Placental bed research: I. The placental bed: from spiral arteries remodeling to the great obstetrical syndromes

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Reconstructing the sequence of investigations that led to the present knowledge of the unique structure in which the fetus and the mother come in contact and exchange all kinds of substances and messages is neither simple nor easy.

Indeed, work on this subject spanned more than 125 years, starting in 1893 when, for the first time, Bumm[1] described unique physiological changes occurring in the uterine vasculature during pregnancy.

The acquisition of knowledge in this field can be subdivided into 2 distinct periods: first, the classic morphological studies and, more recently, a series of functional investigations, including biophysical studies, such as Doppler flow evaluations, uteroplacental perfusion studies, the identification of factors and markers, and a careful evaluation of immunological parameters involved. These more modern investigations will be the subject of a separate successive article.[2]

In 1953, Browne and Veall,[3] using a technique involving the local injection of radioactive sodium, provided the first direct evidence of a reduced maternal blood flow through the placenta in pre-

The term placental bed was coined to describe the maternal-fetal interface (ie, the area in which the placenta attaches itself to the uterus). Appropriate vascularization of this area is of vital importance for the development of the fetus; this is why systematic investigations of this area have now been carried out. Initially, the challenge was the identification and classification of the various successive branching of uterine arteries in this area. These vessels have a unique importance because failure of their physiological transformation is considered to be the anatomical basis for reduced perfusion to the intervillous space in women with preeclampsia, fetal growth restriction, preterm labor, preterm premature rupture of membranes, abruptio placentae, and fetal death. To investigate in depth the pathophysiology of the placental bed, some 60 years ago, a large number of placental bed biopsies, as well as of cesarean hysterectomy specimens with placenta in situ, from both early and late normotensive and hypertensive pregnancies, were carefully dissected and analyzed. Thanks to the presence of a series of specific physiological changes, characterized by the invasion and substitution of the arterial intima by trophoblast, this material allowed the identification in the placental bed of normal pregnancies of the main vessels, the uteroplacental arteries. It was then discovered that preeclampsia is associated with defective or absent transformation of the myometrial segment of the uteroplacental arteries. In addition, in severe hypertensive disease, atherosclerotic lesions were also found in the defective myometrial segment. Finally, in the basal decidua, a unique vascular lesion, coined acute atherosis, was also identified This disorder of deep placentation, coined defective deep placentation, has been associated with the great obstetrical syndromes, grouping together preeclampsia, intrauterine growth restriction, preterm labor, preterm premature rupture of membranes, late spontaneous abortion, and abruptio placentae. More recently, simplified techniques of tissue sampling have been also introduced: decidual suction allows to obtain a large number of decidual arteries, although their origin in the placental bed cannot be determined. Biopsies parallel to the surface of the basal plate have been more interesting, making possible to identify the vessels' region (central, paracentral, or peripheral) of origin in the placental bed and providing decidual material for immunohistochemical studies. Finally, histochemical and electron microscopy investigations have now clarified the pathology and pathogenetic mechanisms underlying the impairment of the physiological vascular changes.

Key words: abnormal physiological transformation, abruptio placentae, acute atherosis, defective deep placentation, fetal death, fetal growth restriction, placental bed biopsies, placental vascular anatomy, preeclampsia, preterm labor, preterm premature rupture of membranes, spiral arteries, trophoblastic invasion, uteroplacental arteries

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eclampsia. Then about 60 years ago, 2 groups, one in Jamaica and one in Belgium, independently started to take placental bed biopsies for the investigation of uterine arteries supplying the fetal side of the placenta. The assumption was that the reduction in maternal blood flow to the placenta observed in preeclampsia must be secondary to alterations in its maternal blood supply.

The term, placental bed, to describe the area in which the placenta attaches itself to the uterus, was introduced by Dixon and Robertson[4] in 1958. The area

has been previously referred to as the Niemandsland (no man's land) by German authors.[5] It has its own histological and pathological aspects, and its study is most useful to investigate and describe the maternal vascular part of the placenta in contrast to the fetal portion. Its primary function is to adapt through modification of the uteroplacental spiral arteries to establish and maintain an adequate maternal blood supply to the intervillous space of the placenta.

This represents a vital adaptation because it has been correctly held that embryonic and fetal growth is dependent on the capacity of the uterine vascular system to satisfy increasing embryonic/fetal oxygen demand throughout gestation. This hypothesis is substantiated by investigations in primates showing that the marked increase in uterine vascular density during late gestation coincides with the phase of rapid growth in embryo mass and concomitant increase in metabolic rate.[6]

Modifications in the uterus in preparation for pregnancy begin already during the second, secretory phase of the menstrual cycle with the decidualization of endometrial stromal cells (see *Decidualization and arterial transformation. Role of decidual natural killer [NK] cells and of the trophoblast*), and there is evidence that disruption of this process can trigger a cascade of events resulting in failed deep placentation.[7]

A unique feature of pregnancy is that during the course of a normal gestation, the endothelium disappears progressively from the uteroplacental arteries, being replaced by trophoblast and the deposition of a fibrofibrinoid structure. This process constitutes the so-called physiological transformation of uterine spiral arteries[8,9] (Figure 1).

Focusing the attention on uterine vasculature, as schematically shown in Figure 2, 3 types of decidual arteries have been distinguished[10]: uteroplacental spiral arteries, basal arteries that do not open into the intervillous space, and spiral arteries outside the placental bed (see *Identification of uteroplacental arteries*).

For a long time, the identification of the uteroplacental spiral arteries remained a mystery, and even today it can be a challenge, particularly in cases of decidual and basal plate studies. For this reason, it is important to retrace how the process through which maternal blood supply to the placenta is progressively established, as a means to better understand the role that alterations of this supply have in the pathogenesis of the syndromes called the great obstetrical syndromes.[11]

Indeed, it is today recognized that defective placentation in the human is a cause of many pregnancy complications, including spontaneous abortion, preterm labor and delivery, preeclampsia, intrauterine growth restriction, fetal death, and abruptio placentae.[10] This is because spiral arteries in which physiological transformation has not taken place are prone to develop atherosclerotic-like lesions, including one coined acute atherosis (see *Atherosclerotic and arteriosclerotic lesions of uteroplacental arteries*), and striking similarities have been observed between lesions found in preeclampsia and atherosclerotic disease and between lesions of atherosis and atherosclerosis.[12,13]

A new, very important finding is that these clinical disorders can have for the newborn long-term consequences going into adulthood, causing cardiovascular disease, obesity and diabetes in the offspring as well as an increased risk of premature death in the mother.[14]

Methods of sampling

Obtaining meaningful samples of the placental bed is not an easy task because, to be useful, biopsies must include trophoblastic cells.

In addition to the technique utilized by Dixon and Robertson[4] and named the placental bed biopsy, several other techniques have been used for more than a century.

Caesarean hysterectomy specimens with placenta in situ: identifying spiral arteries from the myometrium to the intervillous space

It seems that in 1903, Seitz[15] was the first to study hysterectomy specimens

with the placenta in situ, although for half a century no other such investigation appeared. By 1963 a series of 16 cesarean hysterectomy specimens were collected at the University Hospital in Leuven, Belgium, where a technique was developed for keeping the placenta in situ during the caesarean section. Immediately after extraction of the newborn, the uterus was packed by a large amount of gauze and in some cases a large incision was made through the peritoneum and myometrium overlying the placental area before performing the hysterectomy.[16]

This series included 7 hysterectomy specimens with placenta in situ from normotensive and 9 from hypertensive pregnancies (Table 1). In the uteri from the normotensive group, a total of 100 uteroplacental arteries were traced by large step serial sections, whereas in the hypertensive group, the total was 82. These vessels were followed in their course from their origin in the inner myometrium till their opening in the basal plate of the placenta. Apparently, with the exception of an investigation by Kadyrov et al[17] on the effect of maternal anemia on extravillous trophoblast invasion, no similar studies have been published since.

The benefits of the investigation of the cesarean hysterectomy specimens have been multiple. First, the intact specimens have shown that placental bed in normal pregnancy has a concave shape with physiological changes of the uteroplacental arteries in the central and paracentral zone but not at the periphery of the placental bed.

Second, defective deep placentation in severe preeclampsia is characterized by the absence of physiological changes in the myometrial segment of the uteroplacental arteries in the paracentral zone of the placental bed (Figures 3 and 4). In preeclampsia, a direct relationship between pathology of the uteroplacental arteries and placental lesions, such as thrombosis and infarcts, has been documented.[13]

Finally, the study of uteri with placenta in situ has shown that the

FIGURE 1
Progressive physiological modifications occurring in uteroplacental arteries during pregnancy
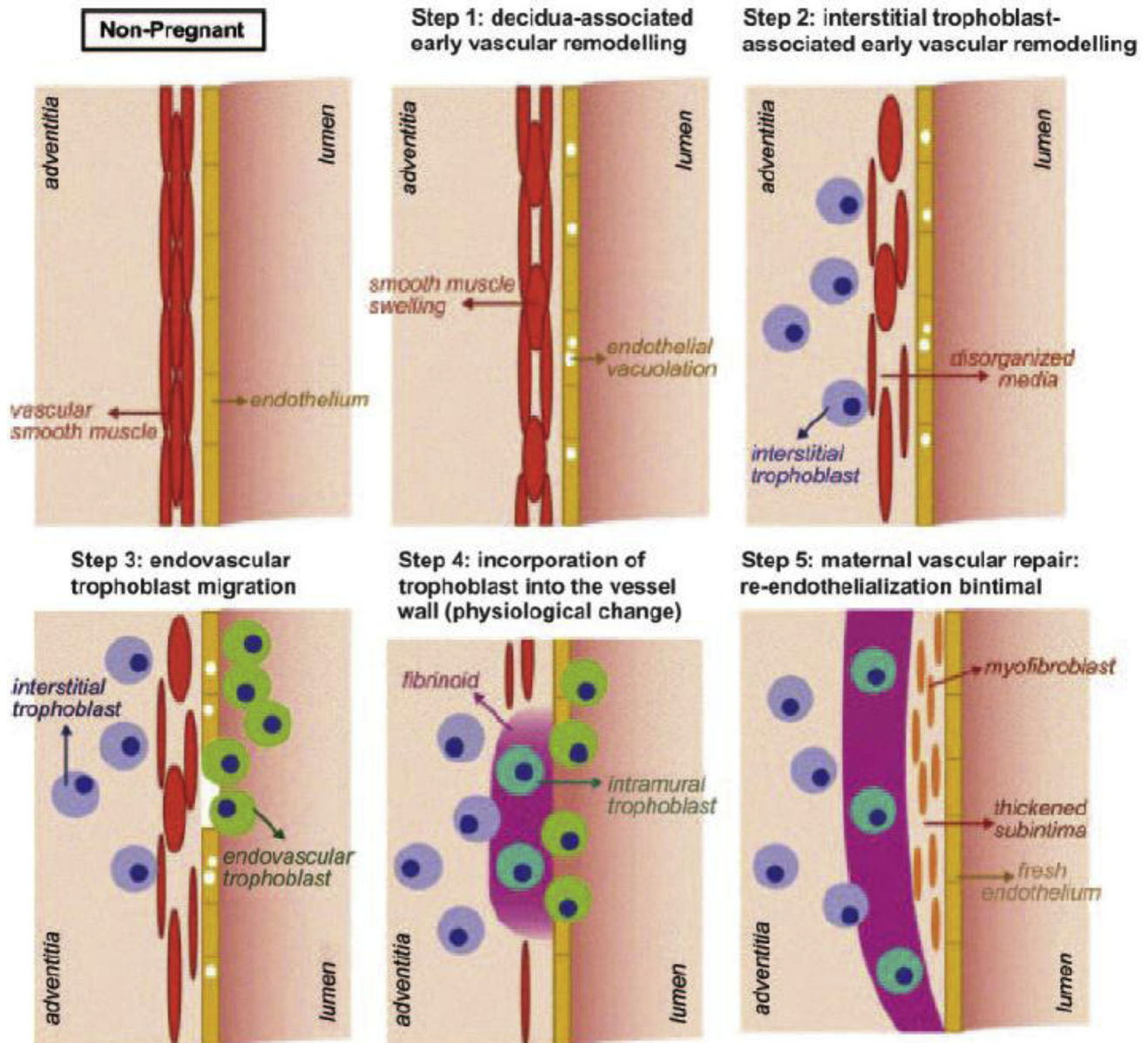
Schematic view of the progressive physiological modifications occurring in uteroplacental arteries during pregnancy. From Pijnenborg et al. (2006).[9]

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uteroplacental spiral artery has a significantly larger diameter, varying between 200 and 500 μm, while the basal artery has a diameter less than 120 μm[16] (Table 2). In their definition, Alnaes-Katjavivi et al[18] applied the criterion of $\geq$140 μm for identifying uteroplacental spiral arteries; this agrees with the findings in hysterectomy studies.[14]

Placental bed biopsies: from myometrium till basal plate
Half a century ago, 2 groups, in Jamaica and in Belgium, started taking placental bed biopsies using different techniques: the first group obtained the biopsies at the time of caesarean delivery and used a cervical biopsy forceps,[4] while the second group obtained biopsies

transvaginally as well, at the time of manual removal of the placenta after vaginal delivery; they used a sharpened ovum forceps for obtaining a large biopsy from the placental bed area.[16]

Because of the blind technique in obtaining the biopsy, confirmation of the origin through the identification of the decidua basalis of the placental bed is of

FIGURE 2
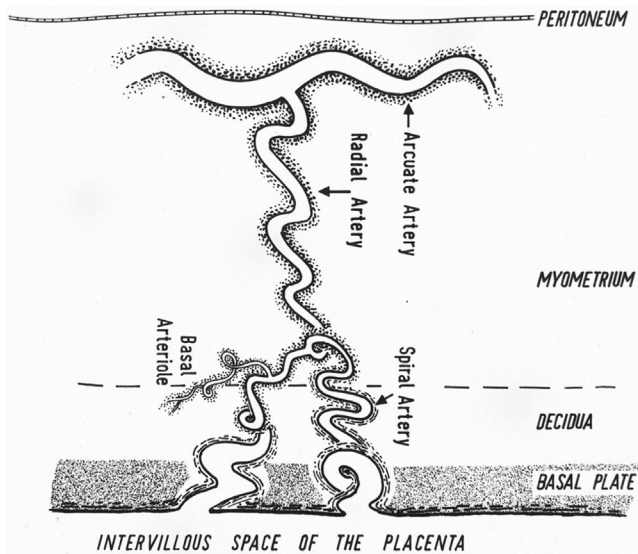**The vascular tree of the placental bed**

Diagram of the maternal blood supply to the placental bed and intervillous space showing physiological changes of the spiral arteries in the basal plate, decidua, and junctional zone myometrium. From Ivo Brosens, PhD thesis, Unversity of London, 1965.

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vital importance. From the experience gained with cesarean hysterectomy specimens with placenta in situ, 3 criteria have been found to prove that the sample is indeed from the placental bed, namely the presence of the following: (1) trophoblastic giant cells in the decidua and/or myometrium, (2) villi attached to the decidua, and (3) physiological changes in spiral arteries.[18] Although it is possible that a biopsy may in fact originate from the edge of the placental bed, every biopsy not satisfying at least 1 of these histological criteria of placental origin should be excluded as not representative.

In addition, 3 caveats should be considered on taking representative placental bed biopsies. First, the uteroplacental artery is a large vessel and, in the absence of physiological changes, it needs to be differentiated from the basal artery both in the myometrium and in the basal decidua by the difference in the external diameter of the vessel.[18]

Second, it should be considered that at term there is 1 spiral artery for approximately 2–3 cm^2 of basal plate.[19] Therefore, the information, particularly in smaller studies, on the exclusion rate of biopsies for the absence of any spiral artery segment is of critical importance. In a systematic review of biopsy techniques, Veerbeek et al[20] reported recently that, depending on the technique used, the likelihood of sampling a spiral artery and trophoblast in a placental bed biopsy is 51–78%. However, the percentage of successful biopsies appears not to increase with the number of biopsies taken.

Third, considering the concave shape of deep placentation with complete transformation of the spiral arteries in the center of the placenta, even in case of severe defective deep placentation, representative biopsies for its diagnosis should be not be taken from the central but rather from the paracentral zone of the placental bed.[21] The tissue may be similar to basal plate tissue and may fail to include the typical vascular pathology of the inner myometrium.

Remarkably, the placental bed biopsy methods are safe because no short- or long-term complications have been reported. Specifically, Brosens[16] mentioned that in 400 placental bed biopsies obtained after vaginal delivery by sharpened ovum forceps, there were no major complications. Veerbeek et al,[20] in their systematic review of the field, also mention that no significant complications had been reported, even in the long-term follow-up (38–60 months) after vacuum suction.

Decidual cells from the placenta and fetal membranes: the battlefield between decidua and trophoblast
More than 60 years ago, Wynn[22] described the fetomaternal junctional zone as "an active placental battleground on which there are heavy casualties on both sides." Robertson and Warner[23] found that a large area of the battleground is left behind in the uterus when the placenta is expelled or removed, indicating the hemochorial nature of human placentation, in which tissue destruction is inevitable and physiological.

The study of uteroplacental arteries in the basal plate of the placenta may offer the opportunity of investigations that would not be feasible with placental bed biopsies. In this area of the placenta, fetal cells can be distinguished by immunohistochemical techniques. To this end, Khong and Chambers[24] recommended to take en face blocks (ie, horizontal sections) for the histological assessment.

An additional benefit is that biopsies can be obtained from the paracentral part, in which implantation may be more representative for spiral artery pathology, such as thrombosis, than in the central part. The study of Labarrere et al[13] documented that using the technique of basal plate biopsy, a median of 4 vessels per placenta can be obtained. Moreover, in a series of 123 placentas they demonstrated the presence of complete or partial physiological transformation in pregnancy complications including preeclampsia, intrauterine growth restriction, fetal death, spontaneous preterm labor, and preterm prelabor rupture of membranes.

Decidual suction: basal decidua
The suction of the decidua method was developed by Harsem et al[25] to obtain a large volume of decidual tissue from the

placental bed. The tissue is harvested at the time of cesarean delivery by vacuum suction of the placental bed. After routine preparation, the tissue is stained with a panel of antibodies and morphologically examined for the presence of trophoblast and spiral arteries. In Harsem's study, in 86% of the specimens (n = 44), 1 random section from the decidual suction material demonstrated at least 1 spiral artery. In 37% (n = 19), 6 or more spiral arteries were present. All sections revealed extravillous trophoblasts. No short- or long-term morbidity was recorded.

Unraveling the vascular anatomy

As mentioned, the identification of the different types of arteries in the placental bed for years remained both a major challenge and a mystery (Box).

Identification of uteroplacental arteries

Our knowledge of how to identify and study the uteroplacental vascularization is based on the investigation of the entire uterus with the placenta in situ and, although clearly cumbersome, this method has been utilized for more than a century.[15] In 1936, Spanner[26] investigated in 4 uteri with placenta in situ the maternal and fetal blood flow anatomy, using corrosion preparations. In one specimen from a pregnancy in the eighth month, he counted 94 spiral arteries with a total of 488 openings into the intervillous space. In 1956, Boyd,[27] on the basis of partial counts, found 180, 310, and 320 openings in 3 term uteri with placenta in situ and estimated that there are approximately 100 spiral arteries in the placental bed.

In 1966, Brosens and Dixon,[21] after serial sectioning of two fifths of a term placenta, estimated a total of 120 uteroplacental spiral arteries. They confirmed an old observation by Bumm[1] that most uteroplacental arteries open in close relation to a placental septum and, interestingly, frequently in the center of an attached cotyledon.

The decidua suction technique seems useful for the study of a unique lesion, coined decidual acute atherosis (see *Acute atherosis of the basal arteries in and*

outside the placental bed), although in several publications utilizing the technique, uteroplacental spiral arteries may not have been clearly differentiated from basal arteries.

Following the publication by Kitzmiller and Benirschke[28] linking diminished perfusion of the placenta to acute atherosis of decidual vessels, as mentioned in the previous text, Robertson et al[10] defined 3 classes of maternal arteries in the placental bed. First, the large, tortuous funnel-shaped

spiral arteries affected by physiological changes that are the de facto vessels supplying the intervillous space; they are easily seen with the naked eye on the cesarean hysterectomy specimen when the placenta is carefully peeled from the placental bed, although, because of their size and distended state, they may be confused with veins. The severed terminations of these vessels, adherent to the basal plate of the placenta, can also be distinguished, with some difficulty, from veins.

TABLE 1
The Leuven collection of cesarean hysterectomy specimens

Reference	Age	Parity	Gestation weeks	Birth weight, g	Clinical data
Normotensive pregnancies (n = 7)					
B57/7774	38	3	38	3700	
B63/22236	30	3	40	3450	
B86/28507	30	6	36	2220	Abruptio placentae
B65/17254	25	3	39	3750	Antepartum hemorrhage at 36 weeks
B68/20751	36	4	38	3470	
B71/27133	27	2	38	2460	
B30/	23	?	39	3240	
Hypertensive pregnancies (n = 4)					
B33/24645	26	0	29	1350	BP 150/100, albumin+, nephrotic syndrome
B60/9874	37	1	28	?	BP 180/110, albumin +++
B66/10469	33	4	?	1250	BP 180/110, abruptio placentae
B70/18857	37	5	37	3120	BP 180/110, albumin negative
Borderline hypertension (n = 5)					
B26/20282	40	9	38	3600	BP 140/90
B43/23651	26	1	40	4200	BP 140/85
B67/26957	39	0	38	2580	BP 150/85; at 37 weeks constrictive pericarditis
B69/	36	7	39	4120	BP 140/80
B72/22543	41	5	28	3640	BP 125/90

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FIGURE 3
Appearance of infarcted zone of a uterus and transformaion
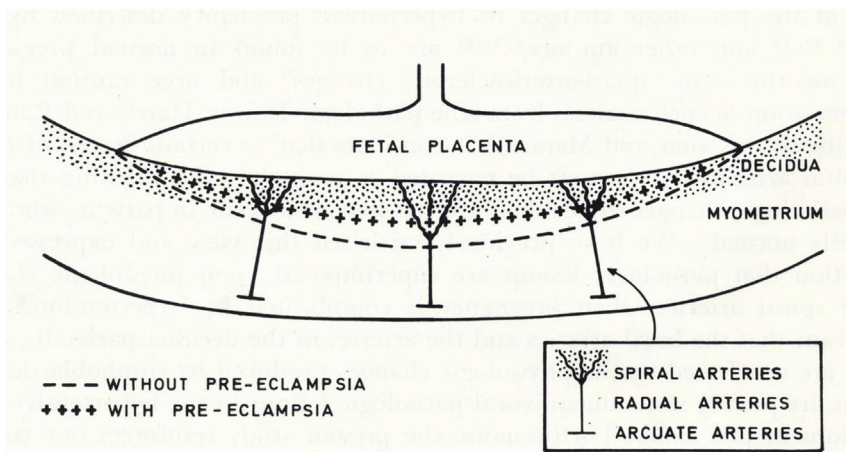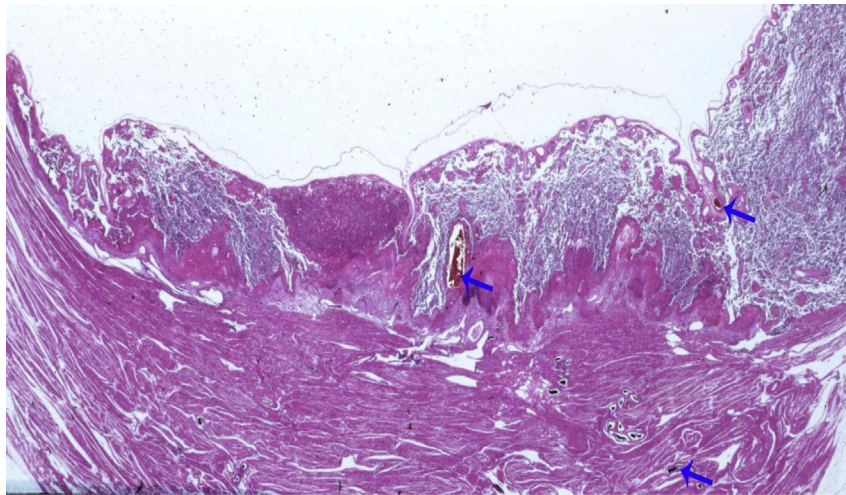
Top, Microscopic appearance of an infarcted zone of a uterus with placenta in situ in severe pre-eclampsia. The intravascular injection of Chinese inkt via the uterine artery shows up in the patent radial and spiral arteries in the central part of the placental bed (*blue arrows* on the right and center) but is absent in the arteries underlying a large intervillous thrombus (*blue arrow* on the left). **Bottom,** Schematic diagram of placental vessels' transformation showing normal (bottom line) and defective deep placentation. From Ivo Brosens, PhD thesis, University of London, 1965.

Brosens. Placental bed research. Am J Obstet Gynecol 2019.

Second, the basal arteries are seen only on histological sections; they are small branches, about 100 μm in diameter, of the radial or spiral arteries that ramify in the inner myometrium and terminate in the decidua basalis, but do not open into the intervillous space.[16]

Third, again seen only on histology, the spiral arteries that are outside the placental bed; they do not undergo physiological changes but terminate in the decidua vera or parietalis; they play no part in the blood supply to the placenta itself but may nourish the chorionic aspect of the membranes.

In conclusion, the study of uteri with placenta in situ has shown that the uteroplacental spiral artery has a significantly larger diameter, varying between 200 and 500 μm, while the basal artery has a diameter less than 120 μm.[16] In their definition, Alnaes-Katjavivi et al[18] applied the criterion of $\geq$140 μm for identifying uteroplacental spiral arteries; this agrees with the findings in hysterectomy studies.[16]

Decidualization and arterial transformation: role of decidual natural killer (NK) cells and the trophoblast

During the secretory phase, the endometrium transforms into a well-vascularized receptive tissue characterized by increased vascular permeability, edema, proliferation and differentiation of stromal into decidual cells, invasion of leucocytes, vascular remodeling, and angiogenesis.[29] If fertilization occurs, the process of decidualization continues and is characterized by an influx of immune cells and trophoblast; vascular adaptation also begins.

Role of dNK in pregnancy
As mentioned in previous text, vascular changes in pregnancy include spiral artery remodeling, angiogenesis, and the induction of angiogenic factors.[30] An important observation was made some 20 years ago by Craven et al,[31] who showed that decidual spiral artery remodeling begins before vascular cellular interactions with cytotrophoblast occur.

A similar observation was made by Pijnenborg et al,[32] confirming that vascular changes precede trophoblast invasion of the spiral arteries. These are transformed into low-resistance vessels by dilatation, loss of the elastica, and disorganization of smooth muscle cells. The surrounding decidual NK (dNK) cells and macrophages seem to prime the decidual spiral arteries for extravillous trophoblast invasion and to play a role in recruiting these cells to line the vessel wall.

These decidual natural killer cells (identified as tissue-resident CD56[superbright] dNK cells) are phenotypically and functionally distinct from conventional NK cells in the circulation.[33,34] Accumulation of dNK cells in the endometrium is primarily governed by the process of decidualization of endometrial stromal cells. During a normal menstrual cycle, dNK cells accumulate rapidly in the endometrium during the midluteal implantation window; levels then continue to rise in the late-luteal phase.[35,36] It has been recently shown that dNK cells play a critical role in

maintaining tissue homeostasis by targeting and eliminating acutely stressed decidual stromal cells through granule exocytosis.[35]

In the event of pregnancy, dNK cells continue to proliferate and their abundance peaks during the first trimester when they constitute 70% of all immune cells in the decidua.[37,38] Single-cell transcriptomic analysis of first-trimester decidua identified 3 main dNK subpopulations,[39] which likely exert distinct roles in tissue homeostasis,[35] maternal allo recognition of placental trophoblast,[40] spiral artery remodeling,[41] and immunomodulation of local myeloid cells and T cells.[39] The discovery of distinct NK subsets in human endometrium is in keeping with growing evidence that they likely arise from different sources; these include resident progenitor cells in the basal endometrium (uNK), hematopoietic progenitor cells, and extravasation and reprogramming of conventional NK cells.[42–44]

The role of dNK cells in pregnancy has been studied extensively also through the use of animal models.[45–47] Despite notable placental differences between humans and mice,[33] there is broad agreement that cytokines and chemokines produced by dNK cells play a pivotal role in hemochorial placentation by regulating angiogenesis, spiral artery remodeling, and extravillous trophoblast invasion through a complex mechanism.[48]

In this connection, 2 important genes, the one expressing the killer immunoglobulin-like (KIR) receptors and that expressing the major histocompatibility complex, class C (HLA-C) are polymorphic and certain types of these genetic variants are believed to predispose for the great obstetrical syndromes,[49–51] including preeclampsia.

Specifically, the frequency of maternal KIR AA genotypes in combination with a paternally derived HLA-C allele bearing a C2 epitope is increased in women with pregnancy disorders associated with poor placentation.[49,52] Furthermore, compelling evidence suggest that decidual factors can inhibit uNK cell-mediated angiogenesis.[53,54] In other

FIGURE 4
Appearance of uteroplacental artery with and without physiological changes
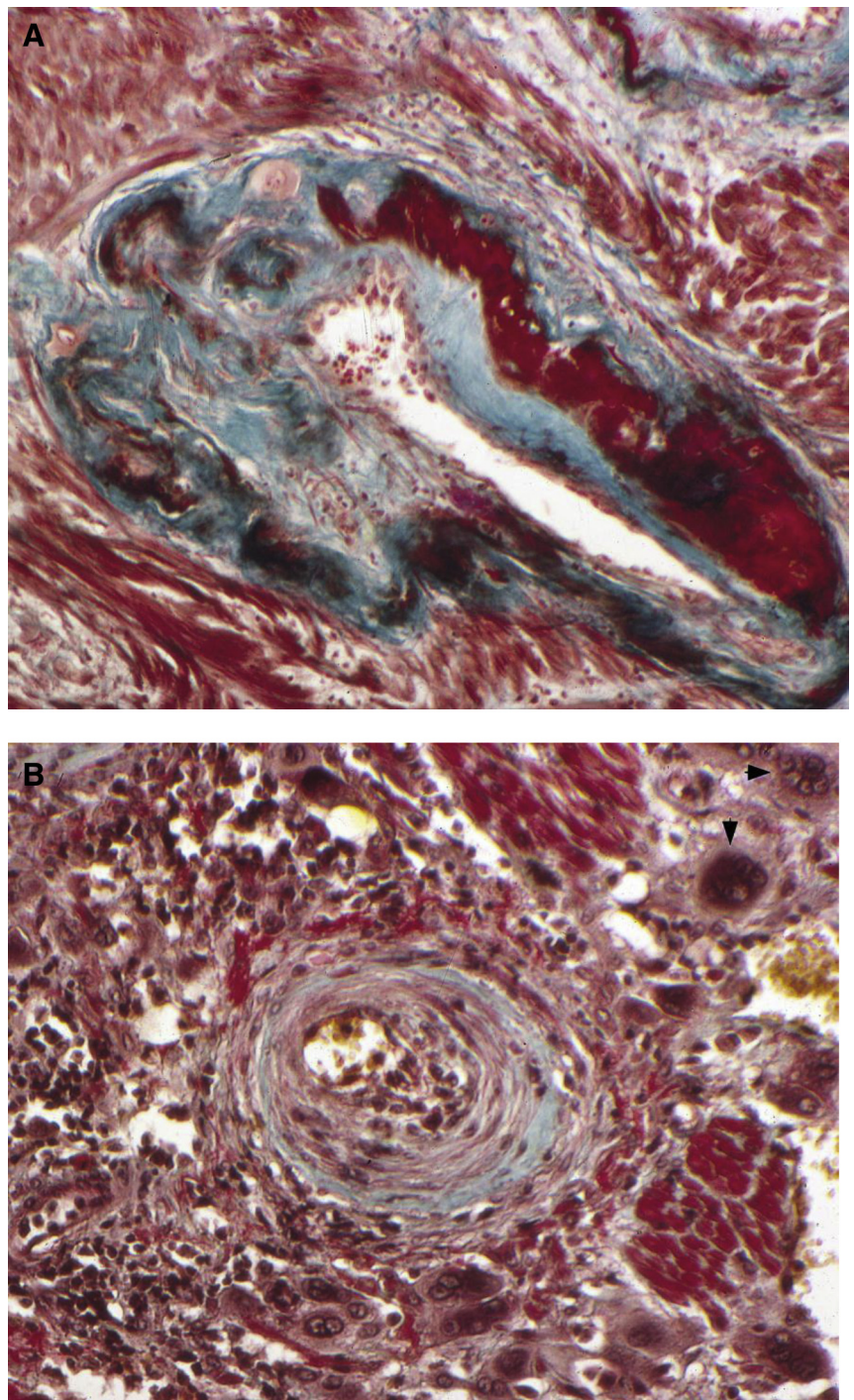
Histological appearance of a uteroplacental artery with and without physiological changes (Masson trichrome staining). **A,** Uteroplacental artery showing marked distension and replacement of the muscular and elastic tissue wall by fibrinoid and invaded trophoblast. **B,** A spiral artery in the junctional zone myometrium in severe preeclampsia showing absence of physiological changes and surrounded by interstitial trophoblast.

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TABLE 2
Structural alterations of the placental bed arteries in obstetrical hypertensive disorders

	Physiological changes	elastica	Diameter (microns)	Hyperplasia	Acute atherosis
Control	+	−	500	−	−
Preeclampsia	−	+	200	−	+
Severe preeclampsia	−	++	200	+	+

After Brosens et al (Obstet Gynecol Annual, 1972.[16]

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words, uNK cells appear to contribute to the pathogenesis of preeclampsia by amplifying the impact of an aberrant decidualization process on uteroplacental adaptation in pregnancy.

Interestingly, pregnancy itself appears to impose a memory on dNK cells. This emerging concept grew from the discovery of a dNK population unique to pregnancies of parous women.[55] These pregnancy-trained dNK cells are characterized by high expression levels of the inhibitory natural killer group A2 receptor and the leukocyte immunoglobulin-like receptor B1. Activation of these receptors leads to increased secretion of vascular endothelial growth factor A and interferon-gamma, 2 major vascular modulators in pregnancy.[56] Whether these pregnancy-trained dNK cells play a role in lowering the incidence of preeclampsia in parous women requires further investigation.

Role of the cytotrophoblast
From a large collection of intact pregnant uteri removed for therapeutic reasons collected at the Department of Obstetrics and Gynecology at the University of Bristol, Pijnenborg et al[9] selected 48 specimens ranging from 8 to 18 weeks of pregnancy. Their analysis showed that cytotrophoblast invades the distal segments of the spiral arteries to become endovascular while at the same time diffusely infiltrating the decidua as an interstitial invader.

With the increase in size, lateral spiral arteries come to lie oblique and new openings into the intervillous space may be created resulting in decidual necrosis in the periphery. Apparently, in the upper decidua, the physiological changes converting spiral arteries into

BOX
Chronology of placental bed research

- 1953. Browne and Veall[3] show that maternal uteroplacental blood flow is reduced in women with preeclampsia.
- 1957. The anatomists Hamilton and Boyd[108] recommend to collect uteri with placenta in situ from women with and without hypertension to study the uteroplacental arteries on serial sections from their origin in the myometrium.
- 1958. Dixon and Robertson[4] at the University of the West Indies, Kingston, Jamaica, obtain biopsies at the time of caesarean section using punch biopsy forceps. They introduce the term, placental bed.
- 1962. Renaer and Brosens[132] at the Catholic University of Leuven, Leuven, Belgium, obtain biopsies both at the time of cesarean delivery and at vaginal delivery, using a sharpened ovum forceps. The main problem they encountered was the identification of the uteroplacental artery in the biopsy specimen.
- 1964. Two buckets filled with cesarean hysterectomy specimens are transported from Leuven, Belgium, to London, United Kingdom, to be investigated by step serial sectioning using a sledge microtome at the Hammersmith Hospital.
- 1965. The first PhD thesis, "The Placental Bed," is presented at the University of London by Ivo Brosens.[111]
- 1972. The examination of placental bed biopsies and cesarean hysterectomy specimens from 400 normotensive and 58 preeclamptic gestations show that in preeclamptic pregnancies physiological changes tend to be restricted to the decidual branches and fail to reach the myometrial trunks. When preeclampsia complicates chronic hypertension, there is not only restriction of physiological changes to the decidual segment but also the myometrial segment shows hyperplastic arteriosclerosis. These morphological features imply a failure of adequate placentation and explain the reduced blood supply to the fetus in preeclamptic pregnancies.[16]
- 1975. The proceedings of the first Leuven symposium, "Human Placentation," are published by Excerpta Medica.[133]
- 1976. Robert Pijnenborg, as visiting scientist at the University of Bristol, Bristol, United Kingdom, investigates a series of 45 hysterectomy specimens with pregnancy in situ between 8 and 18 weeks of gestation, and in 1980 the article reporting on "trophoblast invasion of human decidua from 8 to 18 weeks of pregnancy," is published.[59]
- 1986. Publication of the most cited article on the placental bed by Khong et al.[76]
- 2010. Robert Pijnenborg, Ivo Brosens, and Roberto Romero edit a comprehensive summary of findings in the vascular tree of normal and pathological gestations: a book entitled *Placental Bed Disorders. Basic Science and Its Translation to Obstetrics.*[12]
- 2018. On Aug. 8 2018, there were 1192 published documents on the placental bed.

Brosens et al. Placental bed research. Am J Obstet Gynecol 2019.

FIGURE 5
Spiral artery remodeling between 8 and 18 weeks' gestation
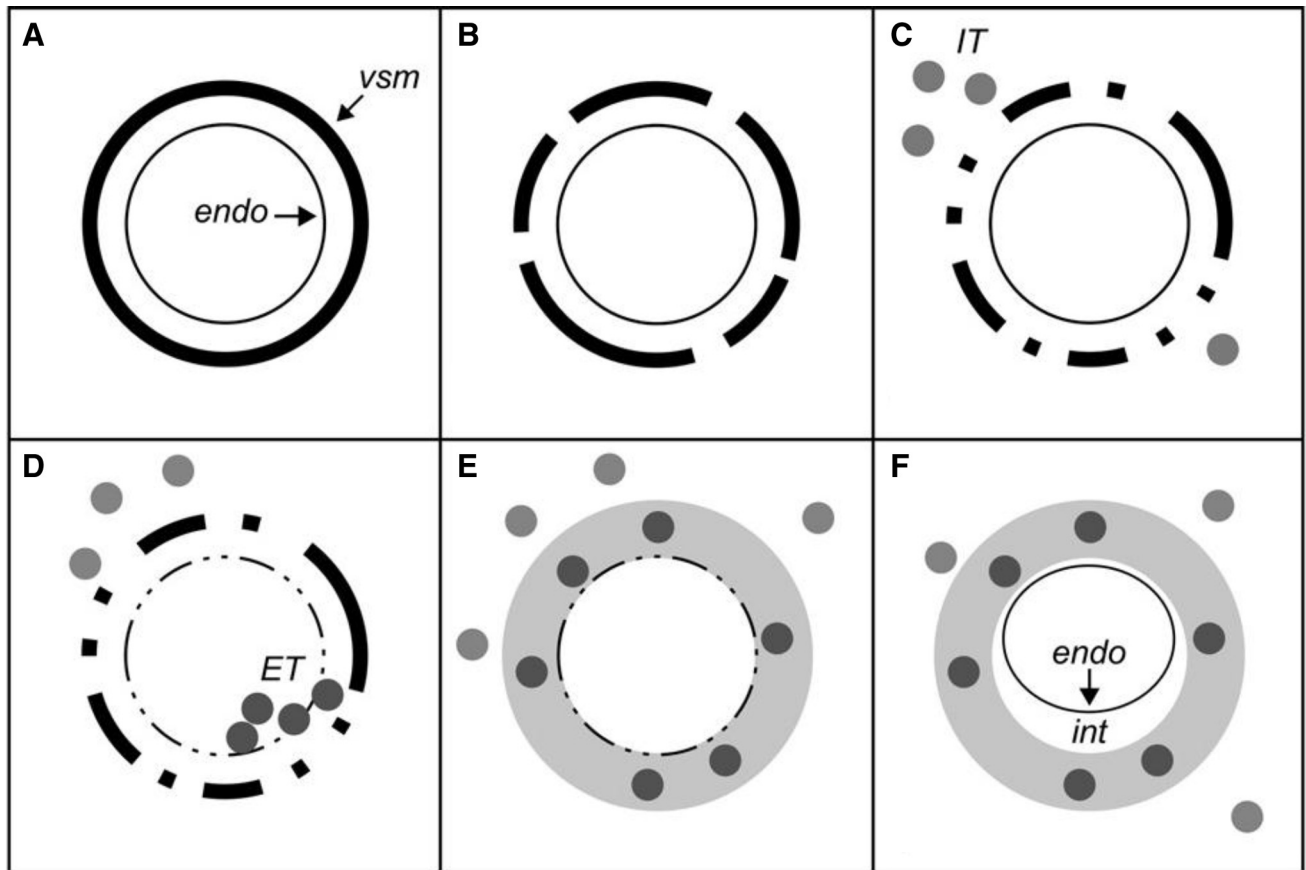
Diagrammatic steps in spiral artery remodeling between 8 and 18 weeks' gestation are shown. **A,** Unmodified spiral artery with endothelium and vascular muscle cell. **B,** Decidua-associated remodeling with disorganization of vascular smooth muscle. **C,** Interstitial trophoblast invasion enhances vascular smooth muscle disorganization. **D,** Endovascular trophoblast temporarily replaces the endothelium; intramural incorporation of endovascular trophoblast is shown. **E,** Deposition of fibrinoid, replacing the vascular smooth muscle. **F,** Reendothelialization and intimal thickening. From Pijnenborg et al (1983).[32]

endo, endothelium; *ET*, endovascular trophoblast; *int*, intimal thickening; *vsm*, vascular muscle cell.

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uteroplacental arteries are affected by the action of endovascular and perivascular trophoblast, whereas in the deeper decidua endovascular trophoblast is principally involved.

The morphometric study of the myometrial interstitial trophoblast invasion in 27 of these intact hysterectomy specimens showed that some changes, such as swollen endothelium and hypertrophy of individual medial smooth muscle cells, are noted also in spiral arteries outside the placental bed, although to a less degree than in it.[57] The migration of endovascular trophoblast into the myometrial spiral arteries in the second trimester occurs only after these arteries are considerably altered in their morphology. Otherwise the vascular changes in the placental bed are a time-related continuum.

The development of physiological changes
A recent observation indicates that in early pregnancy invasion of extravillous trophoblast affects uterine veins as well as arteries. Moser et al[58] have shown that uterine veins are invaded by extravillous trophoblast significantly more than uterine arteries (29.2% ± 15.7%) during early pregnancy and consider that this phenomenon is responsible for draining waste and blood plasma from the intervillous space.

At any rate, the endovascular trophoblast-associated remodeling starts with myometrial trophoblast invasion at around gestational age 14–15 weeks; it has been described in detail by Pijnenborg et al[59] and, as schematically shown in Figure 5, is composed of 5 steps (image A indicates the artery before any alteration occurs):

- Step 1 involves endothelial vacuolization (B).

- Step 2 consists of early media disorganization and weakening of the elastica, which is associated with the beginning of vessel dilatation (C).
- Step 3 starts with the appearance of endovascular trophoblast in the arterial lumen (D).
- Step 4 begins with the incorporation of endovascular trophoblast into the vessel wall, a process associated with fibrinoid deposition. The original smooth muscle layer and elastica are replaced by this fibrinoid material, while the embedded trophoblast acquires a spidery shape (E).
- Step 5 involves endothelial repair and occasional intimal thickening (F).

Therefore, the process begins with the decidua-associated disorganization of the vascular smooth muscle, followed by interstitial and endovascular trophoblast invasion. Progressively, a new wall is formed by deposition of fibrinoid and intimal thickening, lined by endothelial cells. Toward the end of pregnancy, spiral arteries in the placental bed are converted into large, tortuous channels by replacement of the normal musculoelastic wall with a mixture of fibrinoid material and fibrous tissue, and a thickening of the intima, attributed mostly to the organization of mural thrombi.[57]

Structural alterations extend proximally into the myometrial segment of the spiral arteries and even in the terminal segments of radial arteries. These are relatively unaffected by pregnancy, although they may show muscular hyperplasia and a loss or alteration of their elastic membrane.[8] Because structural alterations in the maternal uteroplacental spiral arteries occur in normal pregnancies, the term, physiological changes, has been proposed to characterize them.[59]

In late pregnancy, these changes usually involve the myometrial segment of the spiral arteries, except at the periphery of the placenta. The mean outer diameter of the myometrial segment of spiral arteries is around 500 μm. In vessels affected by physiological changes, the internal elastic lamina is usually not seen,

although a few fragments of elastic tissue can be demonstrated in the altered vessel wall. There is in fact an inverse relation between the degree of physiological change and the quantity of elastic tissue seen.[9]

As mentioned in previous text, basal arteries have an external diameter of less than 120 μm and, although they are branches of the spiral or radial arteries, show no physiological changes and do not communicate with the intervillous space but supply only the decidua and superficial myometrium. On the other hand, the uteroplacental spiral arteries can be identified and localized in the basal plate by their larger diameter.

The Nitabuch membrane
A historical recounting of research on the human placenta[60] showed that the first microscopic analyses carried out in the 1830s revealed the presence of an epithelial lining separating fetal capillaries from maternal blood. This was successively considered to be first maternal endothelial, then decidual, and finally trophoblastic in nature. The presence of unusual endovascular cells was first described by Carl Friedländer, but their trophoblastic nature was recognized only in the early 20th century.

In 1887, in a doctoral thesis based on the study of the autopsy of a pregnant woman, Raissa Nitabuch analyzed the uterus and provided an accurate description of the uteroplacental circulation. She observed in the decidua the presence of a fibrinous layer that in her view was the site of detachment of the placenta from the uterine wall after the baby's delivery. Since then, this fibrinous layer has been coined the Nitabuch membrane, although the findings of this investigation were never published.[61]

The significance of this layer was discussed more than 50 years ago by Bădărău and Gavriliță,[62] who believed that "the striae of Rohr, Nitabuch, and Langhans" made biological sense, constituting a peripheral fibrinoid barrier capable of arresting the trophoblast's "invasive proliferation by the same general process of cellular necrosis."

More recently, Pijnenborg and Vercruysse[60] discounted even the existence of a continuous fibrinoid layer underneath the basal plate representing a borderline separating the trophoblast-invaded upper decidua from the deeper noninvaded uterine tissue.

The ultrastructure of physiological changes
Several basic aspects of deep placentation, including potential fusion of cytotrophoblastic and decidual elements early in pregnancy, spiral artery trophoblast invasion, ultrastructure of uteroplacental arteries, and atherosis of the myometrial segment in hypertensive pregnancies, have been investigated by electron microscopy.[63] Robertson and Warner[23] observed that in the basal plate the intimate contact between trophoblast and decidua is accompanied by cell degeneration, necrosis, and the production of fibrinoid.

Decidua and trophoblast appear to secrete protein material as a contribution to the proteinaceous complex. Despite cell degeneration, ultrastructural evidence favors the hypothesis of an origin of the characteristic placental bed giant cells from trophoblast, which probably also produces the intermediate form, in early studies called X cells. Almost 50 years ago, these giant X cells were identified as having, although not exclusively, a fetal origin.[64] Vernof et al[65] have found evidence that in the presence of a placental infarction, the so-called pregnancy-associated major basic protein, a potent cytotoxin, is deposited in close proximity to chorionic villi and is localized in X cells that undergo proliferation.

On the other hand, the hypothesis that the function of the decidua is to restrict the invasiveness of trophoblast, and that, in this context, placental fibrinoid constitutes an effective immunological barrier, does not seem substantiated.[23,66,67] There is increasing evidence that some form of humoral blocking or immunological enhancement, rather than deficiency or masking of trophoblastic antigens, may be the primary mechanism in the prevention of placental rejection.[68]

Electron microscopic investigations of uteroplacental arteries at the end of normal human pregnancy confirmed that the musculoelastic tissue is replaced to a greater or lesser extent by a fibrillar and granular material in which giant cells are found.[69] These cells, by morphological criteria, are identical to trophoblastic cells, while part of the granular and fibrillar material shows the characteristics of fibrin. Furthermore, it is suggested that another part of this fibrinoid material is derived from the degeneration of trophoblastic cells in the spiral artery wall (Figure 6).

These structural modifications to the arterial wall are probably the direct consequence of invasion of the wall by trophoblastic cells; they are more pronounced in the decidual than in the myometrial portions of the spiral arteries, but the mechanism of their production is presumably the same for both segments. Interestingly, Kalkunte et al[70] have demonstrated that first- and third-trimester trophoblasts respond differently to interactive signals from endothelial cells when cultured on Matrigel. Trophoblasts around term fail to respond to signals from endothelial cells and even inhibit endothelial cell tube formation. In contrast, first-trimester trophoblast cell lines with invasive properties undergo spontaneous migration and synchronize with the endothelial cells in a capillary network.

The mechanism of trophoblast invasion of the wall of uteroplacental arteries was investigated in biopsy specimens from the placental bed obtained in 12 cases of hysterotomy or hysterectomy, between the 14th and 22nd weeks of gestation.[71] It was found that during this period, the trophoblast from the young conceptus reaches endometrial capillaries and arteriolar terminations of the spiral arteries and erodes both, moving retrogradely in the lumen of the spiral artery and simultaneously infiltrating the subendothelial space of the maternal intima.

This defect in the endothelial lining results in the leakage of plasma into the vessel wall, disruption of the internal elastic lamina and some fibroid degeneration of the media. While the intramural trophoblast does not appear to infiltrate the media, the altered intima is overgrown by endothelium. Remarkably, the disruption of the endothelial lining is only occasionally accompanied by the deposition of platelets and fibrin and absence of thrombosis. This may be explained by the production of prostacyclin by the intramural trophoblast, as suggested by Elder and Myatt.[72]

Occasionally, mural and even occlusive thrombosis is encountered in the uteroplacental arteries in normal pregnancies. Nevertheless, the thrombotic response and inflammatory reaction to vessel damage so characteristic of pathological processes, are kept within acceptable bounds in normal placentation. In the vessel wall, trophoblastic cells are always surrounded by, and separated from, the other constituents of the wall by a band of fibrinoid material.

Ultrastructural findings support the hypothesis that the intercellular fibrinoid material is partly the result of apocrine secretion by the trophoblast.[73] As these physiological changes develop, they probably account, at least in part, for the remarkable distension and increase in caliber of the lumen of uteroplacental arteries in the second and third trimester of pregnancy.

Vascular pathology

In view of the extensive physiological changes occurring as pregnancy progresses, the vascular pathology of the placental bed is complex and characterized by a decrease of the changes occurring physiologically.

Defective remodeling of uteroplacental spiral arteries

In the biopsy specimens of pregnancy complicated by preeclampsia, Brosens et al[74] experienced difficulty in identifying the presence of large remodeled spiral arteries in the inner myometrium, pointing to a substantial reduction in their number. This observation was confirmed by subsequent studies.[75-82]

The possibility that preeclampsia might be associated with minimal or absent physiological changes in the myometrial segment of the uteroplacental arteries prompted Brosens et al[74] to review all their material in an effort to discover whether the extent of the changes could be related to the presence or absence of preeclampsia. After reviewing cesarean hysterectomy specimens and more than 300 placental bed biopsies, they confirmed that in normal pregnancy physiological changes extend from the decidual terminations of the spiral arteries as far as the radial arteries deep into the myometrium, except for the periphery of the placental bed. They also documented that in the presence of preeclampsia, physiological changes are reduced and occur only in the central portion of the placental bed, as diagrammatically shown in the scheme of Figure 3.

More recently, Espinoza et al[83] reviewed the anatomy and physiology of the uterine circulation, detailing the physiological remodeling of spiral arteries during normal pregnancy, including timing and anatomical pathways of trophoblast invasion of the spiral arteries. The authors also examined the role of extravillous trophoblast and the criteria used to diagnose failure of physiological transformation of the spiral arteries. In this context, they evaluated the use of uterine artery Doppler velocimetry as a surrogate marker of chronic uteroplacental ischemia.

The relationship between placental bed oxygen tension curve with indication of the successive steps in the endovascular and interstitial trophoblast invasion of the decidua and junctional zone myometrium is illustrated in Figure 7.[84,85]

Finally, it must be pointed out that defective physiological changes have been documented in a series of obstetrical disorders

Atherosclerotic and arteriosclerotic lesions of uteroplacental arteries

The study of cesarean hysterectomy specimens and a large number of placental bed biopsies has made possible to describe accurately the vascular picture in normal patients and in hypertensive disease.[86] In preeclampsia and eclampsia without essential

FIGURE 6
Ultrastructural appearance of progressive physiological alterations in uterine spiral arteries
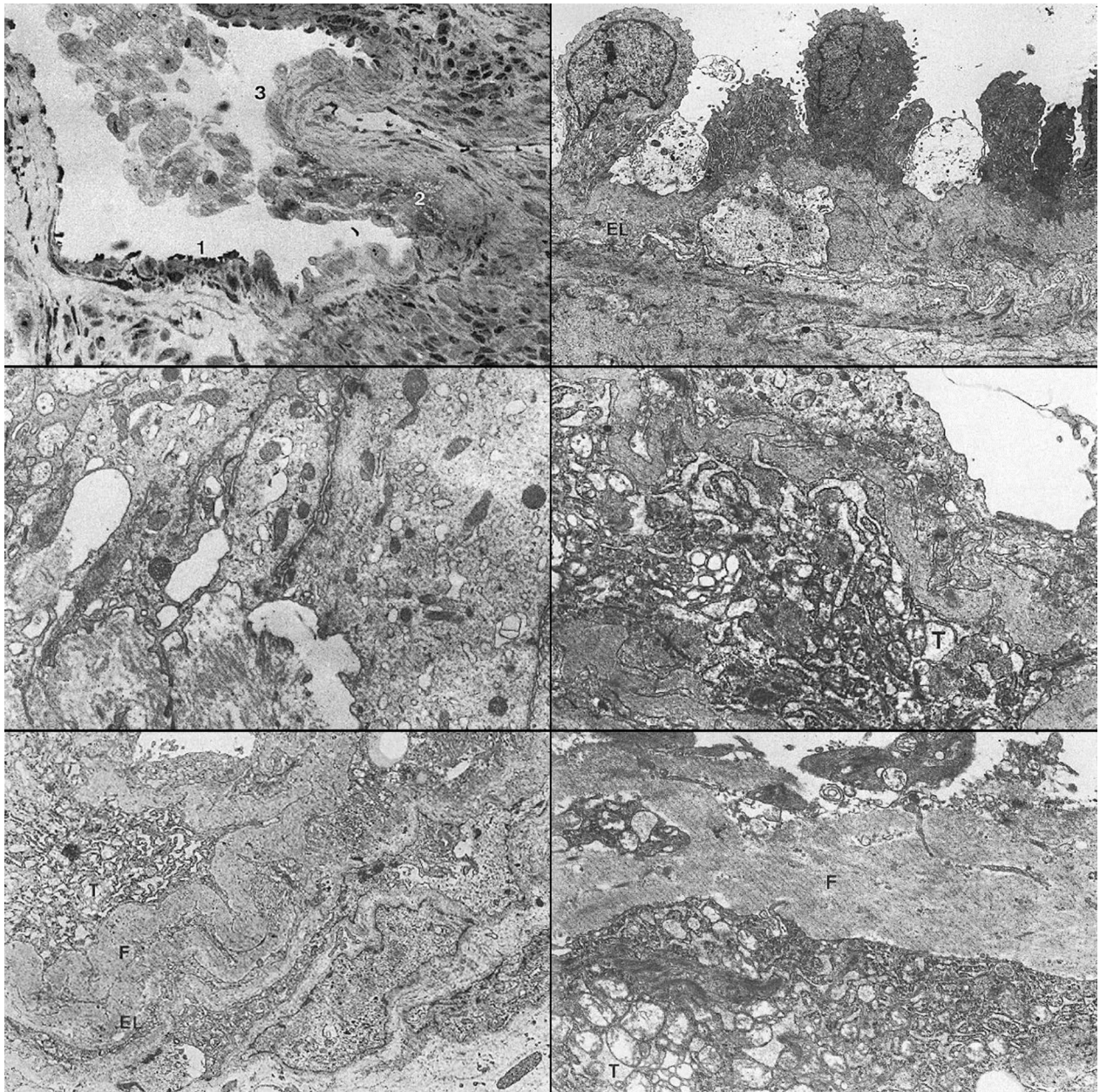
Ultrastructural appearance of the progressive physiological alterations in uterine spiral arteries during the second trimester of pregnancy is shown. **Top, left,** Epon-embedded section showing a spiral artery with 3 different stages of modifications. Stage 1 has obvious alteration but still contains musculoelastic elements. Stage 2 has plugs of intraluminal cells in close contact with the modified vessel wall. Stage 3 shows the vessel wall with typical physiological changes (magnification, ×160). **Right,** In between hypertrophic endothelial cells, translucent cytoplasmic fragments are shown; fenestrations in the internal elastic lamina (magnification, ×5.400) are also shown. **Middle, left,** Stage 1 modification with electron empty clefts between the endothelial cells and their underlying basement membrane (magnification, ×14.400). **Right,** Stage 1 modification with trophoblastic cell (T) is seen in the intima; overlying endothelium is intact (magnification, ×14.400). **Bottom, left,** Stage 2 modification: intimal trophoblastic cell is associated with disrupted elastic and deposition of much fibrinoid material. The normal distinction between intima and underlying media has disappeared (magnification, ×8.400). **Right,** Stage 3 modification: totally disrupted endothelium but without surface platelets or fibrin. Beneath the disrupted endothelium is a thick layer of fibrinoid overlying normal trophoblast (magnification, ×14.400). From De Wolf et al (1980).[71]

EL, elastic; *F*, fibrinoid material; *T*, trophoblastic cell.

Brosens. Placental bed research. Am J Obstet Gynecol 2019.

hypertension, physiological changes are almost completely restricted to the decidual segment of the spiral arteries except for the center of the placental bed. The characteristic lesion is an acute arterial necrosis with intramural foam-cell infiltrates, representing a form of plasmatic vasculosis as described by Lendrum et al.[87]

The extent and severity of acute atherosis as described in the following text is directly related to the severity of preeclampsia. At the same time, disagreement exists on its interpretation. Hertig[88] suggested that infiltration of the vessel with foam cells is the primary factor and that the particular vascular lesion in preeclampsia is an acute fibrinoid necrosis. He proposed that the vessel first becomes damaged and dilated and only later an infiltration of lipophages into the damaged vessel occurs.

When preeclampsia is superimposed upon essential hypertension, combinations of necrotizing and proliferative lesions are found in the placental bed arteries and the internal elastic lamina is frequently split or reduplicated. Elastic tissue can be demonstrated in the hyperplastic intimal layer. The combination of essential hypertension and preeclampsia produces very severe vascular damage and the number of uteroplacental arteries affected by atherosclerosis is usually in excess of the number showing this change in preeclampsia without essential hypertension.[74]

Because of the severity and distribution of the arterial lesions and their limitation to the placental bed, Robertson et al[89] suggested that placental bed vessels are more sensitive than vessels elsewhere to the effect of hemodynamic disturbances. It must be noted that, unfortunately, their large series of biopsy specimens did not include biopsies from adolescents with preeclampsia or eclampsia. Therefore, their findings must be considered representative of the vascular pathology in the mature woman with hypertensive disease and may not apply to younger women in whom the pathogenesis of preeclampsia may be different.[14]

FIGURE 7
Spiral artery remodeling and uteroplacental blood flow in first trimester
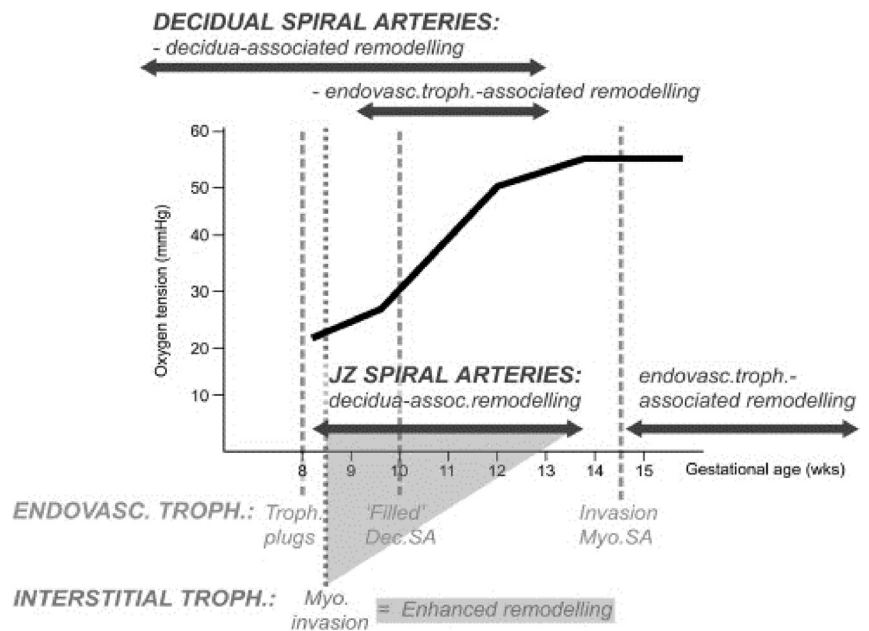
Spiral artery remodeling in relation to uteroplacental blood flow in first trimester of pregnancy is shown. Placental bed oxygen tension curve shows the successive steps in the endovascular and interstitial trophoblast invasion in the decidua and junctional zone myometrium. From Pijnenborg et al (2010).[59] In this figure, the oxygen tension curve was redrawn from Jauniaux et al (2000).[84]

Brosens. Placental bed research. Am J Obstet Gynecol 2019.

Acute atherosis of the basal arteries in and outside the placental bed

Since the early investigations, the delivered placenta and fetal membranes have been the most common tissues for the study of spiral artery pathology. Zeek and Assali[90] were the first to describe a process subsequently coined by acute atherosis in preeclamptic toxemia; in hypertensive pregnancies these lesions are associated to hyperplastic arteriolar sclerosis of spiral arteries.

Back in 1945 a similar lesion had been described in the uterus from subjects with hypertensive albuminuric toxemia of pregnancy.[88] The lesion has been observed in preeclampsia, hypertensive disease not complicated by preeclampsia,[16,91] normotensive intrauterine growth restriction,[80,92–95] preterm prelabor rupture of membranes,[96] and systemic lupus erythematosus.[97,98]

More complex is a possible relationship between acute atherosis and diabetes. While some did not find acute atherosis in patients with uncomplicated diabetes mellitus or gestational diabetes,[94,99] others have described the lesion in diabetic patients[94,100,101] but not in gestational diabetes. Unfortunately, the positive cases were complicated by hypertensive disease or by intrauterine growth restriction; therefore, it is unclear whether it occurs in women with uncomplicated diabetes.

In a series examining placental bed basal plates and amniochorial membranes, the incidence of acute atherosis ranged from 41% to 48%.[102] Some investigators have found an inverse relationship between the presence of acute atherosis and birthweight,[94,103] but this is not supported by critical statistical analysis of the data. No significant relation was found between the severity of the lesion, degree of proteinuria, fetal outcome, including birthweight, and severity or duration of the hypertension.[94]

The lesion is seen in vessels that have not undergone the physiological changes of pregnancy and can also be seen on the

TABLE 3
Percentage of cases with presence of acute atherosis in basal plate and placental bed biopsies in different pathological conditions°

Preeclampsia	10.2
Fetal death	8.9
Spontaneous abortion	2.5
Chronic hypertension	2.3
Small for gestational age	1.7
Gestational hypertension	1.3
sPTL-PPROM	1.2
Normal	0.4
Others	3.0

PPROM, preterm prelabor rupture of membranes; *sPTL*, spontaneous preterm labor.

After Kim et al (J Matern Fetal Neonatal Med, 2015).[110]

Brosens. Placental bed research. Am J Obstet Gynecol 2019.

maternal vessels in the decidua parietalis as well as in those of the placental bed.[89] In established cases, the lesion is characterized by fibrinoid necrosis of the arterial wall, a perivascular lymphocytic infiltrate, and, at a later stage, by perivascular lymphocytic infiltrate associated to the presence of lipid laden macrophages within the lumen and the damaged vessel walls.

A fibrinoid necrosis is sometimes seen without either the lipophages or the perivascular lymphocytic infiltrate, suggesting that this represents the earliest lesion found in acute atherosis.[89] This is consistent with ultrastructural studies aimed at identifying the pathogenesis of this arteriopathy in which endothelial disruption and an occasional vessel luminal obstruction by lipophages or thrombosis can be found.[104] Endothelial disruption can be associated to acute atherosis and observed by immunohistochemistry.[105]

In addition, immunolabeling with lipoprotein (a), which is thrombogenic and atherogenic, has been also observed.[78] Finally, aneurysmal formation associated with acute atherosis is sometimes seen, and this may be the result of the weakened wall as a consequence of the fibrinoid necrosis.[105]

It is understandable that the anatomists Hamilton and Boyd,[106–108] in the absence of clinical notes to properly identify their specimens, found no major vessel changes in association with hypertensive conditions. As mentioned in previous text, acute atherosis occurs in basal arterioles and, to a less extent, outside the placental bed and is characterized by subendothelial lipid-filled foam cells, fibrinoid necrosis and perivascular lymphocytic infiltration. The lesion is generally confined to nontransformed arteries.[109]

In a recent study based on delivered placentas, Kim et al[110] found that acute atherosis is rare in normal pregnancies and occurs more frequently in patients with pregnancy complications, including preeclampsia, spontaneous preterm labor, preterm premature rupture of membranes (PPROM), midtrimester spontaneous abortion, fetal death, and a small-for-gestational-age baby (Table 3).

A study of lipids in the placental bed has shown that a range of obstetrical syndromes can be associated with diffuse lipid infiltration, particularly preeclampsia, intrauterine growth restriction, and postmaturity.[111] Therefore, atherosclerosis affects the large spiral artery in the junctional zone myometrium in the presence of defective deep placentation when the musculoelastic structure is preserved, while acute atherosis affects the decidual basal arterioles in the placental bed as well, but less frequently the basal arterioles in the decidua parietalis.

Interestingly, the presence of fetal growth restriction in maternal hypertensive disorders increases significantly the presence of acute atherosis. Therefore, its presence in and outside the placental bed may reflect the hypoxic stage of the hypertensive condition. This is reflected by a significant correlation between fetal growth restriction and the presence of hypertensive conditions.

Ultrastructure of acute atherosis

In light of the electron microscopic observations by De Wolf et al,[112] acute atherosis is, similarly to human atheromas, characterized by accumulation of lipid in intimal smooth muscle cells or myointimal cells, which eventually perish, freeing their lipids to be taken up by macrophages.

In the end, 2 populations of lipid-bearing cells coexist in the damaged intima. A similar state of affairs is found in the ultrastructural features of acute atherosis but with the significant difference that in atherosis there is also necrosis of the medial smooth muscle and infiltration of the damaged wall by plasma constituents including fibrin.

Robertson et al[113] wondered why acute atherosis in pregnancy should have features in common to atheroma outside pregnancy, while the arterionecrosis of systemic accelerated essential hypertension does not; they wondered whether immunological factors may play a role in causing this discrepancy. Acute atherosis occurs most frequently in obstetrical conditions associated with fetal distress; however, in contrast with atherosclerosis, acute atherosis can occur in normal pregnancy.

The study of the ultrastructure of acute atherosis in the myometrial segment of the uteroplacental arteries from preeclamptic pregnancies confirmed, as previously shown by Marais[109] and Brosens,[16] that in this syndrome the myometrial segment fails to undergo physiological changes.[104] The early stage of the vascular lesion is characterized by endothelial damage,

insudation of plasma constituents into the vessel wall, proliferation of myointimal cells, and medial necrosis. Fat accumulation is seen first in the myointimal cells, and later macrophages engulf the lipid-rich debris released from disintegrating myogenic foam cells (Figure 8). Gross endothelial damage, massive fibrin deposition, luminal thrombosis, and vessel rupture with hemorrhage are epiphenomena.

In an ultrastructural study, Wynn[63] found that in the floor of the human placenta, ultrastructurally well-preserved trophoblast and decidua are rarely in direct contact but remain separated by regressive tissues of fetal and maternal origin, by fibrinoid, or by both. The ultrastructural findings suggest that some form of humoral blocking, or immunological enhancement, rather than deficiency or masking of trophoblastic antigens, may be the primary mechanism in the prevention of placental rejection and a variety of reproductive disorders.

Obstetrical syndromes associated with vascular pathology

In their review of the association of great obstetrical syndromes with disorders of deep placentation, Brosens et al[11] summarized the salient types of defective deep placentation, and proposed criteria for its classification into 3 types, based on the degree of remodeling restriction and the presence of obstructive lesions in the myometrial segment of the spiral arteries. Romero et al[114] emphasized the importance of understanding the physiology and pathology of transformation of the spiral arteries in obstetrical syndromes including spontaneous preterm labor, PPROM, spontaneous abortion, and abruptio placentae.

In fact, the failure of physiological transformation of the spiral arteries has been studied in several obstetrical syndromes, and, contrary to what was originally believed, this anomaly is not restricted to preeclampsia and/or intrauterine growth restriction (Tables 4 and 5).

Hypertensive disease

In preeclampsia, physiological changes tend to be restricted to the decidual

FIGURE 8
Atherotic lesions observed in pathological pregnancies
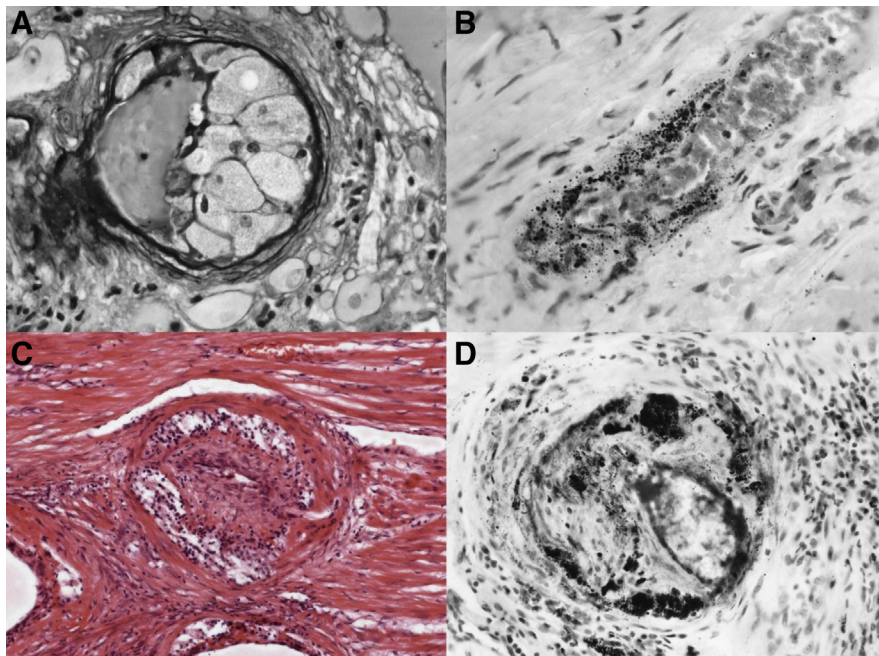
Top, Acute atherosis of decidual arteries with Oil red O staining on the right, **Bottom,** Arteriosclerosis of uteroplacental arteries in severe preeclampsia with Oil red O staining on the right. From Ivo Brosens, PhD thesis, University of London, 1965.

Brosens. Placental bed research. Am J Obstet Gynecol 2019.

branch of the spiral arteries and fail to reach the myometrial trunks, except for the center of the placental bed[7] (Table 2). When preeclampsia complicates preexisting essential hypertension, there is again restriction of the physiological changes to the decidual segments of the spiral arteries, and, in addition, the myometrial segment shows hyperplastic arteriosclerosis or atherosclerosis.[89] The ensuing picture of defective deep placentation is therefore characterized by the presence of the physiological changes of spiral arteries only in the very center of the placental bed, giving it a concave shape, with the small area of deep placentation in the center.[7] Importantly, this concave shape implies that the picture at the center of the placental bed is not representative of the true situation when evaluating defective deep placentation.

Preterm premature rupture of membranes

In an extensive cross-sectional study of the placental bed and placenta

including 59 patients with normal pregnancies, 31 with PPROM, and 23 with preeclampsia, Kim et al[110] evaluated histopathological findings in the placental bed using immunohistochemistry with cytokeratin-7 and periodic acid-Schiff. They found that the mean number of spiral arteries with failure of physiological transformation of the myometrial segment was significantly higher in patients with PPROM and preeclampsia than in normal pregnant women at term ($P = .006$ and $P < .0001$, respectively).

In contrast, the mean number of the spiral arteries with failure of physiological transformation of the decidual segment of the spiral arteries in the basal plate of the placenta was not significantly different in patients with PPROM from that in normal pregnant women ($P > .05$). Placentas from patients with PPROM had a higher frequency of vascular lesions than those from normal pregnant women ($P = .02$).

TABLE 4
Acute atherosis in basal plate and placental bed biopsies

Preeclampsia	10.2
Fetal death	8.9
Spontaneous abortion	2.5
Chronic hypertension	2.3
Small for gestational age	1.7
Gestational hypertension	1.3
sPTL-PPROM	1.2
Normal	0.4
Varia	3.0

sPTL-PPROM, spontaneous preterm labor and preterm prelabor rupture of membranes. From Kim et al (2015).[104]

Brosens. Placental bed research. Am J Obstet Gynecol 2019.

In a similar study of physiological changes in patients with spontaneous preterm labor and intact membranes, the same group[81] found that failure of physiological transformation of the spiral arteries in both the myometrial and decidual segments of the placental bed is frequent in patients with preterm labor and intact membranes. It seems, therefore, that a variable type of defective deep placentation can also be frequently present in PPROM.

Second-trimester bleeding detected by ultrasound

Some 20 years ago, Signore et al[115] in a case-control study retrospectively investigated the presence of specific risk factors in women with second-trimester vaginal bleeding. Through ultrasonography, they ascertained the presence of an intrauterine clot, membrane separation, and placenta previa. Second-trimester vaginal bleeding was associated with increased risk of preterm delivery (relative risk [RR], 1.9; 95% confidence interval [CI], 1.4—2.8); fetal death [RR, 6.3; 95% CI, 1.9—2.1); and perinatal death (RR, 5.4; 95% CI 2.1—13.7). They concluded that bleeding during the second trimester increases perinatal morbidity and mortality and that these risks are compounded when ultrasonography shows abnormalities.

In 1973, Wallenburg et al[116] conducted a careful evaluation of 536 well-defined infarcts obtained from 1240 consecutively delivered placentas, searching for possible pathologic changes related to circulatory obstruction in fetal or maternal vessels. They found that most of the uteroplacental arteries showed evidence of obstruction, with thrombosis being a frequent finding. They concluded that a placental infarct consists of the necrosis of a fetal cotyledon caused by occlusion of the supplying uteroplacental artery.

More recently, Kofinas et al[117] found that an increased size of hypoechoic placental lesions is associated with a higher risk for adverse perinatal outcome. The reason is that probably such lesions are the result of intervillous space thrombosis. Therefore, ultrasound may be a useful tool in the identification of patients with prothrombotic abnormalities.

Finally, Aurioles-Garibay et al[118] have studied a lesion associated with abruptio placentae, fetal death, and adverse perinatal outcome, termed placental infarction hematoma. They described in one such case a progressive deterioration of the fetal and placental Doppler parameters caused by a placental infarction hematoma.

Given this situation, in preterm delivery it would be important to identify and compare the types of uteroplacental arteries in the paracentral zone of the placental bed between hypertensive disease and preterm birth (Figure 2).

Abruptio placentae

Structural changes in the uteroplacental arteries in association with abruptio placentae were investigated by Dommisse and Tiltman[119] in a prospective descriptive study. Of 18 specimens collected, 6 did not show the presence of trophoblast in the myometrium and were discarded as not representative of the placental bed. Of the 12 representative specimens, 7 showed the absence of physiological transformation of the uteroplacental arteries (4 of these were from subjects with hypertension). The authors concluded that vascular malformations

TABLE 5
Myometrial spiral artery remodeling in major obstetrical disorders

Remodeling of myometrial uteroplacental artery	Obstetric disorder
Absent	Preeclampsia Early-onset fetal growth restriction
Absent with obstructive pathology	Chronic hypertension with superimposed preeclampsia
	Chronic hypertension with fetal growth restriction
	Abruptio placentae
Partial	Preterm labor and intact membranes
	Preterm premature rupture of membranes
	Fetal growth restriction without hypertension

Information presented in this table was obtained from the 3 centers: St George's Hospital Medical School, London (United Kingdom); the Department of Obstetrics and Gynecology, University of Leuven (Belgium); and the Department of Obstetrics and Gynaecology, Trinity College, University of Dublin (Ireland). Modified from Robertson et al (1986).[134]

Brosens. Placental bed research. Am J Obstet Gynecol 2019.

in association with placental abruption may be the result of inadequate trophoblastic invasion and could be the site of vessel rupture.

Risk of progesterone resistance in the adolescent pregnancy

In a retrospective cohort study, Traisrisilp et al[120] found that early adolescent pregnancy was associated with higher risks of adverse pregnancy outcomes, in particular preterm labor and fetal growth restriction, although most maternal morbidity was comparable with that in the control groups.

The epidemiological study of Leppälahti et al[121] and other smaller cohort studies[122,123] also demonstrated that the risk of preeclampsia in adolescents is higher the younger the age of the teenager. These findings suggest the presence of a link between defective trophoblast invasion, remodeling of the uteroplacental spiral arteries and preeclampsia.

The hypothesis is based on the possible existence of 2 different types of defective deep placentation: in the young adolescent, this seems to be due to a persisting ontogenetic progesterone resistance of the endometrium,[124,125] whereas in the adult it is a consequence of hypertensive vascular changes.[3,4] Clinical observations suggest the persistence in some young adolescents of the ontogenetic progesterone resistance present at birth in 95% of the newborns. This phenomenon denotes blunted progesterone response in various target tissues including the endometrium.

A specific version of this anomalous response refers to the observation that the endometrial stromal and vascular compartment is not progesterone responsive at birth as proven by Harvard neonatal pathologists Ober and Bernstein,[126] who, in a large series of autopsies, documented that the neonatal endometrium is in most cases and, in a variable degree, progesterone resistant.

Although there are, as yet, no studies that have investigated the impact of gynecological age on decidualization and spiral artery remodeling in placental bed biopsies of adolescents, there is an old observation

documenting that the villous/capillary surface area in placentas from adolescent mothers does not correlate with either maternal chronological age or bone age. This study, however, did find an inverse correlation between the placental villous/capillary surface and gynecological age, further suggesting that uterine immaturity is the primary driver of placental dysfunction during early adolescence.[127]

It has been suggested that the ontogenetic progesterone resistance may decrease and disappear with cyclic menstruations, a phenomenon coined as menstrual preconditioning.[128] On the other hand, the severe vascular lesions may not only be present in association with borderline hypertensive disease, but occasionally atherosclerotic lesion may be more severe than would be expected in hypertensive disease.[114]

Conclusion

A variety of sampling techniques have enabled a detailed description of the complex uterine arterial (and venous) modifications that physiologically occur during pregnancy, starting in the first trimester. These changes are initiated by the dNK cells and macrophages surrounding the vessels and are believed to prime the decidual spiral arteries for an extravillous trophoblast invasion. Thanks to this process, spiral arteries are transformed into low-resistance vessels capable of accommodating the major increase in blood flow characteristic of normal pregnancy.

Research has also identified a series of vascular anomalies in pathological pregnancies, beginning with gestations complicated by preeclampsia, where physiological changes are reduced and only occur in the central portion of the placental bed.[129–131] These disorders of deep placentation are present in a wide range of complications of pregnancy. In these situations, atherosclerotic lesions can be observed, affecting the large spiral arteries in the junctional zone myometrium when the musculoelastic structure is preserved. Another anomaly, called acute atherosis, seems to affect the decidual basal arterioles in the placental bed.

The ensuing defective deep placentation is characterized by the presence of physiological changes only in the very center of the placental bed, thereby limiting blood supply to the fetus.

In spite of major progress, however, much work remains to be done. As an example, Romero et al[114] have proposed that, in addition to the known causes described in previous text, changes in the population and in the function of immunocytes at the maternal-fetal interface can be part of the pathogenetic mechanism of these disorders, something that requires further investigation.

Finally, in addition to morphological studies, also functional investigations of the placental bed have been carried out. These will be reviewed in a separate article.[2] ∎

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