

# Learning from the STRIDER trial<sup>☆</sup>

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## Abstract

The STRIDER is an international consortium of five randomised trials of the use of sildenafil to treat fetal growth restriction. We describe the scientific rationale and processes undertaken to take advantage of such a joint approach to studying new interventions in pregnancy. We also describe the challenges faced during recruitment and the further challenges faced after initial publication. We discuss concerns about fetal wellbeing identified in the Netherlands STRIDER trial and the implications of this on other studies and the wider maternity research community.

**Keywords** fetal growth restriction; FGR; stillbirth

## Background

Severe early-onset fetal growth restriction (FGR) has a significant risk of fetal mortality and is associated with iatrogenic preterm delivery and subsequent neonatal morbidity. There is no treatment for FGR and as such conservative management with close fetal monitoring is often adopted, although termination of these high risk pregnancies may be considered.

The scientific rationale for the use of sildenafil to treat FGR came from a number of animal studies and ex-vivo and in-vivo human studies. These studies demonstrated significant improvements in placental structure, fetal weight animal models and improvements in weight and Doppler studies in a small number of human studies. In addition, sildenafil had a good safety profile including no evidence of harm in the limited number of pregnancy studies with available safety data. Based upon the evidence of potential benefit and relatively low risk there were anecdotal accounts of empirical use of sildenafil off license in private obstetric practice.

Several research groups interested in this area formed the STRIDER consortium to study the use of sildenafil for the

treatment of FGR. Each of the five originally planned studies (Australia/New Zealand, UK, Netherlands, Canada and Ireland) was to be nationally funded with a broadly similar protocol but with an a priori agreement to perform independent patient data meta-analysis. Following ethical approval the Australia/New Zealand study began recruitment first, followed by the UK, Netherlands and Canadian studies. The study was managed using a Risk-adapted Approach which categorises trials based on the risk of the investigational medicinal product (IMP) compared to standard care. STRIDER UK was categorised as Type B, which is 'somewhat higher than the risk of medical care' and received Competent Authority approval by the Medicines and Healthcare Products Regulatory Agency (MHRA). The UK trial completed 20 months of active recruitment and the results were published in January 2018.

## Challenges facing international STRIDER

There were initial concerns about the willingness of women to be randomised although these soon proved unfounded with the STRIDER UK study achieving a consent rate of 80% and recruitment completed in July 2016 ahead of schedule.

The STRIDER UK study demonstrated no beneficial effect of treatment with sildenafil over placebo in either prolonging pregnancy or in fetal or neonatal outcomes. However, there were no signals of harm from sildenafil use. Fetal mortality was 32% with a further 13% neonatal mortality, confirming the very high risk nature of the population.

The Australia/New Zealand STRIDER study completed recruitment soon after STRIDER UK and showed broadly similar findings to the UK study. The Netherlands STRIDER study was also recruiting well until it was stopped prematurely on the advice of the independent safety data monitoring committee (ISDMC) due to concerns about an observed increased risk of neonatal death and persistent pulmonary hypertension of the newborn in babies whose mothers had been treated with sildenafil. Naturally the closure of a trial due to concerns about a drug causing neonatal deaths caused a significant degree of concern in the global media. The Canadian STRIDER trial and other studies of sildenafil use in pregnancy were also stopped as a consequence of these findings.

Subsequently, a brief summary of all known neonatal deaths was published with no conclusive evidence of causation but further review is planned in the context of the IPD meta-analysis.

## Discussion

So what has the experience from the STRIDER trials taught us so far? It demonstrates quite clearly that caution should always be exerted when translating high quality laboratory evidence into clinical practice as unforeseen effects can be observed (the Northwick Park disaster is a further example of this). This uncertainty is even more pertinent in pregnancy due to the difficulty in identifying fetal effects due to the lack of adequate animal models. However, under normal circumstances, repurposing of drugs with a strong safety profile, such as sildenafil, remains the best opportunity to lead to clinical improvements in pregnancy conditions.

Further caution should be exerted when studies are performed across global regions as differences in terminology (definitions)

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and disease management between countries may lead to inconsistencies that may then be interpreted incorrectly. We have attempted to mitigate this by agreeing an IPD protocol.

It took a full two years to publish the Australia/New Zealand study, despite the authors' strenuous efforts to put the full results in the public domain. The negative findings of the first consortium publication (STRIDER UK), and subsequent concerns from the Netherlands study are likely to be important contributing factor to journals' unwillingness to publish, commonly referred to as 'publication bias'. This is a serious concern as it is even more pertinent that any 'negative' results are open to scientific scrutiny in light of the recent concerns.

In summary, the STRIDER experience presents a challenge to future drug studies in pregnancy as despite vigorous laboratory and animal testing and a drug with an excellent safety profile and evidence of improvement in a clinical condition, we have been unable to demonstrate a benefit from treatment. Of greater concern is the potential harm caused by this treatment from the Netherlands study. It is possible that when the full

analysis and review of all cases is performed and also when combined as part of the IPD we may not observe a significant effect. However, much of the damage to confidence in maternity drug research will already have been done due to the perception of harm which poses a fresh challenge to research in this field. ◆

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#### FURTHER READING

Ganzevoort W, Alfrevic Z, von Dadelszen P, et al. STRIDER: sildenafil Therapy in Dismal prognosis Early-onset intrauterine growth Restriction—a protocol for a systematic review with individual participant data and aggregate data meta-analysis and trial sequential analysis. *Syst Rev* 2014 Mar 11; **3**: 23.

Sharp A, Cornforth C, Jackson R, et al. Maternal sildenafil for severe fetal growth restriction (STRIDER): a multicentre, randomised, placebo-controlled, double-blind trial. *Lancet Child Adolesc Health* 2018 Feb; **2**: 93–102.