Incidental Findings of Sex Chromosome Aneuploidies in Routine Prenatal Diagnostic Procedures

A qualitative study on the perspectives of parents and professionals

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Incidental Findings of Sex Chromosome Aneuploidies in Routine Prenatal Diagnostic Procedures

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Parents-to-be are generally eager to know more about their fetus. There may be various reasons for early prenatal assessment by ultrasound, for instance: viability judgment, sex determination, or possible increased risk of a genetic anomaly. However, a salient issue regarding early fetal assessment is the potential risk of discovering incidental findings that may have important medical or social implications unrelated to the reason for testing.

Incidental findings come unforeseen to the parents; nevertheless, they may sometimes be a benefit. An early finding of a fetal anomaly, whether intended or incidental, allows parents and medical professionals to perform additional tests and take appropriate measures. Sex chromosomal aneuploidies (SCAs) may be diagnosed as incidental findings in prenatal diagnostic testing procedures. These SCAs cause syndromes little known to most parents, and their postnatal phenotypes are variable. Some individuals may suffer from health, fertility, or behavioral disturbances; others may go through life without ever knowing they have a chromosomal abnormality. However, these incidental findings of fetal SCA may give rise to difficult dilemmas in decision-making about whether or not to continue the pregnancy.

The studies in this thesis analyze and discuss the different aspects of parental attitudes and dilemmas, as well as professional opinions about the benefit or disadvantage of an incidental finding of a fetal SCA.

1.1 CHARACTERISTICS OF SEX CHROMOSOMAL DISORDERS

Phenotypic spectrum

Sex chromosomal aneuploidies (SCAs) encompass both full-blown and mosaic numerical aberrations, which may influence the individual's phenotype to a greater or lesser extent. Sex chromosomal aneuploidies give rise to syndromes that interfere with normal male or female sexual development, preventing the testicles or ovaries from functioning normally and reducing the levels of testosterone and estrogen[1-5], even though it is known that SCA individuals may go through life without knowing they have a genetic anomaly.[6-8] A multidisciplinary approach to the screening and treatment of the domains of risk is strongly recommended.[1,2,3]

45,X, Turner syndrome

In 1938 American endocrinologist Dr Henry Turner first described the main characteristics of the syndrome. These included small stature, lack of sexual development and webbed neck.[9] In 1959 the genetic background was demonstrated as 45,X. Several health risks that occur during childhood, puberty, or adult life threaten general health and life expectancy. Approximately 3% of the expected conditions are diagnosed prenatally; approximately 20% at birth because of lymphedema with or without a congenital heart defect; 43% in the pediatric population because of otologic problems and small stature; approximately 30% in adolescence because of pubertal delay or small stature; and 3% after the age of 18 years because of secondary amenorrhea or infertility.[10,11]

Early otologic disease with adult deafness[12,13] is a major problem. Growth disturbance with small stature, osteoporosis,[14,15] cardiovascular, aortic,[16,17] auto-immune[18] and metabolic disease[1,19] may occur. Some mosaic 45,X girls may exhibit a relatively normal growth and may spontaneously enter puberty. There is an increased cancer risk.[20] Psychosocial problems may vary from low self-esteem or slight autistic traits to important psychiatric disease such as psychosis and schizophrenia.[2,21] All full-blown 45,X women are infertile; those with mosaic 45,X have a serious risk of premature ovarian insufficiency.[22] Assisted reproduction techniques (ART) with oocyte donation enable procreation.

47,XXY, Klinefelter syndrome

Klinefelter syndrome was first described by Harry F. Klinefelter in 1942 as a clinical entity characterized by gynecomastia, small testes, absent spermatogenesis and increased levels of FSH.[23] The general health of 47,XXY individuals may be normal, but the existing hypergonadotropic hypogonadism and the clinical effects of androgen insufficiency often affect it to a greater or lesser extent.[24] While many 47,XXY individuals remain undiagnosed, it is estimated that approximately 10% of the diagnoses are made prenatally, approximately 10% in the pediatric population, and approximately 20% in the adult

population. Metabolic and auto-immune disease[25-27] and low bone mineral density[28] may be diagnosed in some men with 47,XXY. Thus, two-thirds remains undiagnosed.[7,8,29] The syndrome may seriously affect social interactions, due to mild cognitive and socialization impairment, learning disorders, delayed language development, and/or certain behavioral disorders.[7,30-33] Most 47,XXY individuals are infertile due to degeneration of the seminiferous tubules and sclerosis.[34] For some 47,XXY men, the diagnosis of the syndrome occurs when their infertility is ascertained. In some cases, ART may enable procreation with testis sperm extraction and intracytoplasmic sperm injection (ICSI) techniques.[4,24,35]

47,XXX, Triple X syndrome

Triple X syndrome was first described in 1959 in a 35-year-old woman with normal intellectual abilities who presented with secondary amenorrhea at 19 years of age.[36] Approximately 10% of the cases are ascertained clinically. There is considerable variation in the phenotype, with some individuals being very mildly affected and others displaying more significant physical and psychological features. They may be taller and have longer legs than average. There are reports of increased prevalence of thoracic kyphosis, a short neck and scoliosis, developmental delay, hypotonia, learning disabilities, and emotional or behavioral difficulties. Delayed language development, low self-esteem, motor coordination problems, and certain behavioral difficulties may occur. Psychotic disorders are rarely described. There is a certain elevated risk of premature ovarian insufficiency.[5,37,38] Preventive management for developmental and educational delay is recommended.

Other X–Y aneuploidies ("47,XXY variants" or "X polysomy women")

The negative effects on physical and mental development increase with the number of extra Xs, and each X reduces the overall IQ by 15 to 16 points. Men with extra Ys have a higher overall adaptive scale in daily living skills, socialization, and communication.[5] Women with supernumerary Xs have an increased risk of mortality because of cardiovascular and respiratory disease and cancer.[39]

The incidences of specific features such as decreased height, hypertelorism, clinodactily, pes planus, dental problems, and medical conditions such as asthma, deep vein thrombosis, and type 2 diabetes appear to be greater than the corresponding incidences in the general population.[40] Certain neurodevelopmental and behavioral disturbances may exist, along with mood or tic disorders.[40] Boys with extra Xs may be at risk of maladaptive behavior and may have little tolerance of rejection or teasing. Specific recommendations and interventional strategies may benefit their psychosocial functioning.[5,30] Males may have a small penis and small testicles. Infertility and gynacomastia as a result of hypogonadism have been reported.[41,42]

In conclusion: the most serious problems are encountered in individuals with 45,X and 47,XXY. They entail growth disturbance, cardiovascular and metabolic disease, autoimmune diseases, increased cancer incidence, endocrinological insufficiency, puberty failure, and infertility. An early diagnosis of SCA can enhance the general quality of life of SCA individuals because it makes early treatment and preventive programs possible.

Incidence

The incidence of all SCAs in humans is 1 in 400 newborns.[41,43] The incidence of SCA mosaicisms is not exactly known, as mosaic individuals are not always diagnosed because of very mild or no evident clinical features. In mosaicism, the co-existence of a normal cell line modifies the effect of the aneuploid cells.[44]

The incidence of SCA diagnosis after prenatal invasive testing is 1 in 250 to 1 in 300 individuals.[41,45] There is no direct causality to maternal age, but it is important to realize that in prenatal testing procedures for advanced maternal age, the incidence of the finding of a fetal SCA is comparable to the incidence of Down syndrome.[41,46]

Postnatal versus prenatal incidences

Due to a high rate of fetal demise, the postnatal incidence of 45,X is 1 in 2000 to 2500 newborn girls,[2,3] resulting in a worldwide occurrence of 1.5 million 45,X women.[47,48] The incidence of diagnosis of 45,X in prenatal testing depends on the presence of fetal ultrasound abnormalities and the indication for the testing procedure.

The 47,XXY abnormality occurs with an incidence of 1 in 500 to 1000 newborn boys;[4,6,49,50] many 47,XXY individuals remain undiagnosed. Prenatally, the incidence of 47,XXY diagnosis is 1 in 650 fetuses;[50] it includes 25% of all chromosomal abnormalities after invasive prenatal testing.

The postnatal incidence of 47,XXX is 1 in 1000 newborn girls, the same incidence as in prenatal testing.[37,38,51] Prenatally, the syndrome is diagnosed in 0.1% of all cases with chromosomal abnormalities, generally as an incidental finding.[6,38,52] The addition of more than one extra sex chromosome is rare; the prevalence of other X–Y aneuploidies is estimated at 1 in 18,000[5] or less.[41]

Diagnosis of SCAs

Except for 45,X, prenatal ultrasound abnormalities are not encountered in most SCAs and no prenatal indication is given of the fetal genetic abnormality. Postnatally, these children may have a different phenotype than children with the same SCA for whom a prenatal ultrasound abnormality has been found.[11] Certain fetal ultrasonographic abnormalities are associated with a poor prognosis for the child after birth because they reflect early disturbances in organ functioning. Some full-blown SCAs show fetal abnormalities that may be discovered with prenatal ultrasound investigation, such as

an enlarged nuchal translucency or cardiac abnormalities in 45,X. These ultrasound abnormalities may indicate somatic problems, such as heart, lymph, or kidney defects.[11,53] Some case reports of 47,XXY or variant forms of 47,XXY (polysomy X or Y), have described ultrasound abnormalities.[54-56] The detection of these ultrasound abnormalities may be considered as additional karyotype-independent features.[49] Generally, no fetal ultrasound anomalies are found for most cases with 47,XXX.[38] One case report described prenatal ultrasound dilated fetal stomach and upper part of the duodenum in duodenal atresia (double bubble phenomenon).[57]

The diagnosis of a fetal SCA may be unforeseen in invasive prenatal testing procedures for determining whether the risk of a fetal genetic disorder is increased. Girardin[7] and Bondy[2] described the postnatal phenotypes of fetuses with incidentally diagnosed SCAs as less problematic, whereas Zeger[58] found no clinical differences between individuals with prenatally and postnatally ascertained SCAs. As these syndromes are generally unfamiliar to the parents, professionals who are involved in post-test counseling require specific knowledge and counseling skills so that they can provide adequate guidance and care for these parents.[8,59,60]

Table 1 shows relevant prenatal and postnatal characteristics associated with SCAs.

Table 1. Pre- and postnatal phenotypical aspects of SCAs

Sex chromosomal aneuploidy	Prenatal aspects	Phenotypical postnatal aspects
45,X **Turner syndrome**	· Nuchal translucency enlargement · Septated hygroma colli · Fetal edema · Cardiac abnormality · Growth restriction	· Webbed neck · Puffy hands and feet · Small stature · Health problems: heart, kidney, autoimmune, and metabolic diseases · Estrogen deficiency · No or late puberty · No mammary growth · Infertility · Risk of gonadal dysplasia · Behavioral disturbances
47,XXY **Klinefelter syndrome**	· None	· Large stature · Health problems: autoimmune and metabolic diseases · Testosterone deficiency · Risk of bone fragility · No or late puberty · mammary growth, risk of mammary carcinoma · Infertility · Risk of gonadal dysplasia · Behavioral disturbances

Table 1. Pre- and postnatal phenotypical aspects of SCAs (continued)

Sex chromosomal aneuploidy	Prenatal aspects	Phenotypical postnatal aspects
47,XXX **Triple X syndrome**	· None	· Large stature · Risk of premature ovarian insufficiency · Behavioral disturbances
Other X or Y polyploidies	· None	· Variable · Behavioral disturbances

1.2 SEX CHROMOSOME ANEUPLOIDY: EMERGENCE, X INACTIVATION, GENETICS, AND COUNSELING ASPECTS

Emergence of fetal SCA

Most genetic abnormalities are the result of a random event that occurs during the formation of the haploid reproductive cells followed by a fusion to generate the diploid embryo. Partly because of this, all pregnant women have an approximately 3% risk of carrying a child with a genetic abnormality; 0.5% of this risk is of chromosomal autosomal or sex chromosomal aneuploidies.[61]

In the normal human genotype, each cell contains 46 chromosomes, including two sex chromosomes: either XX or XY. The normal female genotype is 46,XX, while the normal male is 46,XY. The fusion of two haploid cells creates the fetus – a woman's egg and a man's sperm. Each fetal cell is then diploid – it contains 46 chromosomes. During meiosis, the formation of four haploid cells from one precursor cell is of fundamental importance. However, this process does not always work perfectly and may sometimes lead to aneuploidy due to misdivision of a chromosome pair. A more complex situation occurs after a mitotic misdivision of a chromosome pair. This event creates an embryotic cell-line with an extra copy of a chromosome and another cell-line lacking this chromosome next to the normal cells. Such co-existence of genetically different cells within the same individual is called mosaicism.

X inactivation

In normal 46,XX women, one of the X chromosomes is inactivated during the early blastocyst stage of embryonic development and does hardly contribute to transcription. The inactivated X chromosome may be of maternal or paternal origin. This inactivation occurs randomly, and it leaves only one X chromosome fully functioning in each cell of the body.[62-65] The remaining condensed and inactivated X takes only very little part in the transcription of genetic information. Its genes, therefore, contribute much less to the function of the cell.

In normal 46,XY men, the X chromosome is of maternal origin and is normally active. The number of genes on the Y-chromosome is limited, while the SRY gene, which is located on the short arm of the Y chromosome acts as the primary factor for developing the testes. The long arm contains several genes, necessary for spermatogenesis. These genes are typically situated in three regions of Yq11 (AZFa, AZFb and AZFc). Deletions in AZFc are the most common ones, and they are associated with oligozoospermia or the complete absence of germ cells.[66-68]

In men and women who have SCAs with supernumerary X chromosomes the relative small number of transcribed genes from the inactivated X chromosomes probably contribute to the phenotypical abnormalities of individuals with an SCA.[63,69,70]

Sex chromosome aneuploidies and genetics

45,X, Turner syndrome

Monosomy 45,X, or having only one X-chromosome in all cells, is the most frequently occurring karyotype in Turner syndrome anomalies (50%) and is the only chromosomal monosomy compatible with life. A significant number of the X chromosome genes escape inactivation, and the loss of these non-inactivated X genes cause the phenotypic manifestations characteristic of the Turner syndrome.[69,71] The incidence of this genetic anomaly is 3% of all female conceptions, 99% of which are lost during early pregnancy.[48]

Thirty to forty percent of these individuals have a mosaicism, with two or more chromosomally different cell lines, for example 45,X/46,XX; 45,X/47,XXX; or 45,X/46,XY. The level of mosaicism depends on the time of the occurrence in the embryo after fertilization. A mitotic error that occurs at a later stage after fertilization may lead to an abnormal line of cells confined to the placenta or a certain area or tissue in the developing individual.[72-75]

Other patients have structural sex chromosome anomalies such as deletions or ring chromosomes or a karyotype with a duplication of the long arm of the X chromosome together with a deletion of the short arm (isochromosome, 46,X,i(Xq)), showing the complete Turner phenotype.[1,47,76,77] Prenatally, 45,X is diagnosed after prenatal invasive testing often because of fetal ultrasound anomalies; fetal hydrops and septated nuchal hygroma are typically associated with 45,X.[77-79] Other anomalies may come forward as incidental findings in prenatal testing procedures aimed at the exclusion of another genetic anomaly.[80,81] Due to the complexity of the post-zygotic mechanism of emergence of this SCA, 45,X mosaicism may be present in cell lines that are not easily detectable in prenatal diagnostic testing.

The exact nature of the abnormality on the X chromosome will determine the effect on the phenotype. For instance, deletions in the long arm of one of the X chromosomes (Xq) may lead to gonadal dysgenesis, whereas deletions in the short arm (Xp), including the SHOX gene, may be compatible with normal gonadal function, but lead to a

small stature and other skeletal anomalies in the affected women.[80] The presence of Y chromosome material in certain cell lines increases the risk of androgen-producing gonadal tumors, such as gonadoblastoma and dysgerminoma,[82,83,84] and may result in in genital abnormalities ranging from hypospadias to genitalia ambiguity. The use of sensitive polymerase chain reaction (PCR) techniques enables the detection of such Y-chromosome-specific material in 12% of the initially pure 45,X females.[84] Women who present with the complete Turner phenotype often have a mosaicism of 45,X cell lines in combination with an isochromosome Xq.[3,80]

47,XXY, Klinefelter syndrome

The karyotype of males with supernumerary X chromosomes will be full-blown 47,XXY in 90% of the diagnosed cases,[85] but mosaicism with normal male or female cell lines, mosaicisms with trisomy cell lines of chromosome 18 and 21, and polyploidy of the X or Y chromosomes have been described: 47,XXY/46,XY; 47,XXY/46,XX; 48,XXY+18; 47,XXY+21; 48,XXXY; and 48,XXYY. The occurrence of a double aneuploidy often leads to a miscarriage.[49] The additional sex chromosome is almost as likely to come from the father as from the mother.[86]

It has been firmly established that a higher polyploidy of X chromosomes is negatively correlated with the phenotype of the patient, while the role of X chromosome inactivation leading to the variability in 47,XXY phenotypes has not yet been completely unraveled.[70,87] Most importantly, the postnatal phenotype mainly affects behavior and mental capacity.[7]

47,XXX, Triple X and other supernumerary X syndromes

Women with supernumerary X chromosomes usually have the 47,XXX karyotype, but 48,XXXX and 49,XXXXX also occur. Ninety percent of the extra X chromosomes are of maternal origin as a result of nondisjunction in meiosis I.[37,52] The extra X chromosomes are always inactivated (n-1 rule), although, as mentioned before, not completely,[88] and unbalanced expression of X chromosomal genes may therefore contribute to suboptimal brain development.

Most 47,XXX women have normal phenotypes, but there are risks of premature ovarian insufficiency and behavior disturbances. Like in males, a higher polyploidy of X chromosomes increasingly affects the phenotype, which in turn affects behavior.[5]

A certain association of a 47,XXY or 47,XXX outcome with advanced maternal age has been reported,[6,45] but not for 45,X. Of all 45,X cases, 55%[89] to 83%[90] appeared to be diagnosed by routine karyotyping after the detection of ultrasound abnormalities. The detection of most other SCAs were incidental findings during prenatal testing aimed at the exclusion of another genetic anomaly.[11,49,91]

Sex chromosome aneuploidies and counseling

In general, counseling parents after a prenatal diagnosis of SCA is a complex issue because of the large variability in the postnatal phenotypic consequences of the diagnosed genetic abnormality. Differences in attitude and approach of the genetic specialists and the obstetrical or neonatal counselors may influence the communication of the information about the fetal abnormality.[59,92-95] It has been shown that a highly structured home environment has an important positive influence in reducing the emergence of psychological disorders in SCA.[44]

45,X

The prenatal diagnosis of 45,X after invasive diagnostic testing provides difficulties for the counselor because phenotypic consequences may be hard to predict. In the case of fetal ultrasound anomalies, the prognosis of phenotypic outcome depends on the exact nature of the fetal anomaly. If no ultrasound anomalies are detected in the fetus, the prenatal diagnosis of 45,X is often an incidental finding in testing aimed at the exclusion of another genetic anomaly.[2]

Due to the possibility of mosaicisms, two or more cell lines may co-exist in the fetus, some of which may not be detectable in amniotic fluid or chorion villus tissue. After the prenatal finding of a 45,X without the presence of any fetal abnormality, this cytogenetic diagnosis has limited predictive value because low grade mosaicism is difficult to exclude. These circumstances result in a wide range of possible associated phenotypes. The more aberrant cell lines co-exist within a SCA individual, the more they affect the phenotype, but the complete genetic scale of co-existing cell lines is not necessarily visible prenatally. The presence of a cell line with a normal female genotype is favorable to the prognosis of the postnatal phenotype.[44,80]

Parents are often counseled about the typical small stature, the webbed neck, the cardiovascular diseases, the behavioral difficulties and the infertility, but there is no guarantee that the postnatal phenotype will indeed lead to all of these problems in incidentally diagnosed cases.[2,59,80,94,95]

47,XXY

Prenatal diagnosis of 47,XXY is generally an incidental finding in a testing procedure aimed at excluding another genetic anomaly. Fetal ultrasound anomalies are not often encountered, whereas the presence of more X chromosomes (such as 49,XXXXY) often corresponds to abnormal fetal growth.[5,96]

The co-existence of two or more cell lines in 47,XXY mosaicism may have a major impact on postnatal phenotype. The presence of a mosaicism and another chromosomal anomaly (such as a trisomy 21) negatively influences the phenotype. This is also the case for 47,XXY syndromes with more X chromosomes: these genotypes correspond with

more postnatal phenotype abnormalities in health, behavior, and fertility associated with specific brain anomalies.[5,40,96,97] Co-existence with a normal male cell line is prognostically beneficial. The individual shows very few phenotypic aspects, so that fertility may not be completely disturbed and adolescent sperm recovery may be possible to enable procreation in a later stage of life.[4]

The counseling after an incidental prenatal finding of 47,XXY entails providing the parents with information about the very broad scale of the postnatal phenotype of these males. On one side, this scale shows a normal, self-supporting male individual without any health or behavior problems,[95] but ultimately he will discover his genetic anomaly in his medical search for the reason for his infertility. On the other side of the scale, a male individual may have many health and behavior problems, and even very serious metabolic, auto-immune or psychiatric disorders.[7]

47,XXX

In most cases, the prenatal diagnosis of 47,XXX is an incidental finding in a testing procedure aimed at excluding another genetic anomaly. Fetal ultrasound anomalies that typically correspond with this genotype are uncommon. There are some case reports in which 47,XXX was diagnosed after the detection of fetal ultrasound abnormalities,[98,99] but a typical association of specific fetal anomalies that point to 47,XXX have not been described.

Mosaicism with normal cell lines may occur, and it influences the postnatal phenotype positively. The opposite is true of mosaicisms with genetically abnormal cell lines. More X chromosomes correspond with a more abnormal phenotype in health and behavior.[5] Counseling after the incidental prenatal finding of a 47,XXX entails the description of a relatively normal physical appearance, the risk of premature ovarian insufficiency, and the possibility of slight behavior disturbances, which may benefit from early support treatment.[37,38]

1.3 FETAL INVESTIGATION: SCREENING AND DIAGNOSTIC TESTS, NON-INVASIVE AND INVASIVE TESTS, TARGETED OR GENOME-WIDE TESTING, AND INCIDENTAL FINDINGS ASSOCIATED WITH SCAS

Screening tests

Non-invasive: first-trimester screening

All pregnant women are now offered a non-invasive, first trimester, screening test via nuchal translucency measurement (Figure 1A-C) combined with serum measurement of pregnancy-associated plasma protein A (PAPP-A) and free beta human chorionic gonad-

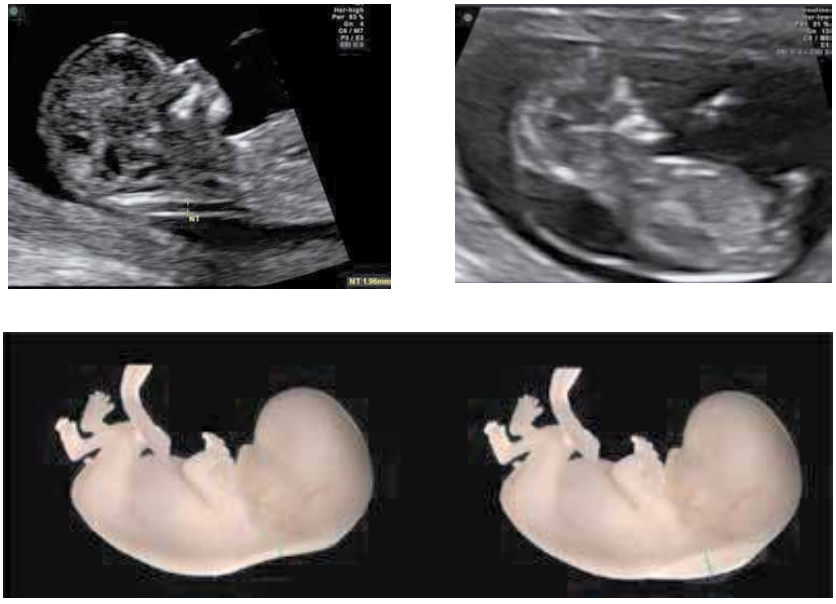
otropin (hCG).[100-102] The purpose of the screening test is to identify a well-defined target population, i.e., pregnant women at risk of having a child with Down syndrome.[103-106] If the screening result is positive, subsequent invasive diagnostic testing in conjunction with karyotyping is offered. Since karyotyping is a full-scale test, all chromosomal aneuploidies with potential diagnostic and prognostic significance are detected. First-trimester ultrasound may also reveal important structural defects in the fetus, such as anencephaly. These findings may have important implications for the parents' decision-making about continuing the pregnancy.[107]

The first-trimester screening test reveals no major abnormalities for most SCAs, but for 45,X, early fetal hydrops or a septated nuchal translucency is associated with a negative prognostic outcome: survival to term is reported to be less than 10%.[2]

Non-invasive: ultrasound findings in the second-trimester screening

Most parents consider fetal assessment by ultrasound to be a social ritual of meeting the baby,[108] but from the professionals' point of view, it is an important tool for prena-

Figure 1A-C First-trimester screening test, ultrasound:
(source: Department of Obstetrics and Gynecology, Division of prenatal diagnosis and therapy. Radboud University Nijmegen Medical Centre Nijmegen, the Netherlands)



A. Normal nuchal translucency measurement
B. Enlarged nuchal translucency
C. Anatomic view: left fetus with normal nuchal translucency, the right fetus with an enlarged nuchal translucency

tally detecting many fetal congenital abnormalities.[109,110] Second-trimester ultrasound screening may reveal structural fetal defects that may be associated with certain chromosomal aberrations. Soft markers for chromosomal abnormalities may be detected, such as choroid plexus cysts (Figure 2A), renal pelvic dilatation (Figure 2B)[111-114] in which case, karyotyping of the fetus is advised. An incidental discovery of a skeletal dysplasia on routine ultrasound screening or fetal biometry that does not fit exactly within the standard fetal growth cards is a reason for additional diagnostic karyotyping.

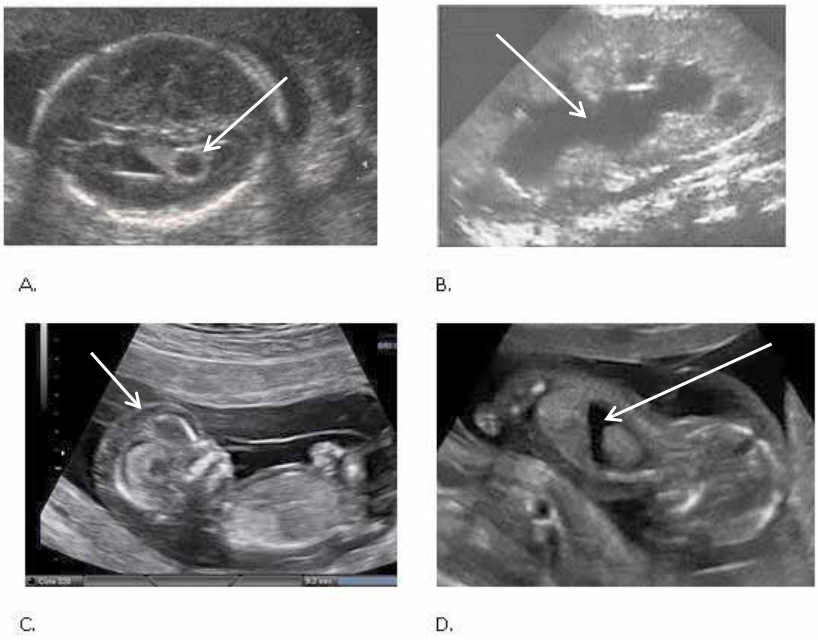
No important ultrasound abnormalities are found for most SCAs except 45,X. Nuchal septated hygroma, cardiac abnormalities, fetal hydrops (Figure 2CD) and growth restriction are often encountered, and subsequent karyotyping may reveal the syndrome.[2] No specific second-trimester ultrasound findings for other SCAs point to a fetal syndrome, apart from some cases with supernumerary X chromosomes. Intra-uterine growth restriction and sporadically major structural defects can be found in these cases.[5]

Diagnostic tests: non-invasive and invasive

Non-invasive test: ultrasound as diagnostic tool

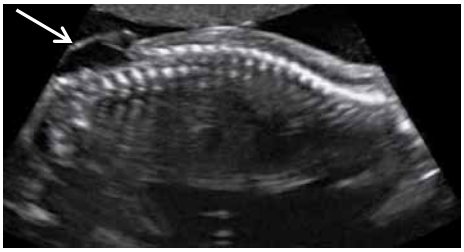
Major congenital defects, such as neural tube defects (Figure 3AB), kidney malformations as well as lymphatic system (Figure 4) or cardiovascular anomalies (Figure 5ABC) possibly associated with a fetal aneuploidy may be diagnosed.[1,103,115] The accuracy of ultrasound imaging of fetal abnormalities has improved in recent years due to the introduction of 3D and 4D ultrasound.[116,117]

Figure 2 A-D. Second-trimester screening test, ultrasound : (source: Department of Obstetrics and Gynecology, Division of prenatal diagnosis and therapy. Radboud University Nijmegen Medical Centre Nijmegen, the Netherlands)



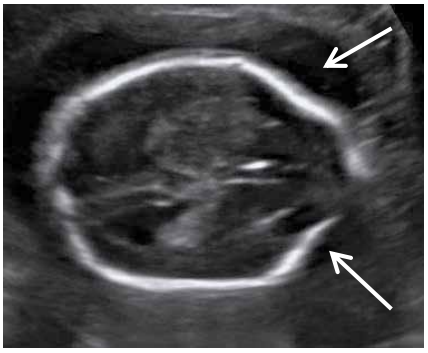
A. isolated plexus chorioideus cyst in fetal brain. Choroid plexus cysts are believed to be caused by abnormal folding of the epithelium lining of the choroid plexus which traps fluid and debris. More than 90% of choroid plexus cysts resolve spontaneously by 28th weeks' gestation.
B. fetal hydronephrosis, dilation of the renal collecting system. The collecting system is the structure that collects urine directly from the kidney tissue and routes it by way of the ureter to the bladder. Blockage of urine flow can possibly lead to infections, scarring, and long term damage of the kidney.
C. D. fetal hydrops, an accumulation of fluid, or edema, in at least two fetal compartments. Here, pleural effusion results in skin edema (C) and hydrothorax (D).
A-D are soft markers for fetal aneuploidy

Figure 3A. Non-invasive diagnostic test, ultrasound:
(source: Department of Obstetrics and Gynecology, section prenatal diagnosis and ultrasound. Radboud University Nijmegen Medical Centre Nijmegen, the Netherlands)



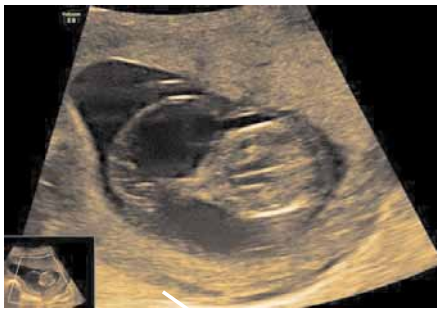
Neural tube defect, one of the most common birth defects. It is an opening in the spinal cord or brain that occurs very early in human development. In the 3rd week of pregnancy called gastrulation, specialized cells on the dorsal side of the fetus begin to fuse and form the neural tube. When the neural tube does not close completely, an NTD develops. Examples of open NTDs are anencephaly, encephaloceles, hydranencephaly, iniencephaly, schizencephaly,and spina bifida. Rarer types of NTDs are called closed NTDs. Closed NTDs occur when the spinal defect is covered by skin.

Figure 3B.



Associated "lemon sign" of the fetal head, a characteristic scalloping of the frontal bones. This is a result of the tethering of the spinal cord with subsequent downward displacement of the brain as the fetus grows (Sebire 1997).

Figure 4. Ultrasound malformation associated with fetal SCA:



Large hygroma colli, an anomaly of the lymphatic system characterized by single or multiple cysts within the soft tissue, usually involving the neck. It contains a clear or cloudy fluid-like lymph. Here a septated hygroma is shown, typically associated with bad prognosis in 45,X.

Figure 5 A-C.

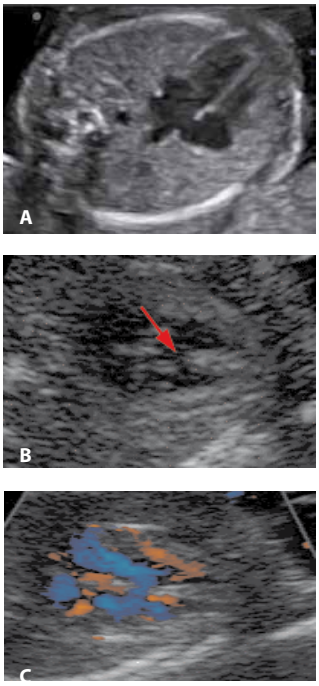


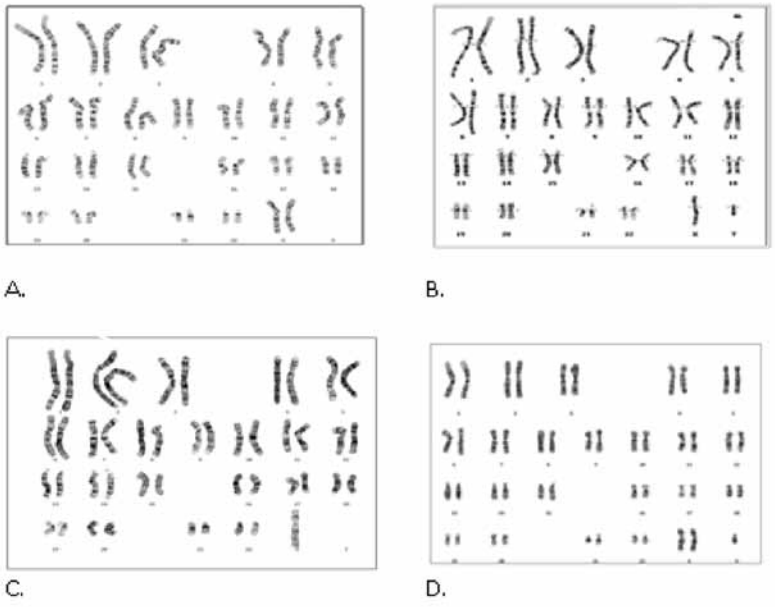
Figure 5A. Normal 4-chamber view of the fetal heart, normal dimensions of atria and ventricles, normal foramen ovale, normal and continuous ventricle septum.
Figure 5B. Ventricular septal defect. Abnormal 4-chamber view of the fetal heart, with abnormal dimensions of the atria and ventricles with a defect seen in the ventricle septum.
Figure 5C. Color doppler technique will reveal the blood flow from left to right ventricle through the defect. This abnormality may be associated with 45,X

Invasive test: karyotyping

Traditional karyotyping of the fetuses of pregnant women with an elevated risk of fetal aneuploidy can be performed using an invasive procedure, namely, chorion villus biopsy or amniocentesis, between 10-11 and 15 weeks of gestation (Figure 6A-D). In human embryology, the chorion is defined as the layer consisting of the trophoblast plus the underlying extraembryonic mesoderm. Amniotic fluid contains amniocytes in addition to fetal cells from the skin, genitourinary system, and gut, along with biochemical products that may be removed for analysis. Mosaicisms found in the chorion may only be related to placental tissue;[72] (mosaic) aneuploidies found in amniocentesis directly relate to the fetus.

If fetal ultrasound abnormalities are detected in the second-trimester, amniocentesis may be performed, with a slightly smaller risk of miscarriage. Overall, invasive prenatal testing carries a certain risk of pregnancy loss (0.2-0.5%).[118]

Figure 6A-D. Invasive diagnostic test, karyotyping:
(source: Department of Human Genetics, Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands)

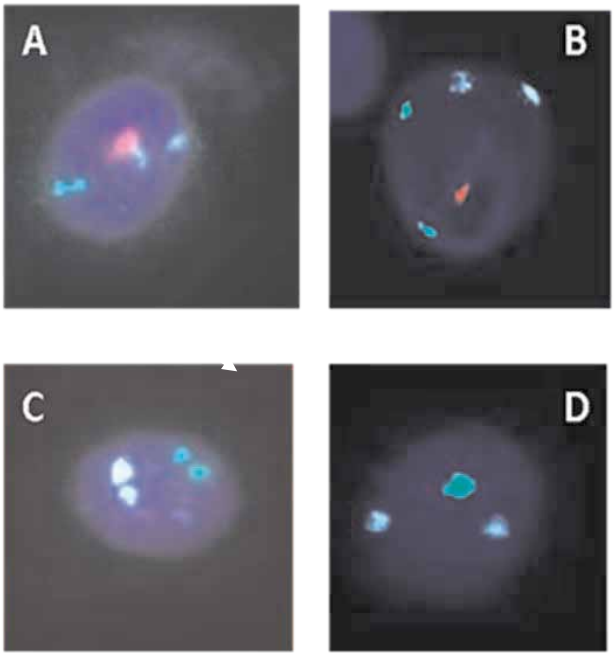


A. 46,XX, karyotype of normal female
B. 46,XY, karyotype of normal male
C. 45,X, karyotype of female, missing one X-chromosome, a condition associated with Turner syndrome
D. 47,XXY, karyotype of male with an extra X-chromosome, a condition associated with Klinefelter syndrome

Rapid aneuploidy detection

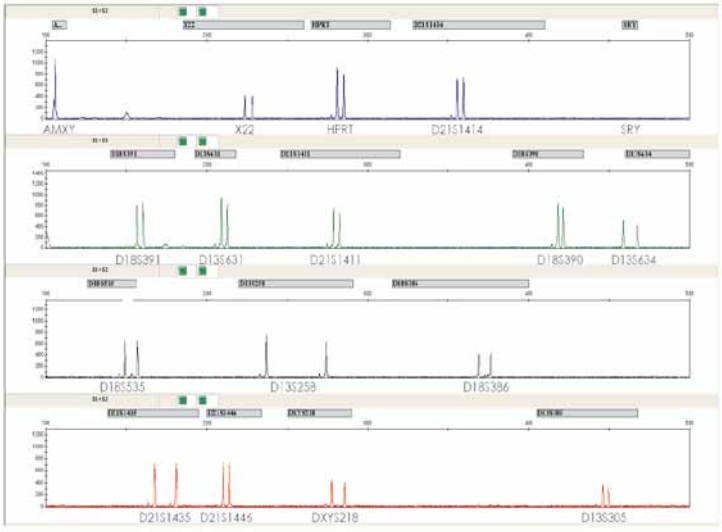
Interphase fluorescent in situ hybridization (FISH) (Figure 7A-D), multiplex ligation-dependent probe amplification (MLPA) and quantitative fluorescence polymerase chain reaction (QF-PCR) (Figure 8AB) are available for rapid aneuploidy detection (RAD) of the most common chromosome anomalies, specific for chromosomes 13, 18, 21, X and Y. These techniques may be useful in cases with fetal ultrasound abnormalities, and enable rapid diagnosis in 2 or 3 days.[119] The accuracy of these rapid testing techniques in detecting non-mosaic common aneuploidies is similar to that of traditional karyotyping,[120] but low grade mosaicisms and uncommon aneuploidies are not detected.[121,122]

Figure 7A-D. Rapid aneuploidy detection, *FISH*:
(source: Department of Human Genetics, Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands)

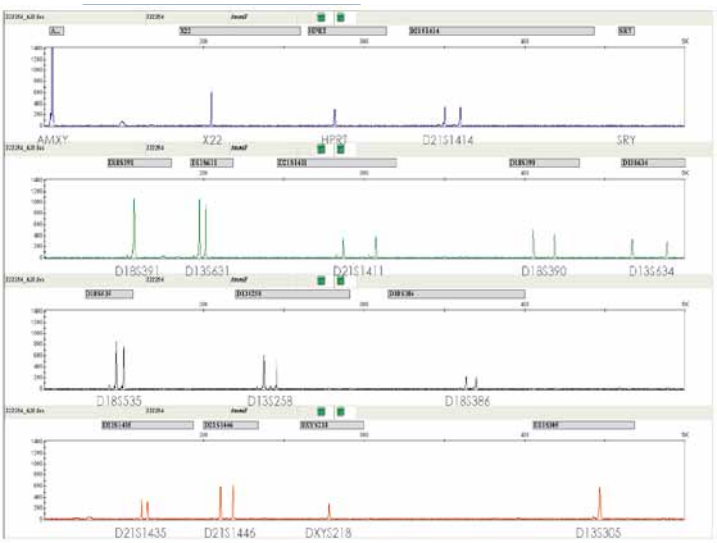


A. normal male: 1 green signal for X chromosome, 1 red signal for Y chromosome
B. Klinefelter male: 2 green signals for X chromosome, 1 red signal for Y chromosome
C. normal female: 2 green signals for X chromosome
D. Turner female: 1 green signal for X chromosome
(2 blue signals for chrom. 18: control for disomy)

Figure 8AB. Rapid Aneuploidy Detection, *QF-PCR*:
(Source: Aneufast User's Manual Revised 2007)



A. Normal XX female sex chromosome constitution
Only the X- specific product of the AMXY is present and SRY is not amplified.
Both pseudoautosomal markers (X22 and DXYS218) and the X-linked HPRT are normal heterozygous, reflecting a normal XX sex chromosome complement. Four markers on chromosome 21 (D21S1414, D21S1411, D21S1446, D21S1435), 18 (D18S535, D18S391, D18S386, D18S390) and 13 (D13S631, D13S634, D13S258, D13S305) are normal heterozygous, confirming the presence of normal chromosome copy number for these autosomes.



B. Detection of monosomy X
X chromosome monosomy is indicated by the single fluorescent products for the two pseudoautosomal markers (X22 and DXYS218) and the X-linked HPRT, in the absence of Y-specific products of AMXY and SRY.

New technological advances and future:

Micro-array testing

Recent implementation of array genomic hybridization technology in prenatal diagnostics may give rise to the diagnosis of genetic aberrations that may or may not be associated with the observed fetal ultrasound abnormalities. In these cases, certain postnatal prognoses cannot always be given.[123-125] Micro-array testing is used usually after the exclusion of a fetal aneuploidy, to represent genome-wide screens for detecting sub-microscopic chromosomal deletions or duplications that are associated with serious fetal ultrasound abnormalities. The array test provides the possibility to reveal the deletion of a gene that is known to prevent cancer. Such a deletion significantly increases the lifetime risk of developing cancer. Genetic aberrations may come forward of which the clinical significance is as yet unclear, or family members may be diagnosed with a genetic abnormality that may have a negative effect on their (future) health.

Next-generation sequencing of cell-free fetal DNA in maternal plasma

Application of fetal cells and fetal cell-free genetic material in the maternal blood are two approaches currently being investigated. They are promising with regard to the rapid and reliable detection of fetal genetic abnormalities.[126-130]

1.4 The right to inform and to be informed about incidental findings and ethical and policy dilemmas

While the novel molecularly targeted approaches focus on the diagnosis of specific genetic diseases, current discussions tend to focus on the possibility of full-scale testing using microarray-based techniques with a maximum of genetic information at an unequaled detection level. The use of these novel molecular genetic technologies for prenatal diagnoses gives rise to many ethical, social, and medico-legal problems and dilemmas.[131,132] From the ethical point of view, the parents' autonomous "right to know" versus "the right not to know" is of topical interest.[133] In view of these new technological developments, it is relevant to examine the parents' preference, i.e., whether women considered to be at high risk of having a child with Down syndrome who undergo invasive testing would opt for full-scale genetic testing for other disorders for which they do not have an a priori increased risk.

The right to be informed has been the basis of current laws and regulations "Everyone has the right to seek, receive and impart information".[134] The debate about patients' right to be informed of their health status and treatment began in the mid-twentieth century in the United States, where these rights have now been consolidated and can still be considered an example for many countries in the world.[135] In its Charter of Fundamental

Rights of the European Union of 2000, the European Union states that free and informed consent of the patient must be respected according to the procedures laid down by the law of each country. These codes refer to the Hippocratic Oath, which obliges physicians never to harm their patients.[136,137] The right to information can be understood as an update of the Hippocratic obligation that refers to the relationship between physicians and patients. The patients' right to information can be considered a result of mutual trust. In the case of an incidental finding in pregnancy with an uncertain prognosis, two patients are involved: the pregnant woman and the fetus. The benefits for each of them are unclear.

New communication technologies are both a risk and an opportunity. There is an increasingly important role for the Internet to provide additional medical information, aside from professional information. The access to and acquisition of large amounts of information has become an obvious right. The relevance of the acquired information varies for each person, and this applies to all kinds of genetic information. The Internet service can be critical in providing extended medical information, which should always be discussed with a professional.[138]

In view of the new technological developments in prenatal testing, the parental preference is an important factor.[119,139,140] The question is whether women considered at high risk of having a child with Down syndrome and who undergo invasive testing would opt for full-scale genetic testing, even for disorders for which they do not have an a priori increased risk. It is not always easy to choose between full-scale testing using microarray-based techniques with a maximum of genetic information and molecularly targeted approaches that focus on the diagnoses of specific genetic diseases. Chromosome abnormalities are associated with severe, moderate, or mild disease, although sometimes the clinical relevance is uncertain. Many women who undergo invasive prenatal tests are unaware of the possible adverse effects of an uncertain prognosis.[141] Herein lies an important task for the professionals who are responsible for the pre-test counseling.

1.5 Aim and outline of the thesis

Aim

The aim of the thesis was to examine the value - in a positive or negative sense - of the incidental finding of a fetal sex chromosomal aneuploidy in invasive prenatal diagnostic procedures. The main study question was whether the incidental finding of a fetal sex chromosomal abnormality is a diagnostic gain or whether it should be omitted because of diagnostic damage.

Outline of the thesis

In order to answer the main study question, we have formulated some questions that are closer to the heart of the matter:

1. What are the attitudes of women in low-risk pregnancies towards full-scale genetic testing? **Chapter 2** reports the answers.
2. What is known about the problems most often encountered by SCA-afflicted individuals? What has recently been published in the medical literature about incidental prenatal findings of sex chromosomal aneuploidies and the postnatal phenotypes of these individuals? **Chapter 3** reports a review of this selected literature and its conclusions.
3. What are the perspectives of parents who have been confronted with an unforeseen prenatal finding of a sex chromosome aneuploidy (full blown or mosaic) when they think about the events in retrospect? What were their reasons for continuing or terminating the pregnancy? Two qualitative interview studies were set up – one with parents who decided to continue the pregnancy and one with parents who decided to terminate the pregnancy. **Chapters 4 and 5** present their responses.
4. What are the views of medical professionals who counsel the parents and treat SCA individuals? These experts may decisively affect the parents' considerations and decision-making, and they are involved in future medical policy changes. **Chapter 6** reports the results of our qualitative interview study with several experts in this field.

During the study period, we had a scientific discussion with authors of a recently published review of factors that may influence the decision-making of parents confronted with a prenatal diagnosis of an SCA. **Chapter 7** presents a letter to the editor of the journal *Genetics in Medicine* and the response of the authors to this letter.

The most important items that emerged for the literature study, as well as the results and conclusions of the three qualitative studies, have been assembled in a such way that they provide a practical answer to our main study question. **Chapter 8** presents this material in relation to recent literature (General Discussion).

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Chapter 2

Parent's attitudes towards full-scale prenatal testing for genetic disorders

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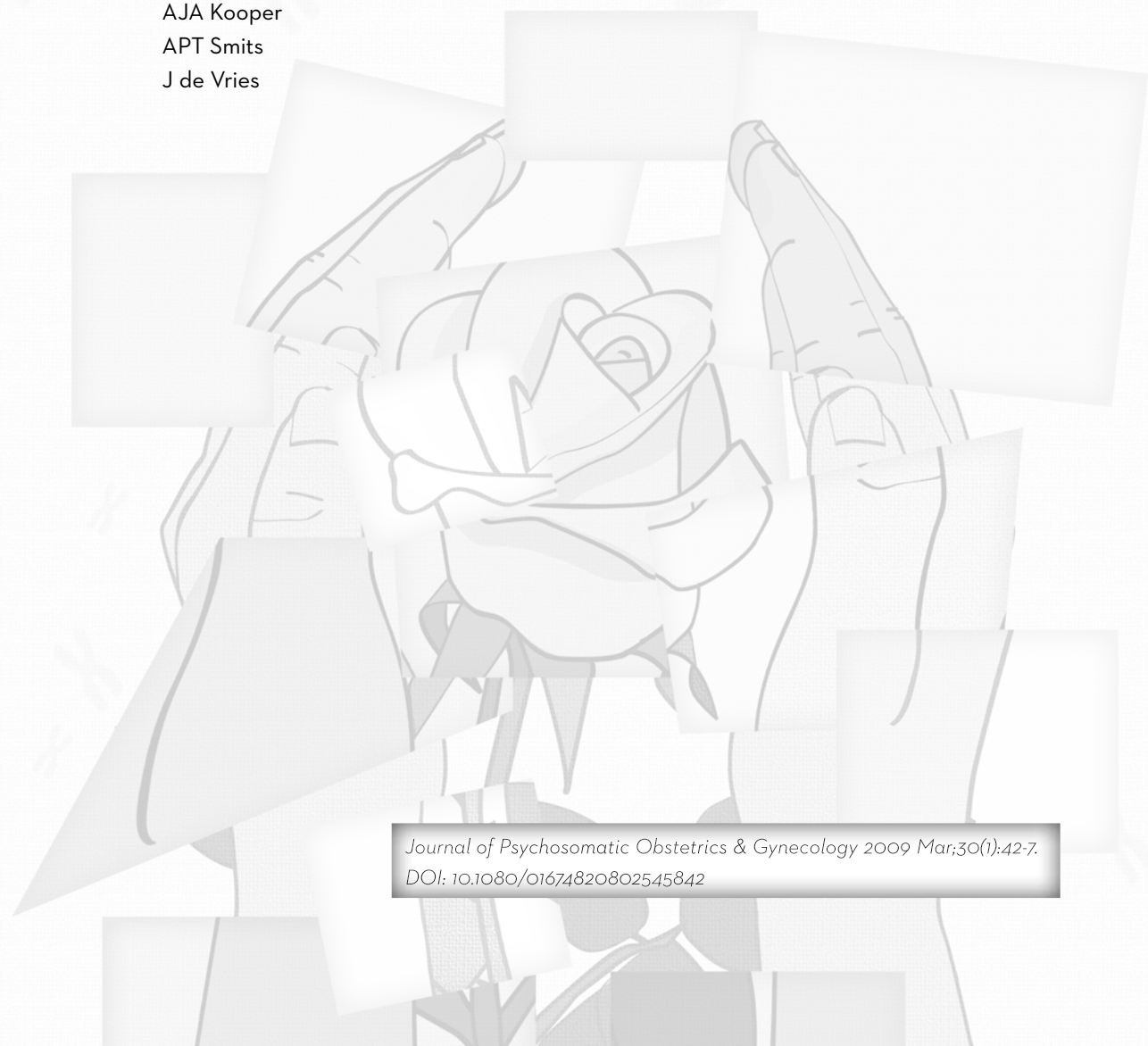

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ABSTRACT

Objectives

Innovations in the field of prenatal diagnostic testing have led to the development of molecular tests that allow the rapid detection of specific genetic defects, such as Down syndrome. In addition, full-scale tests have been developed allowing the detection of many genetic disorders in a single test. Here we examined the attitudes of pregnant women in low risk pregnancies towards full-scale genetic testing and explored relationships between demographic characteristics and the level of interest.

Methods

A prospective study was performed on 115 consecutive pregnant women. They completed the same structured questionnaire at two different time points, before counselling (T1) and after 4 weeks (T2), to assess a possible change of attitude.

Results

At T1, 33% of the respondents were in favour of full-scale testing of their unborn child, whereas at T2, this percentage had dropped to 18%. Except for educational level, no significant relationships were noted between the demographic variables and the wish to opt for full-scale testing. A low educational level was significantly related to the interest in full-scale testing.

Conclusions

Low risk pregnant women expressed little interest in full-scale genetic testing. Educational level appeared to affect their views.

INTRODUCTION

Since January 2006, the guidelines on prenatal tests have changed in the Netherlands.[1] All pregnant women are now offered the opportunity to undergo a non-invasive first trimester Down syndrome screening test via nuchal translucency measurement combined with serum measurement of PAPP-A and free beta hCG.[2-4] The objective of the screening test is to identify a well-defined target population, i.e., pregnant women at risk for having a child with Down syndrome. If the screening result is positive, subsequent invasive testing in conjunction with karyotyping is offered. Since karyotyping is a full-scale test, next to trisomy 21 (Down syndrome) other chromosomal aberrations with potential diagnostic and prognostic significance may be detected. In addition to traditional karyotyping, recent molecular genetic innovations have led to the development of microarray-based genomic profiling technologies that allow full-scale screening for chromosomal anomalies at an until recently unprecedented resolution.[5-7] This technique might be particularly useful for those cases in which fetal malformations are manifested by ultrasound investigation. In contrast, the recent introduction of quantitative PCR-based techniques have led to the development of tests that allow the detection of specific genetic defects such as trisomy 21.[8-11]

Recently, we implemented targeted testing for Down syndrome by multiplex ligation-dependent probe amplification (MLPA) in our diagnostic clinical service. Within this service, the parents have the autonomy to choose between targeted testing and full-scale testing. This new possibility is of topical ethical interest in terms of the parent's autonomy to make their own decisions. In a Dutch national study, M.A.K.E. (MLPA and karyotyping, an evaluation) the parent's preference for MLPA and traditional karyotyping is examined.[12]

While the novel molecularly-targeted approaches focus on the diagnoses of specific genetic diseases, current discussions tend to focus on the possibility of full-scale testing using microarray-based techniques, with a maximum of genetic information at an unequalled detection level. The use of these novel molecular genetic technologies for prenatal diagnoses gives rise to many ethical, social and medico-legal problems and dilemmas.[13,14] From the ethical point of view, the parent's autonomous 'right to know versus not to know' is of topical interest.[15] In view of these new technological developments, we examined the parent's preference, i.e., whether women considered at high risk of having a child with Down syndrome and undergoing invasive testing, would opt for full-scale genetic testing also for disorders for which they do not have an a priori increased risk. In this prospective pilot study, being part of a larger study on general knowledge on prenatal testing, we examined whether specific demographic variables affected the women's preferences towards full-scale testing.

METHODS

From October 2004 to March 2005, pregnant women who visited the prenatal outpatient clinic at the St. Elisabeth Hospital Tilburg, the Netherlands were approached before their intake consultation and invited to take part in this prospective pilot study. During this intake consultation all possibilities of prenatal screening and diagnostic tests were explained by the genetic counsellor. After this consultation, the women were asked to make an appointment for performing of one of the tests. The test population comprised a non-selected group of pregnant women, whether or not referred by a midwife or general practitioner, mostly accompanied by their partner. Women who were not proficient in the Dutch language were excluded.

All participants completed the same questionnaire at two different time points (T1 and T2), with an interval of at least 4 weeks. The reason for using the same questionnaire was to examine the basic knowledge at T1 and the possible increase in knowledge (and change of views) at T2, thus after prenatal intake consultation. This same interval period is also used in studies examining the effect of an intervention.[16,17] Completion of the questionnaire at T1 took place before the prenatal intake consultation, whereas completion at T2 took place by telephone 4 weeks later at a pre-arranged time.

The two questions that are relevant for this study were:

1. Imagine that you undergo amniocentesis or chorionic villus sampling and the technique is so advanced that a whole range of abnormalities or diseases can be detected, even abnormalities that will not affect your child until later in life. Would you want to know all possible genetic information of your future child? When the answer was yes, the second question was asked.
2. Would you be willing to wait a little longer for the results, or would you rather hear them quickly and in brief?

The questionnaire contained also a few multiple choice questions, which could give some insight in their general knowledge and comprehension of the prenatal test that they had asked for and were about to undergo. This information, however, will not be evaluated here and lies beyond the scope of this article.

Demographic data were obtained on age, parity, a priori risk, educational level (low versus middle/high), previous experience with fertility treatment and previous experience with prenatal testing. To analyse possible relationships between these demographic data and the dependent variables, responses were analysed using Phi and Cramer's V tests. Logistic regression analysis was performed to identify demographic characteristics that could predict a respondent's attitude towards full-scale testing of her unborn child. The study was approved by the medical ethics committee of the St. Elisabeth Hospital.

RESULTS

The response rate before prenatal counselling (T1) was 100%, i.e., all couples who were eligible for the study and were asked to participate indeed answered our questionnaire. At the second time point, 4 weeks later (T2), 20 respondents dropped out with no clear reasons given, which turns the response rate at T2 into 83%.

Low educational level influenced the number of couples dropping-out

Table I shows an overview of the obtained demographic variables of the respondents at T1 and T2. The majority of patients had a middle/high educational level (87.8% at T1; 92.6% at T2). As stated above, a total of 20 respondents dropped out between T1 and T2. Low educational level of the respondents (Table II) was significantly related to this dropping out (p=0.002). The other demographic variables were not found to be associated with the decision to drop out of the study.

Table I. Demographic characteristics of the participants at T1 and T2.

Study variables	N (%) at T1	N(%) at T2	Study variables	N(%) at T1 (115)	N(%) at T2 (95)
Age<36	66 (57.4)	56 (58.9)	**Age>36**	49 (42.6)	39 (41.1)
Primigravida	40 (34.8)	31 (32.6)	**Primigravida**	75 (65.2)	64 (67.4)
No earlier PND	96 (83.5)	79 (83.2)	**No earlier PND**	19 (16.5)	16 (16.8)
No earlier fertility treatment	95 (82.6)	79 (83.2)	**No earlier fertility treatment**	20 (17.4)	16 (16.8)
Educational level					
A: low	14 (12.2)	7 (7.4)	**Educational level**	101 (87.8)	88 (92.6)
No risk a priori			**B/C: middle/high**		
	113 (99.1)	94 (98.9)		2 (1.7)	1 (1.1)

Table II. Educational level of the participants, drop-out.

Educational level	Type of schooling	Education no. of years	N (%) at T1 (115)	N(%) at T2 (95)
A: low				
		Max. 12	14 (12.2)	7 (7.4) p=0.002
B: middle	Primary school, lower secondary vocational education, junior secondary education	12 or more	45 (39.1)	40 (42.1)
C: high	Senior secondary vocational education			
	First degree level vocational education, university or equivalent	12 or more	56 (48.7)	48 (50.5)

Limited interest in full-scale testing and association with educational level

At T1, 33% of the respondents (38/115) were interested in full-scale testing. This number decreased to 18% (17/95) at T2, 4 weeks after the intake consultation. The respondents with a low educational level had higher preference for full-scale testing (T1: p=0.026; T2: p=0.049). None of the other demographic variables showed a significant relationship (Table III).

Table III. Influence of demographic variables on interest in full-scale testing at T1, T2.

Independent variables	*T1: interested in full-scale testing*	*T2: interested in full-scale testing*
Age (yrs)	p=0.472	p=0.418
Parity	p=0.262	P=0.256
Educational level*	P=0.026	P=0.049
Earlier PND	P=0.569	P=0.484
Fertility treatment	P=0.504	P=0.624
Risk a priori	P=0.693	P=0.842

*Low versus middle/high.

Negative attitude towards invasive diagnostics and association with low educational level

This pilot study enquired specifically about the respondent's attitudes towards invasive diagnostics (amniocentesis and chorionic villus sampling). The results showed that educational level was significantly related (p=0.031) to the respondent's attitudes. More respondents with a low educational level had a negative attitude towards invasive techniques than those with a higher educational level.

Decrease in interest in full-scale testing

In our study population, 15% of the respondents retracted their original decision to opt for full-scale testing after 4 weeks. The vast majority of these respondents had a middle/ high educational level (92.3%), as respondents with low educational level mostly adhered to their prior wish to opt for full-scale testing. In contrast, one respondent who did not opt for full-scale testing at T1 opted for this possibility at T2. At T1, 71% (27/38) of the respondents who opted for full-scale testing indicated that they would be willing to wait longer for the results, whereas at T2 this percentage had dropped to 47% (8/17). None of the demographic variables appeared to be related to this change in opinion.

Taken together, we conclude that the respondent's interest in full-scale testing was generally limited and that this applied particularly to women with a middle/ high educational level. Women with a low educational level did not exhibit a positive attitude towards invasive testing but, in contrast, appeared to be more interested in full-scale

testing. This latter result may be explained by limited understanding and knowledge about the procedure and the implications of full-scale testing within this group. There appears to be a positive relationship[18] between the level of education and correctly answering general questions about prenatal diagnostic tests before counselling (Table IV). The higher the level of education, the more correct answers were given at T1. Therefore, the level of education appears to be a significant predictor of giving the correct answers at T1 (Table V).

Table IV. Significant relationship between high level of education and correctly answering the individual knowledge items at T1.

Prenatal tests: question asked	Level of education	p
NTM: when performed	Cramer's V = 0.353	0.000
Ultrasound: what is examined	Cramer's V = 0.239	0.016
What entails CVS	Cramer's V = 0.268	0.006
CVS: what is examined	Cramer's V = 0.246	0.0125
Amniocentesis: what is examined	Cramer's V = 0.269	0.006

From Ref. 18.

Table V. Level of education as a significant predictor of answering the individual knowledge items correct at T1.

Prenatal tests: question asked	Level of education; p-value
Purpose of NTM	0.0025
NTM: when performed	0.006
Ultrasound: what is examined	0.0125
What entails CVS	0.0035
CVS: what is examined	0.0295

From Ref. 18.

DISCUSSION

The results of this prospective pilot study indicate that if full-scale testing was made available for low risk pregnant women as part of invasive diagnostics, they would not accept this unquestioningly. An additional aim of the questionnaire survey used was to determine whether certain demographic variables may affect the respondent's attitudes towards full-scale testing. Special attention was given to the relationship between educational level and the answers given to our two questions. The majority of the respondents (67%) stated that they would not opt for full-scale testing and this percentage increased to 82% 4 weeks after the intake consultation.

No demographic characteristics could be found that were significantly associated with the decision to refuse full-scale testing. A low educational level, however, appeared to

be significantly linked with an interest in full-scale testing. As yet, it remains to be established which motives may underlie this latter finding, but it is possible that the impact of full-scale testing was not fully understood by this group of respondents. Interestingly, we found respondents with a low educational level having a negative attitude towards invasive techniques, which is inconsistent with the overall positive attitude within this group towards full-scale testing. Earlier studies reported lower rates of informed choice for women from socio-economic disadvantaged groups.[19] Also the necessity of providing extra information to women with a low educational level has been investigated.[20] Our data confirm that the general basic knowledge on prenatal testing appears to be positively linked with the educational level. In addition, we found that, relative to T1, at T2 the overall interest in full-scale testing was decreased in all groups of respondents (33% at T1 versus 18% at T2). Actively informing pregnant women about the risk of genetic defects in their unborn child may decrease their demand for full-scale testing and, therefore, more knowledge does not inevitably lead to higher demand. It is not yet clear whether anxiety acts as a causal factor for this notion.[21] In addition, it cannot be excluded that a majority of the parents that we questioned chose not to opt for a full-scale test because of a limited understanding of the procedure and a limited insight into the implications of full-scale testing.

The fact that informing patients about serious diseases does not always lead to an increase in testing is in agreement with the results obtained by earlier studies on late-onset diseases, with a specific familiar risk such as Huntington's disease.[22] Even within this population in the Netherlands only 2% of the persons at risk make use of the test offered to them. he choice for parents to achieve comprehensive knowledge or to restrict to one or more certain conditions has now become a reality in prenatal diagnostic testing. This novel development will certainly have important implications on the counselling process and the specific knowledge and skills of the counsellor concerned. Indeed the parent's autonomy to provide a valid consent to be tested for genetic conditions is highly dependent on the adequacy of the counselling they receive.

Offering only full-scale testing to pregnant women who have a referral reason for invasive diagnostics is a matter of debate because this may introduce treatment inequality, i.e., women who do not have an a priori increased risk for a specific genetic defect and, therefore, do not have a referral reason for invasive diagnostics would thus be excluded from full-scale testing. This is in conflict with the principle of equality of care for patients.

At present, parents can choose between molecular targeted testing and traditional karyotyping. This choice is of topical ethical interest in terms of the parent's autonomous 'right to know versus not to know' genetic information on the unborn child. As noted in the report of the human genetics commission: specific ethical considerations relevant to genetic issues in healthcare, a competent patient must give valid consent to be tested for genetic conditions. Some people, however, prefer not to know, particularly

if it contains a disease of late onset and when the likelihood of manifestation of the disease is uncertain.[15]

The technologies to prenatally diagnose genetic defects are undergoing a rapid evolution. Application of molecular targeted testing for the detection of common aneuploidies is already a fact and it is technically possible to increase the number of targets by adding probes for the detection of specific severe diseases such as cystic fibrosis. However, full-scale testing by microarray-based technologies provides an almost unlimited scope to detect genetic anomalies. The decision to apply this technique for prenatal diagnostic purposes, however, still remains to be made. This is because of recent observations that normal copy number variation within the human genome is unexpectedly high,[23] thus hampering the interpretation of the test results and putatively leading to uncertainty and anxiety in the prospective parents. Besides this notion, the ethical-moral question has been raised whether full-scale testing should be offered to pregnant women at all.

In conclusion, our results show that the opportunity to undergo full-scale testing was not accepted casually by pregnant women. Educational level and limited knowledge of genetic defects may have played a role in their decisions. Further research is indicated to gain better insight into the factors that may be of influence to prospective parents in their decisions. The choice to make use of new techniques in the field of prenatal diagnostics is a precious one to be counselled carefully, taking into account the different levels of resolution.

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CURRENT KNOWLEDGE ON THIS SUBJECT

The use of modern molecular genetic technologies for prenatal diagnoses gives rise to many ethical, social and medico-legal problems and dilemmas, because of the possibility of full-scale testing at an unequalled detection level.

- Undergoing prenatal diagnostic tests has been shown to give rise to a scale of psychological, relational and emot
- A competent patient must give valid consent to be tested for genetic conditions. However, some people prefer not to know; particularly if it contains a disease of late onset and when the likelihood of manifestation of the disease is uncertain.
- Low educational level is a factor of concern when providing information to patients to help them making an informed choice in medical decisions. Counselors should take this factor into account in daily practice when offering information.
- Earlier studies described lower rates of informed choice for women from socio-economic disadvantaged groups. Earlier studies described the low uptake of tests available for patients with an a priori risk of late-onset diseases.
- Anxiety possibly plays an important role when making decisions whether undergoing prenatal screening and diagnostic tests.

WHAT THIS STUDY ADDS

- New technologies will soon replace the classic procedure of karyotyping, offering the opportunity to detect thousands of genetic variations in one test, which means full-scale testing at an unequalled detection level. Before these new techniques are implemented in routine clinical care, it is important to explore the sentiments of future parents and the possible problems it will cause when counseling them.
- In view of these new technological developments, the interesting question arises whether pregnant women want to undergo genetic testing for disorders that a priori do not have an increased risk of being present.
- This study showed that the opportunity to undergo full-scale testing was not accepted casually by pregnant women. The majority of our respondents stated that they would not opt for full-scale testing.
- Educational level and limited knowledge of genetic defects may have played a role in their decisions. A low educational level appeared to be significantly linked with interest in full-scale testing.
- This prospective pilot provides insight into the apparent need of a different approach when counseling and explaining difficult choices to parents with a lower educational level.
- Further research is indicated to gain better insight into the choices that prospective parents will make concerning the different levels of targeted testing.

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Chapter 3

Incidental prenatal diagnosis of sex chromosome aneuploidies: health, behaviour and fertility A systematic descriptive review

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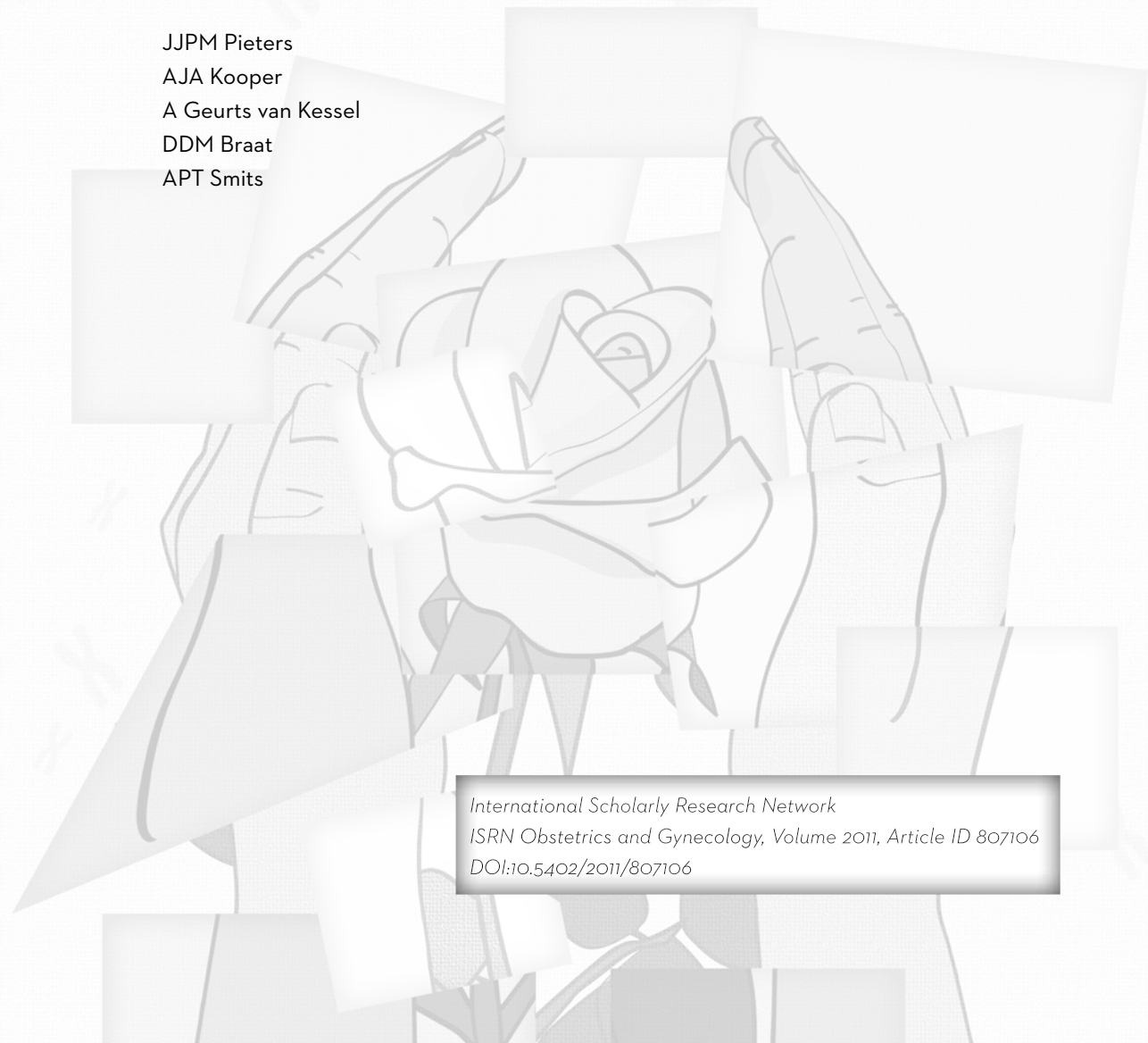

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ABSTRACT

Objective

To assess the diagnostic relevance of incidental prenatal findings of sex chromosome aneuploidies.

Methods

We searched with medical subject headings (MeSH) and keywords in Medline and the Cochrane Library and systematically screened publications on postnatally diagnosed SCAs from 2006 to 2011 as well as publications on incidentally prenatally diagnosed SCAs from 1980 to 2011.

Results

Postnatally diagnosed SCA's demonstrated three clinical relevant domains of abnormality: physical (22-100%), behavior (0-56%) and reproductive health (47-100%), while incidentally prenatally diagnosed SCAs demonstrated, respectively: 0-33%, 0-40% and 0-36%.

Conclusion

In literature incidental prenatal diagnosis of SCAs is associated with normal to mildly affected phenotypes. This contrasts sharply with those of postnatally diagnosed SCAs and highlights the importance of this ascertainment bias towards the prognostic value of diagnosis of fetal SCAs. This observation should be taken into account, especially when considering excluding the sex chromosomes in invasive prenatal testing using Rapid Aneuploidy Detection.

INTRODUCTION

Sex chromosomal aneuploidies (SCAs) are usually diagnosed postnatally in association with specific physical, developmental, and psychological health problems, diminished fertility, or infertility (incidence 1 in 400).[1] Prenatally, the overall incidence of SCAs is 1 in 435,[2] depending on the reason for referral for invasive prenatal testing. For pregnant women whose unborn children are at risk for Down syndrome (e.g., maternal age > 35 years or a positive first trimester screening result without ultrasound abnormalities); the incidence of SCAs is comparable to that of Down syndrome (1 in 300),[3] which represents 25% of all abnormal karyotypes identified.[4] Diagnoses of SCAs in routine prenatal invasive testing are often incidental and present unforeseen findings to the parents, whereas their diagnostic significance is uncertain.[5] As such, these SCAs may be considered as nondiscretionary test information. They are indicative for an abnormality that in the end may not cause any relevant symptoms, or only mild symptoms such as a slightly reduced intelligence and/or a diminished fertility. Taking into account that parents are primarily tested to exclude Down syndrome the diagnosis of an SCA may elicit unforeseen dilemmas about whether or not to terminate the pregnancy.[6] A recent study revealed that in 36% of prenatally detected sex chromosome trisomies these findings have resulted in pregnancy termination.[7] Early and pre-symptomatic diagnoses may, however, provide opportunities for early treatment of certain health and developmental problems and, as such, may represent an advantageous step towards future healthcare for the child. This latter issue has amply been discussed in the literature.[8-12]

Since molecular diagnostic technologies based on Multiplex Ligation-dependent Probe Amplification (MLPA) or Quantitative Fluorescent Polymerase Chain Reaction (QF-PCR) are designed for rapid aneuploidy detection (RAD) of the most common aneuploidies (i.e., of chromosomes 13, 18, 21, X, and Y),[13] the question of whether or not to continue the inclusion of probes for the sex chromosomes arises, since sex chromosome detection does not always provide useful information to parents referred for advanced maternal age.[14] Replacement of full karyotyping with stand-alone RAD for chromosomes 13, 18, and 21 only, would avoid incidental SCA findings. An advantage of early SCA detection may provide opportunities for preventive programs aimed at ameliorating the quality of life. This study consists of a systematic literature review assessing the syndrome-specific, health-related, quality of life (QOL) aspects of patients with postnatally diagnosed SCAs and comparing these results with those of prenatally incidentally diagnosed SCAs.

METHODS: SOURCES, SEARCH STRATEGY, AND STUDY SELECTION

Sources and search strategy

We performed systematic electronic searches during the period of August 2010 until March 2011 in Medline (PubMed) and the Cochrane Library (Database of Systematic Reviews and the Cochrane Pregnancy and Childbirth Group's Trials Register) using medical subject headings (MeSH), filters and keywords. We employed a two-stage process for our searches: first, we assessed the literature over the last 5 years (2006–2011) aimed at gathering information about specific phenotypes associated with postnatally diagnosed SCAs. Second, we assessed the literature from 1980 onward aimed at gathering information about the difference in phenotype after an incidental prenatal detection of SCAs and the associated phenotypes that were ascertained postnatally.

Study selection:

We used the following terms in our PubMed literature search: sex chromosome aberrations "or" sex chromosome disorders "or" X chromosome "or" chromosome human X "or" Y chromosome "or" Turner syndrome "or" 45,X syndrome "or" Klinefelter syndrome "or" 47,XXY syndrome "or" Triple X syndrome "or" Trisomy X syndrome "or" 47,XXX syndrome, and "not" Fragile X syndrome. We used filters for publications in English dealing with human subjects.

We prepared a PICO research query in order to focus our search for the period 1980–2011 (Table 1). The accountability for this research period is the fact that the first studies on ultrasonographically abnormal fetuses were published around 1980. We double-checked all retrieved publications for the following MeSH inclusion criteria and keywords: prenatal diagnosis; disease; prognosis; quality of life; postnatal; phenotypic; prospect; prognosis; unforeseen; unintended; accidental. We combined all search terms and keywords with [MeSH, tiab].

Table 1. PICO research query used to focus literature search and data abstraction

How does a prenatal diagnosis of SCA affect quality of life for individuals, whether intended or not?
PICO-research query:
P: fetus/child with SCA
I: invasive prenatal diagnostic test with *incidental* finding of fetal SCA
C: prenatal ultrasound abnormality or postnatal diagnosis SCA
O: postnatal prognosis in syndrome-specific health related quality of life

Inclusion criteria (stage 1)

All publications used were published in peer-reviewed journals listed in the Science Citation Index. We included original articles, reviews, randomized trials, cohort studies, case-control studies, case reports, letters, expert opinions, and consensus meeting reports dealing with either full-blown or mosaic SCA.

Inclusion criteria for publications according to the research query (stage 2)

We used the criteria of stage 1, publications concerning the incidental prenatal SCA findings in relation to the postnatal, syndrome-specific, QOL prognosis and a comparison with this prognosis for postnatally ascertained SCAs.

Exclusion criteria

We excluded all publications dealing with ultrasonographic fetal abnormalities, epidemiology, registration or counseling issues in relation to SCAs, cytogenetic or molecular technical prenatal diagnostic research and animal studies.

Publication selection for stages 1 and 2

In both stages, the authors (JP and AK) screened the titles of all potentially relevant publications and marked them as "included" (title clearly related to SCA and meeting the inclusion criteria set for both stages) or "excluded" (not related, other syndrome, or not meeting the inclusion criteria). Next, the authors (JP and AS) screened the abstracts of the remaining titles, again marking them as "included" or "excluded". All authors discussed the items that were unclear until they reached agreement. Finally, we grouped all included publications by syndrome.

RESULTS

Stage 1: SCA and syndrome-specific quality of life, 2006-2011

Using the criteria set (see Methods) we retrieved 1093 potentially relevant publications from the period 2006-2011. Specifically, we screened for issues concerning syndrome-specific, health-related, QOL prognoses for persons exhibiting SCA. This resulted in 607 selected publications dealing with either Turner syndrome (TS, *n*=400), Klinefelter syndrome (KS, *n*=193), Triple X syndrome (Tr X, *n*=7), or other SCAs (*n*=7), see Table 2.

Syndrome-specific, health-related, quality of life domains

Based on the results, we were able to determine three domains that could be considered the core outcome domains in assessing the syndrome-specific QOL of patients with SCA, i.e., physical health, behavior, and reproductive health (Table 2, Table 3).

Table 2. Number of publications on SCA in the period 2006-2011. Syndrome-specific quality of life domains

Publications per domain	45,X (n,%)	45,X mosaic (n,%)	47,XXY (n,%)	47,XXY mosaic (n,%)	47,XXX (n,%)	47,XXX mosaic (n,%)	Other SCA (n,%)	Other SCA mosaic (n,%)
I: physical health (n=446)	295 (78.5%)	21 (87.5%)	117 (61.6%)	2 (66.7%)	4 (66.7%)	-	5 (100%)	2 (100%)
II: behavior (n=73)	41 (10.9%)	-	31 (16.3%)	-	1 (16.7%)	-	-	-
III: reproductive health (n=88)	40 (10.6%)	3 (12.5%)	42 (22.1%)	1 (33.3%)	1 (16.7%)	1 (100%)	-	-
N= 607	376 (100%)	24	190 (100%)	3	6 (100%)	1	5 (100%)	2

N= number of publications found 2006-2011
(%)= percentage of total number of publications on that type of SCA

Table 3. Categorization of disease-specific QOL domains related to SCA

domain I - physical health	growth and bone mineral density cardiovascular, metabolic and other disease auto-immune disease other SCA-associated health problems overall disease susceptibility and mortality
domain II - behavior	psychosocial functioning quality of life sexuality
domain III - reproductive health	puberty fertility assisted reproduction techniques disease

Domain 1: physical health

Physical health was characterized by abnormal growth, diminished bone mineral density, cardiovascular, metabolic, and other disease, autoimmune disease, increased cancer risk, dental problems, otologic problems, and overall disease susceptibility and mortality. Also, early screening and preventive programs for health were mentioned. All SCA-related health hazards and overall QOL were said to benefit from early recognition, prompt diagnosis, and pharmacologic or psychosocial treatment in an early stage. Other SCAs were associated with the exacerbation of certain medical conditions relative to the burden of these conditions among the general population. Examples of such conditions are asthma, congenital heart defects, and increased morbidity or mortality rate caused by epileptic insults, cardiovascular disease, or respiratory disease. Most health hazards

were described in association with TS and KS, while Tr X syndrome and other SCA-related disorders were only rarely discussed in relation to domain 1. A relevant finding was the importance of early recognition and preventive treatment of certain health problems.

Domain 2: behavior

Problematic psychosocial functioning and learning capacities, diminished QOL, and problems with relationships and sexuality were discussed in association with SCA. Certain behavioral weaknesses (DSM IV: Adjustment Disorder with Mixed Disturbance of Emotions and Conduct) and limited skills associated with specific brain asymmetries, especially in TS and KS, have been found, and a high body mass index has been related to a negative body attitude. Early psycho-educational support and medical therapy were found to positively affect the patients concerned. Health aspects, infertility, aberrant stature, and psychosocial disabilities negatively influenced the QOL. Positive effects of early growth hormone and estrogen treatment on the psychosocial functioning and self-esteem of girls with TS and of testosterone treatment on the pubertal changes, behavior, and sexuality of boys with KS have been reported. Domain 2 was a focal point of attention both for individuals with Tr X syndrome and those with other SCAs. Attention deficit disorders, autism spectrum disorders, mood disorders, and tic disorders were found.

Domain 3: reproductive health

A variety of aspects of fertility and endocrinology were denoted as problematic in TS and KS, including problematic puberty or abnormal gonadal development (TS: n=25 and KS: n=33 reports, respectively), but there were very little reports of infertility associated with other SCAs. Although assisted reproduction techniques (ART) created new possibilities of procreation, associated risks were mentioned.

Most patients with a non-mosaic SCA karyotype (TS and KS) were infertile, whereas those with mosaicisms were usually fertile. Also here, early gamete cryopreservation and ART have made procreation possible, but medical hazards and the risk of transmission of aneuploidy to the next generation have been discussed.

Domain 1 (physical health) was mostly discussed in the SCA literature in general and, specifically, in conjunction with all types of SCA. Behavior was not a prominent issue, and reproductive health was mostly discussed in relation to KS. For further details about the incidence of the domains discussed per syndrome in the period 2006-2011, see Table 3 and Figure 1; the study selection process is shown in Figure 2.

Figure 1. Publications on SCA 2006-2011, syndrome-specific quality of life domains
Incidental prenatal detection vs postnatal diagnosis

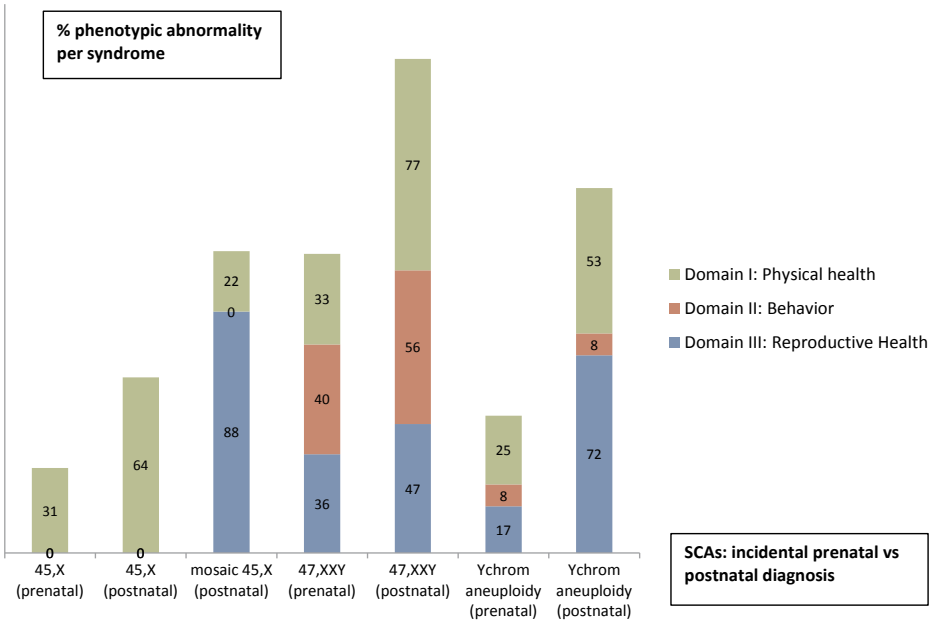
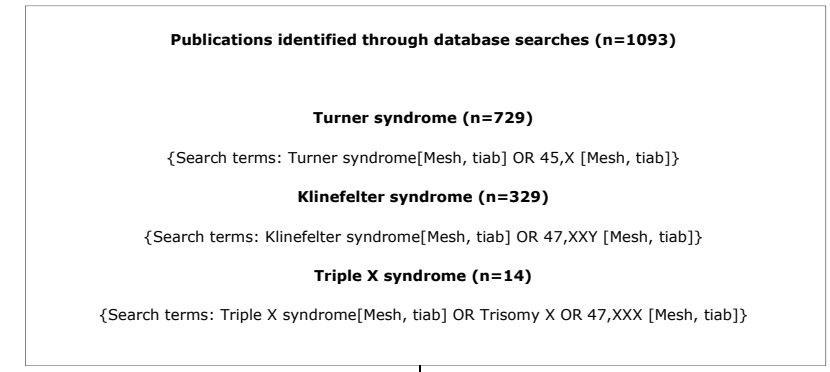


Figure 2. Prisma Flowchart of systematic study selection (stage 1: 2006-2011)



Publications included for judging domains (n=607)

	Domains		
	I (%)	II (%)	III (%)
Turner syndrome (n=376)	78.5	10.9	10.6
mosaic 45,X (n=24)	87.5	-	12.5
Klinefelter syndrome (n=190)	61.6	16.3	22.1
mosaic 47,XXY (n=3)	66.7	-	33.3
Triple X syndrome (n=6)	66.7	16.7	16.7
mosaic 47,XXX (n=1)	-	-	100
Other SCA (n=5)	100	-	-
mosaic (n=2)	100	-	-

Stage 2: Incidental prenatally diagnosed SCA and postnatally ascertained SCA, 1980–2011

We searched PubMed and the Cochrane Library for eligible publications about the incidental prenatal diagnosis of SCA with special attention to our PICO research query. We identified 6345 potentially relevant SCA publications using the MeSH terms, search conditions, and filters described in the Methods section. We excluded publications that did not meet all our inclusion criteria. We included 1278 publications that were subjected to peer review with regard to the relevance of an incidental intrauterine SCA finding for the long-term developmental prognosis. Finally, we included 32 publications for abstract screening and categorization by domain. After abstract screening, 21 potentially relevant publications remained, seven of which were selected after full text screening (Table 4 and Figure 3) relating to the PICO query: an incidental prenatal diagnosis of SCAs, description of the associated phenotype and the syndrome-specific quality-of-life aspects for postnatal life, and a comparison with postnatally ascertained SCAs.

1. Wheeler et al.[15] compared the postnatal phenotypes of six incidental prenatally diagnosed 45,X/46,XY fetuses of couples with an increased risk for a chromosome abnormality. The postnatally diagnosed children were all phenotypically abnormal in domain 3, whereas the incidentally prenatally diagnosed fetuses all developed into phenotypically normal boys.

2. Pettenati et al.[16] reported a comparison of three incidental prenatally diagnosed cases with 45,X/47,XYY mosaicisms with four cases diagnosed postnatally with similar mosaicisms. The three incidental prenatally diagnosed cases were all physically normal at birth, whereas the postnatally diagnosed cases all exhibited phenotypic anomalies (which had been the reason for karyotyping).

3. Hsu[17] reviewed many studies on Y chromosome aneuploidies (except non-mosaic 47,XYY), going back to publications of as early as 1961; and reported in this elaborate review on 600 cases with mosaicisms for genotype-phenotype correlations. Of these, 93 were incidentally prenatally diagnosed while all the other cases were postnatally diagnosed because of phenotypic anomalies. All postnatally diagnosed cases were phenotypically abnormal (which had been the reason for karyotyping), while 67-97% of the prenatally diagnosed cases exhibited a normal male phenotype at birth.

4. Koeberl et al.[18] reported on 12 incidental prenatally diagnosed 45,X/46,XX patients and compared the outcome with 41 postnatally diagnosed girls. They concluded that, although a certain ascertainment bias did exist, the prevalence of a 45,X/46,XX mosaicism was 10 times higher among the group diagnosed prenatally as compared

to postnatally diagnosed TS patients. Absence of hydrops fetalis may account for the milder phenotype of the prenatally diagnosed group.

5. Gunther et al.[19] compared 16 incidental prenatally diagnosed patients with TS with 72 traditionally diagnosed children (typical fetal anomalies on ultrasound or postnatal clinical features). The incidental group exhibited significantly fewer phenotypic TS features than the traditional group. The authors concluded that a significant ascertainment bias does exist in our understanding of TS, with important implications for prenatal counseling in case no fetal abnormalities are found.

6. Zeger et al.[20] compared phenotype data from 55 postnatally diagnosed 47,XXY boys with those from 35 prenatally diagnosed 47,XXY boys and found no significant differences between the two groups. Invariably, all features occurred comparable in both groups.

7. Girardin et al.[21] reported a comparison of clinical symptoms of adolescents with KS after incidental prenatal diagnosis (n=11) with those of adolescents diagnosed because of an abnormal phenotype (n=17). They conclude that there were some differences between the two groups with respect to the presence of gynaecomastia, school delay, and testosterone substitution. Although these differences were not significant, the incidence of phenotypic problems in the postnatally diagnosed group was somewhat higher than in the incidental prenatally diagnosed group. The incidences differed significantly in comparison with the general population.

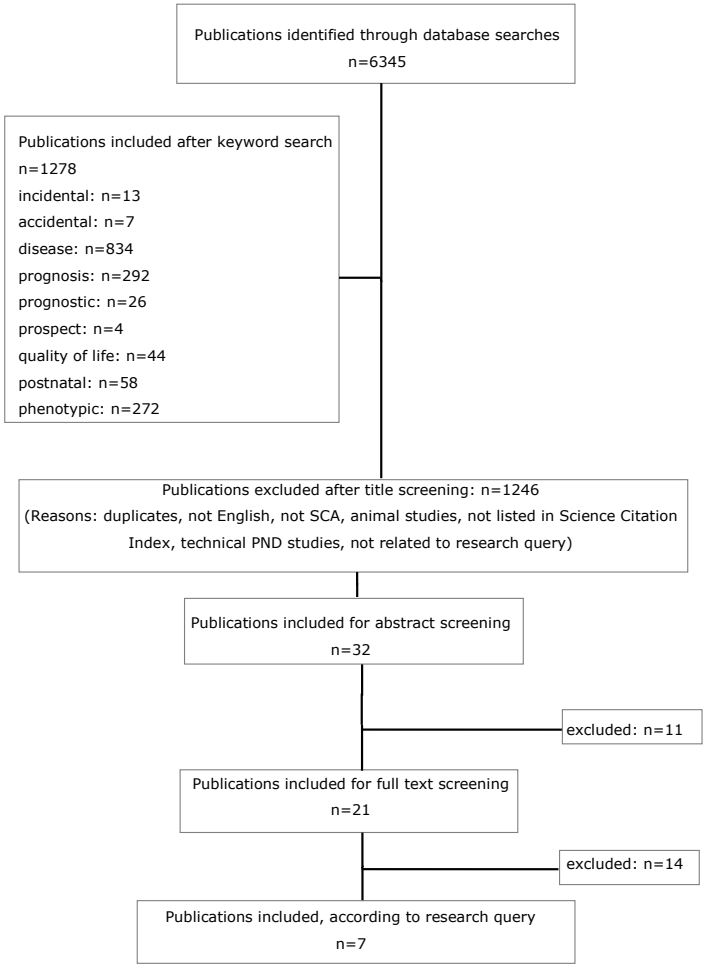
Table 4. Publications on the incidental prenatal diagnosis vs postnatal diagnosis of SCA in period 1980-2011: Case-control studies, clinical comparison, outcome data

author, year	prenatal incidental diagnosis SCA outcome of domains:	postnatal diagnosis SCA outcome of domains:	Type SCA
1.			
Wheeler, 1988	6 pregnancies, 3 term, 1 premature delivered infants, 1 termination, 1 intra-uterine death: 4 healthy children, 2 fetuses normal on autopsy	9 children with abnormal intern / extern genitalia, 7 children with ambiguous genitalia at birth, 2 children with primary amenorrhea at age 17	45,X/46,XY mosaicism
	Domain I: 100% normal Domain II: 100% no mental retardation Domain III: 100% normal reproductive fertility and normal genitalia	Domain I: 22% short stature, webbed neck Domain II: 100% no mental retardation Domain III: 88%: ambiguous genitalia, changed sexual assignment, rudimentary phallus, urogenital sinus, hypospadias, undescended testes; 22%: primary amenorrhea	
2.			
Pettenati, 1991	3 prenatally detected cases; clinical comparison with the postnatally detected cases	4 postnatally detected cases, clinical comparison with the prenatally detected cases	45,X/47,XYY mosaicism
	Domain I: two phenotypically normal term born infants, 1 postermination normal male fetus on autopsy Domain II: normal Domain III: normal external male genitalia in both children; fetus with normal position of testes, normal penis and scrotal development	Domain I: all had phenotypic abnormalities: short statue, short limbs, cubitus valgus, nevi, epicathical folds, depressed nasal bridge, micrognathia, low hair implantation, webbed neck, shield chest, posteriorly rotated ears Domain II: one child developmental delay Domain III: all children had genital abnormalities: ambiguous genitalia, mixed gonadal dysgenesis, streak gonads, hypospadias, small penile length	
3.			
Hsu, 1994	phenotype of 93 prenatally diagnosed cases, liveborn and abortuses	phenotype of 503 postnatally diagnosed cases	Y chromosome aneuploidy (except non-mosaic 47,XYY)
	Domain I: not discussed Domain II: not discussed Domain III: 67-97% normal gonads or genitalia	Domain I: 0-25% phenotypically abnormal stature Domain II: not discussed Domain III: 66-100% abnormal gonads or genitalia	

Table 4. Publications on the incidental prenatal diagnosis vs postnatal diagnosis of SCA in period 1980-2011: Case-control studies, clinical comparison, outcome data (continued)

author, year	prenatal incidental diagnosis SCA outcome of domains:	postnatal diagnosis SCA outcome of domains:	Type SCA
4. **Koeberl, 1995**	12 prenatally diagnosed cases Domain I: all (100%): normal growth, 3 (25%) health problems: ASD, ptosis, dysplastic kidneys Domain II: 8% mental retardation Domain III: 10 (83%) : normal ; 2 (17%): labial fusion, urogenital sinus	41 postnatally diagnosed patients Domain I: 22-53% malformations or phenotypic problems (edema, cardiac, renal otologic, gastrointestinal) Domain II: 8% developmental delay Domain III: 72% no spontaneous menarche	45,X/46,XX mosaicism
5. **Gunther, 2004**	16 incidentally diagnosed cases Domain I: 31% heart defects, 25% renal anomalies, length/ height deficit (-1.1 SDS), weight deficit (-1.0 SDS) Domain II and III: not discussed	72 traditionally postnatal diagnosed cases Domain I: 64% heart defects,19% renal anomalies, length/ height deficit (-1.7 SDS), weight deficit (-1.7 SDS) Domain II and III: not discussed	45,X
6. **Zeger, 2008**	35 prenatally diagnosed boys Domain I: tall stature, hypotonia, increased BMI Domain II: Speech and reading therapy Domain III: below average size penis and testes, low testosterone level, low inhibin B and AMH levels, elevated FSH and LH levels	20 postnatally diagnosed boys Domain I: tall stature, hypotonia, increased BMI Domain II: Speech and reading therapy Domain III: below average size penis and testes, low testosterone level, low inhibin B and AMH levels, elevated FSH and LH levels no significant differences with prenatal group	47,XXY
7. **Girardin, 2009**	11 prenatally diagnosed patients Domain I: gynaecomastia 33%, BMI, height: normal Domain II: school delay 40% Domain III: all had spontaneous puberty, testosterone substitution 36%	17 postnatally diagnosed patients Domain I: gynaecomastia 77%, BMI, height: normal Domain II: school delay 56% Domain III: all had spontaneous puberty, testosterone substitution 47%	47,XXY

Figure 3. Flow diagram of systematic literature search of SCA 1980-2011: phenotype and health of incidental prenatal diagnosis vs postnatal diagnosis



Conclusions of stage 2

Physical health (domain 1) was abnormal for 0-33% of those who were diagnosed incidentally prenatally, whereas it was abnormal for 22-100% of those who were diagnosed postnatally. The behavior (domain 2) was abnormal for 0-40% of the incidental prenatally diagnosed patients, while the behavior was abnormal for 0-56% of the postnatally diagnosed patients. The reproductive health (domain 3) was problematic for 0-36% of the incidental prenatally diagnosed patients, whereas it was problematic for 47-100% of the postnatally diagnosed patients (Table 4, Figure 3).

Four of seven publications regarding the incidental prenatal diagnosis of SCAs dealt with mosaic SCAs, which resulted in normality in the domains of physical health (100%), behavior (100%), and reproductive health (67-100%). For non-mosaic cases, the normality results were: physical health, 67-75%; behavior, 60-100%; and reproductive health, 64-83%. For postnatally ascertained SCAs, the mosaicism-related normality results were: physical health, 0-47%; behavior, 75-100%; and reproductive health, 0-34%, while for non-mosaic cases, the normality results were: physical health, 0-36%; behavior, 0-44%; and reproductive health, 0-53%.

DISCUSSION

A putative change in prenatal diagnosis policy from full karyotyping to stand-alone, rapid aneuploidy detection (RAD) with the standard inclusion of probes for the sex chromosomes needs to be assessed carefully. The purpose of this review was to reveal the clinical relevance of a diagnosis of SCA for the postnatal quality of life (QOL) of symptomatic individuals and for those in whom the prenatal diagnosis was an incidental finding. First, we assessed the SCA literature of the last 5 years, in order to gather information about the specific, phenotypic and clinical problems associated with postnatal SCA detection. By doing so, we found that these publications all addressed one or more domains of syndrome-specific health. Next, we assessed whether the phenotypes of patients with SCA were comparable, irrespective whether the diagnoses were made postnatally or prenatally without any ultrasonographic abnormalities, due to an incidental finding. To this end, we screened all SCA literature between 1980 and 2011. We used 1980 as a starting point since the first studies of fetal ultrasound abnormalities that were associated with a genetic syndrome were published around that time.[22]

We found in our first literature search that physical health (domain 1) is by far most often discussed (74%), followed by reproductive health problems (domain 3, 14%) and behavior (domain 2, 12%), see Table 2 and 3. Problematic physical health is an important issue for patients with an SCA. It manifests itself as disturbances in growth or bone mineral density and cardiac, autoimmune, and other diseases, and it certainly influences the QOL. Many publications dealing with domain 1 mentioned possible early preventive measures. Timely screening and treatment may significantly improve the QOL of patients with certain very health-menacing conditions such as abnormal growth, diminished bone mineral density, and cardiovascular problems. Early detection of SCA-related problems varied between domains. Some authors have elaborated on the minimal negative side-effects of lifelong hormonal treatment, but it is clear that the positive effects of this treatment far exceed the potentially negative effects.[23,24] Apparently, reproductive health problems and behavioral abnormalities trouble these patients

to a much lesser extent than physical health problems. Early preventive management has been described; e.g., induction of puberty and breast development in TS and technical advances in ART increasingly permit parenthood. We are aware of the fact that the number of selected publications is not automatically a measure of its importance, but its frequency is of note.

In the second stage of our literature study, we focused on the impact of the *incidental* finding of a prenatal SCA on the postnatal outcome. The selected publications report on comparisons of patients who were incidentally prenatally diagnosed with patients who were diagnosed through traditional postnatal karyotyping (either non-mosaic or mosaic). In six out of seven publications, the overall phenotypic outcomes affected incidentally prenatally diagnosed SCA patients significantly less than those who were postnatally diagnosed and karyotyped because of phenotypic abnormalities. In one publication,[20] no significant differences in certain phenotypic characteristics were noted after prenatal or postnatal diagnosis.

It is well known that certain fetal ultrasonographic abnormalities are associated with a poor prognosis for the child after birth, because they reflect early disturbances in organ functioning.[18] Genetic mosaicisms are known to be related to mild, or even complete lack of phenotypic features, and those affected may go through life without ever knowing they carry a genetic abnormality.[21,25] Saenger's review[26] showed that most prenatal diagnoses of TS occur by chance after routine invasive procedures for advanced maternal age, and the phenotypes of these women are usually less pronounced.[19] Those with TS detected by ultrasound (increased nuchal translucency or fetal hydrops) exhibit a high rate of spontaneous fetal loss or associated cardiac or renal disease.[18,27] Bondy[10] discusses the fact that incidentally diagnosed TS in prenatal diagnostic tests for advanced maternal age lead to termination of most of these pregnancies, and that the ability to assess clinical outcome is limited. High termination rates for incidentally diagnosed TS reflect overrated pessimistic views, as the phenotype of someone with an incidentally ascertained TS is compared with the phenotypic problems of those who are postnatally diagnosed, or prenatally diagnosed because of fetal abnormalities. Only 10% of those with KS are diagnosed prenatally, another 25% are diagnosed during childhood or adolescence, and 65% remain undiagnosed.[28] KS is the most frequent genetic cause of infertility[29,30] (11% of azoospermic men), and parents often report frustration with the consequences of a delay in diagnosis.[31]

Publications on the diagnosis of Tr X syndrome did not address its incidental prenatal finding and the subsequent clinical consequences. A recent literature review of Tr X[32] (Otter) reports mainly personality and behavioral problems and finds that many of the studies reviewed were "biased because of referral bias". Furthermore, the incidental prenatal finding of Tr X is discussed only in terms of termination rates and intercultural differences. The author concludes that Tr X syndrome is not rare, but often remains un-

diagnosed. Approximately 20% of other SCAs have higher grade chromosome aneuploidies (e.g. 48,XXXY) or mosaicisms and the associated clinical health issues are usually very mild.

To the best of our knowledge, this study for the first time categorizes the abundant SCA literature into three syndrome-specific, QOL-related domains of health. This categorization provides a way to judge the importance of phenotypic problems of an incidental prenatal ascertainment of SCA relative to a postnatal ascertainment of SCA. However, we acknowledge that even if there is an abundance of publications about the clinical implications of SCA for the affected individual, there is little literature that compares the difference in QOL prognoses for incidental prenatally diagnosed patients to those diagnosed postnatally. Despite this limitation, however, we have endeavored to review the literature in a way that is helpful to professionals who wish to use this information in counseling and decision-making processes.

Routine prenatal testing procedures with the standard diagnostic outcome of fetal gender offer a unique opportunity for early prevention and management of SCA-related disease, psychological issues, and fertility issues. This benefit is evident from the professional point of view, but it should be balanced against the possible negative impact of this unexpected diagnosis for the future child. Incidental prenatal diagnosis of a SCA may cause stigmatization and possible damage to the child's self-esteem or distortion of the family's perception of the child. Indeed, parents may consider termination of the pregnancy while being uncertain about the prognosis for the child.[33,34] Molecularly targeted testing through RAD enables the exclusion of the sex chromosomal markers, thus avoiding unexpected sex chromosome-related SCAs. A discussion about this policy has been published.[35] (Hills) It is considered a more or less acquired right in routine prenatal practice that pregnant women can be informed about the sex of their unborn children if they wish to know. However, ultrasonography can also determine fetal gender with high accuracy (98.3%) at 13 weeks of gestation,[36] and an almost 100% accuracy is achieved around 20 weeks of gestation.[37]

CONCLUSION

Early knowledge of a SCA could help the parents and their child to adapt to the consequences of the corresponding syndrome in a timely fashion rather than having the information presented at puberty or even a later stage in life. This fact must be balanced against the ethical concerns about the diagnosis of a genetic condition with an uncertain prognosis. This review shows that, in the medical literature, the syndrome-specific QOL of patients with a SCA contrasts sharply between postnatal and incidental prenatal diagnoses for the three major domains of health. Phenotypic abnormalities in prenatal

or postnatal life were found to be associated with significantly more severe clinical consequences. In contrast, the absence of fetal abnormalities in incidental prenatal diagnoses was found to be associated with a normal to mildly affected phenotype and as such, a significant ascertainment bias may exist in our understanding of SCA. Although it seems rather obvious that the outcome of a child with an incidental discovery of a sex chromosome abnormality is better than one who is diagnosed postnatally, this review of the literature since 1980 shows that counselors may reassure the parents in the knowledge that indeed all studies until now support this conclusion.

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Chapter 4

Parents' perspectives on the unforeseen finding of a fetal sex chromosomal aneuploidy

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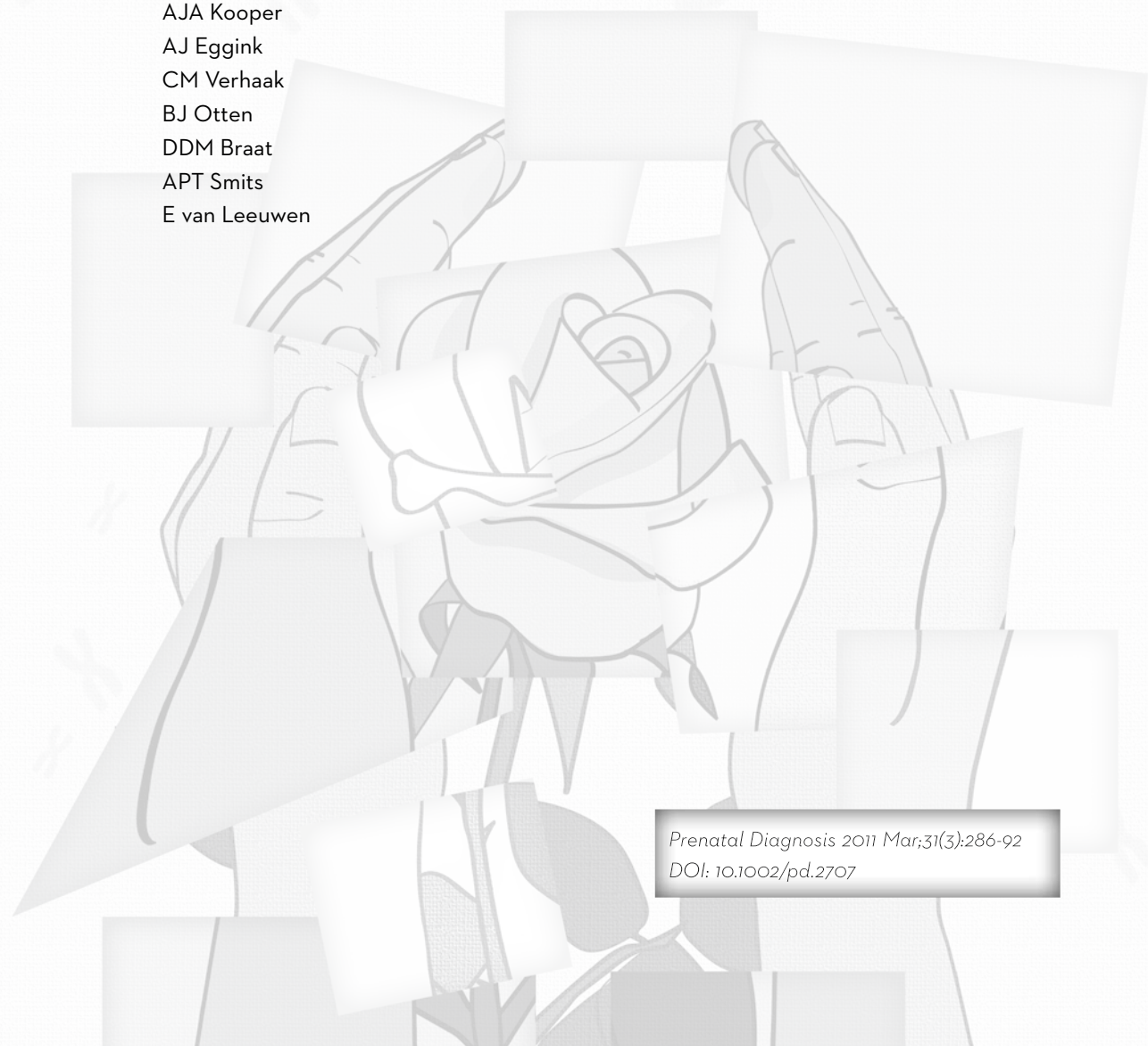

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ABSTRACT

Objective

To investigate the parental perspectives of being confronted with an unforeseen fetal sex chromosomal aneuploidy (SCA), in light of the fact that this accidental finding is avoidable by rapid aneuploidy detection (RAD).

Methods

Exploratory qualitative interview study. We conducted 16 semi-structured interviews with parents who decided to continue pregnancy after the unforeseen finding of a fetal SCA.

Results

The communication of the unforeseen finding of SCA; the informed decision-making process concerning the pregnancy follow-up and the child and its future were the extracted themes. Parents were not prepared to accidental findings in routine prenatal diagnostics. All started an unguided search on the Internet. It is not at all clear whether parents have preference for an RAD test with X and Y probes. Parents were satisfied with the post-test professional information they received to make an informed decision, whereas after birth questions still remained to be answered.

Conclusion

Parents' perspectives may serve as major contributors to research on the question whether or not the X and Y probes should be standard included for purposes of RAD. The fact that RAD has the possibility to avoid accidental findings of SCAs, brings up the question whether any benefits outweigh the potential harms.

INTRODUCTION

Chromosome abnormalities investigated by invasive prenatal testing are associated with severe, moderate or mild diseases, although sometimes there is uncertainty about the clinical relevance. Many women who undergo invasive prenatal tests are unaware of the possible adverse consequences of uncertain prognosis.[1] The birth prevalence of sex chromosomal aneuploidies (SCAs) is 1/426,[2] depending on the reason of referral. In pregnant women 'at risk' for Down syndrome (maternal age >35 years), the risk of SCAs is 1/300.[3]

SCAs are associated with specific physical, developmental and mental health problems, diminished fertility or infertility and are often diagnosed postnatally with an incidence of 1/400.[4] The diagnosis of an SCA in women referred for advanced maternal age (AMA) and 'at risk' for Down syndrome is experienced as unforeseen. To be confronted with an unforeseen finding is a confusing experience and as such a difficult dilemma arises regarding decision-making on continuation of pregnancy. A recent Eurocat study showed that prenatally detected sex chromosome trisomies resulted in termination of pregnancy in 36%.[5] Consequently, there is a need for an exploratory study to determine from parents' perspective the diagnostic relevance of accidental findings, especially SCAs.

As new diagnostic tests, such as MLPA (Multiplex Ligation-dependent Probe Amplification) and QF-PCR (Quantitative Fluorescence Polymerase Chain Reaction), have been implemented in prenatal diagnostics for rapid aneuploidy detection (RAD) of the most common fetal aneuploidies (13, 18, 21, X and Y), the possibility arises to exclude X and Y probes and herewith avoid findings of a fetal SCA. The discussion whether or not to continue the standard inclusion of the X and Y probes in RAD has been ongoing.[6]

The aim of this study was to explore in depth the parental experiences of being confronted with an unforeseen prenatal finding related to the decision of completing or terminating pregnancy.

METHOD AND ANALYSIS

Ethics approval for the study was granted by the institutional Research Ethics Committee (CMO, Arnhem- Nijmegen) and the National Ethics Board for Research on Humans (CCMO, The Hague). General practitioners were contacted to examine the actual status of the parents. The head of the Ob/Gyn Department initiated postal contact with the parents, inviting them to participate in an interview with the principal investigator (JP), along with a response form. Upon receipt of a positive response form, participants were

telephoned to arrange an interview date, time and location. They were asked for verbal consent to record the interview.

Parents referred for AMA and confronted with a fetal SCA who choose to continue their pregnancy were included. The tests were performed in the Department of Human Genetics of the Radboud University Nijmegen Medical Centre in the period between 1994 and 2006. Twelve couples were included: eight couples responded positively, two replied that they wished not to participate, both stated that they had received excellent care but had no wish to talk about the events again; one couple did not reply; one family was not contactable.

All interviews were held by the same investigator after having been trained in theoretical and practical aspects of qualitative research including the grounded theory approach, the scientific status of the interview and the concepts of methodical and systematic analysis of the data to objective and reproducible results. Pilot interviews have been performed as practical training on different stages from thematizing, transcribing, analyzing, verifying and reporting. The interviews took place between October 2008 and December 2009 and lasted between 40 and 80 min (mean: 60 min). Separate semi-structured interviews were held with both parents after the prenatal diagnosis of a full-blown as well as mosaic SCA. In a semi-structured way, parental experiences were investigated in depth, using an interview guide with relevant topics, composed after literature search and consultation with experts. Participants were specifically asked their opinion on the routine inclusion of the X and Y probes in the test kit for prenatal diagnosis. Sixteen separate interviews were completely taped, transcribed verbatim, coded and analyzed. The transcripts of each participant's interview were coded using the Atlas t.i. program for qualitative research. Interview transcripts were read line by line, sentences and phrases were assigned specific codes, using quotes to highlight them. Further conversion resulted in an organized hierarchical list of themes and subthemes. The analysis process was both inductive and iterative, performed by the principal investigator and discussed with three other investigators until agreement was reached. Hereafter, coding was renewed and re-discussed. Theoretical saturation was reached (no more new themes identifiable in additional interview data) according to the definition described by Guest *et al*.[7]

RESULTS

Sample characteristics

At the time of the invasive prenatal test, mean maternal and paternal age was respectively 38.4 years (range 36–40) and 39.7 years (range 36–44). Mean maternal and paternal age at the time of the interview was 47 years (range 42–52) and 48.5 years (range 43–54), respectively. The cytogenetic findings (full-blown or mosaic) were 45,X, 47,XXY and 47,XXX (Turner, Klinefelter and Triple X syndromes, respectively). Demographic details regarding the parents (eligible and non-eligible) are shown in Table 1. During the studied period, 13 171 invasive tests were performed for AMA, 51 (0.3%) SCAs were diagnosed of which 7 (14%) were aborted.

Table 1. Socio-demographic characteristics of participants

diagnosis	**1** **45,XXX**	**2** **47,XXY**	**3** **47,XXY**	**4** **45,X mosaic**	**5** **45,X**	**6** **47,XXX mosaic**	**7** **47,XXY mosaic**	**8** **45,X**	**Mean age [years]**	**9** **47,XXX not interested**	**10** **47,XXX not interested**	**11** **47,XXX moved abroad**	**12** **47,XXY no answer**
numerical code	1A	2A	3A	4A	5A	6A	7A	8A		no code	no code	no code	no code
age mother [years]	36	40	37	38	38	40	40	39	38.4	38	42	41	41
pregnancy nr	1	3	1	1	1	1	1	1		3	2	2	2
education [low, medium, high]	medium	medium	high	high	high	medium	low	high		-	-	-	-
numerical code	1B	2B	3B	4B	5B	6B	7B	8B		no code	no code	no code	no code
age father [years]	38	42	39	37	41	36	44	41	39.7	-	38	44	41
education [low, medium, high]	medium	high	high	high	high	high	low	high		-	-	-	-
marital status	m	d	m	m	m	m	m	m		-	-	-	-

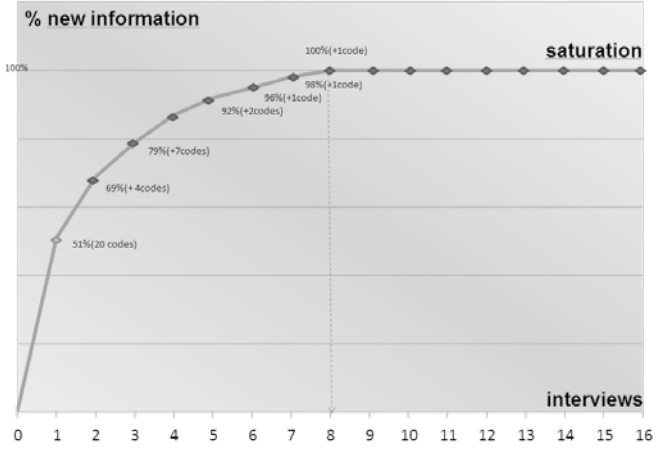
educational level: low =primary school; medium = secondary school; high = high school / university
marital status at the time of the interview: m=married; d= divorced
nr 9-10 : no wish to participate; nr 11: not contactable (moved abroad); nr 12: no answer
missing data: -

Interview findings

Parents' perspectives of fetal SCAs were surveyed and subsequently categorized into themes and subthemes. Saturation of information was reached after eight interviews (Figure 1).

All couples stated that their reason for having the test was to detect Down syndrome. In one couple there was previous experience with invasive prenatal testing, with a normal test result. None of the couples had considered unforeseen findings like a SCA. Six couples intended to terminate the pregnancy if Down syndrome was present, whereas two couples had doubts about termination. The relatively mild clinical features associated with SCAs in comparison with that of Down syndrome prompted all the couples to continue the pregnancy. All the parents communicated with family or friends, and seven parents (three mothers and four fathers out of six couples) said that they were religious, but they said this would not influence their decision-making process. The risk of the invasive test was acknowledged and in two pregnancies a second test was done because of uncertainty about the diagnosis SCA (mosaicism, not enough material); these couples were particularly distressed. Four of the 16 parents (three mothers and one father out of four couples) wanted to know the fetal gender. Almost all the mothers (n = 7) expressed negative effects on emotions during pregnancy and childbirth; only two fathers mentioned this problem. Normal results in the additional tests (amniocentesis, ultrasound) reassured parents; in one case, ultrasound scans repeatedly showed hydronephrosis, which was experienced as very burdensome. All but one of the parents mentioned that they trusted the test result; in two cases, karyotyping was repeated after birth at their request, because the child showed no apparent problems. Most of the parents appreciated knowing about the syndrome, because it enabled them to provide

Figure 1. Saturation of information in interviews with parents



their child with adequate support, whereas one couple would have preferred not to be told at all. Parents were asked to formulate advice for professionals, to help improve future care. Not all the parents were able to give advice (n = 3), some of them gave advice during the interview (n = 5) and others did so when asked (n = 8). All but two of the parents would make the same choice for invasive testing again in a next pregnancy (two couples had already done so).

Analysis of the transcripts revealed three main themes. Subthemes could be defined (Table 2) and relevant quotes were selected to highlight the subthemes. Examples of the advice given by the parents are shown in Table 3.

Table 2. Main themes and sub-themes

1. communication of the unexpected result	1.1 telephone call
	1.2 first emotions
	1.3 comprehension of facts
2. decision-making process	2.1 Internet-search
	2.2 information and support
	2.3 role general practitioner
3. child & future	3.1 quality of life
	3.2 medical concerns
	3.3 knowledge of psychosocial problems
	3.4 need for guidance and support

Table 3. Advises to professionals

		numerical code
communication of the unexpected result	prior to test more information on possibility of an unexpected or uncertain finding	1A 3A/B
	preferably no resident for invasive procedure	5B
	telephone call rather in evening instead of afternoon (quiet hours, husband at home)	8A
decision-making process	guidance by professional when searching for extra information on the Internet	2B
	need for written information or leaflet immediately after the post-test counselling	4A
child & future	need for guidance and support of the child, unclear how to arrange this	8A/B
	need for information leaflets on syndrome after birth	4A

Theme 1: Communication of the unforeseen findings after RAD

Receiving an unexpected telephone call, while waiting for a letter of reassurance

All the parents expected that the test result would be reassuring and had been waiting for a letter with 'good news'. At an unexpected moment, they had been confronted with unforeseen findings.

- *I received this phone call, I was at work. He started to tell me about Turner syndrome, over the telephone. I think the first thing he said was: don't start looking it up on the Internet. (5B)*

Feelings of shock and distress, or even anger, directly after the telephone call about the unforeseen results

All the parents reported feelings of anguish and fear, even anger or panic.

- *About a week later or so, a lady phoned and said that we had to go to the hospital, because something was wrong and that really frightened us. (1A)*

Poor comprehension of the information given in this telephone call, due to emotional turmoil

Generally, the parents showed poor understanding of the information they received during the telephone call about the unforeseen findings, mostly due to strong emotions and grief. In all the cases, an appointment was made for a visit to the hospital within 1 or 2 days.

- *The anger, over the telephone how it was told. I found it very overwhelming and very frightening as well. (1B)*
- *They rang my partner, so he came to pick me up from work in a panic and we were going to have a very large baby, he hadn't understood that very well. (2A)*

Theme 2: The decision-making process of whether or not to continue the pregnancy

After the telephone call, unguided searches were made on the Internet for extra information

All but three of the parents started searching the Internet for information about the findings; one couple only discussed the findings with their general practitioner (1AB). All the parents reported feeling more negative after reading the Internet information. The father who decided not to search for extra information (3B) had confidence in the explanations given by the health care professionals and had no wish for supplementary information. One of the parents (2B) stated that a great deal of the medical information was difficult to understand and should be explained by professionals.

- *I started searching the Internet. And then it became a very emotional evening, you read those chat sites for girls with Turner. I remember crying rivers of tears. It had really frightened me. (4A)*

Post-test counseling was generally perceived to be adequate and the offer of psychosocial support was greatly appreciated

All the parents reported that they had received adequate counseling after being informed of the findings. Their understanding of the prognosis of children with SCAs varied widely and they considered that the syndrome was not as bad as Down syndrome, which resulted in continuation of pregnancy. Decision making was autonomous and all the parents reached mutual agreement. Most of the parents had been offered psychosocial support and they valued this gesture. They all stated that they were able to manage their emotions themselves and provide enough support for each other.

- *He gave us a really good explanation. Well, I didn't feel completely reassured. But he was really calm. (5A)*
- *If you look on the Internet. . . then you don't know what is true. Hearing it from a genetic expert was nice actually. (5B)*

General practitioners made only a marginal contribution to the parents' decision-making process

Only one couple (1AB) discussed the unforeseen findings with their general practitioner; none of the other couples had been in touch with their general practitioner at all.

- *The GP didn't, as far as I can remember, have any role at all in it. (2AB, 3AB, 4AB, 5AB, 6AB, 7AB, 8AB)*

Theme 3: The child and its future

Parents had general faith in a good quality of life for the child

All the parents reported that they had faith in a good quality of life for their child. Most of them appreciated knowing about the syndrome, in order to be able to provide extra care. One couple stated that they would rather not have been told at all.

- *But if you could see the little guy, he is just an easy-going kid, he is really doing his best. It is going extremely well. (2B)*
- *My daughter is 5 years old now I no longer think about it. She is a lovely little girl and she is my daughter. (4B)*

Parents were most concerned about infertility, stature and health

Generally, there was incomplete recall of the information provided about health, fertility and psychosocial issues. Parents confessed that they did not remember all the facts that

had been discussed. Their worries mainly concerned future infertility and stature. One couple expressed faith in new medical advances to treat the fertility problems in their son with Klinefelter syndrome (3AB); one mother hoped that vitrification of oocytes would solve the infertility in her daughter with Turner syndrome (8A). Knowledge about specific health problems was somewhat sparse, except in one couple who were well aware of specific cardiac risks in their daughter with Turner syndrome (8AB).

- *The only thing I found a pity was that he can't have children, I don't know what the future will bring or do. If those legs really get so big, can something be done about it. (2B)*
- *And yes, you are small, well. . . for a woman that's not quite so bad as for a man. The girls probably can't have children. It also makes you think with being able to freeze egg cells, that in 10 or 15 years it might be possible. (8A)*

Very little focus on psychosocial problems

Overall, there were only minor concerns about psychosocial issues. Learning problems were mentioned by several couples. No other psychological and social disturbances were put forward during the interviews, even after specific questioning.

- *If he's having problems learning then we do remedial teaching, the child is really very bright. (2A)*

Much need was expressed regarding extra support and guidance for the child in the future

All the parents reported that they pay special attention to the general health and well-being of their child. Most of the parents explicitly mentioned the need for extra support and guidance for the child in the future. Remarkably, none of the couples had any knowledge of the existence and availability of special care.

- *The growth is something you can see, but the heart valve whether that needs to be tested again, or when. I don't know if it happens automatically from the hospital or whether we have to take the initiative ourselves. (8A)*
- *I would have liked to have a information leaflet 'Turner syndrome'. Not that letter, was pretty full of medical jargon, what I remember. What I should normally be able to cope with, but in emotional circumstances, I couldn't absorb much. (4A)*

Parents' opinions about routine inclusion of the X and Y markers in prenatal diagnosis

Two mothers and three fathers would not want to include the X and Y probes if they chose to have diagnostic testing again; two couples did not express an opinion, whereas all the others (four mothers and three fathers) gave preference to standard inclusion of the X and Y probes.

DISCUSSION

Parents are generally not prepared to accidental findings in routine invasive prenatal testing procedures. Besides providing proper pre-test information, the initial contact with parents in post-test counseling deserves attention. We extracted three themes: the communication of the unforeseen finding of SCA, the informed decision-making process concerning the continuation of pregnancy and the child and its future. We will discuss these themes separately hereafter.

Concerning the communication of SCA, parents referred for AMA and 'at risk' for Down syndrome did not consider the possibility of accidental findings. It is proposed by Ferm *et al*.[8] that pre-test counseling should include the possibility of unintended findings and the lack of complete information has been shown to be experienced as rather problematic.[9] Parents were all hoping for a letter of reassurance concerning the exclusion of Down syndrome, but received a telephone call at an inopportune time to handle the finding of an unfamiliar syndrome. They reported to be overwhelmed by emotions and did not understand the explanation given. This prompted them to make immediate use of the Internet to gather information about SCAs; however, this was generally perceived as very disturbing. The Internet service can play a critical role in providing extended medical information and should therefore always be discussed with a professional.[10] Post-diagnostic counseling in cases of mosaic or full-blown SCAs is widely regarded as a difficult issue,[11] as one argued at the International Society of Prenatal Diagnosis (Amsterdam, 2010) a letter of invitation for personal counselling may be more appropriate than providing clinical details by telephone.

Concerning the informed decision-making process of whether or not to continue the pregnancy, the early diagnosis of SCA provides an opportunity for early guidance and support of the child, but some parents may prefer not to know about syndromes with mild phenotypes. In fact, as RAD is available, parents are becoming increasingly involved in personal and individual choices of targeted testing and its ethical considerations.

The possibility to choose between traditional karyotyping and RAD in women referred for increased risk of Down syndrome has been implemented in Sweden and The Netherlands. Respectively, about 70% and 60% of the women in Sweden and The Netherlands preferred RAD.[12,13]

Offering individualized options for prenatal testing of women following a positive diagnosis of SCA is twofold: preparing for a life with a disabled child or terminating the pregnancy.

The prognosis and phenotype of individuals with SCAs are usually mild as compared to Down syndrome. The high overall termination rates for Down syndrome may reflect a more negative attitude toward giving birth to a child with serious cognitive impairments; the considerable lower overall rate of termination when SCA is detected may

reflect a greater tolerance to children with relatively minor physical and cognitive impairments.[14] The different situations of the pregnant couples should also be taken into consideration; for a couple with previous experience of a child with chromosomal abnormality, even syndromes with mild phenotype may be too much. In a study on attitudes toward termination of pregnancy, 90% of the participants would choose TOP for Down syndrome, whereas 50% would do so for Klinefelter or Turner syndrome.[6] A recent publication showed a termination rate of 36% for sex chromosomal trisomies.[5] As the phenotype of SCAs is usually less predictable, the counseling skills of the medical caregiver is of critical importance and may influence parental decision-making.[9,15] All parents were relieved after post-test counseling; they mentioned to have been provided with useful and reliable facts on the syndrome. Participants reported to have been counseled adequately in order to be able to make a well-informed decision concerning the continuation of pregnancy. Consultation with their general practitioner was in most cases not appreciated.

Concerning the child and its future, parents reported to have faith in a good quality of life for their child. Phenotypic appearance, medical, psychological and fertility problems and also improvement of quality of life for individuals affected with SCAs by early support of the child have been published on Turner syndrome,[16-18] Klinefelter syndrome[18-20] and other XY aneuploidies.[21,22] Preventive medical and psychological screening programs offer these individuals better prospects in terms of health and social adjustment. In this study, parents were most concerned on subfertility and aberrant stature, while psychological problems seemed to be less important for them. Most participants reported that they appreciated knowing about the syndrome and would choose the same procedure again if a next pregnancy would occur. This aspect is an important finding when discussing the option of excluding the X and Y probes using RAD. Although specialized clinics for fetal and pediatric medicine provide specific care, counseling and treatment in cases of SCA, the way to this care is not always easy to find for parents.

The results of this study should be interpreted as indicative rather than conclusive. The choice for qualitative research through in-depth interviews was useful for exploring parental personal feelings, opinions and experiences about unforeseen findings of SCA and may serve as major contributors to research on the question whether or not the X and Y probes should be standard included for purposes of RAD.

CONCLUSION

Parents' perspectives may serve as major contributors to research on the question whether or not the X and Y probes should be standard included for purposes of RAD. The fact that RAD has the possibility to avoid accidental findings of SCAs, brings up the ques-

tion whether any benefits outweigh the potential harms. Research on the experiences of parents who decided termination of pregnancy may shed a more complete light on the desirability of preventing accidental findings, such as fetal SCA.

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Chapter 5

A qualitative interview study of parents' experiences with termination of pregnancy after an unforeseen finding of a fetal sex chromosomal aneuploidy

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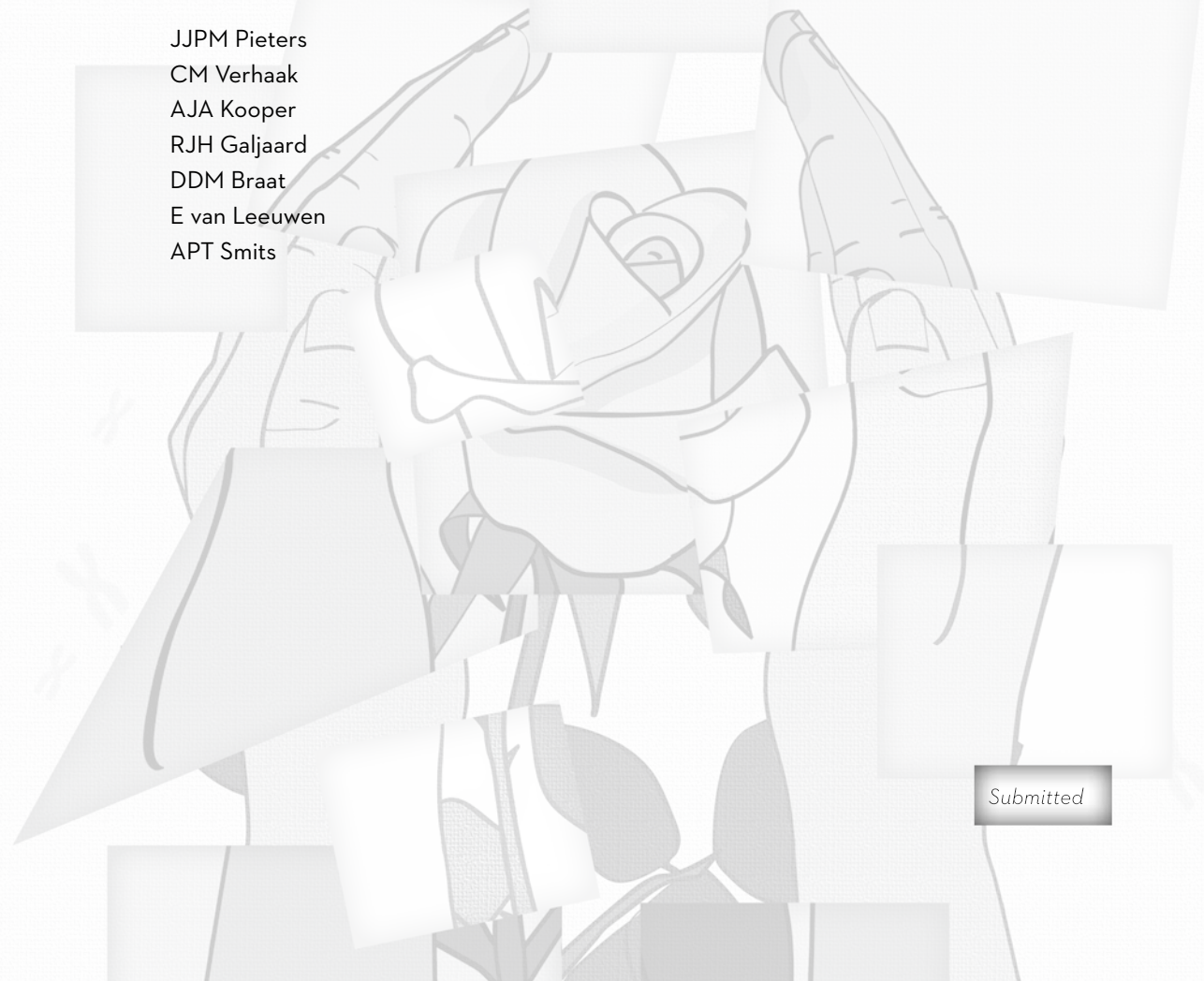

Submitted

ABSTRACT

Objectives

To investigate the parental perspectives of being confronted with an unforeseen fetal sex chromosomal aneuploidy (SCA) and to explore their considerations regarding termination of the pregnancy.

Methods

Exploratory qualitative interview study. We conducted semi-structured interviews with couples who were confronted with the diagnosis of a fetal SCA and decided to terminate the pregnancy. Factors of decisive importance were evaluated.

Results

The percentage of respondents was 31.2. We extracted three major themes: (i) parents' perspectives before performing the prenatal test; they aimed at the exclusion of a severe condition such as Down syndrome, (ii) parents' perspectives after the unforeseen diagnosis of fetal SCA; the impact of the counseling and the perceived burden on the family and (iii) reasons for the decision to terminate; parents had many concerns about the child's future health and socio-psychological wellness. Parents expressed advices for professionals and would include the probes for the sex chromosomes again in a future test.

Conclusion

All couples were satisfied with their decision. The high percentage of selective non-responders might reflect parents' inner feelings and thoughts on the terminated pregnancy. Our study showed that the main reason to terminate was the negative perspective from which the parents judged the child's future.

INTRODUCTION

Sex chromosomal aneuploidies (SCAs) are usually diagnosed after birth; the incidence is 1 in 400.[1] However, SCAs can also be detected with various prenatal tests, such as amniocentesis and chorionvillus biopsy. For pregnant women whose unborn children are at increased risk of Down syndrome (because of advanced maternal age (AMA) or an increased risk found in first trimester screening tests), the incidence of prenatal SCAs is comparable to that of Down syndrome: 1 in 300.[2] The SCAs encompass syndromes caused by the abnormal presence of absence of X or Y chromosomes; they include Turner syndrome (45,X), Klinefelter syndrome (47,XXY), Triple X syndrome (47,XXX) or other aberrant karyotypes (47,XYY, 48,XXXY, 49,XXXXY, etc). The postnatal phenotype of SCA individuals is very variable[3-5] and clinical symptoms may include more or less problematic growth, several health problems such as cardiac, renal and autoimmune disease, neurocognitive or psychosocial impairment as well as infertility and endocrinological problems. In general, when no ultrasound abnormalities are detected in fetuses with an SCA, the postnatal clinical prognosis is likely to be good with no phenotypic symptoms or only mild ones.[6-8]

The SCAs found prenatally are associated with high termination rates (68-100%), despite their non-life-threatening impact.[9-11] Termination rates for the most often encountered types of fetal SCA are quite divergent: the highest rate is for Turner syndrome: 66-100%, for Klinefelter syndrome: 12-70% and the lowest is for Triple X syndrome: 36-50%.[9,11-13] These termination rates vary according to the country where the study took place. A recent review reported that factors that were unique to termination decisions included the parents' anxiety and the directive counseling that they received from medical professionals.[14] The authors conclude that often no statistical association could be found for possible associated factors and that some findings in the literature were inconsistent. They stated that there is a need for qualitative studies examining parents' experiences with decision-making when they are informed of a fetal diagnosis of SCA.

This qualitative study deals with parents' perspectives on the unforeseen finding of a fetal SCA to gain insight into the motives and experiences of couples who had decided to terminate their pregnancy. The clinical impact of the SCA for the future child and for their family life, as well as the other factors that might influence their decision were the main objects of interest to us. This study may help professionals better understand the parental dilemmas and attempts to determine whether an unforeseen prenatal diagnosis of a fetal SCA is useful to the parents and the future child or whether it can harm them.

PATIENTS AND METHODS

We retrospectively interviewed parents who were referred because of AMA and who chose to terminate their pregnancy after being confronted with the accidental finding of a fetal SCA. The institutional Research Ethics Committee (Arnhem-Nijmegen) approved this study. The head of the Department of Obstetrics and Gynecology or the treating gynecologist initiated contact with the parents, inviting them to participate in an interview with the principal investigator (JP). When couples agreed to participate, we telephoned them to arrange an interview date, time and location. We requested their verbal consent to record the interview. The cytogenetic diagnostic tests took place in the Department of Human Genetics at the Radboud University Nijmegen Medical Centre, the Erasmus Medical Centre of Rotterdam and the Utrecht Medical Centre in the period 1994 - 2006.

The same investigator conducted the interviews after successful training in theoretical and practical aspects of qualitative research. The interviews took place between June 2010 and January 2012 and each one lasted between 40 min and 80 min (mean: 60 min). Semi-structured interviews were held with both parents separately after the prenatal diagnosis of a full-blown SCA or a mosaic SCA. One father could not participate, because he often lived and worked in a distant area of the country or abroad (1B). In a semi-structured way, we investigated parental experiences in depth. For this purpose, we used an interview guide with the relevant topics, which we composed after searching the literature and consulting experts. The most relevant topics were: their perspectives before the prenatal testing procedure, their attitudes toward termination of the pregnancy, their conception of risks, the perception of support by close relatives and professionals, their post-test decision-making process and the reasons for their decision to terminate the pregnancy. We specifically asked the participants their opinion of the routine inclusion of the sex chromosomes with X and Y probes besides probes for the common aneuploidies of the chromosomes 21, 13 and 18. We asked parents if they preferred learning about the sex of their child by ultrasonography. We also asked about their main motives to continue or terminate the pregnancy and we finally asked them to formulate advices for the professionals. Nine interviews were completely taped, transcribed verbatim, coded and analyzed. We used Atlas t.i. for qualitative research to code the transcripts of each participant's interview. We read interview transcripts line by line, assigned specific codes to sentences and phrases, using quotes to highlight them. Further conversion resulted in an organized hierarchical list of themes and subthemes. The principal investigator analysis was both inductive and iterative. The points of difference were discussed with the other investigators (EvL, CV and AS) until agreement was reached. Then the coding was renewed and discussed again. Theoretical saturation was reached (no more new themes identifiable in additional interview data) according Guest and colleagues' definition.[15]

RESULTS

Sample characteristics

We contacted 16 couples who decided to terminate pregnancy after the unforeseen finding of a fetal SCA. Five couples were willing to be interviewed (31.2%), four couples replied that they definitely did not want to participate in the study (25%) and the remaining seven couples did not reply at all (43.8%). We did not approach the non-responders again because the protocol did not allow a repeat contact so as not to disturb the couples' rights to privacy.

At the time of the invasive prenatal test, the median maternal and paternal ages were, respectively, 38.5 years (range 36–43 years) and 39 years (range 30–48 years). All the couples had the Dutch nationality. Table 1 shows the socio-demographic personal profiles.

Table 1. Socio-demographic personal profiles

Diagnosis	Age of mother (A) in years at prenatal test	Pregnancy number	Level of education	Age of father (B) in years at prenatal test	Level of education	Time lapse between interview and prenatal test in years
(1A*) 47,XXY	37	2	high	38	high	7
(2AB) 47,XXY	43	2	medium	30	medium	10
(3AB) 47,XXX	39	4	high	40	high	1
(4AB) 47,XYY	36	3	high	38	high	5 /12
(5AB) 47,XXY	40	2	high	48	high	9
	Median: 39			Median: 39		Median: 7

Educational level: low, primary school; medium, secondary school; high, university or other tertiary education
* 1B was not available

Interview findings

We surveyed the parents' perspectives of fetal SCAs and their decision to terminate and then we categorized the data into themes and subthemes. Saturation of information was reached after six interviews. The couples' reason for having the test was to check the baby's health status and to rule out Down syndrome. One couple had a child with Down syndrome, but no prenatal test had been performed (4AB). All the parents talked to family or friends, from whom they said they received much support. One couple stated that they were religious (5AB), but they argued that religion had not influenced their decision. All the parents would make the same choice for invasive testing again for another pregnancy.

Qualitative analysis of the interviews: themes and subthemes

Analysis of the transcripts revealed three main themes. We defined the subthemes and selected relevant quotes to highlight these themes and subthemes (Table 2).

Theme 1: Parents' perspectives before the prenatal test

All women underwent the invasive prenatal test with the intention of ruling out Down syndrome and to check the child's health status. The SCAs were unfamiliar syndromes

Table 2. Themes, subthemes, and quotes

Main themes	Subthemes	Quotes
1. Parents' perspectives before the prenatal test	1a. Deciding beforehand to terminate if there is an abnormality	At the time we did say that there is a result that made us think: if we and our family can't live with that the way we want to, then we would have to terminate the pregnancy. 3A (47,XXX)
	1b. The reason for the test was to rule out Down syndrome	The only thing we were concerned about was Down. Or spina bifida. As for all the other abnormalities, I simply didn't know they existed. 1A (47,XXY)
	1c. Trusting that the result of the test would be reassuring	No, and there was absolutely no reason to think that anything might be wrong, because that only happens to someone else. So it was a very carefree pregnancy.1A (47,XXY)
2. Parents' perspectives after the unforeseen diagnosis of fetal SCA	2a. Unguided Internet searches for extra information	We googled everything. A 40% chance of all kinds of problems, such as underdeveloped language, learning disabilities, and concentration problems. Not to mention height, acne, and possible bone problems. 4A (47,XYY): Domain I–II
	2b. Syndrome was unfamiliar but perceived as very burdensome	The child has no kind of life. We've received enough information. And in the second place, we wouldn't have a life either. So our decision is for both parties, but in the first place it's for the child. 2B (47XXY)
3. Reasons for decision to terminate the pregnancy	3a. No faith in good quality of life for child	We know a boy who has Klinefelter. He is depressive and suicidal. And that was confirmation for me. 5A (47,XXY): Domain II
	3b. Much focus on psychosocial problems	We really wanted to know a lot more about hyperactivity. Behavior problems and being too slow learning to talk. 4A (47,XYY):Domain II
	3c. Would take the same decision if this ever happened again	I would do the same again. It was a good decision; I have never regretted it. 5A (47,XXY)
	3d. Reason for termination primarily considering the child's perspective: 2/9	I put it all together: if he had only 2 or 3 of the 50 possible problems; then I'd think, my God, what have I done to him? Just because we wanted a child so badly. 2A (47,XXY): Domain I–III
	3e. The reason for termination primarily considering the parents' own perspective: 7/9	What I was most afraid of was the child's behavior problems and infertility; and for a lot of going to the doctor, which I would have manage on my own. (1A, 47,XXY): Domain I–III What would your own quality be like? That sounds very egotistical, but it is definitely a factor. (5B, 47,XXY)

to all of them. None of the couples had considered fetal SCA as an unforeseen finding of the test and all the parents said they had agreed beforehand to terminate the pregnancy in case Down syndrome or a relevant clinical abnormality was found. All the parents acknowledged the risk of the invasive test. All the parents wanted to know the gender of the fetus and had asked to be informed before the test.

Theme 2: Parents' perspectives after the unforeseen diagnosis of fetal SCA

One couple (3AB) had a family member (a niece) with perhaps a similar syndrome (47,XXX). This syndrome was in their opinion very burdensome for herself and the rest of the family. Another couple (4AB) already had a child with Down syndrome and thought the burden of extra care would be detrimental to the other two children and the stability of their household (47,XYY). All parents immediately searched the Internet for extra information about the syndrome. They generally found such information useful in their decision-making as a supplement to the professional post-test counseling they received. Three couples (3AB, 4AB, 5AB) stated that they did not appreciate the positive tone of the Internet information.

Theme 3: Reasons for the decision to terminate the pregnancy

All the parents who decided to terminate the pregnancy doubted that the child would have a good life. They expressed concerns about the limited possibilities for providing adequate support for the child, with regard to both health and infertility problems, but most of all they were very concerned about possible behavior problems. They said all these factors would probably be very burdensome to the other children and to the family as a whole, and it would affect their own happiness as parents. They were unanimous in these reasons for deciding to terminate the pregnancy. There was an important role for the midwife in the decision-making for one couple (4AB), neither the family doctor nor the midwife participated in the post-test decision-making for the other couples.

Three domains of health

Recently, we studied the medical literature for SCA and categorized the SCA phenotypical problems in three domains: I health, II behavior and III fertility, endocrinology.[6] We also used these three categories in this study for factors that the parents mentioned as decisive for termination.

The effect of the three domains on termination of pregnancy

The reasons the parents decided to terminate the pregnancy were the uncertain prognosis for the child after birth, the future infertility, no faith in a happy life for the child, the foreseeable burden of the necessary support programs and the negative impact all this would have on the whole family.

The decisive factors were mainly found in domains I and II: parents had many worries about their ability to cope and the poor health of the child. Therefore they doubted that the child would have a happy life. They all felt that the child would be too great a burden on the family because of the necessary support programs.

Table 3 shows the decisive factors in the three domains.

Table 3. Decisive factors and domains

Diagnosis	Domain I: health	Domain II: behavior	Domain III: Fertility and endocrinology	Decisive factors for termination
47,XXY	X	X		Worries about happiness and health
n = 3				Unlikelihood of a happy life for the child
				The child would be too great a burden on the family
47,XXX				Experience of a family member with many behavior problems
n = 1		X		Unlikelihood of a happy life for the child
				The child would be too great a burden on the family
47,XYY				Already have a child with Down syndrome
n = 1	X	X		Worries about behavior and health
				Unlikelihood of a happy life for the child
				The child would be too great a burden on the family

Advice to professionals

We asked the parents to formulate advice for professionals to help improve future care. Some parents (1A, 4AB, 5AB) mentioned the timing and manner of communicating the diagnosis, they thought the professional information and the Internet information were perceived by them as overly optimistic, one parent (3B) said the actual medical initiation of the termination was much too easy and one couple (5AB) stressed the importance of adequately informing parents about the cremation of the fetus by a letter afterwards as promised. Table 4 shows the advice to the professionals.

All couples were satisfied with their decision. The high percentage of selective non-responders might reflect parents' inner feelings and thoughts on the terminated pregnancy. The main reason to terminate was the negative perspective from which the parents judged the child's future.

Table 4. Parents' advice to professionals

Theme	Advice to professionals
1. Parents' perspectives before the prenatal test	Invasive tests should also be available for young women with no a priori risk (2B)
2. Parents' perspectives after the unforeseen diagnosis of fetal aneuploidy	Post-test counseling should be given only by specialists in the field who are very knowledgeable about these syndromes (4B)
	Post-test counseling is much too positive, as is the Internet (4A/B, 5B)
3. Decision to terminate the pregnancy	Information about cremation and farewell rituals should be made available before the actual termination (3 A/B) The initiation of the termination should not be so easy; preferably a contract should be signed (3B) Women should always be given the advice to stay home from work to be able to think things over (4A) The promised information letter about the hospital cremation of the baby has never arrived. That's a very bad thing and it's very unprofessional of the hospital (5A/B)

DISCUSSION

Parents' perspectives on the clinical impact of the SCA syndrome for the future child and for their family life, as well as the exploration of their considerations regarding termination of the pregnancy were our main interest.

A striking result of the study was the low participation rate of the couples who were invited to an interview. Only 31.2% of the parents whom we contacted agreed to an interview. The demographic variables of the total non-responders in this study were comparable to those of the participating couples. Most mothers were also multiparous and the median age (39 years) was not as in the analyzed population. In our previous study of the perspectives of parents who continued the pregnancy after an unforeseen prenatal diagnosis of fetal SCA, 72.7% of the couples were willing to participate.[16] The reason for the large proportion of total non-responders among couples who terminated pregnancy is unknown, we can only speculate. The decision to terminate a wanted or planned pregnancy following prenatal diagnosis of fetal anomaly should be considered a major life event.[17-20] Feelings of grief, guilt and failure after the termination procedure with no apparent decrease in symptomatology of post-traumatic stress symptoms have been reported even up to 7 years after the termination procedure.[21,22]

All the participating mothers who decided to terminate were multiparous (Table 1) and this appeared to be the only difference with the socio-demographic profiles between these parents and those who continued the pregnancy. Most of the participating mothers (87.5%) who continued were nulliparous. Maternal age has been shown to influence termination decisions. The European Surveillance of Congenital Anomalies recently reviewed sex chromosomal trisomy (SCT) cases in the period 2000-2005 from 11 European countries.[11] The review found that the difference in the proportion of terminations for SCTs for the group of mothers 35 years old or less and the group more than 35

years old was statistically significant, with more terminations for the younger mothers. In a study considering termination for Down syndrome, maternal age appeared to be a significant influencing factor, younger mothers more often terminated than older mothers.[23,24] However, another study found no such association.[25] As the indication for referral in our study was advanced maternal age (AMA), we could not compare the interview findings with data from younger mothers.

The median time lapse between the prenatal finding of SCA and the invitation to the interview was 7 years. In the study that described the parental views of continuation, the median time lapse was a comparable 8 years. The time lapse between the events and the invitation for the interview in the population of the total non-responders in this study was median 8 years, which indicates that even after such a long period, many parents are still not willing to talk about their personal perspectives on the decision to terminate. In an earlier study, possible factors of persisting post-traumatic stress symptoms proved to be an important issue,[22] but we cannot draw any conclusions because we have not analyzed for these specific symptoms. Other studies have found non-response to be a problem in qualitative research on traumatic events.[26]

We extracted three main themes and 10 subthemes in the analysis of the interviews (Table 2). The first theme was: "parents' perspectives before the prenatal test". Parents all intended to rule out Down syndrome with the invasive prenatal test, but SCAs were unfamiliar syndromes to all of them. All the couples said they agreed beforehand to terminate the pregnancy if a relevant clinical abnormality was found. In the population that decided to continue,[16] the prenatal test was intended by them to rule out Down syndrome; only 75% of the parents stated that they would terminate, although some hesitated on this point. Garcia and colleagues[27] studied parents' perspectives before the prenatal test and reported that women decide about prenatal testing by balancing the test information against the emotional burden of a disabled child on their well-being and life perspective and on that of their family members.

The second theme was: "Parents' perspectives after the unforeseen diagnosis of fetal SCA". Couples appreciated the post-test counseling information from the medical professionals and they all searched the Internet for additional information about the syndrome. They interpreted the Internet information as much too positive and hopeful; they expected the syndrome would affect the child much more. This was contrary to the findings in the population that continued,[16] where the parents experienced the Internet information as very frightening and worrisome, but decided that it could not be that bad and their child deserved a chance. Not many studies about the interpretation of Internet information by worried and emotional patients are available. One study addresses the Internet service and states that the Internet can play a critical role in providing extended medical information which should always be discussed with a professional because of possible insufficient comprehension of the medical details.[28]

The third theme was: "reasons for decision to terminate the pregnancy". These parents doubted that the child would have a good life. They were concerned about the limited possibilities in providing adequate support and about health and infertility problems, but most of all they were concerned about behavior disturbances. These factors were likely to be very burdensome for the other children and for the family as a whole, as well as being detrimental to their own happiness as parents. The parents in our previous study[16] had faith in the support programs and hoped for medical advances that would cure the infertility problem. They all believed a happy and fulfilling life for the child would be possible. They found no justification for terminating the pregnancy.

A trend towards fewer terminations in the last decade suggests an improved understanding of the pathology associated with SCA.[29-31] In the medical literature, pregnancies with 47,XXY, 47,XXX or 47,XYY karyotype were reported to be continued more often (66%)[31] than pregnancies diagnosed with 45,X genotype (0-30%).[30,32,33] Parental concern about having a child both with infertility and very short stature may account for this finding. The termination rates are comparable to the incidence of termination of pregnancy after a prenatal diagnosis of Down syndrome, which appears to be around 75-92%.[29]

When comparing the parents of both our studies, we found that the parents who decided to terminate were more autonomous, while parents who continued were more dependent on the caregivers.

Phenotypical problems for SCA individuals were categorized into three domains: I health, II behavior and III fertility and reproductive endocrinology.[6] The analysis of these interviews showed that a major factor in the decision to terminate was the expected behavioral problems (domain II). This was mentioned most in the interviews, as worried parents had no faith in a happy life for the child despite the supporting programs. The parents said that fear of health problems (domain I) was burdensome for them and their family, because of the predicted frequent doctors' visits, preventive tests and treatment programs in case of disease (Table 3). This is contrary to our findings in the interviews with the parents who decided to continue pregnancy. The couples in that study said they appreciated the knowledge of SCA in their pregnancy which gave them the opportunity to provide extra medical care and psychosocial support to their child, who they believed had a good chance of a happy life. Parents who continued mentioned problems in domain III (infertility) many times, always as an important and sad fact, whereas the future infertility appeared to be of no great importance to the parents who decided to terminate. Earlier reports of decision-making about a prenatal finding of SCA, conclude that future infertility, sexual development and behavioral problems were the most worrisome for parents and professional support for these aspects was most needed.[33-35]

Parents spontaneously advised better counseling and medical support; a few parents sharply criticized some of the procedures (Table 4). Parents also advised more neutral information and less intervention by a psychologist. One parent would have liked a more formal contract at the start of the termination procedure. The advice of the parents in this study is completely different from the advice the parents in the previous study. Parents in the continuation study mainly emphasized the necessity of extra guidance for them in the process of decision-making and support for the child after birth. Both groups mentioned that test results should always be given in the promised time. Some couples were informed of the unforeseen finding after this period had elapsed, which made them very sad and they thought it very unprofessional.

To highlight the importance of the role of the counselor in this difficult decision-making process, we include this relevant quote: "Nobody gave us any bad news, then we talked to a female specialist and she was the only one that expressed a clear opinion. This was a very important opinion to me, I really held on to it" (5B).

Considering the practical and moral considerations in prenatal diagnostic testing, it should be noted that testing may sometimes lead to processes beneficial to the fetus and the future child in terms of preventive programs or early treatment options,[36] but more often it may be especially beneficial to the parents because it enhances their autonomy and enables them to decide to terminate in certain cases.[37] New technologies in the field of prenatal diagnostic testing, such as MLPA (Multiplex Ligation-dependent Probe Amplification) and QF-PCR (Quantitative Fluorescence Polymerase Chain Reaction), have been implemented for rapid aneuploidy detection (RAD) of the most common fetal aneuploidies (13, 18, 21, X and Y), the possibility arises to exclude X and Y probes and herewith avoid accidental findings of a fetal SCA.[38,39,40] In both populations, the parents stated they had taken the right decision then and would do exactly the same again, they had no regrets. They would all want to include the X and Y probes in a future RAD test because they would want to know about SCA in the fetus.

CONCLUSION

Parents who were willing to talk about their experiences after a diagnosis of an unforeseen finding of SCA followed by termination of the pregnancy on the one hand suffered grief with many emotional feelings, but were nonetheless content with the procedure and their decision. On the other hand, termination of a planned pregnancy might cause the parents significant clinical distress, which may account for the large proportion of total non-responders. Parents who terminated confirmed that they appreciated neutral

medical information about the syndrome and appeared to be rather autonomous in their termination decision, whereas parents who continued the pregnancy asked for more guidance from medical advisers.

PRACTICE IMPLICATIONS

The unforeseen finding of a fetal SCA and the subsequent decision of parents to terminate the pregnancy may be considered a traumatic life event. Even after some years it is possibly still painful for parents to talk about the events again, which we believe to account for the large percentage non-responders in this study. The interpretation of Internet information is variable among couples and may be interpreted as too positive on the one hand, or as very frightening on the other hand. Professional counselors play an important role in guiding and supporting parents to make the right decision.

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Chapter 6

Experts' opinions on the benefit of an incidental finding of sex chromosomal aneuploidy: a qualitative interview survey

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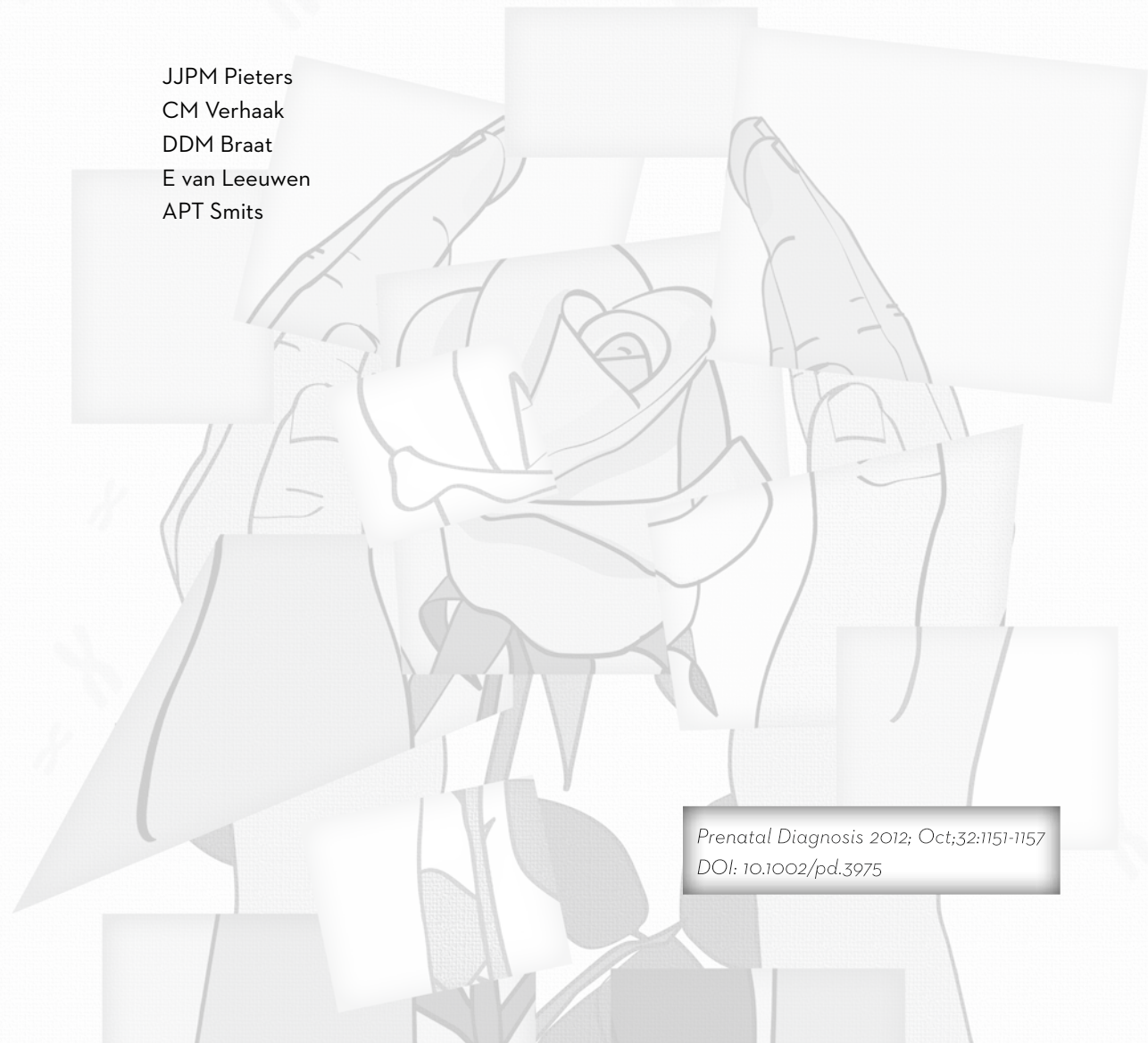

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ABSTRACT

Objective

Incidental findings in prenatal diagnostic testing may or may not have clear prognostic significance for the phenotype. We studied experts' opinions of the benefit and disadvantage of an incidental prenatal diagnosis of a sex chromosomal aneuploidy (SCA).

Methods

We interviewed 16 experts in the field of counseling and treatment of people with SCA and asked 13 clinical geneticists and genetic associates about the clinical relevance of an incidental prenatal diagnosis of SCA.

Results

Most of the experts and clinical geneticists (87.5% and 76.9%, respectively) stated that an incidental prenatal diagnosis of SCA was a benefit for the child and the parents. They acknowledged the possibility of parental decisions to terminate pregnancy. Expert options in screening, training, and treatment of health, behavior, and fertility problems increase with an early diagnosis of SCA.

Conclusion

Most experts favored an incidental prenatal diagnosis of SCA, despite the complex counseling issues and their acknowledgment of possible parental decisions to terminate pregnancy. They believed the benefits greatly outweigh the disadvantages.

INTRODUCTION

In prenatal diagnostic testing procedures, medical experts may be confronted with incidental findings regarding the fetus. Such findings may or may not be important for health and reproduction. Technological advances are causing rapid changes in prenatal diagnosis. For example, the use of genome-wide molecular tests leads to more diagnoses of genetic aberrations, for which the phenotypic significance is relevant, trivial, or uncertain. In good clinical practice, medical experts who are involved in counseling before and after testing inform the parents about the purpose of the test, the potential risks of the procedure, and the odds of a positive or unforeseen finding.[1] Whether it would be an appropriate standard of care to avoid incidental findings with uncertain clinical relevance is a subject of debate. Especially in the case of a fetal sex chromosomal aneuploidy (SCA), the potential gain or damage is unclear and is considered a difficult counseling issue.[2]

The incidental finding of an SCA is considered a challenge to professional counseling skills because its clinical significance is variable.[3] Sex chromosome aneuploidies encompass syndromes caused by the abnormal presence or absence of X or Y chromosomes; they include Turner syndrome (45,X), Klinefelter syndrome (47,XXY), Triple X syndrome (47,XXX), or other aberrant karyotypes (47,XYY, 48,XXXY, 49,XXXXY, etc.). The phenotype of a person with SCA is very variable after birth[4-6], and the clinical symptoms may include problematic growth; health problems such as cardiac, renal, and autoimmune disease; neurocognitive or psychosocial impairment; infertility; and endocrinological problems.[7]

Especially when no ultrasound abnormalities are found, the diagnosis of a fetal SCA (mosaic or full blown) creates a complex counseling issue for medical counselors, as the phenotype is still uncertain after birth, and there may be only mild symptoms or none at all. Some people with SCA may have visible stigma (webbed neck in 45,X or breast enlargement in 47,XXY), some may be karyotyped because of health problems or infertility, and others may go through life without ever knowing they have a genetic anomaly.[8-10] Earlier studies have described the postnatal SCA phenotype after an incidental prenatal diagnosis as very mild compared to the individual phenotypes that are ascertained because of clinical symptoms.[6,9,11,12]

Following the diagnosis of a fetal SCA, the genetic counselor provides unbiased and objective information about the syndrome, the disability of the fetus, its postnatal prognosis, and the necessary extra care. Due to the unpredictability of the postnatal phenotype, future infertility, health, and behavior, parents sometimes decide to terminate the pregnancy.[2,3]

In this study, we asked medical experts who counsel and treat individuals with an SCA to give us their opinion of the benefit or possible disadvantage of a prenatal diagnosis of an SCA. We analyzed expert opinions to determine whether continuing testing

procedures that include the possible incidental diagnosis of a fetal SCA is indeed good medical care.

MATERIAL AND METHODS

Interviews with expert professionals in the field of SCAs

We invited experts involved in the medical and psychosocial treatment of children and adults with SCA in the Netherlands to participate in a structured telephone interview with the principal investigator (JP).

The institutional Research Ethics Committee (CMO, Arnhem-Nijmegen) approved the study. The same investigator (JP) conducted all the interviews after successful training in the theoretical and practical aspects of qualitative research. The participants were asked their opinion of the value of a prenatal diagnosis of an SCA, primarily for the child and secondarily for the parents.

First, we e-mailed the selected experts to explain the purpose of the study, to invite them to participate, and to name a time for the investigator to call them. Second, we assured them of confidentiality: all information from the interviews was to be anonymously reported as part of a larger qualitative survey.

A study of the literature about the phenotypical problems of both children and adults with SCA showed that the experts we needed for this study were working in areas that cover the three domains in which most of the SCA characteristics of clinical health, behavior, and fertility appear.[7] We interviewed 16 nationally known medical experts who are the authors of various articles about care for children or adults with an SCA. Two experts in each domain (health, behavior, and fertility) for each of the three most common SCAs (45,X; 47,XXY; 47,XXX) participated in the study. In the case of 45,X, children are treated by pediatrician-endocrinologists. Then they are treated by gynecologists and endocrinologists from the age of 18 years.

Regarding 45,X, we interviewed two pediatrician-endocrinologists, two endocrinologists, two psychologists, and two gynecologists specializing in fertility. Regarding 47,XXY, we interviewed two endocrinologists, two psychologists, and two urologists specializing in fertility. Regarding 47,XXX, we interviewed two psychologists.

The interviews took place between September 2011 and April 2012, and each lasted between 15 and 40 min (mean: 25 min). The interviewer used an interview guide with the relevant topics, composed after a literature search. We used the same topic list in the same sequence in each interview (Table 1). The first author (JP) encouraged the experts to give their opinions of all the topics in the interview guide. The answers were noted during the interview and categorized afterwards. The interviews were transcribed, coded, and analyzed to retrieve the most important expert counseling aspects. Theoretical

saturation of information was reached (no more new information in additional interview data) according to Guest et al.'s definition.[13]

Questionnaire for clinical geneticists and genetic associates

We presented a short and unannounced questionnaire to seven clinical geneticists and six genetic associates (health professionals with training in genetic counseling who work with clinical geneticists), all of whom were associated with the Radboud University Medical Centre, Nijmegen. We used the same topic list for the questionnaire that we used for the interviews (Table 1). At one of the monthly conference rounds in the Genetic Department of the Radboud University Medical Centre, before the scientific meeting started, we asked the professionals to fill in a questionnaire with three questions about whether a prenatal diagnosis of an SCA is a diagnostic gain or a disadvantage to the parents and/or the child. They were unprepared for the questionnaire, and we asked them to give their intuitive opinion as medical experts in genetics. We assured them that all information would be treated with confidentiality and that only anonymized information would be analyzed. The first author (JP) analyzed the answers and discussed their relevance with the other authors (CV, DB, EL, and AS) until agreement was reached.

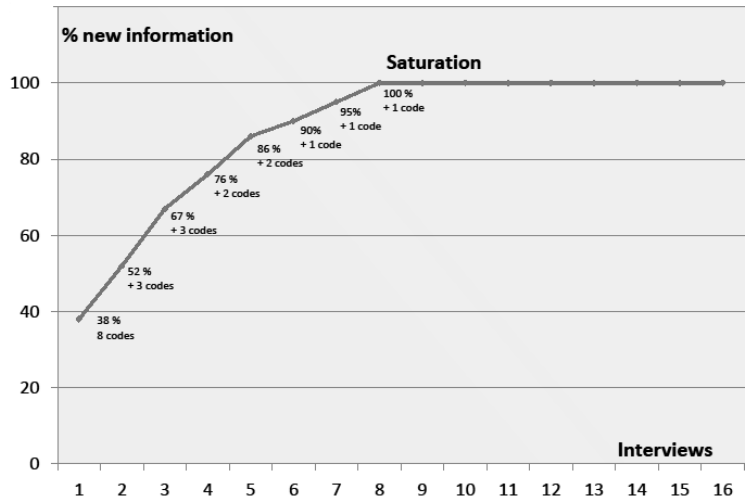
Table 1. Interview guide: topics and sequence
Medical professionals who are experts in the treatment and care for SCA individuals

Burden of disease	To your opinion, what is the burden of disease for the SCA individual, which domain of health is most burdensome?
Advantage of prenatal diagnosis	Is there an advantage in prenatal diagnosis of SCA? a. for the child b. for the parents
Disadvantage of prenatal diagnosis	Is there a disadvantage? a. for the child b. for the parents
Quality of life **prenatal diagnosis vs postnatal diagnosis**	Do you see differences in quality of life between: a. the individuals that know of the SCA diagnosis prenatally or soon after birth or b: the SCA individuals that learn about their syndrome later in life Please explain
Standard inclusion X and Y probe	Would you advise for or against routinely including the X and Y probe in prenatal diagnostic testing? Why?

RESULTS

Saturation of information was reached after eight interviews. Additional interviews brought the number of experts to two for each domain and for each type of SCA, but no new aspects were mentioned in these additional interviews (Figure 1).

Figure 1. Saturation of information in interviews with experts



Expert interviews

Thirteen interviews took place by telephone, while three interviews took place in a face-to-face meeting with the expert.

Aspects of professional post-test counseling

After we qualitatively analyzed the interviews, we extracted five central aspects concerning the professional counseling that is given after an incidental finding of a fetal SCA. All the participating experts mentioned these aspects.

Positive views

1. Early (childhood) knowledge of SCA is favorable in terms of early treatment possibilities.
2. Late diagnosis of SCA deprives experts of the chance to adequately treat growth, behavior, and/or endocrinological insufficiencies.

Critical views

1. The large variability in phenotype creates complexity in the counseling.
2. The incidental diagnosis of fetal abnormalities with uncertain postnatal prognosis poses ethical dilemmas for the parents in deciding to continue or to terminate the pregnancy. However, the experts respect the parental autonomy to decide what they think best.
3. Stigmatization and over-medicalization may occur as result of an incidental prenatal diagnosis of SCA, experts have an important task in guiding the parents in their attitude towards the child.

Early knowledge of SCA is favorable in terms of early treatment possibilities

All experts said that the most important advantage of a prenatal diagnosis of SCA is the early treatment, training, and prevention possibilities for all three domains of health. The participating experts had not treated many prenatally diagnosed SCA cases, as prenatally incidentally diagnosed SCA individuals tend to cause a few or no postnatal phenotypical problems. They all said that the earlier the diagnosis took place, the better for the individual because of early prevention, training, and treatment options. All the experts mentioned the social problems connected with all types of SCA; they had specific problems in mind that were related to their field of expertise.

Late diagnosis of SCA deprives experts of providing adequate treatment

The experts we interviewed about health and behavior were all convinced that a late diagnosis frustrates good quality of life for anyone with SCA because many treatment options are no longer possible. The fertility experts stated that future infertility could neither be prevented nor treated. They also noticed that infertility in SCA might be more of a problem for the parents than for the children with SCA themselves, as they may learn to adapt to this condition. An early diagnosis gives the expert the opportunity to counsel the child and the family regarding the future possibility of artificial reproduction techniques.

Experts have an important task in guiding the parents regarding their attitude towards the child

The risks of stigmatization and over-medicalization of the child were two more problems that the experts named. The experts reported the important role they have in guiding the parents to deal with the weaknesses in health and behavior that are associated with each type of SCA. Professional support is equally important as parental acceptance of the child's opportunities, if properly trained and guided.

The large variability in phenotype creates complexity in counseling

Postnatal phenotype is very difficult to predict in the prenatal finding of SCA, certainly when no ultrasound abnormalities are present in the fetus. All the experts acknowledged the complexity in counseling parents, who are anxiously searching for information about their child's prognosis. The experts said that parents might decide to terminate the pregnancy because of uncertainty about postnatal phenotype and worries about the child's quality of life.

The incidental diagnosis of fetal abnormalities with uncertain postnatal prognosis poses ethical dilemmas for the parents in terms of continuation or termination decisions

Postnatal phenotype is not easy to predict. The experts said that, on the one hand they informed the parents that the child might very well lead a normal and happy life, but on the other hand, they were obliged to provide full information about possible problems in the domains of health, behavior, and fertility. Once they have received all the extensive information from professional counseling, the parents can make an informed decision to continue or terminate the pregnancy. Table 2 gives a summary of the experts' answers to the five questions in the interview guide.

Table 2. Results interviews experts SCA (n=16)

Q-1, advantage prenatal diagnosis SCA
1. early knowledge of SCA is favorable in terms of early treatment possibilities
2. the large variability in phenotype poses difficulties in the counseling
3. late diagnosis of SCA deprives professionals of the possibility to give adequate treatment of growth, behavior or endocrinological insufficiencies
4. professionals have an important task in guiding the parents on their attitude towards the child to prevent stigmatization and over-medicalization
Q-2, disadvantage prenatal diagnosis SCA
Decision to terminate the pregnancy
Stigmatization and overprotection of child
Q-3, Burden of disease for SCA individuals
45,X: infertility and behavior most burdensome, health problems less; quality of life can be improved by early training and acceptance of weaknesses; health problems may benefit by early treatment (growth, puberty induction)
47,XXY: infertility; apart from this, some of these men have perfectly normal lives
47,XXX: behavior may be vulnerable; most girls and women have normal lives
Q-4, Differences in quality of life between prenatally or postnatally diagnosed SCA individuals
The earlier the diagnosis, the better for the individual because of early prevention, training and treatment options.
Q-5, would you advise for or against routinely including the X and Y probe in prenatal diagnostic testing why?
For: 14; reason: prenatal diagnosis offers good possibilities for counseling of parents to enhance their understanding and acceptance of the child; it offers early screening, training and treatment programs for the child which enhances the quality of life
Against: 2; reason: prenatal diagnosis poses difficult dilemma for the parents, risk of parental decisions to terminate the pregnancy because of uncertainties in the postnatal phenotype. Early postnatal diagnosis is early enough.

Experts' opinions on the standard inclusion of the X and Y probes in routine prenatal diagnostic testing

All 16 experts stated that early knowledge of SCA is important for adequate treatment, prevention, and acceptance of postnatal phenotypic problems. The earlier the condition is diagnosed, the better the prospects. Fourteen of the 16 experts were in favor of including the X and Y probe in prenatal diagnostic testing procedures, although all of them were well aware of a possible disadvantage of a prenatal SCA diagnosis: the decision of parents to terminate the pregnancy. Two professionals thought that early childhood diagnosis was early enough and prenatal diagnosis unnecessarily burdened the parents with the dilemma of whether or not to continue the pregnancy.

Questionnaire for clinical geneticists and genetic associates

Thirteen clinical geneticists and genetic associates were asked to spontaneously answer questions about the benefits, disadvantages, and burden of a prenatally diagnosed SCA (45,X; 47,XXY; 47,XXX) for the child and for the parents.

Question 1. Is there an advantage in prenatal diagnosis of SCA (45,X; 47,XXY; 47,XXX)?

a. For the child

b. For the parents

For 45,X, 10 of the 13 agreed with this statement.

For 47,XXY, a minority of 3 agreed with this statement: 6 answered "no" and 4 had "no opinion".

For 47,XXX, only one participant agreed, while 7 said "no" and 5 had "no opinion".

Question 2. Is there a disadvantage?

The complexity of the counseling because of variability in the phenotype and the possibility of a termination decision was mentioned by all the participating staff members.

Question 3. In your opinion, what is the burden of disease for the person with SCA, and which domain of health is the most burdensome?

For 45,X, 6 participants said health was the most problematic domain, 2 said behavior, and 5 said fertility.

For 47,XXY, all the participants said fertility was the most problematic domain.

For 47,XXX, 11 participants said behavior was the most problematic domain, one said health, and one said fertility.

Table 3 shows the clinical geneticists' and genetic associates' answers to the three questions

Table 3. Questionnaire answers clinical geneticists and associates Radboud University Medical Centre

SCA	Question	N=13
	Q-1, advantage prenatal diagnosis SCA	
45,X	yes	10
	no	3
	no opinion	0
47,XXY	yes	3
	no	6
	no opinion	4
47,XXX	yes	1
	no	7
	no opinion	5
	Q-2, disadvantage prenatal diagnosis SCA	
	Complexity of counseling procedure: all experts	
	Decision to terminate the pregnancy: all experts	
	Q-3, Burden of disease for SCA individuals	
45,X	Health	6
	Behavior	2
	Fertility	5
47,XXY	Health	-
	Behavior	-
	Fertility	13
47,XXX	Health	1
	Behavior	11
	Fertility	1

DISCUSSION

Medical experts in the field of counseling and treatment of individuals with an SCA were generally in favor of continuing testing procedures that include the possibility of an incidental diagnosis of a fetal SCA. In their opinion, early treatment of health, behavior, and fertility problems is an important factor in enhancing the child´s quality of life; however, they all acknowledged the possibility of parental decisions to terminate pregnancy. Whether an unforeseen prenatal diagnosis of SCA may be a disadvantage or a benefit to the child or the parents is still a subject of debate.[2]

Experts' opinions on early and pre-symptomatic diagnosis of SCA

Critical views

The experts unanimously acknowledged the complexity of the counseling after a prenatal diagnosis of SCA. This was mainly attributed to the unpredictability and variability of the postnatal phenotype of the person with SCA, especially when no ultrasound abnormalities appeared during the mother's pregnancy. An incidental prenatal diagnosis of SCA may be associated with a phenotype that is even milder than phenotypes diagnosed on traditional clinical grounds.[8,9,11,12] Counseling of the parents is even more challenging after an incidental prenatal finding of a sex chromosomal mosaicism.[3,5,14,15]

Stigmatization of the child was mentioned as a serious risk. The experts stated they had an important task in guiding the parents in their attitude towards the child to prevent stigmatization and over-medicalization. Early professional explanation helps parents accept the child's condition, as has been published for prenatal diagnosis of children with cleft lip and palate.[16-18] Prenatal counseling may add to better understanding and acceptance of the child. The diagnosis of a genetic abnormality may harm the child's self-esteem, distort the family's perception of the child, damage future autonomy, and possibly lead to discrimination of the child.[19]

What are the public, parental, ethical, and medical perspectives of these technologic advances? Pre-symptomatic fetal diagnostics may give rise to moral and ethical dilemmas for parents about whether to continue the pregnancy. In two earlier studies, we have surveyed parents' perspectives of the dilemmas they face after the incidental prenatal finding of a SCA and the reasons they might have for deciding to continue or terminate the pregnancy. Parents in both groups stated clear views of their decisions, and all expressed satisfaction with their decisions (published article and manuscript in progress).[20] Most parents preferred knowing about the fetal SCA and would want to include the X and Y probes again in a prenatal test for a future pregnancy. The experts we interviewed in the current study had concerns about the risk of the parents terminating the pregnancy after an incidental prenatal diagnosis of SCA. The different

view of the geneticists when compared to the clinical experts is an important fact to consider, as most parents-to-be will be provided with post-test counseling information by the geneticist first and thereafter will make the decision to continue or terminate the pregnancy. Our earlier studies have shown that, with professional guidance of medical experts, parents are very capable of handling these dilemmas, and will ultimately reach a satisfactory decision.

The medical experts are involved in counseling parents after an unforeseen diagnosis of a fetal anomaly that is unfamiliar to them. Therefore, these experts require specific knowledge and counseling skills so that they can provide adequate guidance and care for these parents.[21] Termination decisions after a prenatal diagnosis of SCA have been associated with the amount of training and the professional or cultural background of the counselor.[10,22-26] Improved professional knowledge of the conditions associated with SCA have positively influenced a decreasing trend to terminate pregnancy.[27,28] The expert's neutrality in his or her attitude towards pregnancy termination and non-directiveness is a prerequisite for adequate counseling both before and after testing. It has been shown that personal attitude may play a variable influencing role,[29,30] this attitude may be colored by the gravity of the phenotypic aspects of SCA that the expert will have encountered.

Positive views

A prenatal diagnosis of SCA opens options for early screening and treatment of cardiovascular, metabolic, and endocrine disease. Experts can start preventive training for the child's and the parents' acceptance of the behavioral weaknesses. They can also provide coping strategies in an early stage before real problems, such as growth retardation, failed puberty or psychosocial problems come forward. Fertility problems such as the risk of premature ovarian failure or infertility can be disclosed in a very early stage and discussed with the child and the parents, along with the options for assisted reproductive techniques. A late diagnosis of SCA, however, deprives the experts of the opportunity to give adequate early treatment of growth, behavior, and/or endocrinological insufficiencies. Medical or psychological screening options may no longer be possible, and health or behavior problems may have advanced to a stage where treatment options may have become scarce. The recent literature describes the current advice for screening and early treatment programs for children with an SCA.[6,8,31-33] Table 4 lists the experts' opinions of counseling issues and treatment policy after the incidental prenatal finding of a SCA, categorized into critical and positive views.

Table 4. Expert´s remarks on complexity and positive issues for counseling and medical policy after prenatal diagnosis SCA

SCA complexity	Domain I: health	Domain II: behavior	Domain III: fertility
45,X	Phenotype very variable and unpredictable	Phenotype very variable, large scale from normal coping to serious psychiatric disease	No doubts: always infertile
47,XXY	Phenotype very variable and unpredictable	Phenotype very variable, large scale from normal coping to serious psychiatric disease	Sometimes artificial reproductive techniques possible
	Problem of over-medicalization of normal SCA individual		
47,XXX	Sometimes long stature when compared to classmates	Phenotype very variable, most girls have normal behavior and coping	Fertility may be problematic because of premature ovarian failure in some women
Positive issues			
45,X	Early screening program to detect and treat cardiovascular, metabolic and endocrine disease	Preventive training for acceptance of weaknesses and coping strategy	Early disclosure of infertility
	Early start Growth Hormone therapy		Counseling mothers about oocyte donation
	Alertness for dysplastic gonads and timely extirpation		
	Timely start puberty induction		
47,XXY	Early screening program to detect and treat cardiovascular, metabolic and endocrine disease	Preventive training for acceptance of weaknesses and coping strategy	Early disclosure of infertility
	Alertness for mamma carcinoma		Counseling about possibilities of early sperm preservation in young puberty
	Alertness for dysplastic gonads and timely extirpation		
47,XXX		Preventive training for acceptance of weaknesses and coping strategy	Counseling about the risk of premature ovarian failure

Standard inclusion of the X and Y probe in routine prenatal tests

Notwithstanding the difficulties that medical experts encounter in counseling parents after an incidental prenatal finding of SCA, 87.5% were convinced of the benefit of a prenatal diagnosis of SCA. When specifically asked, they were in favor of continuing the inclusion of the X and Y probe in routine prenatal testing procedures because the benefits of early knowledge greatly outweigh the disadvantages.

The questionnaire for clinical geneticists and genetic associates about the benefits, disadvantages, and burden of a prenatally diagnosed SCA revealed that 76.9% agreed that an incidental prenatal finding of 45,X is a diagnostic gain. For 47,XXY, 23.1% agreed it was a diagnostic gain, and for 47,XXX, only one participant saw benefits in prenatal

detection (7.7%). Despite the professional knowledge of these clinical geneticists and genetic associates about SCA, medical experts in the field of care for children or adults with SCA stated that parents might benefit from their additional counseling after an incidental prenatal diagnosis of SCA. Earlier reports have shown that there may be a gap in clinical geneticists' and medical experts' counseling of people with a SCA.[3,22,34] A combination of both counselors might provide a comprehensive view of the child's quality of life for the parents.

CONCLUSION

Most experts were in favor of an incidental prenatal diagnosis of a SCA, notwithstanding the complexity of the counseling issues and the moral dilemma for parents faced with deciding to terminate or continue the pregnancy. Medical experts who are involved in the counseling and treatment of people with SCA had a clear opinion of the incidental fetal diagnosis of SCA: the benefits greatly outweigh the disadvantages. They proposed that the X and Y probes should remain available for rapid and definitive prenatal diagnosis.

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We thank the experts who were willing to share their valuable opinions with us. We also thank the genetic specialists at the Radboud University Medical Centre Nijmegen who spontaneously agreed to answer the three questions in the unannounced questionnaire.

WHAT'S ALREADY KNOWN ABOUT THIS TOPIC?

- Incidental prenatal findings create complex counseling issues for the professionals involved. The variability of the SCA postnatal phenotype puts an extra strain on professional guidance of parents after an incidental prenatal finding of an SCA.

WHAT DOES THIS STUDY ADD?

- Despite the complexity of the counseling and the possibility of parental decisions to terminate the pregnancy, most experts believe that the benefits of a prenatal SCA diagnosis far outweigh the disadvantages.

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Chapter 7

Considering factors affecting the parental decision to abort after a prenatal diagnosis of a sex chromosome abnormality

Letter to the Editor of Genetics in Medicine in reaction to the review of Jeon et al. , published in the October 2011 issue

JJPM Pieters
AJA Kooper
TB Feuth
APT Smits

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LETTER TO THE EDITOR | *GENETICS IN MEDICINE*

CONSIDERING FACTORS AFFECTING THE PARENTAL DECISION TO ABORT AFTER A PRENATAL DIAGNOSIS OF A SEX CHROMOSOME ABNORMALITY

To the Editor:

In their interesting study,[1] Jeon and colleagues evaluated demographic factors to study associations with decisions to terminate or continue pregnancy. While their review is a valuable contribution to the existing literature about the complex issue of decision-making after a prenatal diagnosis of a sex chromosomal aneuploidy (SCA), it does not address some relevant factors that might affect this decision-making. We would like to bring these factors to the readers' attention. Each of a multitude of factors, separately or in combination, may influence parental decisions about terminating pregnancy.

I: Reason for referral

Various studies report that *a fetal ultrasound abnormality* strongly affects the decision to abort.[2] The review reports indications for invasive prenatal testing in 12 of the 19 articles studied, but does not address the reasons for referral. In our opinion, addressing these reasons is necessary. The authors report that young mothers (<36 years old) are more likely to abort after being informed of a fetal SCA. However, as long as the reason for referral is unknown, the maternal age factor must be interpreted with great care. One must take into consideration that these young mothers may have been eligible for invasive prenatal testing on the indication of a fetal ultrasound abnormality. The prognosis is substantially poorer for a fetal ultrasound abnormality than for an incidental finding of SCA. The latter makes the decision-making even more burdensome because the phenotype may be quite normal but uncertainty remains concerning psychosocial development and late-onset diseases.

II: Role of the Internet

The important role of the Internet in providing anxious parents with extensive medical information is not mentioned in the review. We checked whether the informative role of the Internet was considered in the articles reviewed and discovered that it was not, even though the Internet has played an ever greater role in public information since the 1990s. Medical professionals must be aware of the fact that patients check the Internet for extensive information about their disease and/or possible treatments. Parents search the Internet looking for additional information about the syndromes for which their unborn children are diagnosed. In a qualitative interview study (as opposed to a quantitative one), which we published in 2011,[3] all the participating couples independently searched the Internet and stated that the information they found was a shock to them.

After professional counseling they decided that the Internet information was too negative, and ultimately they decided to continue pregnancy. We found two articles regarding the impact of medical information that patients can find on the Internet,[4,5] and we believe that more research on this important issue will follow in the near future. In the complex of emotions after the unforeseen diagnosis of a fetal SCA, parents have a need for additional information; they start searching the Internet even before the post-test counseling appointment. The impact of searching the Internet for their decision-making is an important factor that we believe deserves more attention in future research.

III: The counseling

Directive counseling is an important factor in Jeon colleagues' review. It is associated with the decision to terminate pregnancy, but the authors do not report the professional qualifications of the counselors or consider whether one type of counselor is more tempted to direct parents to abort than another. The profession of the counselor has been reported in 11 of the 19 studies, and the influence of the counselor's profession on the decision to terminate is elaborately discussed in 6 of these studies. Other publications report that counseling by non-geneticists may be associated with more decisions to terminate.[6,7]

The authors used a methodological quality score for the articles they reviewed. It would increase the usability of their review if each of the 19 articles in the table was accompanied with its individual score.

We conclude that: (i) the reason for referral plays a major role in the process of decision- making when a fetal SCA is diagnosed, as fetal ultrasound abnormalities may influence the prognosis. The presence or absence of a fetal ultrasound abnormality was not addressed, this fact importantly affects the results of the review; (ii) the Internet has an increasingly important role in providing additional, but sometimes confusing, medical information to anxious parents who are searching unguided for help in their difficult decision-making; (iii) geneticists can make a significant contribution to the field of decision-making of parents to continue or to abort their pregnancy.

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Response to Pieters *et al.*

To the Editor: We wish to thank Pieters, Kooper, Smits, and Feuth for their interest in our review. We appreciate their thoughtful comments and the important factors raised in their letter "Considering Factors Affecting the Parental Decision to Abort After a Prenatal Diagnosis of a Sex Chromosome Abnormality"[1]. Nonetheless, for the sake of clarity, we would like to point out that our review[2] extends beyond an analysis of demographic factors to include nondemographic variables such as type of sex chromosome abnormality and parents' fears.

No doubt the confounding factors raised by Pieters and colleagues (reason for referral, the role of the Internet, and qualifications of counseling providers) are extremely important for more fully understanding decisions to continue or terminate a sex chromosome abnormality–affected pregnancy. Unfortunately, these factors did not emerge as findings in the studies we reviewed, as they were not sufficiently explored in this body of work. Therefore, we thank Pieters and colleagues for helping to highlight and reinforce both this gap and our call for better-quality studies. To date, assessments of decisions surrounding a sex chromosome abnormality–affected pregnancy have been limited in their ability to identify the multiple factors shaping these decisions, the nuanced variability within those factors, and the complex interactions among them. Studies that (i) tap into the context of decision-making, (ii) examine how parents obtain information on their own through the Internet, and (iii) explore the role played by various types of service providers, in-depth—are urgently needed!

Moreover, as we argue in our review, studies of better methodological quality are also missing from this body of literature. Given the multifactor nature of the topic, it makes little sense to capture complex associations among factors and decisions using descriptive or bivariate statistical analyses without controlling for confounders or covariates. Also missing from this literature are qualitative studies that portray parents' points of view and voices, directly.

Finally, given the below-average methodological quality scores of most studies in the review, we chose not to report each study's score individually. These are available, however, upon request to the authors.

DISCLOSURE

The authors declare no conflict of interest.

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Chapter 8

General discussion and future prospects

GENERAL DISCUSSION AND FUTURE PROSPECTS

1.1 Prenatal findings of sex chromosomal aneuploidies

1.2 Ethical considerations

1.3 Future prospects

8.1 PRENATAL FINDINGS OF SEX CHROMOSOMAL ANEUPLOIDIES

Incidental findings are an inevitable part of medical examinations and may appear in any physical or laboratory test. They usually come as unforeseen to the person involved, even though most medical professionals are aware of the phenomenon. Interpreting the significance of incidental findings may not always be easy for a trained researcher, but it is certainly difficult for the patient.

Prenatal screening and diagnostic testing are widely implemented to gain information about the health of the unborn child. The incidental finding of a sex chromosomal aneuploidy (SCA) in prenatal testing intended to exclude another abnormality is not uncommon. The finding of a fetal SCA in a seemingly normal pregnancy may cause parental anxiety, as SCAs are unfamiliar syndromes to most parents. They cause dilemmas in deciding whether to continue the pregnancy because the postnatal phenotype and quality-of-life prognosis of those with an SCA are so variable. Medical professionals generally consider the post-test counseling very challenging. Counseling is complicated by the fact that many parents use the Internet to collect additional – sometimes incorrect or incomplete – information.

Whether an incidental finding of a fetal SCA provides a diagnostic benefit or creates diagnostic damage is the central study question of this thesis. Some incidental findings may be clearly beneficial to the patient (e.g., the discovery of an ovarian tumor in a routine gynecological ultrasound examination), whereas other findings may be damaging (e.g., the finding of a genetic anomaly with uncertain clinical consequences). In the case of a prenatal finding of SCA, the child may benefit from early parental and professional guidance and may be damaged by stigmatization.

Our study shows that both the parents and the professionals which we interviewed consider the incidental prenatal finding of an SCA a benefit in terms of early treatment and support options. As our study had a qualitative design, the results are indicative rather than conclusive. These results may contribute to the discussion whether testing procedures that include a potential incidental diagnosis of a fetal SCA indeed constitute good medical care.

Considering that the parents and experts in our study favored including the sex chromosomes in prenatal testing, it seems important to continue detecting SCAs and to improve pre- and post-test information. The finding of an SCA in prenatal testing should no longer be considered an incidental finding, and pre-test counseling should adequately inform parents about it.

Pre-test counseling

The incidence of SCAs is 1 in 300 in prenatal tests for advanced maternal age (AMA) or a positive first-trimester screening test result, which is comparable to the incidence of Down syndrome.[1,2] Overall, the incidence of SCA findings at birth is 1 in 400.[3] Parents should be informed beforehand that SCAs can be found in routine prenatal testing; this issue has been addressed in earlier reports.[4-6]

Choosing full-scale prenatal testing by traditional karyotyping, micro-array, next generation sequencing (NGS) or rapid aneuploidy detection (RAD) for selected most common chromosomal aneuploidies, depending on the reason for testing and the parents' preference.[7,8] This choice is of topical and ethical interest in terms of the parents' autonomous "right to know versus not to know" genetic information about the unborn child. Our first study has shown that, if full-scale testing were available to low-risk pregnant women as part of invasive diagnostics, they would not accept it unquestioningly. Low educational level and limited knowledge of genetic defects may play a role in their choices (Chapter 2).

Pre-test counseling concerning prenatal diagnostic testing covers the purposes of the tests and the risks. It should be non-directive in nature,[9] tailored to the circumstances, and preferably with both parents participating.[10] All prenatal tests carry the risk of finding a genetic or structural fetal anomaly for which the parents were possibly unprepared, and its clinical significance is not always clear. Since the prenatal finding of an SCA is not uncommon, we propose that it should be discussed with the parents in pre-test counseling.

Screening and diagnostic prenatal tests

Parents consider fetal ultrasound to be the first pleasant encounter with their unborn child.[11,12] Ultrasound imaging may reassure most pregnant women, yet it is a diagnostic tool that can detect a fetal anomaly. It can miss or falsely detect an anomaly, and it can detect fetal physiology variations with unclear clinical significance (e.g., choroid plexus cysts or echogenic bowel.[13,14] The possibility of finding a major anomaly like anencephaly, or a minor anomaly like a soft marker, is not always discussed beforehand. A similar situation may occur concerning the completeness of the pre-test counseling in invasive diagnostic testing, as increasingly high resolution DNA technology such as micro-array and soon NGS will be applied in prenatal testing. Parents need appropriate

pre-test counseling which means that counselors verify that patients have read and understand the disclosures of the test. In the future, pre-test counseling will be even more challenging.

Mosaicism

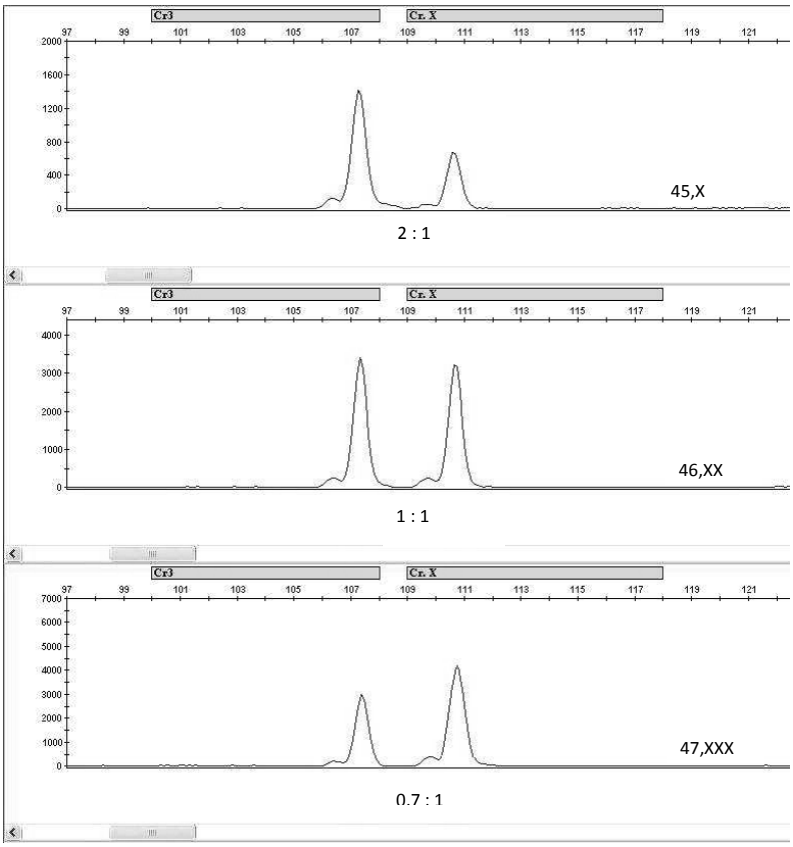
The co-existence of more than one cell line in one person influences the phenotype and the prognosis. The co-existence of a normal cell line has a positive impact, and the co-existence of another aneuploidy has a clearly negative impact on the postnatal quality of life. Mosaicisms are common in all SCAs and are especially associated with 45,X.[4] This is an important complicating factor in the post-test counseling as mosaicisms may have important health consequences. Growth, onset of puberty, fertility, behavior, and general health may be quite normal in the presence of a normal 46,XX cell line.[4,15,16] This is also true of mosaicisms of 47,XXY or 47,XXX combined with a normal cell line.[17] The estimated percentage of Y-chromosome mosaicism in 45,X is 5.5%[18-20] and is associated with hyperandrogenism, virilization, and gonadal tumors.[21-23]

Because of the large variability of co-existing X- or Y-chromosome cell lines, it is virtually impossible to predict the postnatal phenotype of a 45,X fetus, whereas the presence of fetal ultrasound abnormalities is a clear negative prognostic factor.[24-27]

One has to realize that, even if a normal fetal karyotype is found in prenatal invasive testing, there may still be a co-existing aneuploidic cell line that remained undetected in the test. This fact is not usually discussed in pre- or post-test counseling, but the person concerned is diagnosed later in life because of health problems.[28] The huge variability and complexity of the clinical impact of mosaicism in SCAs make it impossible to discuss all the options in pre-test counseling, but counselors can inform parents about the existence of mosaicism by guiding them to specific websites that explain the subject in an understandable way.

A specific back-up marker set should be used to confirm any initial QF-PCR results indicative of (mosaicism) sex-chromosome aneuploidy. This back-up set includes extra markers and primers to amplify chromosome-specific sequences of the paralogous gene TAF9L. This gene has a high degree of sequence identity between chromosome 3 and X, making a relative quantification between chromosome 3 and chromosome X possible. See Figure 1.

Figure 1. Detection of X chromosome aneuploidies by QF-PCR analysis of TAF9L



- X monosomy (Turner Syndrome) is determined by the double dose of chromosome 3-specific product compared to the X.
- Two peaks of equal fluorescent intensity (ratio 1:1) indicate the presence of two X chromosomes.
- Skewed ratio (0,7:1) in favor of the X specific product indicates the presence of three X chromosomes

Post-test counseling

Meeting patients' expectations for information and explanations in genetic pre- and post-test counseling is an issue that earlier studies have discussed.[29,30] The results of our study show that parents were generally shocked by the finding of a fetal SCA, but they were glad to know about the syndrome to better decide whether to continue the pregnancy. They would have preferred to quietly learn about these syndromes beforehand, and pre-test counseling would certainly have been more satisfactory. Other studies of the prenatal diagnosis of SCA have discussed this issue.[4,5]

In our study, most parents complained about the way this unexpected test result was communicated to them, at an unexpected moment, sometimes in an awkward place. They had an appointment with one or more counselors in the days after the disclosure

of the finding for an explanation of the syndrome. Not all counselors gave comparable information, a known fact in post-test counseling of SCA,[31-34] which made them feel insecure, and they reported spending much time in uncertainty and worry (Chapter 4).

Patients increasingly use the Internet to obtain health information. This may affect the patient–health-professional relationship.[35] Searching for additional information about syndromes or diseases without the aid of a medical professional provides a certain risk of getting incorrect or incomplete data, or even misunderstanding information.[36] In the case of the prenatal diagnosis of SCA, anxious parents inevitably visit websites with much positive information coming from parental contact groups, but they also find unilateral negative information regarding the prognosis of the full-blown syndromes. One of the results of our study is that some parents were shocked by the amount of negative information, but at the same time other parents found the information too positively colored; it all depended on the concern they had for their child's future quality of life.

Our review of the SCA literature shows that an incidental prenatal diagnosis usually leads to a less affected or more normal postnatal phenotype (Chapter 3), and this information is generally unavailable on the Internet SCA sites. Reliable information including these specific facts should be available on the Internet; they should adequately inform anxious parents who are faced with an incidental prenatal finding of SCA. Linden et al.[6] have discussed a suggestion for more adequately informing parents about the variability and imprecise prognoses of SCAs.

Parental decision-making

Parents generally found the information they received from the professional counselors satisfactory. This finding confirms the conclusions of other reports.[29,37,38] All the participating couples were able to make a satisfactory decision to continue or terminate their pregnancy. They all stated they would do the same again, and they were content with the procedure and their decision. Parents who terminated confirmed that they appreciated neutral medical information about the syndrome and appeared to be rather autonomous in their termination decision, whereas parents who continued the pregnancy asked for more guidance from medical advisors.

Non-response

In our study of the parental perspectives of the decision to terminate after the incidental prenatal finding of SCA, the parents generally had decided to do so in such a case before the actual diagnostic testing (Chapter 5). The parents whom we invited to participate in the interviews and who were willing to talk about the events and their perspectives again formed a minority (29%). Other studies show that the usual non-response rate is 30%, with peaks to 50%, so that those who refused to take part were probably not a random sub-set of the population to be investigated.[39] We can only speculate about

the reasons for the large proportion of non-responders in our study (71%). Termination of a desired pregnancy has been described as a "major life event", and the grief for the self-chosen loss of a child is associated with feelings of relief, guilt, doubt, and loss of self-esteem.[40] More than 95% of the parents decide to terminate when they receive a prenatal diagnosis of Down syndrome,[41] a fact that is now socially and legally accepted. If the parents acknowledged the possibility of finding a prenatal SCA, they would probably be less shocked when confronted with one, and it might be easier for them to reflect on their perspectives and decision again.

Experts´ opinions

We asked professionals in the field of counseling and treatment of people with SCA about the usefulness of a prenatal diagnosis of SCA. They stated that they considered it a benefit to the child and the parents because of the early prevention and treatment options. This is in line with earlier reports.[4,17,42,43] The experts acknowledged that the child might be stigmatized and that the parents might decide to terminate the pregnancy. After analysis of all the answers, the professionals concluded that the advantages of prenatal SCA detection largely outweigh the disadvantages (Chapter 6).

Literature

Parents who are confronted with an incidental prenatal diagnosis of SCA in the absence of fetal ultrasound abnormalities need different counseling and certainly different additional information than the parents of a child with a postnatal diagnosis of an SCA because of phenotypic problems. Our literature review (Chapter 3) shows that these incidental prenatal findings are associated with phenotypic problems that are much less serious in all domains (health, behavior, and fertility). The currently available information leaflets and Internet websites all describe the condition of people with postnatally ascertained SCAs, and they may reliably report negative and positive aspects of the syndromes. Nonetheless, people with incidentally and prenatally diagnosed SCAs do not fit in this category. These sources of information are thus inadequate and not useful for parents who want to obtain information after an incidental prenatal diagnosis of SCA.

Standard inclusion of the sex chromosomes in prenatal tests

Molecular technologies such as multiplex ligation-dependent probe amplification (MLPA), quantitative fluorescence polymerase chain reaction (QF-PCR) are used for rapid aneuploidy detection (RAD) of the most common fetal aneuploidies (13, 18, 21, X and Y).[44-47] Their implementation makes it possible to reduce certain unwanted findings. Excluding X and Y probes avoids finding a fetal SCA. The discussion whether or not to continue the standard inclusion of the X and Y probes in RAD is ongoing.[48] The results of our study show that excluding the detection of SCAs might not be the best choice.

In conclusion, the results of the studies in this thesis show that both parents and professionals favor prenatal detection of SCAs, whether intended or not. This implies that pre- and post-test counseling deserves attention. Prenatal SCA findings are not uncommon, and this fact should be discussed with the parents before the testing. They can then calmly obtain reliable and neutral information and will then be better prepared for a possible SCA finding, which will increase their psychological adjustment. They will be less shocked by the disclosure of a finding that is unfamiliar to them. The prenatal diagnosis of an SCA should thus be considered a possibility in prenatal testing.

8.2 ETHICAL CONSIDERATIONS

The obligation to inform

Medical professionalism and the interpersonal doctor–patient relationship are summarized and integrated in the Hippocratic Oath (classical or modified),[49] which contains the generally accepted principles of moral values and ethics for physicians. Physicians promise not merely to avoid harm, but to act for the good of the patient.[50] Physicians have a moral obligation to disclose all test information, prenatal or otherwise.

Incidental diagnostic information is becoming common in many areas of medicine. Sometimes the clinical significance of the information remains unclear, but even then it cannot easily be ignored.[51] Other prenatal incidental diagnoses are clearly beneficial, especially when the conditions are treatable or when the information helps parents decide whether to prevent the birth of a seriously handicapped child.[52] However, some disorders are currently untreatable or may lead to late-onset disease (e.g., breast cancer mutations). Some consider that discussing these incidental findings may harm the parents and the child by causing anxiety about a risk of future disease.

An incidental disclosure of a fetal SCA offers a unique opportunity for early prevention and management of SCA-related disease, the psychological issues for parents and children, and the fertility issues in the later life of the child. These benefits are evident from the professional point of view,[4,42,43,53] but they should be balanced against the possible negative impact of the unexpected diagnosis on the future child. Incidental prenatal diagnosis of an SCA may cause stigmatization, damage the child's self-esteem, and/or distort the family's perception of the child.[54] In our studies, the problem of stigmatization did not appear to be an issue for concern (Chapter 4). Nonetheless, future genome-wide testing will likely reveal more genetic aberrations, at which time the clinical significance will not yet be clarified; stigmatization may then become a menace to the future child.[55]

The term "incidental finding" has currently been replaced in some medical publications with "unsolicited finding". One may discuss the use of the term "unsolicited" in the case of the prenatal finding of an SCA, as our studies have indicated that parents and experts

may find the incidental diagnosis of fetal SCA indeed useful and appreciate the information. They all would want to be informed again in the event of another pregnancy. This shows that the professional obligation to inform parents about an "incidental" prenatal finding of an SCA is as much appreciated as the moral obligation to disclose a "solicited finding".

The right to know and the right not to know

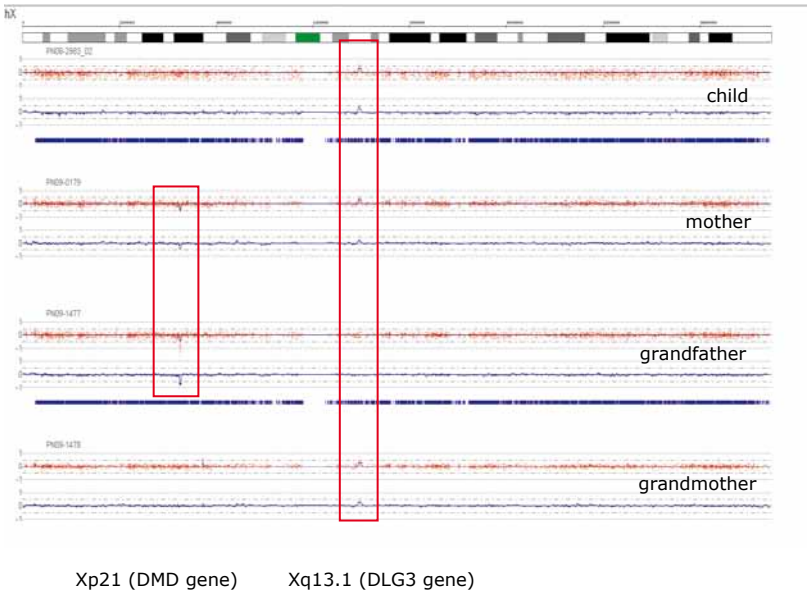
Genetic testing is distinct from testing for other conditions in that it potentially affects the family members as well as the person tested. For all genetic tests, patients must be adequately informed about the implications of genetic screening before they can provide informed consent.[56]

In view of new technological developments, it is interesting to assess the parents' preference, namely, whether women considered at high risk of having a child with Down syndrome and undergoing invasive testing (e.g., because of AMA), would opt for genome-wide genetic testing for other disorders for which they do not have an a priori increased risk (Chapter 2). Women referred because of an increased risk of Down syndrome can now choose between traditional karyotyping and RAD in some prenatal centers in Sweden and the Netherlands. About 70% of the women in Sweden and 60% in the Netherlands who had been offered this choice, preferred RAD.[57,58] One should expect that incidental findings will thus be significantly reduced. The women's preference brings the right not to know to the fore. Women's preferences to have a choice of one of these two prenatal testing techniques have recently been evaluated; most women preferred the choice option (Kooper 2012, data presented at ISPD Miami).[7,8,59,60] From the ethical point of view, the parents' autonomous "right to know" versus "not to know" is of topical interest.[61] Placing knowledge of genetic diseases or predispositions in a well-informed community with integrated clinical and social support systems optimizes its usefulness. These support systems should include counseling services for patients and their families, Such circumstances can lead to better care and management of the patient and ultimately improve the quality of life.[55] If this is also true of conditions that can be diagnosed in fetuses, the question becomes how far the right not to know should be ascribed to the parents. If the quality of life of the future child will clearly benefit from disclosing certain information, a physicians' dilemma arises. Both the pregnant woman and the unborn child are the physician's patients, and they have the right to be cared for properly.[59] The boundaries of the obligation to inform and the woman's "right not to know" can conflict. Researchers are encouraged to consult with a clinical ethics committee regarding the existence of the participant's right "not to know" about incidental findings.

The new technologic advances in prenatal testing may provide genetic information with implications not only for the fetus who is being tested, but also for the parents, other

siblings, grandparents, and other relatives (Figure 2).[52] Adequate, balanced counseling of the parents will lay the groundwork for well-informed choices of the type of prenatal tests. Techniques such as micro-arrays and NGS will oblige medical professionals to adequately assess the parental wish "to know or not to know". The best time to give parents this information is most likely during pre-test counseling; the clarity of thought might not be optimal during post-test counseling when a fetal abnormality or disease has to be disclosed.

Figure 2. Micro-array test result: an incidental finding unrelated to the initial indication for micro-array testing (source: Department of Human Genetics, Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands)



The index patient (child) shows a duplication on Xq13.1 of DLG3 gene: X-linked gene for non-syndromatic mental retardation.
The mother shows the same duplication as well as the grandmother. In addition, the mother shows a second mutation, an in-frame deletion of exons 3 – 9 in the Duchenne Muscular Dystrophy gene (Xp21).
The same deletion size was found in the grandfather of the index patient. Because of the extremely large size of the DMD gene (nearly 2400kb), mutations in the DMD gene correlate between the size of the deletion and the severity of the Duchenne of Becker muscle dystrophia. The medical condition of the grandfather may be characterized by delayed walking.

The upcoming use of informed consent, and disclaimers

Informed consent and disclaimers have become customary items in prenatal practice when micro-array techniques are used. In addition, NGS in the near future, with ever

increasing probe coverage and resolution will increase the detection of small copy number changes.[62] The challenges lie in interpreting the copy number variations (which exhibit reduced penetrance or variable expression), dealing with incidental findings that may be unrelated to the observed fetal anomalies, and handling unclassified variants of uncertain clinical significance. Thus more genetic information about the fetus may not always result in good patient care. Therefore, clinicians need to find a way to adopt policies and guidelines to manage test results that were not intentionally searched for.[51]

The results described in this thesis show that both parents and experts appreciated the disclosure of an incidental prenatal finding of SCA. The increased amount of genetic information of unknown clinical significance or information about the risk of late-onset diseases may justify the legal protection of disclaimers. However, this never absolves us from providing adequate pre-test counseling tailored to the patient.

8.3 FUTURE PROSPECTS

New technologic advances in prenatal testing

Non-invasive prenatal diagnostics using next-generation sequencing (NGS) is rapidly being integrated into prenatal diagnostics and offers considerable potential benefits for the fetus at an unequalled detection level.[63-65] However, NGS entails genome-wide testing of fetal DNA, and incidental findings may be encountered. This could be one of the most difficult obstacles.

The complexity of finding and reporting genetic results which are incidental or unrelated to the reasons for which the test was initially ordered and the options clinicians and laboratories will face as genetic sequencing becomes more common are currently being discussed.[66] To separate the fetal DNA from the mother's, it is necessary to know the mother's nucleotide sequence. This genetic information may also reveal information about family relationships and findings with great or possible net benefit. The procedures are being tested for validation of the sensitivity and specificity in detecting fetal chromosomal aneuploidies, and they will be implemented in clinical prenatal practice soon.[67-71] Both genome-wide testing and selective targeting of the most common aneuploidies 13, 18, 21, X, and Y are possible, and this includes the diagnosis of fetal SCAs.[67,70,72,73]

The diagnostic tests for fetal genetic anomalies in maternal serum samples carry no risk of pregnancy loss, but regulations are needed to respect the parental wish not to know about genetic conditions in what they consider to be unwelcome information. Next-generation sequencing has been discussed as a complex medical test with the power to help, harm, and confuse. Medical professionals have a long-established ob-

ligation to "first, do no harm." That sentiment applies in the discussion about genomic testing as much as in other medical contexts.[74]

Counselors need to learn what patients would want to know about their genome, and management guidelines for counseling patients about incidental genetic findings are necessary. This applies particularly to the new prenatal testing technologies, such as NGS of fetal DNA in maternal plasma.

Improvement of the quality of life for people with SCA

Early recognition of the syndrome and its associated problems in the domains of health, behavior, and fertility offers an opportunity to provide early prevention programs.[42,43,75,76] Besides the problems of gonadal dysgenesis and aberrant stature, some people with SCA have a reduced life expectancy because of certain well-defined health hazards. A diversity and co-existence of factors may influence their quality of life. Early screening and treatment improves health and behavior, and technological advances in fertility treatment offer possibilities of procreation to people with SCA.[4,17,42,43,53,77-80]

Freriks[42] has shown that about one-third of the 45,X population lacks any form of ongoing specialist care. A large proportion of patients with an SCA may not be diagnosed because of the substantial variation of the clinical phenotype;[4,81] still, they have certain health and psychosocial risks. A prenatal diagnosis may be a benefit in terms of early support options.

The information parents receive greatly influences their decision about whether to continue the pregnancy after the incidental prenatal finding of an SCA. It has been shown that there is an association between the amount of negative information parents are given about SCA and the decision to terminate the affected pregnancy.[33] Further, there is a clear influence of the specialty and the knowledge of the counselor on parents' perceptions of the expected disability of the future.[6,31,32,38,82]

Our study shows that some parents expected poor quality of life for their child on the basis of the additional information they found on the Internet. These parents were more inclined to terminate the pregnancy, as they had no faith in the options to improve the quality of life through early treatment programs and they feared these programs would be a burden to their family (Chapter 5). An incidental prenatal finding of SCA may result in the birth of a child with a mild clinical phenotype or no apparent phenotypical problems. The parental fears for the child's future poor quality of life may be unjustified, as has been shown in earlier reports of the mild clinical phenotype of people with SCA after an incidental prenatal diagnosis (Chapter 4).

Improving the quality of life of children with an incidentally prenatally diagnosed SCA may require little effort from the parents, and the early recognition of even a small problem in health or behavior may still be beneficial.[4,43,81,83] Early explanation

of future fertility problems and a joint search for possible solutions, such as fertility preservation or gamete-donation, would most certainly improve the quality of life.[84-87]

Tailored information about SCA for expecting parents: the Internet and hospital brochures

In countries where prenatal screening is routinely offered, some women use testing without considering its consequences.[4,88-90] Early fetal assessment may produce findings that may have important medical or social implications unrelated to the reason for the testing. These findings are beneficial in terms of increasing the parental autonomy in making a personal decision about continuing the pregnancy; for instance, when an important health-threatening fetal abnormality is diagnosed. In other cases, the clinical significance of the findings is unclear, which will lead to concern about the postnatal quality of life.

As prenatal testing has become increasingly complicated because of technological advances in the last years, so will the counseling of the parents. During pre-test counseling, parents should now receive information about the different testing procedures, the associated risks, and the possibility of intended or unintended findings in the tests that they choose. The counseling will be very time-consuming, and it is conceivable that parents will not completely understand all the technical or medical information they receive. Our study of parents' preferences regarding full-scale genetic testing for disorders for which they do not have an a priori increased risk shows that they would not accept this unquestioningly. A low educational level was associated with a negative attitude towards genetic testing, which was inconsistent with the significantly positive attitude of these women towards full-scale testing (Chapter 2). Our data confirm that the general basic knowledge of prenatal testing appears to be positively linked with the educational level, which is in line with other studies about the lower rates of informed choice and the necessity of providing the women involved with extra information.[91,92]

The Internet can be used for assistance in professionally guiding and counseling parents. It may be helpful to the parents to have additional information after the counseling session and to have the counselor guide them to Internet websites with reliable, neutral, tailored, and accurate information. As Internet use broadens access to information, health professionals must be aware that this information is not always accurate.[93]

In the Netherlands, prenatal screening for Down syndrome has become available to all pregnant women.[94] Only licensed prenatal centers are registered to participate and it is a political choice that there should be no signal given that pregnant women should indeed ask for this test. It should be an individual well-informed choice, and attention is paid to guarantee women's right of "not knowing". Accurate information about this nation-wide screening for Down syndrome is available on government-approved websites (www.erfocentrum.nl). However, information about incidental findings that have

an incidence similar to that of Down syndrome, such as SCAs, is not provided. They are not a part of the government-approved screening program, which applies to Down syndrome, recently Edwards and Patau syndrome have been added. Parents who have been confronted with such an incidental finding must resort to non-government-approved websites, and the information on these sites may be unhelpful and unreliable. It would be preferable to inform the parents just as accurately about findings that may no longer be considered incidental or unsolicited.

The Internet successfully provides patients with additional and accurate information about diseases, testing, and treatment programs in other medical disciplines; nonetheless, professional guidance is advisable.[36,93,95] Clear explanations can be given about the different types of prenatal tests which are available, the testing procedures, the associated risks, and the incidental findings in terms of treatable or untreatable disorders. The information can be printed as a hospital brochure and handed out to the parents after the pre-test counseling. The brochure should recommend reliable Internet websites (possibly including one set up by the hospital itself) with adequate information consistent with a prenatal diagnosis of the fetal abnormality in question.

Parents should be informed that new technological advances in prenatal testing can now diagnose genetic abnormalities of unclear clinical significance. It is recommended that parents could choose to receive no elaborate whole-genome information, most importantly their choice should be consistent with their coping style. The results of this thesis show that the parents who participated in the studies did not know that SCAs existed and were shocked to hear about a finding of one. After a period of shock, grief, and anger, they all started an unguided Internet search and then decided whether to continue or terminate their pregnancy. They were content with their decisions, but they might have been spared an anxious time after the disclosure of the finding of SCA.

The variability in phenotypic outcome after a prenatal diagnosis of SCA seriously complicates post-test counseling. Parents who have had a chance to read about SCA after pre-test counseling may be expected to be adequately informed about the likelihood of being confronted with these diagnoses and may have read about the large variability in phenotype. They may not have studied the subject in depth, but they have some idea of these genetic abnormalities. This makes post-test counseling more efficient and less frightening.

Because new technologic advances will result in even more genetic information in prenatal testing, it is of utmost importance that physicians adjust pre- and post-test counseling to the changing circumstances. Since the 1990s, expectant parents and worried patients have had access to an unlimited source of unreliable information: the World Wide Web. In the light of all the new medical diagnosing technologies (not only in the field of prenatal diagnosis), professional guidance of patients to reliable, tailored, and accurate information is essential.

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Chapter 9

Summary / samenvatting

SUMMARY

There are various reasons for prenatal diagnostic tests: to assess fetal viability, to determine the sex of the fetus, and to exclude a structural or genetic abnormality. Early fetal assessment risks incidental findings – findings unrelated to the reason for testing – that may have important medical or social implications. Sex chromosomal aneuploidies (SCAs) may be diagnosed as incidental findings in prenatal diagnostic testing procedures. These SCAs cause syndromes little known to most parents, and their postnatal phenotypes are variable.

In the light of technologic advances in prenatal testing, more genetic information about the fetus will become available, some of which may have uncertain clinical significance.

The studies in this thesis analyze and discuss the various aspects of parental attitudes and dilemmas, as well as professional opinions about the benefits or disadvantages of an incidental finding of a fetal SCA. We discuss how best to provide accurate and balanced pre-test information to parents and to guide them to secure additional information.

Chapter 1 describes the characteristics of sex chromosome disorders. In the variability of the phenotypic spectrum, we see that some individuals are very mildly affected and others have more significant physical and psychological features. The most common SCAs are 45,X (Turner syndrome), 47,XXY (Klinefelter syndrome), and 47,XXX (Triple X syndrome). For better understanding, we briefly describe the phenotypic features of the three most common SCAs. Women with Turner syndrome generally have ovarian failure, subfertility or infertility, short adult height, and increased morbidity and mortality (mainly because of complications from congenital heart disease). Men with Klinefelter syndrome generally present with hypogonadism, subfertility or infertility, are taller than expected, and have small, firm testes. Some have gynecomastia and increased morbidity (due to increased cancer risk or autoimmune, metabolic, or other disease). Women with Triple X syndrome often have tall stature and hypotonia; premature ovarian failure and other SCA-associated diseases may occur. All three types of SCA may lead to psychosocial problems and speech or learning difficulties.

Due to a high rate of fetal demise, the postnatal incidence of 45,X is 1 in 2000 to 2500 newborn girls, resulting in a worldwide prevalence of 1.5 million Turner women. The incidence of diagnosis of Turner syndrome in prenatal testing depends on the presence of fetal ultrasound abnormalities and the indication for the testing procedure. The 47,XXY abnormality occurs with an incidence of 1 in 500 to 1000 newborn boys; many Klinefelter individuals remain undiagnosed. Prenatally, the incidence of 47,XXY diagnosis is 1 in 650 fetuses; it includes 25% of all chromosomal abnormalities after invasive prenatal testing. The postnatal incidence of 47,XXX is 1 in 1000 newborn girls, the same incidence

as in prenatal testing. Prenatally, the syndrome is diagnosed in 0.1% of all chromosomal abnormalities, generally as an incidental finding. The addition of more than one extra sex chromosome is rare; the prevalence of other X–Y aneuploidies is estimated at 1 in 18,000 or less. The incidence of SCA diagnosis after prenatal invasive testing shows no direct causality to maternal age. In prenatal testing for advanced maternal age, the incidence of fetal SCA findings appears to be comparable to the incidence of Down syndrome. Various facets of the diagnosis and some typical pre- and post-natal phenotypic aspects of SCA are described.

The second part of the chapter describes the emergence of SCA and explains the mechanism underlying embryonic folding, along with some basic elements of genetics and the complexity of the counseling. Counseling after a prenatal diagnosis of SCA provides the parents with information about the very broad scale of the postnatal phenotype of these individuals. One end of the scale shows a normal, self-supporting person without any health or behavior problems who may ultimately discover the genetic anomaly in the medical search for the cause of his or her infertility. The other end of the scale shows a person with SCA who may have many health and behavior problems, and even very serious metabolic, autoimmune, or psychiatric disorders.

The third part of the chapter names all the currently available screening and diagnostic prenatal tests: the non-invasive first-trimester screening test, second-trimester ultrasound screening, diagnostic ultrasound assessment, and the invasive procedures for karyotyping the fetus, such as chorion villus biopsy and amniocentesis. The available choices for rapid aneuploidy detection (RAD) or genome-wide testing using micro-array technology or next-generation sequencing are weighed.

The fourth part discusses the difficulties of informing the parents about the incidental findings and addresses some ethical issues.

Chapter 2 describes the attitudes of women in low-risk pregnancies towards full-scale genetic testing and explores relationships between demographic characteristics and the level of interest. Except for educational level, no significant relationships were noted between the demographic variables and the wish to opt for full-scale testing. A low educational level was significantly related to the interest in full-scale testing. The conclusion of this pilot study was that low-risk pregnant women had little interest in full-scale genetic testing, and their interest further diminished as pregnancy progressed. Educational level appeared to affect their views.

Chapter 3 reports a literature review of the diagnostic relevance of incidental prenatal findings of SCAs. Publications about postnatally diagnosed SCAs from 2006 to 2011 as well as publications about incidentally prenatally diagnosed SCAs from 1980 to 2011 were systematically screened. Incidental prenatal diagnosis of SCAs is associated with

normal to mildly affected phenotypes. This contrasts sharply with postnatal diagnoses of SCAs and highlights the importance of this ascertainment bias towards the prognostic value of diagnosis of fetal SCAs. Although it seems rather obvious that the outcome of a child with an incidental discovery of a sex chromosome abnormality is better than one who is diagnosed postnatally on clinical grounds, this review of the literature since 1980 shows that counselors may reassure the parents in the knowledge that indeed all the currently available studies support this conclusion.

Chapter 4 describes the parental perspectives of being confronted with an unforeseen fetal SCA in light of the fact that RAD can avoid this incidental finding. Parents were unprepared for incidental findings in routine prenatal diagnostics, and all of them started an unguided Internet search. Parents reported having faith in good quality of life for their child. Most participants reported that they appreciated knowing about the syndrome and would choose the same procedure again in the event of another pregnancy. This fact is important in discussing the option of excluding the X and Y probes from RAD. The parents' perspectives may serve as major contributors to research into the question whether including the X and Y probes in RAD should be standard.

Chapter 5 shows the parental perspectives of being confronted with an unforeseen SCA and their considerations regarding termination of their pregnancy. Again, parents were unprepared for incidental findings in routine prenatal diagnostics and started an unguided Internet search. They appreciated knowing about the syndrome, and they had many concerns about the child's future health and socio-psychological wellness. The parents gave their advice for professionals and stated their preference of including the probes for the sex chromosomes again in a future test. The main reason for terminating a pregnancy appeared to be the negative perspective from which the parents judged the child's future. The percentage of respondents was 31.2. This high percentage of selective non-responders might reflect parents' inner feelings and thoughts about their terminated pregnancy.

Chapter 6 describes experts' opinions of the advantages and disadvantages of an incidental prenatal diagnosis of an SCA. Most of the experts, who were clinicians in the field of counseling and treatment of people with SCA (87.5%), and clinical geneticists (76.9%) stated that an incidental prenatal diagnosis of SCA was a benefit for the child and the parents. They acknowledged the possibility of parental decisions to terminate pregnancy. Experts favored an incidental prenatal diagnosis of SCA, despite the complex counseling issues and their acknowledgment of possible parental decisions to terminate pregnancy. They believed that the benefits greatly outweigh the disadvantages.

Chapter 7 shows our letter to the editor of *Genetics in Medicine* and the reply from Jeon and colleagues. Their letter is a reflection on a review article *Decision to abort after a prenatal diagnosis of sex chromosome abnormality*: *a systematic review of the literature*, which was published in October 2011. We concluded that some main points were not addressed in the review: (i) the reason for referral (e.g., fetal ultrasound abnormality); (ii) the increasingly important role of the Internet in providing additional, but sometimes confusing, medical information to anxious parents; and (iii) the significant contribution geneticists can make to parents' decision-making to continue or abort their pregnancy. Our letter to the editor commenting on the review was published in the May 2012 issue of *Genetics in Medicine*, together with the reply from the authors of the review.

Chapter 8 discusses considerations regarding the incidental prenatal finding of SCA and the central study question of this thesis: whether an incidental finding of a fetal SCA creates diagnostic benefits or diagnostic damage. Our study shows that both the parents and the professionals who were interviewed considered the incidental prenatal finding of an SCA a benefit in terms of early treatment and support options. As the study design is qualitative, the results are indicative rather than conclusive. The results may contribute to the discussion whether testing procedures that include a possible incidental diagnosis of a fetal SCA is indeed constitutes good medical care. The complexity of pre- and post-test counseling, the problem of mosaicisms, aspects of parental decision-making, the problem of non-responders, the opinion of experts in the field of SCAs, and the issue of providing additional and secure information are addressed. Parents and experts favored the prenatal detection of SCA, whether intended or not. Ethical considerations are discussed: the moral obligation of physicians to inform and the right of the patient "to know" or "not to know" as well as the rights of the fetus. The upcoming use of informed consent and disclaimers in genetic testing and the inevitable increase of the number of incidental findings using genome-wide technologies with high resolution in prenatal testing are addressed. A prenatal diagnosis may positively influence the quality of life because it provides an opportunity for early prevention and treatment programs. Tailored information about possible findings for expecting parents is needed, and pre- and post-test counseling should involve the Internet as a very useful way to provide reliable and accurate information.

SAMENVATTING

Prenatale diagnostische testen worden uitgevoerd om verschillende redenen: om de levensvatbaarheid van de foetus te beoordelen, voor geslachtsbepaling of om een foetale structurele of genetische afwijking uit te sluiten. Vroege foetale beoordeling heeft het potentiële risico van het doen van incidentele bevindingen, losstaand van de reden voor het testen, deze bevindingen kunnen belangrijke medische of sociale gevolgen hebben. Geslachtschromosomale aneuploïdieën (SCA) kunnen worden gediagnosticeerd als incidentele bevindingen in procedures van prenatale diagnostiek. Deze chromosomale afwijkingen veroorzaken syndromen die niet goed bekend zijn bij de meeste ouders en hun postnatale fenotype is variabel.

In het licht van de technologische ontwikkelingen in de prenatale testen, zal meer genetische informatie van de foetus beschikbaar komen, waarvan soms de klinische betekenis nog niet zeker is.

De studies in dit proefschrift analyseren en bespreken de verschillende aspecten van de ouderlijke gevoelens en dilemma's, alsook de professionele opinie over het nut of nadeel van een incidentele vondst van een foetale SCA. De beste manier van accurate en evenwichtige pre-test informatie aan de ouders en het begeleiden van hen naar veilige aanvullende informatie wordt besproken.

Hoofdstuk 1 beschrijft de eigenschappen van de geslachtschromosomale aandoeningen. Er is variabiliteit van het fenotypisch spectrum, waarbij sommigen zeer weinig zijn aangedaan en anderen meer fysieke en psychologische afwijkingen vertonen. De meest voorkomende geslachtschromosomale aneuploïdieën zijn: 45,X (syndroom van Turner), 47,XXY (syndroom van Klinefelter) en 47,XXX (Triple X syndroom). Voor een beter begrip wordt hier een korte beschrijving van de drie meest voorkomende SCAs gegeven. Vrouwen met het syndroom van Turner hebben over het algemeen ovariëel falen, zijn onvruchtbaar, hebben een korte volwassen lengte en een verhoogde morbiditeit en mortaliteit (vooral als gevolg van complicaties van aangeboren hartafwijkingen). Mannen met het Klinefelter syndroom hebben vaak hypogonadisme, zijn sterk verminderd vruchtbaar of onvruchtbaar, hebben kleine vaste testikels, soms borstontwikkeling en een verhoogde morbiditeit (verhoogd kanker risico of auto-immune, metabole en andere aandoeningen). Vrouwen met het Triple X syndroom hebben vaak een grote gestalte en hypotonie, prematuur ovariëel falen kan optreden, evenals een aantal met het syndroom samenhangende aandoeningen. Bij alle drie de vormen van SCA, kunnen zich psychosociale problemen voordoen, evenals spraak- of leermoeilijkheden.
Door een hoog percentage aan foetaal overlijden, is de postnatale incidentie van Turner syndroom 1 op de 2000-2500 meisjes, wat resulteert in een wereldwijde prevalentie van 1.5 miljoen Turner vrouwen. De incidentie van de diagnose Turner syndroom in

prenatale testen wordt beïnvloed door de aanwezigheid van echoscopische foetale afwijkingen en de indicatie voor de testprocedure. Klinefelter syndroom komt voor met een incidentie van 1 op 500-1000 pasgeboren jongens; veel Klinefelter mannen worden nooit gediagnosticeerd. Prenataal is de incidentie van Triple X syndroom 1 op de 650 foetus, dit is 25% van alle chromosomale afwijkingen die worden gevonden bij invasieve prenatale testen. De postnatale incidentie van Triple X syndroom is in op de 1000 pasgeboren meisjes, dezelfde incidentie als gevonden wordt bij prenatale testen. Prenataal wordt Triple X syndroom vastgesteld in 0.1% van alle chromosoomafwijkingen, in het algemeen als een incidentele bevinding. De toevoeging van meer dan een extra geslachtschromosoom is zeldzaam; de prevalentie van andere X-Y aneuploïdieën wordt geschat op 1 op de 18.000 of minder. Er is geen direct causaal verband met de moederlijke leeftijd; in prenatale onderzoeken op indicatie van verhoogde moederlijke leeftijd, was de incidentie van de diagnose foetale SCA vergelijkbaar met de incidentie van het syndroom van Down. Verschillende aspecten van de diagnose en enkele typische pre- en postnatale fenotypische aspecten van SCA worden beschreven.

Het tweede deel van dit hoofdstuk beschrijft het ontstaan van SCA en verklaart het embryologische mechanisme. Een aantal basiselementen betreffende de genetica en de complexiteit van de voorlichting worden beschreven. Counseling na een prenatale diagnose SCA behelst het informeren van de ouders over het zeer brede spectrum van het postnatale fenotype van personen met een dergelijk syndroom. Aan de ene kant van het spectrum is er een normaal persoon die voor zichzelf kan zorgen zonder gezondheids- of gedragsproblemen, maar die uiteindelijk de genetische afwijking kan ontdekken in een medische zoektocht naar de oorzaak van onvruchtbaarheid. Aan de andere kant van het spectrum, kan een persoon met SCA vele gezondheids- en gedragsproblemen ervaren en zelfs ernstige stofwisselings-, auto-immuun of psychiatrische stoornissen hebben.

Het derde deel van het hoofdstuk vermeldt alle screenings en diagnostische prenatale onderzoeksprocedures die momenteel beschikbaar zijn: de niet-invasieve eerste trimester screeningstest, de tweede trimester echo screening, diagnostiek door echoscopische beoordeling en de invasieve procedures voor karyotypering van de foetus, zoals de chorion villus biopsie (vlokkentest) en de amniocentesis (vruchtwaterpunctie), alsmede de keuzemogelijkheden voor gerichte of genoom-brede testen.

Het vierde deel gaat in op de complexiteit van het inlichten van de ouders over de incidentele bevindingen en wordt een aantal ethische kwesties besproken.

Hoofdstuk 2 beschrijft de interesse van zwangere vrouwen in laagrisico zwangerschappen betreffende genetisch testen van het volledige genoom en onderzoekt de relaties tussen hun demografische kenmerken en de mate van interesse. Met uitzondering van het opleidingsniveau, werden geen significante relaties gezien tussen de demografische variabelen en de keuze voor genetisch onderzoek van het volledige genoom. Een laag

opleidingsniveau bleek significant gerelateerd aan de interesse in deze uitgebreide testen. De conclusie van deze pilotstudie was dat de meeste zwangeren met een laag risico weinig interesse hebben in genetische testen waarbij het volledige genoom wordt onderzocht. Hun interesse verminderde naarmate de zwangerschap verder was gevorderd. Het opleidingsniveau bleek van invloed op hun mening.

Hoofdstuk 3 rapporteert een review van de literatuur over de diagnostische relevantie van incidentele prenatale bevindingen van SCA. Publicaties over postnataal gediagnosticeerde SCAs van 2006-2011 en de publicaties over incidenteel prenataal gediagnosticeerde SCAs van 1980-2011 werden systematisch beoordeeld. Een incidentele prenatale diagnose SCA is geassocieerd met een normaal tot licht aangedaan fenotype. Dit staat in schril contrast met het fenotype van postnataal gediagnosticeerde SCA en dit feit benadrukt het vertekende beeld betreffende de prognostische waarde van een diagnose van foetale SCA. Hoewel het nogal voor de hand lijkt te liggen dat de prognose van een kind waarbij een incidentele bevinding van een geslachtschromosomale aneuploïdie wordt gedaan, beter is dan bij iemand waarbij dit na de geboorte op klinische gronden wordt vastgesteld, laat dit overzicht van de literatuur vanaf 1980 zien dat behandelaars de ouders kunnen geruststellen, aangezien inderdaad alle studies tot nu toe deze conclusie ondersteunen.

Hoofdstuk 4 beschrijft de perspectieven van ouders die werden geconfronteerd met een incidentele bevinding van een foetale SCA, in het licht van het feit dat deze toevallige bevinding kan worden vermeden door snelle aneuploïdie detectie (rapid aneuploidy detection: RAD). De ouders waren niet voorbereid op incidentele bevindingen en begonnen een onbegeleide zoektocht op het internet. Deze ouders gaven aan dat zij vertrouwen hadden in een goede kwaliteit van leven voor hun kind. De meeste deelnemers rapporteerden dat zij het prettig vonden om op de hoogte te zijn van het bestaan van het syndroom en dat zij wederom dezelfde procedure zouden kiezen als er een volgende zwangerschap zou optreden. Dit aspect is een belangrijke bevinding bij de bespreking van de mogelijkheid van uitsluiting van de X en Y probes met RAD, de perspectieven van de ouders kunnen een belangrijke bijdrage leveren in het onderzoek naar de vraag of de X en Y probes standaard opgenomen moeten blijven bij gebruikmaking van RAD.

Hoofdstuk 5 toont de ouderlijke perspectieven wanneer zij worden geconfronteerd met een onvoorziene SCA en de verkenning van hun overwegingen om de zwangerschap te beëindigen. Wederom waren de ouders niet voorbereid op incidentele bevindingen in het routine prenatale onderzoek en ook zij begonnen een onbegeleide zoektocht op het internet. Zij vonden het prettig om op de hoogte te zijn van het bestaan van het syn-

droom en zij hadden veel zorgen over de toekomstige gezondheid en het sociaalpsychologische welzijn van het kind. De ouders gaven adviezen aan de professionals en zouden opnieuw de probes voor de geslachtschromosomen includeren in een toekomstige test. De belangrijkste reden om te termineren bleek het negatieve perspectief van waaruit de ouders de toekomst van het kind beoordeelden. Het percentage respondenten was 31.2, het hoge percentage selectieve non-responders zou een reflectie kunnen zijn van hun innerlijke gevoelens en gedachten betreffende de beëindigde zwangerschap.

Hoofdstuk 6 beschrijft de mening van experts betreffende hun mening van het voor- en nadeel van een incidentele prenatale bevinding SCA. Het merendeel van de experts, clinici op het gebied van begeleiding en behandeling van mensen met SCA (87.5%) en klinisch genetici (76.9%) verklaarden dat een incidentele prenatale diagnose SCA een voordeel is voor het kind en de ouders. Zij erkenden de mogelijkheid dat ouders zouden kunnen besluiten tot het beëindigen van de zwangerschap. De experts waren voorstanders van een incidentele prenatale diagnose SCA, ondanks de complexiteit van de voorlichting en de mogelijkheid dat ouders zouden besluiten tot zwangerschapsbeeindiging. Zij geloofden dat de voordelen sterk opwegen tegen de nadelen.

Hoofdstuk 7 toont onze ingezonden brief aan de hoofdredacteur van het tijdschrift "Genetics in Medicine", gevolgd door het antwoord van de auteurs op onze overwegingen. De brief is een reflectie op een overzichtsartikel van Jeon et al.:"Decision to abort after a prenatal diagnosis of sex chromosome abnormality: a systematic review of the literature", welke werd gepubliceerd in oktober 2011. Wij concludeerden dat een aantal belangrijke aspecten niet aan bod kwamen in dit review: (i) de reden voor verwijzing (bv foetale echoscopische afwijkingen); (ii) de steeds belangrijkere rol van het internet in het verstrekken van aanvullende, maar soms verwarrende medische informatie aan bezorgde ouders; (iii) de belangrijke bijdrage die genetici kunnen leveren aan de besluitvorming van de ouders om de zwangerschap te continueren of te beëindigen.
Onze ingezonden brief aan de hoofdredacteur met het commentaar op het review is gepubliceerd in de mei 2012 editie, tezamen met het antwoord van de auteurs van het review waarop we commentaar gaven.

Hoofdstuk 8 behandelt diverse aspecten betreffende een incidentele prenatale bevinding van SCA en de centrale onderzoeksvraag van dit proefschrift: of een incidentele diagnose van een foetale SCA beschouwd moet worden als diagnostische winst of als diagnostische schade. Onze studie toonde aan dat de incidentele prenatale bevinding van een SCA door zowel de ouders als de professionals die werden geïnterviewd, werd beschouwd als een voordeel voor wat betreft de mogelijkheden tot vroege behandeling en ondersteuning. Aangezien onze studie een kwalitatief ontwerp had, zijn de resulta-

ten vooral indicatief en niet zozeer doorslaggevend. De resultaten kunnen bijdragen aan de discussie, of gebruikmaking van test procedures waarin de mogelijkheid bestaat tot een incidentele bevinding van een foetale SCA, ook werkelijk goede medische zorg is. De complexiteit van de pre- en post-test counseling, het probleem van mosaïcisme, aspecten betreffende ouderlijke besluitvorming, het probleem van non-responders, de mening van experts op het gebied van SCA en ook de kwestie van het verstrekken van aanvullende en veilige informatie wordt behandeld. Ouders en deskundigen waren voorstanders van een prenatale detectie van SCA, of deze nu bedoeld is of niet. Ethische overwegingen worden besproken, de morele plicht van artsen om patiënten te informeren, tevens het recht van de patiënt om "te weten" of "niet te weten" alsook het recht van de foetus. Het toekomstige gebruik van informed consent en disclaimers bij gebruikmaking van genetische testen en de onvermijdelijke toename van het aantal incidentele bevindingen met behulp van genoom-brede technologieën met een hoge resolutie in prenataal onderzoek wordt besproken. De kwaliteit van leven kan positief worden beïnvloed door een prenatale diagnose, want dit biedt de mogelijkheid tot vroege preventie en behandel programma's. Informatie op maat voor alle aanstaande ouders over mogelijke bevindingen is nodig en het internet zou betrokken moeten worden bij de pre- en post-test counseling als een zeer bruikbare manier om betrouwbare en nauwkeurige informatie te verstrekken.

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Professor Evert van Leeuwen, hoofd van de afdeling IQ Healthcare, sectie Ethiek, Filosofie en Geschiedenis van de Geneeskunde. Jij hebt mij geleerd om de bevindingen uit het onderzoek steeds onder een zuivere loep te beoordelen. Ik wil je danken voor de begeleiding die ik kreeg bij het doen van kwalitatief onderzoek en analyse, een hele aparte tak van sport.

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Mijn eerste artikel (hoofdstuk 2), de eerste stap op weg naar de promotie, is tot stand gekomen in samenwerking met professor Jolanda de Vries, medisch psycholoog aan de Universiteit van Tilburg en haar student Meeke Hoedjes. Graag wil ik hen bedanken voor de leerzame samenwerking en voor de mogelijkheid om op deze wijze een bijdrage te hebben mogen leveren aan het onderwijs aan studenten medische psychologie en enkele afstudeerscripties.

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CURRICULUM VITAE

Jacqueline Pieters werd geboren in Zuid-Limburg en verhuisde op 12-jarige leeftijd met haar ouders naar Brussel. Zij bezocht daar de Europese School; het eindexamen Gymnasium Bèta deed zij aan het Stedelijk Lyceum te Maastricht. Zij startte haar medische studie aan de Vrije Universiteit te Brussel in oktober 1979. Na het behalen van het kandidaatsexamen in juni 1982 heeft zij haar studie voortgezet aan de Rijksuniversiteit Leiden. Het artsexamen werd behaald in 1987 en in 1988 is zij gestart met het academische deel van de opleiding tot gynaecoloog in Maastricht (Prof. J. de Haan). Na drie jaar heeft ze het perifere deel van de opleiding gedaan in het Reinier de Graaf Gasthuis te Delft (Dr O. van Hemel). In januari 1993 werd zij geregistreerd in het BIG-register als gynaecoloog, destijds de jongste van Nederland. Zij is een jaar chef de clinique geweest in Delft en was vervolgens ruim een jaar als staflid high-risk obstetrie verbonden aan het toenmalige Dijkzigt Ziekenhuis, nu Erasmus MC, te Rotterdam (Prof. H. Wallenburg). Van 1996 tot 2005 maakte zij deel uit van de maatschap gynaecologen in het Elisabeth Ziekenhuis te Tilburg. In deze periode was zij medeoprichter van het Centrum voor Prenatale Diagnostiek Tilburg en ontstond de eerste samenwerking met Nijmegen in een netwerk van prenatale satellietcentra, later het Netwerk Prenatale Diagnostiek Nijmegen (NPDN) geheten. Zij is meeverhuisd met haar echtgenoot naar Noordwijk en heeft twee jaar deel uitgemaakt van de vakgroep gynaecologen in het Kennemer Gasthuis te Haarlem met als aandachtsgebied echoscopie en fertiliteit. Ook hier heeft zij meegewerkt aan het opzetten van een samenwerkingsverband voor Prenatale Diagnostiek met het VUMC. Sinds 2008 is zij als gynaecoloog verbonden aan het volledig op fertiliteit gespecialiseerde zelfstandig behandelcentrum Medisch Centrum Kinderwens te Leiderdorp en sinds een jaar maakt zij ook deel uit van het management en vervult de functie van adjunct-directeur. Zij is met het MCK als eerste centrum in Nederland gestart met een embryodonatie-programma, een initiatief waar collega en directeur Rien Crooij al in 2007 mee naar buiten trad. Sinds 2005 is zij als bestuurslid actief geweest in de Werkgroep Psychosomatische Obstetrie en Gynaecologie van de NVOG, een functie waarvan zij dit jaar afscheid neemt. Zij is getrouwd en heeft drie zonen.