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Prophylaxis and treatment of foetal growth restriction

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A B S T R A C T

Foetal growth restriction (FGR) and associated placental pathologies such as pre-eclampsia and stillbirth arise in early pregnancy when inadequate remodelling of maternal spiral arteries leads to persistent high-resistance low-flow uteroplacental circulation. Current interventions concentrate on targeting the placental ischaemia-reperfusion injury and oxidative stress associated with an imbalance in angiogenic/anti-angiogenic factors. Recent meta-analyses confirm that aspirin modestly reduces the risk for small-for-gestational-age pregnancy in high-risk women. A dose of ≥100 mg starting by 16 weeks of gestation is recommended. *In vitro* and *in vivo* studies suggest that low-molecular-weight heparin may prevent FGR; further research is needed to confirm efficacy. Once FGR is diagnosed, no treatment will improve foetal growth. Potential FGR therapies such as phosphodiesterase type-5 inhibitors or maternal VEGF gene therapy aim to improve poor placentation and/or uterine blood flow. Melatonin, creatine and N-acetyl cysteine have potential as novel neuroprotective and cardioprotective agents in FGR.

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Introduction

Normal placentation is the key to a healthy pregnancy and neonate. In normal pregnancy, trophoblast invasion of the maternal spiral arteries produces a low-resistance, high-flow maternal uterine circulation [1]. These changes are facilitated by the placental production of vasoactive substances such as vascular endothelial growth factor (VEGF) and placental growth factor (PlGF). This leads to angiogenesis and activation of endothelial nitric oxide synthase (eNOS) to produce nitric oxide (NO) and hence vasodilatation. By contrast, poor placentation appears to arise from interactions between inadequate trophoblast invasion, leading to reduced placental perfusion, and oxidative stress, resulting in the production of inflammatory cytokines. Evidence from placental bed biopsies in pregnancies affected by foetal growth restriction (FGR) and pre-eclampsia (PE) confirms that there is a major defect in myometrial spiral artery remodelling that is associated with clinical parameters [2–4]. Placental analysis also shows interstitial extravillous trophoblast, arterial endothelial activation and spiral artery atherosis [5]. The result is a relative reduction in uterine artery blood flow [6], an increase in the soluble VEGF receptor soluble fms-like tyrosine kinase-1 (sFlt-1) and a reduction in the available maternal VEGF and PlGF [7,8]. Other synergistic anti-angiogenic proteins such as soluble endoglin are increased, leading to inhibition of transforming growth factor-β signalling. The phenotype is thus attributable to an anti-angiogenic state.

The ongoing adverse *in utero* environment associated with FGR ultimately leads to hypoxic damage and stillbirth. With no proven therapeutic interventions available, planned early birth must be considered and offered once a foetus reaches a viable gestational age and size. However, prematurity 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 foetal growth and its well-being, which may allow iatrogenic delivery to be delayed and/or to ameliorate the harm of the hypoxic intrauterine environment. This article will focus on strategies to prevent or treat poor placentation that leads to FGR and to prevent the adverse outcomes it produces.

Preventing fetal growth restriction

Diet, supplements, and preconception health

It is now evident that good maternal preconception health sets up a pregnancy to have an optimal outcome. Data from long-term cohort studies such as the Southampton Women's Survey (https://www.mrc.soton.ac.uk/sws/) and the Generation R demonstrate the importance of the pre- and periconceptual diet [9,10]. Delivering a small-for-gestational-age (SGA) infant is more common in women who consume a diet consisting mainly of red and processed meat and high fat dairy [11], whilst a Mediterranean diet reduces the chance [9]. A Cochrane review found that women given antenatal dietary education and a balanced energy and protein supplementation had a reduced risk of SGA and in those undernourished, increased birthweight in their offspring; women with high protein supplementation were at an increased risk of SGA foetus [12]. In low-income countries, supplementation with multiple maternal micronutrients is associated with a decreased incidence of low birthweight and SGA infants [13]. Whether these benefits translate into long-term benefits remains to be studied.

Routine iron supplementation with or without folic acid reduces the risk of maternal anaemia and iron deficiency in pregnancy. In middle- and high-income countries, intermittent supplementation according to maternal haemoglobin level is recommended [14]. Whether there is a positive effect on other maternal and infant outcomes such as low birthweight and SGA is less clear, particularly in low-income countries, and it probably depends on the prevalence of maternal anaemia and malaria [15].

The World Health Organization recommends 1.5–2 g/day of elemental calcium in women at risk of developing PE in pregnant women with low intake of calcium, as systematic review data shows prevention of PE and preterm birth [16,17], although there was no effect on FGR or SGA. Low-dose calcium may also be of benefit but trials suffered from high risk of bias and should be interpreted with caution.

Systematic review data of the use of antioxidants such as vitamins C and E, selenium and fish oil show a reduction in PE and birth of a SGA infant but at the expense of an increase in risk of preterm birth [18]. The studies were of low quality, and routine use of antioxidants is not recommended.

There is an increased risk of delivering low birthweight and very low birthweight infants in pre-pregnancy underweight women [19]. Increased weight gain during pregnancy in underweight women reduces the risk of FGR [20], but other risk factors should be considered when advising such women about changing their weight [21]. On the other hand, a pre-pregnancy high BMI is also a risk factor for FGR, as it is associated with morbidities such as diabetes, hypertension or hypercholesterolaemia, all of which can affect foetal growth, and large population studies show an association between maternal obesity and FGR [22,23]. Studies show a dose-dependent correlation between caffeine consumption throughout the pregnancy and FGR [24], and reducing a high caffeine intake may therefore be of benefit.

There is also increasing evidence for the contribution of paternal health to the development of FGR with an association between fathering FGR offspring with preclinical evidence of the insulin resistance syndrome and smoking [25], and the effect of optimising paternal health pre-pregnancy is now under investigation.

Smoking cessation

The correlation between maternal smoking and low birthweight is well known [26]. Smoking from as early as the first trimester doubles the incidence of a SGA foetus and low birthweight infant [27], while long-term smoking in pregnancy increases the likelihood of overweight in boys at 3 years of age [28]. Interventions that promote smoking cessation in pregnancy reduce the incidence of low birthweight, increases mean birthweight and reduces excessive weight gain in boys [28,29]. Quitting smoking at any time during pregnancy improves foetal biometry in later trimesters [30].

Recreational drugs and alcohol

Most recreational drugs can easily cross the placenta not only affecting birthweight but also causing malformations that can have lifelong implications. Specifically, cannabis (marijuana), cocaine, and amphetamine (speed) use in pregnancy is associated with an increased risk of SGA and low birthweight [31–33].

Alcohol intake in pregnancy has been shown to be associated with SGA foetus and preterm birth [34]. However, a recent meta-analysis found that women who drank low-to-moderate alcohol during pregnancy were at no increased risk for SGA foetus as compared to abstainers [35], with no effect on SGA until consumption reached 10 g of pure alcohol/day (1 drink/day).

Maternal pre-existing disease

Existing medical conditions such as lupus and congenital cardiac disease are associated with an increased risk of FGR, and current antenatal management consists of multidisciplinary care with regular ultrasound assessment of foetal size. Optimising maternal health in the presence of existing medical disease is thought to be associated with pregnancy outcomes including FGR, but evidence is scant. In women with hypertension, systematic review data show that antihypertensive medication halves the risk of severe hypertension, but it has no clear effect on SGA [36]. In the randomised controlled CHIPS trial (Control of Hypertension in Pregnancy Study), where women were randomly assigned to diastolic blood pressure targets of either 85 or 100 mmHg, it was found that maternal treatment of tight control did not reduce the risk of delivering a SGA infant [37].

Maternal infection

FGR is more common in women with viral infections such hepatitis C and HIV, with nearly a quarter of all HIV-infected pregnancies affected in one study [38,39]. Malaria is prevalent in endemic areas such as Southeast Asia or sub-Saharan Africa with up to 40% incidence of FGR. In a meta-analysis, the

use of anti-malarial agents such as chloroquine reduces the incidence of low birthweight by 45% [40]. It is worth noting, however, that many confounders of malaria may exist in study populations, such as poor maternal diet. In addition, there are difficulties in estimating gestational age and in achieving an accurate measurement of birthweight in these settings [41]; further research is needed to understand the association between malaria and FGR.

Aspirin

The cyclo-oxygenase inhibitor aspirin suppresses the production of thromboxane, a powerful vasoconstrictor and prothrombotic antiplatelet agent [42], with the potential to modify placental insufficiency. Although most studies on aspirin have centred on PE as a primary outcome, often FGR is presented as a secondary outcome measure with evidence of benefit. Early trials showed no benefit of low-dose aspirin (50–60 mg) in reducing the incidence of FGR [43,44]. Current guidance by NICE is to administer 75 mg of aspirin to women according to risk factors for prognostication [45]. The use of higher dose of aspirin (150 mg) commenced between 11 and 14 weeks of gestation in high-risk pregnancy showed a reduction in the incidence of preterm PE, but the trial was not powered to detect a difference in the incidence of FGR [46]. There has recently been simultaneous publication of systematic reviews based on study-level meta-analysis and individual patient data (IPD) meta-analysis of randomised trials of aspirin and other antiplatelet agents, which included large numbers of women [47,48]. Both analyses supported pre-existing evidence that aspirin provides a modest risk reduction for FGR (<5th or <10th centile) and SGA at birth. Aspirin initiated before 16 weeks in high-risk women was associated with a significant reduction in the prevalence of FGR in a dose-dependent manner, where the optimum dose appeared to be 100–150 mg.

Heparin

Low-molecular-weight heparin (LMWH) is commonly used in pregnancy for thromboprophylaxis and the treatment of venous thromboembolism. LMWH does not cross the placenta, and *in vitro* data have suggested an angiogenic role for heparin, which is being exploited for the prevention of FGR. The use of LMWH for anticoagulation increases serum PlGF concentration and reduces the sFlt-1/PlGF ratio compared with those of gestation-matched controls [49,50]. Early studies on heparin concentrated on women with thrombophilia, but more recent trials have broadened their entry criteria. Results of early randomised trials were encouraging and suggested that heparin could reduce the risk of FGR (birthweight <5th centile) [51]. Not all published trials show a positive effect of LMWH [52–54], possibly reflecting the heterogeneity of the populations being examined, the type of LMWH being used and early trial discontinuation. An IPD meta-analysis [55] and two further large trials [56,57] have more recently been published and show consistent results that LMWH does not seem to reduce the risk of recurrent placenta-mediated pregnancy complications including FGR in at-risk women.

Treatment of foetal growth restriction

A number of interventions are being developed or reaching the phase of clinical trial in an attempt to improve foetal growth in placental insufficiency. Previous trials have shown no evidence of benefit for maternal oxygen [58] or protein supplementation, or a high protein diet, when maternal diet is adequate. Drug repurposing, the application of known drugs and compounds to treat new indications, is now being used to identify potential drugs for use in pregnancy. The advantage is that safety data for administering drugs in pregnancy are commonly available through postmarketing surveillance; the cost to pharmaceutical industry is lower or the drug may be even off-patent, allowing academic partnerships freedom to operate [59].

Nitrate supplementation

Nitric oxide (NO) is a signalling molecule synthesized from L-arginine and reduces vasopressor effects thus promoting vasodilation and blood flow [60]. It has been shown to regulate placental

vascular tone, reducing the resistance to uterine as well as foeto–placental circulation [61,62]. Reduced NO has been shown to be associated with FGR in animals and humans [63,64]. A pilot study of 26 women with an FGR foetus treated with a transdermal NO patch and plasma volume expansion has shown improvement in maternal haemodynamic indices and foetal size measurements [65]; further trials are anticipated (Table 1). Results are also awaited of a double-blind, placebo, randomised controlled trial (RCT) where a dietary approach to enhance NO production is being tested. Women with hypertension are supplemented with beetroot juice to investigate its effects on uteroplacental resistance and on complications such as FGR and PE (Table 1) [66].

Sildenafil citrate

Sildenafil citrate is a phosphodiesterase-5 inhibitor that prevents degradation of NO, thus producing vasodilatation. The interest in sildenafil citrate stems from *in vitro* studies where it was shown to relax the constricted myometrial vessels in pregnancies with PE [67]. The interest further grew when sildenafil citrate was shown to dilate myometrial vessels in FGR pregnancies without PE [68]. It is disappoint that a double-blind RCT in women with early-onset PE did not show any benefit on foetal outcomes, but there was no evidence of harm [69]. Studies in FGR sheep have given mixed results, with some showing benefit [70] while others show harm, with reduction in uteroplacental blood flow and 23% foetal weight [71]. An open-labelled small pilot study of pregnancies affected with very severe early-onset FGR with dismal prognosis found that sildenafil citrate in a dosage of 25 mg three times a day improved abdominal circumference growth compared to an untreated matched cohort (RR 12.9) [72]. Although there was no significant difference in the intact survival, overall there was some improvement in perinatal survival. Larger RCTs are therefore needed before sildenafil citrate can be considered for clinical use. To this effect, the results of the STRIDER trials that evaluate the benefit of sildenafil citrate in severe early-onset FGR are awaited [73]. The UK study completed recruitment ahead of target [74]. Oral sildenafil (25 mg three times a day) did not prolong pregnancy or improve secondary pregnancy outcomes such as birthweight, perinatal death, neonatal morbidity or neonatal unit treatment. Results from further trials in Australasia, the Netherlands and Canada (Table 1) are awaited and will contribute to a pre-planned systematic review of the topic including IPD meta-analysis [75].

Hydrogen sulphide

Hydrogen sulphide (H_2S) is produced by the enzyme cystathionine gamma-lyase and is known to be a vasodilator [76]; its angiogenic effects appear to be mediated by VEGF and the VEGF receptor 2 [76]. Pregnancies affected with PE have reduced cystathionine gamma-lyase enzyme and therefore a reduction in H_2S. Sodium hydrosulphide (NaHS), a H_2S donor, reduces vascular resistance even in healthy placentas [77]. In a sFlt-1-induced hypertensive, proteinuria rat model, intraperitoneal NaHS injection elevated VEGF levels and reduced sFlt-1 levels leading to less hypertension and proteinuria, without any adverse effects on pups [78]. More research is required in the new area of therapeutic potential of H_2S in improving placental function.

Statins

One of the physiological changes in pregnancy is hyperlipidaemia [79]. Statins are lipid-lowering medications with anti-inflammatory, antioxidant and angiogenic properties. In studies on mice treated with adenoviral vector-containing sFlt-1, which produces a PE phenotype, pravastatin ameliorated hypertension and improved foetal weight [80]. Although studies have shown no increase in congenital anomalies with statins [81], there is some concern that the abolishment of the foetal vasoconstrictor response to hypoxia by increasing NO availability could be harmful [82]. The results of a double-blind RCT of pravastatin in early-onset PE (StAmP) diagnosed between 24 and 31 + 6 weeks' gestation are awaited. Another RCT also investigated the effects of pravastatin between 12 and 16 + 6 weeks in women with PE [83]. Pravastatin has been recently used in women with

Table 1
Summary of planned or recruiting clinical trials investigating treatment options for fetal growth restriction.

Trial Identifier Number	Trial name	Target population	Investigation or Intervention	Primary outcome	Country
NCT02097667[a]	EVERREST – Developing a Therapy for Foetal Growth Restriction	Estimated foetal weight <600 g and <3rd centile at 20 + 0 to 26 + 6 weeks of gestation	Maternal uterine artery VEGF injection to improve uteroplacental blood flow	Not defined but data will be collected for birthweight and various perinatal outcomes	UK
NCT02277132[a]	The Dutch STRIDER (Sildenafil TheRapy In Dismal Prognosis Early-onset for Foetal Growth Restriction)	AC<3rd centile or EFW <5th centile between 20 and 27 + 6 weeks. EFW <700 g between 28 and 29 + 6 weeks	Sildenafil 25 mg three times daily orally from randomisation until delivery Phase II blinded randomisedplacebo-controlledtrial	Intact neonatal survival until term age	The Netherlands
ACTRN12612000584831[b]	STRIDER (NZAus): a randomised placebo-controlled trial of sildenafil therapy to improve foetal growth velocity in dismal prognosis early-onset intrauterine growth restriction (New Zealand and Australia)	Women with intrauterine growth restriction <30 + 0 weeks of gestation	Oral sildenafil, 50 mg three times a day Phase II blinded randomised placebo-controlled trial	The proportion of pregnancies with increased abdominal circumference growth velocity	Australia and New Zealand
NCT02442492[a]	STRIDER Canada: A Randomised Controlled Trial of Sildenafil Therapy In Dismal Prognosis Early-Onset Intrauterine Growth Restriction (Canada)	Women with early-onset IUGR between 18 + 0 and 27 + 6 weeks of gestation and serum PlGF levels <5th percentile for gestational age	Oral sildenafil, 50 mg three times a day Phase II blinded randomised placebo-controlled trial	Gestational age at delivery	Canada
NCT03153215[a]	Sildenafil in Severe Intrauterine Growth Retardation (IUGR)	Severe IUGR [abdominal circumference <5th percentile, gestational age <25 weeks or estimated foetal weight <600 g	Oral sildenafil, 20 mg three times a day Phase II blinded randomised placebo-controlled trial	Foetal growth velocity (25–34 weeks of gestation) proportion of women in each group for whom foetal abdominal circumference growth velocity increased post eligibility.	Egypt
NCT02672566[a]	Low-molecular-weight Heparin in Constituted Vascular Intrauterine Growth Restriction	EFW <10th centile between 22 and 34 weeks of gestation	Enoxaparin 4000 IU daily	Birthweight	France
2011-003730-13[c]	Effects of administering plasma expanders in pregnancies complicated by intra uterine growth restriction	EFW <10th centile with abnormal umbilical artery dopplers between 24 and 32 weeks	hydroxy-ethyl-starch 30 ml/kg	Birthweight	Italy

(*continued on next page*)

Table 1 (*continued*)

Trial Identifier Number	Trial name	Target population	Investigation or Intervention	Primary outcome	Country
NCT03321292	L-arginine in treatment of Intrauterine Growth Restriction	EFW < 10th centile at or after 28 weeks gestation	Phase II blinded randomised controlled trial of oralL-arginine 3000 mg/day + Acetylsalicylic acid 75 mg once daily or only Acetylsalicylic acid 75 mg once daily, until delivery	Birthweight	Egypt

[a] www.clinicaltrials.gov.
[b] www.anzctr.org.au.
[c] www.clinicaltrialsregister.eu.

antiphospholipid syndrome, who developed PE and/or FGR during treatment with low-dose aspirin and LMWH. The addition of pravastatin improved indices of uterine artery resistance and reduced features of PE, but larger trials are needed to investigate effects on foetal growth and neonatal outcome [84].

Proton pump inhibitors

An example of drug repurposing is the use of esomeprazole, a proton pump inhibitor, which may be of benefit in PE due to its upregulation of haem oxygenase-1. This enzyme has antioxidant properties, thereby decreasing the release of the antiangiogenic factors sFlt-1 and sEng and reducing endothelial dysfunction. Currently a double-blind RCT, the PIE trial, is ongoing (PE intervention with esomeprazole), which will randomise 120 women with early-onset PE to either esomeprazole or placebo from 26 to 31 + 6 weeks and evaluate maternal and neonatal outcomes including measures of foetal or neonatal size [85].

Melatonin

The antioxidant property of melatonin makes it an interesting proposition to treat poor placentation and its associated oxidative stress. Melatonin levels are altered in women with PE and FGR [86]. Studies in nutrient-restricted rats with FGR have shown that administering melatonin during the maternal period improves birth weight of the foetus [87]. In a nutrient-restricted sheep model of FGR, melatonin improved umbilical arterial blood flow without affecting uterine artery perfusion but had little effect on measures of foetal size or growth [88]. In a pilot clinical trial that involves administering melatonin orally to women with an FGR foetus, oral maternal melatonin was not associated with adverse maternal or foetal effects and it significantly reduced oxidative stress, as evidenced by reduced malondialdehyde levels, in the FGR-treated placenta compared to the placenta of the untreated group [89]. Further trials should assess if there is any beneficial effect on neonatal outcome.

Plasma exchange and plasmapheresis

PE is associated with circulating toxic mediators; removing these from the circulation generated interest as a potential treatment to improve foetal outcomes and birthweight by delaying delivery in the presence of PE. Selective approaches such as heparin-mediated extracorporeal LDL precipitation (HELP), which removes a range of inflammatory mediators such as tumour necrosis factor-alpha, showed some improvement in maternal parameters such as blood pressure and oedema [90]. A dextran sulphate adsorption (DSA) column (Liposorber® LA-15 system) has been tested in a phase 1b

proof-of-concept study of apheresis to reduce sFlt-1 in pregnant women with pre-eclampsia. Data from the trial are awaited (www.clinicaltrials.gov NCT01404910).

Targeting the uteroplacental circulation

There are a number of 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.

Maternal vascular endothelial growth factor therapy

Vascular endothelial growth factor (VEGF) causes angiogenesis and vasculogenesis and helps to produce NO thus causing vasodilatation. Local increased VEGF expression or therapeutic angiogenesis can be achieved by injection of viral vectors, commonly adenovirus to achieve short-term transgenic protein expression. This technique is being trialled extensively for coronary artery ischaemia and is now reaching phase 3 trials [91]. Adenoviral vectors containing VEGF isoforms (Ad.VEGF) have been shown to improve uterine blood flow short term (4–7 days) and long term (28–30 days) in pregnant sheep [92]. The vector is injected directly into the uterine artery leading to local VEGF expression, increased NO and vasodilatation with reduced vasoconstriction. The reassuring feature was that although no increased VEGF expression was detected after 28 days, uterine arterial blood flow remained increased suggesting the efficacy of VEGF gene therapy in vascular remodelling [93]. Ad.VEGF treatment was also tested in an overnourished sheep model of FGR, where maternal tissue grows at the expense of the foetus leading to FGR in association with reduced uteroplacental perfusion and placental dysfunction. Ad.VEGF injected directly into the uterine arteries in mid-gestation showed improvement in abdominal circumference in serial ultrasound scans, and there were significantly fewer FGR foetuses at birth [94]. The consistent result achieved in the sheep studies makes Ad.VEGF a good candidate for clinical trials. To this end, the EVERREST project started in 2013, which aims to carry out maternal uterine artery VEGF injection in women with severe early-onset FGR (Table 1). 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 [95]. An observational study of severe early-onset FGR is defining inclusion criteria for the trial [96]. The maternal uterine artery gene therapy will be carried out by interventional radiology, which is already in use for the treatment of postpartum haemorrhage [97].

Placental gene therapy with IGF1 and IGF2

Insulin-like growth factors 1 and 2 (IGF1 and 2) are expressed in trophoblast cells and play a mutagenic role in feto–placental growth [98]. IGF1 deficiency in humans manifests as severe growth retardation [99]. Animal studies with intraplacental injection with an adenovirus vector containing IGF1 (Ad.IGF1) has been shown to correct placental insufficiency and may improve foetal growth [100]. Although these results are promising, translating into human trials will need an assessment of the risks involved in intraplacental transfer and foetal effects such as vector modification of foetal germ line.

Other uteroplacental targeting techniques

The tumour-homing peptide sequences CGKRK and iRGD 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 [101]. In the placenta-specific (P0) Igf-2 knockout mouse model of FGR, such nanoparticle IGF-2 treatment improved foetal weight [102]. Recently, a novel NO donor (SE175) encapsulated into targeted liposomes has been delivered systemically to the eNOS−/− FGR mouse leading to increased foetal weight and mean spiral artery diameter and decreased placental weight, indicative of improved placental efficiency [103].

Another approach has used mitochondria-targeted antioxidant MitoQ bound to nanoparticles, to localise and prevent oxidative stress in the placenta [104]. Finally, targeted micro-RNA treatment to the placenta may enhance intrinsic placental growth signalling through enhanced cytotrophoblast proliferation [105]. These approaches will need careful study from a safety and efficacy perspective but they look promising for a targeted FGR treatment.

Clinical trials of interventions to treat foetal growth restriction

For any clinical trial of an intervention or drug, it is important to have a sufficiently comprehensive framework for grading adverse events (AEs). Until now, clinical trials in pregnancy have either not graded their AEs, leading to limited safety data, or AEs have been graded in the absence of standard criteria, leading to variability within and between trials. The EVERREST consortium has addressed this gap through a working group that led in May 2016 to the adoption of a number of new foetal and maternal AE terms by MedDRA, the Medical Dictionary of Regulatory Affairs (www.meddra.org). These standard maternal and foetal AE grading criteria will improve clinical trialling of maternal and foetal therapies in the future.

Summary

Clinicians are now able to identify risk factors for FGR not only in the first trimester but also pre-conceptionally. Getting fit for pregnancy is a message that needs to reach to women of reproductive age, as there is much evidence to show a beneficial effect of a good diet and optimal BMI to prevent the development of FGR. Low-dose aspirin reduces FGR in women at increased risk of PE, but low-molecular-weight heparin cannot be recommended yet. Unfortunately, we are still a long way away from allaying the AEs of poor placentation and its associated foetal and neonatal consequences once it is detected. The only intervention clinicians can offer is iatrogenic preterm birth by administering maternal steroids and magnesium sulphate on time to improve neonatal outcome after early preterm birth. Nevertheless, there are some potential therapeutic strategies emerging from pre-clinical animal studies and repurposing of existing drugs. Translating these therapies to humans is complex owing to a

Practice points

- Pre-conceptionally encourage a healthy diet, folic acid and optimal BMI to achieve best foetal growth.
- Smoking cessation at any gestational age improves birthweight.
- Aspirin modestly reduces the risk for small-for-gestational-age pregnancy in high-risk women, used at a dose of 100–150 mg starting by 16 weeks of gestation at night.
- Further research is needed to confirm if low-molecular-weight heparin may prevent FGR.
- To achieve best neonatal and maternal outcomes in foetal growth restriction, delivery should be planned with optimal timing of administering maternal steroids and magnesium sulphate.

Research agenda

- The value of low-molecular-weight heparin to prevent foetal growth restriction in at-risk women
- Effective dissemination to women of reproductive age that pre-conceptional health optimisation improves pregnancy outcomes and reduces the risk of foetal growth restriction.
- Preclinical development and clinical translation of novel therapeutic strategies or repurposed drugs to improve foetal growth *in utero*.
- Preclinical development and clinical translation of novel neuroprotective and cardioprotective agents in foetal growth restriction.

myriad of factors such as risk/benefit, AEs, cost of drug development, ethics, and informed consent in pregnancy. However, with more trials concentrating on treatment of FGR, there is now hope for a better outcome for pregnancies affected with poor placentation.

Conflicts of interests

ALD is a shareholder in Magnus Growth, a company that is aiming to take therapy for foetal growth restriction into the clinic.

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