Counseling challenges for prenatal diagnosis

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Prenatal genetic counseling is a communication process to help in decision making during or before a pregnancy, which deals with the inheritance patterns, carrier frequencies, recurrence risks, available genetic tests, and potential management options of a genetic disorder in a family. The ethical and technical challenges are significant in the area of prenatal medicine as the fetus has a relatively short medical history, and the morphological assessment is only feasible indirectly through ultrasound. Fetal DNA can be obtained either directly from placental biopsy or amniotic fluid, or indirectly through cell-free fetal DNA circulating in the maternal plasma. For a group of fetal malformations diagnosed during ultrasound evaluation, there is inadequate information to establish a definite diagnosis, and inquiries about the pathogenesis of the fetal abnormalities and their recurrence may be delineated only after postnatal or pathological examination. Uncertainty in diagnosis and prognosis is challenging for physicians and distressing for families. The introduction of chromosomal microarray into the field of fetal medicine has dramatically increased the diagnostic yield of diagnostic tests in several scenarios, including cases of nonimmune hydrops fetalis, and multiple congenital anomalies. New fetal phenotypes evolved by whole-exome sequencing pose a major challenge during pregnancy as the malformations may not yet have manifested during the gestational period when the fetus is assessed. Large-scale efforts to create public databases of whole-exome sequencing findings and their associated fetal phenotypes will greatly enhance counseling abilities. Finally, the increase in use of preimplantation genetic diagnosis poses numerous social, psychological, ethical, clinical, and legal dilemmas, many of which have received little attention.

Keywords:
genetic counseling, prenatal diagnosis, invasive testing, NIPT, PGD

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Introduction

Prenatal genetic counseling deals with inquiries about the risks of genetic disorders for the offspring (Cariati *et al.*, 2019). In the prenatal setting, the most common indications for referral to genetic counseling are advanced maternal age, fetal anomalies identified by ultrasound, current pregnancy with an abnormal genetic screening test, history of a previous child with chromosomal aberration, developmental delay or birth defects, and history of recurrent pregnancy loss or stillbirths (Dobrescu *et al.*, 2018). The advent of amniocentesis in 1960 started the era of prenatal diagnosis (PND). At first, the fetal genetic diagnosis was limited to chromosomal disorders, the few number of monogenic disorders for which biochemical or molecular tests could be tested on the amniotic fluid in addition to the structural malformations detected by ultrasound (Dukhovny and Norton, 2018). The fetal prenatal screening landscape also has improved greatly with the introduction of noninvasive prenatal testing (NIPT) using fetal nucleic acids recovered from the maternal circulation (Hong *et al.*, 2020). Evolving technologies and an increasing number of prenatal screening and diagnostic tools have resulted in more complex genetic counseling issues and challenging case management (Van den Veyver, 2016; Cariati *et al.*, 2020).

Challenging findings detected by invasive prenatal diagnostic methods

The diagnosis of aneuploidy by amniocentesis or chorionic villus sampling (CVS) is the most common reason for referral for prenatal counseling. The possibility of presence of maternal cell contamination in samples of chorionic villus or amniotic fluid represents a potential preanalytical risk for prenatal data interpretation. Therefore, to provide a correct interpretation of the results, maternal contamination testing using maternal markers must be performed on all prenatal samples regardless of the underlying condition and the mode of inheritance (Nagan *et al.*, 2011). The following examples represent challenging results that can create counseling dilemmas (Viotti, 2020).

Structural rearrangements and chromosomal translocations

Chromosomal translocations detected in amniotic fluid cells raise interests regarding possible associated fetal damage as the breakpoints could disrupt the

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functions of genes at the site's breaks (Li *et al.*, 2019). The adverse effects on the fetus are mainly dependent on whether the translocation is inherited from one parent. Thus, the subsequent step is to establish parents' karyotyping, as inherited chromosomal rearrangements are not associated with a significantly increased risk of adverse pregnancy outcome (Priya *et al.*, 2018). On the contrary, identification and follow-up of pregnancies with de novo unbalanced chromosomal inversions and translocations with detailed ultrasound and fetal echo revealed a two to three-fold increase in the fetal malformations risks above the 3% background risk of the general population (Halgren *et al.*, 2018).

Prenatal diagnosis of chromosomal mosaicism

Chromosomal mosaicism is among the most challenging findings to both the prenatal genetic counselors and the parents. It is defined as the presence of two or more cell lines with different karyotypes in an individual or a culture. Prenatally diagnosed mosaicism can be differentiated into confined placental mosaicism, true fetal mosaicism, or pseudomosaicism, resulting from an artifact of culture (Grati *et al.*, 2017). Their clinical significance and possible fetal affection depend on the level of mosaicism, adequacy of the study, and the chromosomal abnormality involved. Further diagnostic testing includes targeted ultrasound examination, fetal echocardiography, repeat amniocentesis, and fetal blood sampling, or skin biopsy, array comparative genomic hybridization (Najafi *et al.*, 2019).

Discrepancy between the chromosomal and ultrasound phenotypic sex

A number of fetal genetic disorders of sexual development must be considered as a possible explanation for a discrepancy between the chromosomal sex revealed by invasive diagnostic tests and phenotypic sex detected by ultrasound examination (Dhamankar *et al.*, 2020). In 46, XX females, genetic disorders associated with excessive androgen production cause virilization; these include congenital adrenal hyperplasia (CAH) caused by CYP21A2 gene mutation, exogenous androgens, or an androgen-producing tumor (Baronio *et al.*, 2019).

In contrast, ambiguous genitalia in a 46, XY fetus can result from the defective formation of the fetal testes (testicular dysgenesis), inability to respond to androgens (androgen insensitivity syndrome), or decreased production of dihydrotestosterone or testosterone (5α-reductase deficiency) (Alimussina *et al.*, 2018). Additionally, ambiguous genitalia can be part of multiple congenital malformations syndromes; this may be explained by the containment involvement of some transcription genes in both sex development and other developmental functions. Examples include campomelic dysplasia resulting from SOX-9 (17q24-25) mutations, and Denys-Drash, and WAGR syndrome, owing to WT-1 gene (11p3) gene mutations (Little *et al.*, 2005; Dhamankar *et al.*, 2020).

Challenging findings detected during first-trimester and second-trimester screening

The utility of maternal serum biochemical tests in screening for fetal birth defects was first recognized in the 1970s following the observation that maternal serum alpha-fetoprotein (MSAFP) at 15 weeks of gestation was usually elevated in cases with open spina bifida or an open ventral wall defect (Wilson, 2014). By the mid-1980s, the association between fetal Down syndrome and decreased MSAFP concentration led to widespread Down syndrome serum screening in the early mid-trimester. This was shortly followed by the incorporation of other serum markers into the screening paradigm (Sharony *et al.*, 2016). The combination of MSAFP, human chorionic gonadotropin (hCG), unconjugated estriol (uE3), and inhibin A screen was correlated with maternal age and created the quadruplet test that allowed the detection of approximately two-thirds of Down syndrome pregnancies with a 5% false-positive rate (Benn, 2002). Over the past 15 years, the advent of high-resolution ultrasound and the widespread adoption of first-trimester risk assessment with nuchal translucency (NT) evolved the field of first-trimester aneuploidy screening to improve PND and optimize pregnancy outcomes. This includes maternal serum free b-hCG and pregnancy-associated plasma protein-A at 9–10 weeks and first-trimester NT measurement as part of an anomaly scan at 12 weeks (Nicolaides, 2011).

Much time is spent by prenatal genetic counselors on counseling women about their individual risk for aneuploidies as derived from noninvasive testing in the first trimester of pregnancy. A mathematical method to derive an overall risk from marker variables and maternal age and extended for multiple markers was first proposed by Cuckle *et al.* and extended for multiple markets by Wald *et al.* (1988). The method is based on the conversion of all marker concentrations to multiples of the normal gestational median (multiple of the median) and the log transformation of these to give Gaussian distributions. A ratio (termed the likelihood ratio) can be calculated from the relative heights of the overlapping distributions in affected and unaffected pregnancies, and this variable is used to modify the *a priori* maternal age risk. The same approach can be used for two or more markers, taking into account any significant correlation between the

markers (Wright *et al.*, 2008). The fetal medicine foundation has developed a new algorithm called Prenatal Risk Calculation to evaluate Down syndrome screening based on free hCGβ, pregnancy-associated plasma protein-A, and NT. The peculiarity of this algorithm is to use the degree of extremeness instead of the multiple of the median (Morin *et al.*, 2013).

Increased nuchal translucency and a normal fetal karyotype

An increased NT measurement detected in the first-trimester scan, in the presence of a normal fetal karyotype, is associated with a large number of genetic syndromes and major structural birth defects (Socolov *et al.*, 2017). Cardiac defects are the most common, followed by skeletal dysplasias. Many, but not all, of the fetal abnormalities associated with an increased NT measurement can be identified by further prenatal assessment including detailed ultrasound to assess the fetal anatomy and to evaluate whether the NT is persistently increased because it is associated with a high risk of underlying fetal pathology (Vayna *et al.*, 2018). Array comparative genomic hybridization to look for gene deletions and duplications undetectable by routine chromosomal analysis would have a low yield in such cases as most of the genetic disorders known to be associated with an increased NT measurement are caused by point mutations, which may be elucidated by whole-exome sequencing (WES) (Su *et al.*, 2019).

Markedly elevated maternal serum alpha-fetoprotein concentration unexplained by a fetal defect on ultrasound

An elevated MSAFP should be followed by ultrasound as unrecognized multiple gestations, incorrect gestational age, and fetal demise must be excluded (Sharony *et al.*, 2016). Other possible explanations for elevated MSAFP include fetal disorders associated with leakage of fetal proteins such as congenital nephrosis, extensive skin lesions including cutis aplasia, large hemangiomas, and epidermolysis bullosa (Jeong *et al.*, 2015).

Very low or undetectable concentration of unconjugated estriol

Low uE3 concentrations are often associated with an increased risk for Down syndrome, trisomies 18 and 13, and triploidy, so that amniocentesis is often offered to establish the fetal karyotype (Benn *et al.*, 2002). In a male fetus with a low uE3 concentration, X-linked ichthyosis owing to steroid sulfatase deficiency is the most common pathologic explanation; therefore, FISH analysis can be performed on amniotic fluid cells to look for common deletions on the X chromosome associated with steroid sulfatase deficiency (Dreyer *et al.*, 2018). Smith–Lemli–Opitz syndrome, a disorder of impaired cholesterol metabolism caused by mutations in the DHCR7 gene, is characterized prenatally by low levels of uE3 in addition to nonspecific ultrasound findings, including such as microcephaly, genital anomalies, and cardiac defects (Lazarin *et al.*, 2017).

Challenging findings detected by ultrasound

Pregnancies complicated by multiple fetal congenital malformations constitute a distinctive challenge in prenatal genetic counseling, mostly in the absence of a definite diagnosis. Accurate counseling is crucial during the prenatal period to help parents in making informed decisions (Dobrescu *et al.*, 2018).

Recurrent nonimmune hydrops fetalis

Hydrops fetalis occurs in approximately one in 1700 pregnancies and is diagnosed in the presence of at least two abnormal fluid collections in the fetus, including pericardial effusion, pleural effusion skin edema, or ascites (Mardy *et al.*, 2019). A large group of genetic and maternal causes may result in nonimmune hydrops fetalis; therefore, detailed thorough genetic and phenotypic assessments are crucial in determining the etiology, anticipating neonatal care requirements, and counsel families about prognosis and recurrence risk (Deng *et al.*, 2020). An algorithm for the evaluation of nonimmune hydrops fetalis should include detailed ultrasound with Doppler evaluation, fetal echo, chromosomal analysis, and lysosomal enzyme evaluation. However, the lack of feasibility of testing for a large number of single-gene disorders associated with fetal hydrops often precludes a diagnosis (Deng *et al.*, 2020).

Recurrent nonmotile ciliopathies

Nonmotile ciliopathies are a group of hereditary disorders caused by mutations of different genes playing crucial roles in cilia structures, and inheritance is mainly autosomal recessive (Waters and Beales, 2011). All of these disorders are characterized by both clinical and genetic heterogeneities. Common features are cystic renal/or hepatic disease; brain malformations; neural tube defects; skeletal disorders including abnormal shortening of ribs, limbs, and polydactyly; and situs inversus (Waters and Beales, 2011). Prenatal findings of renal abnormalities, encephalocele, and postaxial polydactyly are features of Bardet–Biedl syndrome, Meckel–Gruber syndrome, and Joubert syndrome. These abnormalities can also be seen in Jeune syndrome (asphyxiating thoracic dystrophy), but the fetus lacks the skeletal findings (Chung *et al.*, 2014). The constellation of these abnormal ultrasound

findings could be explained by trisomy 13. After delivery, pathologic examination of the fetus and molecular testing to confirm a clinical diagnosis of one of the ciliopathies associated with multisystem abnormalities is recommended (Grochowsky and Gunay-Aygun, 2019).

Challenging findings in noninvasive prenatal testing

Since 1997, following Dennis Lo detection of fetal DNA in the maternal plasma, the use of cell-free fetal DNA (cffDNA) for NIPT is considered as one of the greatest achievements in prenatal care (Chitty and Lo, 2015). The advent of NIPT for aneuploidy screening provides precise information about the risk of common aneuploidies when compared with maternal serum marker screens and is reducing the need for invasive testing (Mackie *et al*., 2017). NIPT is a highly accurate screening test that can be used from 10 weeks in pregnancy to detect Down syndrome (trisomy 21) with high sensitivity (99%) and specificity (99.5%) (Gil *et al*., 2015). NIPT has a much greater sensitivity than traditional screening methods such as the combined test that measures NT and maternal serum biochemistry, and a growing number of studies have confirmed that the introduction of NIPT into the screening pathway has significantly reduced the need for invasive testing (Dondorp *et al*.,2015). However, NIPT is not diagnostic, and confirmation of a positive result by invasive testing (CVS or amniocentesis) is mandatory (Hill *et al*., 2017).

There is a major difference between NIPT and noninvasive prenatal diagnosis, which is considered diagnostic and does not require subsequent invasive testing. The noninvasive diagnostic testing has been successfully used for de novo mutations for autosomal dominant conditions, such as craniosynostosis syndromes and skeletal dysplasias. Moreover, it is useful in paternally inherited disorders for which the fetus and the mother were discordant, including fetal sex determination and Rhesus (Rh) status (Zhang *et al*., 2019).

Prenatal fetal sex discordance following cell-free fetal DNA testing

Noninvasive determination of fetal sex creates ethical challenges arising from sex selection for nonmedical reasons. Therefore, it is recommended that noninvasive fetal sex testing to be restricted for selected cases including those at risk of CAH to provide pregnant women with steroids to avoid virulization of female fetuses' genitalia or serious X-linked disorders. Occasionally, cffDNA testing can give fetal sex results not matching the ultrasound imaging of fetal genitalia or the diagnostic karyotyping results (Smet *et al*., 2020). Counseling in these cases is challenging, as there are very few published cases; moreover, it usually raises concerns about the possibility of analytical errors. Causes usually include co-twin demise, low fetal fraction, or fetoplacental mosaicism, or a maternal transfusion/transplantation (Cariati *et al*., 2019; Smet *et al*., 2020).

False-positive and false-negative noninvasive prenatal testing results

cffDNA screening has a sensitivity and specificity of more than 99% for trisomy 21. False-negative and false-positive results can occur owing to biologic factors, including low fetal fraction (FF), confined fetal mosaicism, and maternal undiagnosed disorders, in addition to statistical or technical causes (Hu *et al*., 2019). False-positive results mostly result from inconsistency between the fetal and placental chromosome count as in vanished twin and fetoplacental mosaicism (Wilkins-Haug *et al*., 2018). On the contrary, the most common explanations for false-negative or inconclusive results include a low FF, which is measured by specific fetal DNA markers. Additionally, failed results owing to low FF has been correlated with an increased aneuploidy risk, especially trisomy 13, trisomy 18, and triploidy, ranging from 2.7 to 23.3%. The management of women with failed NIPT results owing to low FF must include ultrasound assessment and discussion of the available options including alternative screening tests, NIPT redraw, and invasive diagnostic testing (Chen *et al*., 2020).

Challenging aspects of noninvasive prenatal testing in maternal obesity

Obesity is considered a limiting factor to all methods of prenatal screening; the best method for antenatal screening in obese pregnant women has not been delineated. Moreover, obese women are at an increased risk of NIPT test failure resulting from low FF (Kruckow *et al*., 2019). In such cases, postponing NIPT collection till the time of the 12-week anomaly scan is advisable to minimize test failures at 10–11 weeks; this would also allow an opportunity for an early fetal structural evaluation with transvaginal ultrasound (Togneri *et al*., 2019).

Prenatal challenges in multiple gestations

The incidence of multiple pregnancies has grown in the last years, mostly related to the increased use of assisted reproductive techniques (Gil *et al*., 2017).

Despite the progress in prenatal care, twin gestations still have more unfavorable outcomes and pose a multitude of challenges and controversies. Several issues on screening, classification, and management remain under debate; moreover, they are less frequently incorporated in clinical trials (Galeva *et al.*, 2019).

Twins discordant for congenital anomalies

The frequency of congenital anomalies in monochorionic (MC) twins is generally higher than in dizygotic and in singleton pregnancies, and in 90%, only one twin of the monozygotic twins is affected. The anomalies in one twin elevate the risk of morbidity owing to intrauterine death of the abnormal co-twin, preterm delivery, and low birth weight. Given the shared placenta and circulation, the management of MC twin discordant for structural anomalies poses a clinical challenge (Corroenne *et al.*, 2020). Counseling regarding the management must involve a detailed evaluation of the abnormality (lethal vs. nonlethal), the gestational age, and the patient choices. The main options for managing the cases of MC twins discordant for congenital anomalies include selective feticide, termination of the entire pregnancy, or expectant management. However, there are no studies showing that one strategy is superior to the others (Corroenne *et al.*, 2020). Moreover, aneuploidy is less frequently encountered in MC twins, but usually, both fetuses are affected. Infrequently, only one twin may harbor the chromosomal aberration, a phenomenon known as hetero-karyotypic twinning, which can be diagnosed only by an amniocentesis of both sacs. Therefore in MC twins, CVS of a single placenta may miss these rare cases, and a double amniocentesis from both sacs must be performed (Vink *et al.*, 2012).

Challenges in prenatal counseling for disorders with atypical modes of inheritance

These groups of disorders have inheritance patterns that do not follow Mendel's Law of Segregation; examples include multifactorial inheritance and mitochondrial inheritance (McCandless and Cassidy, 2006).

Multifactorial inheritance and birth defects

Disorders with multifactorial inheritance are caused by the effects and complex interactions of multiple susceptibility genes, each usually with a relatively small effect, environmental factors, and epigenetic factors. Isolated birth defects including facial clefting, congenital heart disease, neural tube defects, and talipes equinovarus are examples of disorders that usually follow multifactorial inheritance, with an incidence of 1–8% in newborns (Dixon *et al.*, 2011). For multifactorial disorders, the major factor influencing the risk of recurrence is the degree of relationship; the risk of recurrence is highest among first-degree relatives (Bijanzadeh, 2017). Moreover, there are ethnic and geographic variations in the incidence of some multifactorial disorders, reflecting different genetic and/or environmental influences, which in turn may influence the risk of recurrence (Bijanzadeh, 2017). Folate deficiency, which could be due to genetic variants affecting folic acid metabolism, or nutritional deficiencies, is now recognized as playing an important role in the pathogenesis of some multifactorial disorders such as facial clefting, neural tube defects, and congenital heart disease in some susceptible individuals. Subsequently, periconceptional folic acid supplementation has been shown to reduce the recurrence risk of these disorders (Senousy *et al.*, 2018).

Mitochondrial inheritance

Mitochondrial disorders represent a challenging group of genetic diseases for both prenatal genetic diagnosis and preimplantation genetic diagnosis (PGD). Mitochondrial inheritance differs from Mendelian inheritance because functioning mitochondria are inherited exclusively from the mother, who is usually asymptomatic or less severely affected (Wallace and Chalkida, 2013). Additionally, there is a wide continuum of disease severity within and among affected families; this is largely accounted for by heteroplasmy, the situation in which there is more than one type of mtDNA present within each cell. A high burden of mutant mtDNA will usually result in early-onset and severe disease (Baldo and Vilarinho, 2020). Establishing the molecular basis of a mitochondrial disorder will provide information about recurrence risk in future children, allow for PND in future pregnancies, and permit the identification of at-risk relatives (Craven *et al.*, 2017). Heteroplasmy, tissue specificity, and mutant load represent barriers to performing PGD; the situation is different in non-Islamic countries, as parents have many alternatives to PGD. These include oocyte donation or embryo manipulation to replace the affected mtDNA with a healthy one by different gene replacement techniques; both approaches are prohibited in Islam (Balobaid *et al.*, 2016).

Challenges in genetic counseling for prenatally detected fragile X gene expansions

Fragile X syndrome is an X-linked trinucleotide repeat disorder that is caused by large expansions of a CGG nucleotide triplet repeat in the FMR1 gene; the normal gene has less than 45 repeats. All males with a full FMR1 gene mutation (CGG expansions of – 200 repeats) have moderate to severe mental retardation, and about half of the females with a full

mutation have mild mental retardation or learning disabilities (Macpherson and Murray, 2016). In females, CGG triplet repeats of 55–199 are unstable and are prone to large expansions during meiosis (McKechanie *et al*., 2019). Analysis of DNA obtained from amniotic fluid cells or chorionic villi can establish the FMR1 gene status of the fetus; additionally, PGD is also available for future pregnancies (Man *et al*., 2017). A unique feature of this trinucleotide repeat disorder is the association of abnormal triplet repeat sizes with premature ovarian failure, which occurs in about 20% of women who carry a fragile X premutation but not in those who carry a full mutation. The diagnosis of premature ovarian failure is an indication for fragile X syndrome carrier testing, especially if a woman is considering assisted reproductive technology (Fink *et al*., 2018).

The challenging aspects of Pandora's pregnancy: (a new era for prenatal genetic testing) chromosomal microarray, and whole-exome sequencing

There is a switch from the 'traditional' techniques of conventional karyotyping in PND to the present phase of improved genetic tests, including chromosomal microarray (CMA), and WES (Van den Veyver, 2016). CMA, where small losses and gains of genetic material are detected, has been recommended in the assessment of fetal structural malformations. Moreover, WES, where the coding parts of the fetal genome are evaluated, has been more frequently introduced in cases with congenital malformations (Jelin and Vora, 2018). The advantage of these techniques is their higher detection rate in comparison with conventional methods. However, it is argued that the current 'Pandora's pregnancy' era calls for nondeterministic counseling resulting from the novel findings of 'variants of uncertain significance' (VUS). The challenges created from VUS result from variable phenotypes associated with them or the limited data concerning these variants (Morales and Hershberger, 2018).

The challenges of chromosomal microarray tests in anomalous fetuses

CMA provides genetic information at a higher resolution than the conventional karyotyping by detecting copy number variants – submicroscopic chromosomal duplications or deletions. These copy number variants are interpreted as pathogenic, benign, or VUS depending on the affected genes, its specific location, and the level of available data linking this variant with a specific phenotype (Hashiloni-Dolev *et al*., 2019). Single-nucleotide polymorphism array is a common method of CMA; it can identify triploidy, haploidy, and absence of heterozygosity (AOH). The pathogenesis of AOH includes increased susceptibility to complex disorders and imprinting effects caused by uniparental disomy (UPD) or confined placental mosaicism (Daum *et al*., 2019). When AOH in the imprinting regions is found to be inherited from only one parent, it can result in genomic imprinting disorders, such as Angelman syndrome (paternal UPD15), Beckwith–Wiedemann syndrome (paternal UPD11), and Silver–Russell syndrome (maternal UPD7) (Hattori *et al*., 2019).

Challenges of prenatal whole-exome sequencing: expanding the knowledge of fetal phenotypes

CMA can only detect a small number of severe multiple malformation syndromes, as most of them result from single-gene mutations. The resulting diagnostic gap can be solved by WES, which has a diagnostic yield ranging from 6.2 to 80% in fetuses with multiple malformations (Deden *et al*., 2020). Of great interest is the finding that 'expanded' phenotypes being confronted in fetuses diagnosed using WES tests. As new fetal phenotypes are currently reported in association with the evolving of novel mutations, it is required to have enough evidence to causally link these variants with specific fetal malformations. This evidence usually stems from functional studies, animal models, the detection of the variant fetuses with similar phenotypes, and its absence in normal ones (Deden *et al*., 2020).

The challenges of termination of pregnancy following confirmation of fetal affection

PND and termination of confirmed affected pregnancy represent a challenge to fetal medicine specialists, especially when the pregnant woman presents for the first time to the clinic at a relatively advanced gestational age and/or with an absence of known pathogenic mutations in the index case. In such cases, diagnostic techniques have to be performed under major time pressure, especially in countries with strict laws regarding the termination of pregnancy. Termination of pregnancy is accepted in Islam before 120 days of conception in a grossly malformed fetus or cases with an untreatable severe condition and is based on the parents' request. Other patients not legible for termination are provided with a detailed medical report to seek support from scholars by getting a Fatwa (Balobaid *et al*., 2016).

Challenges in preventative reproductive options: preimplantation genetic diagnosis

Major advances in the field of PGD are needed to combat the medical, social, and financial burden of genetic diseases. PGD options are greatly governed by political and religious factors worldwide (Lemke and Ruppel, 2019). Physicians are using PGD to assess increasing numbers of genes in embryos before transferring the embryos (Lemke and Ruppel, 2019). Genomic imprinting is also a challenging topic, and the field of epigenetic inheritance seems to be an interesting area, especially because assisted reproductive techniques can induce epigenetic modifications that might be transmitted to the next generation (Stuppia *et al.*, 2015).

Ethical, legal, and social aspects of prenatal genetic counseling

The primary ethical concerns in the field of PND are maintaining the well-being of the pregnant woman in addition to ascertaining the health of the developing embryo and treating the fetus as a patient. The use of PND for sex selection and paternity testing should be avoided. Proposed ethical guidelines for PND must include adequate pretest and posttest counseling, ensuring the availability of tests to all those at risk, the uptake of tests, and the decision making following it should be voluntary, and disclosure of all clinically relevant findings to the parents. Moreover, if a PND is medically indicated, it should be available regardless of the couple's view on abortion, as it will help in preparing the birth of an affected child (Vanstone *et al.*, 2018). Regarding the legal challenges in the field of PND, some PND issues present medical dilemmas that cannot be easily solved by legal advice. Those include wrongful test results that would have revealed an abnormality that could have been treated in-utero or avoiding intrauterine fetal death. Additionally, lack of an informed consent stating the risks of invasive diagnostic techniques and limitations of the tests, failure to inform parents of abnormal karyotyping until viability, and failure to diagnose an abnormality by ultrasound also creates challenging legal issues (Pergament and Ilijic, 2014).

Social challenges faced in the field of PND increase in the era of NIPT. The ease and earlier timing of the test might promote certain negative effects of increasing test uptake and therefore higher termination rates, which may lead to stigmatization and discrimination of people with disabilities and their families. Moreover, NIPT is expected to be used in screening for a broader group of fetal disorders, including late-onset diseases with subsequent inquiries about the rights of the coming child (Cernat *et al.*, 2019).

The Egyptian experience

Egyptian scientists began their research in the field of prenatal biochemical screening in 1998. Gaber *et al.* (1988), evaluated the use of biochemical markers in PND. This was followed by a multitude of publications evaluating the role of biochemical markers in predicting pregnancy complications, including preeclampsia, diabetes, and adverse pregnancy outcome including fetal growth restriction and recurrent pregnancy wastage (Afifi *et al.*, 2000; Gaber *et al.*, 2000; Abdel Ghaffar *et al.*, 2003; Abd Al-Kader *et al.*, 2005; Gaber *et al.*, 2006).

Regarding invasive diagnostic testing, Gaber (1999) evaluated the feasibility and benefits of early amniocentesis and later in 2005 published a preliminary report on genetic amniocentesis (Gaber, 2005). Additionally, they published articles about genetic counseling for chromosomal mosaicism in amniotic fluid and later about the sensitivity of real-time quantitative PCR as a rapid PND for Down syndrome and a recent article about screening for parental mitotic nondisjunction as a cause of fetal aneuploidy (Helmy and Gaber, 2003; Helmy *et al.*, 2009; Hussen *et al.*, 2018).

For PND of monogenic disorders, the first assessment of PND of β-thalassemia in Egypt was performed by Hussein *et al.* (2000), followed by later publications on larger number of cases and evaluations of factors affecting parents' attitudes (El-Beshlawy *et al.*, 2012). Additionally; a group of studies was performed to assess the feasibility of PND of a large number of single-gene disorders in the Egyptian families, including CAH, phenylketonuria, hemophilia, Duchenne and spinal muscle atrophy, inborn errors of metabolism, and recessive pediatric neurogenic diseases (Effat and Gaber, 2007; Effat *et al.*, 2007; Essawi *et al.*, 2008; Hussein *et al.*, 2008; Essawi *et al.*, 2012; Gaber *et al.*, 2015; Issa *et al.*, 2020). For multifactorial disorders, the prenatal team in the National Research Centre published articles evaluating the role of folic acid and vitamin B12 and their metabolites in reducing the risk of neural tube defects in the Egyptian Population (Gaber *et al.*, 2007; Senousy *et al.*, 2018).

The literature contains a large number of publications in the field of birth defects and fetal malformations. In an Egyptian study, Temtamy *et al.* (1988) reported that central nervous system anomalies are the most common congenital malformations among Egyptian neonates.

Later in 2000, Gaber and colleagues assessed the PND and management of cystic hygroma colli. This was followed by many publications assessing the success in PND of fetal structural malformations and rare genetic syndromes, with emphasis on fetal cardiac, skeletal, and nervous system anomalies (Hamza and Gaber, 2001; Abdel-Salam *et al*., 2012; Abdel-Salam *et al*., 2015; Afifi *et al*., 2016; El-Ruby *et al*., 2018; El-Dessouky *et al*., 2020). A study was performed in 2012 by Temtamy and Aglan (2012) to assess the effect of consanguinity in the Egyptian population and its relevance to genetic disorders and effect on reproductive health. It was found that consanguinity plays a major role in the high rates of prenatal and infant mortality (Mokhtar and Abdel-Fattah, 2001; Afifi *et al*., 2010). They recommended that shifts in public, political, and professional attitudes are needed to establish a genetic preventive strategy including premarital, preconception, and prenatal genetic counseling.

Conclusion

In the past decades, the emergence of knowledge regarding the human genome and the molecular pathogenesis of several human disorders combined with the increasing availability of highly efficient and fast diagnostic techniques, and the advances in the ultrasound images, greatly transformed the PND field. Additionally, maternal serum biochemical testing combined with the application of cffDNA recovered from the maternal circulation and the new advanced methods of molecular diagnostic techniques including CMA and WES improved our ability to identify abnormalities and to provide accurate pretest and posttest prenatal counseling. However, each of these screening and diagnostic methods has its own limitations and unexpected findings that are infrequently reported in the literature and make prenatal counseling extremely challenging. The advances in elucidating the molecular basis of human disorders have also revealed genetic complexities and mechanisms allowing recognition that different mutations in a single gene can result in greatly diverse clinical presentations in prenatal ultrasound images. In addition, non-Mendelian mechanisms such as mitochondrial inheritance, trinucleotide repeat expansions, and genomic imprinting create another level of complexity when considering prenatal genetic counseling. The exposure to unusual and challenging problems in the field of PND should be an integral part in the training of fetal medicine specialists. Some of these cases may require multidisciplinary team approach that must cooperate in a relatively short period of time of pregnancy to provide the best for both the patient and the fetus. Finally, the ethical, social, and legal challenges in PND must be highlighted and taken into consideration.

Recommendations

The diagnosis, decision-making process, and interpretation of results in the era of advanced genomic technologies need a multidisciplinary team approach composed of prenatal genetic counselors, clinical geneticists, and fetal medicine specialists. Additionally, the exposure to unusual and infrequent clinical challenges in PND should be an essential part of training the fetal medicine specialists and obstetricians. The first prenatal visit is the best timing to inform parents about prenatal genetic screening and testing methods. The amount and quality of information about identifying fetal genetic risks represent special challenges for the initial visit. With increasingly detailed and advanced tests, there is a need to provide families with adequate pretest and posttest counseling. To provide users with information that they will find helpful, the prenatal counseling must focus on accounting for uncertainty in genetic counseling; promoting reproductive choice rather than test uptake as the preferred measure of screening program's 'success;' promoting genetic literacy; developing new counseling methods; and allowing more time to provide a sensitive service with special emphasis on the pretest and posttest counseling. All health care providers including health ministries, patients, and clinicians must cooperate to guide the development of prenatal counseling guidelines and make sure it is implemented in a legally, socially, and ethically acceptable manner.

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None declared.

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