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“Prenatal Genitourinary Anomalies with Normal Sex-Chromosome Screening: A Preliminary Case Series of Ambiguous Genitalia and Posterior Urethral Valves”

Introduction: Cell-free DNA (cfDNA)/NIPT reliably detects trisomy’s 21/18/13 and sex chromosome aneuploidies (SCA) and reports fetal sex, but it does not target differences of sex development (DSD) and has no role in diagnosing structural lower urinary tract obstruction. Two prenatally detected genitourinary (GU) phenotypes, ambiguous genitalia and posterior urethral valves (PUV), therefore illustrate the gap between what cfDNA screens for and the diagnosis that ultimately explains the finding.

Objective: This preliminary case series aims to describe cfDNA/NIPT use and results, the diagnostic pathway, and final diagnoses among fetuses with prenatally detected ambiguous genitalia or PUV, emphasizing how often the definitive diagnosis was one cfDNA cannot detect. This case series is a part of a larger future study that will characterize the types SCAs identified by NIPT, evaluate concordance with confirmatory diagnostic testing, and assess perinatal and neonatal outcomes such as gestational age, birth weight, NICU admission, and congenital anomalies. The goal is to clarify the predictive value of NIPT for SCAs and improve prenatal counseling and postnatal management.

Methods: We conducted a retrospective chart review of pregnancies diagnosed with fetal genitourinary anomalies, between 2023 and 2026 using the LCMC perinatal-neonatology database. Of 117 identified cases, 9 met study criteria after excluding incomplete records, complex multi-system conditions, and isolated upper-tract renal findings (analyzed separately), leaving two subgroups: ambiguous genitalia/disorders of sex development (DSD, n = 4) and posterior urethral valves (PUV, n = 5). For each case, we collected prenatal imaging data (initial and final GU diagnosis, imaging modality, and gestational age at detection), cell-free DNA (cfDNA)/NIPT data (screening performed, predicted fetal sex, and any sex chromosome aneuploidy), maternal demographics (age and BMI), and postnatal diagnostic and outcome data.

Results: Of the genitourinary cases analyzed, two subgroups were characterized: ambiguous genitalia (n=4) and posterior urethral valves (PUV; n=5). NIPT/cfDNA was performed in 4/4 ambiguous genitalia and 3/5 PUV cases; no sex-chromosome aneuploidy was identified in any case (0/9), and every recorded cfDNA result was male or low-risk/negative-male and non-predictive of the postnatal diagnosis. Ambiguous genitalia cases were postnatally diagnosed as isolated hypospadias variants (perineal, penoscrotal, and midscrotal with micropenis); the most striking discordance was a fetus with a female phenotype on ultrasound for whom cfDNA returned male on two separate draws. All PUV cases were male with classic keyhole bladder and bilateral hydroureteronephrosis, and renal outcomes were severe despite reassuring screening.

Conclusion: In this genitourinary cohort, prenatal cell-free DNA screening was consistently normal and did not predict the postnatal diagnosis, and no case harbored a sex-chromosome aneuploidy. These findings underscore that a reassuring NIPT/cfDNA result does not exclude clinically significant genitourinary anomalies, which were instead identified by fetal ultrasound and often carried severe renal morbidity. Recognizing the limits of cfDNA in this setting may help perinatologists appropriately triage imaging findings, counsel families, and coordinate multidisciplinary follow-up for fetuses with suspected genitourinary anomalies.