Annotations

Fetoplacental circulation in health and disease

'The first time [in the year 1743] that I injected the vein of the naval string [cord] while the placenta adhered to the uterus, in separating these two parts it was evident that the injection had nowhere passed further than the placenta. ... From all these experiments and observations, which have been often repeated and diligently attended to with no other desire than to discover the truth, it seems incontestible that the human placenta, like that of the quadruped, is composed of two distinct parts, though blended together, viz, an umbilical, which may be considered as part of the foetus, and a uterine, which belongs to the mother.'
    The Anatomy of the Gravid Uterus, William Hunter 1754

The 250th anniversary of the discovery of the fetoplacental circulation is characterised by a renewal of interest in the placenta, especially with the emergence of data suggesting its influence on adult health and disease.[1] This review will consider the extent of our knowledge of the physiology and pathophysiology of the fetoplacental circulation, and attempt to provide a clinical perspective on these observations.

Physiology of the fetoplacental circulation
The metabolic demands of fetus at term are met through the haemochorial arrangement between maternal and fetal blood within the placenta. On the fetal side as much as 40% of cardiac output enters the umbilical circulation at term[2]; this arrangement implies very low resistance to blood flow in the umbilical circulation as it must 'compete' with the lower fetal body for aortic blood flow. The fetoplacental circulation is unique as it is not innervated,[3] suggesting that the low resistance to blood flow is conferred by either vasomotor or anatomical mechanisms.

An expanding variety of substances are known to influence tone in vessels from the term placenta.[4 5] Vasoconstrictor substances include thromboxane A_2 produced either by platelets or the umbilical vessels,[6] angiotensin II[7] produced either within the fetal kidney[8] or perhaps even within the placenta,[9 10] and endothelin synthesised locally within the placenta.[11]

If low resistance to blood flow at term is brought about by the activities of vasoactive substances then vasodilator mechanisms must predominate. One likely candidate for this role is atrial natriuretic peptide (ANP) which is synthesised by the fetal heart from as early as 7 weeks of gestation.[12] ANP is released by stretching of the heart in response to volume overload, and acts by dilating vascular

smooth muscle and promoting diuresis. Release of ANP by the human fetus has been demonstrated in response to intravascular transfusion for rhesus disease.[13] Biologically active ANP receptors have been characterised within fetoplacental vessels and shown to be functional within the range of circulating fetal ANP within the placenta.[14] Thus ANP is a physiological endocrine signal between the fetal heart and the placenta in vivo.[15]

Another candidate vasodilator of the fetoplacental circulation is endothelium derived relaxing factor (EDRF).[16] Nitric oxide synthase generates EDRF production from L-arginine within endothelial cells and this enzyme has recently been characterised within the human term placenta.[17] Prostacyclin has anticoagulant and vasodilator properties[18] and is synthesised by endothelial cells. However, a physiological role for prostacyclin within the placenta is uncertain as cyclo-oxygenase inhibition within the dually perfused human has no effect on fetoplacental vascular tone.[19]

The fetoplacental circulation is characterised by a progressive fall in vascular resistance as pregnancy advances.[20] The majority of research to date on control of vascular tone within the placenta has been confined to the normal term placenta, but clearly studies which attempt to understand this observation are important. The expression of biologically active ANP receptors within fetoplacental vessels is reduced in preterm deliveries,[14] suggesting that the placenta may become more responsive to the actions of ANP as pregnancy advances. The contractile response of the term umbilical artery to oxygen, which presumably ensures effective closure of the umbilical arteries at birth,[21] is undetectable in umbilical arteries from spontaneous preterm births between 26–32 weeks of gestation.[22] The significance of these findings are as yet difficult to interpret, but such data illustrate the importance of defining the relative role of individual vasoactive factors in the control of vasomotor tone.

An alternative and perhaps more rewarding approach is to view the control of blood flow within the fetoplacental circulation from an anatomical perspective. The fetoplacental circulation has a villous arrangement, beginning as muscularised stem arteries, branching up to 14 times and ending as long dilated capillary loops within the terminal villi; by term the fetal vascular surface area for gas and nutrient exchange is about 8 m².[23] As pregnancy advances the more distal branches of the villous tree continue to branch as part of the process of placental

'maturation' (in much the same way that alveoli continue to bud in the lung after birth). This continued development of the fetoplacental circulation may explain the reduction in fetoplacental vascular resistance as pregnancy advances, though at present the developmental anatomy of the human fetoplacental circulation is not well characterised.

Pathophysiology of the fetoplacental circulation

Doppler ultrasound has provided the obstetrician with a non-invasive method of assessing blood flow within the fetoplacental circulation. Abnormal waveforms (principally the loss of forward end diastolic flow velocity) in the umbilical arteries of many pregnancies complicated by either pre-eclampsia[24] or severe intrauterine growth retardation (IUGR)[25 26] provide an important insight to their pathophysiology as these data suggest that fetoplacental perfusion is abnormal. These pathological pregnancies are often terminated by caesarean section in either the maternal or fetal interest, producing babies with a high rate of perinatal morbidity and mortality.[27] The link between abnormal fetoplacental perfusion and pre-eclampsia/IUGR is therefore crucial to understand.

The numbers of stem villous arteries, as assessed by conventional light microscopy, have been found to be reduced in growth retarded pregnancies complicated by abnormal umbilical artery Doppler.[28 29] Embolisation of the fetoplacental circulation in sheep can reproduce these Doppler findings in an acute setting, which has been used to advance the theory that stem villous arteries are somehow 'obliterated'.[30] The reduction in circulating fetal platelet number observed in pregnancies complicated by IUGR has been taken to imply that they are the source of emboli in small fetoplacental vessels.[31 32] However, no anatomical studies have been conducted to date to prove this association.

Thus it may be more likely that a disorder of vasomotor regulation is responsible for abnormal umbilical Doppler in pathological pregnancies. Endothelin concentration has been found to be raised in umbilical cord plasma from pregnancies complicated by IUGR.[33] Many fetuses with IUGR are known to exist in a chronically hypoxic environment,[25] which is known to stimulate production of endothelin in vitro.[34] Chronic hypoxia probably activates other vasoactive systems, in particular the fetoplacental renin-angiotensin system.[35] The biological action of angiotensin II may be enhanced in placentas from pregnancies where there is IUGR,[36] which may result from an alteration in fetal intrarenal production of renin.[8] Angiotensin II is a growth factor for smooth muscle cells,[37] and it is of interest that proximal fetoplacental stem villous arteries are hypertrophied in placentas from some pregnancies complicated by IUGR.[38]

The vasomotor and anatomical theories of abnormal fetoplacental tone should not be viewed in isolation; it is very likely that they coexist and are responsible, in varying amounts, for the underlying disorder. There is a growing body of evidence indicating a derangement in the anatomy of the fetoplacental circulation in IUGR,[39 40] and from pregnancies delivered at a high altitude.[41] Maternal oxygen delivery to the developing placenta may therefore govern the subsequent anatomical and vasomotor control of the fetoplacental circulation.

Consequences of abnormal fetoplacental blood flow

The pathophysiological mechanisms operating within the fetoplacental circulation of pregnancies complicated by either pre-eclampsia or IUGR may also be present in the systemic circulation of the fetus. It is of interest that low birth weight, and in particular a high placental/fetal weight ratio, may be linked to the development of hypertension in adult life.[42–45] The adverse fetal environment which precipitated a preterm delivery (or perhaps even preterm birth itself) must somehow set in motion events which confer a high risk of cardiovascular disease in adult life.

One such mechanism may be chronic activation of the fetoplacental renin-angiotensin system.[36] Angiotensin II is a vascular growth factor[37] and therefore could cause relative 'overgrowth' of the placenta relative to its fetus. Moreover in the neonatal spontaneously hypertensive rat, inhibition of angiotensin II during the first few weeks of life has been shown to prevent the subsequent development of hypertension.[46]

Our understanding of the pathophysiology of the fetoplacental circulation in pregnancies with abnormal umbilical artery Doppler is only beginning to emerge. It is possible that the fundamental defect may be a failure of normal development of the fetoplacental circulation during early pregnancy: chronic hypoxia results and subsequently activates a variety of vasomotor mechanisms to produce a vicious circle. This sequence of events may finally 'programme' the fetus/neonate towards a greater risk of cardiovascular disease as an adult. Continuing research in this field is thus of unquestionable importance.

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The TORCH screen and intrauterine infections

TORCH (toxoplasmosis, rubella, cytomegalovirus, and herpes) screening has become almost synonymous with the investigation of an unexpected small for dates and/or premature infant with or without other abnormalities, and of apparently unknown cause. If no further direction is given to the house officer, he or she will embark on a series of unnecessary tests and may compound the error by sending inappropriate samples. The futility of such an approach has already been highlighted in a recent editorial.[1] The aim of this annotation is to further hasten the demise of the 'TORCH screen' by considering three specific areas. Firstly, to consider the presentation of congenital infections and to stress that there are now more congenital infections than were originally encompassed by the term TORCH. Rather than expand the screening test clinicians should be aware that many infections present with specific clinical pictures and they should direct investigations accordingly. Secondly, to emphasise the rarity of any congenital infection and thus the poor yield of the blunderbuss approach of the TORCH screen. Thirdly, to consider whether antenatal diagnosis will reduce or even eliminate the need for neonatal TORCH screening.

(1) Postnatal presentation
To request a TORCH screen on a neonate suggests that certain abnormalities are characteristic of congenital infection and the clinical presentation of different agents is similar. Neither supposition is watertight. For example, although growth retardation can occur in congenital herpes[2] or syphilis, 50 infants with cytomegalovirus infection had weights and head circumferences that did not differ significantly from those of 97 controls.[3] In addition, HIV infection, except in babies of seropositive mothers from Zaire,[4] has not been associated with growth retardation.[5] Prematurity is not a *sine qua non* of congenital infection, although typical of congenital syphilis, it is not increased by cytomegalovirus infection. Investigation of a small for dates or premature infant is extremely unlikely to identify any of the congenital infections. Only 10 to 15% of infants infected by toxoplasmosis during pregnancy have abnormalities in the neonatal period,[6] even though 50% develop neurological sequelae or chorioretinitis by the age of 20 years.[7] Parvovirus infection is associated with non-immune hydrops, but rarely causes congenital malformation,[8] indeed there is only one report of a fetal eye anomaly.[9]

Clinical signs that are presumed to be a non-specific clue to congenital infection may, in fact, be characteristic of one particular agent. Syphilis presents with many of the signs expected from a TORCH infection, a vesicular and erythematous skin rash, petechiae, severe non-haemolytic anaemia, and hepatosplenomegaly. In addition, the infant may suffer intestinal malfunction due to syphilitic enterocolitis, respiratory distress because of prematurity and/or pneumonia alba. The associated condylomata are, however, specific as are, in 95% of infants with congenital syphilis, the characteristic long bone changes (symmetrical metaphyseal lesions, horizontal bands of increased/decreased radiodensity, and peripheral porosis.[10] The diagnosis will be further advertised by the peeling of the soles of the feet and palms of the hands and can be confirmed by isolation of the spirochaete from the vesicular lesions. Reliance on the clinical signs described by the TORCH syndrome to identify congenitally infected infants could result in underdiagnosis of other including more recently described infections. Infants with listeriosis may present solely with septicaemia or an unusual pneumonia[11] and this infection should be considered in the differential diagnosis of any infant presenting with septicaemia and/or pneumonia, particularly if premature labour has been complicated by meconium stained liquor.