Fetal Sex Discrepancy Between Non-Invasive Prenatal Testing and Ultrasound: A Retrospective Five-Year Study

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RECEIVED November 13, 2023
ACCEPTED April 25, 2024

DOI 10.20471/acc.2026.65.03.16

SUMMARY

The objective of this study was to investigate discordances in fetal sex between non-invasive prenatal testing (NIPT) and ultrasound, including established causes and other clinical findings.

Cases in which both NIPT and a routine mid-trimester fetal ultrasound scan were conducted were reviewed. When a discordance between NIPT and fetal sex reported on ultrasound was observed, further cytogenomic testing was done.

Among 3320 cases in which both NIPT and a second trimester ultrasound scan were conducted (between 2018 and 2022), discordance was reported in 2 cases (0.06%). In the first, NIPT indicated the female sex, while the fetal ultrasound showed male external genitalia and isolated Blake's pouch cyst. Cytogenetic evaluation revealed a mosaic karyotype with six different cell lines with various abnormalities of sex chromosomes. In the second case, ultrasonography was unremarkable with apparently normal female external genitalia, while NIPT indicated the male sex. Karyotype, FISH and aCGH on amniocytes implicated monosomy X.

Considering the disorders of sexual differentiation, it is of great importance to evaluate the concordance between fetal sex reported by NIPT and ultrasound as a part of the routine second trimester genetic sonogram. Establishing an adequate diagnosis in the early prenatal period is a key step of providing precise information to parents. This involves a multi-team approach in tertiary centers.

KEYWORDS

Blake's pouch cyst; Fetal sex; Gonadal dysgenesis; Non-invasive prenatal testing

Introduction

Cell-free fetal DNA (cffDNA) testing is widely used as a method of sex determination and sex chromosome aneuploidy assessment. The results of a meta-analysis by Mackie et al. demonstrated that cffDNA testing has a high sensitivity and specificity for fetal sex determination, with values of 0.989 and 0.996, respectively[1]. A previous meta-analysis by Devaney at al. demonstrated similar results with an overall sensitivity of 95.4% and specificity of 98.6%. Their results also suggested that testing for fetal sex prior to 7 weeks of gestation is unreliable[2].

Sonographic fetal sex determination has a high level of accuracy when performed in the late first or early second trimester. According to a review by Odeh et al., between 11 and 12 weeks of gestation, sonographic sex determination is inaccurate in 30–40% of cases. However, after 13 weeks of gestation, accuracy is close to 100%[3,4]. Corresponding results were found in a review by Colmant et al.; by 13 weeks of gestation, sensitivity was 100% in most studies[5].

Discordance between fetal sex determined by cffDNA testing and the appearance of fetal external genitalia on a prenatal ultrasound has been reported at a rate of 0.05–0.07%, or 1 in 1 500 to 2 000 pregnancies[6,7]. Detecting phenotype-genotype sex discordance imposes the need for the identification of possible underlying causes, enabling adequate counseling, pregnancy management and postnatal care.

Disorders of sexual differentiation represent one possible cause of discrepant findings. Several cases with NIPT indicating the male sex while ultrasound showed a female fetus were described in association with complete androgen insensitivity syndrome, deletion of region 9p24.3p24.1 including DMRT1 causing a partial or complete 46,XY gonadal dysgenesis (MIM 154230), Smith-Lemli-Opitz syndrome, and mosaic Turner syndrome with a cell line containing the SRY region on the Y chromosome[8,9]. On the contrary, cases where the female sex was detected by NIPT and a male fetus revealed on ultrasound were associated with a vanishing twin, congenital adrenal hypoplasia, or sex chromosome translocations involving the SRY region[2,7].

In this retrospective study, we presented the sex-discrepant results between non-invasive cffDNA testing and ultrasonography, and a review of similar cases published in the literature.

Methods

From 2018 to 2022, a total of 3 320 patients attended Clinical Hospital "Sveti Duh" for a fetal ultrasound scan after NIPT. Discordance between fetal sex determined by cffDNA testing and the sonographic appearance of fetal external genitalia was observed in 2 cases (0.06%).

In the first trimester, the evaluation of fetal sex is based upon the "sagittal sign" — the orientation of the genital tubercle in the mid-sagittal plane[9,10]. An angle of the genital tubercle to the horizontal line through the lower spine of > 30˚ indicates the male sex, whereas an angle of < 30˚ indicates the female sex. In the second trimester, fetal sex is determined as part of a genetic sonogram, usually performed between 18 and 24 weeks of gestation. Genetic sonograms were performed as specialized examinations including an evaluation of fetal anatomy. The aim was to detect any presence of major fetal structural abnormalities, as well as minor ("soft") sonographic markers of fetal aneuploidies. A detailed anatomical survey to detect central nervous system, cardiac, gastrointestinal, genitourinary, and other abnormalities was performed. Fetuses were also scanned for the presence of "soft" markers, most importantly a thickened nuchal fold, echogenic bowel, a shortened femur and/or humerus, pyelectasis (renal pelvis dilatation), echogenic intracardiac foci, an absent or hypoplastic nasal bone, and ventriculomegaly[11,12,13].

Fetal sex was assessed based on direct visualization of the scrotum in males, and labia majora and minora in females[14].

When a genotypic-phenotypic discrepancy was suspected, patients were referred for amniocentesis and cytogenetic analysis as part of further diagnostic procedures. Amniotic fluid samples were cultured using the flask method, and three independent cultures were set up for each sample. A classic cytogenetic analysis using G-banding was performed following the European Cytogeneticists Association guidelines and recommendations for the management of suspected mosaicism by Hsu and Benn[15,16]. At least 20 metaphases from three flasks were examined. Fluorescence in situ hybridization (FISH) was performed on cultured amniocytes according to the manufacturer's protocols using commercially available probes: centromere X (DXZ1) and centromere Y (DYZ3), XYpter and XYqter subtelomeric probes (Kreatech FISH probes, Leica Biosystems, Nussloch, Germany), and a probe specific for the SRY locus (Yp11.31) and Yq heterochromatin region (LSI SRY/DYZ1, Cytocell Ltd, Cambridge, UK). Molecular array Comparative Genomic Hybridization (aCGH) was carried out using SurePrint G3 Unrestricted CGH ISCA v2 8x60K microarray (Agilent Technologies, Santa Clara, CA, USA). The microarray slide was scanned with a G4900DA SureScan Microarray Scanner (Agilent Technologies, Santa Clara, CA, USA), and the data were analyzed by Cytogenomics 5.0.2.5 software (Agilent Technologies, Santa Clara, CA, USA).

After the families received genetic counselling, a written informed consent was obtained in both cases. Ethical approval was acquired from the Ethics committee of Clinical Hospital "Sveti Duh".

Results

Case 1

A 32-year-old primigravida who became pregnant after ovulation induction with clomiphene was referred to our hospital at 12 weeks of pregnancy for the evaluation of fetal morphology. Family history

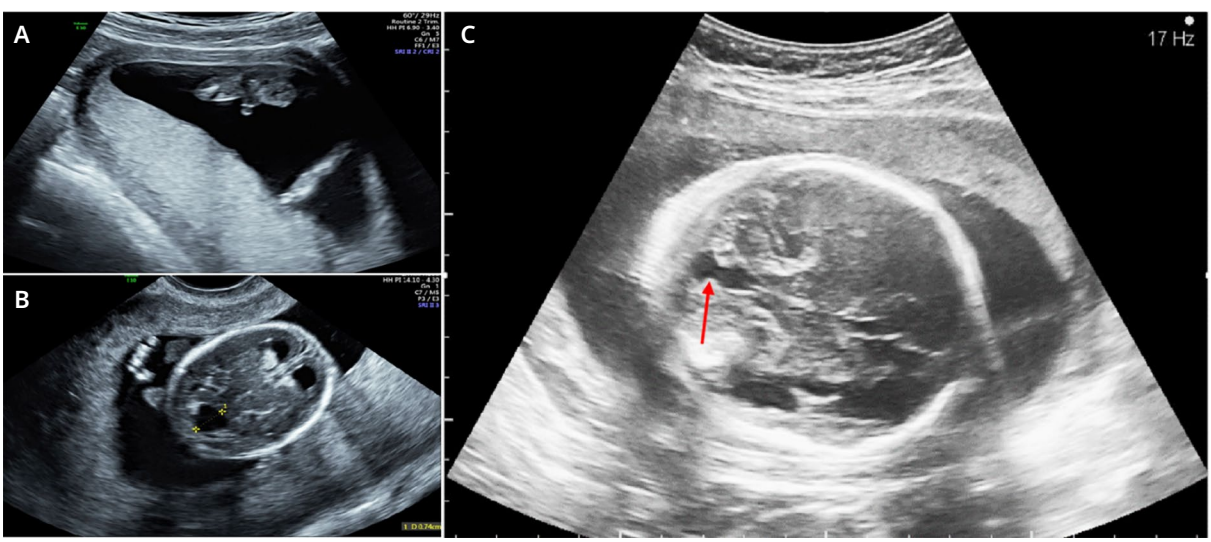


Figure 1. Ultrasound examination in Case 1. (A) Fetal male genitalia; (B) enlarged cisterna magna measured 7.4 mm at 15 weeks of gestation; (arrow, C) suspected Blake's pouch cyst at 18 weeks of gestation with the typical "key hole" sign.

was uneventful. Fetal morphology appeared normal except the impression of an "enlarged cisterna magna". Non-invasive prenatal testing revealed a low risk for common aneuploidies and the presence of 2 X chromosomes indicating a female fetus. An ultrasound examination at 15 weeks of gestation revealed a male fetus (Figure 1A) and an "enlarged cisterna magna" measuring 7.4 mm (Figure 1B). At 18 weeks, ultrasonography showed an expansion of the fourth ventricle into the cisterna magna resulting in a "key hole" sign in the transverse cerebellar view, typical of an isolated Blake's pouch cyst (BPC) (Figure 1C). Other intracranial and echocardiographic findings were normal. A repeated NIPT was concordant with the first result. Amniocentesis was performed at 19 + 5 gestational weeks. Cytogenetic and FISH analyses of the cultured amniocytes revealed a complex mosaicism including five cell lines with various abnormalities of sex chromosomes. In 39% of the analyzed metaphases, a 45,X karyotype was obtained, while in 28.7% an isodicentric Yp (idic(Y)(q11.2) was found (Figure 2A-2C). In 18% of the cells, a structurally normal Y chromosome was found, while in 7.4% a 47,XYY karyotype was revealed. A cell line containing 2 idic(Yp) chromosomes was obtained in 6.4% of the cells (Figure 2D-2F). A variant paternal pericentric inversion of chromosome 9 was found in all analyzed metaphases. After genetic counselling, the parents opted for a termination of pregnancy. The fetal autopsy showed a normal finding of all organ systems and of the posterior cranial fossa. Male sex and normal testicles were confirmed.

Case 2

A 43-year-old G2P1, who conceived after oocyte donation, was referred to our hospital at 24 weeks of gestation. Family history and the obstetric course were uneventful. At 12 weeks of gestation, NIPT was performed, revealing a low risk for common trisomies and indicating a male fetus. Fetal 3D ultrasonography showed female external genitalia.

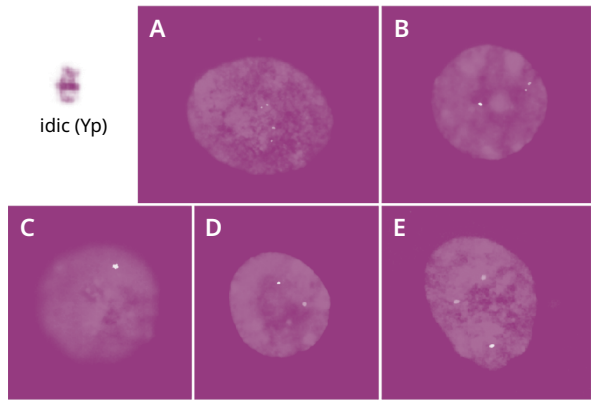


Figure 2. (A) Partial karyotype of the fetus in Case 1 showing isodicentric Yp. (B) Interphase FISH results using probes LSI SRY (Texas Red); (C-F) and CEP X (DXZ1) Spectrum Green / CEP Y (DYZ3) Spectrum Orange: (B) a cell with 2 isodicentric Yp chromosomes; (C) one isodicentric Yp and one normal X chromosome; (D) monosomy X; (E) one normal Y chromosome and one normal X chromosome; and (F) 2 normal Y chromosomes and one normal X chromosome.

The remaining fetal ultrasonography was unremarkable, and echocardiography revealed no cardiac defects. A repeated NIPT was consistent with the initial finding. Amniocentesis was performed at 27 weeks of gestation, and a cytogenetic analysis showed a 45,X karyotype in all analyzed metaphases. A FISH analysis of cultured amniocytes revealed one signal for centromere Y in 2 out of 400 analyzed interphase nuclei, which was declared as a method artefact (Table 1). Array CGH results were also concordant with a 45,X karyotype. After genetic counselling, the parents decided to continue the pregnancy. A female newborn weighing 3010 grams, 49 centimetres long, with Apgar scores of 8 and 10 was vaginally delivered at 39 weeks of gestation. The postnatal presentation demonstrated slight hypotelorism, low-set ears, low posterior hairline and widely-spaced nipples, while the rest of the female phenotype was normal. In order to explain the NIPT results, placental tissue samples were collected at term. Both short-term cytotrophoblast and

Table 1. Distribution of 45,X and 46,XY cell lineages detected by cytogenetic and FISH analyses, performed on placental tissue samples and amniocytes collected after birth in Case 2.

	Cytogenetic analysis		FISH analysis	
	45,X	46,XY	45,X	46,XY
	No. of cells (%)			
Amniotic fluid culture	62 (100)	0 (0)	398 (99.5)	2 (0.5)
STC	6 (22.2)	21 (77.8)	9 (4.5)	193 (95.5)
LTC	24 (82.8)	5 (17.2)	150 (74.6)	51 (25.4)

STC = short-term cytotrophoblast culture; LTC = long-term mesenchymal stroma culture

long-term mesenchymal stroma cultures showed a mosaic karyotype with a different percentage of 45,X and 46,XY cell lines (Table 1).

Discussion

Disorders of sexual differentiation are among the known causes of discordance between fetal sex determined by non-invasive cffDNA testing and ultrasonography. This case study showed that the frequency of discrepancy between fetal sex determined by NIPT and described on ultrasound was 0.06% (2/3320). Our results are in concordance with the previously estimated incidence of about 1 in 1 500–2 000 pregnancies. Also, a common cause of genotype-phenotype discordance is the phenomenon of a vanishing twin. It is, therefore, of great importance to establish the presence of a demised twin prior to NIPT.

Richardson et al.[7] described a case where NIPT indicated the female sex and an ultrasound showed external male genitalia. Array CGH, cytogenetic and FISH analyses revealed an isodicentric Y chromosome, present in 90% of native and 30% of cultivated amniotic fluid cells. Flori et al.[17] reported the case of a pregnant woman, a carrier of hemophilia A, who underwent a non-invasive determination of fetal sex at 13 weeks of pregnancy. Maternal serum was negative for SRY, indicating the fetus was probably female. Chorionic villous sampling showed a 45,X karyotype in direct culture, whereas long-term culture revealed a mosaic form with one cell line showing monosomy X, and the second with an isodicentric Yp (idic(Yp)). The autopsy examination revealed male genitalia. Fetal blood culture showed a more complex karyotype consisting of up to six cell lines. Cytogenetic analysis after amniocentesis in our first case also showed a mosaic karyotype consisting of six different cell lines. The possibility of detecting several different cell lines involving abnormal sex chromosomes is limited by the availability to analyze different cell sources in the prenatal period, their possible presence in kryptic mosaic form, and a dicentric instability during cell division. This is why they are rarely reported. A significant fraction of cells with a present Yp region containing SRY is the most probable cause of the ultrasonographic appearance of external male genitalia in our first case. Xu et al.[18] have suggested that a proportion of idic(Yp) higher than 20% in amniocytes correlated with fetal external male genitalia. This is in accordance with the findings in our first case, but also in the abovementioned published cases[7,17]. The presence of sex chromosome translocations involving the

segment of the short arm of the Y chromosome, including the SRY region, is another possible cause of the male appearance of fetal genitalia.

The common cause of female to male genotype-phenotype discrepancy is congenital adrenal hyperplasia (CAH); an autosomal, recessive, 46,XX disorder of sexual development, which involves a deficiency of enzymes in the adrenal steroidogenesis — most commonly 21-hydroxylase — leading to cortisol deficiency, increased ACTH secretion, a build-up of cortisol precursors, and a consequent increase of androgen production. Virilization of the female genitalia may cause an ambiguous or male appearance of the external genitalia, resulting in a phenotype-genotype sex discordance. A retrospective, observational study of cases with a discordance between NIPT and observed fetal sex reported one case of congenital adrenal hyperplasia among four cases for which the diagnosis of a 46,XX disorder of sexual development was confirmed. A cffDNA test indicated the female sex, whereas an ultrasound reported male external genitalia. A normal female karyotype was confirmed by amniocentesis. Both parents were carriers for 21-hydroxylase deficiency and subsequent amniocentesis confirmed congenital adrenal hyperplasia in the fetus[6].

Richardson et al.[7] also reported a prenatal case with NIPT performed because of an increased nuchal translucency of 3.2 mm showing a low risk of common aneuploidies and indicating a male fetus (Panorama). Ultrasonography, however, showed external female genitalia. A FISH analysis on native amniotic fluid cells showed only one cepX in 91% of the cells and the presence of an additional SRY signal in the remaining 9%. Array CGH was concordant with monosomy X. Srebniak et al.[19] reported a case were NIPT indicated a female fetus with a high risk of Turner syndrome. At 12 weeks of pregnancy, fetal genitalia appeared to be male. An SNP array analysis of cytotrophoblastic cells showed monosomy X, which was in accordance with NIPT results. An analysis of the mesenchymal core showed a mosaic karyotype with 2 cell lines: dominant with idic(Yp) and 7% of cells with 45,X. The array performed from uncultured amniotic fluid cells was suggestive of 100% cells with idic(Yp). In our second case, the cause of an NIPT indicative of male sex was a dominant 46,XY cell line in the syncytiotrophoblast, suggesting fetoplacental mosaicism. The inability to detect the 46,XY cell line in amniotic fluid culture can theoretically be caused by an unequal distribution of cells in the early embryonic period, or cryptic mosaicism in other tissues. Based on the data from mouse aggregation chimera studies, Wolstenholme[20] hypothesized that at a stage of 32–64 cells, only a few progenitor cells possibly become unevenly compartmentalized into the inner cell mass.

Blake's pouch cyst is an anomaly of the posterior cranial fossa mainly diagnosed in the early second trimester of pregnancy. In our first case, the ultrasound finding of the posterior fossa in the first trimester was described as an "enlarged cisterna magna", but the diagnosis of BPC was made at 18 weeks of gestation, showing a typical "key hole" sign on the axial plane. Due to the position of the fetus, it was not possible to obtain an appropriate mid-sagittal plane and fulfil all the recommended ultrasound criteria for the diagnosis of BPC[21,22]. The autopsy showed no existence of BPC. The lack of confirmation of a BPC at fetal autopsy can be explained by the fact that the cyst can deflate post-mortem and the vermis rotates back into normal position[22]. An isolated BPC is generally a benign condition and is rarely associated with chromosomopathies or an impaired neurodevelopmental outcome[23,24]. There are only a few published cases of antenatal detection of an isolated Blake's pouch cyst associated with fetal chromosomal abnormality. For example, one retrospective study described 1 case of fetal mosaic trisomy 22 and 2 cases of trisomy 21 among 19 BPC cases[25]. Our first case is the first reported prenatal case of mixed gonadal dysgenesis associated with an isolated BPC.

There are several other causes of male to female genotype-phenotype discordances. Androgen insensitivity syndrome (AIS) is an X-linked, 46,XY

disorder of sexual development, caused by a mutation of the androgen receptor gene in the Xq12 region, which results in an insensitivity to androgens in the target tissues. The lack of androgen exposure causes phenotype-genotype sex discordance, resulting in genotypic male fetuses exhibiting female external genitalia. In a study conducted by Dhamankar et al., AIS was confirmed in 7 cases of fetal genotype-phenotype sex discordance, either by prenatal or postnatal genetic testing[6]. Zilberman et al. and Richardson et al. also presented cases of prenatal diagnoses of AIS after a discrepancy between cffDNA testing and sonographic external genitalia appearance[7,8]. Another cause is 5-alpha reductase deficiency; an autosomal recessive condition in which the SRD5A2 gene is mutated. As 5-alpha reductase catalyzes the transformation of testosterone to 5α-dihydrotestosterone (DHT) — which is crucial for sexual differentiation in the external genitalia of male fetuses — its deficiency causes various degrees of external genitalia deformation in male fetuses, also resulting in genotype-phenotype sex discordance.

Another autosomal recessive condition causing genotype-phenotype sex discordance is Smith-Lemli-Opitz (SLO) syndrome. It is caused by a homozygote or compound heterozygote mutation in the DHCR7 gene, resulting in cholesterol biosynthesis impairment. Low cholesterol levels lead to abnormal central nervous system development and reduced testosterone production. The syndrome encompasses multiple anomalies, including ambiguous genitalia in male fetuses. Dhamankar et al. reported a case of NIPT and ultrasound sex discordance, where NIPT indicated the male sex, whereas ultrasonography showed female/ambiguous external genitalia, which was later confirmed to be SLO syndrome[6].

About 50% of patients with Turner syndrome exhibit the 45,X karyotype. However, mosaicism for X chromosome monosomy including another cell line with a normal male or female karyotype is not unusual, and can result in a variety of phenotypic presentations, ranging from male to female. In such cases, cryptic mosaicism cannot be detected by classical cytogenetics. Non-invasive perinatal testing might indicate the 46,XY genotype, while female external genitalia are visualized on ultrasound, based on the higher sensitivity of detection of low level mosaicisms. Dhamankar et al. reported 6 such cases for which the diagnosis of monosomy X or mosaic Turner syndrome was confirmed. Prenatal or postnatal karyotyping confirmed the presence of a 46,XY or 47,XYY cell line in addition to the 45,X cell line, and in 2 cases in which placental testing was requested, the results showed a 46,XY genotype consistent with NIPT[6].

Conclusion

Our report and previously published data emphasize the importance of evaluating the concordance between fetal sex reported by NIPT and the ultrasound evaluation of fetal sex as a part of routine obstetric prenatal care. The prevalence of discordant results is highly impacted by the quality of prenatal sonographic sex determination, and is likely underestimated in available data. The proportion of patients diagnosed with disorders of sexual differentiation later in life supports this assumption. Knowledge of potential etiologies, most of which are described in this study, is a prerequisite for further evaluation and adequate counseling. A multi-disciplinary approach, including an experienced sonographer/fetal medicine specialist, the availability of invasive prenatal testing, cytogenetic testing, and genetic counseling, ensures optimal prenatal evaluation and appropriate pregnancy management. ■

References

1. Mackie FL, Hemming K, Allen S, Morris RK, Kilby MD. The accuracy of cell-free fetal DNA-based non-invasive prenatal testing in singleton pregnancies: a systematic review and bivariate meta-analysis. BJOG. 2017 Jan;124(1):32-46. doi: 10.1111/1471-0528.14050. Epub 2016 May 31. PMID: 27245374.
2. Devaney SA, Palomaki GE, Scott JA, Bianchi DW. Noninvasive fetal sex determination using cell-free fetal DNA: a systematic review and meta-analysis. JAMA. 2011 Aug 10;306(6):627-36. doi: 10.1001/jama.2011.1114. PMID: 21828326; PMCID: PMC4526182.
3. Odeh M, Granin V, Kais M, Ophir E, Bornstein J. Sonographic fetal sex determination. Obstet Gynecol Surv. 2009 Jan;64(1):50-7. doi: 10.1097/OGX.0b013e318193299b. PMID: 19099612.
4. Kearin M, Pollard K, Garbett I. Accuracy of sonographic fetal gender determination: predictions made by sonographers during routine obstetric ultrasound scans. Australas J Ultrasound Med. 2014 Aug;17(3):125-30. doi: 10.1002/j.2205-0140.2014.tb00028.x. Epub 2015 Dec 31. PMID: 28191222; PMCID: PMC5024945.
5. Colmant C, Morin-Surroca M, Fuchs F, Fernandez H, Senat MV. Non-invasive prenatal testing for fetal sex determination: is ultrasound still relevant? Eur J Obstet Gynecol Reprod Biol. 2013 Dec;171(2):197-204. doi: 10.1016/j.ejogrb.2013.09.005. Epub 2013 Sep 11. PMID: 24094458.
6. Dhamankar R, DiNonno W, Martin KA, Demko ZP, Gomez-Lobo V. Fetal Sex Results of Noninvasive Prenatal Testing and Differences With Ultrasonography. Obstet Gynecol. 2020 May;135(5):1198-206. doi: 10.1097/AOG.0000000000003791. PMID: 32282607; PMCID: PMC7170435.
7. Richardson EJ, Scott FP, McLennan AC. Sex discordance identification following non-invasive prenatal testing. Prenat Diagn. 2017 Dec;37(13):1298-304. doi: 10.1002/pd.5184. PMID: 29131362.
8. Zilberman D, Parikh LI, Skinner M, Landy HJ. Prenatal diagnosis of androgen insensitivity syndrome using cell-free fetal DNA testing. Ultrasound Obstet Gynecol. 2015 Jan;45(1):114-5. doi: 10.1002/uog.14681. Epub 2014 Dec 4. PMID: 25291542.
9. Salomon LJ, Alfirevic Z, Bilardo CM, Chalouhi GE, Ghi T, Kagan KO, et al. ISUOG practice guidelines: performance of first-trimester fetal ultrasound scan. Ultrasound Obstet Gynecol. 2013 Jan;41(1):102-13. doi: 10.1002/uog.12342. Erratum in: Ultrasound Obstet Gynecol. 2013 Feb;41(2):240. PMID: 23280739.
10. Norton ME, Millar Scoutt L, Feldstein VA, Callen PW, Elsevier (Amsterdam). Callen›s Ultrasonography in Obstetrics and Gynecology. 6th ed. Philadelphia: Elsevier; 2017.
11. Benacerraf BR. The role of the second trimester genetic sonogram in screening for fetal Down syndrome. Semin Perinatol. 2005 Dec;29(6):386-94. doi: 10.1053/j.semperi.2005.12.003.
12. Odibo AO, Ghidini A. Role of the second-trimester ‹genetic sonogram› for Down syndrome screen in the era of first-trimester screening and non-invasive prenatal testing. Prenat Diagn. 2014 Jun;34(6):511-7. doi: 10.1002/pd.4329.
13. Benn KN, Benn P, Campbell WA, Moaddab A, Shamshirsaz AA. Genetic sonogram: components and role in the era of prenatal screening. Fetal Matern Med Rev. 2014;25(3-4):214-31. doi:10.1017/S096553951500008X
14. Smet ME, Scott FP, McLennan AC. Discordant fetal sex on NIPT and ultrasound. Prenat Diagn. 2020 Oct;40(11):1353-65. doi: 10.1002/pd.5676. Epub 2020 Aug 17. PMID: 32125721.
15. Hastings R, Howell R, Bricarelli FD, Kristoffersson U, Cavani S. General Guidelines and Quality Assurance for Cytogenetics. E.C.A. – European Cytogeneticists Association Newsletter 2012;29. Available from: http://www.e-c-a.eu/EN/GUIDELINES.html. Accessed: April 15, 2014.
16. Hsu LY, Benn PA. Revised guidelines for the diagnosis of mosaicism in amniocytes. Prenat Diagn. 1999 Nov;19(11):1081-2. PMID: 10589067.
17. Flori E, Doray B, Gautier E, Kohler M, Ernault P, Flori J, et al. Circulating cell-free fetal DNA in maternal serum appears to originate from cyto- and syncytio-trophoblastic cells. Case report. Hum Reprod. 2004 Mar;19(3):723-4. doi: 10.1093/humrep/deh117. Epub 2004 Jan 29. PMID: 14998976.
18. Xu J, Siu VM. Is there a correlation between the proportion of cells with isodicentric Yp at amniocentesis and phenotypic sex? Prenat Diagn. 2010 Sep;30(9):839-44. doi: 10.1002/pd.2565. PMID: 20658696.
19. Srebniak MI, Diderich KE, Noomen P, Dijkman A, de Vries FA, van Opstal D. Abnormal non-invasive prenatal test results concordant with karyotype

of cytotrophoblast but not reflecting abnormal fetal karyotype. Ultrasound Obstet Gynecol. 2014 Jul;44(1):109-11. doi: 10.1002/uog.13334. Epub 2014 Jun 1. PMID: 24585494.
20. Wolstenholme J. Confined placental mosaicism for trisomies 2, 3, 7, 8, 9, 16, and 22: their incidence, likely origins, and mechanisms for cell lineage compartmentalization. Prenat Diagn. 1996 Jun;16(6):511-24. doi: 10.1002/(SICI)1097-0223(199606)16:6<511::AID-PD904>3.0.CO;2-8. PMID: 8809892.
21. Paladini D, Quarantelli M, Pastore G, Sorrentino M, Sglavo G, Nappi C. Abnormal or delayed development of the posterior membranous area of the brain: anatomy, ultrasound diagnosis, natural history and outcome of Blake›s pouch cyst in the fetus. Ultrasound Obstet Gynecol. 2012 Mar;39(3):279-87. doi: 10.1002/uog.10138. PMID: 22081472.
22. Volpe P, Contro E, De Musso F, Ghi T, Farina A, Tempesta A, et al. Brainstem-vermis and brainstem-tentorium angles allow accurate categorization of fetal upward rotation of cerebellar vermis. Ultrasound Obstet Gynecol. 2012 Jun;39(6):632-5. doi: 10.1002/uog.11101. Epub 2012 May 14. PMID: 22253138.
23. Gandolfi Colleoni G, Contro E, Carletti A, Ghi T, Campobasso G, Rembouskos G, et al. Prenatal diagnosis and outcome of fetal posterior fossa fluid collections. Ultrasound Obstet Gynecol. 2012 Jun;39(6):625-31. doi: 10.1002/uog.11071. Epub 2012 May 14. PMID: 22173885.
24. D'Antonio F, Khalil A, Garel C, Pilu G, Rizzo G, Lerman-Sagie T, at al. Systematic review and meta-analysis of isolated posterior fossa malformations on prenatal ultrasound imaging (part 1): nomenclature, diagnostic accuracy and associated anomalies. Ultrasound Obstet Gynecol. 2016 Jun;47(6):690-7. doi: 10.1002/uog.14900. Epub 2016 May 10. PMID: 25970099.
25. Gholkar N, Singh C, Kaul A. Antenatal detection of mosaic trisomy 22 with a finding of Blake's pouch cyst. J Fetal Med 2018;5:53-57. doi: 10.1007/s40556-017-0144-0.

SAŽETAK

Nepodudarnost spola fetusa između neinvazivnog prenatalnog testiranja (NIPT) i ultrazvučnog pregleda: retrospektivna petogodišnja analiza

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Cilj ove studije bio je istražiti slučajeve u kojima postoji nepodudarnost između spola fetusa utvrđenog neinvazivnim prenatalnim testom (NIPT) i onog utvrđenog ultrazvukom, poznate uzroke navedene nepodudarnosti i dodatne kliničke nalaze.

Pregledani su slučajevi u kojima su rađeni i NIPT i rutinski ultrazvučni pregled drugog tromjesečja. Ako bi se utvrdila nepodudarnost spola fetusa, radila se daljnja citogenetska dijagnostika.

Od 3320 slučajeva u kojima su rađeni i NIPT i ultrazvučni pregled drugog tromjesečja (između 2018. i 2022.) nepodudarnost je zabilježena u dva slučaja (0,06 %). U prvom slučaju, NIPT je pokazao ženski spol dok su ultrazvučno prikazani muški vanjski spolni organi i izolirana cista Blakeove vrećice. Citogenetskom analizom dobiven je mozaični kariotip sa šest različitih staničnih linija raznolikih abnormalnosti spolnih kromosoma. U drugom slučaju, ultrazvučni nalaz bio je neupadljiv uz dojam urednih ženskih vanjskih spolnih organa dok je NIPT pokazao muški spol. Kariotip, FISH i aCGH analiza kulture amniocita pokazali su monosomiju X.

Imajući na umu poremećaje spolne diferencijacije, od iznimne je važnosti potvrditi podudarnost fetalnog spola nađenog NIPT-om s onim prikazanim ultrazvučno u sklopu genetskog sonograma drugog tromjesečja. Postavljanje ispravne dijagnoze u ranom prenatalnom periodu ključni je korak u adekvatnom informiranju roditelja, a moguće je uz multidisciplinarni pristup u tercijarnim centrima.

KLJUČNE RIJEČI

Cista Blakeove vrećice; Spol fetusa; Gonadalna disgeneza; Neinvazivni prenatalni test