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Importance of Prenatal Diagnosis in Patients with History of Chromosomal Abnormalities

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ABSTRACT The researchers retrospectively evaluated the data of patients who underwent invasive prenatal diagnostic tests with respect to the following risk factors: 1) history of chromosomal abnormality in the family (n=36), 2) history of chromosomal abnormality in a previous pregnancy (n=18), and 3) history of chromosomal abnormality in the parents (n=3) between 2000 and 2017. The diagnostic test results of patients with a history of chromosomal abnormality in the family and those with a history of a chromosomal abnormality in a previous pregnancy were compared. A total of 57 invasive procedures were evaluated. The aneuploidy rates were 41.7 percent and 16.7 percent for patients with a history of chromosomal abnormality in the family and patients with a history of chromosomal abnormality in a previous pregnancy respectively (p = 0.085). Invasive prenatal tests should be recommended to patients at high risk of chromosomal aneuploidy.

INTRODUCTION

Chromosomal aneuploidy screening is a routine part of antenatal care program (ACOG 2001; Spencer et al. 2007). The prenatal diagnosis of chromosomal aneuploidies is crucial since they have a relatively high prevalence in the absence of proper prenatal screening programs (approximately 1/600 for Down syndrome and 1/4000 for trisomy 18), and such diseases create a significant socioeconomic burden on the health-care system (Savva et al. 2010). Furthermore, the availability of prenatal diagnosis gives patients the option to terminate the pregnancy if aneuploidy is present (ACOG 2001; Spencer et al. 2007). Thus, the American College of Obstetricians and Gynecologists recommends that screening tests be performed in all pregnant women before 20 weeks of gestation (ACOG 2001).

Choosing the most appropriate screening test may be challenging for physicians since there are various screening tests with different statistical measures (Palomaki et al. 2013). The combined test, triple test, quadruple test, and noninvasive prenatal test (NIPT) (cell-free fetal DNA in maternal blood) are the main options for prenatal screening (Norton et al. 2015). Socioeconomic factors, health-care policies, medicolegal issues, and personal preferences affect the process of determining the optimal screening test. It is critical that risk analyses be performed individually and patient-centered screening tests be chosen by physicians (Hunter et al. 2005). In addition, appropriate counseling should be provided to all patients based on the screening test results (Kuppermann et al. 2014).

Chorion villus sampling (CVS), amniocentesis (AC), and cordocentesis are the invasive procedures that may be used within the framework of prenatal diagnosis programs (ACOG 2007). There is a risk of pregnancy loss due to the invasive nature of the procedures (Akolekar et al. 2015). Due to the possible risk of fetal loss, NIPT may be offered to patients as a second-line screening test because of its high sensitivity and specificity (Gil et al. 2015).

The cost effectiveness of the screening tests is another important topic (Okem et al. 2017). Using the limited options to achieve optimal results should be the main goal of screening protocols. Thus, using NIPT as a second-line screening test seems to be a cost-effective option (Okem et al. 2017). In contrast, a prenatal diagnosis can be offered directly to women with

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poor obstetrical history (for example, conditions such as chromosomal abnormalities in their previous pregnancies), poor family history (for example, presence of translocations) and other risky conditions (like DNA methylation enzyme pathway disorders) (ACOG 2007; Turgal et al. 2013).

This study aims to demonstrate the importance of prenatal diagnosis in patients with a history of chromosomal abnormality in the family, chromosomal abnormality in a previous pregnancy, and chromosomal abnormality in the parents (for example, deletions, duplications, translocations).

Objectives

The researchers retrospectively evaluated the data of patients who underwent invasive prenatal diagnostic tests with respect to the following risk factors: 1) history of chromosomal abnormality in the family, 2) history of chromosomal abnormality in a previous pregnancy, and 3) history of chromosomal abnormalities in the parents (for example, deletions, duplications, and translocations).

MATERIAL AND METHODS

Between January 2000 and December 2017, the researchers retrospectively evaluated the data of patients who underwent invasive prenatal diagnostic tests due to at least one of the following risk factors: 1) history of chromosomal abnormality in the family (uncle, aunt, cousin), 2) history of chromosomal abnormality in previous gestation, and 3) history of chromosomal abnormality in parents (deletions, duplications, translocations, etc.). The necessary information was withdrawn from the electronic database of the Division of Perinatology, Hacettepe University. Written informed consent was obtained from all participants, and the study protocol was approved by the Hacettepe University Ethics Committee (GO 16/690).

All invasive prenatal diagnostic procedures (CVS, AC, cordocentesis) were performed at Hacettepe University Hospital. A total of 3861 invasive procedures were performed at the researchers' institution between this time period (January 2000 and December 2017). Patients gave written informed consent prior to the invasive procedures. All pregnancies were evaluated by the Department of Genetics within the framework of the prenatal diagnosis program.

CVS was performed transabdominally between the 11th and 14th gestational weeks. After a needle insertion site was chosen based on ultrasound findings, the skin was cleaned with an iodine preparation and draped with sterile towels. An 18-gauge spinal needle was inserted percutaneously through the maternal abdominal wall and the myometrium under ultrasound guidance. The tip was then guided into the long axis of the placenta. The needle stylet was withdrawn and a syringe housed in an aspiration device was connected to the Luer lock of the needle. Chorionic villi were obtained by repeated rapid aspirations of the syringe plunger to 20 mL of negative pressure. The needle was then withdrawn under continuous negative pressure. At least 5 mg of villi is required for a chromosomal analysis, but a sample of 10–25 mg is preferred. The chorionic villi were added to 10 mL of transport media. The sample was extensively cleaned of maternal decidua, and a complete karyotype analysis was performed, followed by a G-banded chromosome analysis. Reflex fluorescent in situ hybridization (FISH) was included in the procedure in special circumstances to confirm certain abnormal chromosome results and/or address specific clinical abnormalities.

AC was performed between the 16th and 20th gestational weeks. After ultrasonographic evaluation, a needle insertion site was chosen. The researchers identified the maternal bowel, bladder, fetus, placenta, and umbilical cord insertion site to minimize the risk of procedure-related complications. Next, the maternal skin was cleaned with an iodine-based solution and sterile drapes were placed around the needle insertion site to maintain an aseptic field. A 20-gauge spinal needle was inserted percutaneously through the maternal abdominal wall and the myometrium under ultrasound guidance. Ultrasonographic monitoring with continuous visualization of the needle was provided during the procedure. The first several milliliters of amniotic fluid, which most likely contain maternal cells, were aspirated into a syringe and discarded, as usual. A total of 20–30 mL of amniotic fluid was aspirated and transported to the laboratory. A

complete karyotype analysis was performed via G-banded chromosome analysis, and reflex testing to FISH was performed as necessary.

Cordocentesis was performed after the 20th week of gestation. An ultrasonographic examination of the fetus was performed to assess fetal viability, placental and umbilical cord location, fetal and placental anomalies, and fetal position before the procedure. A suitable site for the needle insertion was selected. The skin was cleaned with an iodine-based solution and sterile drapes were applied. The placental cord root was the preferred site. On the other hand, free loops of cord and the intrahepatic vein were other options. After the percutaneous insertion of the spinal needle into the fetal blood vessel under direct ultrasound guidance, the necessary amount of blood was aspirated (usually <5 mL). Fetal well-being was evaluated after the procedure with ultrasonography, and the mother and fetus were monitored for at least 1 hour. The fetal cord blood was immediately placed into a tube with sodium/lithium heparin to prevent clotting. The specimen was gently inverted several times to mix the blood and vial contents. Rapid analysis of fetal chromosomes was used to determine fetal amniocyte mosaicism. Standard G-banded karyotyping was performed, and reflex testing to FISH was performed, if necessary.

All women at risk of Rh isoimmunization received 300 ìg of anti-D immune globulin following the invasive procedures. The means and standard deviations of maternal age, gravida, parity, miscarriage, living child, invasive procedure week, percentages of invasive prenatal tests, test results, and pregnancy outcomes (birth, termination of pregnancy, miscarriage, karyotype results) were calculated.

Statistical analyses were conducted by IBM SPSS version 22 software. The collected data are presented as mean and standard deviation for symmetrically distributed data and as median value for nonsymmetrical data. Categorical data are presented as percentages.

RESULTS

A total of 57 procedures that fulfilled the required criteria were included in the study (14 CVS, 42 AC, and one cordocentesis). The mean maternal age was 31.90 ± 4.80 (23–43) years. The mean gravida, parity, number of previous miscarriages, and number of living children for the study patients were 3.70 ± 1.60 (2–9), 1.40 ± 1.20 (0–7), 0.80 ± 0.90 (0–3) and 1.00 ± 0.90 (0–5) respectively. Furthermore, the mean gestational week at which the invasive prenatal test was performed was 15.30 ± 1.90 (12–20) weeks. Table 1 shows the patients' demographic features and clinical characteristics.

CVS was performed in 14 women, 10 of whom (72%) had a family history of aneuploidy, three (21%) had a history of aneuploidy in a previous pregnancy, and one (0.7%) had a history of chromosomal abnormality in parents [45,XX,rob (14;21) (q10;q10) in the mother]. Five miscarriages occurred (35.7%) after the application of CVS procedure (two normal karyotypes, one trisomy 21, one trisomy 13, and one triploidy (69,XXX)). Two patients with a normal karyotype experienced early pregnancy bleeding before the invasive procedure; both had hereditary thrombophilia. Three pregnancies (21.4%) were terminated (two trisomy 21 and one Turner syndrome). Although pregnancy termination was recommended as a result of trisomy 13 in one pregnancy, the parents refused the termination and the newborn died on the first postpartum day. A normal karyotype was reported in the remaining five (35.7%) pregnancies (Table 2).

AC was performed in 42 women; among them, 26 (61.9%) had a family history of aneup-

Table 1: Demographic features and clinical characteristics of the patients

Variables	*Mean*	*Std. deviation*	*Minimum*	*Maximum*
Maternal age	31.90	±4.80	23	43
Gravida	3.70	±1.60	2	9
Parity	1.40	±1.20	0	7
Miscarriage	0.80	±0.90	0	3
Living child	1.00	±0.90	0	5
Invasive procedure week	15.30	±1.90	12	20

Table 2: Invasive procedure methods and obstetric outcomes

Outcomes	*AC (n=42)*	*CVS (n=14)*	*Cordocentesis (n=1)*
Birth	76.1% (32/42)	42.8% (6/14)	0% (0/1)
Termination of pregnancy	21.4% (9/42)	21.4% (3/14)	0% (0/1)
Miscarriage	2.3% (1/42)	35.7% (5/14)	100% (1/1)
Healthy	71.4% (30/42)	35.7% (5/14)	0% (0/1)
Aneuploidy	28.5% (12/42)[a]	50.0% (7/14)[b]	100% (1/1)[c]

[a]6 cases with trisomy 21, 2 cases with trisomy 18, 2 cases with triploidy (69, XXX), 1 case with trisomy 15 and 1 case with mosaism (46,XX/47,XX,+21).
[b]3 cases with trisomy 21, 2 cases with trisomy 13, 1 case with Turner syndrome (45, X) and 1 case with triploidy (69, XXX).
[c]1 case with trisomy 21.

loidy, 15 (35.7%) had a history of aneuploidy in a previous pregnancy, and one (2.4%) had a history of a paternal chromosomal abnormality [45,XY,rob(21;22)(q10,q10)]. One miscarriage (2.4%) occurred after the procedure (trisomy 21). Nine pregnancies were terminated (21.4%) [five trisomy 21, one trisomy 18, one trisomy 15, one mosaicism (46,XX/47,XX,+21), and one triploidy (69,XXX)]. Two parents refused pregnancy termination (one trisomy 18 and one triploidy), and both neonates died in the early postpartum period. The remaining 30 pregnancies (71.40%) reportedly had normal karyotypes.

Cordocentesis was performed in one case owing to parental chromosomal abnormality (balanced translocation), and trisomy 21 was detected. This fetus died in utero at the 22nd gestational week (Table 2).

The researchers also compared the diagnostic test results of patients with a history of chromosomal abnormality in the family and patients with a history of chromosomal abnormalities in previous pregnancies. The aneuploidy rates were 41.7 percent (15/36) and 16.7 percent (3/18) respectively (Table 3). However, the difference did not reach statistical significance (p = 0.085).

Table 3: Aneuploidy rates in patients with history of chromosomal abnormality in the family and patients with history of chromosomal abnormality in previous gestation

Group	*Aneuploidy rate*	*p-value*
History of chromosomal abnormality in the family	41.7% (15/36)	0.085
History of chromosomal abnormality in previous gestation	16.7% (3/18)	

DISCUSSION

The management of patients with increased risk of chromosomal aneuploidy is an integral part of antenatal care programs. Researchers worldwide are constantly working on new screening and diagnostic modalities (Norton et al. 2015; Gil et al. 2015). Physicians must aim to maximize the accuracy of test results while preventing unnecessary interventions and procedure-related complications (Scott et al. 2002). Therefore, an individualized approach for each patient should be provided to optimize obstetric outcomes (Kuppermann et al. 2014).

A definitive diagnosis is necessary for patients at risk of chromosomal aneuploidy (ACOG 2007). Choosing suitable candidates for invasive prenatal testing is another challenge for physicians. Physicians should balance the benefits against the procedure-related complications (Scott et al. 2002). Thus, establishing universal management protocols for patients at high risk of chromosomal aneuploidies are debated worldwide (Dondorp et al. 2015; Tanacan et al. 2016). Most leading organizations, institutions, and experts recommend invasive prenatal testing for high risk patients (ACOG 2001; ACOG 2007; Tabor and Alfirevic 2010). In this study, the aneuploidy rates for CVS, AC, and cordocentesis were 28.5 percent (12/42), 50 percent (7/14), and 100 percent (1/1) respectively. Considering the high rates of aneuploidy in this study, suggesting invasive prenatal tests directly without screening tests seems reasonable for patients with a history of chromosomal abnormality in the family, chromosomal abnormality in a previous pregnancy, or chromosomal abnormality in the parents. The use of screening tests in high-risk

populations (including advanced maternal age) may cause loss of time, money, and work force. The researchers must also remember that dysfunctional interventions may cause significant anxiety in these patients (Kuppermann et al. 2014).

Although the miscarriage rate was 35.7 percent (5/14) in the CVS group and 100 percent (1/1) in the cordocentesis group, 3 of the 5 pregnancies that ended in miscarriages in the CVS group [1 trisomy 21, 1 trisomy 13 and 1 triploidy (69,XXX)] and 1 pregnancy that ended in miscarriage in the cordocentesis group (trisomy 21) were reported to have aneuploidy. One pregnancy that ended in miscarriage in the AC group (1/42, 2.4 %) was also reported to have trisomy-21. Aneuploidy itself seems to be a rationale for fetal loss.

Most patients with an aneuploidic fetus accepted the recommendation of pregnancy termination in our study (3 of 4 patients in the CVS group and 9 of 11 patients in the AC group). The karyotyping results gave these patients the opportunity to know the prognosis of their babies, allowing them to make informed decisions about the course of their pregnancies.

When the prenatal diagnosis results of pregnancies with a history of chromosomal abnormality in the family and pregnancies with a history of chromosomal abnormality in a previous pregnancy were compared, the aneuploidy rate was higher in the former (41.7% vs. 16.7%), but the difference did not reach statistical significance ($p = 0.085$). Although the number of patients in the study was relatively small and the difference did not reach statistical significance, physicians should be more cautious when evaluating pregnancies with a family history of chromosomal abnormalities.

CONCLUSION

In conclusion, invasive prenatal tests should be recommended to patients with pregnancies at high risk of being affected by chromosomal aneuploidy.

RECOMMENDATIONS

According to the researchers' experiences and literature findings, invasive prenatal diagnostic tests should be the first choice for the patients with a family history of chromosomal anomalies.

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