Uteroplacental vasculature

W. B. ROBERTSON

From St George's Hospital Medical School, Tooting, London

Pregnancy requires physiological adaptations in every bodily system, not the least important being those involving the cardiovascular system. Associated with an increased plasma volume and cardiac output there are probably changes in the walls of the blood vessels themselves that so far have not been defined (Robertson and Manning, 1974). Suggestive evidence for this is to be found in the remarkable changes seen in the blood vessels of the pregnant uterus (Brosens *et al*, 1967).

The blood supply to the endometrium of the non-pregnant uterus is only a few millilitres per minute whereas something like half a litre of blood per minute must be delivered to the placenta at term (Browne and Veall, 1953). Hypertrophy and hyperplasia of the major uterine and ovarian arteries ensures this supply but if it is to be delivered to the conceptus then the arteries of the placental bed must be considerably modified since human placentation is haemochorial, that is, maternal blood must be brought into direct contact with the villous trophoblast of the fetal placenta. Until we have a better understanding of the topography of the human

placental bed and the mechanisms involved in its establishment and development we will remain in ignorance of the basic defects of many types of abnormal pregnancy.

Development of the Uteroplacental Arteries in Normal Pregnancy

The blood supply to the non-pregnant uterus is shown in figure 1, and particular note should be made of the spiral or coiled arteries (fig 2), hormone-

Fig 1 *Diagram of blood supply to the non-pregnant uterus.*

Fig 2 *Early pregnant uterus, non-placental bed: the myometrial origin of a spiral artery is at the bottom and the coiled portion in the basalis is at the top. A small basal artery is arrowed. Haemalum and eosin (HE) $\times 30$.*

Fig 3 Early pregnancy: the decidual segment of a spiral artery before it is invaded by infiltrating trophoblast. The wall has lost its normal structure and has a rather fibrinoid appearance. Note also round cell infiltrates in the decidua. HE $\times$ 90.

Fig 4 Early pregnancy: decidual arteriole (centre) with cytotrophoblast in the lumen and wall. The decidua is overrun by interstitial mononuclear and multinuclear trophoblast. The glands lined by cuboidal epithelium contain secretion. HE $\times$ 140.

responsive vessels that are destined to become the uteroplacental arteries at the site of placentation. The basal or straight arteries, also branches of the parent radial arteries, are much less hormone responsive than the spiral arteries and are mainly concerned with supplying the basal endometrium and subjacent myometrium.

In the early weeks of pregnancy, after the blastocyst has embedded in the endometrium and the trophoblastic shell has formed, the spiral arteries in what has now become the decidua basalis begin to show morphological changes. Their walls appear to be decidualized and have a smudged, fibrinoid outline not infrequently with round cells in the immediate vicinity (fig 3). Several observers have commented on these changes (Burstein *et al*, 1965; Harris and Ramsey, 1966; Boyd and Hamilton, 1970) and speculated whether they are merely degenerative or due to hormonal influences or immunological reactions. Somewhat later these

target vessels are invaded by the cytotrophoblast proliferating from the trophoblastic shell at the same time as the decidua basalis is overrun by invasive, non-villous forms of trophoblast (fig 4) to produce the condition erroneously labelled in the past as 'syncytial endometritis'. The endovascular trophoblast now produces a remarkable series of morphological alterations in the walls of the spiral arteries. The maternal endothelium is replaced, at least in part, by cytotrophoblast which also infiltrates, or is incorporated, into the walls to become intramural. This latter phenomenon is associated with loss of musculoelastic tissue and the deposition of much fibrinoid material which contains, amongst other things, maternal fibrin and other plasma constituents and proteinous secretion from the trophoblast itself (De Wolf *et al*, 1973). The term 'physiological changes' has been applied (Brosens *et al*, 1967) to these adaptive changes on the reasonable grounds that pregnancy is a physiological state; in any other

Fig 5 Twenty-week pregnancy: second wave of migrating endovascular trophoblast in the myometrial segments of the spiral arteries producing physiological changes in the vessel walls. Note also abundant interstitial trophoblast, including giant cells, in the surrounding myometrium. HE $\times 60$.

Fig 6 Third trimester pregnancy: myometrial segment of a spiral artery showing extensive 'physiological changes'. The wall is altered almost beyond recognition and is composed of a mixture of smooth muscle, fibrinoid containing cytotrophoblast and loose connective tissue. HE $\times 60$.

Fig 7 Diagram of the fully developed blood supply to the placenta. Note that the spiral arteries have been converted (hatching) to the distended, funnel-shaped uteroplacental arteries while the basal arteries (solid black) are not involved in physiological changes.

situation these vascular lesions would be regarded as pathological.

Haemochorial placentation, with transformation of the spiral to the uteroplacental arteries, is now established but the process does not end there. From about the sixteenth to the twentieth week of gestation a second wave of endovascular trophoblast moves retrogradely down the spiral arteries to reach their myometrial segments (fig 5) and even to involve the terminal segments of the parent radial arteries (Robertson *et al*, 1975). Once again there is an interaction between the fetal cells and the maternal arteries to produce the necessary adaptive vascular changes (fig 6). The surrounding myometrium meanwhile has been populated by infiltrating interstitial trophoblast which gives rise to the placental bed giant cells characteristic of human placentation (Robertson and Warner, 1974). Throughout the second and third trimester there is

progressive distension of the uteroplacental arteries, facilitated by the loss of musculoelastic tissue from their walls, to accommodate the increased blood supply required by the growing fetus and placenta. The fully developed blood supply to the placenta is illustrated diagrammatically in figure 7. The exact mechanisms by which these remarkable vascular adaptations are brought about are unknown but no doubt they involve hormonal, immunological, enzymatic, haemodynamic and possibly other factors. One essential consequence is that the physiological changes produce a significant reduction in peripheral vascular resistance in the placental bed allowing a much greater blood flow into and through the intervillous space of the placenta (Moll *et al*, 1975).

The Uteroplacental Arteries in Abnormal Pregnancy

It has been calculated (Boyd, 1956; Brosens and Dixon, 1966) that there are some 100 to 150 spiral artery openings into the intervillous space of the fully developed, normal placenta. There are no data on the number and nature of such arterioplacental communications in defective placentation and relatively little is known about disease of the uteroplacental arteries as a possible factor in many types of abnormal pregnancy. The reason for our ignorance is explained by the fact that the important tissue, the pregnant uterus, is seldom made available to the investigator who usually has to make what he can of the delivered placenta and, when intrauterine or neonatal death occurs, the fetus. The postpartum uterus involutes and gets rid of any incriminating

pathology that may have operated during the pregnancy. The introduction of the placental bed biopsy technique at caesarean section (Dixon and Robertson, 1958) has gone some way to provide tissue for examination but the tissue so obtained is small in quantity and is merely a sample which may not be representative of the large area of the placental bed. It takes a very long time for one centre to collect enough hysterectomy specimens from abnormal pregnancies for the detailed study of a particular condition.

HYPERTENSIVE PREGNANCY

Over the last twenty years some progress has been made in studies of the uteroplacental arteries in hypertensive pregnancy (see Robertson *et al*, 1975 for references) but even more remains to be done. This aspect can only be touched upon here but it will serve as an example of disease of the maternal uterine arteries occurring during pregnancy which explains much that was previously unknown or, at best, guessed at. The various hypertensive complications of pregnancy still present major problems to the obstetrician; essential hypertension, preeclampsia and renal disease are the main categories.

Preeclampsia is a disorder of unknown aetiology but it is associated with a defect in placentation which involves the blood supply to the placenta. In pregnancies that are destined to be complicated by preeclampsia it has been found (Brosens *et al*, 1972) that there is an inadequate maternal vascular response to placentation early in the second trimester. The physiological changes that normally extend retrogradely down into the myometrial segments of

Fig 8 Comparison between normal and preeclamptic pregnancies in the extent of physiological changes in the uteroplacental arteries. Note that in preeclampsia a constricting segment remains throughout pregnancy between the parent radial artery and the distended decidual segments of the uteroplacental arteries.

Fig 9 Preeclampsia: spiral arterioles in the decidua vera (non-placental bed) showing acute atherosclerosis with fibrinoid necrosis of vessel walls, intramural lipophages and perivascular mononuclear cellular infiltrates. HE $\times 150$.

the spiral arteries are restricted to the decidual segments of these arteries leaving the myometrial segments unaffected (fig 8). The implication is that the second wave of migrating endovascular trophoblast, which normally begins about the sixteenth week of gestation, is in some way inhibited so that the myometrial spiral arteries remain throughout the rest of pregnancy as muscular vessels responsive to vasomotor influences.

It is now generally accepted that when the clinical manifestations of preeclampsia, acute hypertension with albuminuria, become manifest a distinctive arteriopathy, usually called acute atherosclerosis (Zeek and Assali, 1950), develops in small muscular arteries in the placental bed, including the spiral arteries, and in similar arteries in the decidua vera near the chorionic membranes. The lesion (fig 9) is characterized by fibrinoid necrosis, ultimately affecting the whole thickness of the vessel wall, accumulation of lipophages in the damaged wall and a mononuclear infiltrate of variable intensity around the affected vessels. To date one can only speculate on the pathogenesis but in our experience (Robertson *et al*, 1967) it is found only in those pregnancies complicated by albuminuria, the hypertension arising *de novo* as in preeclampsia, or already being present as essential or renal hypertension. Suggestions have been made that the arteriopathy may have an immunological basis (Kitzmiller and Benirschke, 1973) or that it is the result of sudden haemodynamic disturbances allied to an inappropriate immune response (Robertson *et al*, 1975).

Women with essential or renal hypertension who

develop preeclampsia later in pregnancy show the same vascular defect of placentation as those women who suffer only from preeclampsia. However, the preexisting hypertension is associated with a remarkable degree of hyperplastic arteriosclerosis in the myometrial segments of the placental bed spiral arteries which are unaffected by physiological changes (fig 10). When preeclampsia then supervenes acute atherosclerosis is superimposed upon the hyperplastic vessels (fig 11). A woman with essential hypertension who proceeds to term without developing preeclampsia will be found to have uteroplacental arteries similar to those of a normotensive pregnant woman except that there may be a degree of arteriosclerosis added to the physiological changes.

Whatever may be the explanation for these vascular phenomena in hypertensive pregnancy there can be little doubt that the vascular lesions offer the most satisfactory explanation for the high incidence in such pregnancies of placental infarcts due to thromboses in the uteroplacental arteries (Wigglesworth, 1969; Brosens and Renaer, 1972), for abruptio due to rupture of these vessels and for much of the fetal morbidity and mortality associated with hypertensive pregnancy.

FETAL GROWTH RETARDATION

Of equal and possibly more importance to the obstetrician is the problem of fetal growth retardation, dysmaturity or the 'small-for-dates' syndrome. Fetoplacental insufficiency is the non-definitive term used to camouflage our ignorance of the underlying pathology in what is almost certainly a heterogeneous group of conditions. In the minority the cause is known, in the majority it is not and it is a pity that, if a term has to be coined, it is not all embracing to include possible maternal factors. There is recent evidence (Bonnar *et al*, 1975) that many cases of non-hypertensive pregnancy exhibiting fetal growth retardation may have vascular lesions in the uteroplacental arteries analogous to, but not identical with, those of preeclamptic pregnancies. It would be interesting to know, but for reasons given earlier difficult to assess, the topography of the placental bed in cases where both the placenta and fetus are small for the gestational age. It may be that an assumption that the conceptus is smaller than normal because the uteroplacental arteries are less than adequate in number and size would prove to be wrong but it has never been tested. Much the same question could be asked in relation to other categories of disordered pregnancy.

ABORTION

Spontaneous abortion can be regarded as nature's

Fig 10

Fig 10 *Essential hypertension plus preeclampsia: the myometrial segments of the spiral arteries have not been invaded by trophoblast but show hyperplastic arteriosclerosis. Note placental bed giant cells in the myometrium confirming placental site. HE $\times$ 90.*

Fig 11

Fig 11 *Essential hypertension plus preeclampsia: myometrial segment of a spiral artery already hyperplastic but now showing fibrinoid necrosis with foam cells (arrow). There are no 'physiological changes' but placental bed giant cells (trophoblast) can be seen in the surrounding myometrium. HE $\times$ 90.*

method of getting rid of undesirable aberrations from the norm of the species as evidenced by the high incidence of genetic abnormalities detected in aborted conceptuses. It is perfectly possible, however, that many abortions result from defective interaction between an otherwise normal conceptus and the uterine tissues and this could include a failure to establish adequate haemochorial placentation. First pregnancies are more liable to end in abortion than subsequent ones and spontaneous abortion tends to occur towards the end of the first trimester, when crucial changes are taking place in the placental bed. These facts may be more than mere hints that defective placentation is the cause of at least a proportion of abortions. There is no direct evidence that such is the case but in those examples of abortion followed by menstrual irregularities and by so-called postabortion endometritis where, in fact,

there is little evidence of infection accompanying or following the abortion, the curetted endometrium often shows interesting features.

Depending upon the time interval between the abortion and the curettage the surviving endometrial glands will show a variety of appearances from involutionary change to active proliferation. The stroma contains a predominantly mononuclear cellular infiltrate in which plasma cells are prominent, indicating a persistence of antigenic material. Another feature not usually commented upon is the frequent presence of hyalinized material, particularly related to the endometrial spiral arteries (fig 12), in which ghost cells, almost certainly effete trophoblast, occasionally can be identified. This finding represents a failure of, or delay in, involution of the placental bed and of the vascular physiological changes following the abortion, a failure that may be due to

Fig 12 Postabortion endometritis: the residuum of the pregnancy is represented by hyaline material in which effete cells (trophoblast) are embedded. The decidual arterioles (top) show involuting physiological changes. HE $\times$ 60.

Fig 13 Secondary postpartum haemorrhage: a leash of decidual segments of the uteroplacental arteries, still distended and partially occluded by very recent thrombus. This indicates subinvolution of the placental bed and of the uteroplacental arteries. HE $\times$ 30.

an early defect in the mechanisms of placentation making it more difficult for the repair process to be effective as quickly as it normally is.

INTRA- AND POSTPARTUM HAEMORRHAGE

It is self-evident that bleeding during pregnancy, concealed or revealed accidental haemorrhage, is due to some catastrophe involving the uteroplacental arteries or the corresponding draining veins or both. When this occurs in pregnancies complicated by hypertension it is reasonably explained by the altered haemodynamics and vascular lesions already described for those conditions. It seems likely that in non-hypertensive cases, which are the majority, thromboses and rupture occasionally occur in the complex arterio-sinusoidal-venous system that has been elaborated over a period of months for the uteroplacental circulation. It is well known that true placental infarction is not confined to hypertensive pregnancy but the factors responsible for triggering

off the vascular catastrophes are largely unknown as, once again, the pathologist usually has only the fetal placenta with its haematomata or infarcts to examine.

Secondary postpartum haemorrhage is often wrongly attributed to retained products of conception when it is assumed that a portion of the fetal placenta, a 'placental polyp', is retained after delivery of the fetus and the bulk of the placenta. In practice this is quite uncommon as a review of the histology of a series of curettage specimens from cases of secondary or late postpartum haemorrhage will readily confirm. Nor is it due in a significant percentage to infection. At parturition separation of the fetal placenta requires a total shearing through the midzone of the basal decidua and this involves the hundred or more spiral (uteroplacental) arteries. Rapid contraction of the uterus and collapse of the amuscular decidual segments of the arteries and veins will achieve much to prevent undue bleeding but there also occurs a rapid change in the coagula-

tion regulatory system (Bonnar *et al*, 1969) to promote occlusive thrombosis in the severed portions of the blood vessels, effectively to stop bleeding from the placental bed. Thereafter, there is a remarkably rapid involutionary process, about which we know virtually nothing, to restore the endometrium and subjacent myometrium to the non-pregnant state by the time of the first menstrual period following parturition. Postpartum bleeding is due in the majority of cases (Ober and Grady, 1961) to imperfect or delayed involution of the placental bed. The evidence for this can be seen in curettage specimens which usually contain the basal decidual portions of the subinvolved uteroplacental arteries, some partially thrombosed (fig 13), some still with a distended lumen and recent haemorrhage in the vicinity of the vessels.

The Systemic Effect of Pregnancy on Blood Vessels

The evidence that pregnancy has a systemic effect on

blood vessels in general is still largely circumstantial but sufficient to encourage further investigation. Vascular catastrophes such as subarachnoid haemorrhage, dissecting aortic aneurysm and rupture of other aneurysms are not common in young women but when they do occur they are likely to do so during pregnancy (Guthrie and McLean, 1972). Normal pregnancy is accompanied by an increase in total body water and, after accounting for that component attributable to the fetus, placenta, liquor amnii and the pregnant uterus, there is a hidden component in the general connective tissues. This latter component is thought to be accommodated by hormone-induced changes in the connective tissue mucopolysaccharides (Hyttén, 1970). Blood vessel walls have similar connective tissue mucins in their ground substance and there seems no reason to suppose that these mucopolysaccharides do not undergo the same hormone-induced changes during pregnancy as the other body connective tissues.

All pathologists are familiar with the histology of the blood vessels of the non-pregnant parous uterus; some are even prepared to hazard a guess at the number of pregnancies the uterus has nurtured from the appearance of the myometrial blood vessels. Even more striking are the vascular lesions seen in the postmenopausal atrophic uterus of the grand multipara (fig 14), an eloquent testimony to the series of changes involving hyperplasia and involution of several pregnancies. The vessels showing such changes are the arcuate and radial arteries, not the much smaller spiral arteries which, during the pregnancies, may have been converted by trophoblast to the uteroplacental arteries. This in itself is surely sufficient evidence to prove that the altered hormonal status of pregnancy does affect blood vessels; it would be useful to know how it is done.

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Fig 14 Multiparous postmenopausal uterus: the arcuate and radial arteries show laminated, hyperplastic changes and around the vessels there are deposits of elastica-like material. Oxidized, orcein-van Gieson $\times 30$.

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