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Sildenafil therapy in early-onset fetal growth restriction: waiting for the individual patient data meta-analysis

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The Sildenafil TheRapy In Dismal prognosis Early-onset intrauterine growth Restriction (STRIDER) Consortium was set up in 2011 to assess the effects of sildenafil for the treatment of fetal growth restriction (FGR). The project included four trials with different but related main outcomes. Once completed, an individual patient data meta-analysis of the four trials was planned to address with adequate statistical power the effects on hard perinatal outcomes.

The results of the randomised controlled trial conducted in Australia and New Zealand are published (Groom *BJOG* 2019;126:997–1006), showing that the proportion of pregnancies with failure to show any improvement in abdominal growth velocity was 47% in the sildenafil group (25 mg/8 h) and 32% in the placebo group. The 95% CI of the risk difference ranged from a 1.4% risk reduction to a 33.4% risk increase. This is relevant because it shows that the study is well powered to detect even small benefits of sildenafil (>1.4%) in improving growth, and leaves little doubt on the lack of benefit regarding this outcome. Remarkably, the inclusion criteria were broad (abdominal circumference <3rd centile before 28 weeks of gestation and estimated fetal weight <700 g from 28 to 29^{+6} weeks of gestation). However, the stratified analysis of those 28 pregnancies with absent or reversed end-diastolic velocities in the umbilical artery showed no difference regarding the lack of effect in improving growth.

One can argue that growth velocity is an intermediate measure rather than a health outcome. In this study, the 95% CI of the risk difference of sildenafil for stillbirth ranged from a 3.7% risk increase to a 22.1% risk reduction; similarly, the 95% CI of the risk difference of sildenafil for death or severe morbidity ranged from a 6.5% risk increase to a 28% risk reduction. Hence, this individual study is only powered to exclude very large benefits of sildenafil, but not more moderate but still clinically relevant effects.

The UK-STRIDER study (Sharp *Lancet Child Adolesc Health* 2018;2:93–102), which only included pregnancies with umbilical artery Doppler abnormalities, also showed no differences between groups in the prolongation of pregnancy (median of 17 days in the sildenafil group versus 18 days in the placebo group). The sample size also rendered the study underpowered to detect moderate but still clinically relevant effects on the rate of fetal and neonatal mortality or neonatal morbidity.

The Dutch-STRIDER trial has been stopped after a planned interim analysis that showed an increased incidence of persistent pulmonary hypertension in the sildenafil group (although causality is still to be established) and also because the chance of neonatal mortality and morbidity was not reduced with the treatment. Likewise, the Canadian-STRIDER trial has been stopped because of the apparent futility and safety concerns.

Therefore, it is now essential to have the results of the individual patient data meta-analysis to definitely rule out clinically relevant benefits of sildenafil therapy in early-onset FGR and confirm the neonatal risks. In the meantime, this treatment should not be prescribed for FGR outside the setting of high-quality randomised clinical trials.

Disclosure of interests

None declared. A completed disclosure of interests form is available to view online as supporting information. ■