

2 Prenatal detection of disorders of sexual development via NIPT and ultrasound sex discordance

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1. Introduction

Disorders of sexual development, or differences of sexual development, (DSDs) are a group of conditions with an estimated incidence of 1 in 4,500-5,500 newborns. The incidence is even higher when including congenital anomalies of the genitalia (e.g. hypospadias)¹. With the rise of non-invasive prenatal testing (NIPT), which can predict the fetal sex chromosome complement, discrepancies between fetal genitalia by ultrasound and predicted fetal sex can be identified earlier in pregnancy. This study reviews a case series from an NIPT laboratory illustrating the identification of DSDs by discordance between ultrasound phenotype and NIPT prediction of fetal sex.

2. Methods

A retrospective review of the clinical outcome database at one commercial NIPT lab was performed, searching for terms related to DSDs, as seen in **Table 1**. Cases and related documentation were reviewed, and cases of a confirmed or strongly suspected DSD with complete outcome information were included. Cases in which a DSD was suspected but had sparse clinical follow-up details were excluded.

3. Results

Figure 1 shows a summary of details for each case. Of note, cases 3 and 5 had relevant family history; in both, a maternal aunt (to the fetus) had a known diagnosis of AIS.

4. Conclusions

Discordances between predicted fetal sex by NIPT and ultrasound phenotype may provide an important clue to an underlying genetic disorder, including DSDs. DSDs are only one potential cause of fetal sex discordance between NIPT and ultrasound. Other explanations include co-twin demise, sample swap or other lab process error, error in cfDNA result interpretation, limitations of ultrasound classification of fetal genitalia, or maternal conditions such as sex chromosome abnormality or transplant.

Most patients who submitted a cfDNA redraw in this series had consistent maternal spikes (identifiers) between samples, which lessens the likelihood of sample mishandling. At current, there are no guidelines for when or how to evaluate for potential DSDs in a pregnancy. Lassey et al propose differential diagnoses for cases of NIPT and ultrasound fetal sex discordance and suggest a clinical algorithm for working up such cases.² Further evaluation may be warranted when other potential causes for fetal sex discordance are reasonably excluded. Collaboration between the ordering provider and the NIPT laboratory is essential in this process.

Despite two cases presented here with family history of a DSD, all cases were initially brought to clinical attention due to the sex discrepancy between NIPT and ultrasound. Without this discordance, these cases may not have been detected in the prenatal period, underscoring the importance of clinical correlation following NIPT

Key Points:

- Discordances between predicted fetal sex by NIPT and ultrasound have many potential etiologies, including DSDs.
- No society guidelines exist outlining the evaluation and management of these cases. Evaluation might be prioritized based on family history, ultrasound findings, or other clinical information.
- Collaboration between the cfDNA lab and ordering provider is critical.

Tables + Figures

Table 1. Clinical outcome database search terms

Disorder of sexual development
DSD
Androgen insensitivity syndrome
AIS
Congenital adrenal hyperplasia
CAH
Reductase (for 5-alpha reductase deficiency)
Dehydrogenase, hydroxysteroid (for 17-hydroxysteroid dehydrogenase deficiency)

Figure 1. Case results



US = Ultrasound, AIS = Androgen Insensitivity Syndrome, CAH = Congenital adrenal hyperplasia

References

1. García-Acero M, Moreno O, Suárez F, Rojas A. Disorders of Sexual Development: Current Status and Progress in the Diagnostic Approach. *Current Urology* 2019; 13:169-178.
2. Lassey S, Wilkins-Haug L, Bromley B, Gbur S. Managing fetal sex discordance in cfDNA. *Contemp Ob Gyn* 2020;65(12).