Third Edition

Scientific Basis of Obstetrics & Gynaecology

Edited by
Ronald R. Macdonald

Churchill Livingstone

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EDITED BY

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Preface

The Royal Commission on Medical Education recommended that the undergraduate should 'understand the *scientific basis* of his profession—to permit him to go forward with medicine as it develops further'. Clinicians find that if they are to give their patients the best treatment they need to understand advances in basic science subjects many of which were not even in the curriculum when they were students.

A book review in the Lancet pointed to the specific integration needed between basic sciences and obstetrics and gynaecology: 'The narrow view of obstetrics must be widened to that of human reproduction, encompassing such disciplines as genetics, physiology, embryology, pharmacology, psychology and sociology. Advancing knowledge in these areas must be co-ordinated and directed towards clinical practice'. The need for further emphasis on the application of basic scientific principles has also been stressed by a select committee in their report to the Royal College of Obstetricians and Gynaecologists on the training of obstetricians and gynaecologists in Britain.

These extracts from the Preface to the First Edition are as true today, and in this third edition we have continued to discuss selected topics in depth from the basic principles through new information to the clinical application. Half the chapters have been completely rewritten or extensively revised from the second edition reflecting the pace of progress, and the others are on new subjects helping to fill some previous gaps.

Thus, for example, Professor Baird's chapter on 'Ovarian function' reintroduces basic endocrinology, Dr Chalmers writes on 'Epidemiology', Profesor Smithells on 'Genetic counselling' and Professor Campbell on 'Ultrasound'. Professor Gunatilake's chapter is primarily for those who practice in the tropics but makes compulsive reading for us all; sadly Professor Gunatilake died suddenly soon after completing his contribution which must stand as a worthy memorial to a great and compassionate clinician. Professor Duncan wondered whether 'Medical ethics' were really 'scientific' but happily he was persuaded to contribute on the grounds that without ethics there would be no basis for our profession.

Once again it has been my privilege to co-ordinate the work of many of the finest teachers, basic scientists and clinicians, who were specially invited to

contribute because of their ability to write with authority, clarity and enthusiasm. I am sure you will appreciate their efforts.

Leeds
1984

Ronald R. Macdonald

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Contents

Placental structure

The placenta is a villous haemochorial organ which serves as a mechanism for gaseous and nutritive transfer between mother and fetus, has a considerable endocrine function and is, in a manner not yet fully understood, of importance in the immunological acceptance of the fetal allograft. Despite the crucial importance of the placenta in fetal development, it is only within the last few decades that any reasonably clear picture of the structure both of the placenta itself and of the maternal utero-placental vasculature has emerged, and even today there are still many facets of placental development and morphology which are either obscure or controversial.

DEVELOPMENT OF THE PLACENTA

(Fig. 1.1) The ovum is fertilised in the Fallopian tube and enters the uterine cavity as a cellular morula which rapidly converts into a blastocyst and loses its surrounding zona pellucida. The outer cell layer of the blastocyst then proliferates to form the trophoblastic cell mass, from which cells infiltrate between those of the endometrial epithelium; the latter degenerate and the trophoblast thus comes into contact with the endometrial stroma, this process

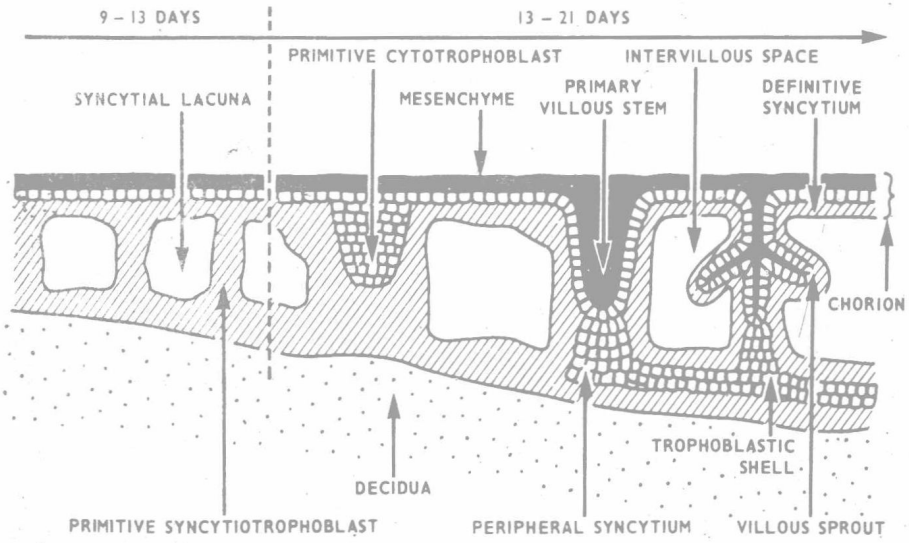

Fig. 1.1 Diagrammatic representation of the early development of the placenta (after Wilkin, 1965)

of implantation being completed by the tenth or eleventh postovulatory day. In the seven-day ovum the trophoblast forms a plaque which rapidly differentiates into two layers, an inner layer of large, clear mononuclear cytotrophoblastic cells and an outer layer of multinucleated syncytiotrophoblast. That the syncytiotrophoblast is derived from the cytotrophoblast, not only at this early stage but also throughout gestation, is now well established, for even when the trophoblast is growing rapidly, synthesis of DNA and mitotic activity occurs only in the cytotrophoblastic cells (Richart, 1961). The syncytiotrophoblast is formed by fusion of cytotrophoblastic cells and, although no true intercellular membranes are present in the syncytial layer, remnants of such structures can occasionally be found on electron microscopy (Carter, 1964; Enders, 1965). Cells having a cytoplasmic and nuclear structure intermediate between those of the two trophoblastic layers have also been identified by electron microscopy (Tighe et al, 1967). It is worth noting that the syncytiotrophoblast is the only true syncytial human tissue; this must have some biological advantage for the trophoblast, and Contractor et al (1977) have suggested that, in teleological terms, the lack of any necessity for the trophoblast to synthesise DNA and undergo mitotic activity allows the full metabolic activity of the tissue to be directed towards its transfer function.

Between the tenth and thirteenth postovulatory days a series of intercommunicating clefts, or lacunae, appear in the rapidly enlarging trophoblastic cell mass; these clefts are probably formed as a result of engulfment within the syncytiotrophoblast of endometrial capillaries (Harris & Ramsey, 1966). The lacunae soon become confluent to form the precursor of the intervillous space, and as maternal vessels are progressively eroded this

becomes filled with maternal blood; at this stage the lacunae are incompletely separated from each other by trabecular columns of syncytiotrophoblast which between the fourteenth and twenty-first postovulatory days tend to become radially orientated (Fig. 1.2a) and come to possess a central cellular core that is produced by proliferation of the cytotrophoblastic cells at their chorionic bases. These trabeculae are not true villi but serve as the framework from which villi will later develop, the placenta at this time being a labyrinthine rather than a villous organ and the trabeculae being therefore best called 'primary villous stems' (Boyd & Hamilton, 1970). Continued growth of the cytotrophoblast leads to its distal extension into the region of decidual attachment and, at the same time, a mesenchymal core appears within the villous stems, this being formed by a distal extension of the extra-embryonic mesenchyme (Fig. 1.2b). Later, the villous stems become vascularised, the vessels arising from the mesenchyme within the stem and not, as previously thought, being formed as a downward extension of the chorio-allantoic arteries. It has been suggested that the vessels are derived from the cytotrophoblastic cells (Cibils, 1968) but the weight of evidence does not favour this view (Dempsey, 1972). In due course the vessels within the stems establish functional continuity with others differentiating from the body stalk and inner chorionic mesenchyme.

The distal part of the villous stems is now formed almost entirely of cytotrophoblast which is anchored to the decidua of the basal plate. These cells, which are sometimes referred to as the 'cytotrophoblastic cell columns',

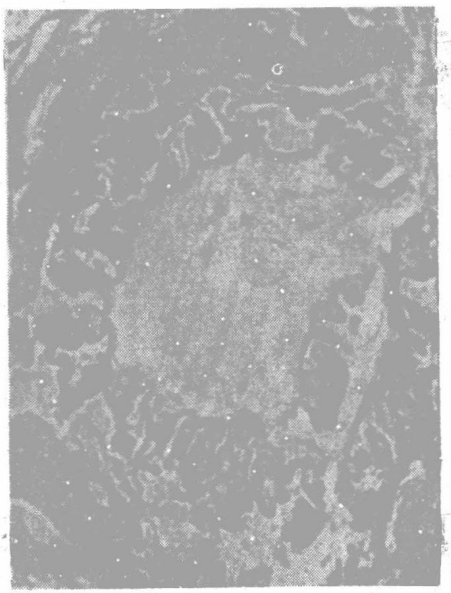

Fig. 1.2a A developing conceptus approximately 14 days after fertilisation. Trabecular primary villous stems are arranged radially and divide the precursor of the intervillous space into a labyrinth. (H. & E. × 24).

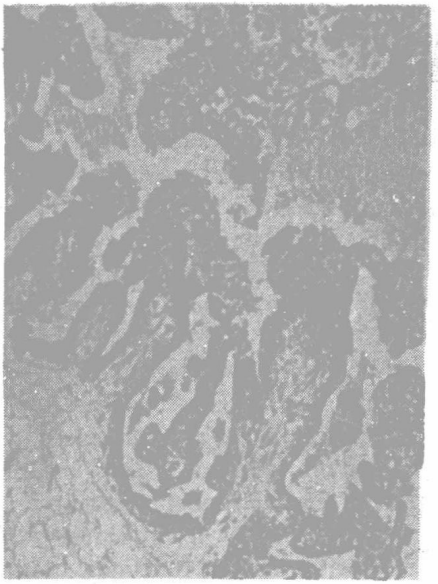

Fig. 1.2b Detail of primary villous stems in a 14-day-old conceptus. The stems have a mesenchymal core and the growing tip of each is formed by a mass of proliferating cytotrophoblastic cells (H. & E. × 68) (from Fox, 1978)

proliferate and spread laterally to form a continuous cytotrophoblastic shell which splits the syncytiotrophoblast into two layers: the definitive syncytium on the fetal aspect of the shell, which persists as the lining layer of the intervillous space, and the peripheral syncytium which largely degenerates and is replaced by fibrinoid material (Nitabuch's layer) that is probably derived from fibrinogen in the maternal blood (Sutcliffe et al, 1982). Cytotrophoblastic cells stream out from the tips of the anchoring villi to colonise extensively the decidua and myometrium, where they often fuse to form syncytial-like giant cells in the placental bed (Pijnenborg et al, 1980, 1981a, 1981b); the function, if any, of this interstitial extravillous trophoblast is unknown. Furthermore, cytotrophoblastic cells grow into the lumens of the decidual portion of the spiral vessels, where they replace the endothelial cells and invade and destroy the musculo-elastic medial tissue (Robertson et al 1975); the vessel wall becomes largely replaced by fibrinoid material which appears to be derived partly from fibrin in the maternal blood and partly from proteins secreted by the intravascular cytotrophoblastic cells. The destruction of the media of the intradecidual portion of the spiral vessels results in weakening of the arterial walls with consequent dilatation induced by the rapidly increasing maternal blood flow to the placenta.

The establishment of the cytotrophoblastic shell is a mechanism to allow for rapid circumferential growth of the developing placenta. This leads to an

expansion of the intervillous space into which sprouts extend from the primary villous stems. These offshoots initially consist only of syncytiotrophoblast, but as they grow they pass through the stages previously seen during the development of the primary villous stems, i.e. intrusion of cytotrophoblast, formation of a mesenchymal core and eventual vascularisation. These sprouts form the primary stem villi and, as they are true villous structures, the placenta is by the twenty-first postovulatory day a vascularised villous organ. Between this date and the end of the fourth month of gestation those villi orientated towards the uterine cavity degenerate and form the chorion laeve, whilst the thin rim of decidua covering this area gradually disappears to allow the chorion laeve to come into contact with the parietal decidua of the opposite wall of the uterus. The villi on the aspect of the chorion orientated towards the decidua basalis proliferate and progressively arborise to form the chorion frondosum which develops into the definitive placenta. During this period there is some regression of the cytotrophoblastic elements in the chorionic plate and in the trophoblastic shell where the cytotrophoblastic cell columns largely degenerate and are replaced by fibrinoid material (Rohr's layer); clumps of cells persist, however, to form the 'cytotrophoblastic cell islands'. Although there is cytotrophoblastic regression in the basal shell there is, during the third to fourth months of gestation, a further proliferation of the endovascular cytotrophoblast which moves retrogradely from the intradecidual into the intramyometrial portion of the spiral vessels; here again it replaces the endothelial cells and invades and destroys the media with resulting fibrinoid change in the vessel wall. The end result of this process is that the spiral arteries are converted into dilated, flaccid, thin-walled, funnel-shaped tubes, this transformation of spiral vessels into uteroplacental arteries being a necessary prerequisite to allow for the greatly augmented blood flow to the placenta as pregnancy progresses.

The placental septa appear during the third gestational month: these protrude into the intervillous space from the basal plate and divide the maternal surface of the placenta into 15–20 lobes. These septa are simply folds of the basal plate, being partly formed as a result of regional variability in placental growth and partly by the pulling up of the basal plate into the intervillous space by anchoring columns which have a poor growth rate (Boyd & Hamilton, 1970). As the basal plate is formed principally by the remnants of the trophoblastic shell embedded in fibrinoid (Kaufmann & Stark, 1971), it follows that the septa are similarly formed; some decidual cells may also be present, and the relative proportions of maternal and fetal elements vary not only from septum to septum but also in different areas of individual septa. The septa are clearly seen to be an incidental by-product of the architectural refashioning of the placenta and have no physiological or morphological role to play.

By the end of the fourth month of pregnancy the placenta has attained its definitive form and undergoes no further anatomical modifications; it has also achieved its full thickness, though growth in circumference continues virtually to the end of pregnancy.

ANATOMY OF THE FETAL PLACENTA

The fetal placenta is formed by a number of sub-units which are now usually known as lobules. There is general agreement that each lobule has a roughly globular structure and that this contains a central hollow space which is relatively empty and villous-free. The injection studies of Wilkin (1965) have shown that the primary stem villi break up just below the chorial plate into a number of secondary stem villi which, after running for a short distance parallel to the chorionic plate, divide into a series of tertiary stem villi. The lobules are derived from the tertiary stem villi which sweep down through the intervillous space to anchor onto the decidua; during their course through the intervillous space they give off multiple branches which ramify into the terminal villous network. As the tertiary stem villi pass down towards the basal plate they are arranged in a circular manner around the periphery of an empty central cylindrical space (Fig. 1.3). Gruenwald (1975 a, b) differs somewhat from this concept by considering that an individual lobule is not derived from a single secondary stem villus but can receive tertiary stem villi from a number of secondary stem villi; this is probably true but is a relatively minor point which does not significantly alter the concept of the lobule. The lobules are separated from each other by interlobular areas which are in continuity with the subchorial space.

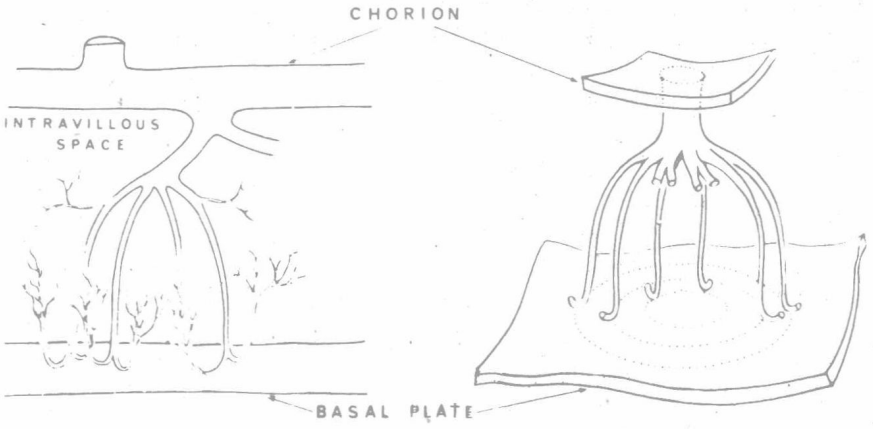

Fig. 1.3 Diagram of the structure of the fetal lobule. The division of the primary stem villi into secondary and tertiary stem villi is shown on the left. On the right the distribution of stem and anchoring villi around a central villous-free space is represented diagrammatically (after Wilkin, 1965)

It is necessary at this point to consider the meaning of the term 'cotyledon' as applied to the human placenta. This name should not be used to describe the lobes seen on the maternal placental surface, for these are merely the areas lying between the septa and lack any other morphological significance. The term 'cotyledon', if used at all, should be restricted to the functional unit of the placental villous tree, and this is best defined as being that part of the villous

tree that has arisen from a single primary stem villus (Ramsey, 1959). According to Wilkin (1965), a single primary stem villus may give rise to a varying number of secondary stem villi and thus to a differing number of lobules, there being no fixed relationship between cotyledons and lobules. Thus centrally placed cotyledons may contain as many as five lobules, whilst those situated more peripherally usually have only one or two lobules. The situation has been unduly confused by the fact that some describe the lobule as a 'cotyledon', whilst others have referred to the same unit as a 'sub-cotyledon'. Others use the term cotyledon to describe the lobes seen on the maternal surface and, overall, there is much to be said for Ramsey's (1975) suggestion that the word 'cotyledon' be abandoned when referring to the primate placenta.

THE FETAL CIRCULATION THROUGH THE PLACENTA

Fetal blood passes to the placenta through the two umbilical arteries which spiral around the umbilical vein. Shortly before reaching the placenta the two arteries are connected by one or two anastomatic vessels and may even fuse into a single trunk which subsequently divides into two rami (Szpakowski, 1974). On reaching the placenta the arteries run in the chorion, usually being of equal size and each supplying one half of the placenta. During their chorionic course the arteries branch, and at each division a proportion of the branches perforate the chorion to enter the placental substance; in addition, a number of perforating vessels are given off directly from the under-surface of the main arteries. As these branches enter the placental substance they run in the primary stem villi and become the lobular arteries. The course of the lobular arteries is usually short and straight, though it has been claimed that they may sometimes run in a spiral fashion, this serving as a mechanism to control the rate of fetal blood flow through the placenta (Romney & Reid, 1951). The lobular arteries soon divide into secondary stem arteries which in turn arborise into tertiary stem vessels. It is the latter which run through the intervillous space in the tertiary stem villi and give off a number of villous branches which eventually break up into a villous capillary system. The villous capiilary networks are found principally on the peripheral aspects of the lobule and are most numerous towards the basal plate.

The villous capillary system was studied by Boe (1953) using an Indian ink injection technique. He showed that not only was there a terminal villous capillary network, but also a paravascular capillary network which is formed by branches arising directly from the main artery (Fig. 1.4): Boe thought that this plexus communicated directly with the main vein, was an arteriolar rather than a true capillary network and served as a shunt arrangement to buffer against focal overloading of the terminal villous circulation. Penfold et al (1981) found no evidence, however, of large diameter vascular shunts within the lobule, and Habashi et al (1982), in a scanning electron microscopic study of corrosion casts (Fig. 1.5), have noted that the paravascular plexus occurs predominantly in

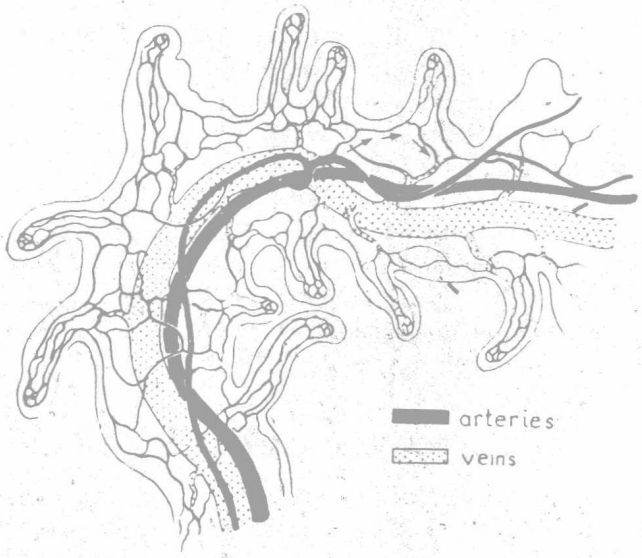

Fig. 1.4 The fetal circulation through the villi shown diagrammatically (after Boe, 1953)

those areas of the villous tree which are bathed with relatively poorly oxygenated maternal blood, i.e. in the stem villi near the chorionic plate, this finding prompting their suggestion that this network could be responsible for the transport of oxygen and nutrients to the stroma of larger villi. Certainly,

Fig. 1.5 Scanning electron micrograph of the cast of a paravascular network encircling a straight vessel of larger calibre (from Habashi et al, 1983)

however, the rather complex system of vascularisation of the fetal placenta allows for considerable flexibility in the control of flow rate through the villi and for ensuring an optimal rate of flow for materno-fetal transfer. The fetal blood flow through the placenta is about 500 ml a minute and, although the main propelling force is clearly the fetal heart, it is possible that there is also a peripheral villous pulse; smooth muscle fibres are present in the stem and anchoring villi (Krantz & Parker, 1963) and it has been suggested that contraction of these fibres may help to pump blood from the placenta to the fetus (Huszar & Bailey, 1979).

THE MATERNAL UTEROPLACENTAL CIRCULATION

The studies of Ramsey and her colleagues, recently summarised in a monograph (Ramsey & Donner, 1980), have shown that maternal blood enters the intervillous space from arterial inlets in the basal plate and is then driven by the head of maternal pressure towards the chorionic plate as a funnel-shaped stream. The head of maternal pressure is gradually dissipated and is further diminished by the baffle-like action of the villi: lateral dispersion of the blood occurs and this forces the blood already present in the intervillous space out through basally placed wide venous outlets into the endometrial venous network. Indian ink injection studies originally suggested that maternal blood entered the intervillous space as a 'spurt' or 'jet', but cineangiography has shown that these terms give an undue impression of both speed and intermittency, the maternal blood entering the space 'much as water from an actively flowing brook penetrates a reed-filled marsh' (Ramsey, 1965).

The physiological basis for this circulatory system is believed to be a series of pressure differentials, with the pressure in the maternal arterioles being higher than the mean intervillous space pressure, which in turn exceeds the maternal venous pressure during myometrial diastole. It has to be remarked, however, that the whole system is a low pressure one, for, whereas in most organs there is a progressive decrease in the diameter of the arteries as they approach their target territories, the reverse is true for the placenta, the uteroplacental arteries dilating progressively as they approach their entry into the intervillous space. Therefore there is a considerable drop in pressure from the proximal non-dilated portions of the uteroplacental vessels to the distal dilated portions, and the full arterial pressure is not transmitted to the intervillous space. The placenta itself offers very little flow resistance to maternal blood and has a high vascular conductance; there is therefore very little drop in pressure across the intervillous space, and the main factor governing the rate of maternal blood flow is the vascular resistance of the proximal part of the uteroplacental vessels (Moll et al, 1975; Moll, 1981). Despite the fact that the pressure differences from arterial to venous sides of the intervillous space are small, they are apparently sufficient to drive arterial blood towards the chorionic plate, to stop short-cutting of the stream into adjacent venous outlets and to prevent mixing of neighbouring arterial streams.