The role of aspirin, heparin, and other interventions in the prevention and treatment of fetal growth restriction

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Fetal growth restriction and related placental pathologies such as preeclampsia, stillbirth, and placental abruption are believed to arise in early pregnancy when inadequate remodeling of the maternal spiral arteries leads to persistent high-resistance and low-flow uteroplacental circulation. The consequent placental ischaemia, reperfusion injury, and oxidative stress are associated with an imbalance in angiogenic/antiangiogenic factors. Many interventions have centered on the 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 the prevention of fetal growth restriction, a 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% confidence interval, 0.81—1.00) and that a dose of $\geq$100 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 randomized control trials is inconsistent. A meta-analysis of multicenter 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% confidence interval, 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 death is high is iatrogenic preterm birth, with the use of peripartum maternal administration of magnesium sulphate for neuroprotection and corticosteroids for fetal lung maturity, to prevent adverse neonatal outcomes. The pipeline of potential therapies use different strategies, many aiming to increase fetal growth by improving poor placentation and uterine blood flow. Phosphodiesterase type 5 inhibitors that potentiate nitric oxide availability such as sildenafil citrate have been extensively researched both in preclinical and clinical studies; results from the Sildenafil Therapy In Dismal Prognosis Early-Onset Intrauterine Growth Restriction consortium of randomized control clinical trials are keenly awaited. Targeting the uteroplacental circulation with novel therapeutics is another approach, the most advanced being maternal vascular endothelial growth factor gene therapy, which is being translated into the clinic via the doEs Vascular endothelial growth factor gene therapy safEly impRove outcome in seveRe Early-onset fetal growth reSTriction consortium. Other targeting approaches include nanoparticles and microRNAs to deliver drugs locally to the uterine arterial endothelium or trophoblast. In vitro and in vivo studies and animal models have demonstrated effects of nitric oxide donors, dietary nitrate, hydrogen sulphide donors, statins, and proton pump inhibitors on maternal blood pressure, uteroplacental resistance indices, and angiogenic/antiangiogenic factors. Data from human pregnancies and, in particular, pregnancies with fetal growth restriction remain very limited. Early research into melatonin, creatine, and N-acetyl cysteine supplementation in pregnancy suggests they may have potential as neuro- and cardioprotective agents in fetal growth restriction.

Key words: aspirin, creatine, esomeprazole, fetal growth restriction, intrauterine growth restriction, low-molecular-weight heparin, melatonin, N-acetylcysteine nitric oxide donor, pravastatin, preeclampsia, sildenafil, small for gestational age, vascular endothelial growth factor gene therapy

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Fetal growth restriction (FGR) describes a group of conditions in which a fetus fails to reach its full growth potential. FGR is difficult to define and measure and so small for gestational age (SGA), defined by birthweight percentile, is often used as the most reliable surrogate marker. FGR and SGA may be caused by fetal issues such as chromosomal anomalies, genetic syndromes, and fetal infection; maternal disease; environmental toxins including cigarette

smoking; and the most common cause, uteroplacental insufficiency. This article will focus on preventative and treatment options for FGR due to uteroplacental insufficiency.

During early pregnancy trophoblast invasion of the maternal spiral arteries remodels and disrupts their smooth muscle layer, creating a low-resistance and high-flow uteroplacental circulation capable of efficient gaseous and nutrient exchange for optimal fetal growth.[1] Inadequate or abnormal trophoblast invasion results in incomplete remodeling of the spiral arteries and persistence of a high-resistance and low-flow circulation.[2,3]

It is hypothesized that this results in a sequence of events including reduced placental perfusion, placental ischemia and reperfusion injury[4]; oxidative stress[5]; an imbalance in angiogenic factors[6-8]; vascular endothelial growth factor (VEGF) and placental growth factor (PlGF), with antiangiogenic factors; soluble fms-like tyrosine kinase 1 (sFlt-1); and soluble endoglin and an increased frequency of atherosis in the placental bed.[9]

Clinically these events present as the placenta-mediated complications of pregnancy: FGR, preeclampsia, placental abruption, and late pregnancy loss. Placental bed biopsies in pregnancies affected by FGR and preeclampsia confirm that there is a major defect in myometrial spiral artery remodeling that is linked to these clinical parameters.[10-12]

The ongoing adverse in utero environment associated with FGR ultimately may lead to hypoxic damage and stillbirth. With no proven therapeutic interventions available planned early birth must be considered and offered once a fetus reaches a viable gestational age and size. However, preterm birth then adds further morbidity and mortality risk to an already compromised neonate.

There is an urgent need to identify early in pregnancy those women at most risk of developing FGR to investigate and offer preventative therapies. Once FGR is diagnosed, other strategies will be required to improve fetal growth and well-being, which may allow iatrogenic delivery to be delayed and/or to ameliorate the harm of the hypoxic intrauterine environment.

Prevention of FGR

Aspirin and other antiplatelet agents

The release of sFlt-1 and soluble endoglin[6,7] into the maternal circulation causes endothelial dysfunction, a feature of the placenta-mediated complications of pregnancy and in particular preeclampsia, and an imbalance in vasoactive factors such as endothelin,[13] nitric oxide,[14] and prostacyclin,[15] resulting in reduced vasodilatation and increased vasoconstriction.

Aspirin has a number of effects at the vascular level that may prevent FGR (Figure). For many years it was understood that aspirin suppresses the production of prostaglandins and thromboxanes through its irreversible inactivation of the cyclooxygenase enzyme. Thromboxane is a powerful vasoconstrictor and prothrombotic antiplatelet agent. Low-dose, long-term aspirin use irreversibly blocks the formation of thromboxane A2 in platelets, inhibiting platelet aggregation. More recently, novel cytoprotective and antioxidant mechanisms of aspirin have been observed that are independent of cyclooxygenase inhibition. Aspirin acetylates endothelial nitric oxide synthase, leading to nitric oxide release from the vascular endothelium.[16] In addition, aspirin increases the activity of heme oxygenase-1 in endothelial cells to catabolize heme, which leads to a reduction in oxidative stress, injury, and inflammation.[17]

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

This year there was simultaneous publication of systematic reviews based on study-level meta-analysis[18] and individual patient data meta-analysis[19] of randomised trials of aspirin and other antiplatelet agents that included 20,909 and 32,217 women, respectively. Both analyses supported preexisting evidence that aspirin provides a modest risk reduction for FGR and SGA (less than the fifth or less than the 10th percentile) at birth (individual patient data analysis relative risk, 0.90, 95% confidence interval [CI] 0.81-1.00).[19] The difference in the conclusions of these meta-analyses arose from assessment of gestational age at initiation of therapy, before or after 16 weeks (Table 1).

The individual patient data meta-analysis found that low-dose aspirin and other antiplatelet agents had a consistent effect on preeclampsia, regardless of whether treatment was started before or after 16 weeks gestation.[19] Data specific to FGR support earlier initiation of therapy where possible. In the study-level meta-analysis, there was a dose-response relationship for SGA when treatment was initiated $\leq$16 weeks, favoring a dose of 100−150 mg.[18]

Studies demonstrating circadian effects of aspirin on plasma renin activity[20] and urinary excretion of cortisol, dopamine, and norepinephrine[21] as well as clinical trials that show a circadian effect of aspirin to treat prehypertension[22] and mild hypertension[23] in nonpregnant adults suggest timing of daily dosing should be considered, particularly with reference to the prevention of preeclampsia.

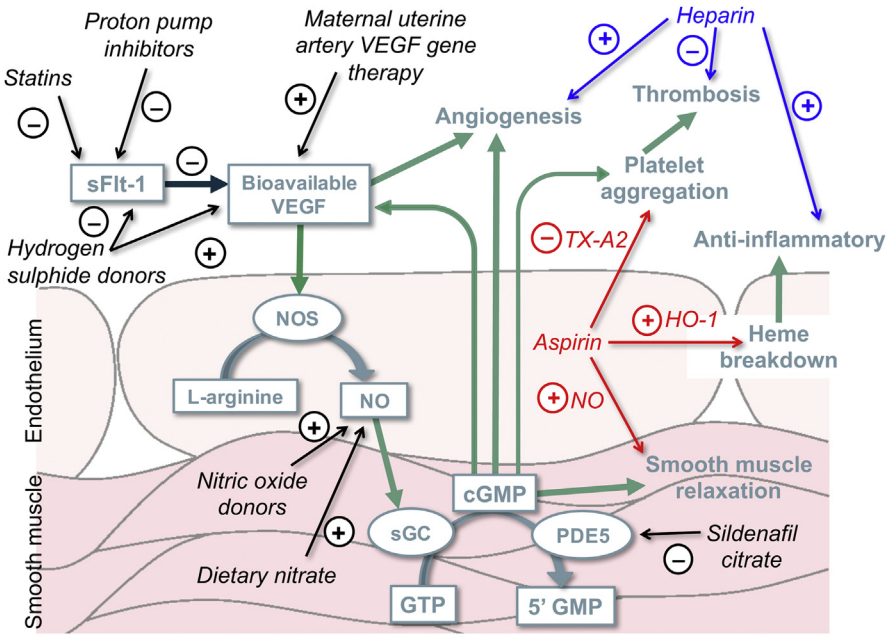
Two small randomized trials in pregnancy have found that evening but not morning administration of aspirin is associated with a reduction in ambulatory blood pressure,[24,25] and in one of these trials, a reduction in the incidence of preeclampsia and FGR was also seen.[24] The circadian mechanism of 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 a 100−150 mg aspirin dose to prevent FGR and SGA pregnancy in women at high risk.[26] However, patient selection and accurate identification of those at most risk of FGR is not clear because, 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, multicenter, randomized trial of aspirin to prevent preterm preeclampsia.

The Aspirin for Evidence-Based Preeclampsia Prevention 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 less than the 10th, less than the fifth, or less than the third percentiles were unchanged,[27] suggesting alternative prediction models are required before being able to truly assess the effect of aspirin on those at highest risk.

FIGURE
Sites of action of interventions under investigation to treat FGR



Sites of action at vascular smooth muscle and endothelium of the interventions under investigation to treat FGR.

cGMP, cyclic guanosine monophosphate; *5′ GMP*, guanosine monophosphate; *PDE5*, phosphodiesterase type 5 inhibitor; *GTP*, guanosine-5′-triphosphate; *HO-1*, heme oxygenase-1; *NO*, nitric oxide; *NOS*, nitric oxide synthase; *sFlt-1*, soluble fms-like tyrosine kinase 1; *sGC*, soluble guanylate cyclase; *TX-A2*, thromboxane A2; *VEGF*, vascular endothelial growth factor.

Groom. Therapeutic interventions in fetal growth restriction. Am J Obstet Gynecol 2018.

Heparin and low-molecular-weight heparin

Unfractionated heparin and low-molecular-weight heparin (LMWH) are commonly used in pregnancy for thromboprophylaxis and the treatment of venous thromboembolism. More recently LMWH is preferred to unfractionated heparin and appears safe and effective for these indications.[28] Unfractionated heparin and LMWH do not cross the placenta[29] and thus pose little direct risk to the fetus.

Initial interest in heparins to prevent placental pathology centered 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 antiinflammatory,[30] complement inhibition,[31] and antitumor[32] actions as well as being proangiogenic[33-37] (Figure). 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.[33,34,36] The mechanism of action is unclear, but enhanced expression of matrix metalloproteinases may be contributory.[38] However, there are inconsistencies in the in vitro study results with some demonstrating suppression of trophoblast invasion,[39] particularly when heparin is used at therapeutic levels.[40] Further caution is raised by the finding of elevated sFlt-1 concentration and impaired VEGF signaling in endothelial cells when placental villi are exposed to LMWH at therapeutic doses,[41] 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 PlGF concentration is increased and there is a lower sFlt-1/PlGF ratio compared with gestation-matched controls,[37] and in a small randomized trial of women at high risk of preeclampsia, plasma levels of PlGF were elevated 1 and 3 hours after LWMH administration, not seen in women at similar risk receiving placebo.[35]

The effect of heparin therapy on uteroplacental circulation is less clear. In a small open-label study of women with gestational hypertension, treatment with LMWH reduced the uterine artery resistance index.[42] However, more sustained use of LMWH in a randomized control trial of LMWH and aspirin vs 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.[43]

Because early evidence suggested a relatively strong association between inherited thrombophilias and preeclampsia and FGR, initial randomized

TABLE 1
Effect of gestational age at initiation of aspirin therapy for prevention of FGR or SGA at birth

	Relative risk	95% CI
Study-level meta-analysis[53] (FGR), wks		
≤16	0.56	0.44–0.70
>16	0.95	0.86–1.05
IPD meta-analysis[54] (SGA), wks		
<16	0.76	0.61–0.94
≥16	0.95	0.84–1.08

Study level meta-analysis[53] used FGR as outcome to assess fetal size, defined as birthweight <10th or <5th percentile for gestational age or similar definition. The IPD meta-analysis[54] used SGA as outcome to assess fetal size; SGA at birth was as defined by individual trialists, including centile charts and cutoff point used. *FGR*, fetal growth restriction; *IPD*, individual patient data; *SGA*, small for gestational age.

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trials of heparin focused specifically on populations of women with or without thrombophilia.[44-46] More recent evidence from prospective cohort studies suggests any association of thrombophilia and placenta-mediated complications, if present, is only weak,[47] 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.[44,45] But a positive effect of LMWH was not seen consistently across all published trials,[44-46,48-52] possibly reflecting the heterogeneity of the populations being examined, the type of LMWH being used, prolonged trial recruitment phases,[44,46] and early trial discontinuations.[45,48]

A study-level meta-analysis of 6 trials (848 women) demonstrated LMWH (included trials used enoxaparin, dalteparin, and nadroparin) was associated with a reduction in a composite outcome (preeclampsia, birthweight <10th 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 <10th percentile and less than the fifth percentile.[53] 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 5 trials from the study-level meta-analysis and 3 additional trials (963 women).[54] Again, a composite primary outcome (early-onset or severe preeclampsia, SGA less than the 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 trial data of LMWH therapy was associated with a reduction in SGA <10th percentile and less than the fifth percentile but not less than the third percentile. However, trial quality also had an impact on these results, with heterogeneity seen between single-center and multicenter trials; there was no effect of LMWH seen when considering only data from multicenter trials (Table 2).

In a 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 subgroup analysis by type of LMWH used but a further study-level meta-analysis including fewer participants (403 women in 5 heterogeneous trials) has compared dalteparin and enoxaparin use. Both types of LMWH were associated with a reduction in preeclampsia, but only dalteparin was effective in reducing the incidence of FGR.[55]

Since the publication of the 2016 individual patient data meta-analysis,[54] 2 further multicenter trials have been published. The Heparin-Preeclampsia[49] and Enoxaparin for Preeclampsia and Intrauterine Growth Restriction (EPPI)[52] trials included only women at high risk of placenta-mediated pregnancy complications, with or without inherited thrombophilia.

The EPPI trial included a higher proportion of women with a prior history of an SGA infant than most other trials.[52] Both trials reported no difference in rates of composite primary outcomes (maternal death, perinatal death, preeclampsia, placental abruption, and/or SGA <10th percentile in the Heparin-Preeclampsia trial and preeclampsia and/or SGA less than the fifth percentile in the EPPI trial) or any secondary outcomes specific to fetal growth.

These recent trials add significant participant numbers (n = 406) and show consistent results with the conclusion of the published individual patient data meta-analysis, that LMWH does not reduce the risk of recurrent placenta-mediated pregnancy complications in at-risk women. If LMWH therapy is protective for the recurrence of placenta-mediated pregnancy complications, then the effect is likely to be modest and, if present, possibly confined to certain subgroups only or specific types of LMWH.

Currently LMWH therapy for the prevention of FGR should be limited to the research setting. Before any future trials are undertaken, further research is required to accurately phenotype women deemed to be at the highest risk to better identify those who may 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 remodeling 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 Table 3.

Preclinical studies

In vitro studies show that when compared with healthy control vessels, myometrial small arteries from pregnancies affected by FGR have increased vasoconstriction and reduced vasorelaxation; preincubation with sildenafil ameliorates this difference.[56]

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 ($COMT^{-/-}$) knockout mouse model of preeclampsia and FGR,[57] sildenafil in maternal drinking water in late pregnancy normalises pup growth measures and abnormal umbilical artery Doppler flow indices when compared with untreated catechol-O-methyl transferase ($COMT^{-/-}$) controls.[58] However, this beneficial effect on fetoplacental 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 vascular phenotype.[59] Alterations in placental weight may be an alternative to vasodilatation as the mechanism of action, a theory that is further supported by studies in ovine models of FGR. In maternal nutrient-restricted FGR sheep pregnancy,

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			Multicenter trials			Single-center trials		
Variables	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
Primary composite outcome[a]	62/444 (14%)	95/433 (22%)	−8.0% (−17.3 to 1.4) *P* = .09	47/263 (18%)	47/255 (18%)	−0.6% (−10.4 to 9.2) *P* = .91	15/181 (8%)	48/178 (27%)	−18.7% (−21.6 to −15.7) *P* < .0001
SGA <10th percentile	61/444 (14%)	94/429 (22%)	−8.2% (−5.4 to −0.1) *P*= .009	47/263 (18%)	53/251 (21%)	−3.2% (−9.6 to 3.1) *P* = .32	14/181 (8%)	41/178 (23%)	−15.3% (−19.1 to −11.5) *P* < .0001
SGA <fifth percentile	27/443 (6%)	38/429 (9%)	−2.8% (−5.4 to −0.1) *P* = .042	22/262 (8%)	23/251 (9%)	−0.8% (−3.7 to 0.2) *P* = .61	5/181 (3%)	15/178 (8%)	−5.7% (−6.1 to −5.2) *P* < .0001
SGA <third percentile	13/443 (3%)	12/249 (3%)	0.1% (−1.9 to 2.2) *P* = .89	13/262 (5%)	9/251 (4%)	1.4% (−1.3 to 4.1) *P* = .32	0/181	3/178 (2%)	[b]

Data are extracted from Rodger et al, 2016.[54] Data are expressed as a number (percentage). *CI*, confidence interval; *LMWH*, low-molecular-weight heparin; *SGA*, small for gestational age.

[a] Primary composite outcome includes early-onset or severe preeclampsia or SGA less than the fifth percentile or placental abruption or pregnancy loss ≥20 weeks' gestation; [b] Expected counts were less than 5, so no formal testing was performed.

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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	Antiinflammatory, antioxidant, and angiogenesis	Phase II/III clinical trials (for preeclampsia only)
Nitric oxide donors	Oral	Selective vascular smooth muscle relaxation and vasodilatation	Phase II nonrandomized (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 nonrandomized
Creatine	Oral	Cellular energy homeostasis	Preclinical
N-acetylcysteine	Oral	Selective vascular smooth muscle relaxation and vasodilatation	Phase II randomized (for preeclampsia only)

VEGF, vascular endothelial growth factor.

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sildenafil increased fetal growth and amino acid availability. In addition, when FGR was created in sheep using uterine artery embolization, sildenafil improved placental and lamb weight and ameliorated the increased umbilical artery resistance but with no effect on maternal myometrial vessel resistance.[60] Not all preclinical studies, however, have demonstrated positive effects of sildenafil treatment on FGR, with some animal models showing no effect and others showing negative and potentially harmful effects.[61,62]

Clinical studies

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

Two small randomized trials have studied sildenafil treatment of preeclampsia in which 30−60% of participants had coexisting FGR.[69,70] Both trials demonstrated positive effects on maternal blood pressure, and in one trial sildenafil was associated with an increase in the mean prolongation of pregnancy (14.4 days vs 10.4 days, $P = .008$). No differences were seen in the measures of fetal growth, but compared with placebo, uterine and umbilical artery Doppler pulsatility index was reduced 24 hours after commencing sildenafil.[70]

More specific to FGR pregnancies, a single-dose, randomized, placebo-controlled trial showed that 2 hours after ingestion of 50 mg sildenafil, there was reduced resistance in the umbilical artery and increased resistance in the fetal middle cerebral artery, showing it can influence the fetoplacental circulation.[71] To date, more prolonged use of sildenafil to treat FGR has been reported only in case reports[72,73] and a small case-control study.[74]

In this open study, 10 women with early-onset FGR received 25 mg three times daily sildenafil and were compared with 17 matched untreated control women. A higher proportion of women taking sildenafil had an increased posteligibility fetal abdominal circumference growth velocity (90% vs 41%, odds ratio, 12.9, 95% CI, 1.3−126) with a tendency toward improved survival and intact survival to hospital discharge. However, it should be noted that the sildenafil-treated group were eligible for the study an average of 10 days later and delivered an average of 9 days after those untreated, delivering at a time (<28 weeks) when gestational age is likely to be the most significant predictor of outcome.

These limited human pregnancy studies to date have not raised specific concerns of maternal and/or fetal side effects. However, sildenafil does have a side effect profile including most commonly headache, flushing, dyspepsia, nasal congestion, and impaired vision and blurred vision.[75] Fetal effects are less well known. Sildenafil is likely to cross the placenta, so effects, in particular, on pulmonary vasculature and cerebral blood flow,[71] must be considered.

In addition, some animal studies suggest a detrimental rather positive effect on uterine blood flow and fetal well-being,[61] and although any delay in delivery is hoped to improve long-term outcome, ongoing exposure to a hostile in utero environment has potential to cause greater harm than that caused by preterm delivery.

The results of randomized 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 5 placebo-controlled randomized trials in the United Kingdom,[76] New Zealand and Australia,[77] The Netherlands,[78] Canada,[79] and Ireland.[80] These trials have been conceived and designed through an 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.[81]

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 cardiometabolic 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). 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 trialed extensively for coronary artery ischaemia and is now reaching phase 3 trials.[82]

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 (1×10^{11} particles), compared with injection of a control nonvasoactive vector, increased uterine artery volume blood flow within 7 days of injection, and long term, this increase in flow persisted for at least 4 weeks until the end of gestation.[83-85]

The mechanism is mediated via short-term VEGF expression detectable in the perivascular adventitia of the treated vessels. This is associated with increased endothelial nitric oxide synthase expression, which results in reduces vascular constriction. In the long term, there is vascular remodeling, with a reduced intima to media ratio, increased endothelial cell proliferation in the perivascular adventitia of injected vessels, and reduced uterine artery contractile response. Importantly, there was no evidence of vector spread or expression in fetal tissues and no effect of the vector on maternal or fetal hemodynamic measures.

In FGR sheep and guinea pig models, fetal growth velocity is increased, and fewer fetuses are affected by severe FGR at birth.[86-89] There appears to be amelioration of the brain-sparing effect in FGR fetuses of treated pregnancies, with a lower brain to liver weight ratio by ultrasound measurement and at birth. Offspring born after treated FGR pregnancies have higher postnatal lean tissue mass, a faster growth rate, and improved cardiovascular phenotype.

In the clinical context, vector delivery into the uterine arteries could be achieved through interventional radiology, which is used as a prophylactic measure before delivery in women at high risk of postpartum hemorrhage.[90] While this is more invasive than administering oral medication, it has the potential advantage of targeting vasoactive changes to the maternal uteroplacental circulation.

The doEs Vascular endothelial growth factor gene therapy safEly impRove outcome in seveRe Early-onset fetal growth reSTriction (EVERREST) Project, which started in 2013, aims to carry out a phase I/IIa clinical trial to assess the safety and efficacy of maternal uterine artery Ad.VEGF gene therapy for severe early-onset FGR.[91] The project, funded by the European Union, involves a multinational, multidisciplinary consortium, including experts in bioethics, fetal medicine, fetal therapy, obstetrics, and neonatology.

A bioethical study found no absolute ethical, regulatory, or legal objections to the use of maternal gene therapy in pregnancy, with patients welcoming the development of new drugs for this untreatable disease.[92] The consortium is performing a prospective observational study of pregnancies with severe early-onset FGR to define their trial inclusion criteria, which is likely to recruit those women who are most at risk of an intrauterine death or neonatal death between 22 and 27 weeks of gestation.[93]

Nanotechnology and other uteroplacental targeting strategies to treat FGR

There are a number of other novel strategies emerging that could target drugs or particles to the uteroplacental circulation and/or the trophoblast with the aim of improving uterine blood flow, placental function, or both (Table 3). Tumor-homing peptide sequences CGKRK (Cys-Gly-Lys-Arg-Lys) and iRGD (Cys-Arg-Gly-Asp-Lys-Gly-Pro-Asp-Cys) bind selectively to the placental surface of humans and mice and do not interfere with normal development. By coating nanoparticles with these sequences, cargoes of proteins such as insulin-like growth factor 2 can be delivered specifically to the placenta.[94]

Insulin-like growth factors promote placental cell proliferation and survival and facilitate the placental uptake of glucose and amino acids. In the placenta-specific insulin-like growth factor 2 knockout mouse model of late-onset FGR[95] such nanoparticle

insulin-like growth factor 2 treatment improved fetal weight.[96] Recently a novel nitric oxide donor (SE175) encapsulated into targeted liposomes has been delivered systemically to the endothelial nitric oxide synthase knockout mouse, which exhibits impaired uteroplacental blood flow and FGR,[97] leading to increased fetal weight and a mean spiral artery diameter and a decrease in the placental weight, indicative of improved placental efficiency.[98]

Another approach has used mitochondria-targeted antioxidant MitoQ bound to nanoparticles to localize and prevent oxidative stress in the placenta.[99] Finally, targeted microRNA treatment to the placenta may enhance intrinsic placental growth signaling. miR-145 and miR675 have previously been identified as negative regulators of placental growth. When applied to human first-trimester trophoblast explants, conjugates of the placental homing placental homing peptide CCGKRK with these peptide-microRNAs enhanced cytotrophoblast proliferation.[100] These approaches will need careful study from a safety and efficacy perspective, but they look promising for a targeted FGR treatment.

Potential drug therapies for FGR

Investigation of new drug therapies remains at the preclinical or very early clinical phases and has focused on treatment of preeclampsia rather than FGR. Statins are lipid-lowering medications with antiinflammatory, antioxidant, and angiogenic properties (Figure). Within small animal models of preeclampsia, pravastatin reduces levels of sFlt-1 and maternal hypertension and increases VEGF and fetal weight.[101,102]

In a single nonrandomized study including 21 women with antiphospholipid syndrome and treated with aspirin and LMWH, the addition of pravastatin in 11 women after the onset of preeclampsia and/or FGR appeared to delay delivery and improve pregnancy outcomes compared with 10 women who did not receive pravastatin.[103]

In the Statins to Ameliorate early onset Preeclampsia randomized trial (STAMP), which completed recruitment in 2014,[104] birthweight is included as a secondary outcome but results are still awaited. A further multicenter pilot study in the United States is expected to have completed recruitment at the end of 2018, with a rate of SGA included as a secondary outcome.[105]

Nitric oxide relaxes vascular smooth muscle cells, resulting in vasodilatation (Figure). In women with preeclampsia, short-term treatment with a nitric oxide donor, isosorbide dinitrate, reduces maternal blood pressure[106,107] and lowers resistance in umbilical artery[107,108] and uterine artery[107] Doppler waveforms. No randomized trials of nitric oxide donors have included long-term therapy or been sufficiently powered to assess any effect on pregnancy outcomes.

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

Repurposing drugs for FGR, proton pump inhibitors

Because the development of new drugs or the testing of unused drugs for the treatment of FGR pregnancy is difficult and costly, the repurposing of existing drugs that have a known safety profile in pregnancy is an exciting area. Proton pump inhibitors such as esomeprazole have long-term safety data about the treatment of gastric reflux in pregnancy. In vitro studies show proton pump inhibitors decrease sFlt-1 and soluble endoglin and improve markers of endothelial dysfunction (Figure),[111] while esomeprazole reduces blood pressure in a preeclampsia transgenic mouse model that overexpresses sFlt-1.[111] The randomized placebo-controlled 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.[112]

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[113-115] and magnesium sulphate for neuroprotection[113,116] is required to prepare for birth with careful consideration of the most appropriate mode of delivery.[117] FGR is associated with long-term neurodevelopmental and cardiac impairment, likely because of oxidative stress.[118-122] 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 the expression of antioxidant enzymes such as glutathione peroxidase and glutathione reductase. Melatonin crosses the placenta[123] and the fetal blood brain barrier[124] and hence has potential to protect the developing fetal brain and heart from damage by oxidative stress.

In an ovine model of FGR, maternal administration of melatonin protects against cardiac infarct and coronary artery stiffness, cerebral white- and gray-matter injury, and abnormal cerebrovascular development, with improvement in some early neurological outcomes in the offspring. A safety study of melatonin in 6 women with early-onset FGR (4 mg twice daily for the duration of pregnancy) found no fetal[125-127] or maternal safety concerns. Cord blood levels of melatonin were higher and placental malondialdehyde concentrations, a marker of oxidative stress, were lower in the melatonin-treated

group compared with the control untreated women.[126] Trials of efficacy to support melatonin as a neuro- and cardioprotective agent[128] are awaited. A single ongoing study in women at risk of imminent preterm delivery (not specific to FGR)[129] may provide additional information.

Creatine

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

Maternal dietary creatine supplementation in a spiny mouse model with late-gestation hypoxic injury increases neonatal survival after birth hypoxia and prevents hypoxic damage to the brain, kidney, and skeletal muscle.[130-132] Studies in larger animal models with more prolonged hypoxic injury are ongoing. Low maternal serum and urine creatine levels have been associated with poor fetal growth,[133] but no randomized trials of maternal dietary creatine supplementation in humans have been undertaken.[134]

N-acetylcysteine

N-acetylcysteine scavenges reactive oxygen species and forms the antioxidant glutathione, thereby counteracting oxidative stress and increasing the bioavailability of nitric oxide.[135] Studies in a rat model of preeclampsia and FGR found that N-acetylcysteine alleviated a rise in maternal blood pressure and increased pup brain weight.[136] 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.[137] However, a small double-blind, randomized controlled trial found that oral N-acetylcysteine did not stabilize the process of established severe preeclampsia or improve neonatal outcome.[138] 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 100−150 mg 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 birth with timely administration of maternal corticosteroids and magnesium sulphate to improve neonatal outcome after early preterm birth. Several potential new therapies are on the horizon, but many of these are being primarily investigated for preeclampsia therapy with FGR as a secondary outcome only. It is important that clinicians wait for the results of appropriately designed and powered randomized controlled trials specific to FGR, which include information on meaningful longer-term outcomes before extrapolating positive preclinical and early clinical study findings into clinical practice. ■

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