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REVIEW

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Chromosomal abnormalities predisposing to infertility, testing, and management: a narrative review

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Abstract

Background: Much interest has not been placed on the role of chromosomal abnormalities in the pathogenesis and rising prevalence of infertility in recent times. This review was conducted to renew public interest on the chromosomal basis of infertility, testing, and management.

Main text: Meiotic and post-zygotic mitotic errors may cause infertility-predisposing chromosomal abnormalities, including Klinefelter syndrome, Jacob syndrome, Triple X syndrome, Turner syndrome, and Down syndrome. Chromosomal abnormalities such as deletion, translocation, duplication, inversion, and ring chromosome may also predispose to infertility. Notable features of male chromosomal infertility include spermatogenic failure, characterized by azoospermia, oligospermia, and gonadal dysgenesis, while females include premature ovarian insufficiency, amenorrhea, spontaneous abortion, and gonadal dysgenesis. The risk of these abnormalities is influenced by maternal age and environmental factors such as chemical exposure, smoking, and alcohol consumption. Most chromosomal abnormalities occur spontaneously and are not treatable. However, early prenatal screening and diagnostic tests can lessen the effects of the conditions. There is also a growing belief that certain diets and drugs capable of changing gene expressions can be formulated to neutralize the effects of chromosomal abnormalities.

Conclusion: Meiotic and mitotic errors during gametogenesis and fetal development, respectively, can cause chromosomal abnormalities, which predispose to infertility. Couples who are at increased risk, particularly those with a family history of infertility and women at an advanced age (≥ 35 years), should seek medical advice before getting pregnant.

Keywords: Amenorrhea, Azoospermia, Infertility, Gonadal dysgenesis, Spontaneous abortion

Background

Infertility is the failure to conceive when a couple engages in regular unprotected copulation for at least a year (Yahaya et al. 2020). At the minimum, 15% of couples worldwide experience infertility, of which males account for 20–30%, females (20–35%), and both shared the remaining (SingleCare 2020; Yahaya et al. 2020). Infertility is more prevalent in low-income nations, especially in West Africa and Southeast Asia (Elhussein et al. 2019). Infertility can be primary (also called sterility), which describes couples who have never conceived despite one year of consistent copulation (Mvuyekure et al. 2020). It can also be secondary, which refers to couples who have had at least one successful conception in the past (Mvuyekure et al. 2020).

Infertility affects all aspects of life. It causes psychosocial problems such as frustration, depression, anxiety, hopelessness, and guilt (Hasanpoor-Azghdy et al. 2014).

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In some countries in Africa and Asia, childless people suffer discrimination, mockery, and divorce or separation (Yahaya et al. 2020). Infertile women face deprivation of financial support and basic needs such as clothes and foods by their husband (Dyer and Patel 2012). In some cases, infertility leads to polygamy or infidelity from both sides. The treatments of infertility may incur huge financial costs, resulting in economic problems, particularly in developing nations where treatment costs are often paid by the patients (Dyer and Patel 2012). Additionally, infertility may reduce the urge for success, resulting in reduced work efficiency and job loss, culminating in reduced income to cater to the family (Nahar and Richters 2011).

The pathologies of infertility include endocrine dysfunction, inflammatory diseases, genital tract abnormalities, gametogenesis failures, implantation failures, and erectile or ejaculatory problems (Okutman et al. 2018). These pathologies can be triggered by lifestyles, environmental, or genetic factors. A thorough understanding of these factors may help reduce the prevalence and burden of infertility. Particularly, more understanding of the genetic factor is important because 15–30% of male infertility alone have a genetic origin (Yahaya et al. 2020). The genetic factor can be chromosomal (numerical or structural anomalies) or single-gene anomalies (Okutman et al. 2018). Chromosomal factor alone accounts for 2–14% of male infertility (Harton and Tempest 2012) and as much as 10% of female infertility (Vicdan et al. 2004). This shows that a thorough understanding of chromosomal abnormalities is imperative to reduce the burden of infertility. Although studies show that a lot of works have been done on the chromosomal basis of infertility, much attention has not been devoted to the topic in the recent past. This review was conducted to renew public interest on the chromosomal basis of infertility, testing, and management.

Main text

Database searching and search strategy

Notable academic repositories including Scopus, Google Scholar, and PubMed were searched individually for literature on the subject. Keywords used for searching include 'infertility,' 'prevalence of infertility,' 'chromosomal abnormalities,' 'numerical chromosomal abnormalities,' 'structural chromosomal abnormalities,' and testing and management of chromosomal abnormalities.' The articles collected from various repositories were merged and sorted to remove double citations.

Inclusion and exclusion criteria

Articles selected are those that were written in the English language and majored in chromosomal abnormality, chromosomal basis of infertility, and testing and management of chromosomal abnormalities. No restriction was placed on the year of publication of articles. However, on articles that treated the same topic with contrasting views, the most unanimous and recent information was prioritized.

One hundred and ten (110) articles were collected from the databases searched, but were reduced to 92 after duplicates were removed. Of the 92 articles, 85 passed the eligibility test, of which 77 fit the objectives of the current study and were thus included.

Chromosome overview

Chromosomes are string-like structures in human cells (Fig. 1). Human cells usually have 23 pairs of chromosomes (46 in all) and contains between 20,000 and 25,000 genes (Genetic Alliance 2009; NHGRI 2020). One set of 23 chromosomes is maternal in origin, while the other is paternal (Genetic Alliance 2009; NHGRI 2020). Chromosomes number 1 to 22 are known as the autosomes, while the 23rd pair is called the sex chromosomes (denoted X and Y chromosome) (Genetic Alliance 2009; NHGRI 2020). Sex chromosomes determine humans' sex in which females possess two X chromosomes (XX), and males possess a X and a Y chromosome (XY) in each cell (Genetic Alliance 2009; NHGRI 2020). The genes on the chromosomes contain the information the body needs to function (Genetic Alliance 2009).

Chromosomal abnormalities

Chromosomal abnormalities often result from meiotic and mitotic errors (NHGRI 2020). Mitosis takes place in somatic cells and results in two daughter cells, each having 46 chromosomes like the parent cell (NHGRI 2020). Meiosis occurs in the reproductive cells (eggs and sperms) and produces four daughter cells, each having half of the chromosome number of the parent cell (NHGRI 2020). However, meiotic and mitotic errors can produce cells with abnormal copies of a chromosome (NHGRI 2020). Most often, chromosomal abnormalities occur spontaneously during meiosis, leading to abnormalities that are found in all cells of the body. However, some abnormalities may occur in somatic cells after fertilization, leading to mosaicism in which some cells express the abnormalities while other cells remain normal (NHGRI 2020).

Maternal age increases the risk of chromosome aberrations (NHGRI 2020). Women inherit all the eggs they will ever produce from their mothers and so the eggs are prone to aging-induced genetic alterations (NHGRI 2020). Thus, women at an advanced age have high chance of producing babies expressing chromosomal abnormalities than young women (NHGRI 2020). On the other

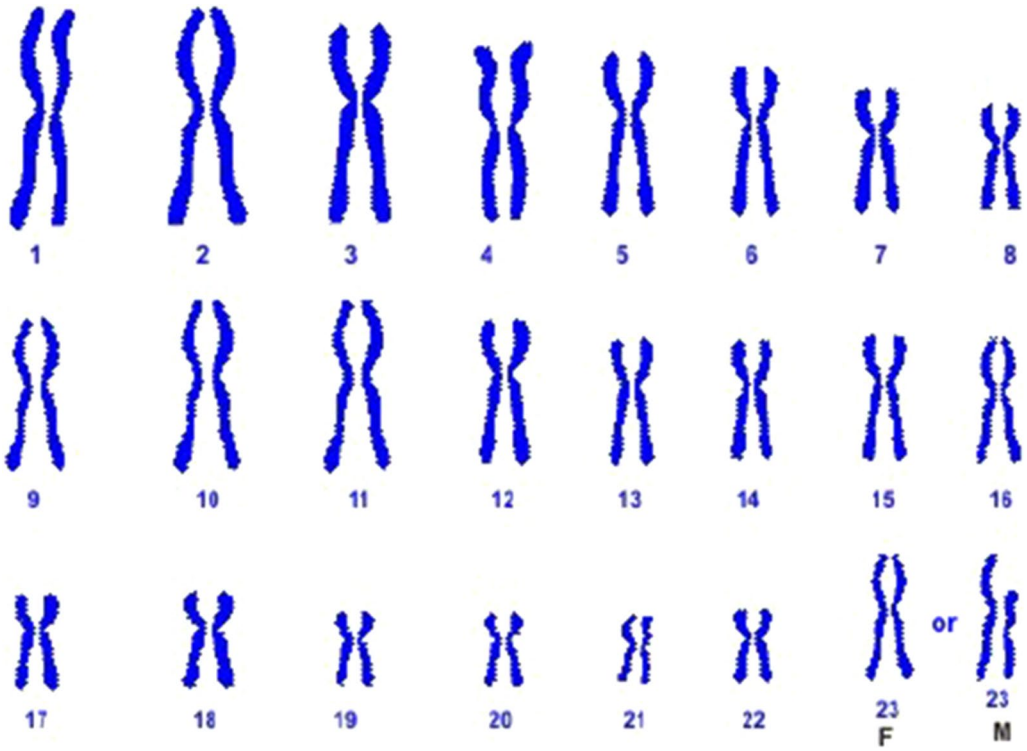

Fig. 1 A karyogram of human chromosome

hand, men produce new sperm daily, so paternal age is less likely to raise the risk of chromosome abnormalities (NHGRI 2020). Maternal and paternal environmental exposures and lifestyles may also influence the pathogenesis of chromosomal abnormalities (NHGRI 2020). There are several types of chromosomal abnormalities, which are grouped into numerical and structural chromosomal abnormalities (Genetic Alliance 2009; NHGRI 2020).

Numerical abnormalities

Numerical abnormalities (also known as aneuploidies) are the most common chromosome abnormalities (Gersen and Keagel 2005). Chromosomal aneuploidies are described as alterations in chromosome numbers of diploid or haploid cells (Harton and Tempest 2012). It is the presence of an unusual number of chromosomes in a cell due to an additional (termed trisomy) or lost (termed monosomy) chromosome (Genetic Alliance 2009; NHGRI 2020). Trisomy is more common than monosomy among individuals suffering from aneuploidy (Genetic Alliance 2009). Chromosomal aneuploidy is the most prevalent cause of spontaneous abortion and developmental errors in humans (Harton and Tempest 2012). Aneuploidy is predominantly maternal in origin. However, sperm aneuploidies are more common among infertile men than fertile men (Harton and Tempest 2012). There are many chromosomal abnormalities. However, the most frequent are Klinefelter syndrome, Jacob syndrome, Triple X syndrome, 45,X0/46,XY mosaicism, Turner syndrome, and Down syndrome.

Klinefelter syndrome (47,XXY)

Klinefelter syndrome (KS) is a chromosomal abnormality that affects males only in which the affected has two copies of the X chromosome (Fig. 2). KS is the commonest gonosomal (sex chromosome) anomaly among men, occurring in 0.1–0.2% of newborns, and as high as 67% and 19% among azoospermic and oligospermic patients, respectively (Huynh et al. 2002; Mau-Holzmann 2005). KS is not inherited and often caused by meiotic nondisjunction or post-zygotic nondisjunction (Bonomi et al. 2017; Los and Ford 2020). Thus, KS exists in several forms, the most common of which is the acquisition of an additional copy of the X chromosome in the cells of the affected (47,XXY), occurring in over 90% of cases (Bonomi et al. 2017). An additional copy of X chromosome may also exist in some cells only and is called mosaic Klinefelter syndrome (46,XY/47,XXY), characterized by fewer symptoms (Bonomi et al. 2017). In rare cases, more than two copies of the X chromosome (e.g., 48,XXXY and 49,XXXXY) may be found in each cell, resulting in severe conditions (Bonomi et al. 2017).

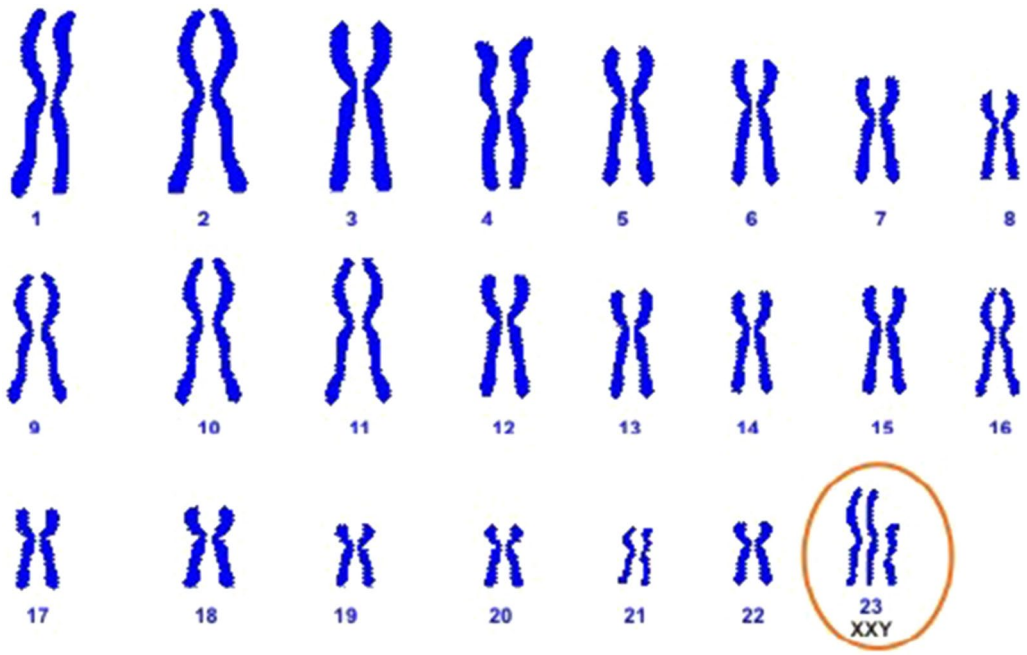

Fig. 2 A karyogram of Klinefelter syndrome

Abnormal copies of genes on the X chromosome can disrupt male sexual development, resulting in genital abnormalities and spermatogenic failure, culminating in infertility (Los and Ford 2020). The testes of individuals expressing KS contain stem cells but degenerate too quickly (Wikström et al. 2007). So much that nothing or few cells will be left for spermatogenesis at puberty (Wikström et al. 2007). The Leydig cells of KS patients are hyperplastic and thus produce insufficient testosterone, resulting in poor libido, erectile dysfunction, and azoospermia (Nieschlag 2013; Zitzmann et al. 2004). At the minimum, 60% of pregnancy with KS result in miscarriage (Bonomi et al. 2017). KS is often accompanied by other features such as speech and learning disabilities, weak bones, enlarged breasts, epilepsy, and type 2 diabetes (Nieschlag 2013). Overall, the severity of these phenotypes correlates with the number of X chromosomes in the cells (Bonomi et al. 2017).

Jacob syndrome (47,XYY)

Jacob syndrome (JS) affects males only (Fig. 3). It is the second most common gonosomal abnormality after KS (Chantot-Bastaraud et al. 2008), occurring in about 1 in 1000 male newborns (Kim et al. 2013; Liu et al. 2020). Most cases of JS are not inherited. It is caused mainly by parental nondisjunction at meiosis II (before conception), leading to an additional Y chromosome (47,XYY) in all cells of the affected offspring (Kim et al. 2013; Latrech et al. 2015). Thus, males with JS have 47 chromosomes. Rarely, nondisjunction may occur from post-zygotic (after conception) mitotic errors, resulting in a mosaic karyotype (46,XY/47,XYY) in which some cells are not affected (Kim et al. 2013; Latrech et al. 2015). Some common features of JS include infertility in adulthood, behavioral and cognitive disorders, facial dysmorphia, micropenis, curved penis with non-palpable testes, and decreased total testosterone (Latrech et al. 2015; MedlinePlus 2020a). However, some men expressing JS are fertile (Kim et al. 2013). In these men, the additional Y chromosome is lost before meiosis, thus preventing infertility (Kim et al. 2013).

Triple X syndrome (47,XXX)

Triple X syndrome (47,XXX), otherwise called trisomy X syndrome, is a sex chromosome aneuploidy in which a female has one additional X chromosome (Fig. 4). It is the commonest female chromosomal abnormality, affecting about 1 in every 1,000 female newborns (Tartaglia et al. 2010; Rafique et al. 2019). Trisomy X syndrome is usually not inherited and results mainly from maternal nondisjunction during meiosis (Rafique et al. 2019). However, post-zygotic nondisjunction is found in almost 20% of cases (Tartaglia et al. 2010). This results in an additional X chromosome in only some cells of the affected, a phenomenon called 46,XX/47,XXX mosaicism (MedlinePlus 2020a, b, c). Women expressing Triple X are often fertile and produce babies with a normal chromosomal number, indicating that the additional X chromosome is

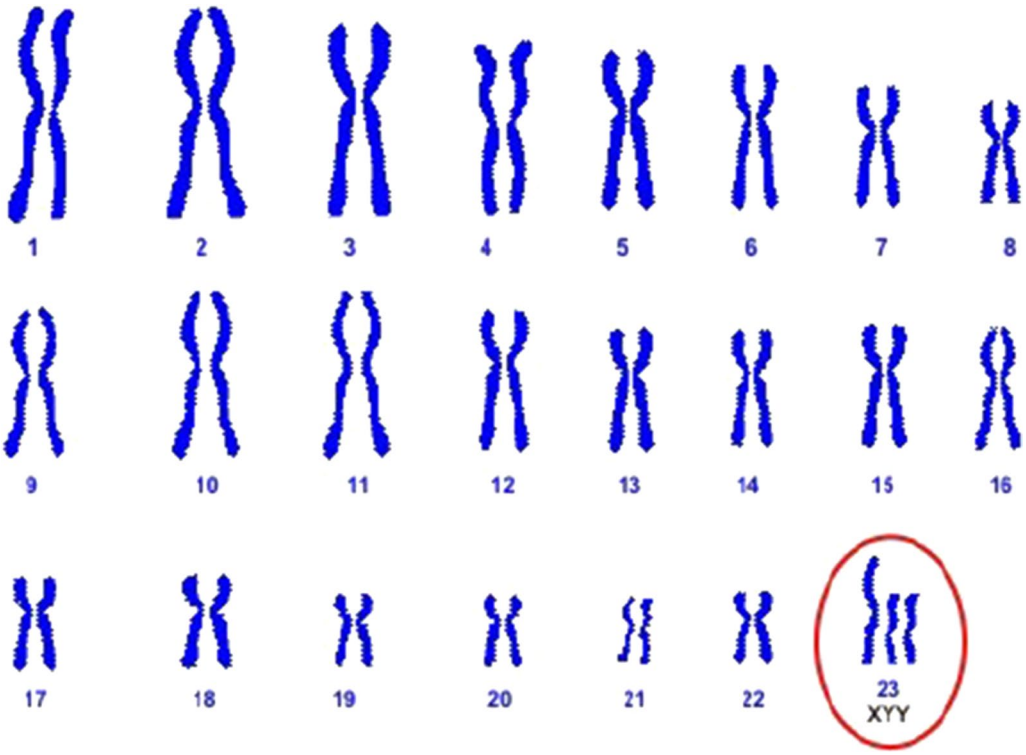

Fig. 3 A karyogram of Jacob syndrome

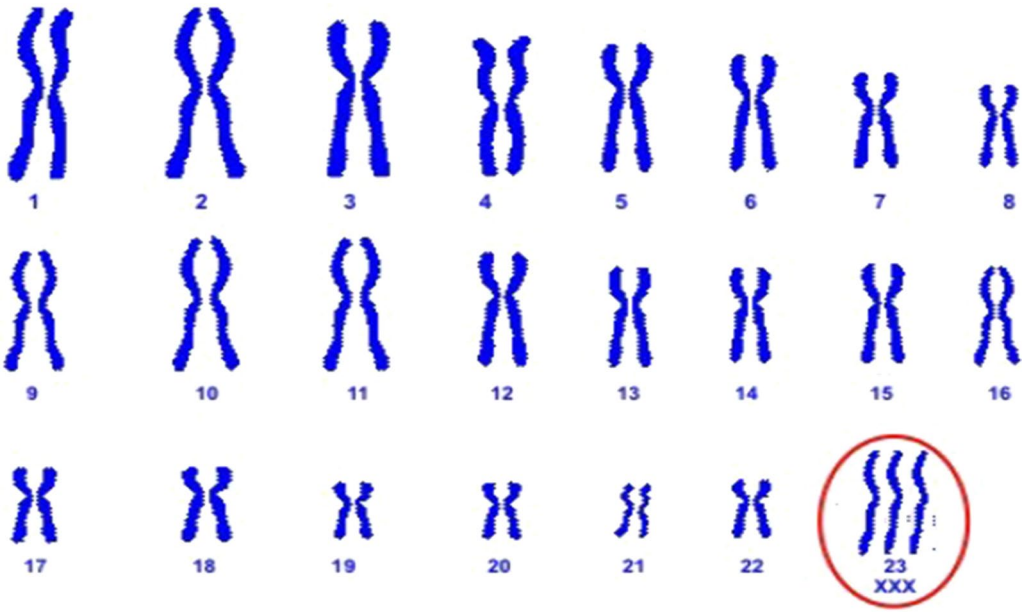

Fig. 4 A karyogram of Triple X syndrome

removed during maternal meiosis (Chantot-Bastaraud et al. 2008). However, Triple X syndrome has been implicated in some cases of primary infertility, characterized by premature ovarian insufficiency (POI), amenorrhea, and premature menopause (Sugawara et al. 2013; Rafique et al. 2019). The notable physical features include tall

stature, congenital urogenital anomalies, epilepsy, speech delays, cognitive and attention deficits, and mood disorders (Tartaglia et al. 2010; MedlinePlus 2020a, b, c).

45,X0/46,XY mosaicism

45,X/46,XY mosaicism, otherwise called X0/XY mosaicism and mixed gonadal dysgenesis, is a rare sex chromosome aneuploidy with a prevalence of approximately 1 in 15,000 newborns (Johansen et al. 2012). In 45,X/46,XY mosaicism, two cell lines exist, of which one has 45,X karyotype (X monosomy) and the other has a normal male karyotype (46,XY). The two cell lines are differently distributed in individuals suffering from the condition which could be responsible for the varied phenotypes expressed by the affected individuals (Rosa et al. 2014). 45,X/46,XY mosaicism is most often caused by the loss of the Y chromosome through nondisjunction in some somatic cells after normal fertilization (Telvi et al. 1999; Rosa et al. 2014). Both the 46,XY and 45,X cell lines divide nonstop, resulting in a baby with 45,X/46,XY (Johansen et al. 2012). The 45,X/46,XY karyotype can also be formed by the malformation, deletions, or translocations of Y chromosome segments (Johansen et al. 2012). This abnormality can repress the SRY genes, resulting in abnormal genitals (incomplete sexual differentiation) and testosterone levels (Johansen et al. 2012). It can also cause conditions such as azoospermia, oligospermia, sperm DNA fragmentation, and increased gonadotropins (Rosa et al. 2014; Ketheeswaran et al. 2019). In some cases, the affected show clinical signs of Turner syndrome (Efthymiadou et al. 2012). Overall, the commonest feature of 45,X/46,XY syndrome is sexual ambiguity, responsible for about 60% of cases, while the least is bilaterally descended testes, occurring in 11–12% of cases (Efthymiadou et al. 2012). However, some individuals expressing 45,X/46,XY mosaicism show normal male sexual development (Efthymiadou et al. 2012).

Turner syndrome (45/X)

Turner syndrome (Fig. 5), also called monosomy X, is a female-only genetic disorder (NHS 2018; Utiger 2020). It is a rare abnormality, found in approximately 1 in 2,000 newborn girls (NHS 2018). However, compared to other chromosomal disorders, Turner syndrome (TS) is common, accounting for one-tenth of all spontaneously aborted fetuses (Utiger 2020). Maternal age has no influence on the occurrence of TS (NHS 2018). It occurs when one X chromosome is completely or partially lost or deleted in females (Cui et al. 2018; Utiger 2020). Thus, a girl expressing TS has one normal X chromosome only, resulting in 45,X karyotype (NHS 2018; Utiger 2020). Aside from 45,X karyotype, some women with TS may express different karyotypes, all lacking X chromosomal material (Gravholt et al. 2019). These include mosaics karyotypes (for example, 45,X/46,XX and 45,X/47,XXX), the presence of

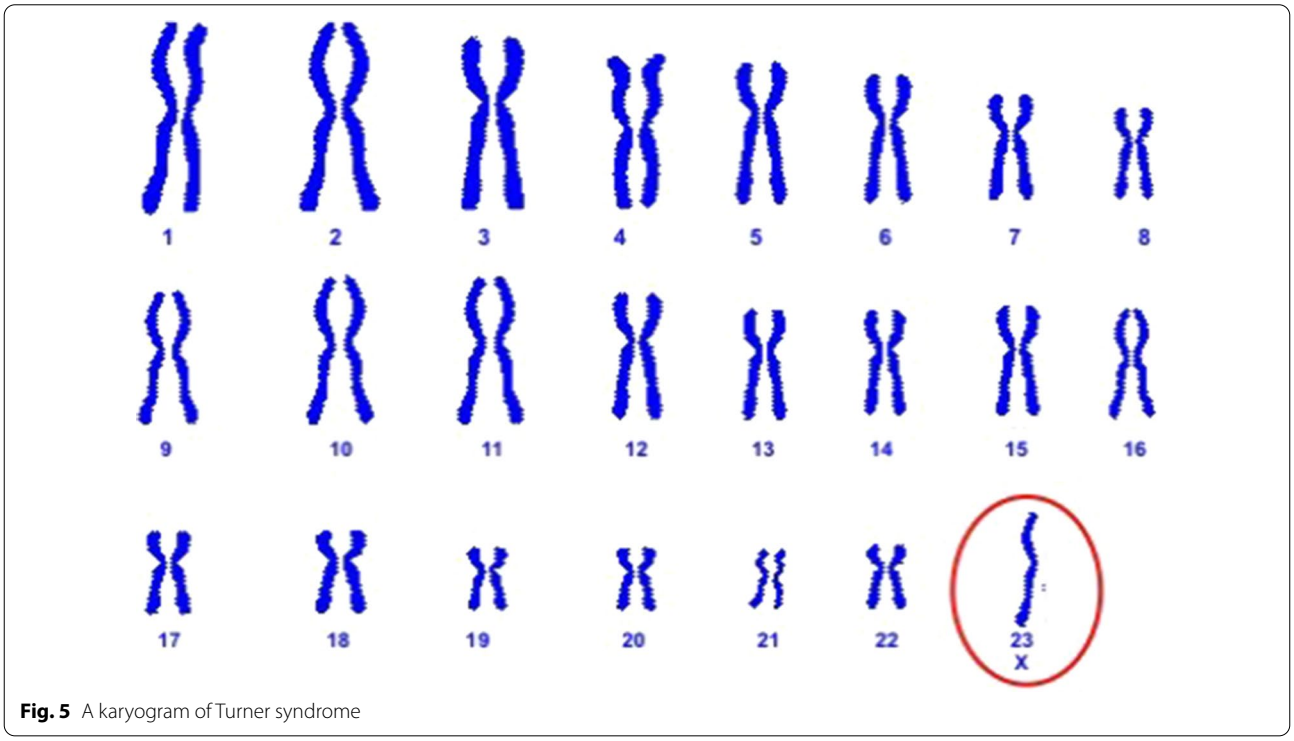

Fig. 5 A karyogram of Turner syndrome

an isochromosome of either the p or q arm, ring chromosomes, and the presence of Y chromosomal material (Gravholt et al. 2019). Approximately 40–50% of women expressing TS have 45,X karyotype, 15–25% have mosaicism (45,X/46,XX), 20% have an isochromosome, and ring X chromosomes occur in few women (Gravholt et al. 2019). In addition, 10–12% of women have varying amounts of Y chromosome material (Gravholt et al. 2019). Individuals with TS often have a wide variety of symptoms and some distinctive features. Most TS patients show delayed puberty, ovarian dysgenesis, hypergonadotropic hypogonadism, ambiguous infantile external genitalia, and infertility (NHS 2018; Gravholt et al. 2019; Utiger 2020). Notable physical features associated with TS include short stature, webs around the neck, layers of skin from tops of shoulders to sides of the neck, low-set ears, and swollen hands (MedlinePlus 2020c). They are also at increased risk for diseases such as cataracts, hypertension, diabetes, cardiovascular diseases, kidney damage, and weak bones (MedlinePlus 2020c; Utiger 2020). Morbidity and mortality among TS patients are high compared with unaffected (Gravholt et al. 2019). However, their intelligence is normal (Hjerrild et al. 2008).

Down syndrome

Down syndrome (DS) is among the best known chromosomal disorders in humans (MacLennan 2020; NHGRI 2020). It is the commonest genetic disease, occurring in almost 1 in 400–1500 newborns (Kazemi et al. 2016; MacLennan 2020). DS, often referred to as trisomy 21, occurs by nondisjunction of chromosome 21 (in either the sperm or egg), resulting in cells with three copies of chromosome 21 (CDC 2020). Thus, the karyotype for female trisomy 21 is 47, XX, +21, while the male is 47, XY, +21 (Fig. 6). DS may also occur when an additional section or a full chromosome 21 is present, but bound or translocated to a different chromosome (usually chromosome 14 or 15), rather than being a separate chromosome 21 (Kazemi et al. 2016; CDC 2020). This translocation could be Robertsonian, isochromosomal, or ring chromosome (Asim et al. 2015). Because these translocations can be transmitted, this form of DS is sometimes called familial DS (Kazemi et al. 2016). The third form of DS is mosaicism, which is due to errors in cell division after fertilization (Asim et al. 2015; CDC 2020). Mosaicism results in two cell lines in the affected in which some cells have 3 copies of chromosome 21, while other cells are unaffected (Asim et al. 2015; CDC 2020). About 95% of people expressing DS have trisomy 21, about 3% have translocation DS, and about 2% have mosaic DS

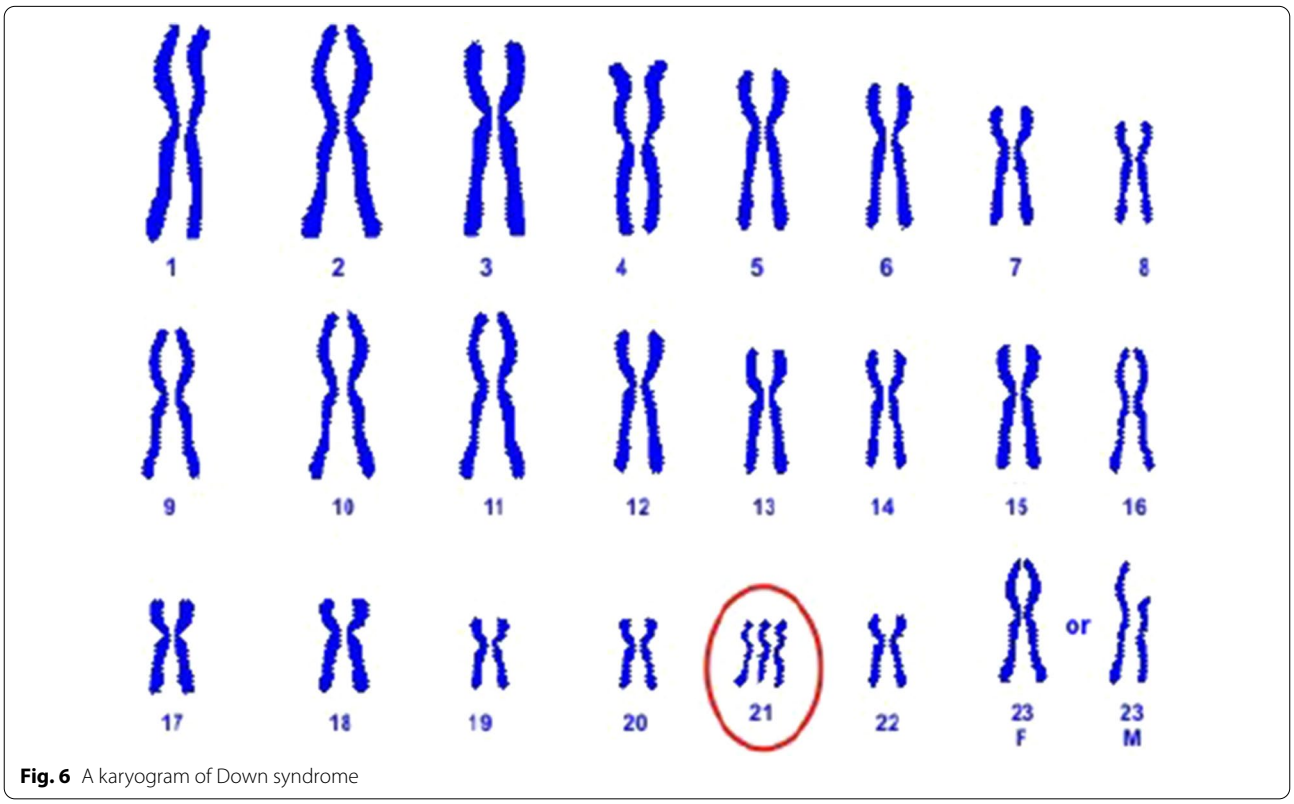

Fig. 6 A karyogram of Down syndrome

(Shin et al. 2010). It is difficult to differentiate each form of DS without looking at the karyotypes because they all have similar physical features and behaviors (CDC 2020). However, mosaic DS may be less severe because some cells have a normal chromosome number (CDC 2020). Pregnancies at advanced maternal age (≥ 35 years) increase the risk of producing a baby with DS (Sherman et al. 2007). However, most babies showing DS are born by women less than 35 years old because younger women give more births (CDC 2020). Trisomic fetuses are at increased risk of miscarriages, defective spermatogenesis in men, and premature menopause in women (Pradhan et al. 2005; Asim et al. 2015; Parizot et al. 2019). Individuals with DS usually show moderately low levels of intelligence and speech disorders (Asim et al. 2015; CDC 2020).

Structural abnormalities

Structural abnormalities occur when a section of a chromosome is deleted, had an additional segment, joined another chromosome, or inverted (Genetic Alliance 2009). It results from splintering and rearrangements of chromosomal segments (Genetic Alliance 2009). The rearrangements are described as balanced if the chromosome is intact, and unbalanced if a piece of information is added or missing (Genetic Alliance 2009). Since all genetic information is retained in balanced chromosomal rearrangements, it is less likely to produce any effect (Genetic Alliance 2009; MedlinePlus 2020d). However, a disease can arise from a balanced rearrangement if the chromosomal break occurs in a gene and cause its malfunctions (Genetic Alliance 2009). A disease may also occur if chromosomal segments bind and produce a hybrid of two genes, resulting in a de novo protein that functionally harms the cell (Genetic Alliance 2009). These showed that individuals expressing balanced rearrangements have a high risk of producing unbalanced gametes, resulting in spontaneous abortion, infertility, or abnormal babies (Aubrey and Jeff 2015). Common chromosome structural abnormalities include translocations, deletions, duplications, inversions, and ring chromosomes (Genetic Alliance 2009).

Chromosome translocations

Chromosome translocation is a phenomenon that occurs when a segment of chromosome breaks and binds to another chromosome, resulting in an unusual rearrangement of chromosomes (EuroGentest 2007; MedlinePlus 2020d). Translocation is the most common chromosomal rearrangement (Reproductive Science Center 2020). Translocation may occur during gametogenesis due to meiotic errors, resulting in abnormalities that feature in all the cells of the baby (Aubrey and Jeff 2015). It may also result from post-zygotic mitotic errors, resulting in two cell lines in which some cells are normal and some are affected (Aubrey and Jeff 2015). Two main types of translocation exist and are reciprocal and Robertsonian translocation (Fig. 7). Reciprocal translocation is a chromosome abnormality in which two different chromosomes (non-homologous chromosomes) exchanged segments (EuroGentest 2007; Aubrey and Jeff 2015). Robertsonian translocation, also known as centric fusion, occurs when the long arm of a chromosome breaks and attached to the centromere of a non-homologous chromosome (Asim et al. 2015). Robertsonian translocations often occur between acrocentric chromosomes (i.e., chromosomes 13, 14, 15, 21, and 22) (EuroGentest 2007; Chantot-Bastaraud et al. 2008). However, the most prevalent translocation occurs between chromosomes 13 and 14 and the next is between 14 and 21 (Anton et al. 2004; Chantot-Bastaraud et al. 2008). Translocations involving chromosomes 13 and 14, in particular, are found in about 1 in 1000 newborns (Anton et al. 2004). Robertsonian translocations often result in one big metacentric chromosome and one very small chromosome that may be eliminated from the organism, producing insignificant effects because it has few genes (Leland 2011). Thus, Robertsonian translocations result in a karyotype having 45 chromosomes, since two chromosomes have merged (Leland 2011). Although patients with balanced Robertsonian translocations are clinically normal, they are at increased risk of producing unbalanced gametes that may result in spontaneous abortion or an abnormal baby (Dong et al. 2012). For example, people expressing Robertsonian translocations involving chromosome 21 have a high risk of producing a baby showing DS (Dong et al. 2012). The maternal chances of transmitting this form of DS are 10%, while the paternal are 1% (Dong et al. 2012). Robertsonian translocation may reduce the volume of testicles and testosterone, impairing spermatogenesis, and resulting in azoospermia

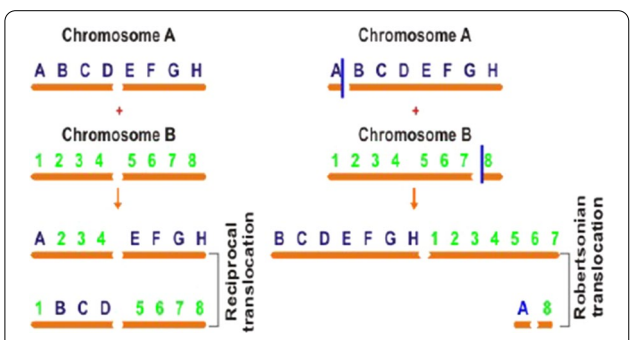

Fig. 7 Chromosomal translocations

or oligospermia (Dong et al. 2012). It may also cause recurrent miscarriage (Stern et al. 1999).

Translocations may also occur between sex chromosomes and autosomes and have been implicated in some cases of infertility (Grzesiuk et al. 2016). X-autosome translocations impair pairing during meiotic recombination, disrupting gametogenesis, and resulting in spermatogenic failure (Grzesiuk et al. 2016). The pairing problem creates unrepaired double-strand DNA breaks, which can result in aneuploid gametes (Grzesiuk et al. 2016). In women, sex-autosome (X-autosome) translocations are rare, occurring in about 1in 30,000 newborns with variable phenotypes (Shetty et al. 2014). However, some clinical studies showed that it can cause the absence of mensuration, insufficient sex hormones, multiple congenital anomalies, and intellectual disability (Shetty et al. 2014).

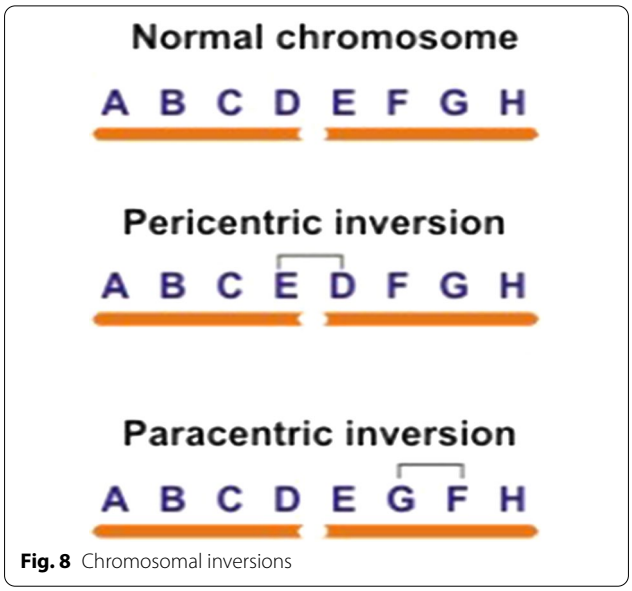

Fig. 8 Chromosomal inversions

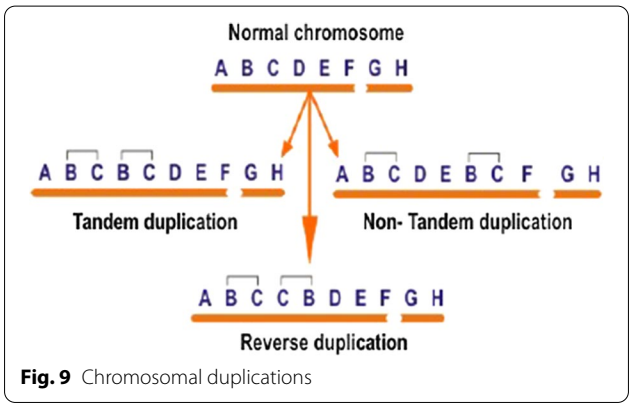

Fig. 9 Chromosomal duplications

Chromosomal inversions

Chromosome inversions are structural intra-chromosomal rearrangements, which occur when two breakpoints exist in a chromosome and the segment between the breakpoints rotates 180° before reattaching with the two broken ends (Griffiths et al. 2000; Chantot-Bastaraud et al. 2008). Inversions are the most prevalent chromosomal rearrangements after translocations (Chantot-Bastaraud et al. 2008). Two types of inversion exist, which are paracentric and pericentric (Chantot-Bastaraud et al. 2008). Paracentric inversions do not include the centromere and both breaks occur in one arm of the chromosome, while pericentric inversions include the centromere and there is a breakpoint in each arm of the chromosome (Fig. 8). Unlike deletions and duplications, genetic information is not lost or gained in inversion; it only reshuffles the genes (Griffiths et al. 2000). In addition, despite that the genes on the inverted chromosome are rearranged backward, the body is still able to read them (NHS 2020). As such, inversions often do not induce any abnormality in the affected so long the rearrangement is balanced (Griffiths et al. 2000; Chantot-Bastaraud et al. 2008). However, there is a high prevalence of abnormal chromatids in people who are heterozygous for an inversion (Chantot-Bastaraud et al. 2008). This occurs when crossing-over takes place within the inverted segment and caused unbalanced gametes, resulting in infertility (Chantot-Bastaraud et al. 2008). Furthermore, in some cases, one of the chromosome breaks may occur within a gene that performs important functions, disrupting its functions (Griffiths et al. 2000). During meiosis, inversions may force chromosomes to create inversion loops to enable homologous chromosomes to pair (Harton and Tempest 2012). The mechanisms involved and time taken to form these loops can cause infertility (Harton and Tempest 2012). Recombination is reduced in these loops, causing meiotic arrest, and resulting in cell death and low sperm count (Harton and Tempest 2012). Even if recombination takes place normally within the inversion loop, it will produce unbalanced gametes (Harton and Tempest 2012). Both paracentric and pericentric inversions also increase the risk of miscarriage due to missing or extra chromosome materials in the sperm or eggs (NHS 2020).

Chromosome duplications

Chromosomal duplications occur when a region of a chromosome is duplicated (Clancy and Shaw 2008). Thus, duplications result in extra genetic materials (NHGRI 2020). Duplication is termed tandem if the duplicated segment is next to the original, but non-tandem or displaced if non-duplicated regions are in-between (Fig. 9). There is also reverse duplication. Duplications affect gene

dosage and thus predispose to diseases. Basically, the amount of a protein produced by a gene often depends on the number of copies of the gene, so additional copies of the genes may result in overproduction of the protein (Clancy and Shaw 2008). Embryogenesis is strictly controlled by balanced levels of proteins, so duplications that produce additional gene copies may disrupt gametogenesis and fetal development (Clancy and Shaw 2008).

Chromosome deletion

Chromosome deletion (Fig. 10) is an abnormality in which a portion of the chromosome is deleted (NHGRI 2020). The effects of a deletion depend on its position on the chromosome (Clancy and Shaw 2008). A deletion that involves the centromere will cause an acentric chromosome that will presumably be eliminated from the cell (Clancy and Shaw 2008). Also, the length of the deletion determines the number of genes affected, and thus the severity of the effects (Clancy and Shaw 2008). Deletions affect gene dosage and thus the phenotype (Clancy and Shaw 2008). Some genes require two copies to produce a normal expression, so if one allele is deleted (called haploinsufficiency), a mutant phenotype will result (Clancy and Shaw 2008).

Chromosomal deletions affecting sex chromosomes will most likely disrupt reproductive development. Y chromosome deletion, in particular, has been implicated in male infertility, often tagged Y-chromosome infertility (MedlinePlus 2019). This condition is usually not inherited as most cases are observed in men with no family history of the disorder (MedlinePlus 2019). Y chromosome deletions cause infertility by deleting Y-linked genes in the AZF regions which are necessary for normal spermatogenesis (Heard and Turner 2011). Loss of Y-linked genes may prevent the synthesis of some proteins needed for normal sperm cell development (MedlinePlus 2019). Y chromosome deletion causes spermatogenic failure, leading to infertility (MedlinePlus 2019). The affected

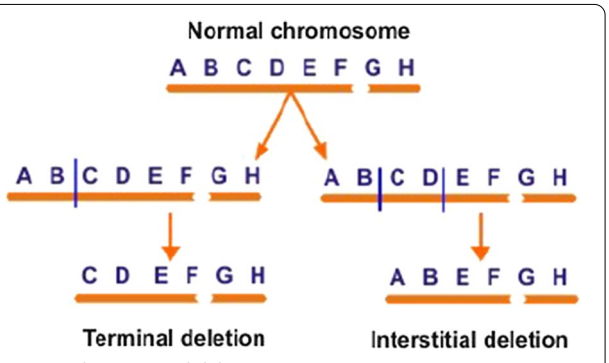

Fig. 10 Chromosomal deletions

may show azoospermia, oligospermia, teratospermia, or sperms with abnormal motility (MedlinePlus 2019). Some men expressing mild to moderate oligospermia may sometime produce a child naturally (MedlinePlus 2019). Furthermore, the majority of men with Y chromosome infertility have some sperm cells in the testes that can be obtained to assist oligospermic to father a child (MedlinePlus 2019). However, when men with Y-chromosome infertility produce children, whether naturally or assisted, they will transmit the abnormality on the Y chromosome to all their male children (MedlinePlus 2019). Consequently, males will also express Y-chromosome infertility (MedlinePlus 2019). This form of inheritance is Y-linked and so females are not affected because they do not inherit the Y chromosome (MedlinePlus 2019).

X chromosomal deletion can affect both male and female fertility. The X chromosome has many genes that are embedded in the testis and ovaries and involve in gametogenesis (Zhou et al. 2013). Male infertility is often caused by spermatogenesis disruption in which X chromosome dosage is implicated (Vockel et al. 2019). Males normally have one X chromosome whose most genes are not on the Y chromosome, so any mutational loss of function of genes on the X chromosome cannot be compensated (Vockel et al. 2019). Deletion in X chromosomes may cause defective chromosomal synapsis, meiotic arrest, and infertility (Zhou et al. 2013). In females, X chromosomal deletion may cause premature ovarian failure, gonadal dysgenesis, and infertility (Ferreira et al. 2010).

Ring chromosomes

A ring chromosome is a chromosome abnormality whose ends fused and formed a ring (Shchelochkov et al. 2008). All human chromosomes can form ring chromosomes (Guilherme et al. 2011). To form a ring, the two ends of the chromosome break and the broken ends fused (Fig. 11). Rarely, the telomeres of the chromosome fuse without losing any genetic information and thus produce no phenotypic effects (Shchelochkov et al. 2008). Ring chromosomes often occur spontaneously and rarely inherited due to instability of ring chromosomes during cell division and so may be lost (Yip 2015). However, if transmitted, ring chromosomes may form new rings in the offspring, which coexists with the normal cell line (Rajesh et al. 2011). This causes a mosaic karyotype in the maternal and fetal cells (Rajesh et al. 2011). Mosaicism is prevalent and influences the severity of the condition (Guilherme et al. 2011). Furthermore, during mitosis, ring chromosomes duplicate and assort regularly to the daughter cells, transmitting the rings (Rajesh et al. 2011). Ring chromosome carriers can be infertile due to

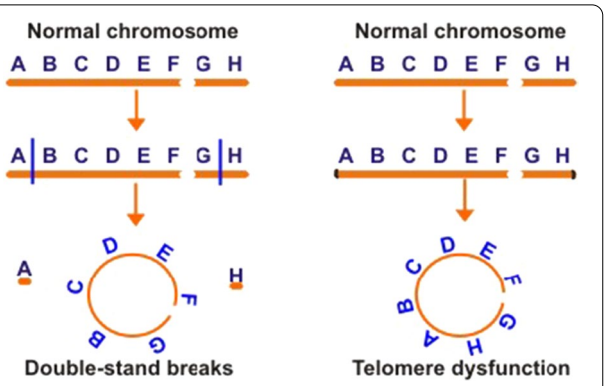

Fig. 11 Ring chromosomes

changes or loss of genetic materials following ring formation (Yip 2015). In males, autosomal ring chromosomes often cause oligospermia and azoospermia, probably due to gamete instability at meiosis (Rajesh et al. 2011). Ring chromosomes rarely impair female fertility (Lazer and Friedler 2019). However, low ovarian reserve has been reported in women expressing ring chromosomes (Lazer and Friedler 2019).

Testing for chromosomal abnormalities

According to Winchester Hospital (2021), most chromosomal abnormalities cannot be cured. However, prenatal screening and diagnostic tests can help lessen the effects of the conditions on both the mother and baby. It can also offer the choice to terminate the pregnancy if an abnormality is detected.

Screening and diagnostic tests are often done to determine the presence and risk of chromosomal abnormalities (Mater Centre for Maternal Fetal Medicine 2017). A screening test searches for signs that may indicate an embryo is at increased risk for a chromosome abnormality; it does not determine if a baby has a certain abnormality or not (Mater Centre for Maternal Fetal Medicine 2017). On the other hand, a diagnostic test confirms the presence or otherwise of certain chromosomal abnormalities.

Screening tests

There are three types of screening tests, which are the first trimester combined screen (FTCS), the triple test or second trimester maternal serum screen and noninvasive prenatal testing (NIPT) (Mater Centre for Maternal Fetal Medicine 2017).

The FTCS involves a combination of an ultrasound scan of the fetus at 11–13 weeks gestation and a blood test of the mother at 10–13 weeks gestation (Mater Centre for Maternal Fetal Medicine 2017; Spencer et al. 2003). The test measures the concentrations of two naturally occurring hormones in the blood, including pregnancy-associated placental protein A and beta-human chorionic gonadotropin (Raising Children Network 2021). In addition to the maternal blood test and baby ultrasound, the test combines the maternal age (the age of the egg if using a donor egg), weight, ethnicity, and smoking status, to score the risk for chromosomal abnormalities (Mater Centre for Maternal Fetal Medicine 2017). The risk level is scored a figure, which is considered high when it is more than 0.0033 and low when less than 0.0033 (Mater Centre for Maternal Fetal Medicine 2017; Spencer et al. 2003).

The triple test is a blood test conducted in the second trimester of pregnancy at 15–20 weeks gestation (Mater Centre for Maternal Fetal Medicine 2017). The test measures the concentrations of certain hormones (alpha-fetoprotein, estriol, human chorionic gonadotropin, and inhibin A) in the placenta and fetal blood to determine the risk of chromosomal abnormalities. The levels of these hormones as well as the baby's gestational age and maternal age and weight are used to determine the risk of certain chromosomal abnormalities (Raising Children Network 2021).

NIPT involves examining the blood of a pregnant woman for maternal and fetal DNA fragments and can be done any time from 10 weeks gestation (Mater Centre for Maternal Fetal Medicine 2017). NIPT, also referred to as cell-free DNA (cfDNA) testing, gives more accurate results than other screening tests, but comparatively expensive (Raising Children Network 2021). The screening counts several maternal and fetal DNA fragments using massive sequencing and assigns them to chromosomes (Rizos 2018). If the result indicates high risk, invasive testing with amniocentesis or chorionic villus sampling may be offered as a diagnostic test (Mater Centre for Maternal Fetal Medicine 2017). Notably, NIPT does not determine the risk of structural abnormalities and the results do not determine a particular abnormality (Mater Centre for Maternal Fetal Medicine 2017).

Diagnostic tests

A diagnostic test examines the tissues of the fetus for chromosomal abnormalities. There are two methods of sampling the tissues, which are chorionic villus sampling (CVS) and amniocentesis (Raising Children Network 2021). The CVS takes the samples from the placenta, while amniocentesis takes samples from the amniotic fluid (the fluid around the baby). The tissues are then tested in the laboratory for chromosomal abnormalities by karyotyping, fluorescence in situ hybridization (FISH), or molecular karyotyping (Raising Children Network 2021).

Chorionic villus sampling (CVS)

Chorionic villus sampling (CVS) is employed to obtain samples of the placenta from the uterus (Raising Children Network 2021). Often, an ultrasound is used to direct a thin needle through the tummy into the uterus to obtain samples of the placenta (Raising Children Network 2021). Rarely, if the placenta is positioned in such a way it is not convenient to insert the needle through the tummy, a soft tube may be inserted through the vagina and cervix to get to the uterus (Raising Children Network 2021). The best time to perform CVS is in the first trimester, between 11 and 14 weeks of pregnancy (Raising Children Network 2021). CVS has a risk of a miscarriage of 1 in 100 (Raising Children Network 2021). This means that for every 100 times a CVS is performed, there is one miscarriage that would not otherwise have occurred (Raising Children Network 2021). So, this risk should be considered before deciding to conduct CVS.

Amniocentesis

Amniocentesis is often offered as an alternative to CVS after 15 weeks of pregnancy. It may also be done if CVS has been performed, but the CVS results are not clear (Raising Children Network 2021). Amniocentesis is used to take samples of the fluid that surrounds the baby in the uterus (Raising Children Network 2021). An ultrasound is used to direct a thin needle into the uterus to obtain samples of the fluid (Raising Children Network 2021). Amniocentesis has a risk of a miscarriage of less than 1 in 200 (Raising Children Network 2021). This shows that amniocentesis is less risky compared to CVS. However, like the CVS, this risk should be considered before embarking on the test.

Management of chromosomal abnormalities

As stated earlier, most chromosomal abnormalities are not treatable. However, some complications that result from chromosomal abnormalities can be treated to improve the quality of life of both the mother and baby (Winchester Hospital 2021). Furthermore, Cody and Hale (2015) believe that chromosomal abnormalities can be treated by changing the expression of some genes. Abnormalities caused by deletions can be treated by up-regulating some genes to induce one gene to perform the work of two. Chromosomal abnormalities resulting from duplications can also be treated by knocking off some genes to normalize the expression level. The same logic can be employed for other structural and numerical abnormalities. Cody and Hale further stated that one of the several ways gene expression can be changed is through diets. The scientists explained the mechanism involved using alcohol dehydrogenases on alcohol metabolism as an example. Individuals that rarely drink alcohol easily feel drowsy after taking a shot. However, the drowsiness disappears after regularly taking the same shot for a long time. This is because repeated drinking of alcohol increases the production of important proteins (alcohol dehydrogenases) that breakdown and metabolize alcohol. Aside from diets, Cody and Hale believe that drugs can be formulated to change gene expression and their proteins. For example, a drug called statin increases the production of important proteins that help the body eliminates bad fats, thus can help treat certain disorders of lipid metabolism.

Preventive measures can also go a long way in cushioning or preventing the occurrence of chromosomal abnormality. Notably, the risk of transmission of an abnormality to a baby increases as the mother ages. So, women above 35 years should see a doctor three months before conceiving a baby (Winchester Hospital 2021). Such individuals should also consider taking prenatal vitamin a day for the three months before becoming pregnant (Winchester Hospital 2021). The vitamin should have 400 μg of folic acid and should be taken through the first month of pregnancy (Winchester Hospital 2021). They should also visit their doctors regularly. Additionally, they should eat healthy foods, especially foods that have folic acids like cereals, grain products, leafy greens, oranges and orange juice, and peanuts (Winchester Hospital 2021). Such individuals should cultivate a healthy weight, avoid smoking and alcoholic drinks, and should not take any drug unless recommended by their doctors (Winchester Hospital 2021).

Conclusion

Several articles reviewed showed that errors during and after gametogenesis may cause infertility-predisposing chromosomal abnormalities. These abnormalities include Klinefelter syndrome, Jacob syndrome, Triple X syndrome, Turner syndrome, and Down syndrome as well as deletion, duplication, inversion, and ring chromosomes. Most often, these abnormalities are not inherited and occur spontaneously. Male chromosomal infertilities are characterized by spermatogenesis arrest, resulting in azoospermia, oligospermia, and abnormal genitals, and female is characterized by premature ovarian insufficiency, amenorrhea, miscarriage, and ambiguous genitalia. Most chromosomal infertilities are incurable. However, early testing, resulting in precautionary measures may lessen the severity of the conditions. There is also a growing belief that changing gene expression through certain diets and drugs may neutralize the effects of chromosomal abnormalities. Women at increased risk of chromosomal abnormalities such as those with advanced age ($\geq$ 35 years) and those with a family history

of infertility should seek medical advice before having a baby.

Abbreviations
CDC: Center for diseases control and prevention; cfDNA: Cell-free DNA; CVS: Chorionic villus sampling; DS: Down syndrome; FISH: Fluorescence in situ hybridization; JS: Jacob syndrome; KS: Klinefelter syndrome; NIPT: Noninvasive prenatal testing; POI: Premature ovarian insufficiency; TS: Turner syndrome.

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TOY conceptualized and did literature search, article writing, and correspondence. EOO did literature search and article writing. DA, BMDA, and CO did proof reading and editing. RS and UUL did article sorting. All authors proofread and approved the final manuscript.

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