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IFPA Gábor Than Award Lecture: Recognition of placental failure is key to saving babies' lives

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ABSTRACT

In high-income countries, placental failure is implicated in up to 65% of cases of stillbirth. Placental failure describes the situation where the placenta cannot meet the fetus' needs and may be the end-result of a variety of underlying pathological processes evident in the placental disc, membranes and umbilical cord. These include lesions with genetic, environmental, infectious, inflammatory, mechanical, metabolic, traumatic or vascular origin. Investigation of placental tissue from stillbirths and from pregnancies at an increased risk of stillbirth has demonstrated changes in macroscopic and microscopic structure which are themselves related to abnormal placental function.

A better understanding and identification of placental failure may improve the management of pregnancy complications and of pregnancies after stillbirth (which have a 5-fold increased risk of stillbirth). The majority of current antenatal tests focus on the fetus and its response to the intrauterine environment; few of these investigations reduce stillbirths in low-risk pregnancies. However, some currently used investigations reflect placental development, structure and vascular function, while other investigations employed in clinical research settings such as the evaluation of placental structure and shape have a good predictive value for adverse fetal outcome. In addition, recent studies suggest that biomarkers of placental inflammation and deteriorating placental function can be detected in maternal blood suggesting that holistic evaluation of placental structure and function is possible. We anticipate that development of reliable tests of placental structure and function, coupled to assessment of fetal wellbeing offer a new opportunity to identify pregnancies at risk of stillbirth and to direct novel therapeutic strategies to prevent it.

1. Introduction

1.1. Stillbirth

Antepartum stillbirth, the death of a baby before labour, remains a challenge to modern obstetrics even in high-income countries (HICs). Internationally, stillbirth is defined as the birth of an infant with no signs of life after 22 weeks gestation or, where gestation is unknown, a birthweight ≥500 g. For international comparisons the World Health Organisation applies a threshold of 28 weeks gestational age or 1000 g [1]. In HICs, the majority of stillbirths (~90%) occur before the onset of labour (described as antepartum stillbirths) and result from diverse causes [2]. Due to its essential role in the maintenance of a healthy pregnancy, placental dysfunction is implicated in a significant proportion of antepartum stillbirths (as opposed to intrapartum stillbirths which relate to an event occurring during labour). Despite extensive research, the clinical tools for screening and diagnosis of placental dysfunction currently lack sensitivity and specificity to prevent stillbirths in a cost-effective way. For example, fetal biometric measurements have a sensitivity of 40–74% and a specificity of 72–81% for the diagnosis of an SGA infant [3–5]. Umbilical artery Doppler has a sensitivity of 19% and specificity of 91% for the prediction of SGA in a low-risk population [6], which rises to a sensitivity of 55% and a specificity of 85% in high-risk cases [7]. Here we argue that a better appreciation of the nature of placental dysfunction in cases of stillbirth could facilitate better identification of placental and fetal compromise

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antenatally, which, in combination with timely and effective intervention, could reduce the number of antepartum stillbirths. We also highlight novel approaches for the identification of placental conditions which may lead to more effective detection of placental dysfunction in the future.

1.2. Linking the placenta and stillbirth

The association between placental disorders and stillbirth has mostly been examined by epidemiological studies describing conditions present in cohorts of stillbirths. The recording of associations and/or presumed cause(s) makes use of classification systems which record placental conditions as the cause of death in 11–65% of cases [8]. Some of the variation in estimates of the placental contribution to stillbirth results from the ability of these classification systems to record placental conditions, which is itself dependent on the ability to detect placental lesions. However, with the exception of placental abruption, placental lesions are infrequently recorded as a primary cause of stillbirth (mean 13.9%, 7.9–21.8%) [8–11]. Involvement of the placenta can also be inferred by the association between stillbirth and pregnancy complications associated with placental abnormalities such as fetal growth restriction (FGR) or preeclampsia (PE) which are more easily identified and recorded. FGR and PE are implicated in 43% and 4.5% of stillbirths respectively [12]. Further evidence of the importance of the placenta in stillbirth is emphasised in the increased pregnancy loss rate seen in confined placental aneuploidy (reviewed in Ref. [13]) and the association between pregnancy loss and imprinted genes in the placenta [14], indicating that primary placental abnormalities can dictate the outcome of pregnancy.

1.3. Placental failure

Organ dysfunction describes the situation when an organ does not perform its expected function; when this dysfunction occurs to such a degree that the normal homeostatic functions do not occur this may be termed organ failure. In this situation, additional intervention is required to support the organ, e.g. haemodialysis in the case of renal failure. Multiple organ failure, also known as multiple organ dysfunction syndrome (MODS), describes the situation when two or more organ systems are failing to maintain their homeostatic roles [15]. The placenta has such diverse homeostatic roles it could be viewed as fulfilling the same role for the fetus as multiple organs in the adult, including: gas and waste exchange (lungs/kidney), nutrient transport (gut), immune protection, hormone synthesis (liver/pancreas/kidney), endogenous and xenobiotic metabolism (liver). Thus, placental failure is synonymous with MODS in ex-utero life. Critically, MODS in children has a high mortality rate (10–56%) [15]; there is no specific treatment and care focuses on adequate oxygenation and organ support. In placental failure, clinicians are fortunate that there is usually no additional fetal organ dysfunction, so delivery with appropriate supportive care offers the opportunity of infant survival.

Despite the use of “organ failure” in medical terminology, this term has not been applied to the placenta, instead terms such as “placental insufficiency” or “placental dysfunction” are used which are less specific and potentially lack the clinical impact attached to organ failure. Placental insufficiency has historically been used to describe a failure of conversion of uteroplacental arteries leading to conditions such as preeclampsia, which is only one cause of placental failure. As stated earlier, placental dysfunction indicates that the organ does not perform as expected, failure describes a more severe phenotype, when the basic homeostatic roles of the placenta such as gas and nutrient exchange no longer occur. We argue that due to the essential and multiple roles of the placenta, placental failure underpins a significant proportion of stillbirths and related pregnancy complications. Furthermore, we propose that placental failure as opposed to placental dysfunction may in part explain the differential outcome between babies born small but alive, where a dysfunctional placenta meets homeostatic requirements, from those who die *in utero*, where it does not. Thus, the survival of the infant may depend upon the magnitude of the placental insult.

1.4. Placental lesions and antepartum stillbirth

Organ failure may be classified by speed of onset as acute or chronic, or by the primary cause of the lesion such as: congenital or genetic problems, environmental (including drugs), infective, inflammatory, mechanical, structural or vascular conditions. These categorisations may be applied to the variety of placental conditions relevant to stillbirth (Table 1), although temporal classification is limited by the small number of conditions that have an acute onset, e.g. placental abruption, cord occlusion or acute chorioamnionitis. Our understanding of the contribution of specific placental lesions to stillbirth is constrained by the quality of evidence, with few high-grade studies such as systematic reviews. In the high-quality assessments that do exist a link has been reported between the recurrence of subchorionic intervillositis and subsequent pregnancy loss [16], but found insufficient evidence to conclusively link villitis of unknown etiology with stillbirth, although an association was seen with FGR [17].

Our systematic review evaluating the utility of histopathological examination of the placenta included 21 studies and confirmed that 11–65% of stillbirths were attributed to a placental cause, and 32–84% were associated with placental conditions (but no causal link was made) [8]. Classification systems such as TULIP that have the largest number of placental categories are most likely to record placental conditions associated with stillbirth [18]. If a modern classification system is used, histological examination of the placenta reduces the proportion of unexplained stillbirths from 26.3% to 10.5% [9]. Of relevance to the identification of placental failure, stillbirths are associated with reduced placental size and increased birthweight: placental weight ratio irrespective of the assigned cause of stillbirth [19].

Despite data supporting histopathological evaluation of the placenta in stillbirths, the origin and significance of specific histopathological lesions remains unclear. Many lesions, including ascending genital tract infection and chronic maternal vascular underperfusion are also seen in apparently normal pregnancies [20], thereby questioning the specificity of placental abnormalities in complicated pregnancies. Secondly, some lesions are reported to have multiple unrelated associations; the best example of this is fetal thrombotic vasculopathy which has variously been reported to be: an artefact of *in utero* retention [21], associated with cord abnormalities/umbilical cord accident [22,23], cytomegalovirus infection [24], thromboembolic damage of essential organs [25], gestational diabetes and FGR [26]. This lack of clarity is not aided by the quality of such studies which are predominantly retrospective, observers are unblinded to outcome, diagnostic criteria are not stated in 75% of cases and only 17% of studies used healthy controls [8]. Thus, methodologically robust studies are required to address the role of specific lesions in cases of stillbirth and related complications.

In the largest and most detailed case-control study of 518 stillbirths, the majority of abnormal histopathological findings were seen more commonly in stillbirths than live births [27]. However, the type of placental lesions changed across gestation, with inflammatory changes and retroplacental haematoma (indicating placental abruption) more common in early gestations, whereas

Table 1
Placental conditions associated with stillbirth categorised by primary aetiological factors using a "surgical sieve" approach to provide a structure to organise individual conditions which are then related to their histological phenotype.

Aetiological category	Placental conditions related to stillbirth and pregnancy loss	Placental histological phenotype
Congenital/genetic disorders	Confined placental mosaicism	Histologically normal placenta or dysmorphic villi, increased stroma with poorly formed vasculosyncytial membranes.
	Placental mesenchymal dysplasia	Enlarged oedematous villi containing cisternae/vacuoles with occasional obliterated fetal blood vessels. No evidence of trophoblast hyperplasia.
Environmental (including drugs)	Placental abruption	Retroplacental clot. Possibly no histological abnormality in acute abruption. Old abruption – degenerating erythrocytes, laminated fibrin, pigmented macrophages and destruction of decidua basalis.
Infection	Chorioamnionitis	Acute inflammatory infiltrate to placental villi and membranes with polymorphonuclear leukocytes predominating. Causative organisms may be visible on microscopy.
	Villitis	Dependent on causative agent e.g. cytomegalovirus – chronic lymphoplasmacytic villitis with thrombosis of fetal capillaries, adjacent haemosiderin deposits, villous necrosis and tissue destruction. Toxoplasmosis – diffuse lymphoplasmacytic infiltrate. Chagas' disease (*Trypanosoma cruzi*) – Parasites in placenta accompanied by destructive villitis intervillous accumulation of fibrin and inflammatory cells.
Inflammatory	Villitis of unknown aetiology	Lymphohistiocytic infiltrate comprising maternal T cells and fetal macrophages in the villous stroma with accompanying villous destruction. Lesions are usually focal with surrounding parenchyma appearing normal.
	Subchorionic intervillositis	Intervillous inflammatory infiltrate with macrophages predominating, associated fibrin deposition.
Mechanical	Umbilical cord occlusion	Presence of occlusive knot in umbilical cord.
	Rupture of Vasa Praevia	Presence of ruptured fetal vessels in membrane, placenta may be pale.
Metabolic	Maternal diabetes	Large placenta. Distal villous immaturity
Trauma	Placental abruption	Retroplacental clot. Possibly no histological abnormality in acute abruption. Old abruption – degenerating erythrocytes, laminated fibrin, pigmented macrophages and destruction of decidua basalis.
Vascular	Fetal malperfusion	Vascular ectasia and thrombosis within the umbilical cord, chorionic plate, and/or stem villi. Regional distribution of avascular villi or villi showing stromal karyorrhexis.
	Fetomaternal haemorrhage	May have no histological abnormality, placenta may be pale. If chronic, may have intervillous thrombi and nucleated red blood cells in the fetal circulation. Confirmed by maternal Kleihaur test.
	Maternal malperfusion	Small placenta, increased syncytial knots, increased perivillous fibrin deposition, distal villous hypoplasia, atherosis of decidual arteries.
	Infarction	Intervillous fibrin deposition with villous karyorrhexis, most notable in trophoblast then stroma leading to eventual villous necrosis (ghost villi). Old infarcts may have focal calcification. Surrounding tissue shows increased syncytial knots consistent with local hypoxia.
	Twin to twin transfusion	Anastamotic vessels between placental tissue of co-twins. Donor placenta, small, thinner placental tissue with immature villi. Recipient placenta – plethoric and thicker placenta with small, congested villi.

thrombotic lesions were more common in later gestation [27]. This confirms the need for accurately matched samples to relate placental abnormalities to stillbirths at any given gestation. Furthermore, a broad view incorporating the data regarding smaller placental size and the increased frequency of placental lesions in stillbirth supports the hypothesis proposed by Mitchell and Warland that stillbirth is usually the result of multiple insults to a vulnerable fetus [28]. Interpreting this model, we suggest that placental failure represents a primary insult, which if severe enough or (more commonly) in combination with other complications leads to fetal death.

1.5. Placental findings in conditions related to stillbirth

A better appreciation of placental findings in stillbirth would also enable the understanding of the significance of lesions in clinical scenarios associated with stillbirth such as FGR, maternal perception of reduced fetal movements and advanced maternal age. These conditions linked with increased risk of stillbirth are associated with macroscopic and microscopic changes to placental structure, alterations in fetal and maternal vascular function and nutrient transport [29–32]. Insights from these clinical scenarios are critical to understand the nature of placental failure in stillbirth as functional analyses are not possible after fetal death *in utero*. Identification of altered placental function (by *ex vivo* vascular function or transporter activity measurements) in placentas from conditions linked to increased risk of stillbirth raises the possibility that these changes can be detected antenatally *in vivo*, allowing pregnancies to be targeted for increased surveillance or delivery. For example, in pregnancies complicated by reduced fetal movements, placental size, the amount of infarction and placental biomarkers differ between normal and adverse outcome [33]. Furthermore, detailed characterisation of conditions relating to stillbirth can be used to determine which tests are likely to be useful to identify specific placental abnormalities. For example, early-onset FGR is associated with reduced conversion of maternal spiral arteries with thin, poorly vascularised villi, whereas, late-onset FGR is more heterogeneous linked to placental infarction or inflammatory conditions [34]. Therefore, investigations such as uterine or umbilical artery Doppler, which determine maternal and fetal blood flow to the placenta, have better predictive value for early-onset than late onset FGR.

1.6. Identification of placental failure using current techniques

Current methods of obstetric surveillance are based on the use of ultrasound scanning; its use in late pregnancy largely focuses on assessment of fetal growth, fetal activity and indirect assessment of fetal oxygenation by cardiotocography (Fig. 1). Although these methods are widely employed, their use is not associated with a reduction in perinatal mortality [35,36]. Other measures such as the assessment of volume of amniotic fluid are thought to provide an indirect assessment of placental function, while umbilical artery Doppler provides an assessment of fetoplacental blood flow so, of the widely used investigations, is arguably the closest to reflecting placental phenotype (Fig. 1). Maternal blood flow to the placenta is

assessed by Doppler ultrasound of the uterine artery. Systematic review shows that applying umbilical artery Doppler in high-risk populations reduces perinatal mortality [37], but the same effect is not seen in low-risk populations [38]. As the clinical test that appears most effective in reducing perinatal mortality also most closely reflects placental phenotype, and is in accord with the abnormal placental functions measured in conditions increasing the risk of stillbirth, this suggests that placental tests are worth exploring in more depth.

Placental biomarkers play a significant role in maternal serum screening for Trisomy 21 in the first and second trimester; analyses of these biomarkers has found that women with a low pregnancy-associated plasma protein A (PAPP-A) at 10–14 weeks and high level of alpha-fetoprotein at 15–20 weeks are associated with increased risk of preterm delivery and fetal growth restriction [39]. A low PAPP-A is associated with an increased risk of stillbirth from placental causes [40] (Fig. 1). Abnormal uterine artery Doppler velocimetry which relates to trophoblast invasion [41,42] is

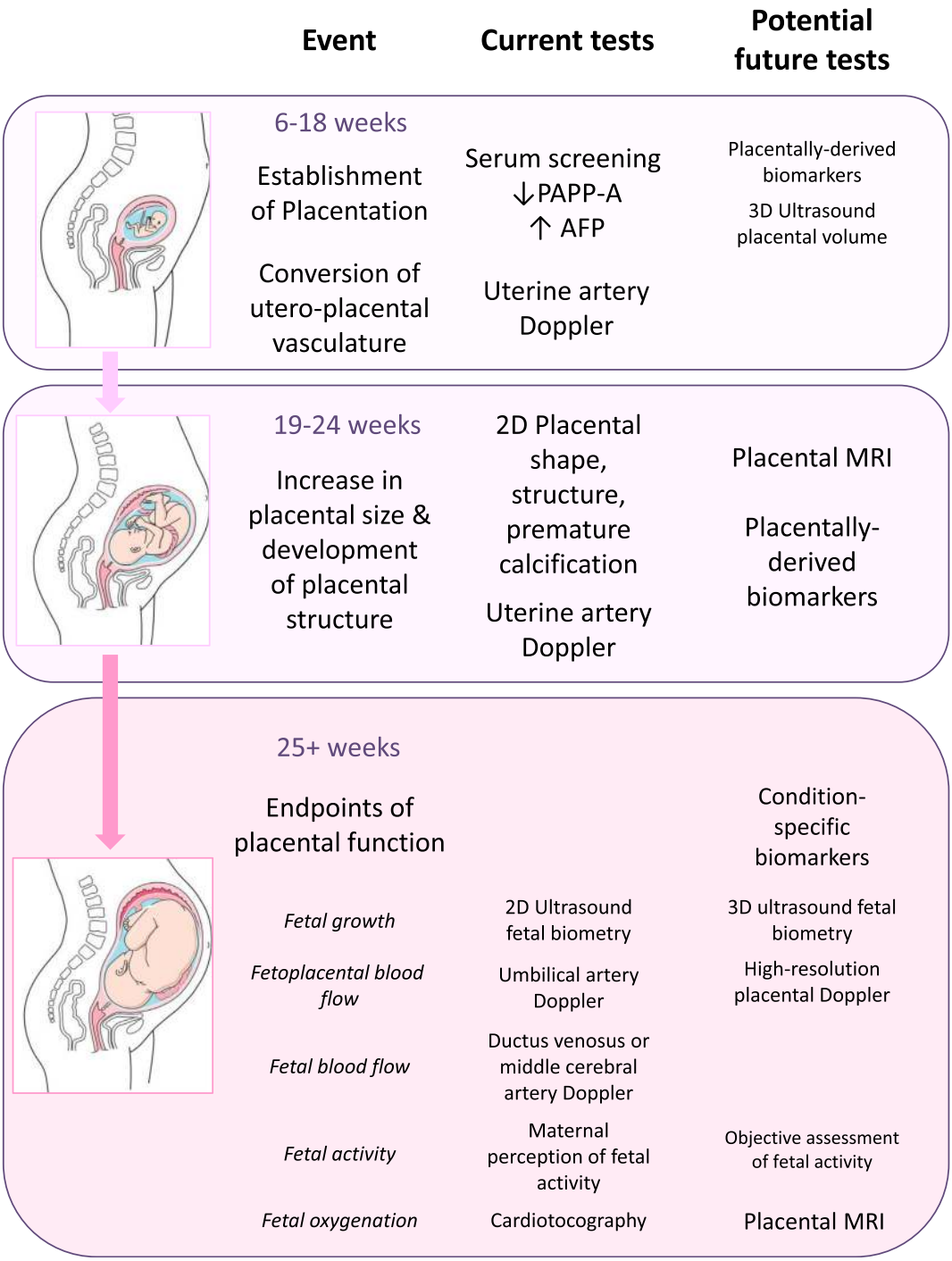

Fig. 1. Schematic representation of current and potential tests to identify placental failure divided by gestation and the event(s) they reflect. Current tests in late pregnancy mostly assess secondary effects of placental dysfunction, specifically fetal growth, fetoplacental blood flow or signs of fetal hypoxia rather than primary assessment of placental function.

associated with a two-fold increased risk of stillbirth when performed in the first trimester of pregnancy [43] and seven-fold increased risk of stillbirth when performed in the second trimester [44]; these risks are greatest for stillbirths from placental causes [45]. Interestingly, abnormal uterine artery Doppler velocimetry in early pregnancy is associated with clinical scenarios associated with placental stillbirth including reduced fetal movements [46] and fetal growth restriction [47].

Applying ultrasound assessment of placental size, structure and blood flow to these high-risk groups enabled prediction of 15/22 stillbirths [48] (Fig. 1). Conversely, a normal placental scan was associated with a risk of preeclampsia, FGR and preterm birth. The

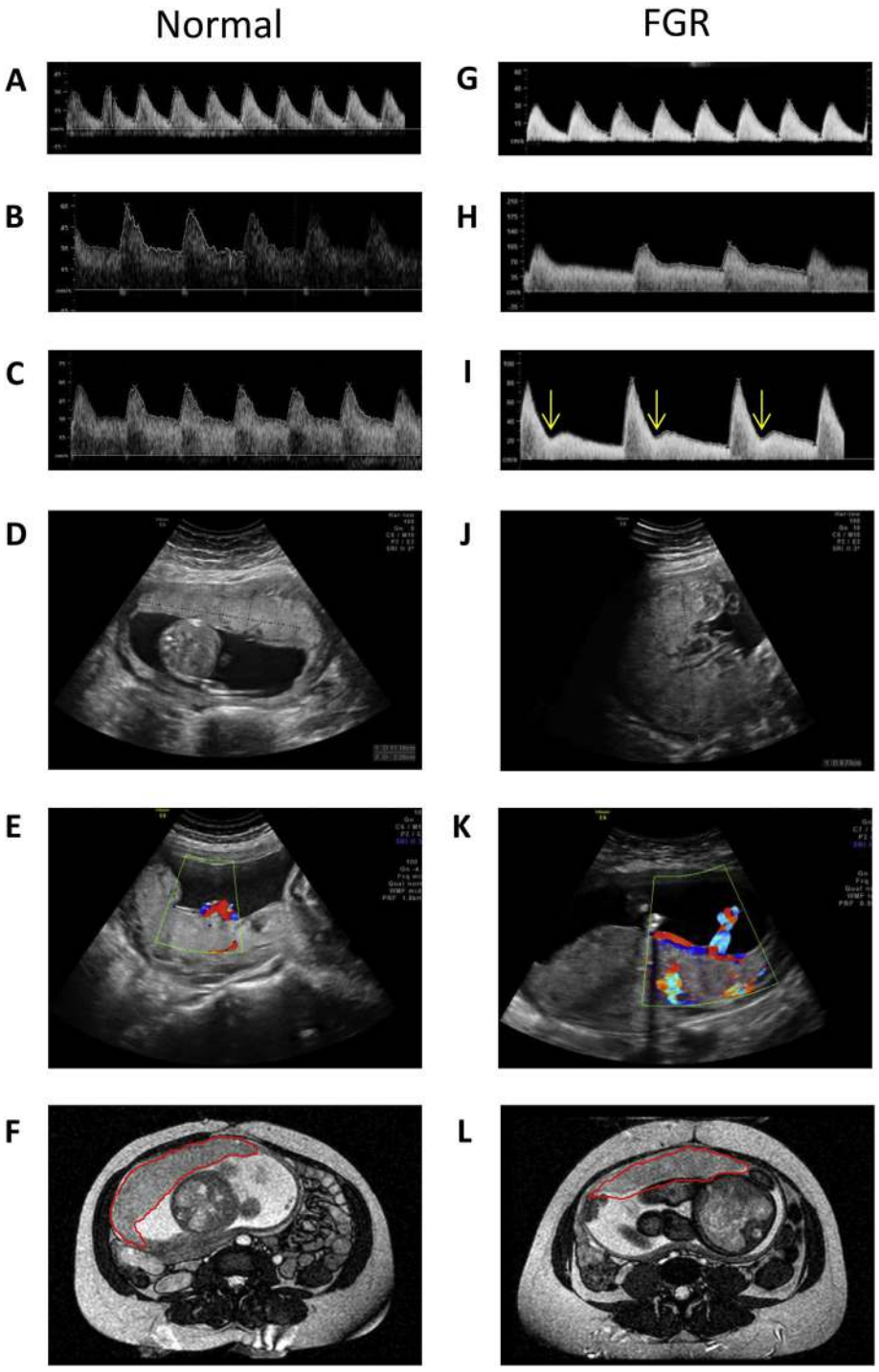

Fig. 2. Assessment of placental structure and blood flow in normal pregnancy and a pregnancy complicated by FGR. A) Normal umbilical artery waveform, Normal B) right and C) left uterine artery waveforms, D) Normal placental appearance of a thin, broad placenta in two dimensions with E) central cord insertion. F) Axial MRI image of placenta in a normally-grown infant (placenta highlighted in red). G) Increased umbilical artery pulsatility index indicating elevated fetoplacental vascular resistance, H) Normal right uterine artery waveform, I) Abnormal uterine artery waveform, notch marked by arrows, J) Placenta with increased thickness and reduced diameters and K) a lateral cord-insertion. L) Axial MRI image of placenta in an FGR infant (placenta highlighted in red).

abnormal placental appearances seen in pregnancies at high risk of stillbirth have been described as a "jelly like" placenta with patchy placental echogenicity with large areas of echo-poor placental tissue and focal echogenic cystic lesions (ECLs); these features are related to intervillous thrombosis and fibrin deposition [49] and with inadequate villous development [50–52]. We employ this ultrasound technique to identify high-risk pregnancies in women with abnormal serum screening or a history of FGR or stillbirth (Fig. 2). Normal placental appearances of a flat, thin placental disc with normal umbilical and uterine artery Doppler waveforms are rarely associated with placental failure <32 weeks gestation. In comparison, abnormal uterine or umbilical artery blood flow and a thickened placental disc is associated with pregnancy complications such as FGR (Fig. 2).

Other assessment of premature placental calcification by placental (Grannum) grading demonstrates an association with FGR and preeclampsia [53] (Fig. 1). The only comparative clinical trial of placental grading demonstrated a reduction in perinatal mortality when the result was revealed to clinicians [54]. However, this trial was over two decades ago and needs to be repeated, particularly in the light of more recent data that there is no clear relationship between placental grading and placental lesions or stereological assessment [55,56].

In addition to ultrasound-based evaluation, placental function in late pregnancy has been assessed by biochemical assessment of placental factors in maternal serum. A systematic review and meta-analysis found that measurement of urinary oestriol, the only placental hormone for which studies meeting the reviewers' inclusion criteria were available at the time of the review, did not improve perinatal outcome [57]. Since the publication of this review, three observational studies suggest that human placental lactogen (hPL) and placental growth factor (PlGF) can identify placentally-mediated adverse pregnancy outcomes in high-risk cases [58–60]. A single-centre feasibility study found that women were willing to participate in a randomised controlled trial using placental biomarker (hPL) as an adjunct to ultrasound, and that this was not related to increased maternal anxiety [61]. These studies suggest that placental assessment using existing techniques may have a role in identifying placental failure and targeting infants for intervention. Currently, intervention is limited to delivery accompanied by administration of corticosteroids to enhance fetal lung maturity in preterm infants. It is important to recognise that most of these tests have not been validated for the detection of pregnancies at high-risk of fetal death and as such are not ready for clinical practice and further trials are needed. However, at early gestations (<34 weeks) when delivery is associated with risks of neonatal mortality and morbidity better placental phenotyping may facilitate the development of novel therapies or inform the timing of delivery.

1.7. The future – identifying placental failure

There is increasing evidence that Magnetic Resonance Imaging (MRI) can provide information for phenotyping the placenta with significant advantages over ultrasound techniques. MRI of the placenta can provide good information on placental structure (Figs. 1 and 2), as shown in a study from our laboratory where we correlated changes in relaxation times, measured close to term, with fibrin deposition in the placenta [62]. MRI can also give reasonable assessment of placental blood flows [63]. However, where MRI measurements have a real advantage over ultrasound is in terms of placental metabolic function. Denison and colleagues have shown that proton magnetic resonance spectroscopy can be used to distinguish metabolic state between placentas of normal versus FGR pregnancies [64]. Furthermore, we have shown that oxygen-enhanced MRI and blood-oxygen-level dependent contrast imaging (BOLD) can be used to give information on the oxygenation of the placenta over gestation [65] and, simultaneously, provide a measurement of fetal brain oxygenation [66]. These MRI techniques are therefore likely to be of great value in the future for diagnosing placental dysfunction and the transition to placental failure.

1.8. The future – phenotyping placental failure

In addition to more detailed description of placental structure and function, the pathogenesis of placental failure could be elucidated by novel approaches. Currently, the majority of antenatal and postnatal investigations aim to identify vascular abnormalities associated with stillbirth (Fig. 1 and Table 1). However, recent studies of women with reduced fetal movements demonstrate placental infiltration with macrophages and a dysregulated placental cytokine profile which is related to a pro-inflammatory profile in maternal serum [67]. This suggests that analysis of maternal serum/plasma not only offers the opportunity to evaluate placental function, but also could be employed to differentiate between different causes of placental failure.

Detailed analysis may also reveal specific pathways affected by placental failure. A case-control study employing metabolomic profiling of maternal serum found decreased levels of several components of the progesterone pathway implying reduced placental synthesis in placental failure [68]. Knowledge of the pathways affected by various causes of placental failure will enable understanding of which may be amenable to therapeutic modulation.

The development of novel tests would allow different causes of placental failure to be accurately determined in the antenatal period. However, current *in utero* phenotyping is limited to exclusion of fetal chromosomal anomalies or infective villitis in cases of severe early-onset FGR [69]. Furthermore, histological identification of placental lesions after pregnancies complicated by stillbirth, FGR or PE could be used to identify lesions (e.g. subchorionic intervillositis, maternal underperfusion/placental bed pathology) which may recur in a subsequent pregnancy [16,70]. Ultimately, we anticipate that more accurate placental phenotyping will allow therapeutic interventions to be targeted to pregnancies (either current or future) most likely to benefit.

1.9. The future – treating placental failure

There are currently no therapeutic treatments for placental failure, other than early delivery. The reasons for this poverty of therapeutic options are many-fold. They include the costs of developing *de novo* drugs versus risk of side effects of administering a drug which could have unwanted effects for both mother and fetus, whatever its intended target, as evidenced by the devastating effect of thalidomide in the early 1960s. Another is the dearth of good animal models of human placental failure for use in preclinical studies to test candidate drugs. We have addressed this latter issue by characterising potential mouse models of FGR and PE, generated by genetic manipulation. As reviewed recently [71], although there are structural differences, the mouse placenta seems to function similarly to the human in many respects and maternal cardiovascular changes in pregnancy are similar in both species [72]. Furthermore, endothelial nitric oxide synthase ($eNOS^{-/-}$), placental-specific *igf2* (P0) and catechol-O-methyl transferase ($COMT^{-/-}$) knockout mice, amongst others, show placental phenotypes similar to those seen in human FGR [71]. Therefore, we have used these mouse models to test drugs that might improve placental function and consequently fetal growth. As no drugs have been developed specifically to target pregnancy

disease, our paradigm has been to select drugs that both improve symptoms in other diseases similar to those related to placental failure, such as poor blood flow, and which have been used safely in pregnant women. The first candidate that we tested, fitting these criteria, was sildenafil citrate (Viagra), a potent phosphodiesterase inhibitor which enhances NO-dependent vasodilatation. It had been used previously to treat pulmonary hypertension in pregnant women [73]. A study in a maternal nutrient restriction sheep model of FGR suggested that sildenafil could improve fetal growth [74] but this was not replicated in a uterine artery ligation sheep model of FGR [75]. However, a small non-randomised clinical trial suggested that sildenafil improved abdominal circumference of an early-onset FGR group of babies [76]. Consequently we tested whether sildenafil would improve fetal growth in the COMT$^{-/-}$ and P0 mouse models of FGR. In both models [77,78] there was a small but significant improvement in fetal growth in the FGR pups, which was not seen in the normally grown wild type pups. Importantly, we showed that sildenafil reduced by a third the number of P0 pups whose weight was below the 5th centile. In the COMT$^{-/-}$ mouse the improvement in fetal growth was associated with improved umbilical artery end diastolic blood flow, and therefore placental function; as yet we have not determined the mode of action of sildenafil in the P0 mouse, which does not have impaired vascular function, but we speculate that there may be a direct action in the trophoblast (see below). These encouraging data have now been translated into an international randomised clinical trial of sildenafil as a treatment for severe growth restriction [79].

We have also now found other drugs that improve fetal growth in our mouse models. Tempol, a superoxide dismutase mimetic, improved fetal growth in the eNOS$^{-/-}$ mouse [80]; resveratrol, an anti-oxidant which improves NO bioavailability increased fetal growth in the COMT$^{-/-}$ mouse, but not in the eNOS$^{-/-}$ mouse [81]; preliminary work also suggests that melatonin, a free radical scavenger, improves fetal growth in wild type pups but not in eNOS$^{-/-}$ pups [82] and that nitrate supplementation, through beetroot juice administration, improves fetal growth in eNOS$^{-/-}$ but not wild type pups [83]. Although, we have done little work so far on mechanisms of action, a common thread running through these drugs that are effective in improving fetal growth in mouse models of FGR is that they all potentially scavenge free radicals and/or improve NO bioavailability. This accords with the view that placental dysfunction in women most often results from ischaemia/reperfusion injury in early pregnancy with consequent free radical damage to the trophoblast with endoplasmic reticulum stress and other consequences, likely to be on the route to placental failure [84]. Altogether the work with genetic mouse models of placental dysfunction so far gives hope that they are of value in testing potential therapies which may be rapidly translated into treatments for placental dysfunction and failure in women.

1.10. Concluding remarks

Placental failure is a critical feature in FGR, PE and the majority of cases of stillbirth. Increased understanding of the underlying mechanisms and distinction between different causes of placental failure is likely to be increasingly important for informing clinical management in current and subsequent pregnancies. For example, disorders of an inflammatory origin are unlikely to respond to a vascular-based therapy such as sildenafil, but may benefit from anti-inflammatory therapies. Importantly, an approach treating the outcome (e.g. severe early onset FGR) rather than the cause (placental dysfunction) will lead to underpowered clinical trials which may underestimate therapeutic efficacy. A better understanding of placental failure is also needed to inform trials of interventions in pregnancies after complications, where drug therapies are presently either ineffective [16] or have low-level evidence of benefit [85,86]. Thus, to address placental failure, a co-ordinated approach between basic science, placental histopathology and clinicians is required. This strategy, combining better identification of placental failure with effective intervention may reduce antepartum stillbirth.

Conflict of interest statement

The authors confirm that they have no conflicts of interest to report in relation to this manuscript.

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