Section 1 Chapter 1

Introducing the placental bed

The placental bed in a historical perspective

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The discovery of the placental bed vasculature

Placental vasculature, in particular the relationship between maternal and fetal blood circulations, has been a contentious issue for a long time. It was indeed a matter of dispute whether or not the fetal blood circulation was separate from or continuous with the circulation of the mother as stated by the Roman physician Galen (129–200). The Renaissance anatomist Julius Caesar Arantius (1530–1589) is usually quoted for being the first who explicitly denied the existence of any vascular connection between the mother and the fetus *in utero* [1,2]. Although this opinion was seemingly based on careful dissections of human placentas *in situ*, he obviously did not have the tools to trace small blood vessels in sufficient detail to provide full support for this idea. Moreover, before William Harvey (1578–1657) anatomists did not understand the relationship between arteries and veins, and thus their knowledge about the uteroplacental blood flow in the placenta must have been rather confused.

The brothers William (1718–1783) and John Hunter (1728–1793) are credited for having demonstrated the separation of maternal and fetal circulations by using colored wax injections of human placentas *in utero*. It was probably the younger brother John who did all the work, and he claimed afterwards most of the credit for this finding [3]. In his magnificent *Anatomy of the human gravid uterus* (1774) William Hunter included the first drawing of spiral arteries ('convoluted arteries'), in what must have been the very first illustration of a human placental bed (Fig. 1.1) [4]. These 'convoluted arteries' are embedded in the decidualized uterine mucosa, the term 'decidua' being used for the first time by William Hunter to describe the 'membrane' enveloping the conceptus, which is discarded at parturition (Latin *decidere*, to fall off). This obviously referred to the decidua capsularis, typical for humans and anthropoid apes, which is formed as a result of the deep interstitial implantation of the blastocyst in these species. John Hunter, however, pointed out that there is also a 'decidua basalis' underneath the placenta. In a tubal pregnancy case he noticed that a similar tissue had developed within the uterus, and he therefore concluded that the decidua originates from the uterine mucosa [5].

Early ideas about placental function

Hunter's demonstration of separate vascular systems coincided with Lavoisier's discovery of oxygen and its role in respiration. It was found that the uptake of oxygen by the blood is associated with a shift in color from a dark to a light red. This color-shift was observed in lungs as well as in the gills of fish, and it was Erasmus Darwin (1731–1802), grandfather of Charles Darwin, who pointed out that exactly the same happens in the placenta [6]. Furthermore, Erasmus Darwin tried to understand how the oxygenated maternal blood is delivered to the fetus. He had noticed that after separation of the placenta, uterine blood vessels start bleeding, while the placental vessels do not. For him this was an indication that the terminations of the placental vessels must be inserted into the uterine vasculature while remaining closed off from the maternal circulation. He thought that structures, referred to as 'lacunae of the placentae' by John Hunter, might represent 'cells' filled with maternal blood from the uterine arteries. It is obvious that these 'cells' referred to compartments of the intervillous space. Erasmus Darwin went as far as to equate these 'lacunae of the placentae' to the 'air-cells' (alveoli) of the lungs. Also interesting is the comparison he made with cotyledonary placentas of cows, which after separation do not result in bleeding of uterine blood vessels. Of course he was unaware of structural differences between the human hemochorial

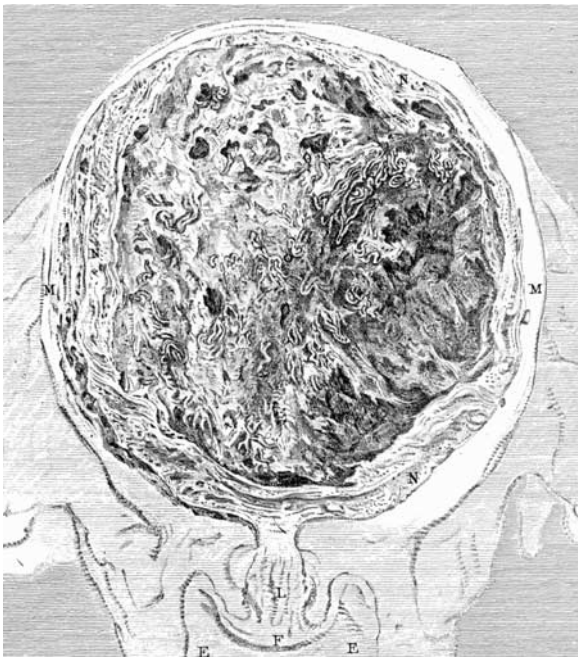

Fig. 1.1 View of the placental bed after removal of the placenta, showing stretches of spiral arteries. Illustration from William Hunter's *Anatomy of the human gravid uterus* (1774).

and the cow's epitheliochorial placenta. His speculation on a 'greater power of contractions' of uterine arteries in cows almost suggests an intuitive grasp about differences in uteroplacental blood supply between humans and cows [7], foreshadowing the later concept of 'physiologically changed' spiral arteries in the human [8].

While the ideas of eighteenth century investigators about the respiratory function of the placenta were essentially correct, opinions about a possible nutritive function of the placenta were very confused. The Scottish anatomist Alexander Monro (1697–1767) thought that, analogous to nutrient uptake in the intestines, a 'succulent' substance appeared between the uterine muscle and the placenta (i.e. the decidual region), which he thought would be absorbed by 'lacteal vessels' of the placenta [2]. In his opinion these placental vessels had to be open-tipped and had to cross the placental–uterine border for absorbing the uterine nutritious material. This idea was of course refuted by Hunter's injection experiments, which clearly showed that fetal vessels never end up in the uterine wall. Transmembrane transport mechanisms for glucose, lipid and amino acid transfer were obviously unknown at that time, and investigators like Erasmus Darwin therefore tended to minimize the idea of a possible nutritive function of the placenta. Instead he favored the view that the amniotic fluid was the main source of fetal nutrition, an idea that he had borrowed from William Harvey, but which became overruled by later findings.

The discovery of trophoblast invasion

A major technological advance in the nineteenth century was the perfection of the microscope together with the development of histological techniques for tissue sectioning and staining. The first microscopic images of the human placenta were obtained in 1832 by Ernst Heinrich Weber, revealing the organization of fetal blood vessels within villi, which are lined by a 'membrane' separating the fetal from the maternal blood. For several decades there was uncertainty about the nature of this outer villous 'membrane', and it was originally thought that this layer represented the maternal lining (endothelium) of the extremely dilated uterine vasculature [9]. The origin of this tissue layer and the real nature of the intervillous space could only be clarified by histological investigations from early implantation stages onwards. An early pioneer was the Dutch embryologist Ambrosius Hubrecht (1853–1915), who undertook the study of implantation in what he considered to be representative species of primitive mammals, hedgehogs and shrews. The idea behind this work was that the implantation events in primitive mammals might offer clues about the evolution of viviparity. His famous hedgehog study revealed early appearance of maternal blood lacunae engulfed by the outer layer of extraembryonic cells. He considered the latter as feeding cells and hence introduced the term 'trophoblast' [10].

Slowly investigators began to realize the invasive potential of this trophoblast. The French anatomist Mathias Duval (1844–1907) was probably the first to recognize the invasion of trophoblast (placenta-derived 'endovascular plasmodium' in his terminology) into endometrial arteries, in this case in the rat [11]. He published his findings in 1892, but he was not the first to have seen endovascular cells in maternal vessels. Twenty years before, in 1870, Carl Friedländer had reported the presence of endovascular cells in 'uterine sinuses' of a human uterus of 8 months' pregnancy [12]. He notified the rare occurrence of arteries in this specimen, obviously not realizing that these might have been transformed by endovascular cell invasion. He was unable to decide whether these cells

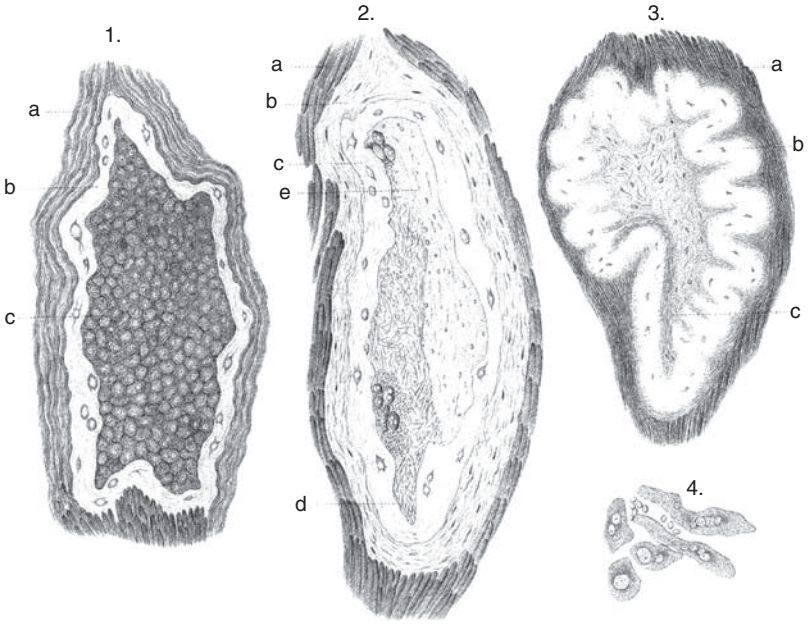

Fig. 1.2 'Uterine sinus' showing a plug of endovascular cells (1) and a similar vessel with embedded cells (2) in an 8 months' pregnant uterus. (3) shows a similar vessel in a postpartum uterus. Details of so-called multinuclear endovascular cells are shown in (4). Reproduced from Friedländer (1870).

were derived from the placenta or the surrounding maternal tissue, but he reported their presence as deep as the inner myometrium. His illustrations show two vessels of his 8 months specimen, one completely plugged, the other containing only a few intraluminal cells (Fig. 1.2). In the latter he noted the presence of a thickened homogeneous 'membrane' containing dispersed cells in the vessel wall (Fig. 1.2, parts 1b and 2c, recognizable as the fibrinoid layer with embedded trophoblast), and also an organized thrombus with young connective tissue (Fig 1.2, part 2e, recognizable as a thickened intima overlying the fibrinoid layer). He also obtained a postpartum uterus in which he thought he could recognize similar 'sinuses' (Fig 1.2, part 3). Surprisingly, Friedländer thought that most intravascular cells were multinuclear (Fig 1.2, part 4). He reasoned that the presence of endovascular cells must considerably slow down and even interrupt the maternal blood supply to the placenta, and considered that failed vascular plugging might result in intrauterine bleeding and maternal death. Friedländer's contemporaries favored the idea that the intravascular cells must have been sloughed off from the maternal vascular wall. It wasn't until the early twentieth century that investigators such as Otto Grosser [13] began to consider these cells as trophoblastic.

The actual depth of invasion was underrated for a long time, partly because of the increasing popularity of the decidual barrier concept. This idea originated in 1887 from Raissa Nitabuch's description of a fibrinoid layer which was thought to form a continuous separation zone between the anchoring 'chorionic' cells in the basal plate and the underlying decidua [14]. It is interesting that she also described cross-sections of decidual spiral arteries close to the intervillous space, mentioning (but not illustrating) a breaching of the endothelium by cells which were morphologically similar to those occurring on the inside of the fibrinoid layer. She did not further comment upon the nature of these cells, and neither did she quote Friedländer's 1870 publication. Unfortunately, the alleged barrier function of Nitabuch's layer was overemphasized in later years, and was also thought to act in the opposite sense by warding off a maternal immune attack on the semi-allogeneic trophoblastic cells [15]. These early concepts had to be considerably modified in later years, when it became clear that deep trophoblast invasion and associated spiral artery remodeling are essential for a healthy pregnancy. Indeed, this research received a considerable boost within the clinical context of preeclampsia and fetal growth restriction, as will be described in Chapters 2 and 3.

Conclusion

The phenomenon of trophoblast invasion – for a long time considered as merely playing a role in anchoring the placenta – has to be understood in the context of growing insights into placental function, notably fetal respiration and nutrition. The elucidation of the anatomical relationship between fetal and maternal circulations was therefore of fundamental importance. Early observations of trophoblast invasion into the spiral arteries set the stage for understanding the maternal blood supply to the placenta via the spiral arteries of the placental bed. This historical context provides an appropriate starting point for understanding the development of the present research directions, which are closely linked to the clinical problems of preeclampsia and fetal growth restriction.

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Chapter 2

Unraveling the anatomy

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Introduction

Although the gross anatomy of the maternal blood supply to and drainage from the intervillous space was well documented by William Hunter [1] in 1774 a considerable degree of confusion persisted, and in particular the understanding of the anatomical structure of the 'curling' arteries remained incomplete and often not based on data. Therefore as an introduction to the chapters on placental bed vascular disorders the early literature on the maternal blood supply to the placenta is briefly reviewed.

The term 'placental bed' was introduced 50 years ago by Dixon and Robertson [2] and can be grossly described as that part of the decidua and adjoining myometrium which underlies the placenta and whose primary function is the maintenance of an adequate blood supply to the intervillous space of the placenta. Certainly, there is no sharp anatomical demarcation line between the placental bed and the surrounding structures, but, as this part of the uterine wall has its own particular functional and pathological aspects, it has proven to be a most useful term for describing the maternal part of the placenta in contrast to the fetal portion.

The uteroplacental arteries

Anatomically the uteroplacental arteries can be defined as the radial and spiral arteries which link the arcuate arteries in the outer third of the myometrium to the intervillous space of the placenta. Before reaching the myometrio-decidual junction, the radial arteries usually split into two or three spiral arteries. When they enter the endometrium the spiral arteries are separated from each other by a 1–6 mm gap [3]. Small arteries, the so-called basal arterioles, branch off from the proximal part of the spiral arteries and vascularize the myometrio-decidual junction and the basal layer of the decidua. They are considered to be less responsive, if at all, to cyclic maternal hormones [4].

Two comments are appropriate here. First, some confusion existed as to whether the spiral arteries of the placental bed should be called 'arteries', which was commonly used in German literature, or 'arterioles', which was more common in the English literature. In view of the size of the spiral vessels, which communicate with the intervillous space, the terminology of 'spiral arteries' was adopted for these vessels in order to distinguish them from the 'spiral arterioles' of the decidua vera. A second comment relates to the spiral course as described by Kölliker [5]. Because during pregnancy these arteries increase in length as well as in size, Bloch [6] suggested that in the human the terminal part of the spiral artery is no longer spiral or cork-screw, but has a more undulating course as was demonstrated in the Rhesus monkey (*Macaca mulatta*) by Ramsey [7].

The origin of placental septa and the orifices of spiral arteries have been the subject of great controversy. Bumm [8,9] pointed out that the arteries are mainly lying in the decidual projections and septa, and eject their blood from the side of the cotyledon into the intervillous space (Fig. 2.1). Bumm's statement has been quoted as implying that the arteries open in the intervillous space near the chorionic plate, while Bumm obviously regarded the subchorionic blood as somewhat venous in nature. Wieloch [10] and Stieve [11] have corrected Bumm's observation in that they specified that the spiral arteries mainly open at the base of the septa. Boyd and Hamilton [4] confirmed that the septa are of dual maternal and trophoblastic origin and that arterial orifices are scattered more or less at random over the basal plate. The orifices of several arteries may be grouped closely together and, in individual vessels, are usually at their terminal portions. Spiral arteries may have initially multiple openings. Such multiple openings can later become separated by the straightening out and dilatation of the artery and the unwinding of the coils during placental growth. When multiple openings are present the segment of the artery between successive ones may show obliteration of the lumen.

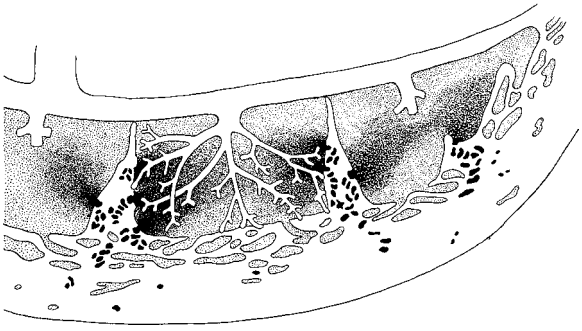

Fig. 2.1 Diagrammatic representation of the course of the maternal circulation through the intervillous space of the placenta. After Bumm [9].

Attempts to count the number of spiral arteries communicating with the intervillous space have been made by several investigators. Klein [12] counted in one separated placenta 15 maternal cotyledons with 87 arteries and 39 veins and in a second 10 cotyledons with 45 arteries and 27 veins. Spanner [13] working with a corrosion preparation of about 6 months' gestation found 94 arteries communicating with the intervillous space. Boyd [3] made calculations of total numbers based on sample counts of openings of the spiral arteries in the basal plate in three placentae of the third and fourth months of pregnancy. The calculations for full-term placentae varied between 180 and 320 openings but all three counts can only be considered as first appreciations. On the other hand, Ramsey [7] showed by serial sections in the Rhesus monkey the uneven distribution of arterial communications with the intervillous space and suggested that partial counts may have introduced errors in the calculations. In an anatomical reconstruction of two-fifths of the maternal side of a placenta *in situ* at term Brosens and Dixon [14] confirmed the irregular arrangement of septa and arterial and venous openings. All arteries opened into the intervillous space by a solitary orifice. They found in a normal placenta 45 openings for a surface area of 32 cm^2 [15] and in a uterus with placenta *in situ* from a woman with severe preeclampsia 10 spiral arteries for a surface area of 7 cm^2 [16], which in both cases amounts to one spiral artery for every 0.7 cm^2 of placental bed.

A bird's-eye view of the three-dimensional basal plate shows septa of various sizes with the majority of arterial orifices at the base of a septum. Septa are likely to represent uplifted basal plate reflecting differences in depth of decidual trophoblast invasion and resulting in a conchiform base for the anchoring of a fetal cotyledon. Arterioles high up in the septa and without an orifice into the intervillous space are likely to be basal arterioles.

The anatomy of the venous drainage has also been the subject of much discussion. Kölliker [5] stressed in 1879 the role of the marginal sinus, partly lying in the placenta and partly in the decidua vera. Spanner [13] revived this theory in 1935, however without quoting Kölliker. The anatomical work by many authors has subsequently shown that venous drainage occurs all over the basal plate. The veins fuse beneath the basal plate to form the so-called 'venous lakes' [7]. The term 'sinusoid' has been applied to these vessels, but has caused much confusion in the literature as the term has been used for the intervillous space and the spiral arteries.

The question of arteriovenous anastomoses in the decidua arose when Hertig and Rock [17] described extensive anastomoses in the decidua. Bartelmez [18], however, after re-examination of the original histological sections of Hertig and Rock [17] cast doubt on the drawings published by these authors in 1941 and the existence of such shunts was later disproved. Recently, Schaaps and collaborators [19] used three-dimensional sonography and anatomical reconstruction to investigate the placental bed vasculature and demonstrated an extensive vascular anastomotic network in the myometrium underlying the placenta. No such network was seen outside the placental bed. It can be speculated that the subendometrial network is formed by the hypertrophied basal arterioles and veins in the placental bed.

Pregnancy changes, intraluminal cells and giant cells

The morphological changes of the uteroplacental arteries were extensively studied, mainly by German investigators, around the turn of the last century and particularly in the context of the mechanism preventing the uterus from bleeding during the postpartum period.

Almost all authors before 1925 agreed that thickening of the intima occurs in myometrial arteries of the uterus as a result of gestation. Wermbter [20] in an extensive study showed that this change is not specific for pregnancy, but is also related to some degree with parity. The importance attached by these authors to intimal thickening was that under the influence of contractions the vessel becomes occluded and that the projections caused by the intimal proliferation

could act as supports for the formation of thrombi causing primary occlusion of the vessel in the postpartum period. The large myometrial arteries of the multigravida are characterized by an abundance of elastic and collagenous tissue in the adventitia, although the amount of increase in elastic tissue does not necessarily correlate with the number of gestations.

While most authors seemed to be agreed on the changes in the myometrial arteries much confusion and discussion existed with respect to vessel changes in the placental bed. Friedländer [21] described in 1870 an outstanding vessel change in the placental bed, which was wrongly described by Leopold [22] as 'die Spontane Venenthrombose'. Friedänder's description is as follows:

> *One finds .... that many of these blood spaces are surrounded by a moderately thick coat e.g. for a sinus of 0.5 mm diameter a coat as thick as 0.04 mm, which contains many apparently large cells with prominent nuclei and a clear, nearly homogeneous ground substance staining intensively with Carmin stain .... The next remarkable phenomenon is that the content of the sinus is no longer made up of red and white blood cells, but contains, in a more or less great number very dark, large and granulated cells .... These cells are sometimes lying singly in the centre of the sinus, sometimes adherent to and lining, as a continuous epithelium, a part of the wall, and, at last, can become so numerous that they completely block the sinus only leaving here and there gaps for an occasional red blood cell.*

In 1904 Schickele [23] drew attention to the fact that the vessel changes described by Friedländer [21] and Leopold [22] occurred mainly in arteries and only occasionally in veins. However, they were incorrect in thinking that the cells in the arterial lumen were most marked in late pregnancy as their description included two different changes which, although related to each other, appear in the spiral arteries at a different time during the course of pregnancy. A confusing terminology has been used to describe the changes which occur in the wall of the spiral arteries communicating with the intervillous space, such as 'physiologische regressive Metamorphose', 'hyalin Rohr mit grössen Zellen', fibrinoid and hyaline structures of bizarre outline in collapsed vessels, and diffuse thickening of the entire wall.

The intrusive cells in the lumen as described by Friedländer [21] were intensively studied by Boyd and Hamilton [24] and Hamilton and Boyd [25,26] using their large collection of uterine specimens with the placenta *in situ*. They demonstrated the continuity of these cells with the cytotrophoblastic cells of the basal plate of the placenta. The intraluminal cells first appear in the arteries when the latter are being tapped by the invading trophoblast; the maternal blood then reaches the intervillous space by percolating through the gaps between the intraluminal cells. They decided that the most acceptable explanation was that these cells were derived from the cytotrophoblastic shell and migrated antidromically along the vessel lumen. The intraluminal cells can pass several centimeters along a spiral artery and, indeed, may be found in its myometrial segment. Such plugging by intraluminal cells was illustrated in a myometrial artery from a pregnant uterus with a fetus of 118 mm CR length [4]. The plugs were present in all the spiral arteries of the basal plate during the middle 3 months of pregnancy, although their numbers varied, and they disappeared altogether in the last months. They were never observed in the veins. Boyd and Hamilton [4] speculated that the intravascular plugs damped down the arterial pressure in arteries that had already lost their contractility.

Kölliker [5] was the first to describe in 1879 the giant cells ('Riesenzellen') in the placental bed and indicated that these cells are restricted to the decidua basalis. Opinions diverged on the origin of these cells. The fetal origin was demonstrated by Hamilton and Boyd [26] when they examined uteri with placenta *in situ* at closely related time intervals during pregnancy and observed continuity in the outgrowth of fetal syncytial elements into the maternal tissue. Suggested functions of the giant cells were the production of enzymes, possibly to 'soften up' the maternal tissue, and the elaboration of hormones. Hamilton and Boyd had the impression that there was no marked effect, cytolytic or otherwise, of the giant cells on the maternal tissue. These cells seemed to push aside the maternal cells and to dissolve the surrounding reticulin and collagen, but there was no apparent destructive effect on the adjacent maternal cells. The possibility of hormone production by giant cells was suggested by their histological and histochemical appearance.

Functional aspects

In the early 1950s the hemodynamic aspects of the maternal circulation of the placenta were investigated using different new functional techniques such as the determination of the ^{24}Na clearance time in the

intervillous space [27], cineradiographic visualization of the uteroplacental circulation in the monkey [28,29], and determination of the pressure in the intervillous space [30].

Measurements of the amount of maternal blood flowing through the uterus and the intervillous space made by Browne and Veall [27] and Assali and coworkers [31] showed that maternal blood flows through the uterus during the third trimester at a rate of approximately 750 ml/min, and 600 ml/min through the placenta. Browne and Veall [27] found a slight but progressive slowing of the flow in late pregnancy up to term. However, in the presence of maternal hypertension a considerable decrease of flow was found and the extent of change appeared to be related to the severity of maternal hypertension.

Pathology of uteroplacental arteries

Vascular lesions of the uteroplacental arteries have been described since the beginning of the last century. Seitz [32] described in 1903 the intact uteri with placentae from two eclamptic patients with abruptio placentae and noted a proliferative and degenerative lesion in the spiral arteries, with narrowing and even occlusion of the vascular lumen. He found occluded arteries underlying an infarcted area of the *in situ* placenta, and related the vascular and decidual degeneration to the toxemic state. In later literature this excellent report on the uteroplacental pathology in eclampsia has been completely ignored, probably because at that time most authors were mainly interested in the presence of inflammatory cells in the decidua as a possible cause of eclampsia.

The delivered placenta and fetal membranes were for many years the commonest method of obtaining material for the study of spiral artery pathology, and there were large discrepancies between the findings in this material. In preeclampsia lesions such as acute degenerative arteriolitis [33], acute atherosis [34], and arteriosclerosis [35] were described.

Dixon and Robertson [2] introduced 50 years ago at the University of Jamaica the technique of placental bed biopsy at the time of cesarean section, while the Leuven group [36,37] obtained biopsies after vaginal delivery using sharpened ovum forceps. Both groups described hypertensive changes that showed the characteristic features of vessels exposed to systemic hypertension, i.e. hyalinization of true arterioles and intimal hyperplasia with medial degeneration and proliferative fibrosis of small arteries.

Physiological changes of placental bed spiral arteries

The method of placental bed biopsy produced useful material, but nevertheless was criticized by Hamilton and Boyd (personal communication). They strongly recommended the examination of intact uteri with the placenta *in situ* for the simple reason that the placental bed is such a battlefield that fetal and maternal tissues are hard to distinguish on biopsy material and maternal vessels are disrupted after placental separation. In 1958, independent from the British group in Jamaica, the Department of Obstetrics and Gynaecology of the Catholic University of Leuven had also started to collect placental bed biopsies, and in 1963 they began to collect uteri with the placenta *in situ* [37,38]. The hysterectomy specimens were obtained from women under normal and abnormal conditions whereas today tubal sterilization would have been performed at the time of cesarean section. The technique for keeping the placenta *in situ* at the time of cesarean hysterectomy was rather heroic. Immediately after delivery of the baby the uterine cavity was tightly packed with towels in order to reduce uterine retraction and prevent the placenta from separating from the wall. The large uterine specimens with placenta *in situ* were examined by semiserial sections to trace the course of spiral arteries from the basal plate to deep into the myometrium. As a result Brosens, Robertson and Dixon [39] described in 1967 the structural alterations in the uteroplacental arteries as part of the physiological response to the pregnancy and introduced for these vascular adaptations the term 'physiological changes' (Fig. 2.2). In 1972 the same authors [40] published the observation that preeclampsia is associated with defective physiological changes of the uteroplacental arteries in the junctional zone myometrium.

In subsequent studies the remodeling of the spiral arteries was investigated during the early stages of pregnancy. While abortion for medical reasons was allowed in the UK, it was not uncommon for older women to have a hysterectomy. When Geoffrey Dixon moved to the Academic Department of Obstetrics and Gynaecology of the University of Bristol in the 1970s he started to collect uteri with the fetus and placenta *in situ* from terminations of pregnancy by hysterectomy. The Bristol collection of uteri with placenta *in situ* was the starting point for the study of the development of uteroplacental arteries by Pijnenborg and colleagues [41].

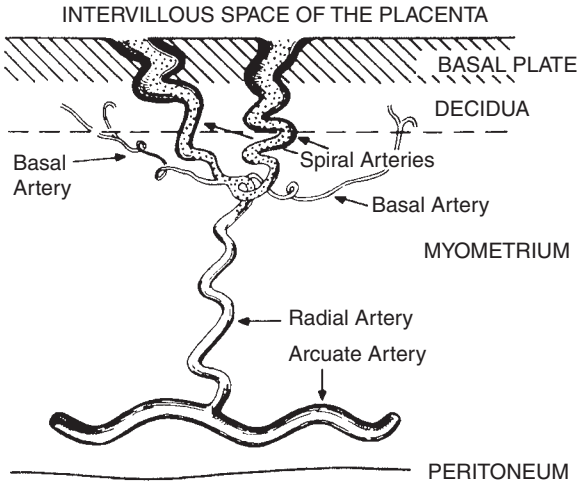

Fig. 2.2 Diagram of the maternal blood supply to the placental bed and intervillous space of the placenta showing physiological changes of the spiral arteries in the basal plate, decidua and junctional zone myometrium. After Brosens *et al.* [39].

Conclusions

The history outlined above illustrates the vascular complexity of deep placentation in humans. The spiral artery anatomy as well as the vascular pathology were only revealed after studying uteri with *in situ* placentae. There is no doubt that the main issue has been the recognition of the structural adaptation of the spiral arteries in the placental bed and the association of defective deep placentation with clinical conditions such as preeclampsia.

The main challenge today is to understand the mechanisms of the vascular adaptations and the role of the trophoblast and the maternal tissues in the interactions that can lead to a spectrum of obstetrical disorders.

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