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SPECIAL ARTICLE

Confounding Factors in Noninvasive Prenatal Testing under Common Benign Gynecologic Conditions

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ABSTRACT

Noninvasive prenatal testing (NIPT) is increasing in use in obstetric practice worldwide, including in Thailand. While the efficacy of NIPT for prenatal aneuploidy detection is accepted, there are some pathologic conditions that can interfere with the NIPT result, such as maternal autoimmune disease or malignancies. Interestingly, some common benign gynecologic conditions, including uterine myoma, endometriosis, and mature ovarian cystic teratoma, have been reported to be confounding effects of maternal cell-free dexoxy ribonucleic acid (DNA) on the NIPT result.

Keywords: noninvasive prenatal testing (NIPT), cell-free DNA (cf-DNA).

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Noninvasive prenatal test

Noninvasive prenatal testing (NIPT) is a modern modality to prenatally screen fetal chromosomal abnormalities. It has been widely implemented in obstetric practice due to its high accuracy and proven clinical validity[1]. NIPT offers intermediate efficiency for prenatal aneuploidy detection, lying between biochemistry serum screening and invasive prenatal diagnostic testing[2]. In Thailand, a previous recent study reported that 91.1% of pregnant women agreed to participate in Down syndrome screening[3]. NIPT can be applied to analyze the fetal aneuploidy risk from fetal cell-free dexoxy ribonucleic acid (cf-DNA) fragments circulating in the maternal blood. Such fetal cf-DNA is derived from apoptotic cytotrophoblasts and it remains in maternal circulation for a few days after delivery[4]. After maternal blood sample collection, the cf-DNA can be extracted and processed for DNA sequencing using shotgun massively parallel sequencing (MPS). Then the sequencing data can be analyzed and compared with a sample obtained from the maternal euploid fetus. An under-presentation or over-presentation of calculated Z-scores is reported as a suspected indication of the fetus being affected by monosomy or trisomy, respectively. However, non-reportable results are shown in some situations. A possible cause of a non-reportable NIPT result is an

insufficient fetal fraction, which may be caused by too early gestation or the effect of a large maternal weight[5]. Besides an insufficient fetal fraction, cf-DNA originating from maternal apoptotic white blood cells and maternal neoplastic cells can be represented in the NIPT result and therefore can interfere in the NIPT analysis[6]. Both epithelium and germ cell malignant ovarian neoplasm have been reported to result in false-positive or non-reportable results for NIPT[7-8]. Moreover, non-gynecologic malignancy, such as gastric cancer, has been also identified during NIPT[8].

Detection of circulating cf-DNA in common cenign gynecologic neoplasm

Uterine leiomyoma, endometriosis, and mature ovarian cystic teratoma are common benign gynecologic diseases. The prevalence of uterine leiomyoma during pregnancy has been reported to be approximately 1.6% to 10.7%, depending on the trimester and method of assessment[9]. Usually, uterine leiomyomas are asymptomatic during pregnancy[10]. Endometriosis is a chronic gynecologic disorder, with a prevalence in all reproductive-age women of around 1% - 2%, who commonly present with infertility, dysmenorrhea, chronic pelvic pain, and dyspareunia[11]. Although infertility is associated with endometriosis, pregnancy can still successfully occur after treatment. Mature ovarian cystic teratoma is usually benign and asymptomatic during pregnancy. The incidence of complicated mature ovarian cystic teratoma during pregnancy, such as torsion, is approximately 15% and it occurs more frequently at 10-17 weeks' gestation[12]. A finding of circulating cf-DNA arising from uterine leiomyoma, endometriosis, and mature ovarian cystic teratoma has been previously reported[6, 13–15]. Circulating cf-DNA originating from maternal cells is called maternal cf-DNA. Analyzed cf-DNA in NIPT has been found to be a mixture of maternal and fetal cf-DNA. Thus, chromosomal copy-number alteration (CNA) of a maternal origin can lead to the NIPT calculated Z-score to show an under-presentation or over-presentation[15].

Confounding factors in NIPT by common benign gynecologic diseases

Non-reportable NIPT is documented when a questionable Z-score is observed. There are several observed Z-score characteristics of NIPT in pregnant women affected by common benign gynecologic diseases, such as[15]:

1. A highly negative Z-score of an autosome, indicating an under-presentation of the Z-scores and suggesting a suspected autosomal chromosome. Most embryos/fetuses with autosomal monosomy or sex chromosomes (lack of one member of a chromosome pair) are not viable. Only some individuals with monosomy of the sex chromosomes (45XO, Turner's syndrome) or partial autosomal monosomy can survive [16].

2. The observation of multiple chromosomal and/or subchromosomal region abnormalities[13], such as abnormal Z-scores for both chromosomes 21 and 18. It is rare for a single fetus to survive with multiple trisomies, especially at an advanced gestational age.

3. The combination indicates an increase (over-presentation) for some genomic regions and a reduction (under-presentation) for others[15].

Clinical suggestions when a confounding NIPT result by common benign gynecologic diseases is suspected

Until now, the clinical importance of a confounding NIPT result by common gynecologic conditions is still controversial. The prevalence of non-reportable NIPT in pregnancy with the presence of uterine myoma has been reported to be approximately 3.75 cases per 100,000 pregnancies[15]. The reasons for the low prevalence can be hypothesized as follows: [i] Only 7 in 13 (54%) leiomyoma hysterectomy or myomectomy specimens

have a clonal chromosome rearrangement detected. The most common chromosomal aberrations in uterine myomas are translocation, which means they should not interfere with the calculated Z-score in the NIPT process[17]; [ii] maternal cf-DNA from a small size tumor with low blood supply is low enough to detect in the NIPT process[15]. Moreover, data on chromosomal aberrations in endometriosis and mature ovarian cystic teratoma are limited. There are few case reports that have found confounding cf-DNA in maternal blood[11-12]. However, the significance of the data remains limited and needs further investigation.

Conclusion

In conclusion, NIPT in pregnancy with benign gynecologic diseases, including uterine myoma, endometriosis, and mature ovarian cystic teratoma, still offers more benefits than the risk of non-reportable results. However, proper pre-test counseling about the non-reportable results should be provided. In contrast, if a non-reportable result is shown in NIPT, the obstetrician should carefully evaluate the causes of the non-reportable result, including the Z-score characteristic, which may be influenced by a maternal confounding cf-DNA arising from common benign gynecologic diseases. Detailed ultrasonographic scanning as part of a pelvic organ survey should be performed and a prenatal diagnostic procedure, such as amniocentesis, may be indicated. Finally, further study is warranted with an adequate sample size to reveal the incidence of confounding cf-DNA from maternal common benign gynecologic diseases.

Potential conflicts of interest

The author declares no conflicts of interest.

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