PLANES - Placental Growth Factor Led Management of the Small for Gestational Age Fetus: a Feasibility Study

Lay summary

Stillbirth happens in about 4 out of every 1,000 pregnancies, and almost half of these cases involve babies who are smaller than expected for their stage of pregnancy (called small for gestational age, or SGA). Delivering these babies early can reduce the risk of stillbirth, but it also increases the chance of medical interventions and may affect the baby's development because they are born before they are fully ready.

A blood test called the sFlt-1/PlGF ratio is already used in women with high blood pressure in pregnancy to check how well the placenta is working. We wanted to see whether using this same test in pregnancies with SGA babies could help doctors decide who might benefit from early delivery and who could safely continue the pregnancy longer.

We carried out a randomised controlled study in two large maternity units in Liverpool and Manchester between April 2022 and October 2023. Pregnant women between 32 and 38 weeks whose babies were found on ultrasound scan to be below the 10th centile for weight were invited to take part. We did not include women with twins, those under 16 years of age, those where the baby had a known abnormality, or women who needed urgent delivery for medical reasons.

Women who participated were randomly assigned to one of two groups, either to receive sFlt-1/PlGF ratio informed clinical management or to have standard care without this additional test being revealed to them. A study pathway was developed which informed the local clinical team of how to manage the woman based on her sFlt-1/PlGF ratio result. If the result was abnormal (≥38 pg/ml) more detailed scans were performed to assess fetal blood flow (Doppler) with delivery planned at 37 weeks. In those women with a normal sFlt-1/PlGF ratio (<38 pg/ml), scans and repeat tests were performed every 2 weeks with birth delayed until 40 weeks.

A total of 78 women joined the study, and most agreed to be randomly assigned to one of the study groups. Many women wished to take part in the study but did not want their care to be determined randomly and as such we adjusted our study to include an additional observational group, where women had standard care with a blood test taken but the result withheld.

We found no differences in newborn health between the groups. Women in the group using the sFlt-1/PlGF test who had a normal result tended to stay pregnant slightly longer and had slightly more vaginal births. There were no safety concerns, and we were able to collect health-economic data successfully.

Interviews with parents revealed the emotional burden of SGA with many describing fear, uncertainty and upset. Uncertainty about clinical management appeared to influence views on the PLANES trial. Across interviews, focus groups and questionnaires parents and clinicians stated their support for research to inform the future care of SGA pregnancies. Mothers and birth partners indicated that the PLANES approach to recruitment and consent was appropriately timed, with sufficient opportunity to ask questions. Many described their preference for being allocated to the reveal arm due to the belief they would receive extra care. The proposed trial was viewed as acceptable as many felt biomarker led care may help identify

potential risk, provided additional reassurance whilst potentially reducing interventions that were not needed.

The strengths of the PLANES study are its randomised nature and the high quality of the evidence for feasibility from qualitative and economic components. This is the first study to use sFlt-1/PlGF ratio to refine care pathway in SGA and as such should stimulate interest in the use of biomarkers to refine risk.

The main weakness of the PLANES study was our failure to recruit to target. We believe the recruitment rate of 60.1%, 85.9% randomisation rate and compliance rate of 86.3%, despite the impact of the Covid-19 pandemic and significant delays in opening the second site, does still suggest that a future study would be feasible. Also, there were higher numbers of women with pre-planned caesarean births in the observation arm (declining randomisation) and 6 (85.7%) women randomised but not complying with the study protocol, did not wish their delivery date to be changed, suggesting that not all women want to extend their pregnancy.

This feasibility study showed that a study using sFlt-1/PlGF ratio to determine clinical management of the SGA fetus is possible, but concerns remain over the willingness of women and clinicians to take part in the study, even though those who did take part had a positive experience. However, because clinical guidelines have recently changed, it is now uncertain whether adding this blood test to routine care for SGA pregnancies would provide meaningful benefit. Before this can be decided, larger studies are needed to find out whether the sFlt-1/PlGF test can reliably predict poor outcomes in SGA pregnancies.