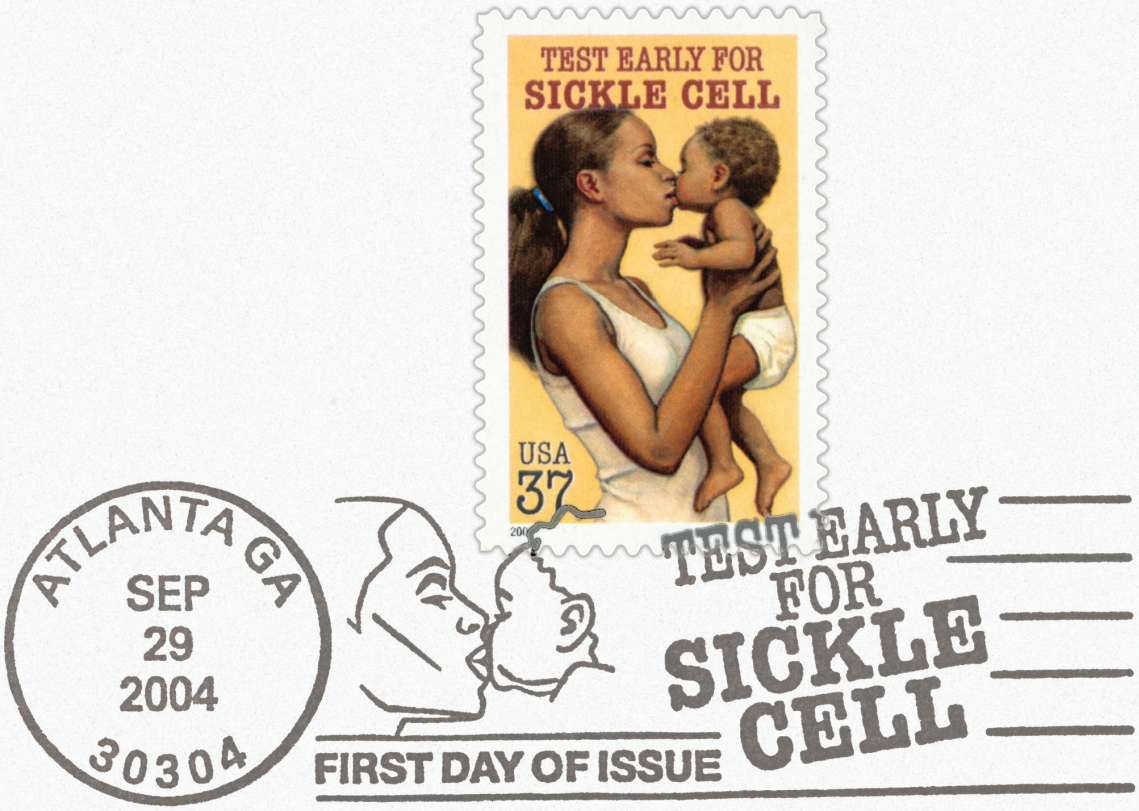
Screening for anaemia and haemoglobinopathy before and during pregnancy

A question of ethnicity?

Suze Jans



SCREENING FOR ANAEMIA AND HAEMOGLOBINOPATHY BEFORE AND DURING PREGNANCY

A question of ethnicity?

Suze Jans

This thesis was prepared by the Department of Primary and Community Care of the Radboud University Medical Centre, Nijmegen, the Netherlands, within the programme of Womens Studies Medicine and the Department of Community Genetics of the VU Medical Center, Amsterdam, the Netherlands.

The thesis (with the exception of chapters 2 and 3) was realised with support of the Centre for Society and the Life Sciences and the Centre for Medical Systems Biology in The Netherlands, funded by the Netherlands Genomics Initiative, [Grant number 70.1.053.1b].

The author received a Travel grant of the EMGO+ Institute of the VU University Medical Center, Amsterdam, the Netherlands.

ISBN: 978-94-6190-173-6

Printing of this thesis was made possible by donations from the Radboud University and the Centre for Society and the Life Sciences and the Centre for Medical Systems Biology in The Netherlands, funded by the Netherlands Genomics Initiative.

Cover based on commemorative stamp of the United States Postal Service designed by James Gurney.

Lay-out and printing: Off Page, www.offpage.nl

Voor Joep Jans: postzegelverzamelaar en psycholoog
(To Joep Jans: stamp collector and psychologist)

SCREENING FOR ANAEMIA AND HAEMOGLOBINOPATHY BEFORE AND DURING PREGNANCY

A question of ethnicity?

Proefschrift
ter verkrijging van de graad van doctor
aan de Radboud Universiteit Nijmegen
op gezag van de Rector Magnificus Prof. mr. S.C.J.J. Kortmann,
volgens besluit van het College van Decanen
in het openbaar te verdedigen op woensdag 14 november 2012
om 13.30 uur precies
door

Suzanna Maria Josephina Philomena Jans
Geboren op 16 mei 1965
te Nijmegen

Promotoren:	Prof.dr. A.L.M. Lagro-Janssen Prof.dr. M.C. Cornel, Vrije Universiteit, Amsterdam
Co-promotoren :	Dr. A. de Jonge, Vrije Universiteit, Amsterdam Dr. L. Henneman, Vrije Universiteit, Amsterdam
Manuscriptcommissie:	Prof.dr. J.A.M. Kremer, voorzitter Prof.dr. H.E. van der Horst, Vrije Universiteit, Amsterdam Prof.dr. V.A.M. Knoers, Universiteit Utrecht

MOTIVATION OF THESIS

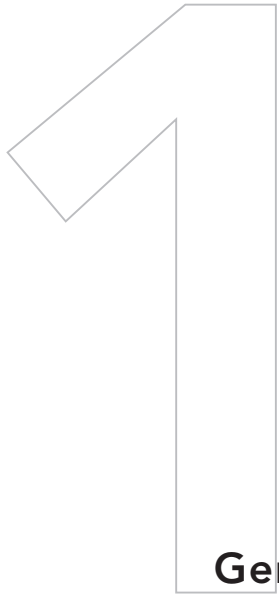
In the late eighties King's College Hospital in England was already offering screening for the carrier status of haemoglobinopathy (HbP). All pregnant women regardless of their ethnic origin were offered a carrier test during the booking visit at the antenatal clinic. During this time I was a student midwife at the hospital. The catchment area of this London based academic hospital involved the areas of Brixton and Peckham; both known for their ethnic diverse populations, especially of African and Afro-Caribbean origin. The prevalence of sickle cell disease and a positive carrier status of HbP were and are high in this area. It was here that I experienced what it means for women to have sickle cell disease. Informing pregnant women about the reproductive risk related to HbP carrier status was the general responsibility of midwives and part of our education on this group of disorders consisted of a mandatory visit to the local Sickle Cell and Thalassaemia Centre which articulated the importance of information on screening.

Great was my surprise that no one seemed to have any knowledge about this group of disorders when I eventually returned to the Netherlands (1992) to work as a primary care midwife. While working in my own midwifery practice in inner-city Amsterdam, which had a very ethnic diverse population, I found myself struggling with anaemia and its possible causes. This and the exposure to clients with different types of anaemia made it easy to decide on the topic of this thesis.

LIST OF ABBREVIATIONS

ASA	American Sociological Association
CBS	Centraal Buro voor de Statistiek (Statistics Netherlands)
CCBH	Centre for Contemporary British History
CCM	Consultative Committee Minorities
CF	Cystic Fibrosis
CI	Confidence Interval
CSG	Centre for Society and Genomics (since 2012 Centre for Society and the Life Sciences)
DoH	Department of Health (Ministerie van Volksgezondheid, Welzijn en Sport; VWS)
FOQ	Family Origin Questionnaire
GP	General Practitioner
Hb	Haemoglobin
HbP	Haemoglobinopathy
HPLC	High-Performance Liquid Chromatography
IDA	Iron Deficiency Anaemia
IUGR	Intra Uterine Growth Retardation
KNOV	Koninklijke Nederlandse Organisatie voor Verloskundigen (Royal Dutch Organisation of Midwives)
MCV	Mean Corpuscular Volume
NHG	Nederlands Huisartsen Genootschap (Dutch College of General Practitioners)
NHS	National Health Service (in United Kingdom)
NNS	Neonatal Screening
NVOG	Nederlandse Vereniging Obstetrie en Gynaecologie (Dutch College of Obstetricians and Gynaecologists)
OR	Odds Ratio
PPH	Post Partum Haemorrhage
PRN	Perinatale Registratie Nederland (Perinatal Registration the Netherlands)
RBC	Red Blood Cells
RR	Relative Risk
SCD	Sickle Cell Disease
SD	Standard Deviation
THD	Transferred Home Delivery
UTI	Urinary Tract Infection
VWS	Ministerie van Volksgezondheid, Welzijn en Sport(Department of Health Welfare and Sports in the Netherlands)
WHO	World Health Organisation

INDEX



General Introduction

The Netherlands has always known migrants; from British monks and travelling gypsies to merchants and labourers from the south and overseas. After World War II migrants from the former Dutch colonies and labourers from especially Morocco and Turkey arrived and the eighties saw an increase in political and economic refugees.[1] This has resulted in the multi-cultural and ethnic diverse society that we live in today: approximately 20% of the Dutch population has a migrant background with much larger percentages among the inhabitants in the four big cities of the Netherlands (www.cbs.nl > themes population. Last accessed 1 May 2012).

Since the nineties, researchers and policymakers have come to the realisation that major ethnic disparities exist in terms of health outcomes.[2,3] This is not only a major issue in the Netherlands but Europe as a whole which experiences similar problems in health care.[4-6] Studies have shown that pregnancy outcomes are not the same for all ethnic groups in the Netherlands[7-10] and that access to health care is still a major issue.[11] In 2009 the report of the Steering Party on Pregnancy and Childbirth advised more attention for women from ethnic minority backgrounds.[12] The research aims set out in this thesis are consistent with this advice. The subject of the thesis concentrates on anaemia and HbP carrier screening related to ethnicity before and during pregnancy.

Screening for anaemia in pregnancy

Anaemia means a low haemoglobin (Hb) level and is determined by a simple measurement of Hb by taking a blood sample. Screening for anaemia in pregnancy is standard midwifery practice, both in the Netherlands and elsewhere.[13-17] The relevance of (screening for) anaemia in the Western world with regards to the outcome of pregnancy is however limited. Circulatory problems are only expected when haemoglobin (Hb) drops below 2.5-3.1 mmol/l.[15] Studies have shown that physical or psychological symptoms in pregnancy are unrelated to a low Hb.[18,19] A causal relationship between a low Hb and prematurity or intrauterine growth retardation (IUGR) has not been confirmed by scientific evidence. Although results are ambiguous, a possible relationship exists between anaemia in pregnancy and prematurity. However it is not certain whether outcomes will improve when anaemia is treated (i.e. with iron tablets in the case of iron deficiency anaemia). It is likely that a low Hb is an indicator for general poor maternal health resulting in a higher risk of prematurity.[15]

There is no literature available to support a relationship between low Hb and an increased risk for postpartum haemorrhage (PPH) or the safety of homebirth.[15] Theoretically more circulatory problems can be expected when a PPH occurs in an extremely anaemic woman. However, an appropriate evidence based reference value cannot not be established. Nevertheless, it is accepted practice to screen for anaemia during pregnancy.[14-16]

Prevalence of anaemia in pregnancy

Anaemia in pregnancy is generally determined by measuring Hb levels. As a result of heterogeneity in definitions used, blood tests, reference values and populations

studied, it is difficult to determine the prevalence of anaemia in pregnancy. The literature presents a range of the prevalence of a low Hb between 2-28% during booking and 2.5-55% in the third trimester of pregnancy.[20-23] The prevalence of iron deficiency anaemia (IDA) is estimated to be between 1-4% in pregnancy.[15]

The World Health Organisation (WHO) definition of anaemia in pregnancy is Hb < 6.8 mmol/l (or < 110 g/l).[24] A Dutch study in 1998 found a prevalence of anaemia in pregnant women of over 42% in the Northern part of the Netherlands, based on these reference values.[20]

Cause of anaemia in pregnancy

A low Hb can be caused by iron deficiency or other pathology but in pregnancy the most likely cause is physiological haemodilution with the greatest drop in Hb occurring around 30-34 weeks gestation.[20,22] Therefore, the parameters for anaemia in pregnancy are different compared to the parameters for non-pregnant women. In the KNOV (the Royal Dutch Organisation of Midwives) anaemia guideline this has resulted in gestation dependent reference values (Table 1).

Measuring Hb alone is insufficient to confirm iron deficiency anaemia (IDA) in pregnancy. The determination of Hb-levels is used as a screening test. If a low Hb is found during pregnancy, the Mean Corpuscular Volume (MCV), which is far less affected by haemodilution, is investigated to confirm physiological haemodilution or the diagnosis IDA.

No studies have been undertaken to describe the prevalence of anaemia in pregnancy according to the reference values used in the midwives' guideline which take physiological haemodilution into account. It would therefore be of interest to know the prevalence of anaemia according to the reference values of the KNOV anaemia guideline.

Table 1. Hb reference values (KNOV 2011)

Preconception	7.5 mmol/l
Pregnancy (in weeks gestation)	
- 13	7.1 mmol/l
14 - 17	6.8 mmol/l
18 - 21	6.5 mmol/l
22 - 37	6.3 mmol/l
38 +	6.5 mmol/l
Postpartum (in weeks)	
1- 5	6.5 mmol/l
6	7.2 mmol/l

Anaemia and ethnic background

There is discussion about a possible difference in Hb reference values amongst women with different ethnic backgrounds.[15,25,26] In the KNOV guideline of 2000 lower Hb reference values were given for Black women than for other ethnic groups.[27] Although some studies have taken possible confounders, such as socio-economic status resulting in poor nutritional status, and geographic status resulting in a higher Hb because of altitude, into account, it is unclear whether results were corrected for the presence of HbP. Besides this midwives have questioned the prevalence of and the policy around anaemia amongst women with different ethnic origins.[28] Few studies have been carried out to substantiate the impression of midwives that pregnant ethnic minority women have a higher risk of anaemia in pregnancy and none according to the KNOV reference values. Before anaemia policy is adjusted for specific groups of pregnant women, we need to establish whether there is a problem and investigate the prevalence of anaemia in different subgroups.

Depending on local policy, anaemia at the end of pregnancy may influence the decision about the place of birth. If anaemia prevalence truly depends on ethnic background, it would mean that some women may have less choice in the place of birth.

Haemoglobinopathy and genetic background

As a result of structural abnormality or a reduced production of normal globin proteins, a link exists between anaemia and HbP. HbP is the umbrella term for disorders such as sickle cell disease (SCD) and thalassaemia. These are autosomal recessive disorders that cause variable but life-long morbidity and a shortened lifespan due to multi-organ ischaemic damage.[29-31] They are considered to be the most prevalent monogenetic disorders worldwide: each year approximately 300,000 babies are born with a severe form of HbP. The prevalence of a positive HbP carrier status has been estimated at 0.03-40% depending on ethnic origin.[31,32]

As a result of the heterozygote advantage in malaria, HbP occur more frequently in those areas where malaria is or was endemic such as Africa, the Mediterranean region, the Middle East and South-East Asia. Because of migration, HbP now also occurs in non-endemic countries. In the Netherlands, each year approximately 60 children are born with a serious HbP disorder.[33] Carrier prevalence has been estimated at 4-26% for Dutch citizens of immigrant descent.[34,35]

Types of haemoglobinopathy

There are over 700 structural Hb variants of which HbS is the most widely known. Homozygotes for HbS suffer from sickle cell disease (SCD). Other structural HbP variants with high frequencies are HbC and HbE.[31] Combinations of HbS and other HbP variants may also lead to SCD. SCD results in red blood cells (RBC) with deviant (sickle) shapes which is caused by a mutation in the haemoglobin gene. This so-called sickling decreases the flexibility of the RBC, resulting in vaso-occlusion and a shortened red cell survival. Patients suffer from acute and extremely painful episodes or so called crisis, causing multi-organ damage and even stroke. Patients are also prone to infections.[29,31,36]

Thalassaemia is an expressional defect, classified according to the globin chain that is affected. Alpha- and beta-thalassaemia are the most common. The alpha chain is produced by four alleles, two paternal and two maternal and the severity of the condition depends on how many of those alleles have been mutated. This includes mild hypochromic anaemia and HbH-disease. The most severe form is Bart's hydrops foetalis which results in stillbirth. Patients with HbH-disease suffer from hepatosplenomegaly, jaundice and occasional bone changes.[31,37]

Beta-thalassaemia also runs a variable course but without adequate treatment such as blood transfusions and chelation therapy, death will occur in early childhood. With adequate treatment children will survive into adulthood. The only known cures for thalassaemia are bone marrow and cord blood transplantations but these treatments are not suitable for everyone and, moreover are expensive[31] (www.nhs.uk. Last accessed 3 May 2012). Other types of HbP are the compound heterozygous SCD such as HbSC; HbSβ0 thalassaemia and HbSβ+ thalassaemia.

Haemoglobinopathy (carrier) Screening

Couples in which both partners are carriers of HbP have a one-in-four chance (25%) in each pregnancy of giving birth to an affected child. However, recessive disorders are not always apparent in families, which means that most couples are unaware of their carrier status[38] and the birth of a child with a severe HbP disorder is therefore usually unexpected. Carriers can be identified by a simple and cheap blood test (High Performance Liquid Chromatography, HPLC). Prospective parents could then be informed about their risk and be given the opportunity to make an informed reproductive decision preferably before or otherwise in early pregnancy.

Despite the advice of the WHO, which advised countries to pay more attention to HbP disorders and to implement screening programmes for risk groups[39], the Netherlands does not have a national screening programme for HbP carrier screening. In 2007, universal screening for SCD, and later beta-thalassaemia, was added to the Neonatal Screening (NNS) programme.[40,41] The primary aim of this addition to the program is health gain for the affected newborn by means of preventing complications of the disorder or even early death. However, the screening method also leads to unsought identification of carriers; about 800 each year.[42] Despite the fact that carrier testing in minors is advised against, in view of privacy, psychological burden, stigmatization and discrimination[43], this unsought finding is reported to parents unless they have declined to be informed about this result by opting-out of the procedure.[44] Those parents whose child is found to be an HbP carrier are invited by their general practitioner (GP) to be tested in order to give them the appropriate reproductive choices in case of a subsequent pregnancy. However, there is evidence that the uptake is minimal.[42]

Although not all carrier parents are identified by NNS, which explicitly is not the aim of the programme, more women will become aware of their HbP carrier status. The genetic relevance has been described above, however the effect, if any, of a positive carrier status on the outcome of pregnancy may also be important.

Textbooks claim an increased risk of urinary tract infection (UTI) or suggest an increased risk of anaemia.[45,46] In the Netherlands no negative effect is assumed for HbP carriers, except perhaps mild anaemia in people with alpha-thalassaemia minor.[34,47] Empirical evidence, however, is inconclusive. It would be important for those involved in maternity care, such as midwives, obstetricians and GPs, to know if any effect of a positive HbP carrier status exists on the outcome of pregnancy, so that appropriate care can be given to those who need it.

Haemoglobinopathy carrier status and ethnicity

Although HbP carrier status can easily be determined by an HPLC test, identification of ethnicity may be necessary regardless of how screening is carried out, not only to investigate mutations as type depends on the couples ethnic origin, but also to inform a couple of their personal risk. In England, where screening was introduced in 2004, ethnicity is determined by means of the Family Origin Questionnaire (FOQ) in both low prevalence areas where targeted screening is practiced, as in high prevalence areas where universal screening is the goal (http://sct.screening.nhs.uk. Last accessed 26 April 2012).

Respect for autonomy and therefore informed choice is an important factor of any screening programme.[48] Identification of risk, in this case by means of ethnicity, enables health care professionals to make adequate risk stratification and support women and couples to make an informed reproductive choice with regards to their (future) pregnancy.

In the Netherlands, midwives and GPs mainly work in primary care. Just like midwives, GPs play an important role in the reproductive lives of women and more than 80% of pregnant women start their antenatal care with a primary care midwife.[49] At present these health professionals might test clients and patients on the basis of unresolved anaemia, a positive family history or consanguinity.[15,17,50-52] An increased risk on the basis of ethnic origin alone is very rarely considered an indication for testing[53], which means that most carriers remain unidentified.

In the Netherlands, many women and couples from those groups at higher HbP risk are probably unaware of the possibilities for carrier testing.[54] However, those who do learn of the possibilities of (ethnicity-based) carrier testing have a positive attitude towards either preconceptional or prenatal carrier testing.[55-57] Some study participants expressed that they preferred to be tested preconceptionally[56,58] and that they want to be adequately informed about testing. One study showed people were in favour of carrier testing provided the costs involved are not too high.[56]

HbP screening did not attract much attention on a national level until the nineties when a discussion erupted in the medical press following a report commissioned by the Consultative Committee Minorities (CCM) of the Department of Health, Welfare and Sports (VWS). On the basis of a low prevalence of HbP, fear of stigmatisation of carriers, lack of knowledge amongst both professionals and those at risk, the report concluded that introducing a screening program was "not opportune".[59] A pilot study of Weinreich et al. among primary health providers and the population

at risk showed that stigmatisation does not seem to be an issue amongst the groups at higher risk of being an HbP carrier.[53] Although it has been subject to debate[60,61], preconceptional and prenatal HbP carrier screening are still not part of routine healthcare in the Netherlands. Both the United Kingdom (UK) and United States (US) have known racial and social conditions related problems regarding the introduction of HbP carrier screening. Considerable barriers of inequality and (institutionalised) discrimination had to be overcome before positive results were achieved by exerting political pressure on the relevant agencies[62] and according to some researchers every aspect of SCD in the US speaks to the problem of race and the social condition of African Americans.[63] Would it be possible that similar issues to those in the UK and the US were part of the decision-making process in the Netherlands? If so it would of interest to know if these issues still exert influence on agenda-setting and the decision making process of today.

Current situation

On a national policy basis carrier screening of any type of disorder is not available at present. The 2007 Health Council report on preconception care advised on a pilot study for HbP and CF carrier screening. However to date no official advice has been issued to set up a broad preconception and/or antenatal carrier screening programme for HbP (and CF) and the Health Council's advice on a preconception programme was rejected by the Minister of Health.[64]

Requests for 'cascade' carrier testing may ensue as a result of the expanded NNS. In addition, increased awareness in society at large may also lead to more frequent requests for carrier testing. However, a more active and broadened policy involving adult carrier testing is also conceivable as the effect of cascade screening has been shown to be limited.[65] Such a policy could go beyond the current NNS program which is primarily meant for morbidity and mortality prevention. Apart from parents who already have an affected child, it would allow reproductive choice for other couples. Primary care providers such as midwives and GPs will be called upon to meet these needs. Achterbergh et al. argued that effective implementation of HbP carrier screening in the Netherlands will require changes among various stakeholders, at several levels of society.[66]

It seems that midwives and GPs have reservations about ordering an HbP carrier test solely on the basis of ethnicity which contrasts with the fact that they do take ethnicity into account, when diagnosing anaemic patients or assessing other aspects of their patients' and clients' health. They were also positive about patient HbP education programs. Despite a positive attitude towards patient education, the participants in this small pilot study did not feel that policy change was needed with respect to their own effectuation of carrier screening.[53] This discrepancy echoes the analysis by Achterbergh et al. and results in an example of inequity in access to health care in the Netherlands that has been shown to exist in other areas as well.[11]

Because attitudes of health professionals may influence clinical practice, the specific attitudes of primary care health professionals such as midwives and GPs

towards ethnicity based HbP carrier screening are of interest. We therefore aimed to investigate midwives' and GPs' attitude, intention and behaviour towards ethnicity based HbP carrier screening as well as their ideas about existing barriers for the implementation of such a program.

THE CONCEPT OF ETHNICITY

In this thesis the term 'ethnicity' will be used when discussing the risk amongst different groups for either anaemia or a positive HbP carrier status. The relationship between ethnicity and health has been described in textbooks and many studies and is currently widely accepted in health care.[3,4,67,68] The aetiology behind this relationship partly depends on which health aspect is being looked at: some disorders have a direct genetic background such as cystic fibrosis (CF) or HbP; others are multi-factorial or not related to genetics at all, such as factors related to lifestyle, infections that are spread by human contacts, living environment and/or use of (preventive) health care services.[69]

As ethnic diversity is increasing, the 'management' of ethnic diversity increasingly becomes a key issue in terms of delivering equitable health care to all groups in society. In order to operationalise ethnicity and to investigate the relationship between health and ethnicity, categorisation of groups is often a necessity, but equally problematic, complex and sensitive. In the second chapter of the thesis, for example, ethnic categories have been used according to the current classification of the National Perinatal Database (http://www.perinatreg.nl. Last accessed 1 May 2012). Although ethnicity and ethnic groups are seen as potentially valuable exposure variables, they are not only difficult to define, but they are also recognised as complex concepts that need to be treated with careful consideration. Critical and cautious interpretation is therefore required, the implications of which are discussed here.

The word 'ethnicity' comes from the Greek word 'ethnos'; meaning nation, people or tribe incorporating geographical and ancestral origins and cultural traditions. However nowadays the term is generally accepted to cover a complex set of values encompassing cultural differences, arising from ancestry, country of birth, migration history, language, lifestyle and religion[68,70] but also of notions of belonging and external recognitions of such claims.[67] It is important to realise that ethnicity, based on this definition, is not static nor simple but rather fluid and complex.

In the US the term 'race' is still acceptable and used by academics. Principally, this term is a biological concept whereby the division is made on the basis of visible physical characteristics.[71] In Europe the term is negatively associated with slavery and colonialism, and is very rarely used. Currently, researchers in the US recognise the fact that 'race' has more meanings than mere physical differences and also emphasize the importance of social (and political) concepts in race.[72,73] Nevertheless, Bhopal cautions against the use of this term for its history of misuse and injustice.[71]

In genetic medicine, ancestral origin is the more accepted concept. All populations originate from the same small group of common ancestors which have

evolved through geographic isolation, regional founder effects, catastrophic natural events and more and have formed the human gene pool that nowadays exists.[74] Ancestral origin determines a priori the risk of genetic disease or the risk of passing on the disease to a person's offspring. This is certainly true for monogenic disorders such as HbP and CF. But in the case of multi-factorial diseases such as diabetes, hypertension or certain cancers, which can have a genetic component but which are also influenced by lifestyle factors, the issue is more complex and the use of ethnicity rather than ancestry might be more appropriate, because it may include both gene and environment. Although determining ancestral origin may appear straight forward, Aspinall et al. argue otherwise quoting a small study carried out by the National Office of Statistics (ONS) in Britain, showing that the term ancestry has its limits because of a lack of understanding by the users. Not all participants were certain how far back they should look at their lineage, uncertainties over their ancestry in Africa or parental origins in the Caribbean and some declined to answer at all, concluding that the term ancestry is therefore unstable.[75] The Canadian Census test is also quoted with a 11.5% non-response mainly because of difficulties remembering the origins of parents and grandparents. Ancestry, whilst seemingly sufficiently describes the information needed for genetic screening such as HbP carrier screening, may not be appropriate in other situations whereby lifestyle and culture play a role such as diabetes. Aspinal also argues that answer categories may be of just as much importance.[75] The same study shows similar answers for ancestry and ethnic group using the same answer categories. Answer categories may also introduce ambiguities for example when primarily based on colour.

The term ethnic origin may therefore be more appropriate especially since ethnicity is the more accepted term in other parts of health care such as midwifery and obstetrics (http://www.perinatreg.nl. Last accessed 1 May 2012). Although not tested, it may be the clearer term for all involved, including health professionals. Fenton argues that what is true of ancestry is true of ethnicity: both are simultaneously socially grounded and socially constructed as the way in which people value and choose their ancestors differs.[76] Context is therefore important.

In the Netherlands, the country of birth and that of (one of) the parents, is accepted in many epidemiological studies as a proxy for ethnicity: so called 'allochtony' a Dutch term meaning "someone with a foreign background" of whom at least one parent was born abroad.[77,78] This "country of birth" definition of ethnicity is used by Statistics Netherlands (or CBS, Central Bureau of Statistics Netherlands as it is known in Dutch), the source of denominator data for many epidemiological studies in the Netherlands. The National Perinatal Registry (PRN) still uses an outdated classification system partly based on the history of the Dutch empire and the history of the first post-war migration waves, but is hoping to replace this soon with country of birth and ethnicity (http://www.perinatreg.nl. last accessed 1 May 2012). CBS also makes a subdivision between Western and non-Western allochtony but interestingly puts Indonesians and Japanese people in the Western allochtony group, allowing

more than just ancestry to enter the municipal registers. Evidently when using the term 'ethnicity', historical context of concepts and terminology cannot be ignored.

Though information on country of birth is generally easy to ascertain, the sought after objectivity and stability may not always be present as argued by Stronks: people's ethnicity may not be consistent with the country they are born in and an adequate gold standard is lacking[78,79]; reflecting the complexity of identity and the contingent nature of ethnicity. Also in genetic studies, self identified ancestry may often lead to a classification that differs from country of birth (of parents).[80] Besides, although the post-war population of immigrant descent is still relatively young, soon if not already, those beyond the second generation will be "lost to statistics" with this method. Stronks et al. have therefore proposed the use of additional indicators such as geographic origin of ancestors, language spoken and self-identified ethnicity.[81]

It is clear that the conceptualisation and the use of ethnicity have been and still are being debated. It has also been argued from an ethical point of view that making ethnic diversity visible may be undesirable. Ahmad and Bradby even go as far to suggest that 'ethnicity' is an over-employed term, sometimes used with such imprecision that it risks losing its analytical value.[67] They argue that using ethnicity as an explanation of inequality ignores underlying, often inequitable, power structures whereby the disadvantage of ethnic minority groups is usually defined by those in power and their disadvantage is related to genetic and dysfunctional cultural inheritance.[82] This doesn't only ignore the real issues at stake but also absolves governments and policymakers from responsibility. For example Agyemang et al. argue that the importance of the influence of the default or host country cannot be ignored when investigating health outcomes as similar ethnic groups have different health outcomes in other countries of residence[83], showing the importance of national context in (in-) equalities in health. Even though all citizens are equal, some groups in society may need different services in order to provide equitable health care for all. As argued by Bhopal, ethnic variations in health and disease are too large to be ignored and that acknowledging and acting upon them is better than ignoring them despite the fact that this may widen ethnic divisions in society.[84]

To add further complexity to these debates, operationalisation of ethnicity and classification of ethnic groups will influence outcomes. Failure to recognise the complexity of terminology and theory involved may lead to poor evidence of ethnic inequalities in health and inappropriate policy and practice. As Craig et al. point out in the introduction of their book; the fact that everyone has an ethnicity is very rarely acknowledged.[85] Ethnic minority groups are usually set aside as 'different' from the default group who are taken for granted. It is essential to realise that inequalities often originate from inequalities in socio-economic status and that complex interactions exist also involving gender and migration status.[76] Set alongside the current political climate in the Netherlands, this becomes an even more important

argument for getting it right. It is conceivable that more than one approach is possible but whatever approach we take, the most important issue before making choices about terminology and definitions, is that we need to understand why we need to make certain distinctions amongst people and what information we are seeking. For example life style related health issues may need a different approach than care surrounding (the risk of) mono-genetic disorders. Since ethnicity is also used in politics, policy and the public debate it is important that the sensitivities involved are understood.

In light of the above the use of the PRN classifications in Dutch research has its limitations. However this is what is currently available to researchers who aim to use this extensive data-base. In the near future the new perinatal database will be implemented. Besides coding according to (parents) country of birth, ethnicity will be classified with a limited ethnicity question (http://www.perintareg.nl. Last accessed 1 may 2012). As argued, more complex issues are at stake. If we want to continue to monitor the health and outcome of pregnancy in the Netherlands, researchers and policymakers will have to think of adequate and sensitive ways of defining the variable 'ethnicity', ultimately depending on the outcome we wish to measure. The fact that most primary health care professionals are more familiar with the term ethnicity, together with the arguments discussed earlier, is the reason why the term ethnicity will be used in this thesis.

AIM OF THESIS

The objective of the first part of this thesis (chapter 2 and 3) is to evaluate screening of anaemia and HbP carrier status against the background of ethnicity.

The second part aims to gain insight into historical background of ethnicity based HbP carrier screening as well as the present attitudes and perceived barriers towards the ethnic registration by midwives and GPs related to preconceptional or antenatal HbP carrier testing.

Research questions

1. What is the prevalence of anaemia in pregnancy according to the cut-off points used in the KNOV anaemia guideline (2000)?
   Is there a difference in the prevalence of anaemia in pregnant women of non-Northern European descent compared with pregnant women of Northern European descent?
   If so, does this difference result in a higher risk of a Transferred Home Delivery (THD), thus reducing the chance for non-Northern European women to choose their place of birth?

2. Does being HbP carrier have any consequences for the health of pregnant women and does it have an effect on the outcome of their pregnancy?

3. When did the issue of preconception, antenatal or neonatal testing of asymptomatic persons at risk of HbP receive attention on the agenda of the Dutch public health authorities and what was the background to this agenda setting?
   To what extent was this influenced by the political climate at the time and potential concerns about the role of ethnicity and the fear of discrimination?

4. What are the attitude, intention and behaviour of midwives and GPs towards ethnic registration and their willingness to undertake carrier testing for clients and patients on the basis of ethnicity?
   What factors play a role in midwives' and GP's attitudes towards ethnic registration related to preconceptional or antenatal HbP carrier testing?
   What are the perceived barriers of these health professionals if ethnicity-based HbP carrier screening would be implemented in the future?

OUTLINE OF THESIS

Chapter 2 describes a retrospective cohort study which was carried out to investigate the prevalence of anaemia in groups of pregnant women of different ethnic origins. The data were also used to see if there was a difference in choice in place of birth for different groups as a result of a difference in anaemia.

Chapter 3 reports on the findings of systematic review of the literature on HbP carrier status, and the (absence or presence of) consequences for the health of pregnant women and the outcome of their pregnancies.

Chapter 4 describes the history of the decision making process surrounding HbP screening in the past and to date and reports on the exploration of the decision making process surrounding the introducing of a broad HbP (carrier) screening programme which is not implemented in the Netherlands (beyond neonatal screening). To what extent was this process influenced by the political climate at the time and potentially deep-seated concerns about the role of ethnicity and the fear of discrimination? The chapter reports on the investigation by means of a witness seminar as developed by the Centre for Contemporary British History (CCBH) in the UK (http://www.kcl.ac.uk/innovation/groups/ich/centres/ccbh/index.aspx. Last accessed 1 May 2012) .

Chapter 5 reports on the quantitative study that used a postal questionnaire to investigate the attitude, intention and behaviour of midwives and GPs towards ethnic registration and the willingness of these primary health care professionals to effectuate HbP carrier testing for clients and patients on the basis of ethnicity.

Chapter 6 describes the qualitative study which used focus group discussions amongst midwives and GPs to explore factors that play a role in their attitudes and understandings of ethnicity and its use in every day practice as well as perceived barriers that prevent these health professionals from offering ethnicity based HbP carrier screening to their patients.

The final chapter (chapter 7) presents the general discussion of the results generated by the studies presented in the thesis, together with the clinical implications and suggestions for further research.

REFERENCE LIST

1. Nicholaas H, Sprangers A. Buitenlandse migratie in Nederland 1795-2006: de invloed op de bevolkingssamenstelling (Foreign migration in the Netherlands 1795-2006: the influence of population composition). www.cbs.nl. 2007.
2. Mackenbach JP. Morbidity and mortality among Turkish subjects in The Netherlands. Ned Tijdschr Geneeskd 1992 May 30;136(22):1044-9.
3. Stronks K. Etnische verschillen in gezondheid en gezondheidzorg (Ethnic differences in health and healthcare). In: Mackenbach JP, van der Maas PJ, editors. Volksgezondheid en gezondheidzorg. Maarssen: Elsevier gezondheidszorg; 2008. p. 175-86.
4. Karlson S, Becares L, Roth M. Understanding the influence of ethnicity on health. In: Craig G, Atkin K, Chattoo S, Flynn R, editors. Understanding 'race' and ethncity.Bristol: The policy Press; 2011. p. 111-28.
5. Mladovsky P, Rechel B, Ingleby D, McKee M. Responding to diversity: An exploratory study of migrant health policies in Europe. Health Policy 2012 Apr;105(1):1-9.
6. Zeitlin J, Combier E, De CF, Papiernik E. Socio-demographic risk factors for perinatal mortality. A study of perinatal mortality in the French district of Seine-Saint-Denis. Acta Obstet Gynecol Scand 1998 Sep;77(8):826-35.
7. Djelantik AA, Kunst AE, van der Wal MF, Smit HA, Vrijkotte TG. Contribution of overweight and obesity to the occurrence of adverse pregnancy outcomes in a multi-ethnic cohort: population attributive fractions for Amsterdam. BJOG 2012 Feb;119(3):283-90.
8. Ravelli AC, Tromp M, Eskes M, Droog JC, van der Post JA, Jager KJ, *et al*. Ethnic differences in stillbirth and early neonatal mortality in The Netherlands. J Epidemiol Community Health 2011 Aug;65(8):696-701.
9. Ravelli AC, Steegers EA, Rijninks-van Driel GC, Abu-Hanna A, Eskes M, Verhoeff AP, *et al*. Differences in perinatal mortality between districts of Amsterdam. Ned Tijdschr Geneeskd 2011;155:A3130.
10. Troe EJ, Raat H, Jaddoe VW, Hofman A, Looman CW, Moll HA, *et al*. Explaining differences in birthweight between ethnic populations. The Generation R Study. BJOG 2007 Dec;114(12):1557-65.
11. Stronks K, Ravelli AC, Reijneveld SA. Immigrants in the Netherlands: equal access for equal needs? J Epidemiol Community Health 2001 Oct;55(10):701-7.
12. Een goed begin: Veilige zorg rond zwangerschap en geboorte (A good start: Safe health care in pregnancy and childbirth). Final report of the Steering Committee Pregnancy and childbirth. 2010 Jan 6.
13. ACOG Practice Bulletin No. 95: anemia in pregnancy. Obstet Gynecol 2008 Jul;112(1):201-7.
14. Beentjes M, Weersma R, Koch W, Offringa A, Verduijn M, Mensink P, Wiersma T, Goudswaard L, van Asselt K. NHG-Standaard Zwangerschap en kraamperiode (NHG guideline pregnancy and puerperium). Utrecht: NHG; 2012. Report No.: M 32.

15. Jans S, Beentjes M. Anemie in de verloskundige praktijk. (Anaemia in midwifery practice). KNOV Guideline. Utrecht; 2010.
16. NICE, the National Collaborating Centre for Women's and Children's Health. Antenatal care. Routine care for the healthy pregnant woman. NICE clinical guideline 62. 2010.
17. Van Wijk MAM, Mel M, Muller PA, Silverentand WGJ, Pijnenborg L, Kolnaar BGM. Anemie (Anaemia). Guideline. Utrecht: NHG; 2003. Report No.: M76.
18. Knottnerus JA, Delgado LR, Knipschild PG, Essed GG, Smits F. Het hemoglobinegehalte van zwangeren en subjectieve klachten. (Haemoglobine levels of pregnant women related to minor complaints). Tijdschr v Soc Gezondheidszorg 1987;65(16):529-33.
19. Lee KA, Zaffke ME. Longitudinal changes in fatigue and energy during pregnancy and the postpartum period. J Obstet Gynecol Neonatal Nurs 1999 Mar;28(2):183-91.
20. Heringa M. Computer-ondersteunde screening in de prenatale zorg (Computer supported screening in antenatal care). PhD thesis, Rijksuniversiteit Groningen; 1998.
21. Schwartz WJ, III, Thurnau GR. Iron deficiency anemia in pregnancy. Clin Obstet Gynecol 1995 Sep;38(3):443-54.
22. Steegers E, Thomas CMG, de Boo T, Knapen MFCM, Merkus JMWM. Klinisch-chemische referentiewaarden in de zwangerschap (Clinical-chemical reference values in pregnancy). Maarssen: Elsevier/Bunge; 1999.
23. Tam KF, Lao TT. Hemoglobin and red cell indices correlated with serum ferritin concentration in late pregnancy. Obstet Gynecol 1999 Mar;93(3):427-31.
24. Worldwide prevalence of anaemia 1993–2005. WHO Global Database on Anaemia. Geneva: WHO Library Cataloguing-in-Publication Data; 2008.
25. Blankson ML, Goldenberg RL, Cutter G, Cliver SP. The relationship between maternal hematocrit and pregnancy outcome: Black-white differences. J Natl Med Assoc 1993 Feb;85(2):130-4.
26. Garn SM, Smith NJ, Clark DC. Lifelong differences in hemoglobin levels between Blacks and Whites. J Natl Med Assoc 1975 Mar;67(2):91-6.
27. Amelink-Verburg M, Daemers DOA, Rijnders MEB. KNOV standaard Anemie in de eerstelijns verloskundige praktijk (Anaemia in primary care midwifery practice). Bilthoven/ Leiden: KNOV en TNO-PG; 2000.
28. Offerhaus P, Fleuren M, Wensing M. De impact van de eerste KNOV-standaard voor eerstelijns verloskundigen (The impact of the first KNOV guideline for primary care midwives). Nijmegen / Leiden: Centre for Quality of Care Research (WOK) / TNO.; 2003.
29. Platt OS, Brambilla DJ, Rosse WF, Milner PF, Castro O, Steinberg MH, *et al*. Mortality in sickle cell disease. Life expectancy and risk factors for early death. N Engl J Med 1994 Jun 9;330(23):1639-44.
30. Dauphin-McKenzie N, Gilles JM, Jacques E, Harrington T. Sickle cell anemia in the female patient. Obstet Gynecol Surv 2006 May;61(5):343-52.
31. Weatherall DJ, Clegg JB. Inherited haemoglobin disorders: an increasing global health problem. Bull World Health Organ 2001;79(8):704-12.
32. Modell B, Darlison M. Global epidemiology of haemoglobin disorders and derived service indicators. Bull World Health Organ 2008 Jun;86(6):480-7.
33. Peters M, Appel IM, Cnossen MH, Breuning-Boers JM, Heijboer H. Sickle cell disease in heel injection screening. I. Ned Tijdschr Geneeskd 2009 May 2;153(18):854-7.
34. Giordano PC, Harteveld CL. Prevention of hereditary haemoglobinopathies in the Netherlands. Ned Tijdschr Geneeskd 2006 Sep 30;150(39):2137-41.
35. Heijboer H, van dT, X, Peters M, Knuist M, Prins J, Heymans HS. One year of neonatal screening for sickle-cell disease in Emma Children's Hospital/Academic Medical Center in Amsterdam. Ned Tijdschr Geneeskd 2001 Sep 15;145(37):1795-9.
36. Bunn HF. Pathogenesis and treatment of sickle cell disease. N Engl J Med 1 997 Sep 11;337(11):762-9.

37. Weatherall DJ. Thalassaemia: the long road from bedside to genome. Nat Rev Genet 2004 Aug;5(8):625-31.
38. Morris JK, Law MR, Wald NJ. Is cascade testing a sensible method of screening a population for autosomal recessive disorders? Am J Med Genet A 2004 Jul 30;128A(3):271-5.
39. World Health Organisation. Sickle cell anaemia. 2006. Report No.: The 59th World Health Assembly; 117th session. Agenda item 4.8; Resolution EB117.R3.
40. Bouva MJ, Mohrmann K, Brinkman HB, Kemper-Proper EA, Elvers B, Loeber JG, *et al.* Implementing neonatal screening for haemoglobinopathies in the Netherlands. J Med Screen 2010;17(2):58-65.
41. Giordano PC. Starting neonatal screening for haemoglobinopathies in the Netherlands. J Clin Pathol 2009 Jan;62(1):18-21.
42. Vansenne F, de Borgie CA, Legdeur M, Spauwen MO, Peters M. Providing Genetic Risk Information to Parents of Newborns with Sickle Cell Trait: Role of the General Practitioner in Neonatal Screening. Genet Test Mol Biomarkers 2011 May 16.
43. Borry P, Evers-Kiebooms G, Cornel MC, Clarke A, Dierickx K. Genetic testing in asymptomatic minors: background considerations towards ESHG Recommendations. Eur J Hum Genet 2009 Jun;17(6):711-9.
44. RIVM-Centrum voor Bevolkingsonderzoek. Draaiboek neonatale hielprikscreening (Scenario Book Neonatal Screening). [Version 8.1]. 2011. Bilthoven.
45. Danforth DN, Gibbs RS, Karlan BY, Haney AF (eds).Danforth's Obstetrics and Gynecology. 9th edition, Lippincott Williams& Wilkins; 2003.
46. Fraser D, Cooper M (eds). Myles Textbook for midwives. 15th ed. Churchill Livingstone Elsevier; 2009.
47. RIVM-Centrum voor bevolkingsonderzoek. Uw kind is drager van sikkelcel (Your child is a carrier of sickle cell). Available from: URL: http://www.rivm.nl/Bibliotheek/Algemeen_Actueel/Brochures/Preventie_Zorg_Ziekte/Hielprik/Uw_kind_is_drager_van_sikkelcel. Last accessed 2 May 2012.
48. Beauchamp TL. Methods and principles in biomedical ethics. J Med Ethics 2003 Oct;29(5):269-74.
49. PRN. Perinatal Registration the Netherlands, major findings.10 years of perinatal registration in the Netherlands. Utrecht: PRN; 2011.
50. De Jong-Potjer LC, Beentjes M, Bogchelman M, Jaspar AHJ, Van Asselt KM. NHG Richtlijn Preconceptie zorg (NHG Guideline Preconception care). Utrecht: NHG; 2011. Report No.: M97.
51. de Jonge A. KNOV Standpunt preconceptie zorg (KNOV position paper Preconception care). Bilthoven: KNOV; 2005.
52. de Jonge A. KNOV Standpunt Prenatale Diagnostiek (KNOV position paper Prenatal Diagnostics). Bilthoven: KNOV; 2005.
53. Weinreich SS, de Lange-de Klerk ES, Rijmen F, Cornel MC, de KM, Plass AM. Raising awareness of carrier testing for hereditary haemoglobinopathies in high-risk ethnic groups in the Netherlands: a pilot study among the general public and primary care providers. BMC Public Health 2009;9:338.
54. Talan D, van Elderen T, Hoogeboom J. Ongelijk verdeeld: migranten vragen minder én ander klinisch genetisch advies [Unequally divided: migrants request less as well as different clinical genetic advice]. Medisch Contact 2004;59:1828-9.
55. Lakeman P, Plass AM, Henneman L, Bezemer PD, Cornel MC, ten Kate LP. Three-month follow-up of Western and non-Western participants in a study on preconceptional ancestry-based carrier couple screening for cystic fibrosis and hemoglobinopathies in the Netherlands. Genet Med 2008 Nov;10(11):820-30.
56. van der Pal S, van Kesteren N, van Dommelen P, Detmar S. Deelnamebereidheid dragerschapscreening op hemoglobinopathieen onder hoogrisicogroepen (Willingness

to participate in HbP carrier screening amongst high risk groups). Leiden: TNO Kwaliteit van Leven; 2009. Report No.: KvL/P&Z 2009.049.

57. van Elderen T, Mutlu D, Karstanje J, Passchier J, Tibben A, Duivenvoorden HJ. Turkish female immigrants' intentions to participate in preconception carrier screening for hemoglobinopathies in the Netherlands: an empirical study. Public Health Genomics 2010;13(7-8):415-23.
58. Locock L, Kai J. Parents' experiences of universal screening for haemoglobin disorders: implications for practice in a new genetics era. Br J Gen Pract 2008 Mar;58(548):161-8.
59. Rengelink-van der Lee JH, van der Most van Spijk MW, Schulpen T. Landelijk onderzoek sikkelcelanemie en thalassemie. Eindrapport (National investigation into sickle cell anaemia and thalassaemia. Final report). Utrecht: onder auspiciën van de Stichting Gezondheid Derde Wereld Kind; 1994.
60. Cornel MC,Detmar S,Plass AMC,Moerman D,Waarlo AJ,de Kinderen M, Giordano PC. Breder screenen op hemoglobinopatie (A broader screening for haemoglobinoptahy). Medisch Contact 2009;Nr. 45(03 november 2009):1874-7.
61. Talan D, van Elderen T, Hoogeboom J. Ongelijk verdeeld. Migranten vragen minder én ander klinisch genetisch advies (Unequal division). `Medisch Contact 2004 Nov 12;59(46):1828-9.
62. Anionwu EN, Atkin K. The politics of sickle cell and thalassaemia. Buckingham Open University Press; 2001.
63. Wailoo K, Pemberton S. A perilous lottery for the black family. Sickle cell, social justice, and the therapeutic gamble. In:The troubled dream of genetic medicine. Baltimore: The John Hopkins University Press; 2006. p. 116-60.
64. Schippers EI. Zwangerschap en geboorte (Pregnancy and Birth). Ministry of Health Wellfare and Sports. [CZ/EKZ 3040205]. 2010.
65. McClaren BJ, Metcalfe SA, Aitken M, Massie RJ, Ukoumunne OC, Amor DJ. Uptake of carrier testing in families after cystic fibrosis diagnosis through newborn screening. Eur J Hum Genet 2010 Oct;18(10):1084-9.
66. Achterbergh R, Lakeman P, Stemerding D, Moors EH, Cornel MC. Implementation of preconceptional carrier screening for cystic fibrosis and haemoglobinopathies: a sociotechnical analysis. Health Policy 2007 Oct;83(2-3):277-86.
67. Ahmad WIU, Bradby H. Locating ethnicity and health: exploring concepts and contexts. In: Ahmad WIU, Bradby H, editors. Ethnicity, Health and Health Care: Understanding Diversity, Tackling Disadvantage. Oxford: Blackwell; 2008. p. 1-15.
68. Bhopal RS. Ethnicity, race and health in multicultural societies. Foundations for better epidemiology, public health and health care. Oxford: Oxford University Press; 2007.
69. Lalonde M. A new perspective on the health of Canadians. A working document. Government of Canada. Minister of Supply and Services; 1974. Report No.: Cat. No. H31-1374.
70. Barot R, Bradly H, Fenton S. Rethinking Ethnicity and Gender. In: Barot R, Bradley H, Fenton S (eds). Ethnicity Gender and Social Change.Houndmills: Macmillan Press; 1999. p. 1-26.
71. Bhopal R. Glossary of terms relating to ethnicity and race: for reflection and debate. J Epidemiol Community Health 2004 Jun;58(6):441-5.
72. Phillips EM, Odunlami AO, Bonham VL. Mixed Race: Understanding Difference in the Genome Era. Soc Forces 2007 Dec;86(2):795-820.
73. Royal CD, Jonassaint CR, Jonassaint JC, De Castro LM. Living with sickle cell disease: traversing 'race' and identity. Ethn Health 2011 Aug;16(4-5):389-404.
74. Peltonen L. Ethnicity and disease. eLS John Wiley & Sons Ltd, Chichester http://www els net [doi: 10 1038/npg els 0005487] 2006;(jan).
75. Aspinall PJ, Dyson SM, Anionwu EN. The feasibility of using ethnicity as a primary tool for antenatal selective screening for sickle cell disorders: pointers from the research evidence. Soc Sci Med 2003 Jan;56(2):285-97.

76. Barot H BHFS. Rethinking ethnicity and Gender. In: Ethnicity, Gender and Social change. Basingstoke: Macmillan Press Ltd; 1999.
77. Keij I. Standaard definitie allochtonen (standard definition allochtony). Index 2000;(10, november/december):24-5.
78. Stronks K, Kulu-Glasgow I, Agyemang C. The utility of 'country of birth' for the classification of ethnic groups in health research: the Dutch experience. Ethn Health 2009 Jun;14(3):255-69.
79. Gill PS, Bhopal R, Wild S, Kai J. Limitations and potential of country of birth as proxy for ethnic group. BMJ 2005 Jan 22;330(7484):196.
80. Lakeman P, Henneman L, Bezemer PD, Cornel MC, ten Kate LP. Developing and optimizing a decisional instrument using self-reported ancestry for carrier screening in a multi-ethnic society. Genet Med 2006 Aug;8(8):502-9.
81. Stronks K, Glasgow IK, Klazinga N. The identification of ethnic groups in health research, additional to the country of birth classification. ZonMW, Comittee Culture and Health.; 2004.
82. Ahmad WI, Bradby H. Locating ethnicity and health: exploring concepts and contexts. Sociol Health Illn 2007 Sep;29(6):795-810.
83. Agyemang C, Kunst AE, Stronks K. Ethnic inequalities in health: does it matter where you have migrated to? Ethn Health 2010 Jun;15(3):216-8.
84. Bhopal RS. Theoretical, ethical and future-orientate perspectives. Evaluating interventions in ethnicity and health. In: Ethnicity, race and health in multicultural societies. Foundations for better epidemiology, public health and health care.Oxford: Oxford University Press; 2007. p. 284-307.
85. Craig E, Atkin K, Chattoo S, Flynn R. Introduction. In: Craig E, Atkin K, Chattoo S, Flynn R (eds). Bristol: Policy Press; 2011. p. 1-13.

2

Are pregnant women of non-Northern European descent more anaemic when compared to women of Northern European descent?

Suze M.P.J. Jans, Darie O.A. Daemers, Rien de Vos, Antoinette L.M. Lagro-Janssen

Midwifery. 2009 ;25(6):766-73.

ABSTRACT

Objectives: to investigate the prevalence of anaemia in pregnancy according to the cut-off points used in the national clinical guideline 'Anaemia in Primary Care Midwifery Practice', and to investigate a possible difference in prevalence between pregnant women of Northern European descent compared with women of non-Northern European descent. The study also investigated whether any difference in prevalence resulted in a higher risk of a transferred home delivery, thus reducing the chance for women to choose the place of birth.

Design: Retrospective cohort study

Setting: Primary care midwifery practices in a highly urbanised area in Amsterdam, the Netherlands.

Participants: All patients in three midwifery practices over 1 year were selected provided that they met the inclusion and exclusion criteria. The practices were selected on the basis of urbanisation, resulting in an adequate ethnic population which was comparable with the ethnic mix in other similarly urbanised areas in the Netherlands. This resulted in a study population of 828 pregnant women of Northern European and non-Northern European descent with low-risk singleton pregnancies during 2003.

Analysis: Mean haemoglobin level and anaemia rate were computed for the total study population as well as separate ethnic groups. Differences between groups were determined using chi^2 tests, and effect sizes were expressed in relative risks including 95% confidence intervals (CI).

Findings: The prevalence of anaemia in pregnancy was 3.4% (n = 28) at booking (first visit) and 2.7% (n = 22) at approximately 30 weeks of gestation. The relative risk of anaemia at booking was 5.9 (95% CI 2.1-16.7) for pregnant women of non-Northern European descent compared with those of Northern European descent. The relative risk of anaemia at approximately 30 weeks of gestation was 22 (95% CI 3-162) for pregnant women of non-Northern European descent compared with those of Northern European descent. The incidence of transferred home delivery was 3.1% in the study population. The relative risk for transferred home delivery was 24.1 (95% CI 3.3-176.7) for pregnant women of non-Northern European descent compared with those of Northern European descent.

Key conclusions and implications for practice: Pregnant women of non-Northern European descent are a specific group in terms of anaemia and are at high risk of a low haemoglobin level for all cut-off values; they have a higher chance of becoming anaemic in pregnancy than women of Northern European descent. As a result, they have a higher risk of a transferred home delivery, taking away their opportunity to choose the place of birth. Haemoglobinopathies did not explain the higher risk of anaemia in pregnant women of non-Northern European descent. Being of non-Northern European descent should be added as a risk factor for anaemia in pregnancy until more is known about the background of this risk factor.

INTRODUCTION

Detection of anaemia in pregnancy is standard practice. However, the question of how this should be done and whether detection of anaemia leads to better pregnancy outcomes has not been answered sufficiently.

In November 2000 the Royal Dutch Organization of Midwives (KNOV) launched its first national clinical guideline entitled 'Anaemia in Primary Care Midwifery Practice'.[1] The guideline is written for midwives working in a primary-care setting looking after women with low risk pregnancies.

The normal or reference values of haemoglobin (Hb) presented in the guideline are based on the observed values in two well-known Dutch studies[2,3] and follow normal haemodilution in pregnancy. Normal values for Black women have been set 0.5 mmol/l lower, based on mainly North American research data that had been adjusted for socio-economic status (SES), dietary influences and geographical factors. Haemoglobinopathies (HbPs) and other possible pathological factors were not taken into account in these studies.[1] According to the World Health Organisation (WHO) 5% of the world's population are carriers for HbP. The prevalence of carriers in the Netherlands is approximately 0.1% among the local Dutch population (1:1300) and 4-13.6% among the Dutch immigrant population (1:25-1:7). Approximately 140,000 immigrants in the Netherlands are estimated to be carriers of HbPs[4,5], but pregnant women of Non-Northern European descent are not routinely screened for HbPs. Discussion whether or not this should be introduced is ongoing.[4-7] The discussion seems to be slowly turning in favour of screening as a result of the new neonatal screening programme which was introduced in the Netherlands on 1 January 2007 and which screens all newborn babies for sickle cell disease.

The guideline operates as a screening instrument for the detection of anaemia in women with normal physiological pregnancies. It recommends Hb investigations at booking (approximately 12 weeks of gestation) and at approximately 30 weeks of gestation. If a pregnant woman belongs to one of the four risk groups for anaemia in pregnancy as defined in the guideline, such as teenage pregnancy, twin pregnancy, poor dietary habits or pregnant within 1 year after a previous birth, she will have an additional Hb investigation at approximately 20 weeks gestation. If an Hb level below the 5th percentile is found, the mean corpuscular volume (MCV) is checked. An MCV of below 80 fL. is considered to be representative of iron deficiency anaemia and therefore iron tablets should be prescribed. If the MCV is below 70fL or above 100fL, or if anaemia is resistant to iron therapy, the woman should be referred to her general practitioner for further investigations. This referral should lead to an adequate detection of anaemia.

In general, the guideline was received positively by midwives[8], but it also has its critics. Elion-Gerritzen argued that the introduction of the guideline would lead to under detection of iron-deficiency anaemia and HbPs in pregnant women, and disagreed with separate cut-off values for pregnant Black women.[6] Midwives, especially those working in highly urbanised areas with large immigrant populations,

have commented that the guideline fails to diagnose anaemia sufficiently early especially in immigrant women of non-Northern European descent.[8]

In the Amsterdam area, it is standard practice for women with an Hb level below 6.0 mmol/l to be transferred to hospital for birth, a so-called 'transferred home delivery' (THD). If women with an immigrant background have a greater risk of severe uncorrected anaemia in pregnancy, than they would also have less chance of being able to choose the place of birth compared with women with a physiological pregnancy. This may result in less favourable outcomes.[9]

The guideline has been in existence for 6 years and is due to be reviewed in 2008. No studies have been undertaken to describe the prevalence of anaemia in pregnancy according to the cut-off points used in the guideline or to substantiate the impression of midwives that pregnant women with an immigrant background have a higher risk of anaemia in pregnancy.

This study aimed to investigate the prevalence of anaemia in pregnancy according to the cut-off points used in the guideline, and to investigate whether there is a difference in the prevalence of anaemia in pregnant women of non-Northern European descent when compared to pregnant women of Northern European descent. The study also investigated whether any difference in prevalence resulted in a higher risk of a THD, thus reducing the chance for women to choose the place of birth.

METHODS

A retrospective cohort study was undertaken to evaluate anaemia in pregnancy between January 2003 and December 2003, when the guideline had been well established. Three primary care midwifery practices in Amsterdam, the Netherlands were selected on the basis that they were all located in highly urbanised areas, served a large multicultural population, and followed the national guideline routinely for Hb investigations (Hb cut-off points and anaemia management when indicated). HbPs were not investigated routinely in any of the practices.

All pregnant women who delivered their baby between 1st of January 2003 and 31st of December 2003, and who were registered with a singleton low-risk pregnancy, at one of the three primary care midwifery practices were included in the study. Women whose care was transferred to hospital before 36 weeks of gestation for medical reasons other than anaemia, and women who suffered from bowel disease or vaginal bleeding other than slight spotting were excluded from the study. Registration with the practice should have been before 20 weeks of gestation; women who booked later than this were also excluded from the study. The guideline recommends that Hb should be investigated routinely at booking and again at approximately 30 weeks of gestation. Women who belonged to any of the four risk groups for anaemia were also investigated at 20 weeks of gestation.

Ethical approval was not required because of the non-experimental nature of the study.

Data collection

Record keeping was computerised in two out of the three practises, and one practice kept their main records on paper. Demographic data collected were date of birth, ethnicity, gravidity, parity, date of booking, expected date of birth and, if applicable, birth year of last previous baby.

All data related to anaemia were collected such as Hb in mmol/l, MCV in fL, HbPs if found, treatment given, referrals for anaemia and risk groups for anaemia.

Ethnicity

Ethnic origin was identified according to the Dutch obstetric registration system. This register classifies women into the following groups: Dutch, Mediterranean, other European, Creole, Hindu, Asian, other and unknown. The guideline makes a distinction between White and Black women. Since people with Turkish and Moroccan backgrounds are two large ethnic groups within Dutch society, Mediterranean women were investigated in depth. To accommodate the guideline, to depict the specific groups in Dutch society and to obtain a sufficiently large enough group for statistical analysis, the study population was divided into Northern European and non-Northern European. The latter group included Black, Mediterranean (Turkish and Moroccan) and 'other' women (consisting of Asians, Hindus, women from Indian descent living in Surinam, others and unknown).

Statistical analysis

Mean [standard deviation (S.D.)] Hb, prevalence of anaemia at booking and at approximately 30 weeks of gestation, and the rate of THD were calculated for the total study population. Subsequently differences in ethnic subgroups were analysed. Mean (S.D.) Hb was determined, as well as rates of Hb below the 5th percentile (considered to be the lowest acceptable normal level of Hb in pregnancy), and anaemia and Hb below 6.0 mmol/l at booking (considered to be a sign of possible pathology) and at 30 weeks of gestation (as this was a reason for THD). Descriptive statistics were used for all of these data.

The differences between pregnant women of Northern European and non-Northern European descent were determined for the rates of low Hb, anaemia and the rate of THD using Chi^2 tests. Effect sizes were expressed in relative risks (RR) and their 95% confidence intervals (CI).

Data were analysed using Statistical package for the Social Sciences version 12.0.1 (SPSS Inc., Chicago, IL, USA) and a p-value of < 0.05 was considered to be statistically significant.

FINDINGS

In total, 1181 cases were retrieved from the three midwifery practices, and 945 (80%) were included in this study.

The mean age of the excluded women was 29.9 years (S.D. 6.5), 42.4% were primiparous, 28.4% were of Northern European descent, 18.2% were Mediterranean, 39.4% were Black, and 13.9% were other ethnic groups. The main reasons for exclusion were a medical indication for secondary care (45.3%) and booking after 20 weeks of gestation (44.5%); in addition, 5.1% of women were excluded because of bowel disease and 5.1% because of vaginal bleeding. Following exclusion of cases wit missing data (i.e. those without Hb taken at booking or approximately 30 weeks of gestation), 828 cases (70%) remained for analysis.

The mean age of the included women was 30.5 years (S.D. 5.8). Approximately half of the study population were primiparous (49.6%). Approximately half of the population was of Northern European descent (48.9%) and the women of non-Northern European descent appeared to be a very heterogeneous group. Of the latter, the subgroups were Mediterranean 19.4%, Black 21.4% and other 10.3% (Table 1).

The 'other' group consisted of 24% Hindus with origins in Surinam, 34% Asians, 32% others (e.g. South American and Middle Eastern women) and 10% unknown.

In this study, mean Hb followed the physiological drop in Hb associated with gestation, ranging from a mean of 7.7 mmol/l (S.D. 0.6) at 10 to 13 weeks of gestation to 6.9 mmol/l (S.D. 0.66) at 22-37 weeks of gestation. The overall rates of

Table 1. Characteristics of studied population (n = 828).

Included pregnant women	**n**	**%**
Mean age (S.D.)	30.5 (5.8)	
Mean gestation in weeks		
Booking (S.D.)	13.3 (2.5)	
30 weeks (S.D.)	30.4 (3.2)	
Primiparous	411	49.6
Multiparous	417	50.4
Ethnicity		
Northern European		
Dutch	379	45.8
Other European	26	3.1
Non-Northern European		
Mediterranean	161	19.4
Black	177	21.4
Other non-Black	85	10.3

SD: Standard Deviation

anaemia at booking and approximately 30 weeks of gestation were 3.4% and 2.7%, respectively (Table 2).

Ethnic differences in Hb and anaemia

At booking

Stratified analysis showed significant differences for the varying cut-off points of Hb in the guideline and for anaemia amongst the different ethnic groups studied (table 3). A significant difference was found in mean Hb at booking, regardless of gestation, between women of non-Northern European descent and women of Northern European descent (p=0.001). Non-Northern Europeans had a significantly higher risk for an Hb below the 5th percentile at booking when the booking took place before 14 weeks of gestation (RR 2.1, 95% CI 1.3–3.3). There was no difference if they booked later than 14 weeks of gestation. The difference between non-Northern Europeans and Northern Europeans was significant for an Hb below 6.0 mmol/l at booking (RR 12.4, 95% CI 1.6–94.7).

Women of non-Northern European descent also had a significantly higher risk for anaemia at booking (RR 5.9, 95% CI 2.1–16.7).

No significant difference was found in mean Hb at booking regardless of gestation, between Mediterranean women and Northern European women. Mediterranean women had a higher risk for an Hb below the 5th percentile when the booking took place before 14 weeks of gestation (3.0, 95% CI 1.8–5.2). The difference between Mediterranean women and Northern European women was significant for an Hb below 6.0 mmol/l (RR 15.1, 95% CI 1.8–124.4). Mediterranean women had a significantly higher risk for anaemia at booking (RR 7.4, 95% CI 2.4–22.8).

A significant difference was found in mean Hb at booking, regardless of gestation, between Black women and Northern European women (p = 0.008). They were not significantly different with regard to an Hb below the 5th percentile

Table 2. Mean haemoglobin (Hb) levels, anaemia prevalence and rate of transferred home delivery (THD) in entire study population.

Gestation	Mean Hb (mmol/l)	S.D.	n	%
At booking				
10 - 13 wks	7.7	0.6		
14 - 17 wks	7.4	0.66		
18 - 21 wks	7.0	0.73		
Anaemia			28	3.4
(mean Hb, SD.)	6.9	0.66		
Anaemia			22	2.7
THD			26	3.1

SD: Standard Deviation

Table 3. Characteristics of ethnic subgroups

	Northern European	Non-Northern European	Mediterranean	Black	Other
	405	423	161	177	85
Mean Hb at booking Mmol/l					
10-13 wks (S.D.)	7.8 (0.59)	7.5 (0.59)	7.5 (0.67)	7.4 (0.51)	7.5 (0.60)
14-17 wks (S.D.)	7.6 (0.60)	7.3 (0.66)	7.4 (0.66)	7.1 (0.69)	7.3 (0.51)
18-21 wks (S.D.)	7.3 (0.64)	6.9 (0.74)	7.1 (0.99)	6.7 (0.59)	7.1 (0.23)
Booking					
Hb< 5th percentile n (%)	30 (7.4%)	82 (19.4%)	31 (19.3%)	12 (6.9%)	13 (15.3%)
Anaemia n (%) (Hb<p5/MCV<80fL)	4 (1.0%)	24 (5.7%)	11 (6.8%)	7 (4.5%)	6 (7.1%)
Unknown n (%)	22 (5.4%)	31 (7.3%)	18 (11.2%)	8 (4.5%)	5 (5.9%)
Hb < 6 mmol/l n (%)	1 (0.2%)	13 (3.1 %)	6 (3.7%)	6 (3.4%)	1 (1.2%)
Hb at +/- 30 wks					
Mean Hb mmol/l (S.D.)	7.2 (0.52)	6.7 (0.70)	6.8 (0.68)	6.7 (0.69)	6.6 (0.73)
Hb < 5th percentile n (%)	12 (3.0%)	63 (14.9%)	23 (14.3%)	18 (10.2%)	22 (25.9%)
Anaemia n (%) (Hb<p5/MCV<80fL)	0 (0)	22 (5.2%)	7 (4.3%)	5 (2.8%)	10 (11.8%)
Unknown n (%)	5 (1.2%)	20 (4.7%)	8 (5.0%)	5 (2.8%)	7 (8.2%)
Hb < 6 mmol/l n (%)	2 (0.5%)	54 (12.8%)	15 (9.3%)	25 (14.1)	14 (16.5%)

Hb: Haemoglobin, MCV: Mean Corposcular Volume, S.D.: Standard Deviation

at booking before 14 weeks of gestation, but had a higher risk for an Hb below 6.0 mmol/l (RR 13.7, 95% CI 1.7–113.2). Black women had a significantly higher risk for anaemia at booking (RR 4.0, 95% CI 1.2–13.4) compared to women of Northern European descent.

No significant difference was found in mean Hb at booking regardless of gestation, between other ethnic groups and Northern Europeans. The other ethnic groups had a significantly higher risk for Hb below the 5th percentile before 14 weeks of gestation, (RR 2.7, 95% CI 1.4–5.0). There was no significant difference between other ethnic groups and Northern Europeans for an Hb below 6.0 mmol/l. Other ethnic groups had a significantly higher risk of anaemia at booking (RR 7.2, 95% CI 2.1–24.9).

At 30 weeks

Non-Northern Europeans had a higher risk for an Hb below the 5th percentile compared with Northern Europeans (RR 5.0, 95% CI 2.8–9.2). They also had a

significantly higher risk for anaemia (RR 22.0, 95% CI 3–162) and an Hb below 6.0 mmol/l (RR 25.8, 95% CI 6.3–105.3) at approximately 30 weeks of gestation.

Mediterranean women had a higher risk for an Hb below the 5th percentile at around 30 weeks of gestation compared with Northern European women (RR 4.8, 95% CI 2.5–9.5). They also had a higher risk of anaemia (RR 20.8, 95% CI 2.6–165.2), and an Hb below 6.0 mmol/l (RR 18.9, 95% CI 4.4–81.6) at approximately 30 weeks of gestation.

Black women had a higher risk for an Hb below the 5th percentile compared with Northern European women (RR 3.4, 95% CI 1.7–7.0). They also had a higher risk for anaemia (RR 13.9, 95% CI 1.7–114.9), and an Hb below 6.0 mmol/l (RR 28.6, 95% CI 6.8–119.4) at approximately 30 weeks of gestation.

Other ethnic groups had a significantly higher risk of an Hb below the 5th percentile compared with Northern European Women (RR 8.7, 95% CI 4.5–17.0). They also had a higher risk for anaemia (RR 55.3, 95% CI 7.2–422.2), and an Hb below 6.0 mmol/l (RR 33.4, 95% CI 7.7–144.1) at approximately 30 weeks of gestation.

Transferred Home Delivery (THD)

According to local policy women with an Hb below 6 mmol/l were scheduled for a THD. This occurred in 26 women (3.1%): one was Northern European, seven were Mediterranean, 14 were Black and four were of other origins.

The RR for a THD for non-Northern Europeans was high when compared to Northern Europeans (RR 24.1 95% CI 3.3–176.7). Within the group of non-Northern Europeans the RR for THD in Mediterranean women was 17.6 (95% CI 2.2–142.0), the RR for THD in Black women was 32.0 (95% CI 4.2–241.7), and the RR for THD in women of other origins was 19.5 (95% CI 2.2–172.4).

Haemoglobinopathies

Due to the multicultural population in the practices studied, some women were investigated for HbPs regardless of the findings that were obtained following the guideline. Twenty-four women were found to have sickle cell trait and five women were found to be positive for thalassaemia, none of which were major. The blood results of six of these women warranted an investigation into HbPs because of uncorrected or unexplained anaemia. The MCV of three women with an Hb below the 5th percentile was not determined; nevertheless, they were investigated for HbPs and found to be positive. In total 234 women were investigated for HbPs.

DISCUSSION

This study confirms the impression held by midwives that Women of non-Northern European descent are a specific group in terms of anaemia, and that they are at high risk of a low Hb for all cut-off values. They have a higher chance of becoming anaemic in pregnancy, and this can result in different care due to the higher risk of THD for this group. This study clearly shows that this group warrants further attention when it comes to anaemia during pregnancy.

Methodological issues

Before interpreting the findings, the methodological issues of this study will be addressed. The study population was a representative sample of the population in highly urbanised areas in the Netherlands in terms of age and parity. The overall mean age of pregnant women living in highly urbanised areas is 29.9 years, whereas the mean age of the women in the study was 30.5 years (S.D. 5.8). Of all singleton pregnancies in the Netherlands, 47% are primiparous women.[10]

The ethnic background of the population of pregnant women depends very much on the degree of urbanisation. In highly urbanised areas in the Netherlands, the percentage of Dutch pregnant women is 57%.[10] The practices studied were all situated in highly urbanised areas. One area is specifically known for its population of African and Surinam origin. This explains the large numbers of pregnant Black women in the study.

The study population was divided into women of Northern European descent and women of Non-Northern European descent. The group of women of Non-Northern European descent was a heterogeneous group. Therefore a stratified analysis for three subgroups was undertaken. The subgroup 'others' was also in itself heterogeneous. However this group was too small for further statistical testing, while omitting the group would have resulted in loss of information. The findings of this latter group should therefore be treated with some caution.

Due to the retrospective nature of the study, it was difficult to complete all data which sometimes made it difficult to deduct the management of anaemia and actions taken from the records. One fifth of the women were excluded. This group consisted mainly of late bookers and women with a medical indication for secondary care. One practice had more exclusions than the other two practices. This practice is situated in an area of Amsterdam which is known for its large multicultural population as well as for its poverty. It is possible that a low SES played a role and may have introduced some selection bias, as it could very well be argued that women with a low SES are more likely to be anaemic. Recently Alderliesten (2006) confirmed that, amongst other factors, low levels of education and communication problems beyond language, such as cultural difference, are related to a late start of antenatal care.[11] However due to the retrospective nature of the study, the presence of selection bias remains speculative.

The overall rate for anaemia was 3.4% at booking and 2.7% at approximately 30 weeks of gestation. The difference between these values and the prevalence suggested by the guideline may be explained by the fact that there were insufficient data for 78 women (9.4%) to determine whether or not they were anaemic. Insufficient data meant that either the MCV was missing or the Hb was not investigated further, despite being extremely low. If all of these 78 women with missing data were anaemic, the prevalences would be 9.1% at booking and 5.7% at approximately 30 weeks of gestation.

When antenatal care was started late, no significant difference was found in anaemia at booking. A possible explanation may be the low SES pathway described above. A late start for antenatal care is not just due to differences in ethnicity but is also related to education, age and communication problems with language barriers.[11]

Transferred Home Delivery

The significantly higher risk for anaemia in women of non-Northern European descent was also reflected in their much higher risk for THD (RR 24.1, 95%CI 3.3-176.7). These women were not able to choose their place of confinement; however, the numbers in this group are small, and this is reflected in the large CI.

Of the 26 women who should have been scheduled for THD, the guideline was not properly used for 14 women. These cases might have been prevented. In most cases the risk factor for anaemia as specified in the guideline was not identified. If ethnic background was added to the guideline as a risk factor, this part of the guideline would need the attention of midwives.

It is difficult to determine the consequences, if indeed there are any, of missing a risk factor with regard to the health of pregnant women and the management of labour. This should be further investigated.

Haemoglobinopathy

It has never been one of the aims of the guideline to screen and find all HbPs. However, they are found occasionally when pregnant women are anaemic and do not respond to treatment. It could be argued that in a multicultural population with a large percentage of women of Non-Northern European descent, (extreme) anaemias could be caused by HbPs. However, this study only found six women who were positive for HbPs on account of anaemia found during pregnancy. Three women had incomplete data, and the 20 women who were found to be positive for HbPs were investigated regardless of anaemia.

The risk of harm to the baby is obvious if both parents are HbP carriers[4,5], and the clinical relevance of sickle cell disease or thalassaemia major is also evident. However, the clinical relevance for pregnant women of being an HbP carrier is not immediately obvious, as not all carriers develop anaemia in pregnancy. If a non-Northern European pregnant woman has an adequate Hb, the question arises whether or not there is any harm in not knowing her HbP status?

It could be argued that if the HbP status of pregnant women was known at an early stage in pregnancy, couples could receive adequate counselling and certain anaemias could be better managed. Women could circumvent an unnecessary long route of finding out the cause of an extreme low Hb that has been allowed to develop in pregnancy, which may have been prevented by timely investigations and simple folate supplements. However, further research is necessary to substantiate this theory.

Key conclusions and implications for practice

In view of the substantial differences found for pregnant women of non-Northern European descent with regard to low Hb and anaemia, special attention should be given to ethnicity when the guideline is revised.

Although the clinical relevance of knowing HbP carrier status in pregnant women is not clear, this can cloud the management of anaemia. Therefore midwives need

to give this issue more attention and should be more aware of its influence on the reproductive lives of women.

The guideline should be revised to enable midwives to give adequate and customised care to women of non-Northern European descent. It is evident from this study that women of non-Northern European descent have a higher risk for anaemia in pregnancy and there for need extra attention with regard to this issue.

Knowledge of HbP status at an early stage in pregnancy could be an advantage in the outcome of pregnancy in several ways. Earlier attention to the possibility of anaemia in pregnancy can prevent extreme low Hb levels in this group, and give these women equal opportunities in their choice of place of birth.

However the true background behind the fact that women of non-Northern European descent have a higher risk of anaemia in pregnancy is not only determined by knowing the HbP status. Further research by midwives into the reasons behind this higher risk is necessary.

Being of non-Northern European descent should be added as a risk factor for anaemia in pregnancy until more is known about the background of this risk-factor.

REFERENCES

1. Amelink-Verburg M, Daemers DOA, Rijnders MEB. KNOV standaard Anemie in de eerstlijns verloskundige praktijk (Anaemia in primary care midwifery practice). Bilthoven/ Leiden: KNOV en TNO-PG; 2000.
2. Heringa M. Computer-ondersteunde screening in de prenatale zorg (Computer supported screening in antenatal care). PhD thesis, Rijksuniversiteit Groningen; 1998.
3. Steegers E, Thomas CMG, de Boo T, Knapen MFCM, Merkus JMWM. Klinisch-chemische referentiewaarden in de zwangerschap (Clinical-chemical reference values in pregnancy). Maarssen: Elsevier/Bunge; 1999.
4. Giordano PC, Harteveld CL. Prevention of hereditary haemoglobinopathies in The Netherlands. Ned Tijdschr Geneeskd 2006 Sep 30;150(39):2137-41.
5. Giordano PC, Bouva MJ, Harteveld CL. A confidential inquiry estimating the number of patients affected with sickle cell disease and thalassemia major confirms the need for a prevention strategy in the Netherlands. Hemoglobin 2004;28(4):287-96.
6. Elion-Gerritzen WE, Giordano PC, Haak HL. The 'Anemia in the midwife practice' standard issued by the Royal Dutch Organisation of Midwives: a risk of not recognizing iron deficiency and hemoglobinopathy. Ned Tijdschr Geneeskd 2002 Mar 9;146(10):457-9.
7. Schulpen TW, van der Lee JH, van der Most van Spijk MW, Beemer FA. Genetic carrier screening for hemoglobinopathies in the Netherlands is not opportune. Ned Tijdschr Geneeskd 1998 May 2;142(18):1019-22.
8. Offerhaus P, Fleuren M, Wensing M. De impact van de eerste KNOV-standaard voor eerstelijns verloskundigen (The impact of the first KNOV guideline for primary care midwives). Nijmegen / Leiden: Centre for Quality of Care Research (WOK) / TNO.; 2003.
9. Wiegers TA, Keirse MJ, van der Zee J, Berghs GA. Outcome of planned home and planned hospital births in low risk pregnancies: prospective study in midwifery practices in The Netherlands. BMJ 1996 Nov 23;313(7068):1309-13.
10. Foundation of Perinatal Registration (PRN). Perinatal Care in the Netherlands, 2001. Bilthoven: Foundation PRN; 2005.
11. Alderliesten M. Quality of perinatal care in a multi-ethnic population. PhD thesis, University of Amsterdam; 2006.

3

Maternal and perinatal outcomes amongst haemoglobinopathy carriers: a systematic review

Suze M.P.J.Jans, Ank de Jonge, Antoinette L.M. Lagro-Janssen

Int J Clin Pract. 2010 ;64(12):1688-98.

ABSTRACT

With the introduction of screening programmes for haemoglobinopathies (HbP), more women will be aware of their HbP status. The genetic risk for women who are carriers of HbP is well known. However, midwives and obstetricians need to know whether there are other risks involved in the pregnancies of women who are carriers of HbP. The objective of this study was to investigate the hypothesis that being a carrier of HbP has no consequences for the health of pregnant women and the outcome of their pregnancies. A systematic search was carried out until August 2008 in the Cochrane Library, Medline, EMBASE and CINAHL databases. All references were inspected to identify further studies. The authors of key publications were contacted for any unpublished research. Selection of studies was made on the basis of the following criteria: Cohort and case-control studies, pregnant women with a singleton pregnancy, exposure: HbAS or thalassaemia minor and the following outcomes: urinary tract infection (UTI), anaemia, (pre-)eclampsia, gestational diabetes, premature labour, low birth weight, intrauterine growth retardation, miscarriage, neonatal death, low Apgar score, neural tube defects. Quality assessment and data extraction were carried out by two researchers. A total of 780 subjects were identified of which nine were included in the study. A protective effect of sickle cell trait was found for premature birth, low Apgar score and perinatal mortality rate. No significant effect was found for low birth weight, growth retardation, UTI or high blood pressure. The risk of anaemia and bacteriuria was increased. In conclusion, the risks amongst pregnant HbP carriers are low. Midwives and obstetricians need to be aware of the risk of anaemia and UTI.

INTRODUCTION

It is generally accepted that the pregnancy of a woman with homozygotic haemoglobinopathy (HbP) disease and some double heterozygous conditions, such as HbSC and HbS-β-thalassaemia, carries a higher risk. While the genetic implications of HbP carrier status are clear, the effect if any, on the outcome of pregnancy remains subject to debate.

Thalassaemia minor (carriers) constitutes of alpha and beta defects and some rare exceptions.[1] The most well known of the structural defects is HbS, like beta thalassaemia this is a beta gene defect that is non-active in the fetus until birth.

Over the years, several studies on the effect on pregnancy have been published but provide inconsistent conclusions. Some studies suggest an increased risk for adverse perinatal outcomes[2-4] whereas others cannot confirm this risk.[5-9] Pregnant women with homozygotic HbP disease need to be referred to a tertiary care centre. Pregnant women who are (known) HbP carriers are usually considered low risk as no risks for their health or the outcome of their pregnancies are assumed. However, it remains unclear whether these women have special needs during pregnancy. As far as we are aware, no systematic review has been conducted on this subject.

Screening for sickle cell disease has been added to the existing neonatal screening program in several countries, such as the Netherlands and England. If a baby has been diagnosed with sickle cell disease or thalassaemia major or is a carrier, the parents will be offered genetic screening tests to confirm their carrier status which will then enable them to make appropriate reproductive choices concerning any subsequent pregnancies. Midwives and obstetricians will therefore increasingly encounter women who are aware of their HbP carrier status. The prevalence of an HbP carrier status is currently estimated to be 4-14% amongst people with non-Northern European background in the Netherlands[10] and according to the World Health Organisation approximately 5% of the world population is a carrier of a significant variant of haemoglobin disorders such as sickle cell disorders or thalassaemias with as many as 40% carriers in some regions.[11] It is therefore important that midwives and obstetricians are aware of any potential risks among HbP carriers during pregnancy.

In this systematic review we will address the possible risks for pregnant HbP carriers and investigate the hypothesis that being an HbP carrier has no consequences for the health of pregnant women and the outcome of their pregnancies.

METHODS

With the aid of a librarian, we searched the Cochrane Library; Medline; EMBASE and CINAHL databases for publications in English, French, German, Spanish and Dutch, examining the effect of sickle cell trait (SCT) and/or thalassaemia minor on maternal morbidity or perinatal morbidity and mortality.

The search was not restricted by publication date and was carried out until august 2008. We only searched for (prospective and retrospective) cohort studies and case control studies.

Keywords used were: Pregnant women, sickle cell, sickle cell trait, sickle cell anaemia, sickle cell disease, thalassaemia, heterozygote thalassaemia, haemoglobinopathy, abnormal haemoglobines, pregnancy outcome, complications of pregnancy, urinary tract infections, iron deficiency anaemia (IDA), folic acid deficiency anaemia, (pre-) eclampsia, gestational diabetes, premature labour, low birth weight, miscarriage, fetal / neonatal death, low Apgar score and neural tube defects.

We inspected the references of all studies found to identify any further studies. The authors of key-publications were contacted for any unpublished research.

The initial selection of studies by title and abstract was carried out by one reviewer (SJ) based on its relevance to the research question and, if possible, by the inclusion criteria (Table 1). The studies found were assessed and scored by two independent reviewers (SJ and AdJ). Details of authors, affiliated institutions, journal name, and year of publication were removed for the second reviewer.

Selection for inclusion into the review was made on the basis of in- and exclusion criteria and quality assessment. The use of checklists is disputed by some.[12] Sanderson et al.[13] highlighted the lack of existence of an adequate tool, but he nevertheless

Table 1. Inclusion criteria

Inclusion criteria
Types of studies All observational (prospective and retrospective) cohort studies and case control studies examining the effect of sickle cell trait and/or thalassaemia minor on maternal morbidity and neonatal morbidity and mortality.
Types of participants Pregnant women with singleton pregnancy.
Types of exposure Sickle cell trait or heterozygous α-/β-thalassaemia or homozygous α+ thalassaemia versus no trait or no thalassaemia. Sickle cell trait is defined as the presence of HbAS. Carrier ship of thalassaemia is defined as α+-thalassaemia heterozygote; α0-thalassaemia heterozygote; α+-thalassaemia homozygote or β-thalassaemia heterozygote.
Types of outcome measures Urinary tract infections Iron deficiency anaemia Folic acid deficiency anaemia (Pre-) eclampsia Gestational diabetes Premature labour Low birth weight Intra uterine growth retardation Spontaneous abortion Fetal / neonatal death Low Apgar score Neural tube defects

advised to use a simple checklist rather than a scale and concluded that it is important to use a small number of key domains for quality assessment. We decided to use the guidelines for assessing the quality of observational and case control studies as defined by the Dutch Institute for Healthcare Improvement to support our quality assessment.[14] These include all the elements mentioned by Sanderson et al.[13], and have been carefully developed by the institute in collaboration with the Dutch Cochrane Centre and are generally accepted as adequate in the Netherlands (Table 2). We awarded a maximum of two points for each item on the list, meaning that each study could score a maximum of 16 points. We excluded any study which obtained a score of < 12 points. This high cut-off point was chosen because almost all studies automatically scored high on 'adequate follow-up' and 'selective loss-to-follow-up'. Some authors were contacted for clarification of the study methods.

Data were extracted independently from the included studies by two investigators (SJ and AdJ) on study design, population and setting, screening method, exposition, outcome variables, confounders and point estimates. Differences were resolved by discussion.

Table 2. Quality assessment

Quality assessment criteria
(The Dutch Institute for Healthcare Improvement (CBO) www.cbo.nl)
Each item scores 0 to 2 points:
- Were the groups that were compared clearly identified?
- Could selection bias be sufficiently excluded?
- Was the exposure factor clearly identified and was the method for assessing the exposure factor adequate?
- Was the outcome clearly identified and was the method for assessing the outcome adequate?
- Was the outcome assessed blinded for the exposure factor?
- Was the follow-up adequate?
- Could selective loss-to-follow-up be excluded?
- Were the most important confounders identified and was correction for the confounders carried out?

(Statistical) analysis

We used population (ethnicity), exposition, screening method and (definition of) outcome variables to assess clinical heterogeneity. Study design, confounders and point estimates were used to assess methodological heterogeneity. Confounders were assessed for all separate outcomes.

Both clinical and methodological homogeneity could not be established; therefore after consultation with a statistician, we decided not to pool the results.

RESULTS

We initially identified 780 studies from which we selected 91 titles (fig.1). After screening the abstracts, we read 36 papers. By inspecting the references of these papers, we identified a further 30 studies of which nine studies were read and assessed. Contact with the authors provided one additional study which was only available as a (PhD-) thesis.[15] In total 46 studies were assessed for methodological quality. The two reviewers disagreed on six out of 46 studies (13%). Consensus was reached by discussion.

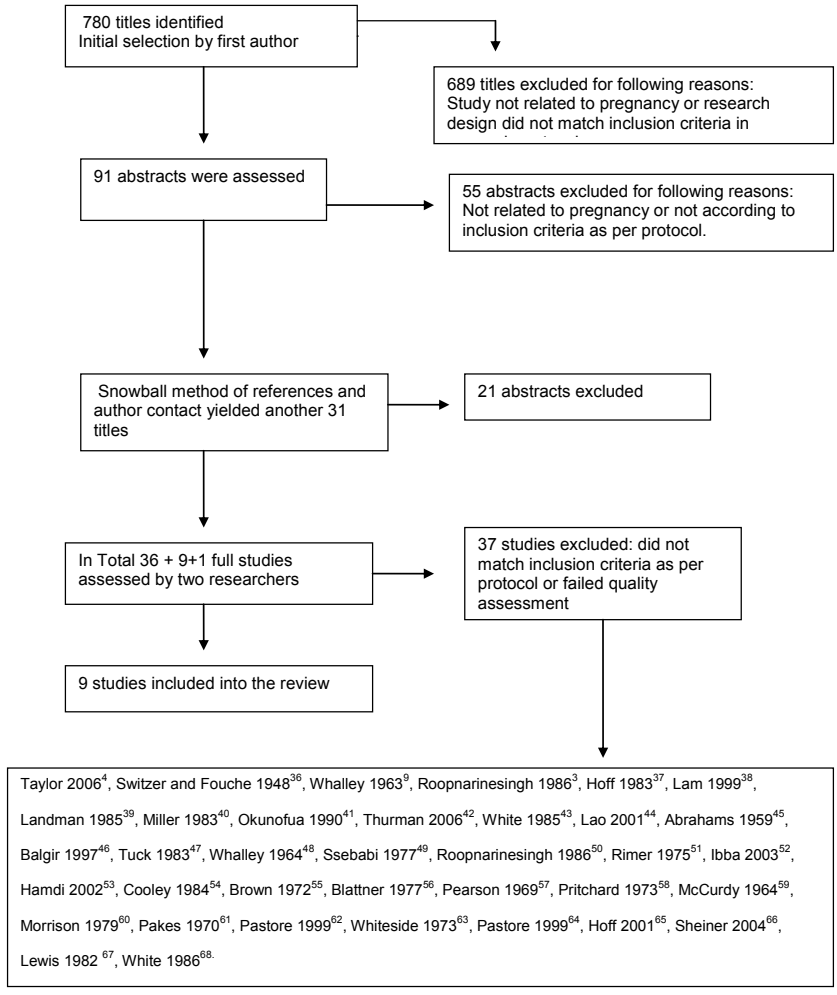


Fig. 1 Flowchart of search

Nine studies on HbAS met the inclusion criteria and scored 12 points or more and therefore were of sufficient methodological quality to be included in the review. Only one of these studies investigated the effect of thalassaemia minor on pregnancy.[15]

Premature birth/(low)birth weight (LBW)/intra uterine growth retardation (IUGR)

None of the studies into premature birth stated whether the expected date of delivery was confirmed by ultrasound scan (Table 3). Bryant et al.[16] showed a significant protective effect for delivery before 32 weeks in women with SCT, whereas Tita et al.[8] showed a protective effect for deliveries at < 37 weeks gestation. Stamilio et al.[7] showed no difference between the two groups. The prospective cohort study of Landman[15] found that HbP carriers had a smaller but non-significant risk of a premature delivery.

The prospective cohort study by Larrabee and Monga[17] only looked at the mean gestational age and showed a significant reduction in the length of gestation by 1 week in women with SCT.

None of the four studies examining the risk of low birth weight in infants of women with SCT showed a significant effect[2,5,7,8] (Table 3).

Four studies[5,8,15,18] looked at IUGR (Table 3). Two studies stated that dates were confirmed by ultrasound scan and only Tan et al.[18] and Landman[15] gave a clear definition of IUGR. Tita et al.[8] supplied the definition of IUGR and Landman[15] confirmed dating by ultrasound scan when contacted. None of the studies found any effect of HbP carrier status on the risk of IUGR.

Risk of urinary tract infection (UTI) and pyelonephritis:

None of the three studies into the risk of UTI in pregnant women with SCT showed an increased risk[2,5,15] (Table 4). In only one study, a definition of UTI was given[15].

Two studies showed a small but statistically significant increased risk for bacteriuria in pregnant women with SCT[8,19] and in one of them the risk of pyelonephritis was also increased.[19]

Iron deficiency anaemia and folate deficiency

Only three included studies looked at anaemia in pregnant HbP carriers[2,5,15] (Table 4). None of them took physiological haemodilution into account. Adeyemi et al.[5] did not give a definition of IDA and found no statistically significant difference between groups. Abdulsalaam et al.[2] found significantly more anaemia in the HbAS group. Landman[15] found a difference between groups when IDA was found in combination with folate deficiency. A significantly higher percentage of anaemia with an Hb ≤ 90 g/l was found in the HbAS group (5.5% vs. 3.6%, p=≤0.05). Looking at the specific causes of anaemia, IDA occurred more often in the control group but this difference was not statistically significant. A combined iron and folate deficiency occurred significantly more frequently in the HbAS group. The group with thalassaemia trait had less IDA but this was not statistically significant. Folate deficiency and combined iron and folate deficiency occurred more in the thalassaemia group but this was not statistically significant.

Table 3. Premature birth / Low Birth weight / IUGR

First Author Country Study design Publication year	N Population Setting	Definition of outcome	Exposure	Premature birth Point estimate (CI / P-value)	LBW Point Estimate (CI / P-value)	IUGR Point Estimate (CI / P-value)
Bryant[16] USA Retrospective cohort study 2007	5028 African American, non-Hispanic > 24 wks pregnant University hosp	< 37 weeks gestation EDD confirmed by US: unclear	SCT (326) vs none-SCT (4702)	AOR 0.76 (CI: 0.52 – 1.12)		
		< 37 wks Singleton gestations		AOR 0.85 (CI: 0.57 – 1.26)		
		< 32 wks		AOR 0.15 (CI: 0.05 – 0.49)		
		< 32 wks Singleton gestations		AOR 0.26 (CI: 0.08 – 0.84)		
Tita[8] USA Retrospective cohort study 2007	35743 African American >22 wks gestation University hospital	< 37 wks EDD confirmed by US: unclear	HbAS (3019) vs HbAA (32724)	AOR 0.8 (CI: 0.7 – 0.9)	AOR = 0.9 (CI:0.8 – 1.1)	AOR = 1.1 (CI:0.9 – 1.2)

Stamilio[7] USA Retrospective cohort study 2003	1996 Ethnicity mixed University hospital *Sub analysis on afro-American women: requested from author: no reply	< 37 wks EDD confirmed by US: unclear	SCT (87) vs none-SCT (1909)	(11% vs 11%) (p=0.89)	AOR = 0.5 (CI:0.1 – 2.1)	
Adeyemi[5] Nigeria Prospective cohort study 2006	420 African University hospital	< 2500 grm EDD confirmed by US: yes	HbAS (210) vs HbAA(210)		15.9% vs 17.8% (p:0.5)	HbAS 2.4% vs HbAA 1.9% (p:0.99)
Abdulsalaam[2] Syria Prospective cohort study 2003	500 Palestinian refugees Health clinics (primary care setting)	No definition given (author contacted; no reply)	HbAS (98) vs HbAA (402)		RR 1.1 (CI:0.7 - 2)	
Bail[19] USA Retrospective cohort study 1990	1828 No information on ethnicity given University hospital	Mean birth weight EDD confirmed by US: unclear	HbAS (914) vs HbAA (914)		3113 g (SD 640g) vs 3062 (SD 638g) n.s	

Tan[18] Uk Retrospective cohort study 2008	16825 All ethnicities University hospital African / Afro-Caribbean	< 10th birth centile (Gardosi) EDD confirmed by US: yes	SCT (505) vs Control (no HbP) (16320)	OR = 1.0 (CI: 0.81 – 1.24) OR = 1.06 (CI: 0.84 – 1.33)
Landman[15] Netherlands Prospective cohort study 1988	1662 Black Asians Mediterraneans 2 University hospitals 2 Peripheral hospitals	< 5th birth centile: corrected for sex, parity and gestational age EDD confirmed by US (author contact)	HbAS (73) vs HbAA (83) ß-thal heterozygote (40) vs controls (160) α-thal trait (8)vs Asian controls (77) Homozygote α-thal.2 (8) vs Black controls (83)	11.1% vs 2.4% (n.s) 10.0% vs 7.5% (n.s.) 12.5% vs 13.0% (n.s.) 12.5% vs 2.4% (n.s.)

SCT: sickle cell trait, OR: odds ratio, AOR: adjusted odds ratio, RR: relative risk, CI: confidence interval, p-value significant if <0.05, ns: not significant, EDD: expected date of delivery, US: ultra sound, LBW: low birth weight, IUGR: intra uterine growth retardation

Table 4. Urinary Tract Infection / anaemia

First author Country Study design Year of publication	N Population Setting	Definition of outcome	Exposure	UTI Point Estimate (CI / P-value)	Anaemia Point Estimate (CI / P-value)
Adeyemi[5] Nigeria Prospective cohort study 2006	420 African University hospital	No definition given	HbAS (210) vs HbAA(210)	9(4.3) vs 9(4.3) p: 1.00	6(2.9%) vs 9(4.3%) (p: 0.61)
Abdulsalaam[2] Syria Prospective cohort study 2003	500 Palestinian refugees Health clinics (primary care setting)	No definition given	HbAS (98) vs HbAA(402)	RR = 1.03 (CI: 0.3 – 3.6)	7(7.1) vs 9(2.2) (p: 0.022)
Tita[8] USA Retrospective cohort study 2007	35743 African American Univ hosp	Bacteriuria: Positive urine culture at booking	HbAS (3019) vs HbAA (32724	AOR = 1.4 (CI: 1.2 – 1.5)	
Bail[19] USA Retrospective cohort study 1990	1828 No information on ethnicity given University hospital	Bacteriuria: >100.000 / ml MSU	HbAS (914) vs HbAA (914)	OR 1.4 (p: 0.011)	

Landman[15]	1662	Iron Deficiency	HbAS (73) vs HbAA (83)	9.6% vs 7.2% (ns)	30.2% vs 54.2% (ns)
Netherlands	Blacks Asians	Anaemia	ß-thal heterozygote (40) vs controls (160)	7.5% vs 9.4% (ns)	15% vs 53.8% (ns)
Prospective cohort study	Mediterraneans	Hb < 110 g/l and Serum ferritine <15µg/l Or Hb<110g/l and low serum iron level and responsive to iron therapy Or Hb< 110g/l and reduction in MCV and responsive to iron therapy	α-thal trait (8) vs Asian controls (77)	- vs 11.7%	25.0% vs 53.2% (ns)
	2 University hospitals		Homozygote α-thal.2 (8) vs Black controls (83)	12.5% vs 7.2% (ns)	37.5% vs 54.2% (ns)
1988	2 Peripheral hospitals	Combined folate and IDA	HbAS (73) vs HbAA (83)		20.6 % vs 4.8 % (ns)
			ß-thal heterozygote (40) vs controls (160)		12.5 % vs 5.0% (p: <0.05)
			α-thal trait (8) vs Asian controls (77)		- vs 5.2% (ns)
			Homozygote α-thal.2 (8) vs Black controls (83)		25.0% vs 2.4% (ns)

SCT: sickle cell trait, OR: odds ratio, AOR: adjusted odds ratio, RR: relative risk, CI: confidence interval, p-value significant if <0.05, ns: not significant, UTI: urinary tract infection, MSU: mid stream specimen of urine.

High blood pressure: pregnancy induced hypertension (PIH) and pre-eclampsia (PE)

Three studies[5,8,15] investigated the relationship between being an HbP carrier and PIH of which two[8,15] gave a definition of PIH (Table 5). None of the three studies was able to demonstrate a significant effect.

Four studies[2,7,8,17] looked at pre-eclampsia of which only one[17] found a significantly increased risk for PE in women with SCT.

Table 5. PIH (PE) / PNMR / Low apgar score

First author Country Study design Publication year	N Population Setting	Definition of outcome	Exposure	PIH (PE) Point estimate (CI / P-value)	PNMR Point Estimate (CI / P-value)	Low Apgar Score Point Estimate (CI / P-value)
Adeyemi[5] Nigeria Prospective cohort study 2006	420 African University hospital	PIH: No definition given Stillbirth: no definition given Low apgar: Apgar 1 min ≤ 6 Apgar 5 min ≤ 6	HbAS (210) vs HbAA (210)	8(3.8%) vs 6(2.9%) (p: 0.81)	2 (1.0%) vs 7 (3.3%) (p: 0.20)	Apgar 1: 11.7% vs 12.9% (p: 0.04) Apgar 5: 0.9% vs 4.9% (p: 0.04)
Tita[8] USA Retrospective cohort study 2007	35743 African American University hospital	PIH: According to NHBP Working Group (systolic ≥ 140 mmHg and /or diastolic ≥ 90 mmHg on 2 occasions) PE: PIH and proteinuria ≥ 300 mg/24 hrs	HbAS (3019) vs HbAA (32724)	AOR : 1.1 (CI: 0.9 – 1.2) AOR: 1.0 (CI: 0.8-1.2)	Stillbirths and neonatal deaths < 28 days post partum: AOR = 0.7 (CI 0.5 – 1.0) Stillbirths: AOR 0.6 (CI:0.3-0.9)	
Landman[15] Netherlands Prospective cohort study 1988	1662 Blacks Asians Mediterraneans 2 University hospitals 2 Peripheral hospitals	PIH: Increase in diastolic blood pressure of 20 mmHg or more as compared to the 1st trimester values	HbAS (73) vs HbAA (83) ß-thal heterozygote (40) vs controls (160) α-thal trait (8)vs Asian controls (77) Homozygote α-thal.2 (8)vs Black controls (83)	8.6% vs 9.6% (ns) 7.5% vs 10% (ns) 12.5% vs 10.4% (ns) 25.0% vs 9.6% (ns)		4.2% vs 2.4% (ns) 5.0% vs 0.6% (ns) - 12.5% vs 2.4% (ns)

Larrabee[17] USA Prospective cohort study 1997	1584 African American University hospital	PE: Hypertension (bloodpressure >140/90 mm Hg, or an increase of > 30/15 mm Hg from baseline) and proteinuria (>300 mg/24hrs. or > 100 mg/dl in 2 random specimens)	SCT (162) vs none-SCT (1422) Nullipara	RR 3.0 (CI 2.0 - 4.6) 33.3% vs 13.3% (p: 0.002)	
Abdulsalaam[2] Syria Prospective cohort study 2003	500 Palestinian refugees Health clinics (Primary care setting)	PE: No definition given PNMR: no definition given	HbAS (210) vs HbAA (210)	RR 1.4 (CI: 0.1 – 13)	RR 2.7 (CI:0.8 – 9.4)
Stamilio[7] USA Retrospective cohort study 2003	1996 Ethnicity mixed University hospital *Subanalysis on afro-american women: author contacted but no reply	PE: Blood pressure of >140/90 mm Hg on 2 separate occasions, at least 6 hrs apart and proteinuria >300mg/24 hrs or 1+ to 2+ on serial quali exam.	SCT (87) vs none-SCT (1909)	AOR = 0.5 (CI: 0.2 – 1.6)	

SCT: sickle cell trait, OR: odds ratio, AOR: adjusted odds ratio, RR: relative risk, CI: confidence interval, p-value significant if <0.05, ns: not significant, PNMR: postnatal mortality rate, PE: pre-eclampsia, PIH: pregnancy induced hypertension.

Miscarriage, fetal and neonatal death

Three studies into the risk of fetal and neonatal death found opposite effects but none of these were significant[2,5,8] (Table 5). Another study[15] found only one case in the control group (results not in table).

Two studies investigated the effect of SCT on stillbirths alone.[5,8] These studies showed a protective effect but in one this was not significant.[5]

Tita et al.[8] found a very small non-significant reduction in fetal death. No studies examined the risk of miscarriage.

Low Apgar score

Two studies looked at the Apgar score (Table 5).[5,15] One study showed a decreased incidence of low Apgar scores among women with HbAS[5] and another study showed an insignificantly increased risk[15].

Gestational diabetes and neural tube defects

None of the included studies examined the effect of HbP carrier status on gestational diabetes or neural tube defects.

DISCUSSION

As far as we know, this is the first systematic review that examines possible risks of pregnant women who are HbP carriers. Besides the obvious need for genetic counselling, it is important for midwives and obstetricians to be aware of any risk factors if these do exist.

Some studies showed a protective effect of SCT for premature birth, low Apgar score and stillbirth: there was some evidence of an increased risk of anaemia and bacteriuria. No significant effect of HbP carrier status was found on low birth weight, growth retardation, UTI or high blood pressure.

These results should be interpreted with caution because of several methodological problems. All studies gave adequate definitions of the exposure factor and of the population under investigation; however, many authors failed to give adequate definitions of the outcomes assessed in their studies and they often did not control for confounders such as socio-economic status (SES). In some studies[7,8,16,20] it was not clear how the expected date of delivery was calculated and if this was confirmed by ultrasound scan. Nevertheless, considering the time frame and the setting in which the studies took place (academic hospitals), it could be assumed that women had an ultrasound scan to assess the expected date of delivery. However, in view of the fact that only one author[8] was able to confirm this when contacted, we need to be cautious with the overall conclusion.

In some studies[7,17] ethnicity was poorly defined and SCT may therefore have been underreported resulting in considerable bias.

The testing method to confirm carrier status was a problem in most studies. Only two studies used adequate methods that identified the presence of thalassaemia.[15,18]

The other studies used a sickle cell test and / or electrophoresis to establish HbP status of pregnant women. Two studies tested all women with a sickle test and confirmed only the positive women with electrophoresis.[7,17] According to The British Committee for Standards in Haematology (BCSH) a sickle test may not detect low levels of HbS and should only be used in an emergency (http://www.bcshguidelines.com). Carriers may have been missed in these studies giving rise to further bias. According to the BCSH, electrophoresis is not recommended for the quantification of HbA2 necessary to establish carrier status of thalassaemia: HPLC or micro column chromatography should be used.[21] Most studies did not specifically state whether other fractions such as HbAC, HbAE or any of the thalassaemias were found and whether or not they were excluded. With the exception of two studies[15,18] none of the studies gave any information on the co-existence of HbS and thalassaemia. Many people of Afro-Caribbean descent with HbAS have a combination of HbAS and α-thalassaemia. High HbA2 β-thalassaemia or any other trait found in early pregnancy and suspected to be associated with thalassaemia major, sickle cell disease or with other severe pathologies, should be confirmed at DNA level in particular when a couple at risk is suspected.[22]

Protective effect

A protective effect was found for preterm labour in carriers of HbP. However in view of the many methodological pitfalls, the conclusion of a protective effect is only tentative. Besides, the patho-physiological pathways underlying these results are unclear.

In order to find a significant effect on stillbirth or perinatal mortality, a large population needs to be studied. Only Tita et al.[8] investigated a large group of women and found a small reduction in perinatal mortality and stillbirth which was borderline significant. Apart from chance playing a role in this study, the antenatal policy of serial urine culture and the reduction in premature labour may also have had an effect on the rate of perinatal mortality.

Two studies found opposite effects on stillbirth.[2,5] Consanguinity may have played a role in the study which found an increased risk.[2] Bittles[23] showed that consanguinity is responsible for 4,4% of deaths between 6 months of pregnancy and 10 years of age. The other studies did not take consanguinity into account. The effect may be particularly important in studies carried out in the Middle East where the incidence of consanguine marriages is relatively high.[24]

HbP carrier status appears to offer a small protective effect on perinatal mortality. However the patho-physiological mechanism behind this remains unclear and in view of the methodological flaws, the results remain questionable.

No effect

No statistically significant difference was found for the risk of low birth weight (as a result of prematurity or growth retardation). Two of the studies were carried out in developing countries where both the health care standards can differ considerably and the population may have different needs than those in developed countries.[25]

As both a poor nutritional status and anaemia increase the risk of low birth weight[26], a difference based on HbP status may not have been detected. On the basis of these studies, it cannot be concluded that HbAS has any effect on the risk of low birth weight. We found no increased risk of intra uterine growth retardation among women with a positive carrier status for HbP.

Only Larrabee and Monga[17] found a significantly higher risk of both (pre-) eclampsia and pregnancy induced hypertension in women who are a carrier of SCT. Other studies found no significant differences.[2,5,7,8,15] This could be due to methodological problems as discussed earlier. None of the authors corrected for maternal weight in their study. We conclude that the relation between HbP carrier status and the risk of (pre-) eclampsia or pregnancy induced hypertension is inconclusive. Further studies are urgently needed to shed light on this issue. Especially since hypertensive disorders in pregnancy are the leading cause of maternal death in the Netherlands[27], rank fourth place in the United Kingdom[28] and are the second direct cause of maternal death in the United States of America (http://www.mchb.hrsa.gov). Moreover, a recent study carried out in the Netherlands showed that non-Western immigrant women had a 1.3-fold increased risk of severe maternal morbidity, including PIH, when compared with Western women.[29]

Increased risk

The generally accepted claim that pregnant sickle cell carriers have a higher risk of UTI in pregnancy[30,31] could not be substantiated in this review. Two of the three included studies[2,5,15] failed to give a definition of UTI which may have led to classification bias.

Although we could not confirm an increased risk for UTI in the pregnancies of HbP carriers, we did find an association between sickle cell trait and an increased risk of bacteriuria in two studies.[8,19] Treatment of asymptomatic bacteriuria reduces the risk of pyelonephritis in pregnancy.[32]

Surprisingly, only three studies were included which investigated the risk of anaemia amongst pregnant women with an HbP-trait. It is generally accepted that a positive carrier status for HbP can give rise to anaemia in pregnancy[32]; however this has not been very well investigated. Although the overall consensus seems to be that SCT is asymptomatic and thalassaemia minor may cause mild microcytic or hypochromic anaemia in the general population at risk[33] (http://www.thalassaemia.org.cy), this systematic review shows that few investigators have adequately studied the effect of HbP carrier status on anaemia in *pregnancy*. Small numbers in all three studies may be the reason that little or no effect was found.

Despite the limited power, Landman[15] found that women with HbAS or ß-thalassaemia trait have a higher chance of having a combined iron and folate deficiency anaemia. This study did not take confounders for anaemia into account, such as twin-pregnancy, poor dietary habits or a low socio-economic status (SES) and the study was carried out amongst a high risk population which may have included women that were already referred because of an increased risk of anaemia.

Abdulsalaam et al.[2] did not use anaemia as an outcome measure but instead used it as a risk factor for the outcomes to be studied and subsequently found a significantly increased percentage of women with HbAS that were anaemic. Whether this is due to iron and/or folate deficiency was not clarified in this study. It is possible that women who were sickle cell carriers had in fact a combination of SCT and α-thalassaemia which was not investigated. It is very likely that a higher risk of anaemia amongst HbP carriers is caused by the (combined) effect of thalassaemias as these are known for ineffective erythropoiesis which in pregnancy because of the increase in blood volume, could result in more pronounced anaemia especially in the second trimester. Because of the disturbed Hb synthesis in HbP carriers, it is very likely that extra folic acid is needed. This may very well be the reason that most textbooks[30,31,34] recommend supplementing these pregnant women with folic acid. However we found no study that investigated and confirmed this theory.

Besides this, a recent study found that women of Non-Northern European descent had a significantly increased risk of becoming anaemic in pregnancy.[35] The researchers were not able to identify the cause of this increased risk. In view of the evidence found in this systematic review the increased risk could partly be explained by women who are a carrier of HbP.

CONCLUSION

In conclusion, the findings of this study show that pregnant women who are HbP carriers have a low risk of adverse outcomes of pregnancy. In expectation of further research on this subject, midwives and obstetricians should be aware of the possibility of anaemia, asymptomatic bacteriuria and the subsequent risk of pyelonephritis and investigate pregnant women who are known HbP carriers more frequently for these conditions.

If carrier status of these women is known and anaemia is present, the cause of it should be investigated further before any treatment is started. Each woman should be correctly diagnosed and be offered partner testing if necessary so that she can make a well informed reproductive choice in order to avoid unexpected outcomes. It also remains important that women with SCT or thalassaemia minor are given correct advice on how this will affect their pregnancy and be reassured that it will not increase their risk of developing complications during pregnancy or shortly thereafter. We found no reason at present to refer pregnant women who are a carrier of HbP to a high risk setting.

This study highlights the lack of evidence of the effect of a positive HbP status on the outcome of pregnancy and the need for large, well controlled prospective studies. With routine investigations into HbP becoming more standard in many countries, it will become easier to conduct further research to thoroughly investigate any possible effect that this may have on pregnancy.

REFERENCE LIST

1. Harteveld CL, Osborne CS, Peters M, van der WS, Plug R, Fraser P, et al. Novel 112 kb (epsilonGgammaAgamma) deltabeta-thalassaemia deletion in a Dutch family. Br J Haematol 2003 Sep;122(5):855-8.
2. Abdulsalam AA, Bashour HN, Monem FS, Hamadeh FM. Pregnancy outcomes among Palestinian refugee women with sickle cell trait in Damascus, Syria. Saudi Med J 2003 Sep;24(9):986-90.
3. Roopnarinesingh S, Ramsewak S. Decreased birth weight and femur length in fetuses of patients with the sickle-cell trait. Obstet Gynecol 1986 Jul;68(1):46-8.
4. Taylor MY, Wyatt-Ashmead J, Gray J, Bofill JA, Martin R, Morrison JC. Pregnancy loss after first-trimester viability in women with sickle cell trait: time for a reappraisal? Am J Obstet Gynecol 2006 Jun;194(6):1604-8.
5. Adeyemi AB, Adediran IA, Kuti O, Owolabi AT, Durosimi MA. Outcome of pregnancy in a population of Nigerian women with sickle cell trait. J Obstet Gynaecol 2006 Feb;26(2):133-7.
6. Blank AM, Freedman WL. Sickle cell trait and pregnancy. Clin Obstet Gynecol 1969 Mar;12(1):123-33.
7. Stamilio DM, Sehdev HM, Macones GA. Pregnant women with the sickle cell trait are not at increased risk for developing preeclampsia. Am J Perinatol 2003 Jan;20(1):41-8.
8. Tita ATN, Biggio JR, Chapman V, Neely C, Rouse DJ. Perinatal and maternal outcomes in women with sickle or hemoglobin C trait. Obstet Gynecol 2007 Nov;110(5):1113-9.
9. Whalley PJ, Pritchard JA, Richards JRJ. Sickle cell trait and pregnancy. JAMA 1963 Dec 28;186:1132-5.
10. Giordano PC, Harteveld CL. Prevention of hereditary haemoglobinopathies in The Netherlands. Ned Tijdschr Geneeskd 2006 Sep 30;150(39):2137-41.
11. Modell B, Darlison M. Global epidemiology of haemoglobin disorders and derived service indicators. Bull World Health Organ 2008 Jun;86(6):480-7.
12. Greenland S, O'Rourke K. On the bias produced by quality scores in meta-analysis, and a hierarchical view of proposed solutions. Biostatistics 2001 Dec;2(4):463-71.
13. Sanderson S, Tatt ID, Higgins JP. Tools for assessing quality and susceptibility to bias in observational studies in epidemiology: a systematic review and annotated bibliography. Int J Epidemiol 2007 Jun;36(3):666-76.
14. The Dutch Institute for Healthcare Improvement (CBO). Guidelines for assessing the quality of observational and case control studies. 2009. http://www.cbo.nl. Last accessed Feb. 2010.
15. Landman H. Haemoglobinopathy and pregnancy. PhD Thesis. State University Groningen, the Netherlands; 1988.
16. Bryant AS, Cheng YW, Lyell DJ, Laros RK, Caughey AB. Presence of the sickle cell trait and preterm delivery in African-American women. Obstet Gynecol 2007 Apr;109(4):870-4.
17. Larrabee KD, Monga M. Women with sickle cell trait are at increased risk for preeclampsia. Am J Obstet Gynecol 1997 Aug;177(2):425-8.
18. Tan TL, Khanapure A, Oteng-Ntim E. Sickle-cell trait and small-for-gestational age babies: Is there a link? J Obstet Gynaecol 2008 Apr;28(3):298-300.
19. Bail IC, Witter FR. Sickle trait and its association with birthweight and urinary tract infections in pregnancy. Int J Gynaecol Obstet 1990 Sep;33(1):19-21.
20. Larrabee K, Cowan M. Clinical nursing management of sickle cell disease and trait during pregnancy. J Perinat Neonatal Nurs 1995 Sep;9(2):29-41.
21. Working Party of the General Haematology Task Force of the British Committee for Standards in Haematology. Guidelines on the laboratory diagnosis of haemoglobinopathies. Br J Haematol 1998;101:783-92.

22. Mosca A, Paleari R, Ivaldi G, Galanello R, Giordano PC. The role of haemoglobin A(2) testing in the diagnosis of thalassaemias and related haemoglobinopathies. J Clin Pathol 2009 Jan;62(1):13-7.
23. Bittles AH. Consanguineaous marriage and childhoodhealth. Dev Med Child neurol 2003 Aug;45(8):571-6.
24. Bittles AH. The global prevalence of consanguinity. 2010. Available from: http://www.consang.net. Last accessed March 2010.
25. Worldwide prevalence of anaemia 1993-2005. WHO Global database on anaemia. 2008. Report No.: WH 155.
26. United Nations Standing Committee on Nutrition. 5th report on the world nutrition situation: Nutrition for improved development outcomes. 2004 Mar.
27. Schuitemaker N, van RJ, Dekker G, van Dongen P, van Geijn H, Bennebroek Gravenhorst J. Confidential enquiry into maternal deaths in The Netherlands 1983-1992. Eur J Obstet Gynecol Reprod Biol 1998 Jul;79(1):57-62.
28. Lewis G. CEMACH. Why mothers die. The confidential enquiries into Maternal Deaths in the United Kingdom. London: RCOG Press. 2004.
29. Zwart JJ, Richters JM, Ory F, de Vries JI, Bloemenkamp KW, van RJ. Severe maternal morbidity during pregnancy, delivery and puerperium in the Netherlands: a nationwide population-based study of 371,000 pregnancies. BJOG 2008 Jun;115(7):842-50.
30. Cunningham FG, McDonald PC.Williams Obstetrics. 20th edn. New York: McGraw-Hill Medical Publishing. 1997.
31. Danforth DN, Gibbs RS, Karlan BY, Haney AF (eds). Danforth's obstetrics and gynecology. 9th edition ed. Lippincott Williams & Wilkins; 2003.
32. CG62 Antenatal care; Nice guideline. 2008 Mar 26. Available from www.nice.org.uk. Last accessed February 2010.
33. Wonke B, Modell M, Marlow T, Khan M, Modell B. Microcytosis, iron deficiency and thalassaemia in a multi-ethnic community: a pilot study. Scand J Clin Lab Invest 2007;67(1):87-95.
34. Fraser D, Cooper M (eds). Myles textbook for Midwives. 15th edn. Churchill Livingstone Elsevier; 2009.
35. Jans SM, Daemers DO, de VR, Lagro-Jansen AL. Are pregnant women of non-Northern European descent more anaemic than women of Northern European descent? A study into the prevalence of anaemia in pregnant women in Amsterdam. Midwifery 2008 Apr 3.
36. Switzer PK, Fouche HH. The sickle cell trait; incidence and influence in pregnant colored women. Am J Med Sci 1948 Sep;216(3):330-2.
37. Hoff C, Wertelecki W, Dutt J, Hernandez R, Reyes E, Sharp M. Sickle cell trait, maternal age and pregnancy outcome in primiparous women. Hum Biol 1983 Dec;55(4):763-70.
38. Lam YH, Tang MH. Risk of neural tube defects in the offspring of thalassaemia carriers in Hong Kong Chinese. Prenat Diagn 1999 Dec;19(12):1135-7.
39. Landman H, Visser GH, Huisjes HJ. Pregnancy complications in women with a (double) heterozygote hemoglobinopathy. Ned Tijdschr Geneeskd 1985 Mar 30;129(13):598-601.
40. Miller JMJ. Sickle cell trait in pregnancy. South Med J 1983 Aug;76(8):962-3, 965.
41. Okonofua FE, Odutayo R, Onwudiegwu U. Maternal sickle cell trait is not a cause of low birthweight in Nigerian neonates. Int J Gynaecol Obstet 1990 Aug;32(4):331-3.
42. Thurman AR, Steed LL, Hulsey T, Soper DE. Bacteriuria in pregnant women with sickle cell trait. Am J Obstet Gynecol 2006 May;194(5):1366-70.
43. White JM, Richards R, Byrne M, Buchanan T, White YS, Jelenski G. Thalassaemia trait and pregnancy. J Clin Pathol 1985 Jul;38(7):810-7.
44. Lao TT, Ho LF. Alpha-Thalassaemia trait and gestational diabetes mellitus in Hong Kong. Diabetologia 2001 Aug;44(8):966-71.

45. Abrams J. The sickle cell trait and pregnancy. Obstet Gynecol 1959 Jul;14(1):123-6.
46. Balgir RS, Dash BP, Das RK. Fetal outcome and childhood mortality in offspring of mothers with sickle cell trait and disease. Indian J Pediatr 1997 Jan;64(1):79-84.
47. Tuck SM, Studd JW, White JM. Pregnancy in women with sickle cell trait. Br J Obstet Gynaecol 1983 Feb;90(2):108-11.
48. Whalley PJ, Martin FG, Pritchard JA. Sickle cell trait and urinary tract infection during pregnancy. JAMA 1964 Sep 21;189:903-6.
49. Ssebabi EC, Bulwa FM. Sickle cell trait anaemia in pregnancy. East Afr Med J 1977 May;54(5):258-65.
50. Roopnarinesingh S, Ramsewak S. The outcome of pregnancy in patients with haemoglobin AS. West Indian Med J 1986 Jun;35(2):96-8.
51. Rimer BA. Sickle-cell trait and pregnancy: A review of a community hospital experience. Am J Obstet Gynecol 1975 Sep 1;123(1):6-11.
52. Ibba RM, Zoppi MA, Floris M, Manca F, Axiana C, Cao A, et al. Neural tube defects in the offspring of thalassemia carriers. Fetal Diagn Ther 2003 Jan;18(1):5-7.
53. Hamdi IM, Karri KS, Ghani EA. Pregnancy outcome in women with sickle cell trait. Saudi Med J 2002 Dec;23(12):1455-7.
54. Cooley JR, Kitay DZ. Heterozygous beta-thalassemia in pregnancy. J Reprod Med 1984 Feb;29(2):141-2.
55. Brown S, Merkow A, Wiener M, Khajezadeh J. Low birth weight in babies born to mothers with sickle cell trait. JAMA 1972 Sep 18;221(12):1404-5.
56. Blattner P, Dar H, Nitowsky HM. Pregnancy outcome in women with sickle cell trait. JAMA 1977 Sep 26;238(13):1392-4.
57. Pearson HA, Vaughan EO. Lack of influence of sickle cell trait on fertility and successful pregnancy. Am J Obstet Gynecol 1969 Sep 15;105(2):203-5.
58. Pritchard JA, Scott DE, Whalley PH, Cunningham FG, Mason RA. The effects of maternal sickle cell hemoglobinopathies and sickle cell trait on reproductive performance. Am J Obstet Gynecol 1973 Nov 1;117(5):662-70.
59. McCurdy PR. Abnormal hemoglobins and pregnancy. Am J Obstet Gynecol 1964 Dec 1;90:891-6.
60. Morrison JC, Schneider JM, Kraus AP, Kitabchi AE. The prevalence of diabetes mellitus in sickle cell hemoglobinopathies. J Clin Endocrinol Metab 1979 Feb;48(2):192-5.
61. Pakes JB, Cooperberg AA, Gelfand MM. Studies on beta thalassemia trait in pregnancy. Am J Obstet Gynecol 1970 Dec 15;108(8):1217-23.
62. Pastore LM, Savitz DA, Thorp JMJ. Predictors of urinary tract infection at the first prenatal visit. Epidemiology 1999 May;10(3):282-7.
63. Whiteside MG, Smith MB. Heterozygous beta-thalassaemia in pregnancy. Med J Aust 1973 Sep 8;2(10):487-90.
64. Pastore LM, Savitz DA, Thorp JMJ, Koch GG, Hertz-Picciotto I, Irwin DE. Predictors of symptomatic urinary tract infection after 20 weeks' gestation. J Perinatol 1999 Oct;19(7):488-93.
65. Hoff C, Thorneycroft I, Wilson F, Williams-Murphy M. Protection afforded by sickle-cell trait (Hb AS): what happens when malarial selection pressures are alleviated? Hum Biol 2001 Aug;73(4):583-6.
66. Sheiner E, Levy A, Yerushalmi R, Katz M. Beta-thalassemia minor during pregnancy. Obstet Gynecol 2004 Jun;103(6):1273-7.
67. Lewis D, Stockley RJ, Chanarin I. Changes in the mean corpuscular red cell volume in women with beta-thalassaemia trait during pregnancy. Br J Haematol 1982 Mar;50(3):423-5.
68. White JM, Richards R, Jelenski G, Byrne M, Ali M. Iron state in alpha and beta thalassaemia trait. J Clin Pathol 1986 Mar;39(3):256-9.

4

A case study of haemoglobinopathy screening in the Netherlands: Witnessing the past, lessons for the future

S.M.P.J. Jans, C.G. van El, E.S. Houwaart,
M.J. Westerman, M.J.P.A. Janssens,
A.L.M. Lagro-Janssen, A.M.C. Plass, M.C. Cornel

Ethnicity & Health 2012;17(3):217-39

ABSTRACT

Objectives: In 2007 neonatal screening was expanded to include screening for sickle cell disease and beta-thalassaemia. Up until that year no formal recommendations for haemoglobinopathy (carrier) screening existed in the Netherlands. Although it has been subject to debate in the past, preconceptional and prenatal haemoglobinopathy carrier screening are not part of routine health care in the Netherlands.

This study aimed to explore the decision-making process of the past: why was the introduction of a screening programme for haemoglobinopathy considered to be untimely and did ethnicity play a role given the history in other countries surrounding the introduction of haemoglobinopathy screening.

Design: A witness seminar was organised, inviting key figures to discuss the decision making process concerning haemoglobinopathy screening in the Netherlands, thereby adding new perspectives on past events. The transcript was content analyzed.

Results: The subject of haemoglobinopathy screening first appeared in the 1970's. As opposed to a long history of neglect of African-American health in the United States, the heritage of World War II influenced the decision-making process in the Netherlands. As a consequence, registration of ethnicity surfaced as an impeding factor. However overall, official Dutch screening policy was restrained regarding reproductive issues caused by fear of eugenics. In the 1990's haemoglobinopathy screening was found to be "not opportune" due to low prevalence, lack of knowledge and fear of stigmatisation. Currently the registration of ethnicity remains on the political agenda, but still proves to be a sensitive subject.

Discussion: Carrier screening in general never appeared high on the policy agenda. Registration of ethnicity remains sensitive caused by the current political climate. Complexities related to carrier screening are a challenge in Dutch health care. Whether carrier screening will be considered a valuable complementary strategy in the Netherlands, depends partly on participation of representatives of high-risk groups in policy making.

INTRODUCTION

Haemoglobinopathies (HbP), such as sickle cell disease (SCD) and thalassaemia, are serious autosomal recessive disorders characterised by severe anaemia, variable but severe and debilitating morbidity and a shortened lifespan. In the past HbPs occured more frequently in areas where malaria is or was endemic, such as Africa, the Mediterranean area, the Middle East and South-East Asia, but they are now common in most countries worldwide due to increasing migration.[1] Globally approximately 5% of the population is a carrier of a significant variant of haemoglobin disorders with as many as 40% carriers in some regional populations.[2] The prevalence of a positive carrier status of HbP in the Netherlands has been estimated at 4-13.6% depending on ethnic background.[3] The birth prevalence of severe hereditary HbP in the Netherlands was 64 infants in 2007 among 182.000 total births.[4]

Parents who are both carriers of HbP, have a one in four chance in each pregnancy of giving birth to a child affected with the disease. Carriers can be identified by simple blood tests (Hb-electrophoresis or High Performance Liquid Chromatography (HPLC)). Couples could then be informed about their risk, preferably before pregnancy.

The first HbP screening programmes were developed during the 1970's in Mediterranean countries such as Italy, Cyprus and Greece and were aimed at thalassaemia. The United States (US) introduced SCD in neonatal screening programmes in some states in the 1970's but screening became more widespread after publication of the consensus document of the National Institutes of Health (NIH) in 1987.[5] In the United Kingdom (UK) the NHS Sickle Cell and Thalassaemia Screening Programme was the first service in the world aiming to link antenatal and neonatal screening. The programme was officially launched in 2001 (http://sct.screening.nhs.uk/accessed 26 May 2011).

In 2006 the WHO urged member states to increase the awareness of sickle cell anaemia and to develop systematic and comprehensive programmes for the screening of (the carrier status of) SCD.[6] HbP programmes based on these recommendations have been developed in several other countries both in and outside Europe and in low, middle and high income countries.[7]

In the Netherlands HbP screening did not attract much attention on a national level until 1994 when a report was commissioned by the Consultative Committee Minorities of the Department of Health investigating the possibility of introducing a screening programme for HbP.[8] On the basis of a low prevalence of HbP, fear of stigmatisation of carriers, lack of knowledge amongst both professionals and those at risk the authors concluded that introducing a screening programme was "not opportune" at that time.[9]

Carrier screening in general never appeared high on the policy agenda in the Netherlands. At the moment of performing the Witness Seminar (July 2009) the National Screening Programme in the Netherlands did not include carrier screening of any type of genetic disorder and public discussion on the subject was also absent.

The programme does include cascade screening for familial hypercholesterolaemia (FH), screening for neural tube defects in pregnancy (since 2007) as well as trisomy 21 for women above the age of 36 and neonatal screening (NNS). In contrast to SCD, cystic fibrosis (CF) was not included in the NNS until 2011. The discussion about CF has mainly been dominated by the suboptimal specificity and the fact that the mutation panel has a different sensitivity for amongst others the Turkish population as compared to western Europeans.

As a result of the discussions on HbP in the 1990's and in the absence of community pressure or sufficient patient demand, no public information on testing for HbP (or the carier status) has been available in the Netherlands before 2007. Until that time testing was only carried out on the basis of unresolved anaemia or established familial risk.[10-13]

Information was only available through non-governmental patient organisations. Following a 2005 Health Council report, the NNS programme was expanded in 2007 including screening for SCD.[14] The primary aim of this screening was to identify SCD patients so that early complications of this disease could be prevented. As a result of discussion at the start of the expanded NNS programme it was decided to report on alpha- and beta-thalassaemia as well. For beta-thalassaemia, optimal sensitivity in the laboratory is pursued. Identifying other HbP is not official policy but remains subject of debate. If a case of HbH disease or other relevant HbP is diagnosed in the NNS programme, the result is reported to the parents because it is clinically relevant, although unintentionally found. Screening also leads to unsought identification of carriers. Parents may opt out from receiving information on carrier status of their child by ticking a box on the test card. In a survey 62 out of 3200 parents (1.9%) indicated to have opted out.[15] Those parents whose child is found to be a carrier of HbS (other carrier states are not communicated) are invited by their family doctor to be tested to allow for possible reproductive choices in subsequent pregnancies. However in 2007 only 20 parents of the 806 children with HbS carrier status were referred for genetic counselling, whereas based on a carrier prevalence of 10%, 80 carrier couples were expected.[16]

In 2007 the Health Council of the Netherlands published a report on the subject of preconception care[17] recommending a pilot study on carrier screening for HbP (and Cystic Fibrosis); however, to date no governmental advice has been issued to introduce a broad preconceptional screening programme for HbP.

In the US, social activism surrounding race relations and disease dramatically altered the issues of race and health because affected minority groups came together themselves to challenge many mainstream assumptions.[18] Previously the top-down implementation of a screening programme met with opposition; the racial identity of white patients was questioned, social concerns about the interbreeding of races were voiced.[19] The community of African Americans viewed screening with suspicion and as part of the long history of interference with self-determination.[20] Indeed according to Wailoo and Pemberton "(…) every aspect of SCD in the United States speaks to the problem of race and the social condition of African Americans".[20] Although

screening for SCD has been accepted since the 1980's, screening for carrier status has been the cause of ongoing controversy. Most recently marked by discussion of the testing of recruits to the US Armed Forces and professional athletes.[21-23]

In the UK it took considerable effort by the community and health professionals to attract policy interest. They had to overcome barriers of inequality and (institutionalised) discrimination before positive results were achieved by exerting political pressure on the relevant agencies.[24] Given the history in the US and the UK, it was questioned whether Dutch policymakers and (health) professionals were aware of the issues of discrimination and stigmatisation thus causing hesitation about the introduction of a screening programme in the Netherlands. It is not apparent whether elements of the history and discussions in both the US and UK had any (indirect) influence on the Dutch discussion in the 1980's and 1990's. It would be interesting to perform a case study focussing on a country other than either the US or the UK to investigate the agenda setting of a disorder with differential sensitivities in different ethnic groups and with a growing prevalence due to a still increasing group of immigrants and their descendants. This is especially relevant in the light of the fact that the 2007 expansion of the neonatal screening programme has raised the discussion whether or not a carrier screening programme should be introduced in the Netherlands, renewing the discussion which followed the publication of the report in 1994.[25-28]

While it would be interesting to make a comparison with the history of the US and the UK, to do so would go far beyond the scope of this study. Attention often focuses on the experience of these two countries whereas the Dutch situation is essentially different. Because programmes such as the ones in the US and the UK cannot automatically be transposed to other countries, we prefer to concentrate on the case history of the Netherlands. Although references are made to the history and situation of these two countries, we explicitly did not aim to carry out a comparative study. The aim of this study was to explore why and when the issue of preconception, antenatal or neonatal testing of asymptomatic persons at risk of HbP did or did not receive any attention on the agenda of the Dutch public health authorities. To what extent was this influenced by the political climate at the time and potentially deep-seated concerns about the role of ethnicity and the fear of discrimination?

METHODS

Witness seminar

The formulated research questions were investigated using a witness seminar. This method was developed by the Institute of Contemporary British History (ICBH) as a special form of oral history, in which several experts, researchers and policymakers who each have been associated with a particular set of circumstances or events, are invited to meet in order to explain and debate their recollections of a certain time period and subject (www.ccbh.ac.uk/witnessseminars.php, accessed 11 Oct. 2010). This enables researchers to elaborate on developments in the past and on traditional

sources of historical research such as the existing literature. The advantage of using this method to investigate the subject of (the absence of) HbP screening in the Netherlands is that it may generate a better understanding of the original definition of the problem, the collaborative relationships and the controversies. Apart from supporting the current discussion with new background material, this method further enables exploration of possible barriers against the introduction of a broader screening programme for HbP and other ethnicity related disorders.

Preparations

The Dutch literature, both scientific and grey literature (information produced on all levels in electronic and print formats not controlled by commercial publishing: www.greynet.org, accessed 14 June 2010), was scrutinized to identify Dutch articles concerned with HbP, both research and otherwise, and to identify those involved in the decision-making process and the discussion about the introduction of a screening programme for HbP.

The search was carried out in the most important Dutch medical journals such as the Dutch Journal of Medicine, General Practitioner & Science, Dutch Journal of Obstetrics and Gynaecology, Journal of Health Science and The Midwives' Journal. All articles identified were scrutinized for further literature by snow-ball method. Authors, the Ministry of Health archives and non-governmental organizations which were possibly involved in the decision making process (such as the patient organization for HbP (OSCAR) and the VSOP (Dutch Genetic Alliance)) were contacted for further documentation, information and correspondence.

Key figures e.g. clinicians, scientists and policymakers were contacted and interviewed by telephone.

The collected material was used to identify themes and to construct a discussion guide for the witness seminar (Box 1) which lasted a full day and was divided into three sessions. Key witnesses were invited to attend the seminar.

The study was approved by the Medical Ethics Committee of the VU University Medical Center, Amsterdam.

Study sample

Fourteen witnesses who were involved in the past discussions or decision making process in the past were invited to participate. They were either active in the field of obstetrics, haematology, paediatrics, genetics, epidemiology, ethics, clinical chemistry, or were working as officials for the Health Inspectorate or the Department of Health. All members of the original advisory committee to the National Investigation into Sickle cell anaemia and Thalassaemia[8] were contacted and invited to attend the witness seminar (all were able to attend apart from one who was subsequently replaced by a colleague).

The meeting was chaired and facilitated by a medical historian (EH). An introduction to the meeting was presented outlining the historical context of the topic in order to activate the memory of those attending the seminar.

Box 1. Discussion program

Discussion program of witness seminar
The meeting was divided into three sessions, each addressing a specific period in time. In each session issues relevant for that particular period were discussed and explored:

Session one
The period after World War II until the eighties: First appearance of studies and articles in the medical press investigating the prevalence and aetiology of HbP and the start of an initial debate.
Were opinions expressed about screening for HbP?
What were local practices of HbP screening?
Was fear of stigmatisation and discrimination present?

Session two
The nineties: Structured around the publication of the report of the National Investigation into Sickle cell anaemia and Thalassaemia.[8]
Why and how was the report initiated?
What was the role and policy of the public health authorities?
Does a comparison to CF elucidate the discussion?

Session three
The new millennium: Transformation of opinions, the introduction of sickle cell disease in neonatal screening and discussion on preconceptional and antenatal screening.
Was a transformation really apparent?
What was the background of the decision to limit neonatal screening to SCD?
What possibilities and limits are there to introduce a broad (carrier) screening program in the future? If so, does ethnicity play a role in this?

Analysis

Socio-technical analysis

For the analysis of our results we used a study which was carried out to obtain more insight into the process of the potential implementation of a screening programme identifying carriers of cystic fibrosis and haemoglobinopathies before pregnancy.[29] The study was based on the model of co-evolution between technology and society[74] and helps to identify constraining and enabling factors factors intrinsic to the introduction of a screening programme for HbP carrier status. For the successful introduction of new technological options, such as screening, attunement between stakeholders on various issues is necessary.[29] These issues range from the technological options necessary to carry out such a screening programme to the necessary facilities and services, the demand particularly by the population at risk, and the political and cultural acceptability of a screening programme for HbP.

We used this model to compare the past to the present situation and to understand why the introduction of a screening programme may or may not have been possible in the past. Including what kind of interactions should be facilitated before the introduction of a screening programme can be possible in the future.

Further Analysis

The meeting was fully recorded and the entire discussion was transcribed verbatim and three researchers (SJ, CvE and AMP) were present to take notes.

A full copy of the transcript was sent to all participants for approval and corrections. Such amendments were only allowed to be stylistic or mistakenly remembered facts such as names or dates. The transcript was independently content-analyzed and relevant themes were identified and categorized by four researchers (SJ, CvE, AMP and EH).

The result of the literature search and additional sources of information, such as correspondence and interviews, were used to resolve any disagreements in the discussion.

The central themes identified are discussed in this article and are illustrated with quotations.

RESULTS AND DISCUSSION

Session one: From World War II until the 1980's

Isolated scientists and doctors

Following World War II and prior to the 1980's, scientists and doctors began to show an interest in (screening for) HbP. Gradually (research) articles began to appear in the Dutch medical press, originating from a few academic centres in the Netherlands.[30-32] Initial policy was ad hoc and local, influenced by the interest of specific clinicians. The interest of scientists in the northern city of Groningen, with few inhabitants of immigrant descent, was generated by a professor of paediatrics who had a specific interest in blood group antagonisms. He created a research collaboration with colleagues from the Dutch Caribbean island of Curaçao which originally generated his interest in HbP.[33] This resulted in the thesis of a gynaecologist entitled *Haemoglobinopathy Screening in Pregnancy*[34] which focused primarily on antenatal screening and investigated the influence of HbP on the outcome of pregnancy. An investigation into the HbP status of the child was also included. In the 1960's, the University of Leiden in the western part of the Netherlands attracted a human geneticist, who subsequently developed what would become a well-known reference laboratory for HbP.

Meanwhile an interest in HbP in Amsterdam had also been generated due to a large population of immigrants in the city and the specific interest of doctors specialised in tropical medicine. High risk individuals who attended the local out-patient clinic for tropical medicine, were offered *ad hoc* (preconception) screening which would inform them of their carrier status. This was carried out as an extra service. Whether this resulted in any further action being taken remains unclear:

> *We didn't screen just because it was interesting and it wasn't done for research purposes either. It was probably meant to offer people the possibility of [reproductive] choice so that they could take this into account when thinking about their [future] offspring.*
> *(Professor of tropical medicine)*

However, doctors and scientists had little or no contact with each other and there was no collaboration between universities and their departments on this subject. An explanation for this may be that one department was self-supporting in terms of diagnostic capacity and another centre was isolated because of geographic location. A sense of urgency was not yet perceived by any of the experts:

> *I think the impact of the research in Groningen has been limited because it was situated in Groningen [and therefore geographically relatively isolated]. The research [on HbP] clearly identified the problems and gave excellent [clinical] advice. But because we were so remotely situated from most of these problems, the results and conclusions weren't picked up by other professionals in the country. No issues of discrimination by colour or anything like that played a part here.*
> *(Prof. of obstetrics, formerly assigned to the University of Groningen in the north of the Netherlands)*

In 1985 a thesis was published in Amsterdam entitled *Sickle Cell Disease in the Netherlands*[35] that primarily investigated the prevalence of HbP, haematological and clinical variables and treatment in the Netherlands. The author touches on the subject of HbP screening with a singular closing statement. "To omit the performance of Hb electrophoresis in a patient with a Mediterranean or "negroid" background should be considered malpractice".[35]

Start of the debate

Before 1980 the population at risk was still relatively small; therefore, HbP received little or no attention. However, due to an increasing influx of migrant workers, the population at risk increased dramatically during the 1980's (www.cbs.nl, accessed 11 Oct. 2010). This resulted in an attempt to supply immigrant minorities with extra support:

> *… It wasn't until the end of the 80's, now over twenty years ago, that the Ministry of Health had the idea that we should do something coordinated for migrant minorities. We should at least do something about the access to health care for migrant minorities. All the departments within the Ministry of Health put together a budget of three million guilders per year [less than one million English pounds]. They appointed a coordinator, a new job function, which was me.*
> *(Civil servant of Dept. of Health)*

In comparison to the US and the UK, it is interesting to note that the initiative for specific health needs for immigrant workers was initiated by the government and not by societal organisations representing the population at risk.

In terms of policy context it is relevant to point out that both in the Dutch Parliament and in society a public debate ensued during the second half of the 1980's when new possibilities for genetic testing and screening became increasingly clear.[36] A documentary series discussing both the possibility of selecting foetuses and the offer of antenatal testing[37] was broadcast in 1987 and stirred alarm about the social and ethical consequences of genetic testing. At the end of that same year, the Ministry of Health produced a report on the prevention of congenital anomalies.[38] By including genetic testing as a means to prevent congenital anomalies and to enact "responsible parenthood", the suggestion was raised unintentionally that the government would favour a eugenic population policy, stimulating prenatal testing and abortion reminiscent of World War II. In the ensuing debate[39], it was made clear that the goal of genetic counselling should be to inform people, to help them cope with genetic conditions and to support them to choose a course of action appropriate to their individual risk, their family planning, and their ethical and religious standards and then to act in accordance with that decision.[40] The general consensus was that governmental prevention policy should refrain from interference with reproductive genetic issues. At this point in time the term "prevention" could no longer be used in context with reproductive genetic screening in the Netherlands. Whereas in other countries, "prevention" is more readily associated with (HbP) screening, "offering a reproductive choice" would be the optimal preferred terminology in the Netherlands (Health Council of The Netherlands 1989).[41] Reproductive choice refers to options parents have available to them when they are both carriers: adoption, remaining childless, change of partner, accept the risk of a possibly affected child, use of donor gametes, or use of prenatal diagnosis and termination of affected pregnancies. Pre-implantation Diagnostics (PID) was not yet available at this time. Concern for the expectations of the at-risk community was not apparent until later on.

In the wake of these debates, governmental policy regarding genetics and reproductive issues became restrained. This probably influenced the 1989 governmental decision led by Christian Democrats and with full support of Parliament not to implement prenatal screening for neural tube defects.[42;43]

Carrier screening for haemoglobinopathies was not discussed until the second half of the 1980's, when a book entitled *Can I Have Your GenePassport?* was published exploring the ethical issues related to carrier screening in reproductive health care.[44] The book resulted from a report that was commissioned by the Department of Health and presented in 1988:

> *Our first conclusion was that carrier screening could be defended from an ethical point of view given certain conditions. One of the important conditions is the aim of the screening: Is this to maximise prevention or to maximise selective abortion, is it about population eugenics or does it facilitate informed choice. We opted for the last one.*
> *(Professor of ethics, author of the book)*

The above statement also illustrates the importance of terminology used at the time and how it also generated some discussion: Some people preferred to use the term "prevention" whereas "informed choice" was the concept that came to be preferred:

> *The professor of my department was like a lion in his cage: he was roaring (with me) in the department that prevention [of HbP] should be implemented. But when he had to explain this in public, he was a lot more careful and said that we were the researchers and prevention was the responsibility of the doctors. But they didn't do very much, so the word "prevention" came from us.*
> *(Clinical chemist and head of reference laboratory for HbP)*

Besides the more general restraint towards screening for reproductive options, another sensitive issue, the registration of ethnicity also became part of the HbP screening debate. Since the 1970's a law on the registration of personal data, was in preparation. The law itself was a result of societal commotion starting in 1970 when organisations and journalists stirred up a public protest against the national census. Intellectuals warned against the danger of a government being able to register religion or ethnicity referring to the misuse of personal data resulting in the mass deportation of Jewish citizens in World War II. In the proposed law, it was explicitly stated that registration of ethnicity is prohibited.[45] This debate continued into the 1980's when the Council of the Sick Fund sent a letter to the State Secretary of Health concerning its statement on the registration of ethnicity:

> *On November 7 1984 the chairman [of the Council of the Sick Fund] received a telex … in which both national trade unions expressed their opinion of not supporting ethnic registration according to nationality. This accurately reflects the mood at that time.*
> *(Former officer of the Health Inspectorate)*

Both researchers and other professionals were aware of these issues which influenced their decision making:

> *I was involved with the introduction of hepatitis B screening in 1989 and this discussion was very relevant, who do you screen: certain ethnicities at risk or the entire Dutch population? It was said at the time that it is impossible to ask women about their ethnicity, the midwives don't want this, nobody wants this. So we subsequently opted for universal hepatitis screening.*
> *(Head of central screening laboratory)*

In the US the debate on sickle cell screening was influenced by suspicions in the Black community that screening was being used to determine racial purity in order to secure white supremacy and specifically Black inferiority.[19] Scientists, policymakers and politicians in the Netherlands seemed to have been oblivious to this debate. Although the authors of the aforementioned book *Can I Have Your Gene Passport?* referred to the situation in the United States:

> *When we focus on sickle cell disease: the classic example of bad management was the United States. This had much to do with failing technology, miscommunication, confusing the disease with carrier status and in our view specifically because it was introduced in a top-down fashion without any interaction with or involvement of the population at risk. This resulted in our recommendation that (…) you need to create support by involving the population at risk. Without support from the population at risk, invariably you will be accused of racism et cetera. (Professor of ethics)*

Session two: The 1990's: introduction of a new law and two reports

This decade was marked by political influence on screening in general and the National Investigation Sickle Cell Disease and Thalassaemia.[8] The strained attitude regarding genetic screening for reproductive issues that was rooted in the 1980's continued in the 1990's. Although this attitude was supported by a broad range of political parties, the leading influence of the Christian Democratic Party (CDA) is relevant to note, because they were part of the government during many years.[46] Their view on genetics was elaborated in a 1992 report called *Genes and Limits*[47] which was motivated by the introduction of new technology and possibilities in reproductive health care. In the report both prenatal screening and preconceptional carrier screening were described as undesirable developments because of both the need to protect the foetus and the psychological burden imposed upon people when knowing their future child may have a serious untreatable condition. The report was to influence the general screening debate for years to come:

> *Genetics is scary, genetics is dirty (…) it [the report of the Christian Democratic Party] was full of a 'German' [based on WW II] aversion against eugenics in the past. It is the additional sum of only negative possibilities. The possibility of empowerment did not occur to them. (Professor of ethics)*

Shortly after the publication of *Genes and Limits* the final report of the National Investigation Sickle Cell Disease and Thalassaemia was published by Rengelink-van der

Lee in 1994.[8] This report was not initiated by the Department of Health itself but instead, was commissioned by the Consultative Committee Minorities of the Department of Health. The conclusions were based on the prevalence of HbP disease (which was mainly found amongst adopted children born outside the Netherlands) and the results of an anthropological study. The latter concluded that only very limited knowledge amongst both the population at risk and professionals existed. The researchers, who were also concerned about stigmatisation, concluded that introduction of a screening programme for HbP was not "opportune" at this point in time:

> *Yes, that was the main question [whether the prevalence of HbP in the Netherlands was high enough to warrant the introduction of a screening programme] and the idea of having preconceptional or antenatal screening. We thought that that would be the best scenario but it didn't seem feasible.*
>
> *Preconceptionally because the knowledge was far too limited and you would have to be able to reach people at a very early stage (…)…and specifically at that time in the 1990's, the knowledge about inheritable diseases was very limited, both with the older immigrants [those who immigrated to the Netherlands a long time ago], e.g. the people from Surinam, as with more recent immigrants. There was no basis on which a screening programme could be introduced. People felt stigmatized which was a very important feeling (…) the fact is that many parents said: I don't want to know if my child is a carrier of a certain disease because I won't be able to find my daughter a suitable wedding partner.*
> *(Professor of paediatrics & co-author of report)*

The report fuelled the discussion and generated opposition among some professionals who were clearly disappointed with the report's conclusion.[48;49] Some argued that developing a neonatal screening programme for SCD would be a first step in the right direction[50] as was alluded to by the report itself.

> *In the end the result was a negative advice, it can easily be said that this was a heavy blow for us and which determined the future for the next ten years.*
> *(Clinical chemist and head of reference laboratory for HbP)*

The criteria of Wilson & Jungner[51] were not explicitly mentioned in the final report of the National Investigation into Sickle Cell Disease and Thalassaemia[8] nor did they surface in the discussion that followed the report's publication. However, the research that was part of the report, investigated the attitude of the target

population which was (unintentionally) an elaboration of one of the criteria of Wilson and Jungner in so far that the test should be acceptable to the target population.

Although the (problematic) registration of ethnicity is not given any attention in this report, it does seem to have influenced the discussion:

> *And of course even then we weren't allowed to screen on the basis of ethnicity. It was unheard of to pick out all the Black kids and submit them to heel prick screening [to investigate for HbP]. That would be ethically impossible […] The Department of Health said to us: well thank you very much, we don't need to implement any policy on this subject. We will put it in a drawer somewhere.*
> *(Professor of paediatrics & co-author of report)*

A professor of preventative and curative health care for children who was interviewed by telephone, confirms this:

> *We talked about screening the population at risk but this was such a sensitive subject: it was considered discrimination and was seen as politically very incorrect, even if it was used as positive discrimination.*

The constraining influence of the existing political climate is further illustrated when researchers and clinicians were clearly relieved with a change in government (1994):

> *I believe the change in government in 1994/5 when the Christian Democrats were no longer in office, was very important. I remember this very clearly. We had a very broad discussion with the Department of Health, including the discussion whether or not to screen for Down syndrome which was of course impossible. When the Christian Democrats left office we were all very relieved.*
> *(Clinical chemist)*

In 1996 a new law was introduced (Population Screening Act, in Dutch: WBO) based on the criteria of Wilson and Jungner, aimed at protecting the general public against the possible hazards of population screening programmes. The sensitivity towards reproductive issues is illustrated by the fact that this law requires a special licence for certain types of screening such as screening for disorders for which no treatment is available, complicating the introduction of prenatal screening.[36]

Despite a change in the political climate, policy towards HbP carrier screening did not change. Although researchers felt more comfortable investigating the subjects surrounding screening and the fact that the population at risk doubled in size during

the 1990's (www.cbs.nl, accessed 2 March 2010), no screening programme for carrier status of HbP has been introduced to date.

Session three: A new millennium: a change in direction

Turning into a new millennium attitudes change and eventually more attention is given to the health needs of the different populations in the Netherlands.

Though at the end of the 1990's attention to the debate on HbP screening decreased, at the turn of the century the debate resurfaced under the influence of an enthusiastic and very driven molecular geneticist.[52]

The Netherland's population had changed dramatically in the previous decades (www.cbs.nl, accessed 6 Oct. 2010); there were now a vast variety of immigrants and their descendants from all over the world e.g. not only from Turkey, Morocco, Surinam and the Dutch Antilles but also from Africa, South-East Asia and the Middle East. Certain ethnic groups had organized themselves (www.ocan.nl accessed 26 Nov. 2010) and SCD and thalassaemia patients had founded their own organisation (OSCAR) in 1989, although the organisation did not become publicly visible until 1998 (www.sikkelcel.nl accessed 26 Nov. 2010).

Certain professionals began to realise that by *not* specifically tailoring health care needs to certain groups that this in fact is discriminatory, for example by not offering HbP screening to groups at risk:

> *[during the nineties] where I spoke to Elizabeth Anionwu [see: Anionwu and Atkin 2001] … she said you might be worried about discrimination if you start screening for HbP, but the discrimination you create by not screening is probably far greater.*
> *(Em. Professor of clinical genetics)*

I was in London at the conference of the European Society of Human Genetics The debate on the registration of ethnicity was renewed and this time it was approached from a different angle; socioeconomic influences in health were being investigated as well as possibilities to reduce them.[53-55] Both education level and ethnicity are analysed to look for possibilities to reduce inequalities in health. In order to use ethnicity and risk factors more constructively and to avoid any negative connotations, some researchers explored the possibility of combining screening for several groups at risk for different disorders.[56] The Netherlands Organisation for Health Care Research and Development funded several projects on HbP screening after 2000.[57-59] Results of these projects have contributed to the debate on potential implementation of HbP (carrier) screening.

In 2005 the Health Council of the Netherlands published a report on neonatal screening which stated that the prevalence of certain disorders is changing, influenced by the composition of the population in the Netherlands.[14] This report resulted in the expansion of the neonatal screening programme when fourteen diseases were

rapidly added to the programme, one of which was SCD. It was the first time since the previous debate that an official report put the issue of an ethnicity related disorder on the (public and political) agenda. The possibility of ethnically targeted screening was dismissed in the report, and universal screening proposed instead. The 2007 Health Council report on preconception care[17] subsequently explicitly mentioned ethnic background as a risk factor, specifically calling attention to HbP, CF and Tay Sachs disease. Comments published in a national newspaper[60] contributed to the debate which led to discussions in Dutch Parliament and official queries at the address of the Minister of Health. In his reply the Minister of Health made the following statement: "However the question is if offering screening to certain preselected groups on the basis of ethnicity is desirable and acceptable in our society".[61]

The issue of screening and ethnicity therefore remains difficult to fathom. The Parliamentary discussion is referred to during the witness seminar:

> *The minister thinks it should be possible to screen by indication but doesn't mention whether pregnancy is seen as an indication. Whether a woman with ancestors from another country wishes to be pregnant is an indication for screening, is not mentioned either. But he does want carrier testing to be carried out in a genetic centre.*
> *(Professor of community genetics)*

Clearly the registration of ethnicity has returned to the current (political) agenda. In January 2008 the Dutch Society of Clinical Geneticists (VKGN) gave the State Secretary of Health positive advice in response to questions of the department regarding the relevance of the registration of ethnicity related to care in clinical genetics.[62] However hospitals and health professionals are reluctant; it is against hospital policy to register the ethnicity of a patient for the benefit of adequate care and the Dutch Federation of Medical Specialists (KNMG) advises restraint in the matter.[63]

Subsequently a report has been published by the Netherlands Organisation for Health Care Research and Development recommending the registration of ethnicity in the health care sector to facilitate further research in order to reduce differences in health outcomes amongst different ethnic groups in Dutch society.[64]

Despite being back on the agenda, the registration of ethnicity still proves to be a sensitive issue when, although not health related, a minister lost her post over this debate in 2008 suggesting ethnic registration as a means to monitor young offenders.

The late 1990's have been politically dominated by a joint Labour and Liberal government but the new millennium is once again marked by religiously influenced political parties. Recently this has led to a renewed discussion concerning the late termination of pregnancies following prenatal screening whereby specifically religious parties but also the right wing Party for Freedom argue against late terminations of pregnancy reducing the options available to parents.[65] The expectation is that the liberal yet right wing government which was installed in October 2010 will not be

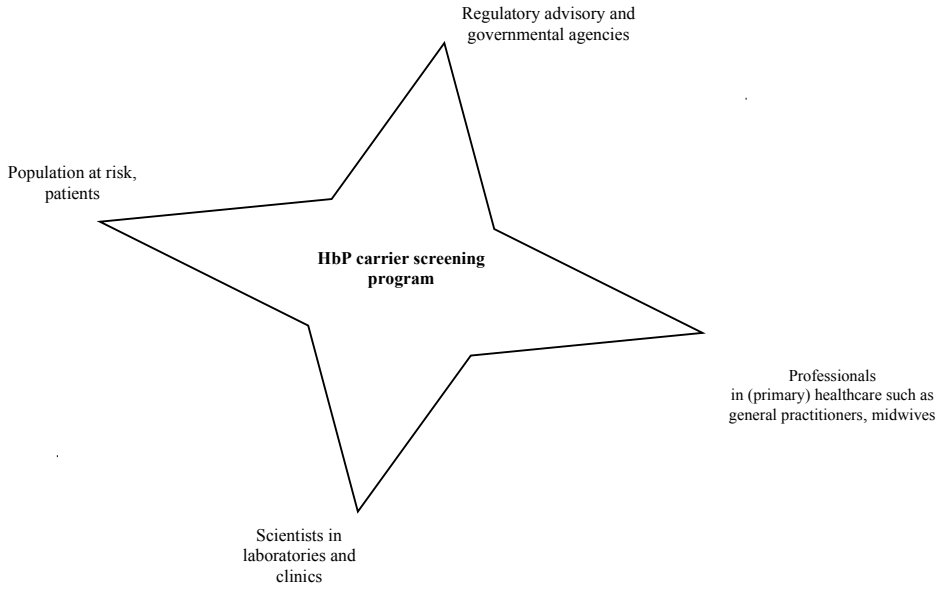


Fig. 1 Network of stakeholders & actors involved

very forthcoming. Moreover, preconception care in general suffered a setback as the Minister of Health recently denounced any further commitment to this subject.[66]

Sociotechnical analysis

After having discussed the findings of the witness seminar and the context of discussions on screening for HbP, we will now address the sociotechnical analysis. The witness seminar and the preceding literature search have identified the actors and stakeholders involved in the former discussions and decision making process about whether or not a screening programme for HbP should be introduced in the Netherlands. These individuals can be categorised into four groups: 1) Scientists in the field, 2) Healthcare professionals, 3) Policymakers and 4) The patients and population at risk (fig.1). We looked at attunement between these stakeholders both in the past and the present on technical options, facilities and services, demand and issues of political and cultural acceptability. Thus more insight was gained into why it was not possible to implement a screening programme in the past and compare this to the current situation.

Technological options

In the 1990's, technological options were acceptable as simple and reliable tests were available. HPLC testing for HbP might not yet have been available in all laboratories, however, electrophoresis was a test available to clinicians.[8] Availability and standardisation of testing methods has only improved since this period.[14;67]

Facilities and services

Facilities and services were clearly limited at the time because preconception care was unavailable to the public. Currently preconception services are being offered in most regions, however; this type of care only reaches a very small part of the target population.[68] Although preconception services have recently been endorsed by the Dutch Steering Committee on Pregnancy and Childbirth[69], the Minister of Health has refused to financially support further policy development regarding this issue.[66]

The National Investigation showed that knowledge amongst professionals was very limited in the early 1990's.[8] Although more attention to the subject has been given since, i.e. neonatal screening has been expanded to include SCD[14], knowledge about these kinds of genetic disorders is still insufficient amongst professionals.[70;71]

Besides this, carrier diagnosis is indicated for certain groups of people in case of (unresolved) anaemia as part of the anaemia guideline of both the midwives and the GPs.[12;13]

Demand

In the past, limited knowledge amongst the groups at risk also made demand for screening low or non-existent (Rengelink-van der Lee *et al*. 1994).[8] Recent research has shown that screening is acceptable amongst the groups at risk[71;72] although cascade screening following a positive carrier status found during the neonatal screening is still limited.[16] After 2000, the patient organisation becomes more established and expresses the need for implementation of screening services, however, it does not feel as if its voice is being heard (OSCAR personal communication 2011).

Political and cultural acceptability

The witness seminar has clearly shown that political and cultural acceptability was non-existent; this was partly caused by the insurmountable discussion on the registration of ethnicity. Moreover, research showed that parents worried about the possible stigmatisation of their affected children.[8] Furthermore, during the 1980's and 1990's the discussion on screening was burdened by the fear of eugenics.[36] The renewed debate seems to be turning in favour of screening[25] supported by the realisation that ethnicity does play a certain role in health care which needs to be investigated further.[64] There is international consensus that a screening programme should be implemented in those countries where HbP is prevalent[6], preferably carried out in a primary health care setting.[2] Although consensus is still lacking at the national level, health professionals seem willing to carry out screening for HbP.[25;71]

Table 1 gives an overview of the various failing processes of attunement in the past on several dimensions and clarifies which issues have changed in the last decade. This model is helpful in understanding the possibilities and barriers that exist for present-day attunement for implementing HbP carrier screening.

Table 1. Sociotechnical analysis of the past and present with regards to an HbP carrier screening program.

Attunement with regard to:	Period in 1990s	Present time
Technological options	– Simple and reliable testing methods	– Well developed testing method for large scale screening
Facilities and services	– Insufficient knowledge amongst health care professionals. – Insufficient collaboration between health care professionals. – Unclear who should offer and carry out screening program. – No support from a national public health institution. – No guideline for anaemia in existence for midwives. – No preconception services available. – Neonatal screening limited, screening for HbP is not part of the screening. – Health authorities decline formulation of recommendations on the basis of report of the National Investigation into Sickle Cell Anaemia and Thalassaemia.	– Insufficient knowledge but willingness is increasing amongst health care professionals. – Carrier diagnosis is part of the anaemia guideline of the midwives and the GPs. – Visible public health authority in place which is able to take responsibility for the coordination of screening programmes (RIVM– Centre for Population Screening). – Improving collaboration between health care professionals under direction of RIVM and professional organisations, but consensus is still insufficient amongst stakeholders. – International consensus that a screening program should be introduced and carried out by primary care professionals. – Endorsement of preconception services by the Dutch Steering Committee on Pregnancy and Childbirth. – Preconception services available in most regions, although funding postponed by ministry of health. – Neonatal screening SCD implemented.
Demand	– Knowledge amongst population at risk is insufficient.	– Knowledge is increasing. OSCAR, patient organisation of HbP, in existence, demanding more (screening) services for group at risk. – Uptake of preconception services is low. – Screening for SCD in Neonatal screening (2007): Carriers are identified > cascade screening as a result of this screening is limited.
Political and cultural acceptibility	– Parents express worries about finding suitable partners for their daughters therefore screening not acceptable in all cultures. – Restrained political attitude on issues of reproductive genetic screening. – Disagreements amongst stakeholders. – Introduction of law on screening (WBO).	– Renewed debate more in favour of screening. – Attitude and culture towards screening in general has changed in The Netherlands e.g. routine prenatal screening for certain abnormalities implemented (once screening for a certain disorder is implemented > easy to add other conditions). – More emancipation of groups at risk. – Screening acceptable amongst population at risk. – Report by the Health Council of the Netherlands endorses preconception care and identifies certain ethnicities as a risk factor for genetic disorders but this is not seen as a basis on which further policy recommendations can be made.

CONCLUSION

By means of a witness seminar the case history of screening policy in the Netherlands was explored and has demonstrated the influence of the heritage of past events on general health care policy, even to this date. Although this method allows researchers to make a further in-depth analysis and explore hidden and sensitive elements of discussions in the past, the method has some weaknesses. The results of the seminar are in part dependent on the participants attending and their recollections which may be hampered by the passing of time. However by using the group dynamics, participants are invited to respond and add to each other's account, thereby helping to reconstruct past events from different perspectives. While being aware of its limitations, the study is able to address an important issue that has long been neglected by elaborating on traditional and often scarce sources.

Policy makers and healthcare workers have been and still are struggling with the challenge of being able to deliver equitable services for an ethnically diverse population.

As opposed to the US where the history of slavery influenced extremely sensitive discussions surrounding the introduction of (carrier) screening for HbP, healthcare policy in the Netherlands is still burdened by the inheritance of WW II when the mass deportations of Jews was supported by a diligent register of the Dutch population which causes ethnic registration still to be problematic until today. In addition genetic screening for reproductive options proves to be a sensitive subject against the same background. Whereas in the US the National Sickle Cell Disease Control Act was introduced in 1972, followed by the Genetic diseases Act of 1976 and the NIH consensus statement in 1987[5], the discussion in the Netherlands is still ongoing. Difficult and sensitive discussions against a background of collective feelings of guilt and penance have influenced the decision making process surrounding screening issues, causing extreme apprehension to debate the registration of ethnicity for the benefit of equitable health services. The issue of ethnicity and the fear of possible discrimination, proved to be a relevant subject but only played a secondary role in the decision making process in the end. In the 1990's the restrained political climate regarding genetic screening for reproductive options as illustrated by the Christian Democrat Party and the law on population screening prevented any further development in the HbP screening discussion.

In addition, the Research Report National Investigation into Sickle Cell Anaemia and Thalassaemia made any initiatives towards the introduction of a screening programme by this department superfluous. Although excellent research exploring the possibilities of a screening programme for carrier status of HbP has taken place over the years both in and outside the Netherlands, the results seem to be "lost in translation".[73] To date, preconceptional and prenatal screening programmes for HbP carrier status have not been introduced in the Netherlands. Screening is still limited to SCD in the neonatal screening programme. The fact that no one, neither at governmental level nor in the scientific community, convened a meeting at the

time to debate and clarify the issues at stake with all professionals and policymakers involved, exemplifies the lack of attunement at the time.

The discussion in the Netherlands has focused primarily on equality (all persons being equal) however the realisation that this may limit health care equity for some has only surfaced in recent years. Under the influence of increasing immigration to the Netherlands (as elsewhere in Europe), and both departmental and political changes, professional opinion concerning the use of information about ethnicity to benefit public health, has begun to change but still remains a sensitive discussion. While a report on the registration of ethnicity by the Health Council of The Netherlands is expected in the near future, a national debate on the introduction of a broader screening programme is urgently required; this should include the voice of the patient organisation which has been insistently calling for further development on this terrain (www.oscarnederland.nl, accessed March 2011).

KEY MESSAGE

Before 2000 reflecting on the inheritance of World War II, reproductive genetic screening and the registration of ethnicity, has been politically unacceptable in the Netherlands, causing a barrier for the introduction of HbP carrier screening. It is clear that carrier screening based on ethnicity would only be acceptable under certain conditions, mainly aimed at a guarantee of informed decision making.

Besides careful analysis of the present situation to resolve existing challenges, future decision making on an extended screening programme needs to include representatives from groups most at risk of HbP to support the possible implementation of such a programme.

REFERENCE LIST

1. Weatherall DJ, Clegg JB. Inherited haemoglobin disorders: an increasing global health problem. Bull World Health Organ 2001;79(8):704-12.
2. Modell B, Darlinson M. Global epidemiology of haemoglobine disorders and derived service indicators. Bull World Health Organ 2008;(86):480-7.
3. Giordano PC, Harteveld CL. Prevention of hereditary haemoglobinopathies in The Netherlands. Ned Tijdschr Geneeskd 2006 Sep 30;150(39):2137-41.
4. Peters M, Appel IM, Cnossen MH, Breuning-Boers JM, Heijboer H. Sickle cell disease in heel injection screening. I. Ned Tijdschr Geneeskd 2009 May 2;153(18):854-7.
5. National Institutes of Health. Newborn Screening for Sickle Cell Disease and other Hemoglobinopathies. Consensus Development Conference Statement. April 6-8, 1987.; National Institutes of Health; 1987.
6. World Health Organisation (WHO). Sickle cell anaemia. 2006. Report No.: The 59th World Health Assembly; 117th session. Agenda item 4.8; Resolution EB117.R3.
7. World Health Organisation (WHO). Management of Hemoglobin disorders. Report of Joint WHO-TIF meeting. Nicosia Cyprus 16-18 November 2007. Geneva Switzerland: WHO; 2008.
8. Rengelink-van der Lee JH, van der Most van Spijk MW, Schulpen T. Landelijk onderzoek sikkelcelanemie en thalassemie. Eindrapport (National investigation into sickle cell

anaemia and thalassaemia. Final report). Utrecht: onder auspiciën van de Stichting Gezondheid Derde Wereld Kind; 1994.
9. Schulpen TW, van der Lee JH, van der Most van Spijk, Beemer FA. Genetic carrier screening for hemoglobinopathies in the Netherlands is not opportune. Ned Tijdschr Geneeskd 1998 May 2;142(18):1019-22.
10. de Jonge A. KNOV Standpunt preconceptie zorg (KNOV position paper preconception care). Bilthoven: KNOV; 2005.
11. de Jonge A. KNOV Standpunt Prenatale Diagnostiek (KNOV position paper Prenatal Diagnostics). Bilthoven: KNOV; 2005.
12. Jans S, Beentjes M. KNOV Richtlijn Anemie in de verloskundige praktijk (Anaemia in midwifery practice, guideline). Utrecht; 2010.
13. Van Wijk MAM, Mel M, Muller PA, Silverentand WGJ, Pijnenborg L, Kolnaar BGM. Anemie richtlijn (Anaemia. Guideline). Utrecht: NHG; 2003. Report No.: M76.
14. The Health Council of the Netherlands. Neonatal screening. The Hague: The Health Council of the Netherlands; 2005. Report No.: 2005/11.
15. Lanting CI, Rijpstra A, Breuning-Boers JM, Verkerk PH. Evaluation of neonatal screening amongst children born in 2007. Leiden: TNO KvL; 2008. Report No.: KvL/P&Z 2008.119.
16. Vansenne F, de Borgie CA, Legdeur M, Spauwen MO, Peters M. Providing Genetic Risk Information to Parents of Newborns with Sickle Cell Trait: Role of the General Practitioner in Neonatal Screening. Genet Test Mol Biomarkers 2011 May 16.
17. The Health Council of the Netherlands. Preconception care: a good beginning. The Health Council of the Netherlands; 2007. Report No.: 2007/19.
18. Wailoo K, Pemberton S. The troubled dream of genetic medicine. Ethnicity and innovation in Tay-Sachs, Cystic Fibrosis and Sickle Cell Disease. Baltimore: The John Hopkins University Press; 2006.
19. Tapper M. In the blood. Philadelphia. Un. Of Pennsylvania press; 1999.
20. Wailoo K, Pemberton S. A perilous lottery for the black family. Sickle cell, social justice, and the therapeutic gamble. In: The troubled dream of genetic medicine. Baltimore: The John Hopkins University Press; 2006. p. 116-60.
21. Bonham VL, Dover GJ, Brody LC. Screening student athletes for sickle cell trait--a social and clinical experiment. N Engl J Med 2010 Sep 9;363(11):997-9.
22. Mitchell BL. Sickle cell trait and sudden death-bringing it home. J Natl Med Assoc 2007 Mar;99(3):300-5.
23. Stein R. Sickle testing of athletes stirs discrimination fears. Washington Post 2010 Sep 20.
24. Anionwu EN, Atkin K. The politics of sickle cell and thalassaemia. Buckingham, Philadelphia. Open University Press; 2001.
25. Cornel MC, Detmar S, Plass AMC, Moerman D,Waarlo AJ, de Kinderen M, Giordano PC. Breder screenen op hemoglobinopatie (A broader screening for haemoglobinopathy. Art. In Dutch). Medisch Contact 2009;Nr. 45(03 november 2009):1874-7.
26. Cornel MC, Lakeman P, Dondorp W. Preconceptional carrier screening should not be delayed. Ned Tijdschr Geneeskd 2011;155:A3205.
27. Giordano PC. Artsen moeten vragen naar etniciteit patient, nieuwsbericht (Doctors should enquire after the ethnicity of their patients. Art. in Dutch). Medisch Contact 2008 May 13.
28. Kievits F, Adriaanse MT. Discriminatie door zorg onder de maat (Discrimination by inadequate care. Art. in Dutch). Ned Tijdschr Geneeskd 2007;151:778-9.
29. Achterbergh R, Lakeman P, Stemerding D, Moors EH, Cornel MC. Implementation of preconceptional carrier screening for cystic fibrosis and haemoglobinopathies: a sociotechnical analysis. Health Policy 2007 Oct;83(2-3):277-86.
30. Huisman TH, van der Schaaf PC, van der Sar A. Studies on hemoglobin abnormality in sickle cell anemia and sickle cell trait. Ned Tijdschr Geneeskd 1954 Oct 9;98(41):2881-8.

31. Muntinghe OG, Pietersz RN, Verhulst JC. Hemoglobinopathies in immigrants from Surinam. Ned Tijdschr Geneeskd 1971 Jul 31;115(31):1306-10.
32. van der Sar. Aplastic sickle cell crisis: a report on four cases. Trop Geogr Med 1967 Dec;19(4):273-85.
33. Jonxis JH. Hemoglobinopathies in families of foreign workers and other migrant groups. Ned Tijdschr Geneeskd 1977 Jun 4;121(23):949-54.
34. Landman H. Haemoglobinopathies and pregnancy. PhD Thesis. Rijksuniversiteit Groningen; 1988.
35. Aluoch JR. Sickle cell disease in the Netherlands. Origin, prevalence, clinical features and management. PhD Thesis. University of Amsterdam; 1985.
36. Van El CG, Pieters,T,Cornel,MC. The changing focus of screening criteria in the age of Genomics: A brief history from the Netherlands. In: Wieser B, Berger W, editors. Assessing Life: on the organisation of genetic testing. Vol.59 ed. München/Wien: Profil; 2010. p. 203-24.
37. Kaizer W. Beter dan god (Better than God) [Documentary] VPRO; 1987.
38. Tweede Kamer der Staten Generaal (The Dutch House of representatives). Prevention of congenital abnormalities (doc. in Dutch). 1987. Report No.: TK 20345:2.
39. De Wert GMWR, Engel GL. Genetic counselling as instrument of population eugenics? Some remarks on the report "Prevention congenital anomalies" (art in Dutch). Medisch Contact 1988 Oct 20;43:843-5.
40. Fraser FC. Genetic counseling. Am J Hum Genet 1974 Sep;26(5):636-59.
41. The Health Council of the Netherlands. Heredity: Society and Science. The Hague: The Health Council of The Netherlands; 1989. Report No.: 31/89.
42. Tweede Kamer der Staten Generaal (The Dutch House of representatives). Population screening neural tube defects. Letter from the State Secretary of Welfare, Health and Culture (doc. in Dutch). 1989. Report No.: Parliamentary documentation. TK 21353:1.
43. Tweede Kamer der Staten Generaal (The Dutch House of representatives). Population screening neural tube defects. report of oral consultation (doc. in Dutch). 2012. Report No.: Parliamentary documentation TK 21353:2.
44. de Wert GMWR, de Wachter MAW. Mag ik uw genenpaspoort? (Can I have your gene-passport?).Baarn. Ambo; 1990.
45. Blessing M. The resistance against the census of 1971 (art. in Dutch). Historisch Nieuwsblad 2005;no.8.
46. van El CG, Cornel MC, Pieters T, Houwaart ES, eds. Debatteren over genetische screeningscriteria (Debating about genetic screening criteria).Houten. Prelum publishers; 2010.
47. Commission of the Scientific Institute of the Christian Demoratic Party (chaired by Prof.E.Bleumink). Genen en grenzen (Genes and their limitations). The Hague: CDA; 1992.
48. van Rhee MA, Holm JP, Niermeijer MF. Genetic carrier screening for hemoglobinopathies: the situation in the Netherlands compared with England. Ned Tijdschr Geneeskd 1998 May 2;142(18):996-7.
49. Wierenga KJ. Neonatal screening for sickle-cell disease. Ned Tijdschr Geneeskd 1997 Jan 25;141(4):184-7.
50. Wierenga KJ, Luteijn AJ. Heterozygote detection for hemoglobinopathies: situation in the Netherlands as compared to the British. Ned Tijdschr Geneeskd 1999 Feb 6;143(6):326-7.
51. Wilson JMG JG. Principles and practice of screening for disease.1968. Geneva: WHO.
52. Giordano PC. Haemoglobinopathies in the Netherlands. Diagnostics, epidemiology and prevention.1998. PhD Thesis. University of Leiden.
53. de Walle HE, van der Pal KM, de Jong-van den Berg LT, Jeeninga W, Schouten JS, de Rover CM, et al. Effect of mass media campaign to reduce socioeconomic differences

in women's awareness and behaviour concerning use of folic acid: cross sectional study. BMJ 1999 Jul 31;319(7205):291-2.
54. Stirbu I, Kunst AE, Bos V, Mackenbach JP. Differences in avoidable mortality between migrants and the native Dutch in The Netherlands. BMC Public Health 2006;6:78.
55. Troe EJ, Bos V, Deerenberg IM, Mackenbach JP, Joung IM. Ethnic differences in total and cause-specific infant mortality in The Netherlands. Paediatr Perinat Epidemiol 2006 Mar;20(2):140-7.
56. Lakeman P, Henneman L, Bezemer PD, Cornel MC, ten Kate LP. Developing and optimizing a decisional instrument using self-reported ancestry for carrier screening in a multi-ethnic society. Genet Med 2006 Aug;8(8):502-9.
57. Giordano PC. Starting neonatal screening for haemoglobinopathies in The Netherlands. J Clin Pathol 2009 Jan;62(1):18-21.
58. Lakeman P, Plass AM, Henneman L, Bezemer PD, Cornel MC, ten Kate LP. Three-month follow-up of Western and non-Western participants in a study on preconceptional ancestry-based carrier couple screening for cystic fibrosis and hemoglobinopathies in the Netherlands. Genet Med 2008 Nov;10(11):820-30.
59. van den Tweel X, Heijboer H, Fijnvandraat K, Peters M. Identifying children with sickle cell anaemia in a non-endemic country: age at diagnosis and presenting symptoms. Eur J Pediatr 2006 Aug;165(8):581-2.
60. Cornel C, Dondorp G, de Wert G. Allow parents the freedom to choose (art in Dutch). Trouw 2008 Nov 22.
61. Klink A. Answers to the queries from Koser Kaya, member of parliament, on preconceptional carrier screening (report in Dutch). 2009 Jan 7. Report No.: 2008Z08008.
62. Knoers VVAM, Leschot NJ. 2008. Genetics and ethnicity in letter to State Secretary of Health, Wellbeing and Sports. PG/e 2807914. 22 January.
63. Baltesen F, Rijlaarsdam B. Levens redden met discriminerende registratie etniciteit (Saving lives with discriminating art. in Dutch). NRC Handelsblad 2008 May 14.
64. ZonMW (The Netherlands Organisation for Health Research and Development. Ethnicity and Health. ZonMW programme recommendations (doc. in Dutch). 2009.
65. Christian Union wants to abolish 20 week ultra sound scan. NRC 2010 Feb 10.
66. Schippers EI. Zwangerschap en geboorte (Pregnancy and Birth). Ministry of Health Wellbeing and Sports,CZ/EKZ 3040205. 2010.
67. Giordano PC. Towards the state of the art neonatal screening for secondary and primary prevention of the hemoglobinopathies in The Netherlands. Validation of technology. Leiden, The Netherlands: Leiden University; 2006 May.
68. Hosli EJ, Elsinga J, Buitendijk SE, Assendelft WJ, van der Pal-de Bruin KM. Women's motives for not participating in preconception counseling: qualitative study. Community Genet 2008;11(3):166-70.
69. A good start: Safe health care in pregnancy and childbirth. Final report of the Steering Committee Pregnancy and childbirth. 2010 Jan 6.
70. Baars MJ, Henneman L, ten Kate LP. Deficiency of knowledge of genetics and genetic tests among general practitioners, gynecologists, and pediatricians: a global problem. Genet Med 2005 Nov;7(9):605-10.
71. Weinreich SS, de Lange-de Klerk ES, Rijmen F, Cornel MC, de Kinderen M., Plass AM. Raising awareness of carrier testing for hereditary haemoglobinopathies in high-risk ethnic groups in the Netherlands: a pilot study among the general public and primary care providers. BMC Public Health 2009;9:338.
72. Giordano PC, Plancke A, Van Meir CA, Janssen CA, Kok PJ, Van Rooijen-Nijdam IH, et al. Carrier diagnostics and prevention of hemoglobinopathies in early pregnancy in The Netherlands: a pilot study. Prenat Diagn 2006 Aug;26(8):719-24.

73. Lenfant C. Shattuck lecture-clinical research to clinical practice--lost in translation? N Engl J Med 2003 Aug 28;349(9):868-74.
74. Rip A, Kemp R. Technological change. In: Rayner S, Malone EL, editors. Human choice and climate change. Columbus: Batelle Press; 1998. p. 327-99.

5

Attitudes of general practitioners and midwives towards ethnicity-based haemoglobinopathy carrier screening

S.M.P.J. Jans, A. de Jonge, L. Henneman
L, M.C.Cornel, A.L. Lagro-Janssen

European Journal of Human Genetics 2012 May 2.
[Epub ahead of print]

ABSTRACT

Haemoglobinopathies are severe autosomal recessive disorders with high prevalence amongst certain ethnic groups. WHO advises implementing screening programmes for risk groups. Research in the Netherlands has shown that general practitioners and midwives do not perceive ethnicity as a risk factor for haemoglobinopathies. Moreover, registration of ethnicity is a controversial societal issue which may complicate the introduction of a national preconception or antenatal carrier screening programme.

This study investigates attitudes, intention and behaviour of general practitioners and midwives towards ethnicity-based haemoglobinopathy carrier screening in general.

A structured questionnaire based on the Theory of Planned Behaviour was sent by mail to a random selection of 2100 general practitioners and1800 primary care midwives. Response was 35% (midwives 44.2%; GPs 27.6%).

Although 45% of respondents thought that offering a carrier test on the basis of ethnicity alone should become national policy, it is currently not carried out. The main factor explaining lack of intention towards ethnicity-based haemoglobinopathy carrier screening was subjective norm, the perception that their peers do not think they should offer screening (52.2% variance explained). If ethnicity-based haemoglobinopathy carrier screening would become national policy, most professionals report that they would carry this out. Most respondents favoured ethnicity registration for health purposes.

Since most practitioners look for role models among peers, debate amongst general practitioners and midwives should be encouraged when new policy is to be developed articulating the voices of colleagues who already actively offer haemoglobinopathy carrier screening. Moreover, primary care professionals and professional organisations need support of policy at national level.

INTRODUCTION

Haemoglobinopathies (HbP) such as sickle cell disease (SCD) and thalassaemia are autosomal recessive disorders with severe anaemia, variable but life-long morbidity and currently with a shortened lifespan due to multi-organ ischaemic damage.[1-3] Couples in which both partners are carriers of HbP have a one-in-four chance in each pregnancy of giving birth to an affected child. HbP is one of the world's main genetic disorders but occur more frequently in current or formerly malaria-endemic areas, such as Africa, the Mediterranean region, the Middle East and South-East Asia. Due to immigration these disorders are now also common in non-endemic countries[3] with an estimated prevalence ranging from 5-40% depending on ancestry.[4] The prevalence of a positive carrier status of HbP in the Netherlands has been estimated at 4-14% depending on ethnic background[5] with a birth prevalence of severe HbP of about 60 infants among 182.000 total births.[6]

In 2006 the World Health Organisation (WHO) urged member states to increase the awareness of SCD and to develop services which integrate carrier detection and genetic counselling within existing primary healthcare systems, in addition to the services of specialists such as clinical geneticists and paediatricians.[4,7] Such genetic population screening programmes have several social, ethical and technological issues which may vary according to the type of screening. Universal neonatal screening as offered in the public health setting, generally serves the purpose of timely detection of a disorder to prevent further illness. Ethical concerns centre primarily on objections to abortion, embryo selection, and concerns on eugenics and medicalization of care, and are especially relevant in the context of prenatal and preconceptional genetic screening, where prevention is *not* the primary purpose. In the preconceptional or prenatal setting the primary aim of any genetic disorder related screening programme is reproductive choice.[8] Although preconception carrier screening provides prospective parents with the most reproductive choice, antenatal carrier screening has practical advantages: it reaches the target population more easily. This article is limited to preconception and antenatal HbP carrier screening. Although (ethnic) diversity and heterogeneous distribution of HbP may make the introduction of such a programme challenging, it is currently thought to be possible to develop an appropriate programme that meets the ethical considerations for the introduction of genetic screening programmes as agreed upon at European level.[9]

England is an example of a country where a linked antenatal carrier screening (both targeted and universal, depending on prevalence) and neonatal screening programme (universal) for HbP is available.[10] This policy is supported by the National Institute for Health and Clinical Excellence (NICE) which recommends (preconception) counselling and carrier testing.[11] Carriers can be identified by a simple and inexpensive blood test (Hb-electrophoresis or High Performance Liquid Chromatography (HPLC)) allowing couples preferably before pregnancy to be informed about their risk, giving them a wider scope of reproductive options.

Although universal carrier screening, in which all women regardless of their ethnicity who are either pregnant or planning to become pregnant are offered carrier screening, may be preferable in equitable terms, this may not always be preferred in economic terms because in some geographical areas prevalence may be too low to warrant universal screening even though this means some cases may be missed.[12] Even if universal screening would be the goal, women should always be offered the choice to opt out. Information on risk based on her ethnic background can be used to support women making an informed choice about whether to accept screening or not. For example, targeted ethnicity-based screening as advised by the American College of Obstetricians and Gynecologists (ACOG), may be more appropriate.[13] This requires health professionals, such as GPs and midwives to identify couples at risk by taking an ethnicity-related history by asking them about their ancestry in conjunction with offering them information about HbP carrier screening when women (and their partners) enter into care. Initiatives have been undertaken to develop instruments to help decide who is eligible for testing and who is not. [10,14,15] Although implemented in England, this still awaits further discussion in the Netherlands.

Pregnant women are mostly cared for in primary care by midwives and occasionally by GPs and are currently at best offered carrier testing on the basis of anaemia, a positive family history or at the personal discretion of midwives and GPs in the Netherlands.[16-18] However if (primary) healthcare services want to adequately meet the needs of the whole population, health professionals should be aware of the specific healthcare requirements of certain ethnic groups.

In the past and even still today, ancestry or ethnicity-based HbP screening has not been without controversy.[19-21] A recent study showed ethnic registration to be a controversial issue in the Netherlands because of its relationship with World War II and lingering feelings of guilt in Dutch society, causing it to be a barrier for the introduction of HbP carrier screening.[22] Moreover, in a pilot study primary care professionals expressed that although they support HbP carrier screening, they do not interpret ethnicity as a risk marker for HbP.[23] In order to offer equitable health services to all groups in society, health professionals need to be aware of ethnicity-related health needs without the fear of raising issues of discrimination or stigmatization. Because attitudes of health professionals may influence clinical practice, the specific attitudes of such professionals towards ethnic registration are of interest.

The aim of this study was to investigate the attitude, intention and behaviour of midwives and GPs towards ethnic registration and their willingness to undertake carrier testing for clients and patients on the basis of ethnicity.

MATERIAL AND METHODS

Questionnaire

A cross sectional study was designed by means of a structured questionnaire based on a previous pilot study[23] including direct measures of the main constructs of

the Theory of Planned Behaviour (TPB) (figure1). TPB interprets the behavioural intentions concerning performance as the most immediate and important predictor of whether people perform a certain behaviour.[24] The behaviour of interest in this study was *offering patients an HbP carrier test on the basis of their ethnicity* which was explained to participants in the introduction to the questionnaire. We underlined the fact that the amount of patients at risk in their practice and whether or not they tested them for (carrier status of) HbP at present was irrelevant to being able to answer the questions.

The relationship between attitudes, subjective norm and perceived behavioural control is described by the theory as the underlying foundational belief about the intention of performing the behaviour.

Attitude was measured by using multiple word pairs to answer two questions. First, *What do you think about offering your patients a carrier test for HbP solely on the basis of ethnicity (regardless of family history)?* A sum-score was then calculated from answers scored on a 7-point scale using the following word-pairs: bad-good, nonsense-important, tough-easy, undesirable-desirable, harmful-beneficial and discriminating-privilege. The results showed good consistency for the total score (Cronbach's alpha 0.86). The one factor model fitted well using exploratory factor analysis, all items loaded onto one factor.

Secondly, *What do you think about registering the ethnicity of your patients?* A sum-score was calculated from answers scored on a 7-point scale using the following word-pairs: wrong-good, harmful-beneficial, nonsense-appropriate, awkward-useful, discriminating-harmless and objectionable-desirable. (Cronbach's alpha 0.89). All items were loaded on one factor using exploratory factor analysis.

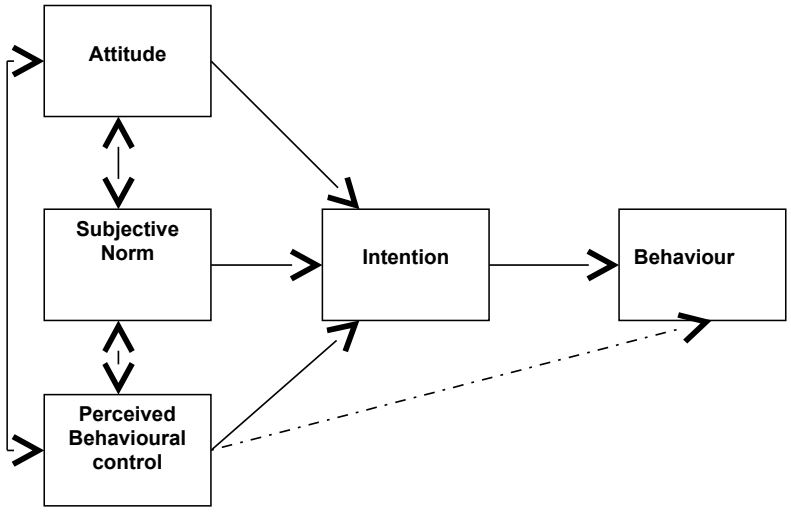


Figure 1. Theory of Planned Behaviour[23]

Subsequent questions were answered with single word pairs. The question *Do you think your colleagues believe a carrier test solely on the basis of ethnicity should be offered to patients (certainly not [1]-certainly [7])*? measured the subjective norm of the professional groups. Behavioural control was measured with the following question: *Are you currently able to offer your patients a carrier test for HbP on the basis of ethnicity alone (certainly not [1]-certainly [7])?*

Two questions measured intention: *Do you intend to offer your patients a carrier test for HbP exclusively on the basis of ethnicity in the future (certainly not [1]-certainly [7])?* and: *Do you intend to offer your patients an HbP carrier test solely on the basis of ethnicity should this become national policy (certainly not [1]-certainly [7])?*

Behaviour was measured by asking the following questions: *Do you at present offer your patients an HbP carrier test solely on the basis of ethnicity (never [1]-always[7])?* and: *Do you offer your patients with unresolved anaemia and no familial history an HbP carrier test (never [1]-always [7])?*

Responders were also asked if they thought that: *An HbP carrier test on the basis of ethnicity alone should become national policy* (binary answer; yes [1] or no [2]). Finally, they were asked some basic characteristics (location of practice, estimated percentage of population from the group at risk in their practice, work experience).

The final version of the questionnaire was approved by members of an expert group which consisted of members of the GP and midwifery professions, a representative from the national patient organisation and researchers in the field of HbP.

Respondents

The questionnaire was accompanied by a letter of introduction explaining the aim of the project i.e. exploring the opinion of health care professionals about offering patients an HbP carrier test on the basis of their ethnicity and underlining the fact that no specific knowledge about HbP was necessary to be able to answer the questions. This was sent by post to 2100 GPs and 1800 primary care midwives between November and December 2009. GPs were randomly selected from the total population of GPs (roughly 8000) by the Netherlands Institute of Health Services research (NIVEL). The total number of midwives is small in the Netherlands; therefore, all primary care midwives were sent a questionnaire. No reminders were sent out and no incentives were offered to participate in the study.

Analysis

Differences between GPs and midwives were assessed by a two-tailed t-test and chi^2: p-values <0.05 are reported as statistically significant.

Direct measures of the main constructs of the TPB (attitude, subjective norm, perceived behavioural control and intention) are reported as a mean. Standard linear regression analysis was applied analysing data obtained according to the TPB in order to explain the behaviour of midwives and GPs towards ethnicity based HbP carrier testing (figure 1). Variables were added backwards. Two tailed values for Pearson correlations are reported between determinants from the TPB. All data were analysed in SPSS 15.01.

RESULTS

The questionnaire was returned by 1346 primary health care workers: 795 midwives (response rate 44.2%) and 551 GPs (response rate 27.6%) resulting in a total response rate of 35%.

Respondent characteristics are presented in table 1. About half of the respondents worked in urban areas. The average working experience was 14 years. More midwives came from urban areas compared to the GPs and they had a significantly longer working experience. The estimated percentage of patients from ethnic minorities in the practices showed a wide distribution of 0-95% with a mean of 16.6% (SD 18.7%). The midwives reported significantly higher estimates of clients from the groups at risk for HbP in their practices.

Results according to items of the TPB are shown in table 2.

Table 1. Characteristics of respondents

	GPs N=551	Midwives N=795
Urban location of practice, n (%)**	255 (46.4)[1]	452 (56.9)
Estimated average percentage of patients from population at risk in practice **	12.9[1]	19.1
Years of experience (mean SD)*	11.3 (9.0)[1]	17.3 (9.3)

[1]Difference between groups significant at p <0.001 *Independent t-test ** Chi[2] GP= general practitioner

Table 2. Constructs of TPB, comparison between GP sand midwives

	GPs Mean score (SD)	Midwives Mean score (SD)
Attitude towards testing on the basis of ethnicity	4.6[1] (1.3)	4.9 (1.3)
Attitude towards the registration of ethnicity in daily practice	4.5[1] (1.4)	5.6 (1.2)
Subjective norm	3.6 (1.4)	3.8 (1.7)
Perceived behavioural control	4.4[1] (2.1)	4.0 (2.1)
Intention on the basis of ethnicity	3.4[1] (1.7)	3.9 (1.7)
Intention on the basis of national policy	5.1[1] (1.8)	5.7 (1.7)
Current behaviour	1.9 (1.4)	1.8 (1.6)
Current behaviour on basis of guidelines	4.2[1] (2.1)	5.2 (2.1)

[1] t-test, two tailed significant p <.001 TBP = Theory of Planned behaviour GP = General Practitioner

Attitude

On average primary care providers have a fairly positive attitude towards offering a test solely on the basis of ethnicity and regardless of family history, midwives being more positive than GPs. The midwives also displayed a more positive attitude towards the registration of ethnicity.

Subjective norm

Both GPs and midwives were less positive about what they thought their colleagues opinions were to ds testing on the basis of ethnicity. Most of them thought their colleagues would not recommend screening based on ethnicity.

Perceived behavioural control

While in practice the laboratory test is easily available, the responses were close to the scale average. GPs felt somewhat more able to actually carry out an HbP carrier test compared to midwives.

Intention

GPs scored the intention of offering an HbP carrier test to their patients on the basis of ethnicity alone more negative compared to midwives, who scored almost neutral. However if this were to become national policy, most participants did express the intention to offer this to their patients: midwives significantly more so than GPs.

Current test behaviour

The scores for the questions on current behaviour showed that both GPs and midwives almost never offer a carrier test for HbP on the basis of ethnicity alone (mean scores 1.9 and 1.8). On the other hand, specifically midwives were prepared to test patients on the basis of unexplained anaemia as instructed by the guidelines of their professional organisations (mean score 5.2). GPs however were less inclined to do so (mean score 4.2); the difference was significant.

Of all primary care providers, 45% thought that offering a test for carrier status on the basis of ethnicity alone should become national policy, GPs thought so significantly less often than midwives.

Explaining intention and behaviour

For both midwives and GPs together, the *intention* of offering patients an HbP carrier test on the basis of ethnicity alone was largely explained by three factors: the attitude towards offering patients a carrier test for HbP only on the basis of ethnicity, subjective norm and control over the ability to effectuate the test. This model explained 52.2% of the variance ($p < 0.001$). The subjective norm, i.e. what GPs and midwives perceived their colleagues' opinion to be, contributed most to the model (Beta=0.49 $p<0.001$).

Variance changed only slightly by adding attitude towards the registration of ethnicity to the model (explained variance 52.5% $p<0.001$). In this model, attitude

towards the registration of ethnicity was the second most important contributor (Beta = 0.31 p<0.001). Characteristics of the participants, such as percentage of population from the group at risk in their practice, work experience and location of practice, did not influence intention towards screening for carrier status of HbP on the basis of ethnicity.

DISCUSSION

Although at present midwives and GPs in the Netherlands do not carry out HbP carrier testing solely on the basis of their patient's ethnic background, they generally have a positive attitude towards ethnicity-based carrier screening. This finding is supported by the results of other studies.[23,25] According to the TPB, subjective norm influences intention and behaviour. Since health care professionals apparently only have very few examples of colleagues who carry out this type of testing, they are not inclined to do so in their own practice environment. However, they are prepared to follow guidance should carrier screening become national policy. Control over the ability to administer the test was also part of the model that explained intention and behaviour. Midwives especially seemed less than secure in their capability of carrying out a test for HbP carrier status as they scored significantly lower on this item (personal control) when compared to GPs. Although ordering an HbP carrier test is relatively simple, the interpretation of the results is not always straight forward. This requires more knowledge than health professionals may have[26,27] and may explain why health professionals are reluctant in offering carrier testing for HbP. Another reason may be that health professionals incorrectly believe they are legally restricted to offer carrier screening because of the Dutch Population Act.[28]

Interestingly the attitude of midwives towards the registration of ethnicity in daily practice was much more positive when compared to GPs. One explanation may be that midwives are already used to registering the ethnicity of their clients and in contrast to GPs also have the possibility to do so in the software they use. It is unclear in which manner midwives (and GPs) determine ethnicity; if and what questions are asked or whether this is self reported or otherwise determined. This important and interesting point needs further investigation in the future.

Since we wanted to know what health professionals thought in general about ethnicity related HbP screening, we did not specify when the screening should take place; either preconceptionally or antenatally. It is not inconceivable that attitudes may differ between the two as reproductive options during the antenatal period are limited for a carrier couple. The questionnaire was used in a previous pilot project[23] and discussed in the expert group. Despite this the question *An HbP carrier test on the basis of ethnicity alone should become national policy* could be interpreted in several ways and is therefore one of the limitations of the study. It is difficult to attribute definitive meanings to the answers with this question: A person who answers 'no' might do so either because he/she believes that screening should only be offered if universal or because they do not believe such screening for HbP should

be offered at all in the Netherlands or that it should be an individual decision at professional level. This needs further study.

Although the response rate was low in this study (35%); it was reached without sending out reminders and the response rate amongst GPs was much lower resulting in a lower overall response rate. We expected to receive more questionnaires from those GPs and midwives practicing in urban areas with a higher percentage of the population at risk. This was not the case, especially in the group of GPs. The spread of practice location, however, corresponds with national spread of GPs indicating a representative sample.[29] Responding GPs estimated only slightly more patients from ethnic minorities in their practice (12.9%) compared to the national population (11.2% non-western). In 2008, 19.6% of women in Dutch midwifery practices were of non-Dutch ethnicity which is comparable to what the midwives in the study estimated.[30] Other surveys have encountered similar problems in terms of response and indicated that a high workload prevented health professionals from participating.[31] A lack of interest or failure to see the importance of the subject and the popularity of GPs as research objects may also have influenced the lack of enthusiasm amongst GPs in returning the questionnaire. Although the response rate was low; there was no evidence of selection bias.

Achterberg et al. argued that effective implementation of screening for HbP will require changes at both regime (suppliers and users) and landscape level (institutions, material social, political and legal infrastructure), but that such change is difficult to achieve without an active orchestrating role of the government.[32] This contradicts present governmental policy which expects the field of health professionals to initiate such policies. The fact that similar programmes in the Netherlands have been initiated by the government in the past[33] makes this all the more curious. Whether or not to test for (carrier status of) HbP during reproductive life (ie preconceptional, antenatal or neonatal) has been debated since the seventies and eighties. Possibly, previous sensitivities surrounding ethnicity and ethnic registration are still applicable today.[22]

Since most women in the Netherlands are cared for by midwives when pregnant[30] and most women will probably meet with their GP at some point during their reproductive life, they would be the professionals of choice to offer HbP carrier screening to women and /or couples.

Morgan et al.[34] showed that fewer than 28% of gynaecologists offered their pregnant patients screening for cystic fibrosis (CF), on the basis of all of the criteria in the guidelines of the ACOG. One explanation given was that almost 60% did not feel familiar enough with genetics to offer screening.[35] This lack of knowledge displays a need for continuing education in genetics, a problem which probably also exists amongst primary healthcare professionals. Vansenne et al. reported a lack of HbP knowledge and clinical experience influencing primary care practitioners' behaviour in neonatal screening which confirms the need for further education.[26]

Besides knowledge development, the use of specific antenatal laboratory forms (such as used for the Antenatal Screening Programme for Infectious Diseases and

Pregnancy Immunisation, PSIE, programme[36]) could prompt health professionals to initiate HbP carrier testing and may encourage implementation of testing. Since the design of this form is not the responsibility of professional organisations such as those of GPs and midwives, it would still require some form of governmental or laboratory experts' initiative.

It has been shown that informed choice is less well facilitated for women from different ethnic backgrounds in other areas of antenatal screening[37], although several researchers have shown that both preconception and antenatal screening is acceptable amongst the population at risk.[38-40] Ethnic diversity poses an extra challenge to health care professionals to deliver equitable services.[41] The discussion in the Netherlands has focused primarily on equality in health care and concerns over stigmatisation of certain groups in society; however, the realisation that this may limit health care equity for some has only surfaced in recent years.[22] If we want to strive to provide equitable healthcare services for all, it is important that health professionals such as midwives and GPs are aware of these issues and that discussions on equity, equality and access are part of (continuing) education programmes to enable them to provide women with the care they need. Introduction of HbP carrier screening should be a part of meeting these needs, as proposed by the WHO.

Many countries have been hesitant about introducing ethnicity-based HbP carrier screening based on negative reports related to discrimination and stigmatization of groups at risk. In the past SCD has been wrongly addressed as a "Black disease" and care for these patients has been and very often still is shadowed by mistrust and health care discrimination.[19,42] Associating (carrier status of) HbP with particular ethnic groups may undermine the success of a possible screening programme. For such a program to be effective, equitable facilities for diagnosis and treatment should be available.[43] Moreover, the correct determination of ethnicity is important but it could also be possible that health professionals and/or their patients find this difficult; they may need to be supported by a tool to determine risk or universal screening should be considered.[15,44]

We conclude that most practitioners are willing to offer screening solely on the basis of ethnicity should this become national policy, however not all. The fact that not all midwives and GPs answered that they are not prepared to implement a national guideline for HbP carrier screening, is unusual. The background of this result and a more in depth analysis of the possible barriers for ethnicity-based HbP carrier screening, warrant further investigation.

In developing and implementing new policy with regard to HbP carrier screening, debate amongst GPs and midwives should be encouraged, articulating the voices of colleagues who already actively offer HbP carrier screening. Opinion leaders and professional organisations of primary health care professionals should be supported by policy at national level when targeting GPs and midwives to implement HbP carrier screening.

REFERENCE LIST

1. Dauphin-McKenzie N, Gilles JM, Jacques E, Harrington T. Sickle cell anemia in the female patient. Obstet Gynecol Surv. 2006 May;61(5):343-52.
2. Platt OS, Brambilla DJ, Rosse WF, Milner PF, Castro O, Steinberg MH, et al. Mortality in sickle cell disease. Life expectancy and risk factors for early death. N Engl J Med 1994 Jun 9;330(23):1639-44.
3. Weatherall DJ, Clegg JB: Inherited haemoglobin disorders: an increasing global health problem. *Bull World Health Organ* 2001;**79**(8):704-712.
4. Modell B Darlison M: Global epidemiology of haemoglobin disorders and derived service indicators. *Bull World Health Organ* 2008;**86** (6):480-487.
5. Giordano PC, Harteveld CL. Prevention of hereditary haemoglobinopathies in The Netherlands. Ned Tijdschr Geneeskd 2006 Sep 30;150(39):2137-41.
6. Peters M, Fijnvandraat K, van dT, X, Garre FG, Giordano PC, van Wouwe JP, et al. One-third of the new paediatric patients with sickle cell disease in The Netherlands are immigrants and do not benefit from neonatal screening. Arch Dis Child 2010 Jun 24.
7. World Health Organisation. Sickle cell anaemia, The 59th World Health Assembly; 117th session. 2006. *Agenda item 4.8; Resolution EB117.R3*.
8. De Wert GM, Dondorp WJ, Knoppers BM. Preconception care and genetic risk: ethical issues. J Community Genet 2011 Dec 29.
9. Population genetic screening programmes: technical, social and ethical issues. Eur J Hum Genet 2003 Dec;11 Suppl 2:S5-S7.
10. National Health Service. Sickle cell & Thalassaemia Screening Programme. 2011. Available from: http://sct.screening.nhs.uk on16 August 2011.
11. National Collaborating Centre for Women's and Children's Health. Antenatal care. Routine care for the healthy pregnant woman: London: National Institute for Health and Clinical Excellence, 2010 Jun 23. Report No: CG62.
12. Hinton CF, Grant AM, Grosse SD: Ethical implications and practical considerations of ethnically targeted screening for genetic disorders: the case of hemoglobinopathy screening. *Ethn Health* 2011;**16**(4-5):377-388.
13. American College of Obstetricians and Gynecologists: Practice Bulletin No. 78: hemoglobinopathies in pregnancy. *Obstet Gynecol* 2007;**109**(1):229-237.
14. Lakeman P, Henneman L, Bezemer PD, Cornel MC, ten Kate LP: Developing and optimizing a decisional instrument using self-reported ancestry for carrier screening in a multi-ethnic society. *Genet Med* 2006;**8**(8):502-509.
15. Dyson SM, Culley L, Gill C, Hubbard S, Kennefick A, Morris P, et al. Ethnicity questions and antenatal screening for sickle cell/thalassaemia [EQUANS] in England: a randomised controlled trial of two questionnaires. Ethn Health 2006 May;11(2):169-89.
16. Jans S, Beentjes M. Anaemia in midwifery practice, guideline. Utrecht, KNOV, 2010.
17. Nederlands Huisartsen genootschap. Preconception care, M97. Utrecht, NHG, 2011.
18. Wijk MAM, Mel M, Muller PA et al Anaemia, guideline, M76. Utrecht, NHG, 2003.
19. Anionwu EN, Atkin K: The politics of sickle cell and thalassaemia. Buckingham, Open University Press, 2001.
20. Dyson, SM: Ethnicity and Screening for Sickle Cell/Thalassaemia. Oxford, Elsevier Churchill, 2005.
21. Tapper M: In the blood. Philadelphia, University of Pennsylvania Press,1999.
22. Jans SM, van El CG, Houwaart ES et al: A case study of haemoglobinopathy screening in the Netherlands: witnessing the past, lessons for the future. *Ethn Health* 2011; Aug 8 [Epub ahead of print].
23. Weinreich SS, de Lange-de Klerk ES, Rijmen F et al: Raising awareness of carrier testing for hereditary haemoglobinopathies in high-risk ethnic groups in the Netherlands: a pilot

study among the general public and primary care providers. *BMC Public Health* 2009; **9**:338.

24. Ajzen I: The theory of planned behaviour. *Organ Behav Hum* 1991; **50**: 179-211.
25. Tsianakas V, Calnan M, Atkin K, Dormandy E, Marteau TM: Offering antenatal sickle cell and thalassaemia screening to pregnant women in primary care: a qualitative study of GPs' experiences. *Br J Gen Pract* 2010; **60**(580):822-828.
26. Vansenne F, de Borgie CA, Legdeur M, Spauwen MO, Peters M: Providing Genetic Risk Information to Parents of Newborns with Sickle Cell Trait: Role of the General Practitioner in Neonatal Screening. *Genet Test Mol Biomarkers* 2011 May 16. [Epub ahead of print].
27. Houwink EJ, van Luijk SJ, Henneman L, van d, V, Jan DG, Cornel MC. Genetic educational needs and the role of genetics in primary care: a focus group study with multiple perspectives. BMC Fam Pract 2011 Feb 17;12:5.
28. van Hellemondt RE, Hendriks AC, Breuning MH. Regulating the use of genetic tests: Is Duch law an example for other countries with regard to DTC genetic testing? Amsterdam Law Forum 2011. Available from: URL: http://ojs.ubvu.vu.nl/alf/article/view/194/368. Last accessed dec. 2011.
29. National Institute for Public Health and the Environment: Dutch National Atlas of Public health. 2011. Available from: www.zorgatlas.nl on 16 August 2011.
30. The Netherlands Perinatal Registry: Perinatal care in the Netherlands 2008. Utrecht, PRN-Foundation, 2011.
31. Poppelaars FA, Ader HJ, Cornel MC et al: Attitudes of potential providers towards preconceptional cystic fibrosis carrier screening. *J Genet Couns* 2004;**13**(1):31-44.
32. Achterbergh R, Lakeman P, Stemerding D, Moors EH, Cornel MC: Implementation of preconceptional carrier screening for cystic fibrosis and haemoglobinopathies: a sociotechnical analysis. *Health Policy* 2007; **83**(2-3):277-286.
33. National Institute for Public Health and the Environment: Pre- and neonatal screening in the Netherlands. 2011. Available from: www.rivm.nl/pns_en on 16 August 2011.
34. Morgan MA, Driscoll DA, Mennuti MT, Schulkin J: Practice patterns of obstetrician-gynecologists regarding preconception and prenatal screening for cystic fibrosis. *Genet Med* 2004; **6**(5):450-455.
35. Committee on Genetics ACOG: Update on Carrier Screening for Cystic Fibrosis. Committee opinion. No 486. *Obstet Gynecol* 2011;**117**(4):1028-1031.
36. National Institute for Public Health and the Environment: Bloodtests for pregnant women. 2011. Available from: www.rivm.nl/pns_en/bloodtest on 16 August 2011.
37. Dormandy E, Michie S, Hooper R, Marteau TM: Low uptake of prenatal screening for Down syndrome in minority ethnic groups and socially deprived groups: a reflection of women's attitudes or a failure to facilitate informed choices? *Int J Epidemiol* 2005 ;**34**(2):346-352.
38. Lakeman P, Plass AM, Henneman L et al*:* Three-month follow-up of Western and non-Western participants in a study on preconceptional ancestry-based carrier couple screening for cystic fibrosis and hemoglobinopathies in the Netherlands. *Genet Med* 2008;**10**(11):820-830.
39. Tsianakas V, Atkin K, Calnan MW, Dormandy E, Marteau TM: Offering antenatal sickle cell and thalassaemia screening to pregnant women in primary care: a qualitative study of women's experiences and expectations of participation. *Health Expect* 2011; March 3. [Epub ahead of print]
40. Pal van der S, Kesteren van N, Dommelen van P, Detmar S: Willingness to participate in carrier screening for haemoglobinopathies amongst high risk groups. Report No.: 09.049. Leiden, TNO KvL, 2009.
41. Darr AR: Ethnic diversity and genetics: implications for families and service providers in the UK; in Broertjes JJS, Henneman L, Beemer FA (eds): Community Genetics. Past and future.Utrecht, Department of Biological Education, 2002.

42. Wailoo K, Pemberton S: The troubled dream of genetic medicine. Baltimore, The John Hopkins University Press, 2006.
43. Wilson JMG, Jungner. Principles and practice of screening for disease. Public health papers No. 34. Geneva, World health Organisation, 1968.
44. Lakeman P, Henneman L, Bezemer PD, Cornel MC, ten Kate LP. Developing and optimizing a decisional instrument using self-reported ancestry for carrier screening in a multi-ethnic society. *Genet Med* 2006 Aug;**8**(8):502-9

6

"A morass of considerations": Exploring attitudes towards primary care ethnicity-based haemoglobinopathy carrier screening

S.M.P.J Jans, L. Henneman, A. de Jonge, C.G. van El, L.H. van Tuyl, M.C. Cornel, A.L.M. Lagro-Janssen

Submitted

ABSTRACT

Background: The Netherlands does not have a national haemoglobinopathy carrier screening program aimed at facilitating informed reproductive choice, even though the WHO advises this. HbP carrier testing for those at risk is at best offered on the basis of anaemia. Registration of ethnicity has proved controversial and may complicate the introduction of a screening programme if ethnicity-based. However, other factors may also play a role.

Objective: To explore perceived barriers and attitudes amongst general practitioners (GPs) and midwives regarding the registration of ethnicity and ethnicity based haemoglobinopathy carrier screening.

Methods: Six focus groups in Dutch primary care with a total of 37 GPs and midwives were conducted, transcribed and content analysed using Atlas-ti.

Results: Both GPs and midwives struggled with correctly identifying ethnicities at risk for HbP. Ethical concerns regarding privacy seem to originate from World War II experiences when ethnic and religious registration facilitated deportation of Jewish citizens, coupled with the current political climate. Some midwives thought the ethnicity question might undermine the relationship with their clients. Despite this, both groups seemed positive and are familiar with identifying ethnicity and use this for individual patient care. Software programs prevent GPs from registering ethnicity of patients at risk. Financial implications for patients were also a concern.

Conclusion: Although health professionals are generally positive about screening, ethical, financial and practical issues surrounding ethnicity-based HbP carrier screening need to be clarified before introducing such a programme. Primary care professionals can be targeted through professional organisations but need national policy support.

BACKGROUND

Haemoglobinopathies (HbP), such as sickle cell disease and thalassaemia, are autosomal recessive disorders with severe anaemia, variable but life-long morbidity and with a shortened lifespan due to multi-organ ischaemic damage.[1;2] HbP occur more frequently in areas such as Africa, the Mediterranean area, the Middle East and South-East but are now also common in other countries due to migration and population admixture, resulting in a varying carrier prevalence of up to 40% depending on the ancestry[2;3] making ethnicity an important determinant of risk. Carrier couples have a 1-in-4 chance in each pregnancy of giving birth to a diseased child. Carrier screening would allow the identification of these couples and give them an opportunity to make informed reproductive decisions. Despite the advice of the World Health Organisation (WHO)[4], the Netherlands, as many other countries, does not have a national HbP carrier screening programme. Although national guidelines advice HbP carrier testing for (unresolved) anaemia or in case of a positive family history[5;6], health professionals such as general practitioners (GPs) and midwives rarely carry this out to facilitate reproductive choice. Several studies have shown that both health professionals and groups at risk support HbP carrier screening.[7-10] One study however showed that primary care professionals do not see ethnicity as a risk factor for HbP.[8] Another study suggested that because HbP testing is influenced by peer behaviour and since colleagues rarely test and official screening policy is lacking[9] could be one of the explanations why testing rarely happens. Subsequently, most carriers remain unidentified, also because recessive disorders are often not apparent in families.

In England, where antenatal HbP carrier screening was introduced in 2004, self identified ethnicity based on a family origin questionnaire is determined to assess HbP risk in both low prevalence areas where targeted screening is practiced, as well as in high prevalence areas where universal screening is the norm.[11] Although HbP carrier status can easily and cheaply be determined by a HPLC test, identification of ethnicity might still be necessary not only to investigate mutations but also to inform a couple of their risk, regardless of how screening is carried out. Identification of the extent of their risk based on ethnicity supports health care professionals to facilitate women and their partners to make an informed choice with regard to their (future) pregnancies as HbP (carrier) prevalence differs across ethnic groups. Additionally, economic arguments may also be used to favour implementation of targeted screening.[12]

Research by Dyson et al. showed that health care workers struggle with the ethnicity question as a screening tool and worry about the sensitivities related to ethnicity.[13] In the Netherlands, ethnic registration proved to be a controversial issue rooted in the history of World War II and linked to the current nationalistic political climate and came up as a barrier for the introduction of HbP carrier screening.[9;14] In order to offer equitable health services to all groups in society, health professionals need to be aware of ethnicity-related health needs without the fear of raising issues of discrimination or stigmatisation.

Objective

This study's objective was to explore the present attitudes towards ethnic registration by GPs and midwives related to every day practice and in particular to identify risk groups for preconceptional or antenatal HbP carrier testing and to explore perceived barriers if ethnicity-based HbP carrier screening is implemented in the future.

METHODS

Design and setting

This qualitative study is part of a broader study examining ethnicity-based HbP screening.[9;14]

As both 'ethnicity' and 'ancestry' are shown to be equally complex terms and ethnicity is supported by the literature as a proxy for ancestral or ethnic origin[15], this term was chosen to be used in the study. Moreover, this term is most common among health professionals.

A focus group study was designed as this method stimulates debate and generates ideas about the topics introduced.

Focus groups were homogenous with regard to health profession in order to generate a sufficient feeling of security among participants. The semi-structured topic guide was based on the literature and the questionnaire results. Topics included experience with HbP carrier testing; attitudes regarding ethnic registration also related to HbP screening and perceived barriers. Prior to the start of the focus group participants received a brief HbP fact sheet by post giving disease background and information on groups at risk and they were asked to complete basic background questions and provide written consent.

The focus group discussions took place at two universities and a midwifery academy; they lasted approximately 90 minutes and were facilitated by one of two moderators, (LvT, health scientist or CvE, sociologist). The primary researcher (SJ, midwife), was only involved in the GP group as note taker to prevent influencing the discussion of her colleagues. Another assistant took notes in the midwives group. Midwives received professional register credits in return for participation. All participants received a €10,- gift voucher but were not informed of this prior to the discussion.

Participant recruitment and data collection

Primary care practitioners were asked to participate by means of a letter included in a postal questionnaire (sent to all primary care midwives and a random GP sample) on ethnicity-based HbP screening. [9] To this letter 29 GPs and 191 midwives responded. We selected a regionally based purposeful sample from the responders, on the assumption that rural health professionals would have less experience with HbP risk groups. Our sample included six focus groups of about six midwives or GPs each, with a total of 37 individuals aged 23-65 years. In the autumn of 2010 four focus groups were held with midwives (n=28) and two with GPs (n=9) after which

saturation was achieved concerning the midwives. Several attempts were made to recruit more GPs but proved unsuccessful. While most midwives were female, the mostly male GPs had more working years experience compared to the midwives. Even so, midwives were more familiar with preconception care and looked after a larger percentage of the population at risk for HbP (table 1). Digital audio recordings of the discussions were collected and anonymously transcribed.

Analysis

The transcripts were checked once to ensure accuracy and to gain familiarity with the data, and were subsequently content analysed (SJ). Transcripts were searched for common themes but also for deviant cases and subsequently indexed as codes. The coding frame was developed by the primary researcher (SJ), in consultation with two other researchers (LH, health scientist and CvE). SJ coded the transcripts and CvE and LH each verified one third of the transcripts as an inter-rater check. The codes were grouped together into key themes. Codes and emerging themes were compared for coding reliability through a process of discussion and deliberation of themes and connections (SJ, LH, CvE). ATLAS.ti software package (version 5.2.0) was used to support the analysis of the transcripts.

RESULTS

General attitudes towards HbP carrier screening were mixed. While practitioners thought it to be good practice and would fulfil a health need, they also questioned cost-effectiveness and necessity because of perceived low prevalence. Data analysis identified four themes related to ethnicity-based carrier screening: Defining ethnicity; Ethical dilemmas and sensitivities; Ethnic awareness and good practice; Practicalities. All are discussed here and illustrated by representative quotations from the discussions translated from Dutch. The participants group and type of health care professional (GP or midwife) are given in brackets.

Table1. **Characteristics** of participants in the focus groups

Characteristics	**Midwives (n=28)**	**General practitioners (n=9)**
Mean age (sd)	35.4 (11.3)	51.4 (11.2)
Female gender, n (%)	27 (96)	2 (22)
Dutch, n (%)	27 (96)	9 (100)
Mean years (sd) of practice experience	10.4 (9.2)	22.0 (11.7)
Estimated percentage of population at risk in practice	27	20
Urban area of practice, n (%)	18 (64)	4 (44)
Gives preconception care, n (%)	14 (50)	4 (44)

Defining ethnicity: Who is at higher risk?

The issue that generated most discussion in all focus groups was the concern of being able to correctly identify those individuals at higher risk for HbP. Participants wondered how ethnicities can be defined, and thus how they could correctly identify those at risk: by appearance; by name; by country of birth?

> *So they might look Hindustani [Surinam people of Indian origin] but there might be some black or something, (…) but how strong… wouldn't you need to test them?*
> *Midwife (group 6)*
>
> *But no, I believe all those Mediterranean people are Caucasian too and that is clearly a different ethnicity. Because I [this GP is of Dutch ancestry] don't have a higher risk of HbP and they do. So yes, the way you define ethnicity puts you immediately in a morass of difficult considerations.*
> *GP (group 2)*

Participants wondered how far back they would have to look into one's ancestry to determine their risk of being a HbP carrier.

> *How strong is HbP in the inheritance? (…) How much white; lets say how much percent of something else do you need to take away the effect? This is what I don't know (…). Percentages will drop the more mixing there is. But it's still only a chance and you have a chance of one in two that it will be passed on to you and that will always remain if your parents have it.*
> *Midwife (group 6)*

Both GPs and midwives also struggled with mixed backgrounds of their patients and clients which made them feel unsure how to handle this in daily practice, and uncertain whom to offer screening:

> *But what do you do with someone who has an Indonesian mother and an Italian father and she is married to a Dutch man, you know, these people can also have carrier (…) The fact that people are so intertwined, so often, well that is, we see a lot of people with mixed backgrounds and what is the limit [cut-off point], with which background?*
> *Midwife (group 3)*

Participants seemed aware that determining ethnic origin with regards to HbP carrier screening entails more than identifying someone's place of birth.

> *I mean, they are from Moroccan descent that's what it's all about of course, the ethnicity on the basis of genetics and not let's say… the ancestors, yes, so the country of birth of their parents counts, but let's say as a person I don't really have someone in front of me with a lot of Moroccan influences, her Dutch influences are much bigger.*
> *Midwife (group 5)*

Ethical dilemmas and sensitivities

Both midwives and GPs had several, sometimes quite strong ethical opinions concerning ethnic registration. Specifically, GPs felt burdened by ethical objections that stem from Dutch experiences during World War II, when ethnic and religious registration facilitated mass deportation of Jewish citizens.

> *But if you think a bit further, at the time of Hitler and the Jewish people et cetera; they carried out all sorts of scary experiments with different ethnic populations, that was on the basis of you know… Jews and Gypsies and I don't know who… And if we would register all of that and it would be registered somewhere that you are Caucasian; Muslim; African or whatever else: Go ahead think about it, in times of, people, well in the craziness of war strange things can happen…*
> *Midwife (group 5)*

One GP said that he would not object to the registration of ethnicity, and that it could potentially be useful, but despite this, he still felt distrust and maintains his recordkeeping to a minimum:

> *I register as little as possible. And well, I wouldn't object [to ethnic registration] if it was possible to do this correctly and in a way that's reproducible. I know we have a huge trauma in the Netherlands caused by World War II when Jewish people were registered with the council and as Dutch citizens we diligently helped the Germans to deport them and we pretend to be the best country in the world. (…)*
> *GP (group 1)*

Participants coupled this with the current political climate (right wing and nationalist) and worried about the misuse of data that could threaten patient confidentiality. GPs especially felt very protective of their patients' privacy and had little confidence in digital record keeping:

> *I have no trust whatsoever in that it [electronic patient record] won't be used for anything but patient purposes. The safety and the trustworthiness of this still have to be verified and demonstrated in my opinion. I believe records can easily be hacked at the moment. Besides, I don't know what governmental authorities will do with this in the long run. At the moment we have a government which says they will only do the right thing but I am sorry the [Nationalist right wing political party] has a very large following and I am not sure what will happen in the future.*
> *GP (group 2)*

The current political climate in which tolerance regarding ethnic and cultural differences is reduced, may also be at the root of midwives' concerns. Participants seemed keen not to be seen as supportive of this and therefore, felt uncomfortable asking the ethnicity question. Some seemed to think that clients might interpret this as a sign of being less welcoming to them compared to a client of Dutch descent and worried that confusion over ethnicity, descent and nationality, might possibly cause tension:

> *Are we just going to ask: 'Hey where are you from? Where are your parents from?' Because really they are just Dutch, but that's what I find difficult; that I'm emphasizing that they are not Dutch originally. Although my impression is that they don't seem to mind themselves. It's more that it makes me feel uncomfortable.*
> *Midwife (group 5)*

In contrast, one midwife said she did not mind at all asking her clients about their ethnicity to determine their risk; she felt the ethnicity question was a positive one which helped her to get to know her clients:

> *People are proud of where they come from, so I mean, that's something; why should it [ethnic registration] be an issue? And what is nice, well that is my opinion anyway, clients who come from elsewhere, they always like to, I mean they enjoy talking about their special things, their culture and traditions. It is always interesting.*
> *Midwife (group 4)*

Midwifery participants voiced other privacy related concerns related to the nature of genetic disorders in relationship with paternity:

> *Well, I think it can be really tricky, it's the same with a rhesus negative status when a woman is convinced that her partner is also rhesus negative and that she doesn't want the anti-D (…) Some things might come out just like with this [HbP testing] he can or cannot be the father.*
> *Midwife (group 6)*

It appears that worries such as above stem from the fact that the midwives have the impression that women or couples may not be able to see the potential impact of accepting screening. Finding an appropriate way of informing women in pregnancy may thus be complicated in more ways.

Ethnic awareness and good practice

Despite the sensitivities voiced by participants, they appeared to be familiar with identifying ethnicity for (other) health purposes and seemed to believe that it is good practice to be aware of different health needs amongst certain ethnic groups. They use their knowledge and earlier experiences to choose the appropriate care for their patients or clients; for example diabetes risk in Suriname people of Indian descent. This awareness also resulted in offering certain patients or clients a test for HbP carrier status:

> *We don't carry out standard [HBP carrier] screening. But we do test people with a low Hb or those who were very anaemic in a previous pregnancy and actually also those people with a Mediterranean background; we test them for sickle cell and thalassaemia when we send them for the usual Hb and MCV tests as our experience tells us that they are very often positive [for HbP carrier status].*
> *Midwife (group 5)*

But again one participant pointed out the fact that in her practice they felt insecure about defining groups at higher risk of a positive HbP carrier status and as a result policy is inconsistent:

> *Part of our practice area is very white and another part has a lot of immigrants; probably 20-25% of our population. We screen Black people for sickle cell but this is quite arbitrary because some people who are mixed [of mixed descent] are sometimes not screened, so our policy is not very consistent.*
> *Midwife (group 5)*

Attention given to ethnic differences in clinical guidelines varies. [16] In this case some participants felt supported by ethnic specific recommendations in their guidelines, underlining the importance of professional and national clinical guidance:

> *I think on the basis of anaemia, of course we currently have a beautiful guideline for this purpose which is really easy to use; you just follow it and arrive at the point where you think it has to be a haemoglobinopathy.*
> *GP (group 1)*

Practicalities in relation to (ethnicity-based) HbP carrier screening

Two practical barriers emerged during the focus group discussions; registration difficulties and financial issues. Despite the presented dilemmas, midwives reported that they have been registering ethnicity in the Netherlands Perinatal Register since the seventies which contains national perinatal data for research purposes and care improvement. Software systems are improving the registration methods:

> *We register by means of our LVR [national perinatal register] but this is only a very general if not limited registration. Mediterranean, other European, the groups are very "broad". We have now started with [new software program for midwives] and with this program you can fill in country of birth, therefore you have the country of birth for everyone.*
> *Midwife (group 3)*

The practical side of implementing ethnic registration appeared to be no problem for the midwifery profession. However this is not the case for GPs because the available GP-software does not provide a simple way of doing this:

> *Yes, there is loads of space [in the software program] but you have to be able to locate it [the information on ethnicity]. Like, it's not a separate field [in the program] for which you can search, which you can select. (…) I think a computer nerd would be able to do it but not GPs in general. It has to be easy otherwise you won't do it.*
> *GP (group 1)*

Although midwifery and GP care is exempt from financial charges to patients or clients in the Dutch health care system, they are sometimes charged for extra (laboratory) services, depending on how insurance companies apply the rules. Those midwives who already tested for HbP carrier status, expressed concern about the financial implications for their clients. Unclear financial regulations are apparently making them feel awkward about offering such tests:

> *That depends whether or not the insurance will pay. (…) And if people, I mean I don't know how much a test like that costs, but if people receive a huge bill which they have to pay themselves…*
> *Midwife (group 4)*

It appeared that midwives easily feel guilty about financially burdening their clients through the care they have proposed. Not being able to give clear explanations about financial implications may also result in complaints from clients.

DISCUSSION

This study took a qualitative thematic approach to provide a deeper understanding of the attitudes and elucidates the perceived barriers of midwives and GPs with regards to ethnicity related HbP carrier screening. Four themes were identified showing that participants use ethnicity in daily practice for a tailored approach towards their patient's or client's health but find it difficult to adequately identify ethnicity whereby uneasy feelings are experienced when broaching the subject. Both participant groups voiced strong concerns over privacy issues of their patients and clients. GPs do not have the possibility to register ethnicity in their software programs. Midwives worried about the financial implications for their clients.

We regret the small number of GP participants in our study. This meant that the intended purposeful sample had to be turned into a convenience sample. Other studies have encountered similar problems in terms of response and indicated that a high workload prevented GPs from participating in research.[9;17] Minimal interest and the GPs popularity as research objects may also have influenced the lack of enthusiasm. One GP in this study mentioned that the subject was low on her priority list considering the magnitude of (social) problems she encountered in her practice. It should further be emphasized that qualitative data are not intended to be generalized.

The discussion on defining ethnicity was one of the most dominant in our study. Information on (perceived) ethnicity can be used to determine risks for certain disorders that occur more often in certain ethnic groups, such as HbP, cystic fibrosis, diabetes mellitus et cetera, but as other researchers have shown, the use of ethnicity is problematic in social and political terms.[14;18] It is interesting to note that none of the participants actually thought of asking patients/clients themselves. Although self-defined ethnicity is favoured by some [19;20] defining ethnicity is still the subject of on-going debate.[15;21;22] A generally accepted way of determining ethnic groups is by country of birth and (grand-) parents' country of birth, but this method misses third and fourth generations.[22] Our study results correlate with the complexity of determining ethnicity as demonstrated by others who have shown that a substantial proportion of ethnic groups give complex answers about their ethnic background (and which do not necessarily fit predetermined categories).[18;21;23]

As opposed to Dyson's results[23] which showed no consistency in how the ethnicity question was interpreted (i.e. meaning place of birth, place of upbringing, family, ancestors or ethnic identity), the participants in this study seemed to have at least some awareness of the importance of ethnic origin with regards to HbP carrier screening. Whether this awareness is also apparent in clinical practice, is unclear. Our study does support Dyson's finding that midwives feel uncomfortable asking the ethnicity question. One way to reduce such feelings may be by offering combined HbP and CF carrier screening, using a tool specifically designed for such purpose.[10]

GPs and midwives in this study are familiar with the use of ethnicity in daily practice for the purpose of tailored health care and are prepared to screen their patients for HbP carrier status in the future. However this also seems to create uncomfortable feelings which require further investigation. Although several instruments are available for determining ethnic HbP risk[10;24], it is not known what women and their partners think about ethnicity-related health care, although Lakeman's study reported no feelings of stigmatisation with the combined screening offer.

Two earlier studies revealed ethnic registration to be a controversial barrier in the past preventing the introduction of a HbP carrier programme, which was rooted in the history of World War II and linked to the current nationalistic political climate. [9;14] This study shows that these issues continue to be important.

Considering the complexity of determining ethnicity, universal screening may be more appropriate. However irrespective of screening method, consideration of ethnicity is still required to adequately inform patients or clients of their risk. A validated tool to support health care professionals to determine risk should therefore be considered. At the same time support by national policy whereby ethical and practical barriers are solved and financial issues clarified before such a program is implemented, is crucial.

It may well be possible that for future generations the necessity to determine ethnicity will become obsolete as ethnic admixture becomes more common in our multicultural societies and complex DNA panels determining a wide range of genetic disorders can be offered in preconception screening.

REFERENCE LIST

1. Dauphin-McKenzie N, Gilles JM, Jacques E, Harrington T. Sickle cell anemia in the female patient. Obstet Gynecol Surv 2006 61(5):343-52.
2. Weatherall DJ, Clegg JB. Inherited haemoglobin disorders: an increasing global health problem. Bull World Health Organ 2001;79(8):704-12.
3. Modell B, Darlison M, Birgens H, Cario H, Faustino P, Giordano PC, et al. Epidemiology of haemoglobin disorders in Europe: an overview. Scand J Clin Lab Invest 2007;67(1):39-69.
4. World Health Organisation. Sickle cell anaemia. 2006. Report No.: The 59th World Health Assembly; 117th session. *Agenda item 4.8; Resolution EB117.R3*.
5. De Jong-Potjer LC, Beentjes M, Bogchelman M, Jaspar AHJ, Van Asselt KM. NHG-Standaard Preconceptiezorg, M97 (Guideline preconceptioncare for GPs). Huisarts Wet 2011;54((6)):310-12.
6. Jans S, Beentjes M. Anaemia in midwifery practice. Guideline. Utrecht; KNOV 2010.

7. van Elderen T, Mutlu D, Karstanje J, Passchier J, Tibben A, Duivenvoorden HJ. Turkish female immigrants' intentions to participate in preconception carrier screening for hemoglobinopathies in the Netherlands: an empirical study. Public Health Genomics 2010;13(7-8):415-23.
8. Weinreich SS, de Lange-de Klerk ES, Rijmen F, Cornel MC, de Kinderen M, Plass AM. Raising awareness of carrier testing for hereditary haemoglobinopathies in high-risk ethnic groups in the Netherlands: a pilot study among the general public and primary care providers. BMC Public Health 2009;9:338.
9. Jans SM, de Jonge A, Henneman L, Cornel MC, Lagro-Janssen AL. Attitudes of general practitioners and midwives towards ethnicity-based haemoglobinopathy-carrier screening. Eur J Hum Genet 2012 May 2;10.
10. Lakeman P, Henneman L, Bezemer PD, Cornel MC, ten Kate LP. Developing and optimizing a decisional instrument using self-reported ancestry for carrier screening in a multi-ethnic society. Genet Med 2006 8(8):502-9.
11. NHS Sickle Cell & Thallassaemia Screening Program. http://sct screening nhs uk/ Last accessed 29 May 2012.
12. Hinton CF, Grant AM, Grosse SD. Ethical implications and practical considerations of ethnically targeted screening for genetic disorders: the case of hemoglobinopathy screening. Ethn Health 2011 Aug;16(4-5):377-88.
13. Dyson S. Ethnicity and Screening for Sickle Cell/Thalassaemia. Edinburgh: Elsevier Churchill Livingstone; 2005.
14. Jans SM, van El CG, Houwaart ES, Westerman MJ, Janssens RJ, Lagro-Janssen AL, et al. A case study of haemoglobinopathy screening in the Netherlands: witnessing the past, lessons for the future. Ethn Health 2011 Aug 8.
15. Aspinall PJ, Dyson SM, Anionwu EN. The feasibility of using ethnicity as a primary tool for antenatal selective screening for sickle cell disorders: pointers from the research evidence. Soc Sci Med 2003 Jan;56(2):285-97.
16. Manna DR, Bruijnzeels MA, Mokkink HG, Berg M. Less ethnic knowledge in the Dutch College of General Practitioner's practice guidelines on type 2 diabetes mellitus, hypertension and asthma in adults than in the supporting literature. Ned Tijdschr Geneeskd 2003 Aug 30;147(35):1691-6.
17. Poppelaars FA, Ader HJ, Cornel MC, Henneman L, Hermens RP, van der Wal G, et al. Attitudes of potential providers towards preconceptional cystic fibrosis carrier screening. J Genet Couns 2004 Feb;13(1):31-44.
18. Royal CD, Jonassaint CR, Jonassaint JC, De Castro LM. Living with sickle cell disease: traversing 'race' and identity. Ethn Health 2011 Aug;16(4-5):389-404.
19. Bhopal R. Glossary of terms relating to ethnicity and race: for reflection and debate. J Epidemiol Community Health 2004 Jun;58(6):441-5.
20. Gomez SL, Kelsey JL, Glaser SL, Lee MM, Sidney S. Inconsistencies between self-reported ethnicity and ethnicity recorded in a health maintenance organization. Ann Epidemiol 2005 Jan;15(1):71-9.
21. Rankin J, Bhopal R. Current census categories are not a good match for identity. BMJ 1999 Jun;19;318(7199):1696.
22. Stronks K, Kulu-Glasgow I, Agyemang C. The utility of 'country of birth' for the classification of ethnic groups in health research: the Dutch experience. Ethn Health 2009 Jun;14(3):255-69.
23. Dyson SM, Cochran F, Culley L, Dyson SE, Kennefick A, Kirkham M, et al. Ethnicity questions and antenatal screening for sickle cell/thalassaemia (EQUANS) in England: Observation and interview study. Critical Public Health 2007;17(1):31-43.
24. Dyson SM, Culley L, Gill C, Hubbard S, Kennefick A, Morris P, et al. Ethnicity questions and antenatal screening for sickle cell/thalassaemia [EQUANS] in England: a randomised controlled trial of two questionnaires. Ethn Health 2006 May;11(2):169-89.

7

General discussion

This thesis has several objectives related to anaemia and haemoglobinopathies (HbP). The first objective is to establish the prevalence of anaemia (low haemoglobin, Hb) in pregnancy, and to investigate whether this was different for pregnant women of non-Northern European descent compared with pregnant women of Northern European descent. Furthermore, the effect of a positive HbP carrier status on the outcome of pregnancy was investigated. HbP is the umbrella name for the group of autosomal recessive disorders that consists of sickle cell disease (SCD) and thalassaemia which are relatively frequent among certain ethnic groups. Subsequently, preconception and antenatal ethnicity-based HbP carrier screening was addressed: First the historical context in the Netherlands of the decision making process surrounding the negative outcome of the discussion whether or not to introduce an HbP screening programme was investigated. Next, a quantitative and a qualitative approach was used to investigate and explore the attitudes of midwives and general practitioners (GPs) towards ethnic registration and their perceived barriers to ethnicity-based preconceptional or antenatal HbP carrier testing.

The previous chapters have described the individual studies in detail. In this final chapter the main findings of the thesis are presented. These findings and methodological issues will be discussed in the context of the existing literature. This chapter ends with implications for clinical practice and recommendations for implementation and further research.

MAIN FINDINGS

Prevalence of anaemia in pregnancy

In a retrospective cohort study (Chapter 2) anaemia was defined according to the reference values of the KNOV anaemia guideline published in 2000.[1] If Hb and MCV are low, iron deficiency anaemia (IDA) is assumed. The overall prevalence of anaemia in pregnancy in the urban population of Amsterdam was 3.4% at booking (first visit; around 12 weeks of gestation at the time of study) and 2.7% at approximately 30 weeks gestation. The relative risk (RR) of anaemia at booking was 5.9 (95% CI 2.1-16.7) for pregnant women of non-Northern European descent, 7.4 (95% CI 2.4-22.8) for Mediterranean women, 4.0 (95% CI 1.2-13.4) for Black women and 'others' 7.2 (95% CI 2.1-24.9) when compared with women of Northern European descent. The RR of anaemia at approximately 30 weeks of gestation was 22 (95% CI 3.0-162.0) for pregnant women of non-Northern European descent, 20.8 (95% CI 2.6-165.2) for Mediterranean women, 13.9 (95% CI 1.7-114.9) for Black women and 55.3 (95% CI 7.2-422.2) for 'others' when compared to women of Northern European descent. The higher risk for anaemia resulted in a higher risk for transferred home delivery (THD) in case of an Hb< 6.0 mmol/l as indicated by local policy, for non-Northern European women: RR 24.1 (95% CI: 3.3-176.7).

Effect of HbP carrier status on outcome of pregnancy

The cohort study was followed by a systematic literature review bringing together the best available evidence on the effect of a positive HbP carrier status on the maternal and neonatal outcome of pregnancy. The systematic review identified nine studies that met the inclusion criteria and that were of sufficient quality for the review. No studies of sufficient quality were found on the effect of a positive thalassaemia carrier status. The heterogeneous non-pooled data showed a protective effect of sickle cell trait (SCT) for premature birth, low Apgar score and perinatal mortality rate. No significant effect was found for low birth weight, growth retardation, urinary tract infection (UTI) or high blood pressure. The risk of anaemia and bacteriuria was increased.

History of HbP screening in the Netherlands

Fourteen multi-disciplinary professionals participated in a so called witness seminar to discuss the past decision-making process regarding the possible introduction of an HbP (carrier) screening programme in the Netherlands. The subject of HbP screening first appeared on the agenda in the 1970s. As opposed to a long history of neglect of African-American health in the United States (US), the heritage of World War II influenced the decision-making process in the Netherlands. This heritage appeared to be multi-layered. Concerns about eugenics cast a shadow over the repro-genetic discussion in general. Complicated aspects of ethnicity and race influenced the discussion and ethnic registration, which was associated with World War II, surfaced as an impeding factor. In the 1990s, HbP (carrier) screening was found to be 'not opportune' due to the low prevalence, lack of knowledge and fear of stigmatization. Discussion of the registration of ethnicity remains on the political agenda, and still proves to be a sensitive subject.[2]

Current HbP (carrier)screening in the Netherlands

A postal questionnaire survey was used to investigate attitudes, intention and behaviour of 795 midwives and 551 GPs towards ethnicity-based HbP carrier screening. The study showed that although 45% of respondents thought that offering a carrier test on the basis of ethnicity alone should become national policy, most of them do not currently offer such a test to their patients and/or clients. The main factor explaining lack of intention towards offering ethnicity-based HbP carrier screening was subjective norm; the perception that their peers do not think they should offer screening. If ethnicity-based HbP carrier screening would become national policy, most professionals report that they would carry this out. Most respondents favoured ethnic registration for health purposes.

A focus group study explored the background of the attitudes of midwives and GPs and of their perceived barriers regarding ethnicity-based HbP carrier screening. Both professionals struggled with correctly identifying ethnicities at risk leading to several complex considerations. Acerbated by the current political climate, ethical concerns regarding privacy originated from World War II when ethnic and religious registration facilitated deportation of Jewish citizens. Some midwives thought

the ethnicity question may undermine the relationship with their clients. Software programs prevent GPs from registering ethnicity of patients at risk. Financial implications of HbP carrier screening for patients are also a concern. Despite this, both professional groups seemed positive about ethnicity based HbP carrier screening and are familiar with identifying ethnicity for individual patient care.

A QUESTION OF ETHNICITY?

The research in this thesis shows that ethnic diversity raises certain questions within the healthcare setting. Clinical health professionals struggle with these questions on a daily basis, especially those who work in areas where this diversity is greatest such as in the urban areas of the Netherlands. The prevalence of certain disorders differs between ethnic groups and therefore, health care professionals and policymakers should take these differences into account in the way health care is delivered to avoid health inequalities. This does not always happen and most professional guidelines lack attention to ethnic differences.[3]

Ethnic differentiation in policy recommendations should be evidence based and lead to appropriate care for all ethnic groups. The first edition of the KNOV anaemia guideline did take differences between ethnic groups into account by introducing separate reference values for pregnant Black women, however when the guideline was evaluated primary care midwives in the Netherlands still commented that the guideline did not meet the needs of all ethnic groups and that anaemia was detected too late.[4] Separate reference values for Black women were based on evidence that Hb levels among Black people are on average lower than among other ethnic groups. However, it is unclear whether these lower levels are physiological or due to underlying pathological conditions which warrant further investigation and treatment instead of separate reference values. Others commented that HbP carrier status should be investigated.[4,5] By carrying out the presented research we have contributed to these issues that were put forward by midwives.

Ethnicity related to anaemia and haemoglobinopathy carrier status

It is evident that the question of ethnicity cannot be ignored when dealing with anaemia in pregnancy and when health professionals want to provide adequate care for all pregnant women and women with a pregnancy wish in an ethnically diverse society.

The assumption voiced by Dutch midwives that pregnant women of non-Northern European descent are at a higher risk of anaemia was confirmed. However, this finding is not easy to interpret. First, ethnicity was defined according to the National Perinatal Register as identified by the midwife: practice based but perhaps with suboptimal validity. Besides these groups, as used in the study, are very heterogeneous. The terms 'Northern European' and 'non-Northern European' are obviously very broad and apply to a large variety of ethnic groups. However, so are the terms used for sub-groups: Mediterranean may mean anything from Italian, Croatian and Turkish to Moroccan whereas "Black" could be anyone with

a background from the wide diversity of the African continent, the former Dutch colonies of Suriname and the Antilles and so on. Besides the obvious geographical and genetic (HbP) differences, combining women in these groups ignores more complex but very relevant issues such as migration, differences between generations, socio-economic factors and culture, which may all influence lifestyle and nutritional factors and therefore also anaemia. Second, although the study confirms a difference in risk for anaemia amongst different ethnic groups, it is unable to elucidate on the factors that lie behind this finding.

From the systematic review which aimed to investigate the effect of HbP carrier status on the outcome of pregnancy, we can conclude that pregnant women who are HbP carriers are at low risk of adverse pregnancy outcomes. On the basis of the available evidence women can be reassured that they can continue to receive care in a low risk setting.

The systematic review also encountered problems with the definition of ethnicity; sometimes absent or not always clearly defined. The lack of definitions was an overall problem in the review. This and the fact that important confounders such as SES were not always reported in the studies and the fact that not all studies used the appropriate diagnostic test for HbP[6], may have influenced the results.

Considerable heterogeneity meant that pooling of the data was not possible. Although the HbP topic yields sufficient results in search engines such as Pubmed, only a few studies evaluated the effect of HbP carrier status on the outcome of pregnancy (see chapter 3). These studies are relatively old and have many methodological problems. It is curious that despite the fact that HbP are some of the world's most prevalent autosomal recessive disorders with a carrier prevalence of up to 40% in some ethnic groups[7], there is an apparent lack of research interest in this specific topic. This fact is also recognized by the WHO which expressed concern over the lack of relevant epidemiological data which may present a challenge to effective and equitable management of sickle cell disease and trait.[8]

The results of this thesis support clinicians such as midwives, obstetricians and GPs in providing tailored health care for pregnant women with different ethnic backgrounds. The European project partners of the Amsterdam declaration towards migrant-friendly hospitals agreed on basic principles in their statement, one of which was identifying the needs of people with diverse backgrounds and monitoring and developing services with regard to these needs.[9] Although the statement is aimed at hospital care, it could easily be transferred to primary care. Paying more attention to those groups at higher risk for anaemia such as women from non-Northern European descent, and the complexities behind this such as the possibility of a positive HbP carrier status supports meeting those needs. This would answer the call of the WHO in 2006 to pay more attention to those a risk for HbP.[8]

Professionals caring for pregnant women with different ethnic backgrounds such as midwives, obstetricians and GPs, should be aware of the possibility of anaemia. If anaemia is present, carrier status should be investigated in at least those women

with a higher risk ethnic background before any treatment is started, since iron treatment may be harmful in carriers. Asymptomatic bacteriuria and the subsequent risk of pyelonephritis may occur more frequently in pregnant HbP carriers; therefore health professionals involved should investigate pregnant women who are known HbP carriers more frequently for these conditions.

Carrier screening and reproductive choice

No medical service exists in isolation. The related effects of a positive HbP carrier status on the outcome of pregnancy and diagnostic clarity when looking at anaemia in pregnancy, testing for HbP carrier status also raises discussion about reproductive choice. Couples who are both an HbP carrier have a 25% chance of giving birth to an affected child with each pregnancy. Some have argued that HbP carrier screening should be part of the midwives' anaemia guideline.[5] However the answer to the question whether or not HbP carrier screening for the purpose of reproductive choice should be offered during the preconception period or in early pregnancy, does not belong in a guideline on anaemia. Moreover, the expanded Neonatal Screening (NNS) which was implemented in 2007 and included a test for SCD raised the same question: As a result of the unintended finding of HbP carriers in the programme, the old discussion whether or not a broad HbP carrier screening programme should be introduced, was renewed.[10] In order to adequately re-address the issue of HbP carrier screening, we need to know about the barriers and sensitivities experienced in the past, which was why the case history of HbP screening policy in the Netherlands was explored.

The case history demonstrates the influence of the heritage of past events on general health care policy such as screening, and more specifically on HbP screening policy, even to this date. The results were generated through a unique research method which allowed for an in-depth analysis and an exploration of hidden and sensitive elements in the past discussion. The results of the seminar are partly dependent on the choice and availability of the witnesses and their recollections which may be hampered by the passing of time. However, by using the group dynamics, participants were invited to respond and add to each other's account, thereby helping to reconstruct past events from different perspectives. We have therefore been able to address an important issue that has long been neglected. Interestingly, the analysis follows on from an earlier witness seminar that was held in the Netherlands[11], which reports on the unholy alliance of political parties and the government against prenatal screening in the eighties out of fear for eugenics. The HbP witness seminar takes this one step further: Not only was reproductive screening politically unacceptable, but the registration of ethnicity was as well and for similar reasons. As opposed to a long history of neglect of African-American health in the US, the heritage of World War II influenced the decision-making process in the Netherlands causing a barrier for the introduction of HbP carrier screening.

Strikingly, during the discussion in the nineties, no role existed for any patient representatives. The anthropological study that was part of the 1994 report on the

possibility of introducing an HbP carrier screening programme, showed very little knowledge amongst groups at higher HbP risk. Those familiar with HbP disorders, expressed a willingness to accept prenatal screening and were open to the possible consequences of such screening.[12] Since then a few studies have been carried out amongst the groups at higher risk in the Netherlands.[13-15] In order to resolve existing challenges, future decision-making on an extended screening programme needs to include representatives from groups most at risk of HbP to support a programme that adequately supports the needs of societal groups and to ensure adequate implementation of such a programme, as is advocated by the International Alliance of Patient Organizations, IAPO, in all aspects of health care.[16]

Long before the introduction of the English sickle cell and thalassaemia screening programme (http://sct.screening.nhs.uk. Last accessed 30 April 2012) researchers commented on the fact that long term neglect of adequate screening and care of HbP conditions by the British health services were pointed to by users as reflecting racist marginalization.[17,18] Since then a comprehensive programme has been introduced in England. Although it does meet with difficulties, the programme has been successfully implemented and evaluated.[19-23] Although the Netherlands has introduced NNS for SCD, societal discussion about HbP carrier screening is practically absent outside the call of a committed few[10,24]; the discussion does not seem to have moved forward from the one held in the nineties as described in the witness seminar.

Definition of ethnicity

Difficulty in defining ethnicity appears as a central thread throughout this thesis and has been shown to also have methodological implications. With such obvious differences in prevalence in both anaemia and HbP, it is important that ethnicity is adequately defined to prevent underreporting. Besides, a recently published guideline on hypertension by the Dutch midwives organization points out that being of African (sub-Sahara) descent is a risk factor for hypertension in pregnancy, making ethnicity in itself a confounder for one of the outcomes in the systematic review[25-27]; again pointing out that an adequate ethnic definition is important.

Although the questionnaire study showed that midwives have a positive attitude towards ethnic registration, the results of the focus group study showed that both midwives and GPs find defining ethnicity problematic and complex. Mixed backgrounds of their patients and clients made them uncertain about whom to offer screening. These results correlate with the complexity of determining ethnicity which is often misleading as demonstrated by others.[28-31] These arguments would therefore support a universal screening offer.

It is unclear how health professionals currently determine ethnicity. As Hinton et al. point out, assessing ethnicity is usually done by health professionals using their own judgment which is prone to errors.[32] The practical problem of GPs who are unable to register ethnicity in their software system, may be easily solved. However the fact that they displayed clear ethical concerns of doing so needs further attention if

ethnicity based HbP carrier screening is introduced in the future. The fact that SCD is characterized as a "Black disease" as has been (and still is) the case in the US and the UK[17,33-35] may further complicate ethical issues as it sets aside certain groups in society, especially in the current politically hostile climate. Although there is no available empirical evidence of racism within the Dutch health system, the uneasy feelings as displayed in the focus group study clearly supports concerns about this issue as has also been pointed out by others who call for greater awareness of such issues.[36]

Government, law and lack of national policy

The fact that midwives (and GPs to a lesser extent) seemed less confident in their capabilities of carrying out a test for HbP carrier screening, may have something to do with a lack of knowledge among health care professionals which has been demonstrated by other studies directly related to HbP and CF (carrier) screening[37,38] or related to genetic knowledge in general.[39] However this may also be related to the incorrect belief that they are legally restricted to offer preconceptional carrier screening because of the Dutch Population Act[40] or to the fact that laboratory (result) forms are sometimes complicated to interpret (see Appendix 4-A). Easily accessible schooling for health professionals may support them to feel more secure about informing clients and patients about HbP carrier testing. But standardised laboratory forms which include advice on correct follow up when results are positive as is used in prenatal screening, or as used by one of the Amsterdam laboratories (Appendix 4-B) would further support health professionals (http://www.rivm.nl/Onderwerpen/Onderwerpen/B/Bloedonderzoek_zwangeren/Voor_professionals. Last accessed 30 April 2012).

Although the results of the questionnaire study show that lack of intention was mostly influenced by negative peer behaviour (social norm), a reluctance to initiate screening is probably largely related to the absence of appropriate policy direction. Normally screening programmes are initiated by government and public health authorities and not individual health professionals. On a European level this is also the advice of the Public and Professional Policy Committee (PPPC).[41] This would suggest that without guidance by national policy, implementation may not be initiated by health professionals. However preconception carrier screening is not legally bound by the Population Screenings Act of the Netherlands (Wet op Bevolkingsonderzoek, WBO) and therefore does not need a governmental license.[42] This, and current political health policy which keeps governmental interference with preventive policy and reproductive choice to a minimum, complicates matters as for this reason the government may refrain from taking action. In the case of *antenatal* carrier screening the discussion may be different: Carrier screening during pregnancy, although also aiming to give parents reproductive choice, options are more restricted and could lead to prenatal diagnosis to identify a foetus with severe HbP, and thus could in principle result in termination of the pregnancy. An HbP carrier screening programme would still be regulated under the WBO but the question as to whether a license is required when screening would be offered in the

early antenatal period remains open to discussion. Unfortunately information on this subject does not give a definitive answer[43,44] and will therefore need guidance from the Department of Health.

Clearly before a genetic screening programme is introduced, it should be evaluated against the background of certain (internationally agreed) criteria.[41,45,46] The potential benefits and harm should be carefully considered before such a programme is implemented. These benefits include pre-symptomatic detection of genetic disorders and prevention of further harm by determining the predisposition of a person that may produce a hereditary disease in offspring[47] and thus providing reproductive choice, which is the case with HbP carrier screening. The potential harm may include anxiety, stigmatisation and discrimination.[45]

The results from the focus group study underlined the necessity to solve ethical and practical barriers and clarify financial issues before an HbP carrier screening programme is implemented. Others have also highlighted the lack of financial resources, a high workload and the absence of a preconception care setting as barriers in the implementation for preconception CF carrier screening.[48] There is no reason why it should be assumed that HbP carrier screening differs in this respect. Others have discussed the possibility of medicalisation: there may be no doubt that when preconception or antenatal carrier screening is introduced about a certain degree of medicalisation will occur, but this is not necessarily a moral problem. The facilitation of adequate informed decision making together with good quality provision of care of those affected by the specific disorder, in this case HbP, will address the main concerns.[49]

Some of these issues can be dealt with by the representative organizations of health professionals but legal, ethical and financial barriers will need academic guidance and negotiation with relevant insurance bodies. The Dutch HbP patient organization OSCAR, indicated in a small unpublished study that their members encounter difficulties requesting a carrier test at their own initiative. OSCAR would prefer government involvement in terms of carrier screening as the organization has little confidence that screening will become more available when patients and clients have to rely on the goodwill of health professionals alone and therefore support the introduction of a programme similar to the one in England.[49-51]

Government leadership would be preferred in order to initiate the appropriate changes, and may be needed in terms of clarifying legal matters. It could be the responsibility of the representative professional organizations of midwives and GPs (and possibly the obstetricians), to find appropriate strategies in dealing with ethnic diversity of their client and patient populations. This is supported by Achterberg's study in which it was argued that effective implementation of screening for HbP will require changes at both regime (suppliers and users) and landscape level (institutions, material social, political and legal infrastructure), but that such change is difficult to achieve without an active orchestrating role of the government.[52]

Ethnicity tailored health care

The focus group study showed that health professionals use ethnicity to deliver appropriate equitable health care for all groups within society. Despite the fact that Manna et al. dispute adequate ethnic related knowledge in guidelines, increasingly guidelines seem to incorporate ethnicity related health care.[3,26,53,54] However, how to operationalise this concept is a question that is less easy to answer. The second part of this thesis shows that health professionals are willing to offer ethnically sensitive care but struggle with the concept in daily practice. A screening instrument based on ancestry has been shown to be effective.[55,56] According to Karlson et al. 'ethnic' classifications draw on phenotypic characteristics in many surveys, in this case a screening instrument, which have genetic underpinnings or geographic and / or environmental ancestry which has been shown to influence genetic profile.[57] Ancestry seems to be less of a social construct than ethnicity. But as we have seen in the introduction of this thesis, some scientists belief that ancestry also has its limits because of a lack of understanding by the users.[58] However the authors argue that even in the apparently clear case of a monogenic disorder such as sickle cell disease or thalassaemia, where genetic factors can offer insight into ethnic variations of these disorders, there is a complex interplay between genetic, environmental and socio-economic characteristics to be taken into account before the extent of genetic influences can be definitively established.[57] For instance the life-span of a person with sickle cell disease or the potential influence of a positive carrier status on the outcome of pregnancy is influenced by more than just the genetic component which means that ethnic origin may be more appropriate for tailoring (midwifery or obstetric) health care.

Both the available screening instruments as developed by Lakeman and Dyson, use the term *family origin*[55,56] but the self-assessment screening instrument by Lakeman et al. offers a combined offer of CF and HbP carrier screening in order to reduce feelings of discomfort when asking the ethnicity question, which was an emerging theme in our study and which was also found by others.[28] If the implementation of a targeted screening programme is agreed upon, this would be the instrument of choice.

Introduction of an HbP carrier screening programme in the Netherlands

In England as opposed to the Netherlands which only introduced sickle cell screening as part of NNS, a successful combined screening programme was introduced in 2004 (http://sct.screening.nhs.uk. Last accessed 25 April 2012). England conducts ethnicity based or targeted antenatal HbP carrier screening in low prevalence areas and universal screening in high prevalence areas. NNS for SCD and thalassaemia is conducted on the basis of universal screening as in the Netherlands.

The programme in England is still hampered by some implementation problems two of which are late screening offers when first appointments do not occur until 18-19 weeks of pregnancy[21,22] and only half of the fathers of those pregnant women who

are found to be a carrier, are tested.[19] Besides, preconception screening is not really an issue (yet) in England. In general women in the Netherlands are seen between week 10 and 12 of pregnancy for a first visit with their midwife and sometimes even earlier, although it is known that some women from certain ethnic backgrounds have a tendency to come late into antenatal care.[59,60] Preconception care has been initiated by all health professionals involved[61-63], although the necessary financial support by health authorities was halted last year delaying adequate implementation.[42] The Netherlands is in a good position to implement a similar broad programme because of early pregnancy bookings and interest of health care professionals in preconception care. Previous research projects have shown that groups at higher risk of a positive HbP carrier status are interested in the offer of screening[14,15,64] and that screening can work.[65,66] Experience in England shows that about 30% of identified carrier couples during antenatal screening opt for prenatal diagnosis.[19]

Targeted or universal screening?

Whether to offer HbP carrier screening on a targeted or universal basis, is a discussion initiated by the balance between genetic distribution and the use of public funds to implement such a programme.[32] The fact that targeted screening on the basis of ethnicity is problematic, both from an ethical and practical point of view as this thesis and research by others have shown[32], would favour universal preconception and antenatal screening. A combined offer of HbP and CF carrier screening such as suggested by Lakeman et al. may also circumvent issues of stigmatisation.[56] OSCAR, the Dutch patient organisation for HbP, has expressed the view that the accent should not be placed upon certain ethnic groups and has indicated that there is a considerable group of carriers amongst their members of so called "autochtony descent" (Dutch term for a person whose parents were both born in the Netherlands).[50] SCD has been wrongly addressed as a "Black disease" and care for these patients has been and very often still is shadowed by mistrust and health care discrimination.[17,35]

The ethnic structure of the Dutch population is not static as history has shown.[67] This influences the prevalence of HbP and HbP carrier status. Besides, the association with minority ethnic groups will dilute over time as the number of inter ethnic relations grows and ethnic admixture becomes more common. This will make ethnicity less suitable for stratification of the risk of HbP carrier status. How this will influence other health issues is unsure but this would certainly be an interesting question in the future although midwives and GPs have indicated in the focus groups discussions that they already find this concept difficult to deal with. HbP should therefore be repositioned in our thinking as a health issue and not as an ethnic issue.[68] Associating (carrier status of) HbP with particular ethnic groups may undermine the success of a possible screening programme.

Considering all these factors, a universal offer of preconception and / or antenatal HbP carrier screening would therefore be the most equitable option. Extensive literature on cost effectiveness of antenatal HbP carrier screening does

not exist. However some argue that the potential of preconception counselling to prevent significant lifetime costs for affected children, may ultimately result in a favourable cost-savings balance. Recent research has indicated that health-sector costs are about 180.000 euro's per 10.000 pregnancies.[70] However this is based on the English health service model whereby most women receive hospital based antenatal care. The study was carried out in a high prevalence area and a cost-effectiveness study may yield different results in a low prevalence area. Because of the involvement of public funding, it was decided that ethnicity based neonatal screening was unacceptable.[32] Although preconception or antenatal screening does not have the same rational of preventing death or severe morbidity, the notions of equality and equity can still be applied for a preconception or antenatal offer of screening. Although funding for an HbP screening programme in the Netherlands would probably not be paid from public funds but rather through the insurance system, similar arguments may still apply. That aside, costs should not be the most important motive when deciding to implement a carrier screening programme.

In order to support women and their partners to make an informed reproductive choice, they need to be adequately informed about their risk which is different amongst ethnic groups. This and the fact that HbP comprises a broad group of haemoglobins of which new ones are still being identified[71,72] means that the ethnicity question may still have to be asked in order to facilitate correct diagnosis, especially when specific mutations need to be confirmed. As the field of genetics is developing rapidly, complex DNA panels determining a wide range of genetic disorders including (carrier status of) HbP, may be offered to women and couples in the future eliminating the need to specify ethnicity. Indeed some have argued screening should be expanded to include autosomal recessive disorders such as HbP, CF and the Jewish panel which for example includes Tay Sachs disease.[73]

In the mean time health professionals should be adequately supported with an evidence based screening instrument[55,56] and guidance both from government and their professional organizations in order to solve ethical and practical barriers.

Based on this thesis a universal offer of preconception and antenatal carrier screening linked to NNS is proposed. If this is not feasible, i.e. for economic reasons, targeted screening such as is implemented in the programme in England, could be introduced but only if supported by an evidence based instrument to determine ethnic origin.

If we want to strive to provide adequate and accessible healthcare services for all, we need to find the right balance between providing equitable health care for all but without setting certain groups aside. If the discovery of ethnic health variations does more harm than good, we may need to retrace our steps.[74] It is important that health professionals such as midwives and GPs are aware of these issues and that discussions on equity, equality and access are part of (continuing) education programmes to enable them to provide women with the care they need.

IMPLICATIONS FOR PRACTICE

The implementation of appropriate anaemia care in pregnancy should be sought through the representative organisations of the health professionals involved such as the KNOV and NHG. Publication of some of the results of this thesis was timely which meant that the studies were included in the literature which informed the current and updated KNOV guideline on anaemia in pregnancy (Appendix 1).[75] Since the publication of the updated KNOV anaemia guideline, the NHG has updated its guideline on care during pregnancy and postnatal period.[76] This NHG guideline was written in collaboration with the KNOV which meant that the KNOV anaemia guideline was fully incorporated into the NHG guideline. Both guidelines now tailor more to the needs of an ethnically diverse population of pregnant women. Further implementation has been encouraged by the formulation of local multidisciplinary guidelines based on the updated national guidelines.

Being of non-Northern European descent has been added as a risk factor for anaemia in pregnancy. Pregnant women who are at higher risk of being an HbP carrier should have timely investigations into the cause of anaemia preferably during the first trimester of pregnancy so that anaemia can be appropriately managed, over-subscription of iron therapy will be prevented and pregnant women can use the knowledge of their carrier status to make appropriate reproductive choices.

The integration of preconception care into the basic offer of health care for women and couples in their fertile period of life, should not be delayed any further and should be properly implemented and supported by the Ministry of Health (VWS), insurance companies and the Health Care Insurance Board (CVZ). Preconception care should be part of the basic insurance package for it to be accessible to all groups in society, especially to those groups who may need it most. Health professionals involved have already taken the necessary measures supported by their professional organizations and public information is available (http://www.strakszwangerworden.nl and http://www.zwangerwijzer.nl. Both last accessed 08-05-2012).

Following this, the introduction of HbP carrier screening should be considered possibly combined with other disorders such as CF and Tay Sachs disease as suggested by other researchers and the Dutch Health Council.[49,77-79] Neonatal screening for SCD, has already been introduced in the Netherlands[80], and the programme also identifies thalassaemia patients. This primarily benefits newborns with the disorder. Carrier status of the child is found as an unintended side-effect meaning that at least one of the parents is also an HbP carrier. Although parents have a possibility to opt-out on receiving this information about their child, most of them will be caught by surprise by this finding and few of them are adequately counseled by their GP.[81] The knowledge for the child itself will not become relevant until he or she is an adult, besides, carrier testing in minors has many ethical considerations.[82]

As the English programme has shown, it is also possible to use the same simple and cheap test to offer women an antenatal HbP carrier test. Offering the test during the preconception period would be preferable because it would give women the

most reproductive choices.[14,50] This would be consistent with the advice of the Health Council.[78] Adequate support by the Department of Health and health insurers would ensure that this type of care is available for all, especially those who need it most.

For a variety of reasons preconception care reaches only very few women and couples at present[48,83] and therefore an antenatal offer for HbP carrier screening should also be considered as almost all women attend antenatal services.

So far, sufficient research data have been collected to consider a combined preconception, antenatal and neonatal HbP (carrier) screening programme. This should not be done without thorough consultation of appropriate patient organizations and the target populations such as couples with a pregnancy wish.

RECOMMENDATIONS FOR FURTHER RESEARCH

During the period of the studies on which this thesis is based, more questions related to the subject of screening for anaemia and HbP before and during pregnancy surfaced. Based on the results and discussion of this thesis, the following suggestions for further research have been formulated:

Patho-physiology of anaemia and HbP carrier status

The diversity of factors involved in the aetiology of a higher risk of anaemia in women of non-Northern European descent, should be thoroughly investigated by a larger prospective cohort study allowing for adequate consideration of possible confounders such as SES and HbP carrier status.

Such a cohort study could also find more evidence on the effect of a positive HbP carrier status on the outcome of pregnancy as highlighted by chapter 3. As ethnic diversity grows in our society the need for more knowledge on this subject increases as well. Following the advice of the WHO, routine investigations into HbP should become more standard in many countries making it easier to conduct a large well controlled prospective study to investigate any possible effect a positive HbP carrier status may have on pregnancy.

The results of such a study could be incorporated into a study on how best to treat IDA in pregnancy, especially since very little evidence is available about the most optimal dosage of iron treatment for IDA in pregnancy. Iron metabolism in pregnancy is different when compared to non-pregnant women and iron absorption increases, in fact haemodilution is an essential and physiological component of pregnancy.[84] It is unknown whether when IDA is treated, the outcome of pregnancy will improve. A randomised controlled trial would be able to answer this question.

Ethnicity in daily practice

The research in this thesis showed that midwives and GPs are familiar with the use of ethnicity in daily practice for the purpose of tailored health care and are prepared to screen patients for HbP carrier status in the future. However this also seemed to create uncomfortable feelings. It is important to investigate how to deal with these

feelings and how to operationalize ethnicity in such a way that neither health care professionals nor patients and clients are left feeling uncomfortable, stigmatised or discriminated against, as ethnic background becomes more important in the delivery of tailored and equitable care to all pregnant women.

The assumption is that most midwives and GPs interpret the ethnicity of their clients and patients either by looking at their appearance or based on their country of origin. By only determining country of birth (and that of parents) third, fourth etc. generations will be missed. Besides, country of birth fails to address cultural and other issues that may be of importance depending on the condition. Moreover, the research in this thesis has shown that primary health care professionals find defining ethnicity and determining risk difficult, especially when mixed backgrounds are apparent. Dysons' research has shown that even when asking "the ethnicity question", the distinction becomes confused with other factors such as nationality or citizenship.[28] Misplaced ideas about ethnicity may therefore ultimately influence quality of care, reproductive choice, especially in the case of screening for disorders which have a different prevalence amongst ethnic groups, such as HbP, CF and Tay Sachs. According to Stronks et al, in the Dutch context, country of birth complemented with additional indicators may be a more useful indicator for ethnicity.[85,86]

Several instruments are available for determining ethnic HbP risk.[55,56] Lakeman et al. studied the combined offer of targeted CF and HbP carrier screening during the preconception period and looked at the psychological effect of such a screening offer. However it is not known what women and their partners think about ethnicity related health care. Moreover the idea of ethnic targeting of carrier screening might reflect undesirable stereotyping of disease with specific ethnic groups as demonstrated in the literature from the US and England. The experience of health professionals with these types of instruments has not been investigated in the Netherlands. Both a qualitative and a quantitative approach would provide more information on this subject.

Screening for carrier status

Although considerable research has been produced in the Netherlands on the possibilities of HbP carrier screening, much of it has been on preconception care. Considering the limited access to preconception care at present, it may be more feasible to screen in pregnancy. Opportunities for reproductive choice are essentially different before pregnancy when compared to during pregnancy: they are more limited in pregnancy and may have more serious consequences such as decision whether or not to maintain the pregnancy if the baby is affected. Only two small pilot studies have been carried out in pregnancy.[65,87] The voice and opinion of the target population, pregnant women and their partners, is absent in this. It is unknown what pregnant women would think of such an offer and what they would do with the knowledge of their carrier status. Moreover the role of fathers is under exposed in Dutch HbP related research. The English programme has shown that only half of those who are eligible are screened.[19] It would be of interest to know

what the background is to this and if this would be applicable to the Dutch situation. This needs to be investigated.

Equal access

As we have seen, there are many reports from researchers and authors from different countries across the world that highlight the ethnic controversies of social disadvantage attached to the services available for those who are either patients or carriers of HbP but very little is known about the situation in the Netherlands. A recent study in the Netherlands concluded that the results imply that reduced health related quality of life in children with SCD is mainly related to the low SES of this population.[88] Another study on prenatal screening (unrelated to HbP) found ethnic differences in knowledge about prenatal screening could mainly be attributed to differences in levels of educational attainment.[89] These are serious issues that affect equal access to health care. How this affects HbP carriers (and other ethnicity related autosomal recessive disorders such as CF and Tay Sachs) is unknown Further studies into experiences of those who are a carrier are needed. If equitable access to appropriate health care may be further compromised when people who are possible HbP carriers or those with HbP disorders are disproportionately from lower socio-economic groups, policy needs to be developed based on good evidence to ensure that the target groups are reached. This can be done by investigating the needs of those groups, thereby giving groups at higher risk of a positive HbP carrier status more say in the health care they need. The discomfort of establishing ethnicity should not stand in the way of establishing equal access to health and health care for all groups in our society but should rather strive to support this.

REFERENCE LIST

1. Amelink-Verburg M, Daemers DOA, Rijnders MEB. KNOV standaard Anemie in de eerstelijns verloskundige praktijk (Guideline: Anaemia in primary care midwifery pratcice). Bilthoven/Leiden: KNOV en TNO-PG; 2000.
2. Raad voor Maatschappelijke Ontwikkeling (RMO). Tussen afkomst en toekomst. Etnische categorisering door de overheid. (Between ancestry and future. Ethnic categorisation by Government). Den Haag; 2012. Report No.: NUR 740.
3. Manna DR, Bruijnzeels MA, Mokkink HG, Berg M. Less ethnic knowledge in the Dutch College of General Practitioner's practice guidelines on type 2 diabetes mellitus, hypertension and asthma in adults than in the supporting literature. Ned Tijdschr Geneeskd 2003 Aug 30;147(35):1691-6.
4. Offerhaus P, Fleuren M, Wensing M. De impact van de eerste KNOV-standaard voor eerstelijns verloskundigen (The impact of the first KNOV guideline for primary care midwives). Nijmegen / Leiden: Centre for Quality of Care Research (WOK) / TNO.; 2003.
5. Elion-Gerritzen WE, Giordano PC, Haak HL. The 'Anemia in the midwife practice' standard issued by the Royal Dutch Organisation of Midwives: a risk of not recognizing iron deficiency and hemoglobinopathy. Ned Tijdschr Geneeskd 2002 Mar 9;146(10):457-9.
6. The laboratory diagnosis of haemoglobinopathies. Br J Haematol 1998 Jun;101(4):783-92.
7. Modell B, Darlinson M. Global epidemiology of haemoglobine disorders and derived service indicators. Bull World Health Organ 2008;(86):480-7.

8. World Health Organisation. Sickle cell anaemia. 2006. Report No.: The 59th World Health Assembly; 117th session. Agenda item 4.8; Resolution EB117.R3.
9. The MFH Project Group, DG Health and Consumer Protection. The Amsterdam Declaration Towards Migrant-Friendly Hospitals in an ethno-culturally diverse Europe. 2005.
10. Cornel MC, Detmar S, Plass AMC, Moerman D, Waarlo AJ, de Kinderen M, GiordanoPC. Breder screenen op hemoglobinopatie (A broader screening for haemoglobinoptahy). Medisch Contact 2009;Nr. 45(03 november 2009):1874-7.
11. Witness seminar Debatteren over genetische screening (Debating genetic screening). Houten: Prelum uitgevers BV; 2010.
12. Rengelink-van der Lee JH, van der Most van Spijk MW, Schulpen T. Landelijk onderzoek sikkelcelanemie en thalassemie. Eindrapport (National investigation into sickle cell anaemia and thalassaemia. Final report). Utrecht: onder auspiciën van de Stichting Gezondheid Derde Wereld Kind; 1994.
13. Lakeman P, Plass AM, Henneman L, Bezemer PD, Cornel MC, ten Kate LP. Three-month follow-up of Western and non-Western participants in a study on preconceptional ancestry-based carrier couple screening for cystic fibrosis and hemoglobinopathies in the Netherlands. Genet Med 2008 Nov;10(11):820-30.
14. van der Pal S, van Kesteren N, van Dommelen P, Detmar S. Deelnamebereidheid dragerschapscreening op hemoglobinopathieën onder hoogrisicogroepen (Willingness to participate in HbP carrier screening amongst high risk groups). Leiden: TNO Kwaliteit van Leven; 2009. Report No.: KvL/P&Z 2009.049.
15. van Elderen T, Mutlu D, Karstanje J, Passchier J, Tibben A, Duivenvoorden HJ. Turkish female immigrants' intentions to participate in preconception carrier screening for hemoglobinopathies in the Netherlands: an empirical study. Public Health Genomics 2010;13(7-8):415-23.
16. International Alliance of Patients' Organizations (IAOP). Patient Involvement. Policy Statement. London; 2005. Available from www.patientsorganisaztions.org. Last accessed 11 May 2012.
17. Anionwu EN, Atkin K. The politics of sickle cell and thalassaemia. Buckingham. Open University Press; 2001.
18. Atkin K, Ahmad WI, Anionwu EN. Screening and counselling for sickle cell disorders and thalassaemia: the experience of parents and health professionals. Soc Sci Med 1998 Dec;47(11):1639-51.
19. NHS Sickle Cell and Thalassaemia: Annual Report 2010-11. London: NHS Sickle Cell and Thalassaemia Screening Programme; 2011. Available from www.sct.screening.nhs.uk. Last accessed 11 May 2012)
20. Brown K, Dormandy E, Reid E, Gulliford M, Marteau T. Impact on informed choice of offering antenatal sickle cell and thalassaemia screening in primary care: a randomized trial. J Med Screen 2011 Jun;18(2):65-75.
21. Dormandy E, Gulliford MC, Reid EP, Brown K, Marteau TM. Delay between pregnancy confirmation and sickle cell and [corrected] thalassaemia screening: a population-based cohort study. Br J Gen Pract 2008 Mar;58(548):154-9.
22. Tsianakas V, Calnan M, Atkin K, Dormandy E, Marteau TM. Offering antenatal sickle cell and thalassaemia screening to pregnant women in primary care: a qualitative study of GPs' experiences. Br J Gen Pract 2010 Nov;60(580):822-8.
23. Tsianakas V, Atkin K, Calnan MW, Dormandy E, Marteau TM. Offering antenatal sickle cell and thalassaemia screening to pregnant women in primary care: a qualitative study of women's experiences and expectations of participation. Health Expect 2011 Mar 3;10-7625.
24. Talan D, van Elderen T, Hoogeboom J. Ongelijk verdeeld (Unequal division). Medisch Contact 2004 Nov 12;59(46):1828-9.

25. Caughey AB, Stotland NE, Washington AE, Escobar GJ. Maternal ethnicity, paternal ethnicity, and parental ethnic discordance: predictors of preeclampsia. Obstet Gynecol 2005 Jul;106(1):156-61.
26. de Boer J, Zeeman K, Verhoeven C. KNOV standaard: Hypertensieve aandoeningen tijdens de zwangerschap, bevalling en kraamperiode. Aanbevelingen voor risicoselectie, diagnostiek en beleid. (Guideline: Hypertensive disorders in pregnancy, labour and puerperium). Utrecht: KNOV; 2011.
27. Knuist M, Bonsel GJ, Zondervan HA, Treffers PE. Risk factors for preeclampsia in nulliparous women in distinct ethnic groups: a prospective cohort study. Obstet Gynecol 1998 Aug;92(2):174-8.
28. Dyson SM, Cochran F, Culley L, Dyson SE, Kennefick A, Kirkham M, et al. Ethnicity questions and antenatal screening for sickle cell/thalassaemia (EQUANS) in England: Observation and interview study. Critical Public Health 2007;17(1):31-43.
29. McAuley J, De SL, Sharma V, Robinson I, Main CJ, Frank AO. Describing race, ethnicity, and culture in medical research. Self defined ethnicity is unhelpful. BMJ 1996 Aug 17;313(7054):425-6.
30. Rankin J, Bhopal R. Current census categories are not a good match for identity. BMJ 1999 Jun 19;318(7199):1696.
31. Royal CD, Jonassaint CR, Jonassaint JC, De Castro LM. Living with sickle cell disease: traversing 'race' and identity. Ethn Health 2011 Aug;16(4-5):389-404.
32. Hinton CF, Grant AM, Grosse SD. Ethical implications and practical considerations of ethnically targeted screening for genetic disorders: the case of hemoglobinopathy screening. Ethn Health 2011 Aug;16(4-5):377-88.
33. Moxley Rouse C. Uncertain Suffering. Racial health care disparities and sickle cell disease. Berkeley: University of Calefornia Press; 2009.
34. Tapper M. In the blood. Philadelphia: University Of Pennsylvania press; 1999.
35. Wailoo K, Pemberton S. A perilous lottery for the black family. Sickle cell, social justice, and the therapeutic gamble. In: Wailoo K, Pemberton S. The troubled dream of genetic medicine. Baltimore: The John Hopkins University Press; 2006. p. 116-60.
36. Agyemang C, Seeleman C, Suurmond J, Stronks K. Racism in health and health care in Europe: where does the Netherlands stand? Eur J Public Health 2007 Jun;17(3):240-1.
37. Morgan MA, Driscoll DA, Mennuti MT, Schulkin J. Practice patterns of obstetrician-gynecologists regarding preconception and prenatal screening for cystic fibrosis. Genet Med 2004 Sep;6(5):450-5.
38. Vansenne F, de Borgie CA, Legdeur M, Spauwen MO, Peters M. Providing Genetic Risk Information to Parents of Newborns with Sickle Cell Trait: Role of the General Practitioner in Neonatal Screening. Genet Test Mol Biomarkers 2011 May 16.
39. Baars MJ, Henneman L, ten Kate LP. Deficiency of knowledge of genetics and genetic tests among general practitioners, gynecologists, and pediatricians: a global problem. Genet Med 2005 Nov;7(9):605-10.
40. van Hellemondt RE, Hendriks AC, Breuning MH. regulating the use of genetic tests: Is Dutch law an example for other countries with regard to DTC genetic testing? Amsterdam law forum 2011. Available from: http://ojs.ubvu.vu.nl/alf/article/view/194/368. Last accessed 4 May 2012.
41. EUROGAPPP PROJECT 1999 - 2000 Public and Professional Policy Committee (PPPC) Population genetic screening programmes: Proposed recommendations of the European Society of Human Genetics. Eur J Hum Genet 2000 Dec;8(12):998-1000.
42. Schippers EI. Zwangerschap en geboorte (Pregnancy and Birth). Ministry of Health Wellfare and Sports. [CZ/EKZ 3040205]. 2010.
43. Klink A. Beschikking van de Minister van VWS, PG/OGZ 3.000.241, houdende vergunningverlening op grond van de wet op het bevolkingsonderzoek voor prenatale

screening op trisomie 13 en 18.(Ministerial Order on antenatal screening for trisomy 13 and 18). [PG/OGZ 3.000.241]. 21-5-2010.
44. The Health Council of the Netherland, Commission WBO. Proeve toepassing Wet bevolkingsonderzoek cystische fibrose (Model application Population Screenings Act:cystic fibrosis). The Hague: Gezondheidsraad;1996. Report No.: 1996/20.
45. Population genetic screening programmes: technical, social and ethical issues. Eur J Hum Genet 2003 Dec;11 Suppl 2:S5-S7.
46. The Health Council of the Netherlands. Genetic Screening. The Hague: Gezondheidsraad; 1994. Report No.: No.1994/22E.
47. Godard B, ten KL, Evers-Kiebooms G, Ayme S. Population genetic screening programmes: principles, techniques, practices, and policies. Eur J Hum Genet 2003 Dec;11 Suppl 2:S49-S87.
48. Poppelaars FA, van der WG, Braspenning JC, Cornel MC, Henneman L, Langendam MW, et al. Possibilities and barriers in the implementation of a preconceptional screening programme for cystic fibrosis carriers: a focus group study. Public Health 2003 Nov;117(6):396-403.
49. Lakeman P. Preconceptional carrier couple screening for cystic fibrosis and hemoglobinopathies PhD Thesis. Vrije Universiteit Amsterdam; 2008.
50. Expertmeeting: Actief informeren op HbP risico Waarom, wanneer en hoe? (Expert Meeting: active information about HbP risk: Why, when and how). Book of abstracts. 2011.
51. Bosma AR, Cornel MC, Donker M. De ontwikkeling en evaluatie van patientgebonden voorlichtingsmateriaal over dragerschap van hemoglobinopathieen voor de 1e lijn. (Developement and evaluation of patient oriented information about HbP carrier status in primary health care). Master Thesis Gezondheidswetenschappen, Vrije Universiteit; 2008.
52. Achterbergh R, Lakeman P, Stemerding D, Moors EH, Cornel MC. Implementation of preconceptional carrier screening for cystic fibrosis and haemoglobinopathies: a sociotechnical analysis. Health Policy 2007 Oct;83(2-3):277-86.
53. NICE, the National Collaborating Centre for Women's and Children's Health. Antenatal care. Routine care for the healthy pregnant woman. NICE clinical guideline 62. 2010.
54. ACOG. Update on carrier screening for cystic fibrosis, 486, The American College of Obstericians and Gynecologists A, (2011). Available from www.acog.org. Last accessed 12 May 2012)
55. Dyson SM, Culley L, Gill C, Hubbard S, Kennefick A, Morris P, et al. Ethnicity questions and antenatal screening for sickle cell/thalassaemia [EQUANS] in England: a randomised controlled trial of two questionnaires. Ethn Health 2006 May;11(2):169-89.
56. Lakeman P, Henneman L, Bezemer PD, Cornel MC, ten Kate LP. Developing and optimizing a decisional instrument using self-reported ancestry for carrier screening in a multi-ethnic society. Genet Med 2006 Aug;8(8):502-9.
57. Karlson S, Becares L, Roth M. Understanding the influence of ethnicity on health. In: Craig G, Atkin K, Chattoo S, Flynn R, editors. Understanding 'race' and ethncity. Bristol: The policy Press; 2011. p. 111-28.
58. Aspinall PJ, Dyson SM, Anionwu EN. The feasibility of using ethnicity as a primary tool for antenatal selective screening for sickle cell disorders: pointers from the research evidence. Soc Sci Med 2003 Jan;56(2):285-97.
59. Alderliesten ME, Vrijkotte TG, van der Wal MF, Bonsel GJ. Late start of antenatal care among ethnic minorities in a large cohort of pregnant women. BJOG 2007 Oct;114(10):1232-9.
60. Chote AA, Koopmans GT, Redekop WK, de Groot CJ, Hoefman RJ, Jaddoe VW, et al. Explaining ethnic differences in late antenatal care entry by predisposing, enabling and need factors in The Netherlands. The Generation R Study. Matern Child Health J 2011 Aug;15(6):689-99.

61. De Jong-Potjer LC Beentjes M, Bogchelman M, Jaspar AHJ, Van Asselt KM. NHG-Standaard Preconceptiezorg, M97 (Guideline preconceptioncare for GPs). Huisarts Wet 2011;54((6)):310-12.
62. de Jonge A. KNOV-Standpunt preconceptie zorg (KNOV position paper preconception care) Bilthoven: KNOV; 2005.
63. NVOG. Nota Preconceptie zorg. 2008. Available from www.nvog-documenten.nl. Last accessed 11 May 2012.
64. Weinreich SS, de Lange-de Klerk ES, Rijmen F, Cornel MC, de KM, Plass AM. Raising awareness of carrier testing for hereditary haemoglobinopathies in high-risk ethnic groups in the Netherlands: a pilot study among the general public and primary care providers. BMC Public Health 2009;9:338.
65. Giordano PC, Plancke A, Van Meir CA, Janssen CA, Kok PJ, Van Rooijen-Nijdam IH, et al. Carrier diagnostics and prevention of hemoglobinopathies in early pregnancy in The Netherlands: a pilot study. Prenat Diagn 2006 Aug;26(8):719-24.
66. Kaufmann JO, Mirel-Gungor G, Selles A, Hudig C, Steen G, Ponjee G, et al. Feasibility of nonselective testing for hemoglobinopathies in early pregnancy in The Netherlands. Prenat Diagn 2011 Dec;31(13):1259-63.
67. Nicholaas H, Sprangers A. Buitenlandse migratie in Nederland 1795-2006: de invloed op de bevolkingssamenstelling (Foreign migration in the Netherlands 1795-2006: the influence of population composition). www.cbs.nl. 2007. Last accessed 5 April 2012.
68. Dyson S. Chapter 1. Sickle cell, thalassaemia and haemoglobinopathy counselling. In: Dyson S. Ethnicity and Screening for Sickle Cell/Thalassaemia. Edinburgh: Elsevier Churchill Livingstone; 2005.
69. de Weerd S, Polder JJ, Cohen-Overbeek TE, Zimmermann LJ, Steegers EA. Preconception care: preliminary estimates of costs and effects of smoking cessation and folic acid supplementation. J Reprod Med 2004 May;49(5):338-44.
70. Bryan S, Dormandy E, Roberts T, Ades A, Barton P, Juarez-Garcia A, et al. Screening for sickle cell and thalassaemia in primary care: a cost-effectiveness study. Br J Gen Pract 2011 Oct;61(591):e620-e627.
71. Phylipsen M, Traeger-Synodinos J, van der KM, van DP, Bakker G, Geerts M, et al. A novel alpha(0) -thalassemia deletion in a Greek patient with HbH disease and beta-thalassemia trait. Eur J Haematol 2012 Apr;88(4):356-62.
72. van Zwieten, R, Kaufmann JO, Vuil H, Kouwenberg J, Verhoeven AJ, Fogelberg K, et al. Hb Nile[A1] and Hb Nile[A2]: novel identical [alpha77(EF6)Pro-->Ser] variants found in either the alpha1- or alpha2-globin genes. Hemoglobin 2009;33(3):188-95.
73. Metcalfe SA. Carrier screening in preconception consultation in primary care. J Community Genet 2011 Dec;20.
74. Bhopal RS. Theoretical, ethical and future-oriented perspectives. Evaluating interventions in ethnicity ad health. In: Bhopal RS. Ethnicity, race,and health in multicultural societies. Foundation for better epidemiology, public health, and health care.Oxford: Oxford University press; 2007. p. 285-307.
75. Jans S, Beentjes M. KNOV Standaard Anemie in de verloskundige praktijk. (Guideline Anaemia in midwifery practice). KNOV Guideline. Utrecht; KNOV, 2010.
76. Beentjes M. Weersma R, Koch W, Offringa A, Verduijn M, Mensink P, WiersmaT, Goudswaard L,van Asselt K. NHG-Standaard Zwangerschap en kraamperiode (NHG guideline pregnancy and puerperium). Utrecht: NHG; 2012. Report No.: M 32.
77. Henneman L. Preconceptional cystic fibrosis carrier screening. Desirability and feasability in the Netherlands. PhD Thesis. Vrije Universiteit Amsterdam; 2002.
78. The Health Council of the Netherlands. Preconception care: a good beginning. Den Haag. The Health Council of the Netherlands; 2007. Report No.: 2007/19.
79. Weijers-Poppelaars F. Preconceptional cystic fibrosis carrier screening. Opportunities for implementation. PhD Thesis. Vrije Universiteit Amsterdam; 2004.

80. Peters M, Appel IM, Cnossen MH, Breuning-Boers JM, Heijboer H. Sickle cell disease in heel injection screening. I. Ned Tijdschr Geneeskd 2009 May 2;153(18):854-7.
81. Peters M, Fijnvandraat K, van dT, X, Garre FG, Giordano PC, van Wouwe JP, et al. One-third of the new paediatric patients with sickle cell disease in The Netherlands are immigrants and do not benefit from neonatal screening. Arch Dis Child 2010 Jun 24.
82. Borry P, Evers-Kiebooms G, Cornel MC, Clarke A, Dierickx K. Genetic testing in asymptomatic minors: background considerations towards ESHG Recommendations. Eur J Hum Genet 2009 Jun;17(6):711-9.
83. Mazza D, Chapman A. Improving the uptake of preconception care and periconceptional folate supplementation: what do women think? BMC Public Health 2010 Dec 23;10:786.
84. Milman N. Iron and pregnancy-a delicate balance. Ann Hematol 2006 Sep;85(9):559-65.
85. Stronks G&K. The identification of ethnic groups in health research, additional to the country of birth classification. ZonMW, Comittee Culture and Health.; 2004.
86. Stronks K, Kulu-Glasgow I, Agyemang C. The utility of 'country of birth' for the classification of ethnic groups in health research: the Dutch experience. Ethn Health 2009 Jun;14(3):255-69.
87. Kaufmann JO, Mirel-Gungor G, Selles A, Hudig C, Steen G, Ponjee G, et al. Feasibility of nonselective testing for hemoglobinopathies in early pregnancy in The Netherlands. Prenat Diagn 2011 Dec;31(13):1259-63.
88. Hijmans CT, Fijnvandraat K, Oosterlaan J, Heijboer H, Peters M, Grootenhuis MA. Double disadvantage: a case control study on health-related quality of life in children with sickle cell disease. Health Qual Life Outcomes 2010 Oct 26;8:121.
89. Fransen MP, Wildschut HI, Vogel I, Mackenbach JP, Steegers EA, Essink-Bot ML. Ethnic differences in considerations whether or not to participate in prenatal screening for Down syndrome. Prenat Diagn 2009 Dec;29(13):1262-9.

Summary / Samenvatting

SUMMARY

The topic of this thesis is the screening of anaemia and haemoglobinopathies (HbP) against the background of ethnicity in pregnancy and the preconception period. Haemoglobinopathy is the umbrella term for the autosomal recessive disorders such as sickle cell disease (SCD) and thalassaemia. The thesis consists of two parts: The first part looks at anaemia in pregnancy amongst different ethnic groups in an Amsterdam population and at the effect of a positive HbP carrier status on the outcome pregnancy. The second part investigates the attitudes and barriers concerning the introduction of a ethnicity-based HbP carrier screening programme.

Chapter 1 discusses the background to and the relevance of the studies and introduces the research questions. Screening for anaemia, a low haemoglobin (Hb), in pregnancy is world wide common practice. As a result of heterogeneity in definitions used, blood tests, reference values and populations studied, it is difficult to determine the clear prevalence of anaemia in pregnancy. In the Royal Dutch Organisation of Midwives' (KNOV) anaemia guideline, gestation specific reference values are designed to account for physiological haemodilution. The anaemia prevalence according to these reference values is also unknown. Besides midwives have questioned the policy around anaemia amongst women with different ethnic origins. Before anaemia policy is adjusted for specific groups of pregnant women, the prevalence of anaemia in different ethnic groups needs to be investigated. Depending on local policy, anaemia at the end of pregnancy may influence the decision about the place of birth. If anaemia prevalence depends on ethnic background, it would mean that some women may have less choice in the place of birth.

HbP are considered to be the most prevalent monogenetic disorders worldwide. The prevalence of a positive HbP carrier status has been estimated at 0.03-40% depending on ethnic origin. Western Societies have become more and more multicultural and ethnically diverse, causing the prevalence of (carrier status of) HbP to increase. In the Netherlands, each year approximately 60 children are born with a serious HbP disorder. Carrier prevalence has been estimated at 4-26% for Dutch citizens of immigrant descent.

Despite the advice of the World health Organisation (WHO) in 2006, the Netherlands does not have a national programme for HbP carrier screening. To prevent complications and to promote health gain, universal screening for SCD added to the Neonatal Screening (NNS) in 2007. However the screening method also leads to unsought identification of carriers. In the Netherlands no negative effect is assumed for HbP carriers, except perhaps mild anaemia in people with alpha-thalassaemia minor. Empirical evidence, however, seems inconclusive. It would be important for those involved in maternity care, such as midwives, obstetricians and GPs, to know if any effect of a positive HbP carrier status exists on the outcome of pregnancy, so that appropriate care can be given to those who need it.

The expansion of the NNS renewed the old discussion whether or not a broad HbP carrier screening programme should be introduced. Both the United Kingdom

(UK) and United States (US) have known Regarding the racial and social conditions related problems in both the United Kingdom (UK) and United States (US) related to the introduction of HbP carrier screening, the question was raised if similar issues were part of the decision-making process in the Netherlands.

If a broader HbP carrier screening programme would be introduced in the future, primary care providers such as midwives and GPs, will be primarily called upon to carry out such a programme.

Following the example of the UK where an HbP screening programme was introduced in 2004, screening may be ethnicity based. It is unknown what primary health care professionals think of such a programme.

We therefore aimed to investigate midwives' and GPs' attitude, intention and behaviour towards ethnicity based HbP carrier screening as well as their ideas about existing barriers for the implementation of such a program.

As both 'ethnicity' and 'ancestry' are shown to be equally complex terms and ethnicity is supported by literature as a proxy for ancestral or ethnic origin, this term was chosen to use in the study (Chapter 1). Moreover, it seems to be the acceptable term for health professionals.

The following research questions will be answered in this thesis:

1. What is the prevalence of anaemia in pregnancy according to the cut-off points used in the KNOV anaemia guideline (2000)?
   Is there a difference in the prevalence of anaemia in pregnant women of non-Northern European descent compared with pregnant women of Northern European descent?
   If so, does this difference result in a higher risk of a Transferred Home Delivery (THD), thus reducing the chance for non-Northern European women to choose their place of birth?
2. Does being HbP carrier have any consequences for the health of pregnant women and does it have an effect on the outcome of their pregnancy?
3. When did the issue of preconception, antenatal or neonatal testing of asymptomatic persons at risk of HbP receive attention on the agenda of the Dutch public health authorities and what was the background to this agenda setting?
   To what extent was this influenced by the political climate at the time and potential concerns about the role of ethnicity and the fear of discrimination?
4. What are the attitude, intention and behaviour of midwives and GPs towards ethnic registration and their willingness to undertake carrier testing for clients and patients on the basis of ethnicity?
   What factors play a role in midwives' and GP's attitudes towards ethnic registration related to preconceptional or antenatal HbP carrier testing?
   What are the perceived barriers of these health professionals if ethnicity-based HbP carrier screening would be implemented in the future?

Chapter 2 describes the results of a retrospective cohort study into the prevalence of anaemia in pregnant women in Amsterdam according to the reference values used in the guideline *Anaemia in Primary Care Midwifery Practice* of the KNOV, and investigates a possible difference in prevalence between pregnant women of Northern European descent compared with women of non-Northern European descent. The study also investigated whether any difference in prevalence resulted in a higher risk of a transferred home delivery, thus reducing the chance for women to choose the place of birth. All pregnant women with a singleton low-risk pregnancy, who delivered their baby between 1st of January 2003 and 31st of December 2003, and who were registered, at one of the three primary care midwifery practices were included in the study. The practices were selected on the basis of urbanisation, resulting in an ethnic population which was comparable with the ethnic mix in other similarly urbanised areas in the Netherlands. This resulted in a study population of 828 pregnant women.

The results showed a prevalence of anaemia in pregnancy of 3.4% (n = 28) at booking (first visit) and 2.7% (n = 22) at approximately 30 weeks of gestation. The relative risk (RR)of anaemia at booking was 5.9 (95% CI 2.1-16.7) for pregnant women of non-Northern European descent compared with those of Northern European descent. The RR of anaemia at approximately 30 weeks of gestation was 22 (95% CI 3.0-162.0) for pregnant women of non-Northern European descent compared with those of Northern European descent. The incidence of transferred home delivery was 3.1% in the study population. The RR for transferred home delivery was 24.1 (95% CI 3.3-176.7) for pregnant women of non-Northern European descent compared with those of Northern European descent.

The conclusion of this chapter is that pregnant women of non-Northern European descent have a higher chance of anaemia in pregnancy than women of Northern European descent: RR 5.9, (95% CI 2.1-16.7) at booking and RR 22.0, (95% CI 3.0-162.0) at 30 weeks pregnancy. As a result, they have a higher risk of a transferred home delivery, taking away their opportunity to choose the place of birth. HbP did not explain the higher risk of anaemia in pregnant women of non-Northern European descent and it was not possible to correct for socio-economic status. Being of non-Northern European descent should thus be added as a risk factor for anaemia in pregnancy until more is known about the background of this risk factor.

In **chapter 3** the results of a systematic literature review into the effect of a positive HbP carrier status on the outcome of pregnancy are presented. The reproductive risk for women who are carriers of HbP is well known. However, midwives, GPs and obstetricians need to know whether there are other risks involved in the pregnancies of women who are carriers of HbP. On the basis of the following criteria a selection for the inclusion of studies into the review was made: Cohort and case-control studies, pregnant women with a singleton pregnancy, exposure of HbAS or thalassaemia minor and the following outcomes: urinary tract infection (UTI), anaemia, (pre-) eclampsia, gestational diabetes, premature labour, low birth weight, intrauterine

growth retardation, miscarriage, neonatal death, low Apgar score, neural tube defects. Quality assessment and data extraction were carried out by two researchers. A total of 780 scientific articles were identified of which nine were included in the study. As a result of considerable heterogeneity, pooling of the data was not possible.

A protective effect of sickle cell trait was found for premature birth, low Apgar score and perinatal mortality. No significant effect was found for low birth weight, growth retardation, UTI or high blood pressure. The risk of anaemia and bacteriuria was increased.

Many methodological problems were identified in the studies. The appropriateness of a large well controlled prospective cohort study is called for. Until further knowledge on this subject is generated, health care professionals need to be aware of the risk of anaemia and bacteruria. In conclusion, the risk for an adverse outcome of pregnancy in HbP carriers is low and they can continue to receive primary care.

Chapter 4 describes the results of a one-day witness seminar that was held in 2009 to explore the decision-making process around the possible introduction of a HbP carrier screening programme in the Netherlands in the past. The central question that the participants, fourteen multi-disciplinary key figures, were asked to answer during this seminar was why the introduction of a screening programme for HbP was considered to be untimely, and whether ethnicity played a role given the race-related history in other countries surrounding the introduction of HbP (carrier) screening? The full transcript of the day was content-analysed together with the available grey and scientific Dutch literature identified on the subject.

The results of this study show that the subject of HbP (carrier) screening first appeared in the literature in the 1970s. As opposed to a long history of neglect of African-American health in the United States, the heritage of the Second World War influenced the decision-making process in the Netherlands. As a consequence, registration of ethnicity surfaced as an impeding factor. Overall, official Dutch screening policy was restrained regarding reproductive issues caused by fear of eugenics. In the 1990s HbP (carrier) screening was found to be 'not opportune' due to low prevalence, lack of knowledge and fear of stigmatisation. Currently the registration of ethnicity remains on the political agenda and still proves to be a sensitive subject due to the political climate. Carrier screening in general never appeared high on the policy agenda. Complexities related to carrier screening are a challenge in Dutch healthcare. Whether carrier screening will be considered a valuable complementary strategy in the Netherlands, depends partly on participation of representatives of high-risk groups in policy making.

In **chapter 5** the results are described of a quantitative questionnaire based on the Theory of Planned Behaviour which investigated the attitudes, intention and behaviour of midwives and GPs towards ethnicity-based HbP carrier screening. Moreover, registration of ethnicity is a controversial societal issue which may complicate the introduction of a national preconception or antenatal carrier screening programme.

The questionnaire was sent by mail to the total population of 1800 primary care midwives and a random selection of 2100 GPs. The response rate was 35% (midwives 44.2%; GPs 27.6%).

Most respondents favoured ethnicity registration for health purposes. Although 45% of respondents thought that offering a carrier test on the basis of ethnicity alone should become national policy, it is currently not carried out. The main factor explaining lack of intention towards ethnicity-based HbP carrier screening was subjective norm, the perception that their peers do not think they should offer screening (52.2% variance explained). If ethnicity-based HbP carrier screening would become national policy, most professionals reported that they would carry this out.

Since most practitioners look for role models among peers, debate amongst general practitioners and midwives should be encouraged when new policy is to be developed articulating the voices of colleagues who already actively offer HbP carrier screening. However, implementation of HbP carrier screening by GPs and midwives cannot be achieved without policy support at national level.

The aim of **chapter 6** was to explore attitudes and perceived barriers amongst GPs and midwives regarding ethnicity-based HbP carrier screening. Six focus group discussions were held with a total of 9 GPs and 28 midwives. GPs and midwives were consulted separately. The study showed that both GPs and midwives struggled with correctly identifying ethnicities at risk leading to several complex considerations such as what to do with mixed backgrounds and how far back they would have to look into someone's ethnic origin. Acerbated by the current political climate, ethical concerns regarding privacy originated from the second World War when ethnic and religious registration facilitated deportation of Jewish citizens. Some midwives thought the ethnicity question might undermine the relationship with their clients. Software programs prevent GPs from registering ethnicity of patients at risk. Financial implications for patients were also a concern. Despite this, both groups seemed positive and are familiar with identifying ethnicity and use this for individual patient care. The chapter concluded that although health professionals are generally positive, ethical, financial and practical issues surrounding ethnicity-based HbP carrier screening need to be clarified before introducing such a programme. Primary care professionals can be targeted through professional organisations, but still need national policy support.

Finally **chapter 7**, the general discussion of the thesis, presents a brief overview of the findings which are discussed against the background of the existing literature. Besides this, limitations of the studies in the thesis are discussed, as well as implications for practice and advice on further research based on the results of this thesis.

Overall the study findings show that ethnic diversity poses certain questions within the healthcare setting and challenges health care professionals to deliver equitable health services. The results of this thesis support clinicians such as midwives, obstetricians and GPs in providing tailored health care for pregnant women with different ethnic backgrounds. Professionals should therefore be aware of the

increased possibility of anaemia and HbP (carrier) status in different ethnic groups. The prevalence of anaemia between ethnic groups differs and ethnicity affects the prevalence of HbP carrier status. Since anaemia, asymptomatic bacteriuria and the subsequent risk of pyelonephritis may occur more frequently in HbP carriers, health professionals involved should investigate pregnant women who are known HbP carriers more frequently for these conditions.

On the basis of the available scientific evidence it can be concluded that a positive HbP carrier status does not seriously affect the outcome of pregnancy which means that carriers can continue to receive primary care during their pregnancies, it may influence reproductive choice. Health professionals use ethnicity to deliver appropriate equitable health care for all groups within society, but the results show that they struggle with the operationalisation of this concept, making them uncertain whom to offer ethnicity-based screening. A screening instrument based on ancestry has been shown to be effective. Although primary health care professionals are reasonably positive about a national HbP carrier screening programme, ethical, practical and financial barriers need to be solved if an ethnicity-based programme would be introduced.

The discussion in the Netherlands has focused primarily on equality in health care and concerns over stigmatisation of certain groups in society. Considering the complexity of determining ethnicity, increasing ethnic admixture, the view of the patient organisation OSCAR that the accent should not be placed on certain ethnic groups, a universal offer of preconception and / or antenatal HbP carrier screening would therefore be the most equitable option. If we want to strive to provide equitable healthcare services for all, it is important that health professionals such as midwives and GPs are aware of these issues. They must be supported in giving appropriate care and discussions on equity, equality and access should be part of (continuing) education programmes to enable them to provide women with the care they need. As part of meeting the needs of all societal groups, the introduction of HbP carrier screening should be considered, as proposed by the WHO.

Based on this thesis a universal offer of preconception and antenatal carrier screening alongside the NNS is proposed. If this is not feasible, i.e. for economic reasons, targeted screening such as is implemented in England, could be introduced but only if supported by an evidence based instrument to determine ethnic origin.

The results from the studies in this thesis underline the necessity to solve ethical and practical barriers and clarify financial issues before a HbP carrier screening programme is implemented. This can only be done with adequate governmental leadership. Once these issues are solved health care professionals and their professional organisations can be called upon to meet the implementation requirements of such a programme.

SAMENVATTING

Het onderwerp van dit proefschrift is het screenen op anemie en hemoglobinopathie (HbP) tijdens de preconceptieperiode en in de zwangerschap in het licht van etniciteit. Hemoglobinopathie is de samenvattende term voor de autosomaal recessieve aandoeningen sikkelcelziekte (SCZ) en thalassemie.

Het proefschrift bestaat uit twee delen: Het eerste deel concentreert zich op anemie tijdens de zwangerschap bij verschillende etnische groepen in een Amsterdamse populatie en het effect van een positieve HbP dragerschapstatus op de uitkomst van de zwangerschap. Het tweede deel onderzoekt de attitudes en de barrières met betrekking tot de introductie van een HbP dragerschapscreening programma gebaseerd op etniciteit.

Hoofdstuk 1 gaat over de achtergrond en de relevantie van de studies en introduceert de onderzoeksvragen. Het screenen op anemie, dat wil zeggen een laag hemoglobinegehalte (Hb), tijdens de zwangerschap is wereldwijd geaccepteerd beleid. Vanwege de heterogeniteit in de gebruikte definities, de gebruikte bloedtesten, referentiewaarden en de onderzochte populaties, is het lastig een eenduidige prevalentie van anemie vast te stellen. In de richtlijn anemie van de Koninklijke Nederlandse Organisatie voor Verloskundigen (KNOV) zijn referentiewaarden ontwikkeld die rekening houden met fysiologische hemodilutie en die daarom verschillen, afhankelijk van de zwangerschapstermijn. De prevalentie van anemie op basis van de KNOV referentiewaarden is onbekend. Bovendien hebben verloskundigen vragen gesteld bij het beleid rondom anemie bij vrouwen met verschillende etnische achtergrond. Voordat het anemiebeleid aangepast kan worden voor specifieke groepen zwangere vrouwen, is het van belang de prevalentie in verschillende etnische groepen vast te stellen. Afhankelijk van regionaal beleid, kan het vóórkomen van anemie aan het eind van de zwangerschap invloed hebben op de plaats van bevalling. Indien anemie tijdens de zwangerschap inderdaad vaker voorkomt bij bepaalde etnische groepen, dan zou dit betekenen dat sommige vrouwen minder keuzemogelijkheid hebben ten aanzien van de plaats van bevalling.

HbP zijn wereldwijd de meest voorkomende monogenetische aandoeningen. De prevalentie van een positieve dragerschapstatus wordt geschat op 0,03-40% afhankelijk van etnische afkomst. Aangezien de westerse samenleving steeds multicultureler en etnisch divers wordt, wordt ook dat de prevalentie van HbP (dragerschap) in de samenleving steeds groter. In Nederland worden ieder jaar ongeveer 60 kinderen geboren met een ernstige vorm van HbP. De dragerschapprevalentie wordt geschat op 4-26% voor Nederlanders van niet-westerse afkomst. Ondanks het advies van de Wereld Gezondheidsorganisatie (WHO) in 2006, bestaat er in Nederland geen landelijk dragerschapprogramma voor HbP. Ter voorkoming van complicaties en het bevorderen van gezondheidswinst, werd de neonatale screening (NNS) in 2007 met SCZ uitgebreid. Als nevenbevinding van het programma wordt echter ook HbP dragerschap bij de pasgeborenen

vastgesteld. In Nederland gaat men er van uit dat HbP dragerschap geen negatieve gezondheidseffecten heeft behalve een lichte anemie bij dragers van alfa-thalassemie. Er is echter wat betreft de gezondheidseffecten op de uitkomst van de zwangerschap geen duidelijke conclusie beschikbaar op basis van wetenschappelijk onderzoek. Hulpverleners zoals verloskundigen, gynaecologen en huisartsen, zouden gebaat zijn bij wetenschappelijk onderbouwde kennis over het effect van een positieve HbP dragerschapstatus op de uitkomsten van de zwangerschap. Indien er inderdaad negatieve gevolgen zijn, kan de zorg worden aangepast.

De uitbreiding van de NNS zorgde voor een hernieuwde discussie over het al dan niet invoeren van een HbP dragerschap screeningsprogramma. Zowel Groot Brittannië (GB) als de Verenigde Staten (VS) zijn bekend met bepaalde sociale en raciale kwesties met betrekking tot de introductie van HbP dragerschapscreening. De vraag is dan ook of en hoeverre er in Nederland sprake is geweest van soortgelijke kwesties ten tijden van het besluitvormingsproces over het al dan niet introduceren van een screeningsprogramma.

Een breed HbP screeningsprogramma zal mogelijk gebaseerd zijn op etniciteit, zoals in Engeland waar in 2004 een dergelijk programma werd geïmplementeerd. Indien in de toekomst een breed HbP programma in Nederland zal worden geïntroduceerd, is de verwachting dat dit voornamelijk zal worden uitgevoerd door verloskundigen en huisartsen in de eerstelijn. Het is onbekend wat deze eerstelijns hulpverleners van een dergelijk programma zouden vinden. Het doel van het onderzoek was daarom de attitude, de intentie en het gedrag ten aanzien van HbP dragerschapscreening programma op basis van etniciteit te onderzoeken en de mogelijke knelpunten in beeld te brengen die volgens deze hulpverleners zouden kunnen bestaan bij de invoering van een dergelijk programma.

Zowel 'etniciteit' als 'herkomst' blijken complexe termen. In de bestaande literatuur wordt 'etniciteit' vaak gebruikt als een ander woord voor 'herkomst', oftewel etnische herkomst. Daarom wordt er in dit onderzoek gekozen voor het gebruik van deze term. Bovendien lijkt etniciteit de term die het meest bekend is bij hulpverleners.

De volgende onderzoeksvragen zullen in dit proefschrift worden beantwoord:

1. Wat is de prevalentie van anemie tijdens de zwangerschap gebaseerd op de KNOV-referentie waarden?
   Is er een verschil in de prevalentie van anemie tussen zwangeren van niet Noord Europese afkomst in vergelijking met zwangeren van Europese afkomst? Indien dit zo is, hebben deze zwangeren dan een verhoogde kans op een verplaatste thuis bevalling waardoor zij minder keuze hebben ten aanzien van de plaats van bevalling?
2. Wat is het effect van HbP-dragerschap bij vrouwen op de uitkomst van de zwangerschap
3. Wanneer verscheen de discussie over het preconceptioneel; prenataal en / of neonataal testen van asymptomatische personen met een verhoogd risico voor het eerst op de agenda van beleidsmakers in de Nederlandse gezondheidzorg en

tegen welke achtergrond gebeurde dit? Heeft het politieke klimaat van destijds en de rol van etniciteit en de angst voor discriminatie hier enige invloed op gehad?

4. Wat is de attitude; de intentie en het gedrag van verloskundigen en huisartsen ten aanzien van de registratie van etniciteit en hun bereidheid om hun cliënten en/of patiënten een op etniciteit gebaseerde HbP dragerschaptest aan te bieden? Welke andere factoren spelen hierin een mogelijke rol en wat zijn de knelpunten die deze hulpverleners voorzien bij de implementatie van een op etniciteit gebaseerd HbP dragerschapprogramma?

Hoofdstuk 2 beschrijft de resultaten van een retrospectieve cohortstudie naar de prevalentie van anemie bij zwangere vrouwen in Amsterdam op basis van de referentiewaarden in de KNOV richtlijn *Anemie in de eerstelijns verloskundige praktijk.* In de studie is een mogelijk verschil in de prevalentie tussen zwangere vrouwen van Noord Europese en niet-Noord Europese afkomst onderzocht. Tevens is nagegaan of, indien er een verschil in prevalentie bestaat, dit resulteert in een hoger risico op een verplaatste thuisbevalling (de zogenaamde D-indicatie) waardoor deze groep vrouwen minder kans heeft om zelf de plaats van bevalling te kiezen.

Alle zwangeren met een laag risico die tussen 1 januari en 31 december 2003 bevielen van een eenling in één van drie eerstelijns verloskundigenpraktijken, werden geïncludeerd in de studie. De praktijken werden geselecteerd op basis van urbanisatie zodat de etniciteit van de onderzoekspopulatie vergelijkbaar was met die van vergelijkbare gebieden in Nederland. Dit resulteerde in een onderzoekspopulatie van 828 zwangere vrouwen.

De resultaten van deze studie laten een anemie prevalentie zien van 3,4% (n=28) onder zwangere vrouwen tijdens de eerste controle en 2,7% (n=22) bij ongeveer 30 weken graviditeit. Het relatieve risico (RR) op anemie tijdens de eerste controle was 5,9 (95% BI 2,1-16,7) voor zwangere vrouwen van niet-Noord Europese afkomst vergeleken met vrouwen van Noord Europese afkomst. Het RR op anemie bij 30 weken graviditeit was 22 (95% BI 3,0-162,0) voor zwangeren van niet-Noord Europese afkomst in vergelijking met vrouwen van Noord Europese afkomst. De incidentie van de verplaatste thuisbevalling was 3,1% in de bestudeerde populatie. Het RR op het risico van een verplaatste thuisbevalling was 24,1 (95% BI 3,3-176,7) voor zwangeren van niet-Noord Europese afkomst in vergelijking met zwangeren van Noord Europese afkomst.

Dit hoofdstuk concludeert dat zwangeren van niet-Noord Europese afkomst meer kans hebben op anemie tijdens de zwangerschap waardoor zij minder kans hebben om zelf de plaats van bevalling te kiezen vanwege een hogere kans op een indicatie voor een verplaatste thuisbevalling. HbP bleek het verschil in anemie niet te verklaren en voor sociaal economische factoren kon niet worden gecorrigeerd. Niet-Noord Europese afkomst zou daarom als risicofactor voor anemie moeten worden toegevoegd tot meer bekend is over de achtergrond van dit risico.

In **hoofdstuk 3** worden de resultaten van een systematisch literatuuronderzoek gepresenteerd naar het effect van HbP dragerschap op de uitkomst van de

zwangerschap. Het genetische risico voor vrouwen met een positieve HbP dragerschapstatus is bekend. Echter verloskundigen, gynaecologen en huisartsen zouden ook moeten weten of er nog andere risico's voor zwangere HbP-dragers zouden kunnen zijn.

Cohort en patiëntcontrole onderzoeken werden geïncludeerd op basis van de volgende criteria: Vrouwen zwanger van een eenling met een HbAS of thalassemie minor expositie en een van de volgende uitkomsten: urineweginfectie; anemie; (pre-) eclampsie; diabetes gravidarum; laag geboortegewicht; prematuriteit; dysmaturiteit; spontane abortus; perinatale mortaliteit; lage apgarscore; neuraal buisdefect. Kwaliteitsbeoordeling en data-extractie werden uitgevoerd door twee onderzoekers. Er werden in totaal van 780 wetenschappelijke artikelen gevonden waarvan er negen werden geïncludeerd in de studie Door aanzienlijke heterogeniteit van de studies was het poolen van de data niet mogelijk.

Er werd een beschermend effect gevonden van sikkelceldragerschap, op het voorkomen van prematuriteit; lage apgarscore en perinatale mortaliteit. Er werd geen significant effect gevonden voor laag geboortegewicht; dysmaturiteit; urineweginfectie of hoge bloeddruk. Het risico op anemie en bacteriurie was verhoogd bij sikkelceldragerschap.

Er werden nauwelijks studies gevonden die het effect van dragerschap op thalassemie onderzochten. Er werden veel methodologische knelpunten in de studies geïdentificeerd. Het zou daarom zinvol zijn om een grote prospectieve cohortstudie uit te voeren om een betere uitspraak te kunnen doen over het effect van HbP dragerschap op de uitkomst van de zwangerschap. Tot er meer bekend is over dit onderwerp moeten verloskundige hulpverleners er van uitgaan dat er een grotere kans op anemie en bacteriurie bestaat bij dragers. Concluderend is het risico op een ongunstige uitkomst van de zwangerschap laag bij HbP dragers en kan de zorg in de eerstelijn plaats vinden.

Hoofdstuk 4 beschrijft de resultaten van een *witness* seminar, gehouden in 2009 waarbij gedurende één dag het besluitvormingsproces in het verleden rondom de eventuele introductie van een Nederlands screeningsprogramma voor HbP-dragerschap werd onderzocht. Deelnemers, veertien multidisciplinaire sleutelfiguren, werden gevraagd de volgende centrale vragen te beantwoorden: Waarom werd de introductie van een HbP screeningprogramma in de jaren '90 niet opportuun geacht en heeft de factor etniciteit een rol gespeeld gezien de raciaal gerelateerde geschiedenis in andere landen met betrekking tot de introductie van een dergelijk dragerschapprogramma? Het volledige transcript van die dag en de beschikbare wetenschappelijke en grijze Nederlandse literatuur over dit onderwerp werden op inhoud geanalyseerd.

De resultaten van dit hoofdstuk laten zien dat het onderwerp HbP (dragerschap-) screening voor het eerst in de jaren '70 in de literatuur verscheen. Door raciale tegenstellingen is HbP dragerschap in de Verenigde Staten lang verwaarloosd. In Nederland daarentegen hebben de erfenis van schuldgevoelens en ervaringen uit

de Tweede Wereldoorlog de besluitvorming beïnvloed. De registratie van etniciteit is gezien de geschiedenis een beladen onderwerp en dit kwam dan ook als een belemmerende factor naar voren. Over het algemeen was het officiële Nederlandse beleid ten aanzien van reproductieve keuzemogelijkheden beperkt wat voornamelijk veroorzaakt werd door de angst voor eugenetica. In de jaren '90 werd verondersteld dat HbP (dragerschap-) screening 'niet opportuun' zou zijn, voornamelijk vanwege een lage prevalentie; gebrek aan kennis en angst voor stigmatisering.

Momenteel staat de registratie van etniciteit nog steeds op de politieke agenda en in verband met het huidige politieke klimaat blijft dit een gevoelig onderwerp. Over het algemeen heeft het onderwerp dragerschapsscreening nooit hoog op de politieke agenda gestaan. De complexiteit rondom dragerschapsscreening blijft een uitdaging in de Nederlandse gezondheidzorg. Of dragerschapscreening zal worden gezien als een waardevolle strategie in Nederland is deels afhankelijk van de deelname van vertegenwoordigers van de bevolkingsgroepen met een hoger HbP (dragerschap-) risico aan de beleidsvorming.

In **hoofdstuk 5** worden de resultaten beschreven van een kwantitatief vragenlijstonderzoek, gebaseerd op de Theorie van Gepland Gedrag. Hierin werden de attitude, intentie en gedrag onderzocht van verloskundigen en huisartsen met betrekking tot HbP dragerschapscreening gebaseerd op etniciteit.

Daarbij is het zo dat de registratie van etniciteit gezien wordt als een controversieel maatschappelijk onderwerp wat de introductie van een landelijk preconceptioneel en prenataal screeningprogramma zou kunnen bemoeilijken. De vragenlijst werd per post verstuurd aan alle 1800 eerstelijns verloskundigen in Nederland en aan een gerandomiseerde steekproef van 2100 huisartsen. De respons was 35% (verloskundigen 44,2%; huisartsen 27,6%).

Respondenten zijn voorstander van etniciteitsregistratie, het bevordert volgens hen het geven van zorg op maat. Hoewel 45% van de respondenten voorstander is van een op etniciteit gebaseerd landelijk screeningsbeleid voor HbP dragerschap, voert geen van hen dit momenteel uit. Dit lijkt vooral te worden verklaard doordat zorgverleners vermoeden dat hun collega's ook niet screenen (52,2% verklaarde variantie). Indien HbP dragerschapscreening landelijk beleid zou worden, zouden de meeste eerstelijns hulpverleners dit uitvoeren.

Omdat de meeste hulpverleners hun collega's gebruiken als rolmodel zou het goed zijn om de collega's die deze screening al wel aanbieden te betrekken bij implementatie van een eventueel toekomstig HbP screeningsbeleid. Het is echter wel zo dat de implementatie door verloskundigen en huisartsen van een dergelijk screeningprogramma niet zal plaatsvinden zonder landelijke beleidsondersteuning.

Het doel van **hoofdstuk 6** was het exploreren van de attitudes en de te verwachte barrières van huisartsen en verloskundigen ten opzichte van op etniciteit gebaseerde HbP dragerschapscreening. Er werden zes focusgroepdiscussies gehouden met een totaal van negen huisartsen en 28 verloskundigen. De groepen met verloskundigen en huisartsen werden apart bevraagd.

De studie liet zien dat zowel huisartsen als verloskundigen moeite hebben met het correct identificeren van etniciteit met een verhoogd risico. DIt leidde tot complexe overwegingen, zoals wat te doen bij een gemengde afkomst en hoever moet worden terug gekeken naar iemands etnische afkomst bij het vaststellen van een verhoogd risico. Verergerd door het huidige politieke klimaat, komen de ethische bezwaren voort uit de Tweede Wereldoorlog toen etnische en religieuze registratie de deportatie van joodse inwoners heeft gefaciliteerd. Een aantal verloskundigen had het gevoel dat door de etniciteitvraag de relatie met hun cliënt op het spel zou komen te staan. Softwareprogramma's weerhielden de huisartsen ervan om de etniciteit van hun patiënten te registreren. Financiële gevolgen voor patiënten waren ook een zorg voor hulpverleners. Desondanks leken beide groepen eerstelijns hulpverleners positief over en zijn zij bekend met het identificeren van etniciteit in individuele patiëntenzorg. De conclusie van dit hoofdstuk is dan ook dat hulpverleners over het algemeen positief zijn over op HbP dragerschapscreening gebaseerd op etniciteit. Ethische, financiële en praktische zaken moeten echter nog worden opgehelderd voordat een screeningsprogramma kan worden geïntroduceerd. Eerstelijns hulpverleners kunnen worden bereikt via hun beroepsorganisaties, maar hebben bij de implementatie landelijke beleidsondersteuning nodig.

De algemene discussie van het proefschrift, **hoofdstuk 7**, geeft een kort overzicht van de resultaten in het licht van de bestaande literatuur. Daarnaast worden besproken: de beperkingen van het uitgevoerde onderzoek, de betekenis van de resultaten voor het veld en aanbevelingen voor verder onderzoek t.

Over het algemeen laten de studieresultaten zien dat etnische diversiteit leidt tot een aantal vraagstukken in de gezondheidszorg die een uitdaging zijn voor hulpverleners bij het leveren van gelijkwaardige zorg. De resultaten van dit proefschrift ondersteunen clinici zoals verloskundigen; huisartsen en gynaecologen bij het geven van zorg op maat aan zwangeren met verschillende etnische achtergronden. Hulpverleners zouden zich meer bewust moeten zijn van een grotere kans op anemie en een positieve HbP (dragerschap-) status in verschillende etnische groepen. De prevalentie van anemie verschilt tussen etnische groepen en etniciteit heeft invloed op de prevalentie van HbP dragerschap. Omdat anemie en asymptomatische bacterurie en het daaraan gerelateerde risico op pyelitis vaker kunnen voorkomen onder zwangere HbP dragers, moeten verloskundige hulpverleners hier alerter op zijn bij deze groep zwangeren.

Hoewel er momenteel geen bewijs bestaat dat een positieve HbP dragerschapstatus ernstige gevolgen heeft voor de uitkomst van de zwangerschap en deze zwangeren daarom in de eerste lijn onder zorg kunnen blijven,, kan dit wel van invloed zijn op hun reproductieve keuzes. Etniciteit wordt door zorgverleners gebruikt om gelijkwaardige zorg te geven aan alle groepen in onze maatschappij, maar de resultaten laten zien dat zij worstelen met de operationalisatie van dit concept waardoor zij onzeker zijn aan wie zij screening zouden moeten aanbieden. Een screeningsinstrument dat is gebaseerd op oorspronkelijke afkomst is

bewezen effectief. Eerstelijns hulpverleners zijn redelijk positief over een landelijk dragerschapsprogramma voor HbP, maar ethische, praktische en financiële barrières moeten eerst worden opgelost alvorens een op etniciteit gebaseerd programma wordt geïntroduceerd.

In Nederland heeft de discussie zich voornamelijk gefocust op gelijkheid in de gezondheidszorg en zorgen over stigmatisering van bepaalde groepen in de maatschappij. Gezien de complexiteit van het vaststellen van etniciteit, de steeds groter wordende smeltkroes van etniciteiten, de mening van de patiëntenorganisatie OSCAR die vindt dat de nadruk niet moet worden gelegd op bepaalde etnische groepen, lijkt een universeel aanbod om tijdens de preconceptieperiode of aan het begin van de zwangerschap op HbP dragerschap te screenen de meest gelijkwaardige optie. Indien we willen streven naar gelijkwaardige gezondheidszorg voor iedereen dan is het van belang dat hulpverleners zoals huisartsen en verloskundigen zich hiervan bewust zijn en worden ondersteund in het uitvoeren van deze zorg. De discussie over gelijkwaardigheid, gelijkheid en gelijke toegankelijkheid van zorg horen onderdeel te zijn van het (continue) opleidingsproces zodat zorgverleners in staat worden gesteld vrouwen de zorg te geven die zij nodig hebben. De introductie van een screeningsprogramma voor HbP dragerschap zoals voorgesteld door de WHO ligt in het verlengde hiervan en zou daarom moeten worden overwogen.

Gebaseerd op dit proefschrift is een universeel aanbod van preconceptie en prenatale screening op HbPaan te bevelen, naast de NNS. Indien dit niet mogelijk is, bijvoorbeeld om economische redenen, dan is doelgerichte HbP dragerschapscreening op basis van etniciteit een mogelijkheid, zoals geïmplementeerd in Engeland. Wel moet dit worden ondersteund door een wetenschappelijk ontwikkeld instrument om etniciteit te bepalen.

De uitkomsten van de studies in dit proefschrift benadrukken de noodzaak om ethische en praktische barrières op te lossen en financiële onduidelijkheden op te lossen alvorens een screeningsprogramma te implementeren. Dit kan alleen met een duidelijke beleidsuitspraak van de overheid. Wanneer deze zaken zijn opgehelderd, kan de vraag bij de betreffende beroepsorganisaties worden neergelegd om het voorgestelde programma te implementeren.

DANKWOORD / ACKNOWLEDGEMENTS

In het boemeltje van Bilthoven naar Utrecht, daar is het begonnen: "Ga nou gewoon met haar praten; je kunt altijd kijken wat je doet en er altijd weer mee ophouden." Maar ik ben opgevoed met het idee dat waar je aanbegint dat maak je ook af. Daarom ligt er nu dit boekje. Een boekje dat er nooit was geweest zonder de aanmoediging en ondersteuning van velen die ik hierbij graag wil bedanken.

Allereerst wil ik mijn collega's bedanken (daarbij tel ik voor het gemak ook de huisartsen) die mij hun vertrouwen schonken en mij toe hebben gelaten in hun praktijk of deelgenomen hebben aan het onderzoek. Ook de deelnemers aan het witness seminar horen hierbij. Zonder jullie was het simpelweg niks geworden.

Prof. ALM Lagro-Janssen en Prof. MC Cornel. Lieve Toine als ik bij jou vandaan kwam had ik altijd vleugeltjes: je geloof in mij heeft me veel goed gedaan. Toen ik eenmaal bij je langs was geweest kon en wilde ik niet meer terug. Je was een geweldige coach. Dank voor het vertrouwen dat je me altijd hebt gegeven.

Beste Martina je leerde mij verder kijken dan de verloskunde. Je hebt een enorme kennis en wist mij vaak met een paar woorden de juiste richting op te sturen. Ik heb veel geleerd op de afdeling Community Genetics en had mijn tijd daar voor geen goud willen missen. Dank.

Veel dank ben ik uiteraard ook verschuldigd aan mijn co-promotoren Ank de Jonge en Lidewij Henneman. Ik geloof dat ik de promovendus ben met de twee meest energieke co-promotoren ooit… Ank, I am your first, daar ben ik trots op! Je hebt een enorme drive en eeuwig optimisme. Zonder jou had ik hier niet gestaan, echt.

Lidewij je scherpzinnige blik en onaflatende enthousiasme zijn geweldig en je zakelijke en nuchtere aanpak een verademing. Wat was (en ben) ik blij met je.

De leden van de promotiecommissie, prof. Kremer, prof. van der Horst en prof. Knoers wil ik hartelijk danken voor de tijd die zij hebben besteed aan het lezen en beoordelen van mijn proefschrift en voor de bereidheid plaats te nemen in de promotiecommissie, evenals de overige leden van de oppositie: Prof. Karl Atkin, Prof. Hub Zwart, Piero Giordano en Marianne Amelink-Verburgt.

Prof. Karl Atkin at the University of York: thank you for your hospitality and support in writing the sub-chapter of the introduction of the thesis and for opening my eyes to the interesting but complex subject of ethnicity and health.

Prof. Eddy Houwaart wil ik bedanken voor zijn uitstekende voorzitterschap tijdens het witness seminar.

Dank aan al mijn collega's: bij Community Genetics, de KNOV, de redactie van het Tijdschrift voor Verloskundigen en Midwifery Science.

Bij Community Genetics wil ik vooral Carla van El bedanken. Ook jij was een van mijn begeleiders. Er is geloof ik niemand zo precies en doortastend als jij; als enorme sloddervos heb ik veel van je geleerd. Dank voor je bijdragen, ondersteuning en je kennis.

Uiteraard ook mijn roomies: Tessel, google-fanaat, dank voor alle computersteun als ik weer es met mijn handen in mijn zeer "blonde" haar zat. En Sarah; is it a Z or an S? We had a good spelling exchange going! Maar ook de rest van mijn collega's op deze afdeling, dank voor de gezelligheid en de ongelofelijke hoeveelheid (altijd zelfgemaakte) taart.

De Mariannes en Wilma ben ik dank verschuldigd voor de secretariële ondersteuning en al het andere; Hans Bor (Radboud universiteit) en Piet Kostense (VUmc) voor het statistische advies en Elmie Peters voor de literatuur ondersteuning in hoofdstuk 3. Lilian van Tuyl dank voor het begeleiden van de verloskundige focusgroepen.

Anne Marie Plass dank voor de start van het tweede deel van het onderzoek in dit proefschrift en daarbij ook dank aan je zonen voor al het invoer- en plakwerk.

Dank aan alle mede-auteurs (zie lijst) voor alle waardevolle ondersteuning en toevoegingen aan de diverse hoofdstukken.

Mijn collega's bij de KNOV dank voor alle aanmoediging, collegialiteit en vriendschap. Mieke B: we hebben samen toch maar een mooie richtlijn neergezet! Ook ben ik veel dank verschuldigd aan mijn collega's bij het Tijdschrift voor Verloskundigen, Wil, Kristel en Relinde: Jullie hebben me de tijd gegeven om mijn proefschrift af te maken; dat heb ik enorm gewaardeerd. Wil van Veen; je geeft ons altijd alle ruimte, je bent je gewicht waard in goud!

Dank voor de fijne samenwerking aan mijn collega's in het organiserend comité van de Expertbijeenkomst gehouden op 10 juni 2011: Piero Giordano; Symone Detmar; Sylvia van der Pal en Marjolein Peters. Als ook Soroya Beecher en Elmas Citak van OSCAR voor hun bijdrage aan die dag.

Dank voor de ondersteuning van het organiseren van het symposium bij mijn promotie aan de leden van de Werkgroep Migranten en genetica, in het bijzonder Marja de Kinderen.

Steve: You eat, but you don't shoot, or you don't eat shoots (but just about everything else): make sure you never leave. Thank you for your friendship and for all the (language) editing that you did. I loved our discussions! It is great that you and Quirine both agreed to be my paranymphs: thank you both. Thanks also to Clifton & Alex for a last English-english language check en Aimee en Kristel voor het redigeren van de Nederlandse samenvatting.

Heel veel dank ook aan al mijn familie, vrienden (bonbonnes!) en dansers die het leven naast het schrijven van een proefschrift zoveel fijner maken: zonder jullie was het eerder af geweest, maar dan was het niet half zo leuk geweest.

Mama, mijn bewondering voor het feit dat je me altijd hebt laten gaan wordt met de jaren groter. Zonder dat had jouw eigenwijze dochter dit boekje nooit geschreven.

En als laatste Nico. Dank… voor alles.

Y ahora: que sigue la Milonga!
Suze

C.V.

Suze Jans was born in Nijmegen from parents with a mixed Limburg-Dutch and German ethnic origin. She travelled for a couple of years after completing her secondary education. In order to become a midwife she first trained as a Staff Nurse at Newham General Hospital in the East End of London (qualified in 1985). Before starting her midwifery training at King's College Hospital (KCH), she worked during six months at the Samaritan Hospital for Women in London. After obtaining her midwifery qualification in 1990 she continued working in London at KCH for one year.

In 1991 she returned to the Netherlands to follow her dream of attending homebirths and worked as a primary care or independent midwife in Amsterdam. She returned to London for one year to work as a team midwife at the Chelsea & Westminister Hospital from 1993-1994.

In 1994 the charity Medical Aid for Palestinians (MAP) asked her to complete the teaching course for Palestinian midwives in Southern Lebanon: During one year she taught Palestinian student midwives in el Hamshari Hospital in Sidon and Haifa Hospital in Bourj el-Barajneh refugee camp in Beirut, after which she chose to return to the Netherlands. After several locum contracts in different primary care midwifery practices, she settled in Amsterdam where she joined the midwifery practice in the Ruyschstraat.

In 2006 she completed her Master degree (midwifery / epidemiology) at the University of Amsterdam which subsequently led to a position as policy advisor to the Royal Dutch Organisation of Midwives (KNOV). Along side her policy work, she started her PhD in 2007 at the Radboud University in Nijmegen, first in her private time, but a year later, in November 2008, she was able to join the department of Community Genetics at the VU University Medical Center in Amsterdam as a researcher, where she worked on the CSG-project Neonatal screening and beyond.

In October 2010 she exchanged her policy position for a position as (scientific) editor at the Journal for Midwives. As of September 2012 she also works as senior researcher at the department of Midwifery Science at the VU University Medical Center in Amsterdam.

C.V.

Suze Jans is geboren in Nijmegen en is van Limburgs-Nederlandse en Duitse afkomst. Na het afronden van haar middelbare school, verbleef zij een paar jaar in het buitenland. Om verloskundige te kunnen worden, behaalde zijn in 1985 eerst haar verpleegkundige diploma in het New Ham General ziekenhuis in oost Londen. Na een half jaar op de afdeling gynaecologie van het Samaritan Hospital for Women ten westen van het centrum van Londen gewerkt te hebben, startte zij haar opleiding tot verloskundige in King's College Hospital in Londen, welke zij in 1990 met succes afrondde. Na het behalen van haar diploma werkte zij nog een jaar als verloskundige in het zelfde academische ziekenhuis.

In 1991 keerde zij terug naar Nederland om invulling te geven aan haar droom om thuis bevallingen te begeleiden en was zij werkzaam als eerstelijns verloskundige in Amsterdam. Van 1993-1994 keerde zij terug naar Londen om in het Chelsea & Westminister Hospital te werken als team midwife.

In 1994 vroeg de organisatie Medical Aid for Palestinians (MAP) haar de opleiding verloskunde voor Palestijnse studenten verloskunde in het zuiden van Libanon af te ronden: Gedurende een jaar gaf zij les in el Hamshari ziekenhuis in Sidon en Haifa ziekenhuis in Bourj el-Barajneh vluchtelingenkamp in Beirut. Hierna keerde zij terug naar Nederland. Na een aantal waarneemcontracten bij verschillende praktijken startte zij in 1999 in de verloskundige praktijk aan de Ruyschstraat in Amsterdam waar ze toe trad tot de maatschap.

In 2006 behaalde ze haar Master diploma (verloskunde / epidemiologie) aan de Universiteit van Amsterdam. De opleiding werd opgevolgd met een baan als beleidsmedewerker bij de beroepsorganisatie voor verloskundigen (KNOV). Naast haar baan als beleidsmedewerker, startte zij in 2007 haar promotie-traject aan de Radboud Universiteit, in eerste instantie in haar eigen tijd. In november 2008 kon zij haar promotie traject vervolgen met het CSG-project Neonatal screening and beyond bij de afdeling Community Genetics van het VU Medisch Centrum in Amsterdam.

In oktober 2010 ruilde zij haar beleidsbaan bij de KNOV om voor een part-time baan als (wetenschaps-) redacteur bij het Tijdschrift voor Verloskundigen. Vanaf september 2012 is zij eveneens werkzaam als senior onderzoeker bij de afdeling Midwifery Science van het VU Medisch Centrum in Amsterdam.

LIST OF CO-AUTHORS & AFFILIATIONS

- Prof. dr. Martina Cornel, MD, PhD
  Clinical Genetics, section Community Genetics
  EMGO Institute for Health and Care Research
  VU University Medical Center, Amsterdam
- Darie Daemers, RM
  Academie Verloskunde Maastricht
- Dr. Carla van El, PhD
  Clinical Genetics, section Community Genetics
  EMGO Institute for Health and Care Research
  VU University Medical Center, Amsterdam
- Dr. Lidewij Henneman, PhD
  Clinical Genetics, section Community Genetics & Public and Occupational Health
  EMGO Institute for Health and Care Research
  VU University Medical Center, Amsterdam
- Prof. dr. Eddy Houwaart, MD, PhD
  Department of Medical Humanities
  EMGO Institute for Health and Care Research
  VU University Medical Center, Amsterdam
- Dr. Rien Janssens, PhD
  Department of Medical Humanities
  EMGO Institute for Health and Care Research
  VU University Medical Center, Amsterdam
- Dr. Ank de Jonge, RM, PhD
  Midwifery Science
  EMGO Institute for Health and Care Research
  VU University Medical Center, Amsterdam
- Prof. Dr. Toine Lagro-Janssen, MD, PhD
  Department Primary Care and Community Care
  Women Studies Medicine, Radboud University Medical Center
  Nijmegen
- Dr. Anne-marie Plass, PhD
  NIVEL, Utrecht
- Dr.ir. Lilian van Tuyl, PhD
  Department of Rheumatology
  VU University Medical Center, Amsterdam
- Dr. Rien de Vos, PhD
  Faculty of Health, Hoge School van Amsterdam, Amsterdam & Academic Medical Center, Amsterdam
- Dr. Marian Westerman, PhD
  Departement of Methodology and Applied Biostatistics
  Faculty of Earth and Life Sciences, VU University, Amsterdam

LIST OF PUBLICATIONS & PRESENTATIONS

Publications

- Jans S. Een afwijkend Hb. TvV april 2006; 43-44.
- Verstappen WHJM; Jans SMPJ; van Egmond N; van Laere A, Schippers-van Mourik MM; Labots-Vogelesang SM; van Luin MJ; Oldenziel JH. LESA Anemie tijdens zwangerschap en kraamperiode; Huisarts wet 2007:50(7): S17-S20.
- Verstappen W, Jans S; van Egmond N; van Laere A, Schippers-van Mourik MM; Labots-Vogelesang SM; van Luin MJ; Oldenziel JH. LESA Anemie in zwangerschap en kraambed; TvV; 2007; 14-18.
- de Jonge A; Jans S; Buitendijk S. Het 'niet-pluisgevoel' in de kraamperiode. TvV okt. 2007; 17-21.
- Jans S, Merkus HMWM; Curven voor geboortegewicht, nieuwe Nederlandse referentie. TvV, jan 2008; 8-9.
- Jans SMPJ; Hammelburg R; van Balen JAM; de Boone MM; Klomp GMT; Lubbers WJ; Oldenziel JH; Somford RG; Wijnsma MK; Flikweert S; LESA Onderzoek van de pasgeborene; Huisarts Wet 2008:51(13) S15-S19.
- Wiersma T; Offerhaus P; Jans S; Schagen van Leeuwen J. Baten van extra vitamine D voor zwangeren en zogenden nog steeds onduidelijk. Huisarts en Wetenschap; 2009; 8:408-409.
- Jans SM, Daemers DO, de Vos R, Lagro-Jansen AL. Are pregnant women of non-Northern European descent more anaemic than women of Northern European descent? A study into the prevalence of anaemia in pregnant women in Amsterdam. Midwifery. 2009 Dec;25(6):766-73.
- Jans SMPJ, de Jonge A, Lagro-Janssen ALM. Maternal and perinatal outcomes amongst hameoglobinopathy carriers: a systematic review. Int J Clin Pract, November 2010, 64, 12, 1688-1698.
- S.Jans, M.Beentjes. Anemie in de verloskundige praktijk. KNOV standaard. dec. 2010.
- Jans SMPJ, van El CG, Houwaart ES, Westerman MJ, Janssens RJPA, Lagro-Janssen ALM, Plass AMC, Cornel MC. A case study of haemoglobinopathy screening in the Netherlands: witnessing the past, lessons for the future. Ethnicity & Health. 2011. aug. 8. [Epublication ahead of print].
- Beentjes M, Jans S. Herziene beroepsstandaard 'Anemie in de verloskundige praktijk'. Ned Tijdschr Geneeskd. 2012;156:A3711
- Jans SM, de Jonge A, Henneman L, Cornel MC, Lagro-Janssen AL.
- Attitudes of general practitioners and midwives towards ethnicity-based haemoglobinopathy-carrier screening. Eur J Hum Genet. 2012 May 2. [Epub ahead of print]

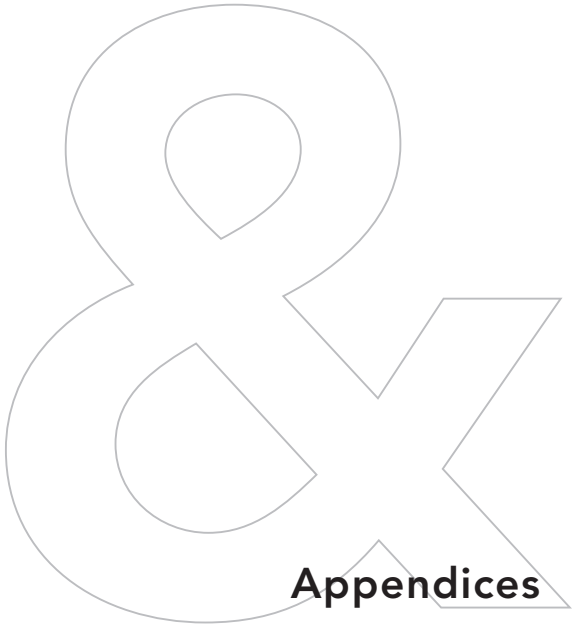
Presentations

- Are pregnant women of non-Northern European descent more anaemic than women of Northern European descent? A study into the prevalence of anaemia in pregnant women in Amsterdam.
  Symposium Verloskunde & Wetenschap, AMC, Amsterdam, 2006
- Dragerschap sikkelcelziekte (workshop)
  RIVM; Landelijke bijeenkomst pre- en postnatale screening, 2007
- Workshop Onderzoek van de Pasgeborene
  NHG congres, de Doelen, Rotterdam, 2008
- Verkenning rondom het beperkte aanbod van hemoglobinopathie-screening in Nederland.
- Nationaal Congres PCZ, 2009
- Witnessing the past, lessons for the future.Conference: Sickle cell the next 100 years, Leicester april 2010.
- Maternal and perinatal outcomes of haemoglobinopathy carriers.Normal Birth Conference. Vancouver. July 2010.
- Witnessing the past, Lessons for the future.
- First European Preconception Congress. Brussels. October 2010.
- Attitudes of midwives and general practitioners towards ethnicity based haemoglobinopathy screening: exploring current behaviour and future intentions.
- First European Preconception Congress. Brussels. October 2010.
- Attitudes of midwives and general practitioners towards ethnicity based haemoglobinopathy screening: exploring current behaviour and future intentions.
- Landelijk symposium NACCG. November 2010. Utrecht.
- Attitudes of midwives and general practitioners towards ethnicity based haemoglobinopathy screening: exploring current behaviour and future intentions. Triennial congres of the International Confederation of Midwives (ICM). Durban june 2011.

Poster presentations

- Jans SM, Daemers DO, de Vos R, Lagro-Jansen AL.
  Hebben zwangeren vrouwen van niet-Noord Eurpese afkomst een grotere kans op het ontwikkelen van anemie dan zwangeren van Noord Eurpoese afkomst?
- Kennispoortconferentie Verloskunde, Amersfoort, 2007.
- Jans SM,van El C, Houwaart E, LagroJanssen ALM, PLass AMC, Cornel MC.
  Witnessing the past, lessons for the future.
- CSG conference Ten years after, mapping the societal landscape of genomics, Amsterdam, May 2010.
- Jans SM,van El C, Houwaart E, Lagro-Janssen AM, Plass AMC, Cornel MC.
  Witnessing the past Lessons for the future.

- European Meeting of psycho-social aspects of genetics, EMPAG, Gothenburg, June 2010.
- Jans SM, van El C, Houwaart E, Lagro-Janssen AM, Plass AMC, Cornel MC. Witnessing the past, Lessons for the future.
- First European Preconception Congress, Brussels, October 2010.
- Jans SM, van El C, Houwaart E, Lagro-Janssen AM, Plass AMC, Cornel MC. Witnessing the past, Lessons for the future.
- Triennial congres of the International Confederation of Midwives (ICM), Durban, june 2011.
- Jans SM, de Jonge A, Henneman L, Cornel MC, Lagro-Janssen AM.
- Hemoglobinopathie dragerschapscreening op basis van etniciteit: Attitudes en ervaren barrières bij verloskundigen en huisartsen.
- Kennispoort conferentie Verloskunde, Utrecht, 2012.
- Jans SM, Henneman L, de Jonge A, van El CG, van Tuyl LH, Cornel MC, Lagro-Janssen AM.
- "A morass of considerations": Exploring attitudes towards primary care ethnicity-based haemoglobinopathy screening.
- European Meeting of psycho-social aspects of genetics, EMPAG, Nurnberg, June 2012.



Appendices

APPENDIX 1: KNOV GUIDELINE SUMMARY

Anemie in de verloskundige praktijk

praktijkkaart behorend bij de gelijknamige KNOV-standaard 2010

Tijdens de zwangerschap wordt het Hb gecontroleerd op de volgende momenten:

- Tijdens de eerste controle
- Rond 20 weken: indien risicogroep voor anemie
- Rond 30 weken: alle zwangeren
- 3-6 wk na start behandeling (vervolgcontrole)

Hb-referentiewaarden (p5-waarden) in mmol/l

Preconceptioneel	7,5
Zwangerschap (in wk Am))	
tot en met 13	7,1
14 tot en met 17	6,8
18 tot en met 21	6,5
22 tot en met 37	6,3
vanaf 38	6,5
Postpartum (in wk)	
1-5	6,5
6	7,2

Risicogroepen met verhoogde kans op anemie in de zwangerschap (20 wk controle)

- Zwangere tieners
- Zwangere vrouwen van niet-Noord-Europese afkomst
- Vrouwen die binnen een jaar na de geboorte van een vorig kind zwanger zijn
- Zwangeren met slechte voedingsgewoonten
- Zwangere vrouwen die bekend zijn met dragerschap van hemoglobinopathie
- Vrouwen met een meerlingzwangerschap

Schema A. Eerste controle hemoglobinebepaling (referentiewaarde tot 14 wk) — A

Hemoglobinegehalte in mmol/l	actie
≥ 7,1 (p5)	• vervolgcontrole bij 20 weken bij risicogroepen • vervolgcontrole bij 30 weken bij alle zwangeren (inclusief risicogroepen) ga door naar schema B
< 7,1 (p5) maar ≥ 5,6	MCV-bepaling — ga door naar schema C Niet-Noord-Europese afkomst: HbP-bepaling
< 5,6	Verwijzing huisarts voor nadere diagnostiek

Schema B. Vervolgcontrole hemoglobinebepaling bij 20 of 30 weken — B

zwangerschapsduur	hemoglobinegehalte in mmol/l	actie
20 weken	≥ 6,5 (p5)	vervolgcontrole Hb bij 30 weken
30 weken	≥ 6,3 (p5)	geen verdere vervolgcontrole meer nodig
20 weken	< 6,5 (p5)	MCV- bepaling — ga door naar schema C
30 weken	< 6,3 (p5)	MCV- bepaling — ga door naar schema C
Gehele zwangerschap	< 5,6	Verwijzing huisarts voor nadere diagnostiek

Schema C. Aanvullende diagnostiek d.m.v. MCV-bepaling bij een laag Hb — C

MCV-gehalte (in fL)	actie
80-100	Geen verdere vervolgcontrole Hb meer nodig (hemodilutie)
70-80	IJzergebreksanemie: schrijf ijzermedicatie voor — ga door naar schema D
< 70	Verwijzing huisarts voor nadere diagnostiek, cave HbP
≥ 100	Verwijzing huisarts voor nadere diagnostiek, cave Vit B12/foliumzuurdeficiëntie

Schema D. Vervolgcontrole na 3-6 weken ijzersuppletie

D

vergelijking met vorige Hb-bepaling	actie
Hb gestegen en ≥ p5	6 weken onderhoudsdosering: 1 tablet ferrofumaraat 200 mg, om de dag
Hb gestegen maar nog < p5	Controleren therapietrouw Voortzetting ijzermedicatie Opnieuw Hb-controle na 3-6 weken
Hb gezakt of gelijkgebleven	Bij adequate inname: verwijzing huisarts voor nadere diagnostiek

Schema E. Preconceptiezorg

E

- Bepaal het Hb bij vrouwen die één of meer risicofactoren voor anemie hebben.
- Veronderstel een ijzergebreksanemie bij een te laag Hb (< 7,5 mmol/l)
  Schrijf 1 tablet ferrofumaraat 200 mg per dag voor, voor een periode van 6 weken
- Verwijs in alle gevallen de vrouw met anemie naar de huisarts
- Bespreek de mogelijkheid van dragerschapsdiagnostiek naar HbP met vrouwen van niet-Noord-Europese afkomst

Schema F. Hemoglobinecontrole tijdens de postpartumperiode

F

Indicatie Hb-controle	Hb	Actie
Einde kraambed; bij fluxus zonder ingezette behandeling	< 6,5 mmol/l	Start ijzermedicatie en controle na 6 weken
Controle ingezette behandeling, **3-6 weken na start ijzerbehandeling** in zwangerschap of kraambed	< p5	Verwijzing huisarts
	≥ p5	Onderhoudsdosering 6 weken
Bij de nacontrole **6 weken post partum** wanneer de vrouw:	< 7,2 mmol/l, maar gestegen	Continueren behandeling en na 3-6 weken een Hb-controle bij de huisarts.
- op dat moment nog (een onderhoudsdosis) ijzertherapie heeft; - postpartum is behandeld in verband met een fluxus	< 7,2 mmol/l, niet gestegen	Indien therapietrouw adequaat: Verwijzing huisarts voor verdere diagnostiek
	≥ 7,2 mmol/l	Stoppen behandeling

Verwijzing voor verdere diagnostiek naar de huisarts

- Bij een Hb van < 5,6 mmol/l
- Bij een MCV van < 70 fL of een MCV ≥ 100 fL
- Indien iemand niet reageert op ijzertherapie
- Onderzoek naar (dragerschap van) hemoglobinopathieën

Medicatie

- 1 tablet ferrofumaraat 200 mg (1 x 65 mg elementair ijzer)
- Inname vóór de maaltijd
- Bij gastro-intestinale klachten: inname ná de maaltijd of dosering verminderen

Hemoglobinopathie (dragerschap)

Bepaal bij zwangeren die bekend zijn als drager van HbP en een laag Hb/MCV hebben, eerst een serumferritine alvorens te behandelen met ijzermedicatie.
Zwangeren die bekend zijn met dragerschap van HbP worden gesuppleerd met foliumzuur 0,5 mg/dag.

APPENDIX 2: QUANTATIVE SURVEY

Uw mening over advisering over dragerschaptest erfelijke bloedarmoede

Er ontstaan steeds meer initiatieven om verschillende etnische bevolkingsgroepen voor te lichten over erfelijke bloedarmoede (hemoglobinopathieën (HbPs)), zoals sikkelcelziekte en thalassemie en de mogelijkheid om zich op dragerschap hiervan te laten testen. Sinds 2007 wordt op landelijk niveau via de hielprik gescreend op sikkelcelziekte. Ook dragers van deze ziekte worden daarbij opgespoord. Onbekend is wat u als eerstelijns hulpverlener vindt van het testen op dragerschap van hemoglobinopathie op basis van etniciteit.
Wij vragen u daarom onderstaande vragen te beantwoorden **ongeacht of u cliënten uit de risicogroep in uw praktijk heeft en ongeacht of u deze dragerschaptest aanbied**. Dit kost u niet meer dan vijf minuten, maar levert belangrijke en onmisbare informatie op. Uw antwoorden worden strikt vertrouwelijk en anoniem verwerkt.

Alvast hartelijk dank voor uw medewerking!

---

1. Wat vindt u ervan om uw cliënten uitsluitend op basis van etniciteit een test op dragerschap van erfelijke bloedarmoede (HbP) aan te bieden (zonder dat er sprake is van een positieve (familie) anamnese en/of anemie verschijnselen)?

Graag per item op een schaal van 1-7 uw mening weergeven (omcirkelen); svp <u>ALLE</u> items scoren.

• **goed**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**slecht**
• **belangrijk**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**onzin**
• **bezwaarlijk**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**gemakkelijk**
• **wenselijk**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**onwenselijk**
• **schadelijk**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**bevorderlijk**
• **discriminerend**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**een voorrecht**

2. Biedt u cliënten ***zonder*** positieve (familie) anamnese en/ of anemie verschijnselen aan om zich te laten testen op dragerschap van erfelijke bloedarmoede (HbP), uitsluitend op basis van etniciteit?

nooit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**altijd**

3. Bent u van plan om in de toekomst uw cliënten een test op HbP dragerschap aan te bieden ***uitsluitend*** op basis van etniciteit (dus zonder dat er sprake is van familiegeschiedenis of anemie)?

zeker niet	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**zeker wel**

4. Denkt u dat uw collega's vinden dat aan cliënten ***uitsluitend op basis van etniciteit*** een test naar dragerschap van erfelijke bloedarmoede (HbP) moet worden aangeboden?

zeker niet	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**zeker wel**

5. Kunt u op dit moment *daadwerkelijk* elke cliënt een test op HbP-dragerschap aanbieden uitsluitend op basis van etniciteit als u dat zou willen?

zeker niet	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**zeker wel**

Kunt u uw antwoord kort toelichten:
……..

6. Biedt u cliënten met een onbegrepen anemie, maar zonder positieve familieanamnese, aan om zich te laten testen op HbP dragerschap?

nooit **1** **2** **3** **4** **5** **6** **7** **altijd**

7. Vindt u dat standaard aanbieden van een HbP dragerschaptest uitsluitend op basis van etniciteit landelijk beleid moet worden?

ja **nee**

8. Bent u van plan om uw cliënten een test op HbP dragerschap aan te bieden ***uitsluitend*** op basis van etniciteit (dus zonder dat er sprake is van familiegeschiedenis of anemie) indien dit landelijk beleid wordt?

zeker niet **1** **2** **3** **4** **5** **6** **7** **zeker wel**

9. Wat vindt u van het registreren van de etniciteit van uw cliënten?

Graag per item op een schaal van 1-7 uw mening weergeven, graag <u>ALLE</u> items scoren

- **goed** **1** **2** **3** **4** **5** **6** **7** **fout**
- **schadelijk** **1** **2** **3** **4** **5** **6** **7** **bevorderlijk**
- **zinvol** **1** **2** **3** **4** **5** **6** **7** **onzin**
- **lastig** **1** **2** **3** **4** **5** **6** **7** **handig**
- **discriminerend** **1** **2** **3** **4** **5** **6** **7** **onschuldig**
- **bezwaarlijk** **1** **2** **3** **4** **5** **6** **7** **wenselijk**

Tenslotte volgen hier nog een paar algemene vragen:

- Kunt u een schatting maken van het percentage cliënten die u jaarlijks ziet en die afkomstig zijn uit etnische minderheidsgroepen?
  Ongeveer ☐ **%**

- Heeft u de afgelopen twee jaar bijscholing gevolgd op het gebied van erfelijke bloedarmoede (HbP) (kruis het juiste hokje aan)?
  ☐ **Ja** ☐ **Nee**

- Hoe lang bent u werkzaam als verloskundige ? (of als huisarts)
  ☐ **Jaar**

- Mijn praktijk bevindt zich (kruis het juiste hokje aan)

  ☐ **In een stad in de Randstad** ☐ **In een dorp in de Randstad**
  ☐ **In een stad buiten de Randstad** ☐ **In een dorp buiten de Randstad**

Heeft u verdere opmerkingen over dit onderwerp en/ of de vragenlijst? Graag hier vermelden.

Hartelijk dank voor uw medewerking!

U kunt de vragenlijst versturen in de bijgevoegde antwoordenveloppe.
(een postzegel is niet nodig)

APPENDIX 3: QUESTION ROUTE

Focusgroep discussie

Algemeen welkom (15 min):
Welkom allemaal op deze focusgroep bijeenkomst over het screenen op hemoglobinopathie in de eerstelijn. Heel fijn dat jullie tijd hebben willen vrij maken om mee te doen aan dit onderzoek.
*Korte introductie van jezelf (discussieleider & secondant)
Graag wil ik jullie allereerst vragen om jullie mobiele telefoons uit te zetten.
Jullie hebben vorig jaar allemaal de vragenlijst over dit onderwerp ingevuld. Naar aanleiding hiervan willen wij graag dieper ingaan op het onderwerp. Het gaat dus om jullie mening over het screenen op hemoglobinopathie op basis van etniciteit.

> OZ vraag:
> Wat zijn de gedachten en ideeën van eerstelijns hulpverleners met betrekking tot preconceptie en prenatale screening van hemoglobinopathieën gebaseerd op etniciteit?
> Wat zijn de mogelijkheden en wat zijn de knelpunten?

Start van discussie

Eerste helft 45 min.

1) Introductie deelnemers dmv kennismakingsrondje (kort!):
   Wat is je naam en in wat voor een gebied ben je werkzaam (stad / platteland)
   Wordt er in jouw praktijk getest op hemoglobinopathie?
   Wie test je wel en wie test je niet?

2) Registratie etniciteit
   Als we het hebben over het aanbieden van screenen is dan iedereen gelijk?
   Met andere woorden zijn er groepen die wel of geen screening aan wordt geboden?
   Je kunt bijvoorbeeld ook screening aanbieden aan bepaalde groepen op basis van vooraf gestelde criteria.
   Screenen op basis van etniciteit is bijvoorbeeld een mogelijkheid.

   Wat is het eerste dat bij je opkomt als de term "screenen op basis van etniciteit" hoort?
   Wat vinden jullie van het registreren van etniciteit (algemeen)?
      Voordelen
      Nadelen
      Is dit überhaupt wel nodig (het registreren)? (je zou bijv. wel op basis van etniciteit kunnen screenen maar de etniciteit hoef je bijvoorbeeld niet te registreren)

Gebruiken jullie etniciteit op andere momenten in de zorgverlening?

Bijvoorbeeld bij het inschatten van risico, denk aan bijv. diabetes, hoge bloeddruk etc.

Stel dat screening op HbP zou worden geïntroduceerd in Nederland, zou etniciteit hier dan een rol in moeten spelen?

Hoe bepaal je iemands etniciteit?

Wie bepaalt tot welke etnische groep iemand behoort?

In hoeverre verwachten jullie knelpunten bij het registreren van etniciteit?

Wat hebben jullie nodig om te kunnen screenen op basis van etniciteit?

Hoe zouden jullie omgaan met iemand met een gemengde etniciteit?

Hoe zouden patiënten/cliënten dit ervaren naar jullie mening?

Zou universele screening beter/handiger zijn?

PAUZE (15 min)

Tweede helft : 45 min.

3) Neonatale screening (hielprikscreening) > **kort!**

Is met name om even te laten "mopperen" en als bruggetje naar volgende stap in discussie.

Jullie zijn al bekend met het screenen op bepaalde erfelijke ziektes tijdens de neonatale periode, nl het hielprikprogramma dat in 2007 is uitgebreid.

Wat vinden jullie van deze screening, wat zijn jullie gedachten hierover?

Heeft implementatie aan behoefte voldaan? > *NB hier opletten dat de discussie niet verzandt in klagen over hielprikprogramma, eventueel een kort rondje om gal te spuien.*

Wat vinden jullie van de nevenbevinding, nl dat dragerschap van HbP wordt gerapporteerd?

In hoeverre zijn er knelpunten?

4) Preconceptionele & prenatale screening

NB Voor het preconceptioneel screenen op HbP is geen vergunning vereist

Screening op HbP kan ook uitgebreider worden aangeboden: We willen het nu gaan hebben over het screenen niet alleen na de geboorte maar ook hiervoor, nl tijdens de preconceptie periode en in de zwangerschap.

Wat zouden jullie er van vinden indien ook preconceptioneel en prenataal op HbP wordt gescreend?

Wat zijn jullie gedachten hierover?
Wat zou er voor zorgen dat jullie screening op HbP zouden gaan uitvoeren in de toekomst?

Stel dat we in Nederland uitgebreide screening zouden gaan invoeren, hoe zouden we dat dan het beste kunnen doen ?
Wat zouden jullie nodig hebben voor de implementatie hiervan?
Wat zijn de kansen / positieve kanten van dergelijke screening?
In hoeverre verwachten jullie knelpunten hierbij?

Bijvoorbeeld in Engeland is in 2004 een uitgebreid screeningsprogramma geïntroduceerd. Hierbij wordt preconptioneel, prenataal en postnataal screening op HbP aangeboden. In de hoogrisico gebieden, dus daar waar een hoge prevalentie van (dragerscha) op HbP is, wordt iedereen gescreend. In de gebieden waar de prevalentie van (dragerschap van) HbP laag is, wordt op basis van een vragenlijst de etnische afkomst bepaald en op basis daarvan wordt al dan niet gescreend.
(familie oorsprong vragenlijst uitdelen > is vertaalde versie van die in Engeland

Wat vinden jullie van een dergelijk overheidsprogramma?
Zou een dergelijk instrument ondersteunend zijn?
Verwachten jullie knelpunten hierbij? Zo ja, welke?

5 Als er uigebreide screening wordt aangeboden dan is er blijkbaar toch nog een groep hulpverleners die niet van plan is screening op basis van etniciteit uit te voeren (dit kwam uit de vragenlijst) indien dit landelijk beleid zou worden.
Wat vinden jullie hiervan > hoe kan dit ?
Wat zou de mogelijke uitleg kunnen zijn van deze bevinding?
Wat verstaan jullie onder een landelijke beleid? (bv waar komt dit vandaan?)
Maakt het uit waar de richtlijn / landelijk beleid vandaan komt > beroepsvereniging / overheid?

Afsluiting

Wij wilden graag jullie mening horen over de eventuele knelpunten bij het invoeren van een screeningsprogramma op hemoglobinopathie. Dat hebben we geprobeerd boven water te krijgen met de vragen die we gesteld hebben.

- Is er nog iets dat we vergeten zijn te vragen?
- Had een van jullie nog iets willen zeggen waarvoor je eerder niet de kans hebt gekregen?

Heel hartelijk dank voor jullie komst. Mochten jullie achteraf nog vragen hebben dan kunnen jullie contact opnemen met Suze Jans s.jans@vumc.nl

Verloskundige kunnen uren schrijven voor het kwaliteitsregister van de KNOV. Dit valt onder “vrije ruimte” Jullie ontvangen van Suze Jans een mailtje ter bevestiging van deelname.

- Graag op de lijst je emailadres nakijken> dit geldt dus alleen voor de verloskundigen
- Graag aftikken op lijst of deelnemer aanwezig was

Ook worden er declaratieformulieren uitgedeeld. Deze kunnen worden ingevuld en opgestuurd in bijbehorende enveloppe.

APPENDIX 4A: SAMPLE OF LABORATORY RESULTS A

Rapport Hemoglobinopathieën Onderzoek

Aanvraagdatum: Datum uitslag:

Onderzoeksnr.: Onze ref.:
Uw referentie:

Naam :
Geboortedatum: BSN: onbekend
Materiaal :
Webinfo :
Vraagstelling: Anemie/hemolyse e.c.i.

Test : Hematologische parameters (Micros 60)
Resultaat : Microcytair hypochroom
Test : Hb scheiding d.m.v. Capillaire Electroforese en HPLC
Resultaat : HbA2% verlaagd, indicatief voor alfa of delta thalassemie
Test : Deletie PCR voor alfa-thalassemie: -alfa3.7(Rightward),-alfa4.2(Leftward),--SEA --Med1, -(alfa)20.5,--THAI en --FIL.
Resultaat : Homozygoot voor deletie: -alfa3.7 (Rightward)

Conclusie
Er werd een homozygote -alfa3.7 (Rightward) deletie aangetoond, de patiënt heeft hierdoor alfa-thalassemie trait (type:-,alfa/-,alfa).

(Klin. mol. biochem. geneticus)

Deze brief is elektronisch geautoriseerd en derhalve niet ondertekend.

CC.

APPENDIX 4B: SAMPLE OF LABORATORY RESULTS B

Pat.naam :
Geb.datum :
Adres :
Plaats :
Pat.nummer:
Ext.pnr :

Klinisch Chemici:

&

DAGRAPPORT

DATUM	TIJD	BEPALING	RESULTAAT		EENHEID	REF.WAARDEN
			HEMATOLOGIE ALGEMEEN			
		Hemoglobine	8.4	#	mmol/l	6.5 - 10.0
		MCV	76	#	fl	75 - 95
			HEMATOLOGIE DIVERSEN			
		Hb-onderzoek	:	#		
		Hb type	AC	#		
		Hb-A	58	#	%	
		Hb-A2	3.0	#	%	1.9 - 3.2
		Hb-F	<1.0	#	%	0.1 - 1.5
		Hb-C	39	#	%	
		opmerking:	TKST	#		

opmerking:
In de erytrocyten van de patient zijn zowel hemoglobine-A als hemoglobine-C aanwezig, hetgeen op de heterozygote hemoglobinopathie HbAC wijst.
Gezien het percentage hemoglobine-C is er geen aanwijzing voor alfa of beta-thalassemie.
Het HbA2 en HbF gehalte is normaal.
Het MCV is normaal/licht verlaagd.

Algemene opmerking:
Ouders die beiden drager zijn van een hemoglobinopathie lopen een groot risico op ernstige vormen van hemoglobinopathie in het nageslacht.
Daarom is het geindiceerd om alle relevante bloedverwanten met dit risico, op de hoogte te brengen van deze afwijking en op dragerschap voor hemoglobineafwijkingen te laten controleren.
Voor dragers met een kinderwens is het geindiceerd om ook de partner te laten controleren.