Low fetal fraction in cell-free DNA testing is associated with adverse pregnancy outcome: analysis of a subcohort of the TRIDENT-2 study

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OBJECTIVE

It is hypothesized that the amount of cell-free fetal DNA (cfDNA) released in the maternal circulation reflects placental health. A low fetal fraction (FF) is suggested to indicate placental dysfunction. This study assesses the association between low FF in prenatal cfDNA testing and adverse pregnancy outcomes.

METHODS

We conducted a retrospective cohort study of participants of the TRIDENT-2 study* who received a failed cfDNA test result due to low FF (<4%) between April 2017 until February 2018. Data from one of the three NIPT-laboratories (Amsterdam UMC-VUMC) were included. Patient characteristics and pregnancy outcomes were collected and compared to the general Dutch obstetric population.

Primary outcome measures were pregnancy-induced hypertension (PIH), pre-eclampsia (PE), small for gestational age neonates (SGA), spontaneous preterm birth (sPTB), and gestational diabetes mellitus (GDM). Secondary outcome measures were aneuploidy and congenital structural anomalies.

RESULTS

During the study period, a total of 26,226 cfDNA tests were performed. Test failure due to low FF occurred in 295 women (1.12%) on initial testing. Information regarding pregnancy outcomes was available for 284 of these women (96.3%).

Women with low FF had a significantly higher BMI (28.7 vs. 23.7, p<0.001), were more often nulliparous (64.8% vs. 44.5%, p<0.0001), and smoked more often (12.3% vs. 9%, p=0.049) as compared to the general Dutch obstetric population.

There were significantly higher incidences of PIH, PE ≥ 34 weeks of gestation, and GDM in women with low FF. Additionally, higher prevalences of aneuploidy, and congenital structural anomalies were found in women with low FF **(Table 1)**.

*** Study offering first-tier cfDNA screening within the Dutch government-supported screening program for fetal aneuploidies**

Table 1. Adverse pregnancy outcomes in women with low FF compared to the general Dutch obstetric population

Pregnancy outcome	Women with low FF (%) n=284	General Dutch obstetric population (%)	p-value
Pregnancy induced hypertension	11.2	5.3	<0.0001
Total preeclampsia	4.1	2.3	0.07
▪ ≥ 34 weeks GA	3.7	1.9	0.04
▪ < 34 weeks GA	0.4	0.4	1.00
Small for gestational age neonates	7.3	7.2	0.98
Total spontaneous preterm birth	5.1	4.3	0.54
▪ Spontaneous preterm birth (32-37 weeks)	4.7	3.8	0.44
▪ Spontaneous preterm birth (<32 weeks)	0.4	0.5	1.00
Gestational diabetes mellitus	14.8	4.9	<0.0001
Aneuploidies	1.4	0.4	0.03
Congenital structural anomalies	4.1	1.7	0.006

CONCLUSION

Low fetal fraction is associated with pregnancy-induced hypertension and preeclampsia ≥ 34 weeks of gestation, gestational diabetes mellitus, aneuploidy, and congenital structural anomalies. Further large-scale studies are needed to solidify these associations.