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Management of late-onset fetal growth restriction: anlysis and prediction of neonatal outcome

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Objective

International guidelines recommend delivery from 37 weeks in late fetal growth restriction (FGR) fetuses mostly because of stillbirth concerns. Differentiating between normal small babies from FGR is challenged by the limited prospective evidence to guide management. We implemented a novel protocol that used ultrasound criteria to classify women with suspected late FGR into two groups: low-risk with expectant management until 41 weeks and high-risk with delivery at 37-38 weeks. We compared the neonatal outcome of this prospective cohort with a historical cohort of women with suspected late FGR, to evaluate the impact of implementation of the new protocol and a multiparameter prediction model.

Methods

This was a time series analysis in women managed at University College London Hospital, UK between 2017-2019 with a singleton non-anomalous fetus at ≥32 weeks and any of the following inclusion criteria: • estimated fetal weight (EFW) ≤10th centile, • ≥50 centiles decrease of the abdominal circumference (AC) from previous scans, • umbilical artery Doppler pulsatility index >95th centile or • cerebroplacental ratio <5th centile. Management of women in the historical cohort (2017-2018) was guided by individual clinician's expertise, and when available, according with national guidelines in the UK. Women in the new cohort (2018-2019) were classified as high-risk and delivery was planned at 37-38 weeks if they had: 1) EFW <3rd centile, or 2) EFW ≥3rd and ≤10th centile, and AC centile drop or umbilical Doppler >95th centile or cerebro-placental ratio <5th centile. Otherwise, low-risk women were delivered at 40-41 weeks. Women managed according with the new protocol were compared with a historical cohort of women, delivered prior to the implementation of the new protocol (2017-2018) and classified retrospectively into low- and high-risk using the same criteria. The primary outcome was adverse neonatal outcome including any of: hypoglycaemia (serum glucose <2.5mmol), hypothermia (temperature <36.5C), neonatal unit admission, jaundice requiring treatment, suspected infection, feeding difficulties, Apgar score <7 at 1 minute, hospital readmission and any of the severe adverse neonatal outcome (perinatal death, resuscitation using inotropes or mechanical ventilation, Apgar score <7 at 5 minutes, metabolic acidosis, sepsis, cerebral, cardiac or respiratory morbidity). Secondary outcomes were adverse maternal outcome (operative delivery for abnormal fetal heart rate) and severe adverse neonatal outcome. Multiple logistic regression analysis was performed to adjust for characteristics' differences between the two cohorts. A sample size of 152 women per risk group was required to observe a reduction in adverse neonatal outcome of 15% (alpha 0.05, power 80%). We estimated the probability score of adverse neonatal outcome between 34 and 42 weeks (gestational age as a continuous variable), fitting a model based on logistic regression using observed data from the new cohort and applied the model to the historical cohort and simulated data (low/high-risk women were represented by a dichotomous variable). A non-linear relationship with the gestational age was captured by adding a quadratic term. The probability of adverse outcome ranges from 0 to 1, whereas 0 is the minimal and 1 the highest risk of adverse neonatal outcome.

Results

321 women were included in the new and 323 in the historical cohort. Most women delivered between 37 and 40 weeks. In new versus the historical low-risk group the mean gestational age at delivery was later: 39^{+5} (38^{+5}-40^{+2}) versus 39^{+1} (38^{+1}-40^{+1}), p=0.023; and the birthweight <3rd population centile was lower (8% versus 17% respectively; p= 0.012). In women classified as high-risk, mean gestational age at delivery was lower in women managed in the new compared with the historical cohort [38^{+2} (37^{+5}-39^{+0}) versus 38^{+5} (37^{+4}-39^{+6}); p=0.02]. There was a reduction in rate of adverse neonatal outcome in low-risk women of the new versus the historical cohort [45% versus 58%, adjusted odds ratio (aOR): 0.6, 95% confidence intervals (CI): 0.4-0.9; p=0.026], whereas in the high-risk women there was no significant difference in adverse neonatal outcome (56% versus 63%, aOR: 0.8, 95%CI: 0.5-1.3; p=0.319). There was no difference in severe adverse neonatal and maternal outcome between new and historical cohort, both in the low- and high-risk group. The probability of adverse neonatal outcome by the multiparameter model was highest prior to 37 weeks of gestation, reporting a value of 1 at 34 weeks, probably due to prematurity, and it reached a nadir at 39-40 weeks, increasing again after 40 weeks of gestation. At any gestation, the probability score for adverse neonatal outcome was on average lower in the low- versus the high-risk group, with the nadir score range being 0.3-0.4 and 0.4-0.5 in the low- and high-risk group respectively.

Conclusion

Appropriate risk classification to define management in low- and high-risk FGR groups was associated with reduced adverse neonatal outcome in the low-risk group. In clinical practice a policy of expectantly managing women with late-onset low-risk FGR pregnancies at term could improve neonatal outcome. A predictive model supports the hypothesis of high risk of abnormal neonatal outcome due to late prematurity at less than 39 weeks and increased risk after 41 weeks due late placental insufficiency implications. Randomized controlled trials are needed to assess the effect of an evidence based conservative management protocol of late FGR on perinatal morbidity, mortality and long-term neurodevelopment.