

**Title:** The Role of Aspirin, Heparin and Other Interventions in the Prevention and Treatment of Fetal Growth Restriction.

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9

10 **Condensation:** A review of the current evidence for preventative and treatment  
11 options for fetal growth restriction with some insights into new therapies on the  
12 horizon.

13

14 **Short version of title:** Therapeutic Interventions in Fetal Growth Restriction.

15

## Abstract

Fetal growth restriction and related placental pathologies such as pre-eclampsia, stillbirth and placental abruption are believed to arise in early pregnancy when inadequate remodelling of the maternal spiral arteries leads to persistent high-resistance and low-flow uteroplacental circulation. The consequent placental ischaemia, re-perfusion injury and oxidative stress are associated with an imbalance in angiogenic/anti-angiogenic factors. Many interventions have centred on prevention and/or treatment of preeclampsia with results pertaining to fetal growth restriction and small for gestational age pregnancy often included as secondary outcomes because of the common pathophysiology. This renders the study findings less reliable for determining clinical significance.

For prevention of fetal growth restriction, recent large study level meta-analysis and individual patient data meta-analysis confirm that aspirin modestly reduces small for gestational age pregnancy in women at high risk (relative risk 0.90, 95%CI: 0.81-1.00) and that a dose of  $\geq 100\text{mg}$  should be recommended, and to start at or before 16 weeks of gestation. These findings support national clinical practice guidelines. *In vitro* and *in vivo* studies suggest that low molecular weight heparin may prevent fetal growth restriction, however, evidence from randomised control trials is inconsistent. Meta-analysis of multi-centre trial data does not demonstrate any positive preventative effect of low molecular weight heparin on a primary composite outcome of placenta-mediated complications including fetal growth restriction; 18% vs 18%, absolute risk difference 0.6%, 95%CI: 10.4-9.2); use of low molecular weight heparin for the prevention of fetal growth restriction should remain in the research setting.

There are even fewer treatment options once fetal growth restriction is diagnosed. At present the only management option if the risk of hypoxia, acidosis and intrauterine

1 death is high is iatrogenic preterm birth, with the use of peri-partum maternal  
2 administration of magnesium sulphate for neuroprotection and corticosteroids for  
3 fetal lung maturity, to prevent adverse neonatal outcomes.

4 The pipeline of potential therapies employ different strategies, many aiming to  
5 increase fetal growth by improving poor placentation and uterine blood flow.  
6 Phosphodiesterase type-5 inhibitors that potentiate nitric oxide availability such as  
7 sildenafil citrate have been extensively researched both in preclinical and clinical  
8 studies; results from the STRIDER consortium of randomised control clinical trials  
9 are keenly awaited. Targeting the uteroplacental circulation with novel therapeutics is  
10 another approach; the most advanced being maternal VEGF gene therapy which is  
11 being translated into the clinic via the EVERREST consortium. Other targeting  
12 approaches include nanoparticles and microRNAs to deliver drugs locally to the  
13 uterine arterial endothelium or trophoblast. *In vitro* and *in vivo* studies and animal  
14 models have demonstrated effects of nitric oxide donors, dietary nitrate, hydrogen  
15 sulphide donors, statins and proton pump inhibitors on maternal blood pressure,  
16 utero-placental resistance indices and angiogenic/anti-angiogenic factors. Data from  
17 human pregnancies, and in particular, pregnancies with fetal growth restriction  
18 remains very limited. Early research into melatonin, creatine and N-acetyl cysteine  
19 supplementation in pregnancy suggests they may have potential as neuro and  
20 cardio-protective agents in fetal growth restriction.

21  
22 **Keywords:** Fetal growth restriction, FGR, intrauterine growth restriction, IUGR, small  
23 for gestational age, SGA, preeclampsia, low molecular weight heparin, aspirin,  
24 sildenafil, VEGF gene therapy, pravastatin, nitric oxide donor, esomeprazole,  
25 melatonin, creatine, N-acetylcysteine.

## 1 Introduction

2 Fetal growth restriction (FGR) describes a group of conditions in which a fetus fails  
3 to reach its full growth potential. FGR is difficult to define and measure and so small  
4 for gestational age (SGA), defined by birthweight percentile, is often used as the  
5 most reliable surrogate marker. FGR and SGA may be caused by fetal issues such  
6 as chromosomal anomalies, genetic syndromes and fetal infection; maternal  
7 disease; environmental toxins including cigarette smoking; and the most common  
8 cause, utero-placental insufficiency. This article will focus on preventative and  
9 treatment options for FGR due to utero-placental insufficiency.

10 During early pregnancy trophoblast invasion of the maternal spiral arteries remodels  
11 and disrupts their smooth muscle layer creating a low-resistance and high-flow utero-  
12 placental circulation capable of efficient gaseous and nutrient exchange for optimal  
13 fetal growth.<sup>1</sup> Inadequate or abnormal trophoblast invasion results in incomplete  
14 remodelling of the spiral arteries and persistence of a high-resistance and low-flow  
15 circulation.<sup>2, 3</sup> It is hypothesized that this results in a sequence of events including  
16 reduced placental perfusion, placental ischaemia and re-perfusion injury<sup>4</sup>, oxidative  
17 stress,<sup>5</sup> an imbalance in angiogenic factors<sup>6-8</sup>; vascular endothelial growth factor  
18 (VEGF) and placental growth factor (PIGF), with anti-angiogenic factors; soluble fms-  
19 like tyrosine kinase 1 (sFlt-1) and soluble endoglin and an increased frequency of  
20 atherosclerosis in the placental bed.<sup>9</sup> Clinically these events present as the placenta-  
21 mediated complications of pregnancy; FGR, preeclampsia, placental abruption and  
22 late pregnancy loss. Placental bed biopsies in pregnancies affected by FGR and pre-  
23 eclampsia confirm that there is a major defect in myometrial spiral artery remodeling  
24 that is linked to these clinical parameters.<sup>10-12</sup>

1 The on-going adverse *in utero* environment associated with FGR ultimately may lead  
2 to hypoxic damage and stillbirth. With no proven therapeutic interventions available  
3 planned early birth must be considered and offered once a fetus reaches a viable  
4 gestational age and size. However, preterm birth then adds further morbidity and  
5 mortality risk to an already compromised neonate. There is an urgent need to identify  
6 early in pregnancy, those women at most risk of developing FGR to investigate and  
7 offer preventative therapies. Once FGR is diagnosed other strategies will be required  
8 to improve fetal growth and wellbeing, which may allow iatrogenic delivery to be  
9 delayed and/or to ameliorate the harm of the hypoxic intrauterine environment.

## 11 **Prevention of FGR**

### 12 **Aspirin and other anti-platelet agents**

13 The release sFlt-1 and soluble endoglin<sup>6, 7</sup> into the maternal circulation cause  
14 endothelial dysfunction, a feature of the placenta-mediated complications of  
15 pregnancy and in particular preeclampsia, and an imbalance in vasoactive factors  
16 such as endothelin<sup>13</sup>, nitric oxide<sup>14</sup> and prostacyclin<sup>15</sup>, resulting in reduced  
17 vasodilatation and increased vasoconstriction. Aspirin has a number of effects at the  
18 vascular level that may prevent FGR (Figure 1). For many years it was understood  
19 that aspirin suppresses the production of prostaglandins and thromboxanes through  
20 its irreversible inactivation of the cyclooxygenase enzyme. Thromboxane is a  
21 powerful vasoconstrictor and pro-thrombotic antiplatelet agent. Low-dose, long-term  
22 aspirin use irreversibly blocks the formation of thromboxane A2 in platelets, inhibiting  
23 platelet aggregation. More recently, novel cytoprotective and antioxidant  
24 mechanisms of aspirin have been observed that are independent of cyclooxygenase

1 inhibition. Aspirin acetylates endothelial nitric oxide synthase leading to nitric oxide  
2 release from vascular endothelium.<sup>16</sup> In addition aspirin increases the activity of  
3 heme oxygenase-1 in endothelial cells to catabolize heme which leads to a reduction  
4 in oxidative stress, injury and inflammation.<sup>17</sup>

5 Most aspirin studies have centred on preeclampsia as a primary outcome measure  
6 with FGR included as a secondary outcome only. The volume and quality of  
7 evidence however does allow meaningful interpretation and implementation of  
8 findings.

9 This year there was simultaneous publication of systematic reviews based on study  
10 level meta-analysis<sup>18</sup> and individual patient data meta-analysis<sup>19</sup> of randomised trials  
11 of aspirin and other antiplatelet agents that included 20 909 and 32 217 women  
12 respectively. Both analyses supported pre-existing evidence that aspirin provides a  
13 modest risk reduction for FGR and SGA (<5<sup>th</sup> or <10<sup>th</sup> percentile) at birth; individual  
14 patient data analysis relative risk 0.90, 95% CI 0.81-1.00.<sup>19</sup> The difference in the  
15 conclusions of these meta-analyses arose from assessment of gestational age at  
16 initiation of therapy, before or after 16 weeks (Table 1). The individual patient data  
17 meta-analysis found that low-dose aspirin and other antiplatelet agents had a  
18 consistent effect on preeclampsia regardless of whether treatment was started  
19 before or after 16 weeks gestation.<sup>19</sup> Data specific to FGR supports earlier initiation  
20 of therapy where possible. In the study level meta-analysis there was a dose-  
21 response relationship for SGA when treatment was initiated ≤16 weeks, favouring a  
22 dose of 100-150mg.<sup>18</sup>

23 Studies demonstrating circadian effects of aspirin on plasma renin activity<sup>20</sup> and  
24 urinary excretion of cortisol, dopamine and norepinephrine<sup>21</sup> as well as clinical trials  
25 that show a circadian effect of aspirin to treat pre-hypertension<sup>22</sup> and mild

hypertension<sup>23</sup> in non-pregnant adults suggest timing of daily dosing should be considered, particularly with reference to the prevention of preeclampsia. Two small randomised trials in pregnancy have found that evening but not morning administration of aspirin is associated with a reduction in ambulatory blood pressure<sup>24, 25</sup> and in one of these trials a reduction in the incidence of preeclampsia and FGR was also seen.<sup>24</sup> The circadian mechanism of action in the prevention of FGR seems less clear. However, if recommending daily aspirin therapy it seems prudent to recommend evening dosing.

Most national and international guidelines recommend 100-150mg aspirin dose to prevent FGR and SGA pregnancy in women at 'high risk'.<sup>26</sup> However, patient selection and accurate identification of those at most risk of FGR is not clear as, like most studies of therapies for the prevention of placenta-mediated complications of pregnancy, prediction studies have been more focussed on preeclampsia rather than FGR. This is highlighted by a recent large multicentre randomised trial of aspirin to prevent preterm preeclampsia. The Aspirin for evidence-based preeclampsia prevention (ASPREE) trial used a complex algorithm including maternal factors, mean arterial pressure, uterine artery Doppler pulsatility index, and maternal serum biomarkers (maternal serum pregnancy-associated plasma protein A and placental growth factor) to identify women at high risk. Although aspirin use was associated with a reduction in preterm preeclampsia, rates of SGA <10<sup>th</sup>, <5<sup>th</sup> or <3<sup>rd</sup> percentile were unchanged<sup>27</sup> suggesting alternative prediction models are required before being able to truly assess the effect of aspirin on those at highest risk.

## **Heparin and Low Molecular Weight Heparin**



Unfractionated heparin and low molecular weight heparin (LMWH) are commonly used in pregnancy for thrombo-prophylaxis and the treatment of venous thromboembolism. More recently LMWH is preferred to unfractionated heparin and appears safe and effective for these indications.<sup>28</sup> Unfractionated heparin and LMWH do not cross the placenta<sup>29</sup> and thus pose little direct risk to the fetus. Initial interest in heparins to prevent placental pathology centred on their anticoagulant properties and presumed ability to prevent placental thrombosis and subsequent infarction leading to miscarriage. *In vitro* and *in vivo* data suggest heparins have a variety of other biological properties including anti-inflammatory<sup>30</sup>, complement inhibition<sup>31</sup> and anti-tumour<sup>32</sup> actions as well as being pro-angiogenic<sup>33-37</sup> (Figure 1). These additional effects may positively influence trophoblast development and invasion making them potential candidates for the prevention of placenta-mediated complications of pregnancy including FGR.

#### Preclinical studies of unfractionated heparin and LMWH on angiogenesis

*In vitro* studies using placental villous explants found that both unfractionated heparin and LMWH promote angiogenesis.<sup>33, 34, 36</sup> The mechanism of action is unclear, but enhanced expression of matrix metalloproteinases may be contributory.<sup>38</sup> However, there are inconsistencies in *in vitro* study results with some demonstrating suppression of trophoblast invasion<sup>39</sup> particularly when heparin is used at therapeutic levels.<sup>40</sup> Further caution is raised by the finding of elevated sFlt-1 concentration and impaired VEGF signalling in endothelial cells when placental villi are exposed to LMWH at therapeutic doses,<sup>41</sup> although this was most significant in healthy early and term pregnancy placentae but not in placentae from pregnancies with preeclampsia and/or FGR.

## Clinical studies of LMWH

*In vivo* use of LMWH appears to have a more positive effect on markers of angiogenesis. When used in pregnancy for anticoagulation, serum PIGF concentration is increased and there is a lower sFlt-1/PIGF ratio compared with gestation matched controls<sup>37</sup> and in a small randomised trial of women at high risk of preeclampsia plasma levels of PIGF were elevated one and three hours after LMWH administration, not seen in women at similar risk receiving placebo.<sup>35</sup>

The effect of heparin therapy on utero-placental circulation is less clear. In a small open label study of women with gestational hypertension, treatment with LMWH reduced uterine artery resistance index.<sup>42</sup> However, more sustained use of LMWH in a randomised control trial of LMWH and aspirin versus aspirin alone found no differences in uterine artery Doppler resistance index at 22-24 weeks or in umbilical artery Doppler pulsatility index at 22-24 weeks and later gestational ages.<sup>43</sup>

As early evidence suggested a relatively strong association between inherited thrombophilias and preeclampsia and FGR, initial randomized trials of heparin focused specifically on populations of women with or without thrombophilia.<sup>44-46</sup> More recent evidence from prospective cohort studies suggests any association of thrombophilia and placenta-mediated complications, if present, is only weak<sup>47</sup> and so more recent trials have included women regardless of thrombophilia status. Many trials have diverse inclusion criteria identifying women not only at high risk of FGR and preeclampsia but also earlier pregnancy complications such as recurrent miscarriage and non-placenta related conditions such as venous thromboembolism.

Results of early randomized trials were encouraging and suggested that heparin could reduce the risk of preeclampsia and FGR.<sup>45,44</sup> But a positive effect of LMWH was not been seen consistently across all published trials<sup>44-46, 48-52</sup> possibly reflecting the heterogeneity of the populations being examined, the type of LMWH being used, prolonged trial recruitment phases<sup>44, 46</sup> and early trial discontinuations.<sup>45, 48</sup>

A study level meta-analysis of six trials (848 women) demonstrated LMWH (included trials used enoxaparin, dalteparin and nadroparin) was associated with a reduction in a composite outcome (preeclampsia, birthweight <10<sup>th</sup> percentile, placental abruption or pregnancy loss >20 weeks) 18.7% vs 42.9% (relative risk 0.52, 95%CI 0.32–0.86) with similar risk reductions for a number of secondary outcomes including SGA <10<sup>th</sup> percentile and <5<sup>th</sup> percentile.<sup>53</sup> However, there were high levels of heterogeneity across trials and trials of higher-quality suggested no treatment effect. The same authors have subsequently completed an individual patient data meta-analysis including five trials from the study level meta-analysis and three additional trials (963 women).<sup>54</sup> Again a composite primary outcome (early-onset or severe preeclampsia, SGA < 5th percentile, placental abruption, and late pregnancy loss after 20 weeks).was used but with no difference seen between those treated and those untreated, 14% vs 22% (relative risk 0.64, 95%CI 0.36-1.11). Reviewing all trials data LMWH therapy was associated with a reduction in SGA <10<sup>th</sup> percentile and <5<sup>th</sup> percentile but not <3<sup>rd</sup> percentile. However, trial quality also impacted on these results with heterogeneity seen between single-centre and multicentre trials; there was no effect of LMWH seen when only considering data from multicentre trials (Table 2). In subgroup analysis, including only women with a history of a SGA infant, LWMH was not associated with any reduction in the composite primary outcome. These meta-analyses did not include sub-group analysis by type of LMWH used but

1 a further study level meta-analysis including fewer participants (403 women in five  
2 heterogeneous trials) has compared dalteparin and enoxaparin use. Both types of  
3 LMWH were associated with a reduction in preeclampsia but only dalteparin was  
4 effective in reducing the incidence of FGR.<sup>55</sup>  
5 Since the publication of the 2016 individual patient data meta-analysis<sup>54</sup> two further  
6 multicentre trials have been published. The Heparin-Preeclampsia (HEPEPE)<sup>49</sup> and  
7 Enoxaparin for Preeclampsia and Intrauterine Growth Restriction (EPPI)<sup>52</sup> trials  
8 included only women at high risk of placenta-mediated pregnancy complications,  
9 with or without inherited thrombophilia. The EPPI trial included a higher proportion of  
10 women with a prior history of a SGA infant than most other trials.<sup>52</sup> Both trials  
11 reported no difference in rates of composite primary outcomes (maternal death,  
12 perinatal death, preeclampsia, placental abruption and/or SGA < 10th percentile in  
13 the HEPEPE trial and preeclampsia and/or SGA <5<sup>th</sup> percentile in the EPPI trial).or  
14 of any secondary outcomes specific to fetal growth. These recent trials add  
15 significant participant numbers (n=406) and show consistent results with the  
16 conclusion of the published individual patient data meta-analysis, that LMWH does  
17 not reduce the risk of recurrent placenta-mediated pregnancy complications in at-risk  
18 women. If LMWH therapy is protective for the recurrence of placenta-mediated  
19 pregnancy complications, then the effect is likely to be modest and, if present,  
20 possibly confined to certain subgroups only or specific types of LMWH. Currently  
21 LMWH therapy for the prevention of FGR should be limited to the research setting.  
22 Before any future trials are undertaken further research is required to accurately  
23 phenotype women deemed to be at the highest risk to better identify those who may  
24 benefit from treatment.

## Treatment of FGR

### Phosphodiesterase type-5 inhibitors

Phosphodiesterase type-5 inhibitors block the phosphodiesterase enzyme preventing the inactivation of the intracellular second messenger cyclic guanosine monophosphate within vascular smooth muscle cells which potentiates the action of nitric oxide leading to vasodilatation. Maternal spiral arteries that have not undertaken complete remodelling early in pregnancy have intact or partially intact muscular layers and so potentially remain responsive to nitric oxide and amenable to vasodilatation. The majority of work investigating phosphodiesterase type-5 inhibitors and FGR has used sildenafil but more recently other agents, including the longer acting tadalafil, have been studied.

#### Preclinical studies

*In vitro* studies show that when compared to healthy control vessels, myometrial small arteries from pregnancies affected by FGR have increased vasoconstriction and reduced vasorelaxation; pre-incubation with sildenafil ameliorates this difference.<sup>56</sup> Work in animal models predominantly support the theory of improved fetal growth with maternal sildenafil use, however, interestingly raises some questions over the mechanism of action. In the catechol-O-methyl transferase (COMT<sup>-/-</sup>) knockout mouse model of preeclampsia and FGR<sup>57</sup>, sildenafil in maternal drinking water in late pregnancy normalises pup growth measures and abnormal umbilical artery Doppler flow indices when compared to untreated COMT<sup>-/-</sup> controls.<sup>58</sup> However, this beneficial effect on feto-placental blood flow and fetal growth was not associated with increased uterine artery blood flow. Sildenafil use also increased pup weight in an alternative mouse model of FGR that has a normal

1 vascular phenotype.<sup>59</sup> Alterations in placental weight may be an alternative to  
2 vasodilatation as the mechanism of action, a theory that is further supported by  
3 studies in ovine models of FGR. In maternal nutrient restricted FGR sheep  
4 pregnancy, sildenafil increased fetal growth and amnio acid availability. In addition,  
5 when FGR was created in sheep using uterine artery embolization, sildenafil  
6 improved placental and lamb weight and ameliorated the increased umbilical artery  
7 resistance but with no effect on maternal myometrial vessel resistance.<sup>60</sup> Not all  
8 preclinical studies however have demonstrated positive effects of sildenafil treatment  
9 on FGR with some animal models showing no effect and others showing negative  
10 and potentially harmful effects.<sup>61, 62</sup>

## 11 12 Clinical studies

13 Several case reports and a small randomised trial of sildenafil to selectively reduce  
14 pulmonary vascular resistance in pregnant women with pulmonary arterial  
15 hypertension demonstrate improved maternal cardiorespiratory performance and  
16 echocardiography status with better neonatal outcomes.<sup>63-66</sup> It also appears to be a  
17 useful adjunctive therapy for persistent pulmonary hypertension of the newborn.<sup>67, 68</sup>  
18 Use in pregnancy and the early neonatal period for these indications have not raised  
19 safety concerns.

20 Two small randomised trials have studied sildenafil treatment of preeclampsia in  
21 which 30-60% of participants had co-existing FGR.<sup>69, 70</sup> Both trials demonstrated  
22 positive effects on maternal blood pressure and in one trial sildenafil was associated  
23 with an increase in mean prolongation of pregnancy (14.4 days vs 10.4 days,  
24  $p=0.008$ ). No differences were seen in measures of fetal growth but compared to

1 placebo, uterine and umbilical artery Doppler pulsatility index was reduced 24 hours  
2 after commencing sildenafil.<sup>70</sup>

3 More specific to FGR pregnancies, a single dose randomised placebo controlled trial  
4 showed that two hours after ingestion of 50mg sildenafil there was reduced  
5 resistance in the umbilical artery and increased resistance in the fetal middle  
6 cerebral artery, showing it can influence the feto-placental circulation.<sup>71</sup> To date,  
7 more prolonged use of sildenafil to treat FGR has only been reported in case  
8 reports<sup>72, 73</sup> and a small case-control study.<sup>74</sup> In this open study, 10 women with  
9 early-onset FGR received 25mg TDS sildenafil and were compared to 17 matched  
10 untreated control women. A higher proportion of women taking sildenafil had an  
11 increased post-eligibility fetal abdominal circumference growth velocity (90% vs 41%,  
12 odds ratio 12.9, 95% CI 1.3-126) with a tendency towards improved survival and  
13 intact survival to hospital discharge. However, it should be noted that the sildenafil  
14 treated group were eligible for the study an average of 10 days later and delivered  
15 an average of nine days after those untreated, delivering at a time (<28 weeks) when  
16 gestational age is likely to be the most significant predictor of outcome.

17 These limited human pregnancy studies to date have not raised specific concerns of  
18 maternal and/or fetal side effects. However, sildenafil does have a side effect profile  
19 including most commonly headache, flushing, dyspepsia, nasal congestion and  
20 impaired vision and blurred vision.<sup>75</sup> Fetal effects are less well known. Sildenafil is  
21 likely to cross the placenta and so effects, in particular, on pulmonary vasculature  
22 and cerebral blood flow<sup>71</sup> must be considered. In addition some animal studies  
23 suggest a detrimental rather positive effect on uterine blood flow and fetal  
24 wellbeing<sup>61</sup> and although any delay in delivery is hoped to improve long-term  
25 outcome, on-going exposure to a hostile *in-utero* environment has potential to cause

greater harm than that caused by preterm delivery. The results of randomised trials of sildenafil and other phosphodiesterase type-5 inhibitors are keenly awaited. The international Sildenafil Therapy In Dismal Prognosis Early-Onset Intrauterine Growth Restriction (STRIDER) Consortium includes five placebo-controlled randomised trials in the United Kingdom<sup>76</sup>, New Zealand and Australia<sup>77</sup>, the Netherlands<sup>78</sup>, Canada<sup>79</sup> and Ireland.<sup>80</sup> These trials have been conceived and designed through international collaboration and include women with early onset-FGR. Although independently funded and executed, shared data management systems and outcomes will allow assessment in prospectively planned systematic reviews including individual patient data meta-analyses.<sup>81</sup> Trials in the United Kingdom and New Zealand and Australia have completed participant recruitment and results are expected soon. Both these trials have childhood outcome studies underway to assess surviving children at the age of 2-3 years and provide important data on longer-term neurological and cardio-metabolic outcomes.

## **Maternal VEGF Gene Therapy**

An alternative approach to treating FGR is to increase the levels of VEGF in the maternal uterine arteries, thus improving local vasodilatation and angiogenesis (Figure 1). This can be achieved with an adenoviral (Ad) gene therapy vector, either injected into the uterine arteries or applied to the outside of the vessels, which produces short-term VEGF expression (Ad.VEGF). This technique, called therapeutic angiogenesis has been trialled extensively for coronary artery ischaemia and is now reaching phase 3 trials.<sup>82</sup> Studies in large and small FGR animal models have confirmed the efficacy of this approach for improving fetal growth before birth. In normal sheep pregnancy, injection of Ad.VEGF ( $1 \times 10^{11}$  particles), compared with



1 injection of a control non-vasoactive vector, increased uterine artery volume blood  
2 flow within 7 days of injection, and long term, this increase in flow persisted for at  
3 least 4 weeks until the end of gestation.<sup>83-85</sup> The mechanism is mediated via short  
4 term VEGF expression detectable in the perivascular adventitia of the treated  
5 vessels. This is associated with increased endothelial nitric oxide synthase  
6 expression, which results in reduces vascular constriction. Long term there is  
7 vascular remodelling with a reduced intima to media ratio, increased endothelial cell  
8 proliferation in the perivascular adventitia of injected vessels, and reduced uterine  
9 artery contractile response. Importantly, there was no evidence of vector spread or  
10 expression in fetal tissues and no effect of the vector on maternal or fetal  
11 haemodynamic measures. In FGR sheep and guinea pig models, fetal growth  
12 velocity is increased, and fewer fetuses are affected by severe FGR at birth.<sup>86-89</sup>  
13 There appears to be amelioration of the “brain sparing effect” in FGR fetuses of  
14 treated pregnancies, with a lower brain to liver weight ratio by ultrasound  
15 measurement and at birth. Offspring born after treated FGR pregnancies have higher  
16 postnatal lean tissue mass, a faster growth rate and improved cardiovascular  
17 phenotype. In the clinical context, vector delivery into the uterine arteries could be  
18 achieved through interventional radiology, which is used as a prophylactic measure  
19 before delivery in women at high risk of postpartum haemorrhage.<sup>90</sup> While this is  
20 more invasive than administering oral medication, it has the potential advantage of  
21 targeting vasoactive changes to the maternal uteroplacental circulation.

22 The EVERREST (doEs Vascular endothelial growth factor gene therapy safEly  
23 impRove outcome in seveRe Early-onset fetal growth reSTriction) Project, which  
24 started in 2013, aims to carry out a phase I/IIa clinical trial to assess the safety and  
25 efficacy of maternal uterine artery Ad.VEGF gene therapy for severe early-onset

1 FGR.<sup>91</sup> The project, funded by the European Union, involves a multinational,  
2 multidisciplinary consortium, including experts in bioethics, fetal medicine, fetal  
3 therapy, obstetrics, and neonatology. A bioethical study found no absolute ethical,  
4 regulatory or legal objections to the use of maternal gene therapy in pregnancy, with  
5 patients welcoming the development of new drugs for this untreatable disease.<sup>92</sup> The  
6 consortium is performing a prospective observational study of pregnancies with  
7 severe early onset FGR to define their trial inclusion criteria, which is likely to recruit  
8 those women who are most at risk of an intrauterine death or neonatal death  
9 between 22 and 27 weeks of gestation.<sup>93</sup>

## 12 **Nanotechnology and other uteroplacental targeting strategies to treat FGR**

13 There are a number of other novel strategies emerging that could target drugs or  
14 particles to the uteroplacental circulation and/or the trophoblast with the aim of  
15 improving uterine blood flow, placental function or both. Tumor-homing peptide  
16 sequences CGKRK and iRGD bind selectively to the placental surface of humans  
17 and mice and do not interfere with normal development. By coating nanoparticles  
18 with these sequences, cargoes of proteins such as insulin-like growth factor 2 can be  
19 delivered specifically to the placenta.<sup>94</sup> Insulin-like growth factors promote placental  
20 cell proliferation and survival, and facilitate the placental uptake of glucose and  
21 amino acids. In the placenta-specific insulin-like growth factor 2 knockout mouse  
22 model of late-onset FGR<sup>95</sup> such nanoparticle insulin-like growth factor 2 treatment  
23 improved fetal weight.<sup>96</sup> Recently a novel nitric oxide donor (SE175) encapsulated  
24 into targeted liposomes has been delivered systemically to the endothelial nitric  
25 oxide synthase knockout (eNOS<sup>-/-</sup>) mouse which exhibits impaired uteroplacental

1 blood flow and FGR<sup>97</sup> leading to increased fetal weight and mean spiral artery  
2 diameter, and decreased placental weight, indicative of improved placental  
3 efficiency.<sup>98</sup>

4 Another approach has used mitochondria-targeted antioxidant MitoQ bound to  
5 nanoparticles, to localise and prevent oxidative stress in the placenta.<sup>99</sup> Finally,  
6 targeted micro-RNA treatment to the placenta may enhance intrinsic placental  
7 growth signaling. miR-145 and miR675 have previously been identified as negative  
8 regulators of placental growth. When applied to human first trimester trophoblast  
9 explants, conjugates of the placental homing peptide CCGKRK  
10 with these peptide-microRNAs enhanced cytotrophoblast proliferation.<sup>100</sup> These  
11 approaches will need careful study from a safety and efficacy perspective but they  
12 look promising for a targeted FGR treatment.

#### 14 **Potential drug therapies for FGR**

15 Investigation of new drug therapies remains at the preclinical or very early clinical  
16 phases and has focussed on treatment of preeclampsia rather than FGR. Statins are  
17 lipid lowering medications with anti-inflammatory, antioxidant and angiogenic  
18 properties (Figure 1). Within small animal models of preeclampsia pravastatin  
19 reduces levels of sFlt-1 and maternal hypertension and increases VEGF and fetal  
20 weight.<sup>101, 102</sup> In a single non-randomised study including 21 women with  
21 antiphospholipid syndrome and treated with aspirin and LMWH the addition of  
22 pravastatin in 11 women after the onset of preeclampsia and/or FGR, appeared to  
23 delay delivery and improve pregnancy outcomes compared with 10 women who did  
24 not receive pravastatin<sup>103</sup>. In the Statins to Ameliorate early onset Pre-eclampsia  
25 (STAMP) randomised trial which completed recruitment in 2014<sup>104</sup>; birthweight is

1 included as a secondary outcome but results are still awaited. A further multicentre  
2 pilot study in the United States is expected to completed recruitment at the end of  
3 2018 with rate of SGA included as a secondary outcome.<sup>105</sup>

4 Nitric oxide relaxes vascular smooth muscle cells resulting in vasodilatation (Figure  
5 1). In women with preeclampsia short term treatment with a nitric oxide donor,  
6 isosorbide dinitrate, reduces maternal blood pressure<sup>106, 107</sup> and lowers resistance in  
7 umbilical artery<sup>107, 108</sup> and uterine artery<sup>107</sup> Doppler waveforms. No randomised trials  
8 of nitric oxide donors have included long term therapy or been sufficiently powered to  
9 assess any effect on pregnancy outcomes.

10 Hydrogen sulphide, like nitric oxide, is a gas that produces vasodilatation by acting  
11 on smooth muscle cell adenosine triphosphate-sensitive potassium channels, while  
12 its angiogenic effects appear to be mediated by VEGF and the VEGF receptor 2  
13 (Figure 1).<sup>109</sup> In a sFlt-1 induced hypertensive, proteinuric rat model sodium  
14 hydrosulfide treatment resulted in elevated VEGF levels and reduced sFlt-1 levels.<sup>110</sup>  
15 Further work is now needed to investigate the therapeutic potential of hydrogen  
16 sulphide donors in poor placentation.

## 18 **Repurposing drugs for FGR, proton pump inhibitors**

19 As the development of new drugs or the testing of unused drugs for treatment of  
20 FGR pregnancy is difficult and costly, repurposing of existing drugs that have a  
21 known safety profile in pregnancy is an exciting area. Proton pump inhibitors such as  
22 esomeprazole have long term safety data about treatment of gastric reflux in  
23 pregnancy. *In vitro* studies show proton pump inhibitors decrease sFlt-1, soluble  
24 endoglin and improve markers of endothelial dysfunction (Figure 1),<sup>111</sup> while

esomeprazole reduces blood pressure in a pre-eclampsia transgenic mouse model that overexpresses sFlt-1.<sup>111</sup> The randomised control Preeclampsia Intervention with Esomeprazole (PIE) trial will assess esomeprazole to treat early-onset preeclampsia, however, limited secondary neonatal outcomes do not include measures of fetal growth.<sup>112</sup>

## **Preventing the adverse outcomes of FGR**

Amelioration of the adverse effects of FGR before delivery is an important therapeutic option. When the risks of hypoxia, acidosis and intrauterine death are deemed high and the fetus is considered to have reached a viable gestational age and size, iatrogenic preterm birth should be offered. Timely antenatal administration of corticosteroids for fetal lung maturation<sup>113-115</sup> and magnesium sulphate for neuroprotection<sup>113, 116</sup> is required to prepare for birth with careful consideration of the most appropriate mode of delivery.<sup>117</sup> FGR is associated with long term neurodevelopmental and cardiac impairment, likely due to oxidative stress.<sup>118-122</sup> Interventions are now being developed to ameliorate this antenatal insult.

## **Melatonin**

Melatonin, an endogenous lipid soluble hormone produced by the pineal gland, exerts its powerful antioxidant effect directly by scavenging reactive oxygen species and indirectly by increasing expression of antioxidant enzymes such as glutathione peroxidase and glutathione reductase. Melatonin crosses the placenta<sup>123</sup> and the fetal blood brain barrier<sup>124</sup> and hence has potential to protect the developing fetal brain and heart from damage by oxidative stress.

1 In an ovine model of FGR maternal administration of melatonin protects against  
2 cardiac infarct and coronary artery stiffness, cerebral white- and grey-matter injury,  
3 abnormal cerebrovascular development with improvement in some early neurological  
4 outcomes in the offspring. A safety study of melatonin in six women with early-onset  
5 FGR (4mg BD for duration of pregnancy) found no fetal<sup>125-127</sup> or maternal safety  
6 concerns. Cord blood levels of melatonin were higher and placental  
7 malondialdehyde concentrations, a marker of oxidative stress, were lower in the  
8 melatonin treated group compared to control untreated women.<sup>126</sup> Trials of efficacy  
9 to support melatonin as a neuro- and cardio-protective agent <sup>128</sup> are awaited. A  
10 single on-going study in women at risk of imminent preterm delivery (not specific to  
11 FGR)<sup>129</sup> may provide additional information.

## 13 **Creatine**

14 Creatine is a naturally produced amino acid derivative that facilitates recycling of  
15 adenosine triphosphate and is essential for cellular energy production. As creatine  
16 can cross the placenta, maternal supplementation may increase fetal intracellular  
17 creatine and prolong cellular energy homeostasis during hypoxia, potentially  
18 providing protection for the brain and other organs in FGR pregnancies.

19 Maternal dietary creatine supplementation in a spiny mouse model with late  
20 gestation hypoxic injury increases neonatal survival after birth hypoxia and prevents  
21 hypoxic damage to the brain, kidney and skeletal muscle.<sup>130-132</sup> Studies in larger  
22 animal models with more prolonged hypoxic injury are on-going. Low maternal  
23 serum and urine creatine levels have been associated with poor fetal growth<sup>133</sup>, but

no randomised trials of maternal dietary creatine supplementation in humans have been undertaken.<sup>134</sup>

#### **N-acetylcysteine**

N-acetylcysteine scavenges reactive oxygen species and forms the antioxidant glutathione, thereby counteracting oxidative stress and increasing the bioavailability of nitric oxide.<sup>135</sup> Studies in a rat model of pre-eclampsia and FGR found that N-acetylcysteine alleviated a rise in maternal blood pressure and increased pup brain weight.<sup>136</sup> In a guinea pig model of maternal chronic hypoxia, administration of N-acetylcysteine did not affect pup weight but did ameliorate oxidative stress responses to hypoxia in the fetal liver.<sup>137</sup> However a small double-blind randomised controlled trial found that oral N-acetylcysteine did not stabilise the process of established severe preeclampsia, or improve neonatal outcome.<sup>138</sup> Further studies are needed to investigate whether N-acetylcysteine may prevent fetal complications of FGR.

#### **Implications for practice**

Currently clinicians have limited ability to enhance placentation and prevent FGR, partly due to the paucity of proven therapeutic options but also our inability to accurately identify those at highest risk. A 100-150mg evening dose of aspirin commenced prior to 16 weeks gestation provides a modest risk reduction in women at risk using conventional obstetric history based risk factors.

There are no proven treatments of FGR that will improve fetal growth or outcome once it is diagnosed. The only intervention clinicians can offer is iatrogenic preterm

1 birth with timely administration of maternal corticosteroids and magnesium sulphate  
2 to improve neonatal outcome after early preterm birth. Several potential new  
3 therapies are on the horizon but many of these are being primarily investigated for  
4 preeclampsia therapy with FGR as a secondary outcome only. It is important that  
5 clinicians wait for the results of appropriately designed and powered randomised  
6 control trials specific to FGR which include information on meaningful longer-term  
7 outcomes before extrapolating positive preclinical and early clinical study findings  
8 into clinical practice.



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1   **Glossary**

- 2   Ad.: Adenovirus
- 3   COMT: catechol-O-methyl transferase
- 4   eNOS: endothelial nitric oxide synthase knockout
- 5   FGR: fetal growth restriction
- 6   IPD: individual patient data
- 7   SGA: small for gestational age
- 8   sFlt-1: soluble fms-like tyrosine kinase 1
- 9   PlGF: Placental Growth Factor
- 10  VEGF: Vascular Endothelial Growth Factor

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## Tables

**Table 1.** Effect of gestational age at initiation of aspirin therapy for prevention of FGR or SGA at birth.

	Relative Risk	95% CI
<b>Study level meta-analysis<sup>53</sup> (FGR)</b>		
<b>≤16 weeks</b>	0.56	0.44-0.70
<b>&gt;16 weeks</b>	0.95	0.86-1.05
<b>IPD meta-analysis<sup>54</sup> (SGA)</b>		
<b>&lt;16 weeks</b>	0.76	0.61-0.94
<b>≥16 weeks</b>	0.95	0.84-1.08

Study level meta-analysis<sup>53</sup> used FGR as outcome to assess fetal size, defined as birthweight <10th or <5th percentile for gestational age or similar definition

IPD meta-analysis<sup>54</sup> used SGA as outcome to assess fetal size; SGA at birth was as defined by individual triallists, including centile charts and cut-off point used

FGR – fetal growth restriction

SGA – small for gestational age

IPD – individual patient data

**Table 2.** Primary and fetal growth outcomes from individual patient data meta-analysis of LMWH trials for the prevention of recurrence of placenta-mediated pregnancy complications.

	All trials			Multicentre trials			Single-centre trials		
	LMWH	No LMWH	Absolute difference (95%CI), p value	LMWH	No LMWH	Absolute difference (95%CI), p value	LMWH	No LMWH	Absolute difference (95%CI) p value
<b>Primary composite outcome†</b>	62/444 (14%)	95/433 (22%)	-8.0% (-17.3 to 1.4) p=0.09	47/263 (18%)	47/255 (18%)	-0.6% (-10.4 to 9.2) p=0.91	15/181 (8%)	48/178 (27%)	-18.7% (-21.6 to -15.7) p<0.0001
<b>SGA &lt;10<sup>th</sup> percentile</b>	61/444 (14%)	94/429 (22%)	-8.2% (-15.4 to -0.1) p=0.009	47/263 (18%)	53/251 (21%)	-3.2% (-9.6 to 3.1) p=0.32	14/181 (8%)	41/178 (23%)	-15.3% (-19.1 to -11.5) p<0.0001
<b>SGA &lt;5<sup>th</sup> percentile</b>	27/443 (6%)	38/429 (9%)	-2.8% (-5.4 to -0.1) p=0.042	22/262 (8%)	23/251 (9%)	-0.8% (-3.7 to 0.2) p=0.61	5/181 (3%)	15/178 (8%)	-5.7% (-6.1 to -5.2) p<0.0001
<b>SGA &lt;3rd percentile</b>	13/443 (3%)	12/249 (3%)	0.1% (-1.9 to 2.2) p=0.89	13/262 (5%)	9/251 (4%)	1.4% (-1.3 to 4.1) p=0.32	0/181	3/178 (2%)	*

Data extracted from Rodger et al 2016<sup>54</sup>

Data expressed as number (percentage)

LMWH - low molecular weight heparin

SGA - small for gestational age

1 †Primary composite outcome includes early-onset or severe preeclampsia, or SGA <5<sup>th</sup>

2 percentile or placental abruption, or pregnancy loss ≥20 weeks gestation.

3 \*Expected counts less than five and so no formal testing performed.

4

1 **Table 3.** Summary of progress of experimental treatments for fetal growth restriction.

Experimental Treatment	Method of Administration	Potential Mechanisms of Action	Current Stage of Investigation
Phosphodiesterase type-5 inhibitors	Oral	Selective vascular smooth muscle relaxation and vasodilatation	Phase II/III clinical trials
Maternal VEGF Gene Therapy	Injected into uterine arteries or applied to outside of vessels	Local vasodilatation and angiogenesis	Phase I/IIa clinical trial
Nanoparticles	Intravenous injection	Uterine blood flow, placental function	Preclinical
microRNAs	Intravenous injection	Uterine blood flow, placental function	Preclinical
Statins	Oral	Anti-inflammatory, antioxidant and angiogenesis	Phase II/III clinical trials (for preeclampsia only)
Nitric oxide donors	Oral	Selective vascular smooth muscle relaxation and vasodilatation	Phase II non-randomised (for preeclampsia only)

Hydrogen sulphide	Oral	Selective vascular smooth muscle relaxation and vasodilatation	Preclinical
Proton pump inhibitors	Oral	Angiogenesis	Phase II/III clinical trials (for preeclampsia only)
Melatonin	Oral	Antioxidant	Phase II non- randomised
Creatine	Oral	Cellular energy homeostasis	Preclinical
N-acetylcysteine	Oral	Selective vascular smooth muscle relaxation and vasodilatation	Phase II randomised (for preeclampsia only)

1

2

1 Figure 1 Sites of action at vascular smooth muscle and endothelium of the  
2 interventions under investigation to treat FGR. TX-A2, thromboxane A2; sFlt-1,  
3 soluble fms-like tyrosine kinase 1; VEGF, vascular endothelial growth factor; NOS,  
4 nitric oxide synthase; NO, nitric oxide; HO-1, heme oxygenase-1; sGC, soluble  
5 guanylate cyclase; GTP, guanosine-5'-triphosphate; cGMP, cyclic guanosine  
6 monophosphate; 5' GMP, guanosine monophosphate; PDE5, phosphodiesterase  
7 type 5 inhibitor.  
8

**Figure(s)**

