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MATERNAL-FETAL MEDICINE

Indications for genetic testing leading to termination of pregnancy

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Abstract

Purpose In this study, we aimed to assess the distribution of genetic abnormalities leading to termination of pregnancy and its fluctuation during the past 8 years in light of those technical advances.

Methods Our cohort consisted of all pregnant women who underwent termination of pregnancy because of genetic aberrations in their fetuses from January 2010 through April 2018 in our medical center. The information that was gathered included: maternal age, results of the nuchal scan, results of the first- and second-trimester biochemical screening, ultrasonographic findings, reasons for conducting a genetic evaluation, gestational age at which termination of pregnancy was carried out, and the type of genetic aberration.

Results 816 women underwent termination of pregnancy at our institution due to genetic aberrations, most of them because of positive biochemical screening ($n=297$, 36%) or because of maternal anxiety ($n=283$, 35%). Findings in chromosomal microarray led to termination of pregnancy in 100 women (100/816, 12%). Chromosomal microarray had been performed due to maternal choice and not because of accepted medical indications among most of the women who underwent termination of pregnancy due to findings on chromosomal microarray (69/100, 69%).

Conclusion Performing chromosomal microarray on a structurally normal fetus and identifying abnormal copy number variants may give the parents enough information for deciding on the further course of the pregnancy.

Keywords Chromosomal aberrations · Chromosomal microarray analysis (CMA) · Single gene mutation · Termination of pregnancy · Trend

Introduction

Both anatomical and genetic fetal abnormalities are among the leading causes of perinatal death and a major contributor to permanent disability and prolonged hospitalization, thus constituting to a major health burden [1, 2]. Improving technologies in the field of prenatal imaging have led to an increase in prenatal detection of fetal malformations, but the most telling advance was probably in novel molecular methods for prenatal genetic diagnosis, such as chromosomal microarray analysis (CMA). CMA provides a powerful tool for detecting chromosomal imbalances in a much higher resolution (up to 1000-fold) than that of conventional karyotyping [3]. Such genomic imbalances are known as copy number variants (CNVs), and they constitute a major cause of congenital malformations and neurodevelopmental disorders. This is the reason that CMA has been recommended since 2013 as the first-line test in the evaluation of fetuses with congenital malformations, with an added detection rate of 5–7% over standard karyotyping [4, 5]. The American Congress of Obstetrics and Gynecology and the Society for Maternal–Fetal Medicine also recommended that it be offered to women who have structurally normal fetuses and who are undergoing diagnostic testing for routine reasons, such as positive aneuploidy screening or maternal anxiety [6, 7]. Other advances in molecular genetics, such as next-generation sequencing, led to new opportunities in single-gene sequencing by enabling the sequencing of a large number of genes and even the sequencing of the whole exome much more rapidly and at a reduced cost. These recent advances and recommendations have led to a deeper understanding of

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the genetic components of the fetus, as well as to changes in the management of pregnancies.

It is widely accepted worldwide that parents can request termination of pregnancy (TOP) when the fetus is diagnosed as having severe structural and genetic abnormalities. Studies in Israel demonstrated that early genetic counseling and early prenatal diagnosis influence the decision about pregnancy termination even among population where abortions are not readily acceptable [8]. In Israel, under the stringent terms specified in the laws governing abortions [9], TOP involving a fetus with genetic aberrations is permitted at any gestational stage as long as approval is given by a specially appointed committee. The local committees are responsible for pregnancies at < 24 weeks of gestation, while regional supreme committees consider a request for termination of pregnancies at > 24 weeks of gestation. Ours is one of the main referral centers for a request for TOP at all stages of pregnancy.

The purpose of our study was to assess the distribution of genetic abnormalities leading to TOP and its fluctuation during the past 8 years. We also aimed to identify the indications leading to genetic queries in those cases in a single high-volume medical center.

Materials and methods

Currently, every pregnant Israeli woman is offered routine first-trimester screening that includes nuchal scan combined with biochemical markers (BhCG + PAPP-A), as well as triple test and second-trimester anomaly scan under mandatory national health insurance. In addition, all women are offered the opportunity to screen for genetic syndromes according to their ethnic origin. They also have the option to undergo noninvasive prenatal screening (cell-free fetal DNA) and early (14–17 weeks' gestation) as well as third trimester (30–32 weeks' gestation) anomaly scanning in the private sector.

Study participants

All compliant women with a singleton pregnancy who underwent TOP because of a genetic aberration(s) in their fetus as the major finding on prenatal invasive testing (chorionic villus sampling or amniocentesis) from January 2010 through April 2018 were recruited into the study. Our medical center is a tertiary referral center for pregnancies in which severe malformation is suspected, and most of the cases were from outside its catchment area. After completion of the genetic assessment and a workup that included genetic consultation, the woman or couple was given the choice to either obtain further information [e.g., additional genetic studies, fetal magnetic resonance imaging (MRI)] or undergo TOP. The woman or couple that opted for TOP was evaluated by a multidisciplinary medical team consisting of a geneticist, an expert in the field of obstetrics and gynecology and a social worker (when required), and the decision of pregnancy termination was then taken by a special committee in accordance with the stipulations of the Israeli law.

Study design

Three different assays were used to detect the genetic aberrations. Chromosomal aberrations greater than 10 megabases (Mb) were detected by standard G-banding karyotype analysis. Submicroscopic aberrations, defined as aberrations below the detection of light microscopy (typically less than 10 Mb), were detected by CMA. Copy number variants (CNVs) were classified as *pathogenic*, *benign*, or *variant of uncertain clinical significance* (VOUS) in accordance with the recommended guidelines from the American College of Medical Genetics, as previously described [10, 11]. Sanger sequencing was used to detect single gene mutations. All the women underwent detailed multidiscipline workup (described by us in a previous publication) [12] and genetic counseling. The woman or couple was then offered the choice of terminating the pregnancy and decisions to do so were evaluated by a special committee in accordance with the national law. TOP was carried out upon the receipt of legal approval.

Methods

In this retrospective study, we reviewed the medical charts in our registry and located all the TOPs that were performed due to genetic aberration throughout the time frame. Further demographic information was obtained from the women's medical records, including maternal age, the results of the nuchal scan, the results of the first and second trimester screens, ultrasonographic findings, reasons for conducting genetic evaluation during the pregnancy, gestational age at which TOP was carried out, and the type of genetic aberration. The study was approved by the ethics committee of the Assaf Harofeh Medical Center (approval 0008-17-ASF). Descriptive parameters are expressed as medians (range) and frequencies are given as percentages. SPSS software (Version 25 Chicago, IL, USA) and GraphPad (version 7, San Diego, CA, USA) were used for the statistical analyses and the presentation of the data.

Results

Between January 2010 and April 2018 (100 months), 816 women underwent TOP due to fetal genetic aberrations at our institution. The median age of these women at the time

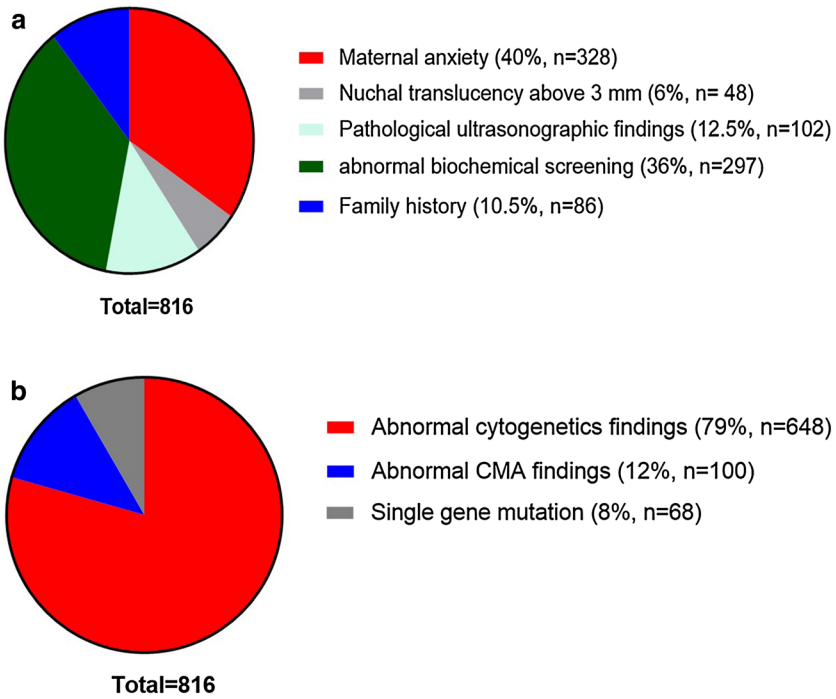

Fig. 1 **a** Distribution of the reasons that led to genetic testing. **b** Distribution of the genetic aberrations that led to the termination of pregnancy. *CMA* chromosomal microarray analysis

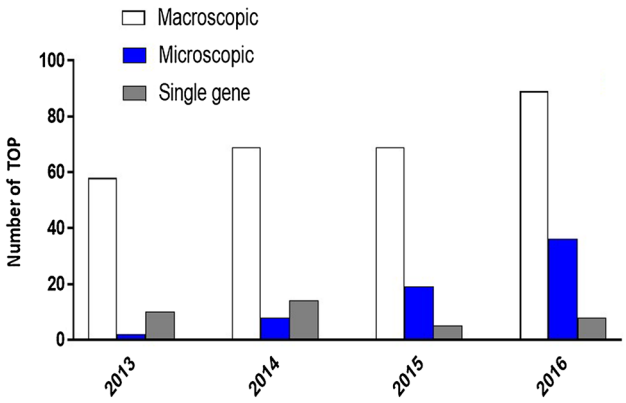

Fig. 2 Distribution of the genetic aberrations that led to the termination of pregnancy (TOP) according to years

of TOP was 36 years (range 20–47). Most women underwent genetic testing either because of positive findings on biochemical screening ($n=297$, 36%) or because of maternal anxiety ($n=283$, 35%) (Fig. 1a). During the entire study period, genetic reasons led to TOP in 816 women in whom findings in CMA led to TOP in 100 of them (100/816, 12%) (Fig. 1b). CMA results were classified by the geneticist as pathogenic in 65 of those 100 (65%), while 30 (30/100, 28%) were classified as likely pathogenic, and the rest (5%) were classified as variable of unknown significance. The number of TOP due to abnormal CNV findings rose from 2 in 2013 (2/70, 2.9% of all TOP) to 36 in 2017 (36/133, 27.1% of all TOP) (Fig. 2). Interestingly, CMA was mainly performed due to maternal anxiety and, to a lesser extent, to ultrasound findings or family history (69/100, 69%) (Fig. 3).

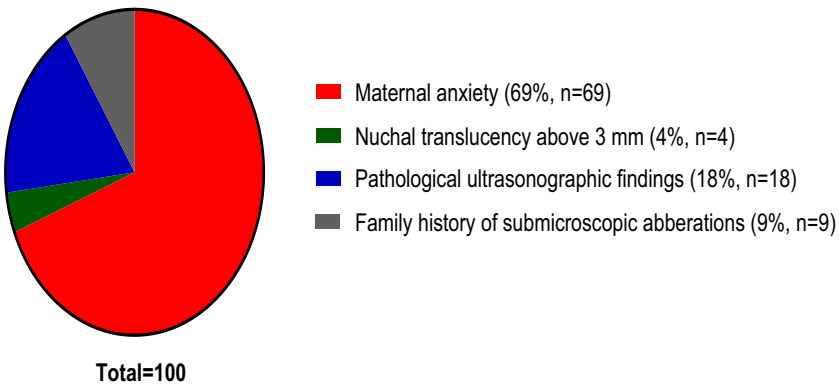

Fig. 3 Distribution of the reasons that led to the women undergoing chromosomal microarray

Discussion

CMA has a significantly higher detection rate of chromosomal aberrations compared to routine karyotyping, and it has been gradually becoming the standard of care for prenatal testing of fetuses with congenital malformations [5, 13]. The use of CMA for prenatal testing in the population of structurally normal fetuses is still a matter of controversy among physicians. The dilemma stems from the fact that the frequency of pathogenic CNVs diagnosed by CMA in structurally normal fetuses has been reported to be around 1%. A recent study in our population reported a 1:131 (0.76%) chance for detecting clinically significant CMA findings in low-risk population [14, 15], enough to lead some authorities to advocate performing CMA for all invasive prenatal diagnostic test (CVS and amniocentesis) regardless of whether or not there is another indication for those procedures [3, 16]. There are, however, some disadvantages in performing CMA when there is a structurally normal fetus, such as an incidental finding of low-penetrance neurosusceptibility loci [17], which could be a source of considerable maternal/couple anxiety. Secondly we must remember that for every low-risk fetus tested, there is around 99% chance for a negative CMA result and that amniocentesis is not a riskless procedure: a recent meta-analysis estimates procedure-related risk of amniocentesis to be 0.1% [18].

Our study presents a new perspective to this dilemma by demonstrating that most women who opted for pregnancy termination as a result of CMA findings had undergone the test on a structurally healthy fetus without any medical indication. We demonstrated not only that CNVs can be detected in this population, but also that once that information is given to the pregnant women, some of them will choose to terminate their pregnancy. As far as we know, this is the first study that provides quantitative data on the consequences of genetic testing that takes into account the wishes of the woman/couple with regard to abnormal CNVs found in a structurally normal fetus.

A potential limitation of our study is the fact that we do not have the total number of women who underwent CMA on structurally normal fetuses nationally during the study period and therefore we cannot extract the exact prevalence of CNVs in that group. In addition, this is a retrospective survey from a single referral center which might introduce some bias.

Conclusion

Our findings lead us to the conclusion that performing CMA on a structurally normal fetus and identifying abnormal CNVs may provide the parents enough information to decide on the further course of the pregnancy.

Author contributions SR: project development, data collection, manuscript writing. PM: data collection, manuscript writing. RU: statistical analysis, manuscript writing. MR: project development, manuscript writing.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent The local IRB committee approved this retrospective study (approval 0008-17-ASF), without requiring informed consent since this is a retrospective study, all the data were gathered using complete anonymity, and it is not applicable to our manuscript.

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