Scientific Basis of Clinical Practice

The Placenta—An Environmental Problem

D. I. RUSHTON

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Clinical obstetrics has long been considered an art rather than a science. It is only in relatively recent times that scientific measurements of the progress of mother and fetus during pregnancy and labour have become possible. These advances have re-awakened interest in the placenta, an organ which in many instances is destined for the incinerator without examination.

The placenta is frequently incriminated in otherwise unexplained intrauterine or intrapartum deaths. The term placental insufficiency is widely used in clinical obstetrics, yet there is little evidence that primary placental insufficiency is a pathological entity. Many current tests of placental function are assessments of the functional capabilities of the trophoblast or of the feto-placental unit. There is no single method of assessing total placental function as there is no single method of assessing hepatic function. This is not unexpected in an organ with so many diverse metabolic activities. While biochemical studies of placental function are throwing new light on normal and abnormal intrauterine growth and development, very little is understood of the inter-relationship of the various indices which are measured. Further, the correlation between metabolic and morphological abnormalities is very limited though the pathologist is often hard pressed by obstetric colleagues to find a placental cause for intrauterine death of the conceptus.

Genetic and Environmental Factors

In any living organism the success of the species is dependant on a balance between the genetic constitution and the environment. Man has been particularly successful in adapting and modifying his environment after birth. In recent years he has attempted, with very limited success, to modify the intrauterine environment. Indirectly, improved standards of living, better antenatal care, and the advent of new drugs have had some effect. The improved control of the diabetic mother, the development of methods for the prevention of and intrauterine treatment of rhesus isoimmunization, and the intensive management of the hypertensive mother have clearly had a more direct effect on the intrauterine environment. It is therefore necessary to consider some of the genetic and environmental factors which act in utero to clarify the role of placental disease in clinical obstetrics.

SPONTANEOUS ABORTION

Probably most of those embryos and fetuses with genetic disorders are lost before the end of the first trimester. The most gross genetic abnormalities—the chromosomal anomalies—give

a clear indication of the extent of this selection. About 20% of spontaneous abortions have an abnormal karyotype. The intra-uterine survival rate of these abnormal conceptuses varies from under 1% in triploid and tetraploid embryos to almost 100% in some sex chromosome anomalies. This loss of embryos probably reflects the failure of the conceptus to provide an adequate hormonal environment for the continuation of pregnancy. It is equally probable that many other unexplainable intrauterine deaths and abortions in early pregnancy are due to less detectable genetic disorders resulting in failures of maturation and development at a biochemical level.

The majority of the genetically and metabolically inadequate conceptuses having been lost, the role of the environment becomes of paramount importance. Today much obstetric research is devoted to measuring the effects of pathological changes in the intrauterine environment in the hope that it may be possible to prevent or correct these disturbances. Why is the uterine environment so critical? An understanding of this problem requires knowledge of the basic properties of trophoblast and of utero-placental anatomy.

The Trophoblast

Trophoblast is a unique tissue. It forms the junction between two genetically dissimilar organisms, it is the site of placental hormone production, and it is the site of active and passive transport of the metabolites necessary for fetal growth and development. The trophoblast is derived from the early cytotrophoblast, which differentiates on the surface of the blastocyst and therefore has the same genetic constitution as the embryo. Two major histological types are recognized: the inner cytotrophoblast and the outer syncytial trophoblast (Fig. 1), which is in contact with the maternal blood. Only the cytotrophoblast can divide and the syncytial component is derived from it.

Fig. 1—Syncytial and cytotrophoblast at 8 weeks gestation (Haematoxylin and eosin $\times 155$).

Birmingham Maternity Hospital, Edgbaston, Birmingham

D. I. RUSHTON, M.B., M.R.C.PATH., Senior Lecturer in Pathology

Trophoblast is a naturally invasive tissue and during implantation penetrates the endometrial surface. The adjacent maternal cells undergo orderly necrosis, the debris being phagocytosed by the syncytial cells. As invasion continues lacunae form within the syncytium and these become filled with maternal blood as the endometrial vessels are eroded. These lacunae are the forerunners of the intervillous space.

As pregnancy progresses some trophoblastic cells break away from the conceptus and migrate into the deeper layers of the decidua, endometrium, and myometrium, forming the "wandering cells". In the past the changes associated with these cells were known as "syncytial endometritis" (Fig. 2), a term which falsely suggests an inflammatory origin for these changes. Further groups of syncytial cells become detached from villi and form emboli which can be commonly found in the lungs of patients dying during pregnancy.

FIG. 2—"Syncytial endometritis"—large wandering trophoblastic cells in myometrium (Haematoxylin and eosin $\times 62$).

The uterine environment plays a major part in preventing uncontrolled trophoblastic invasion. In animals extrauterine blastocysts—for example, blastocysts implanted in the brain or testis—show uncontrolled trophoblastic proliferation, which destroys these organs. Similarly, if blastocysts are implanted into uteruses without decidua growth of the trophoblast continues until the uterine wall is penetrated. Hence evidently the decidua plays an important part in controlling trophoblastic growth and the full invasive potential of this tissue is not realized in normal pregnancy. It is of interest that in the rare condition of placenta accreta or percreta the trophoblast may invade or penetrate the myometrium and no intervening decidua can be demonstrated (Fig. 3).

FIG. 3—Placenta percreta—myometrium (left) and villi (right) with no intervening decidua (Haematoxylin and eosin $\times 62$).

Immunological Barrier

The immunological effectiveness of the trophoblast against host rejection of the conceptus depends, at least in part, on the presence of a layer of acid mucopolysaccharide containing sialic acid on the cell surface. This endows the cell surface with a strong negative charge. The human lymphocyte also possesses a strong negative charge and since cell to cell contact is required for the detection of a transplantation antigen the trophoblastic antigen is not apparent to the host's immunological cell and rejection does not occur. This is an over-simplification of the host-graft relationship in pregnancy, but the barrier is extremely effective since there is no conclusive evidence that immunological rejection occurs after implantation in man. Changes in the maternal hormonal environment also modify the response to grafted tissues during pregnancy, but the roles of immunological factors in fertilization and implantation are outside the scope of this discussion.

Dependence of Trophoblast on Mother

Trophoblast is, however, entirely dependent for its survival on an adequate maternal blood supply. The oxygen consumption of trophoblast is twice that of the embryo or fetus on a weight for weight basis. Equally the fetus is dependent on the placenta for its survival, so that it may be argued that the immediate environment of the fetus is the maternal blood in the intervillous space. If this blood flow is modified quantitatively or qualitatively the survival of the placenta and fetus may be jeopardized.

Basic Placental Anatomy

The basic anatomical unit of the placenta is the cotyledon or placentome. Both maternal and fetal cotyledons are described.

The maternal cotyledon is frequently visible on the decidual surface of a freshly delivered placenta as an ill-defined lobule. It may consist of one or more fetal cotyledons. The fetal cotyledon consists of a group of villi which receive their fetal blood supply from a major trunk of the chorionic vessels. About 30-50 such units exist in a normal full-term placenta. This group of villi forms a bell-shaped structure ("système tambour" of Wilkin), the base of the bell being attached to the uterine surface. The maternal blood enters the centre of this structure through the decidual termination of a uterine spiral artery (Fig. 4).

FIG. 4—Diagrammatic representation of a fetal cotyledon (a—termination of spiral artery, v—decidual veins, d—decidua, c—chorionic plate.)

Each cotyledon is supplied by one spiral artery. This implies that cotyledons develop at the termination of the spiral arteries and the greater density of the villi adjacent to the openings of these vessels may facilitate the even distribution of maternal blood in the intervillous space. It also presents the greatest surface area to the most highly oxygenated maternal blood.

Placental Pathology

The commoner pathological lesions of the placenta may be readily and logically explained using the above model. If changes secondary to intrauterine embryonic or fetal death are excluded most placental lesions can be related to disturbances of the maternal circulation—for example, the placental environment. The common lesions are infarction, haematoma, thrombus, and fibrin deposition (Fig. 5). It is notable that the most significant lesions clinically are related to maternal hypertension (see Table.)

FIG. 5—Common placental lesions (After Wigglesworth¹) (i—infarct, h—haematoma, t—thrombus, f—fibrin deposition.)

Common Lesions in the Placenta

Lesion	Aetiology	Clinical Association
Infarct	Placental ischaemia Spiral artery disease	Maternal hypertension Fetal growth retardation Intrauterine death As for infarction
Haematoma ..	Spiral artery disease	—
Thrombosis ..	Spiral artery disease	—
Arterial	Eddies, stasis	? erythroblastosis fetalis
Venous	Placental ageing and repair (Present in 20% of normal term placentae)	—
Fibrin deposition		

Placental infarction follows ischaemia and is frequently associated with complete occlusion of the termination of a spiral artery. True infarcts show a well-defined correlation with the cotyledonary structure. Infarction does, however, invariably reflect severe placental ischaemia since it is unlikely, except in marginal areas, that it follows occlusion of a spiral artery in the absence of disease in other similar vessels. This situation may be considered analogous to coronary artery disease and myocardial infarction. The significance of an infarct to the fetus is variable, depending on the placental reserve and the extent of the necrosis. Fetal death may occur immediately; placental function may be reduced so as to retard fetal growth either permanently or temporarily; there may be minor fetal disturbance; or there may be no demonstrable effect on the fetus. In addition to the loss of the maternal blood supply, in the early stages the fetal circulation continues through the infarcted villi and this leads to shunting between the umbilical arterial and venous circulations. The effect on the fetus will clearly depend on the size of the shunt and its duration.

Closely related to placental infarction is the placental haematoma. This may follow rupture of the wall of the termination of a spiral artery, with subsequent sudden cessation of the maternal blood supply and clotting of the blood in the centre of the cotyledon. The lesion is usually situated in the central part of the cotyledon and is made up of fresh non-laminated thrombus and may be surrounded by or lie within the centre of an infarct.

Laminated intervillous thrombus is frequently seen in term placentae. In many instances these thrombi are related to local disturbances in intervillous blood flow and are analogous to laminated thrombi in other situations—for example, in arterial aneurysms. Laminated thrombi are more common in placentae from cases of rhesus isoimmunization. Much argument has centred on the hypothesis that these thrombi may follow haemorrhages from the fetal vessels into the maternal circulation. Nevertheless, it may be equally argued that the swollen oedematous villi of the hydropic placenta may interfere with normal blood flow in the intervillous space leading to slowing and subsequent thrombosis.

The origin and nature of placental fibrin and fibrinoid are still not completely resolved. Deposits are evident macroscopically as

firm indurated pale grey-yellow areas with a slightly translucent cut surface. They are most frequently found at the margins of the placenta and beneath the chorionic plate. The latter are evident on the fetal surface of the placenta as white plaques (subchorionic fibrin plaques). Fibrin is also deposited on the maternal surface between the villi and the basal plate (stria of Rohr) and within the basal plate (stria of Nitabuch.) Microscopically, small deposits are found on the surface of villi, the number of these deposits increasing with the duration of pregnancy. There is little evidence that fibrin and fibrinoid have an important role in the clinical problems of obstetrics. The heaviest deposits of fibrin and fibrinoid are found in placentae retained in utero after death of the embryo or fetus, particularly in early pregnancy.

PLACENTAL INSUFFICIENCY

Finally the role of the placental environment in clinical placental insufficiency must be considered. It has been suggested that the fetal part of the placenta may, in part, control the maternal blood flow since the pressure gradient in the maternal circulation is related to the density of the villi. It follows that a reduction in maternal blood flow could lead to a reduced villous population and therefore a smaller placenta. In hypertensive pregnancy the blood flow in the intervillous space is reduced. Measurements of the functional surface area of the villi have shown an appreciable reduction in placentae derived from hypertensive pregnancies. Small or light-for-dates babies are particularly common in association with such pregnancies and placental function tests are frequently in the low normal or sub-normal range. Evidence that these placental changes are secondary comes from studies of placental bed biopsies. These have shown severe vascular lesions in the maternal uterine vessels, particularly in pre-eclamptic and eclamptic pregnancies. This form of secondary placental insufficiency is therefore better termed utero-placental insufficiency. It is a chronic process which may terminate in fetal death unless the function of the fetoplacental unit is adequately monitored and clinical action dictated by deteriorating results.

Nevertheless, while maternal hypertensive vascular lesions are implicated in some cases of light-for-dates babies, there are many other genetic and environmental factors including parity, maternal stature, socio-economic group, multiple pregnancies, maternal smoking, chromosomal anomalies and intrauterine infections. In many instances no adequate explanation is forthcoming.

Acute utero-placental insufficiency may occur in an otherwise uneventful pregnancy after retroplacental haemorrhage, partial placental separation, or obstruction of the umbilical cord. There is a greater hazard if acute changes are superimposed on chronic insufficiency. This is particularly likely to occur during labour, when the haemodynamic changes in the maternal circulation during uterine contractions may further diminish placental perfusion and lead to fetal distress.

Thus evidently the placental environment is the key to many current obstetric problems. Modern management of the "at risk" pregnancy includes careful monitoring of this environment and balancing the risks of delivery against those of a continued intrauterine existence.

Many tests of placental function have been employed but in an organ which synthesizes several hormones—and functionally replaces the fetal lung, alimentary tract, and kidney—no single test can be truly representative of the placental sufficiency. Furthermore the inter-relationships of many of these tests are ill understood so that they are more closely correlated to the clinical conditions than to each other.

Assessment of Placental Function

There are four major methods of assessing placental function.

MORPHOLOGICAL STUDIES

As has been indicated above, the correlation between placental function and pathology is frequently very limited.

Complex morphometric techniques for the determination of placental surface area, while of value as a research tool, are too time-consuming for routine laboratory usage. Placental weight is unreliable since these measurements usually include undetermined quantities of fetal and maternal blood. Probably placental insufficiency resulting from small placental size is rare.

A further disadvantage of these techniques is that they are retrospective, and while they may be of academic interest they contribute in no way to the obstetric management of individual pregnancies.

It is possible to biopsy the placenta during pregnancy but, apart from the possible dangers of this procedure, it is unlikely that it has anything to recommend it over less risky methods.

TROPHOBLASTIC FUNCTION

Estimates of trophoblastic function depends on the hormone-synthesizing properties of this tissue. It has not yet been possible to accurately correlate hormone synthesis with transport function. Two hormones are widely estimated in clinical practice to assess trophoblastic function.

Human Chorionic Gonadotrophin (HCG)

Immunofluorescent histological studies have indicated the main site of HCG synthesis is the syncytiotrophoblast, the layer of trophoblast in contact with the maternal blood.

There is some evidence that the cytotrophoblast may also synthesize HCG. Since the syncytium is derived from the cytotrophoblast this suggests that synthesis begins before syncytial differentiation is complete.

Measurement of HCG is widely used as the basis of many pregnancy tests. It is also of considerable value in the detection and follow-up of molar pregnancy and choriocarcinoma. It is of limited value in later pregnancy because of wide fluctuations in individual patients in normal pregnancy. In early pregnancy it is of some value in the prediction of the outcome of threatened abortion.

Human Placental Lactogen (HPL)

This hormone has also been shown to be produced in the syncytiotrophoblast. It is an extremely sensitive indicator of trophoblastic function since it has a half-life in maternal blood of about 20 minutes. It is as yet still not used very widely in clinical obstetrics.

Both these hormones reflect the amount of functioning trophoblast but they do not give a direct indication of the condition of the fetus. It is therefore necessary to combine these estimations with the clinical assessment of the fetus and usually with a biochemical parameter of fetal well being.

THE FETO-PLACENTAL UNIT

The most widely used biochemical index for the assessment of fetoplacental function is maternal urinary oestriol (or in some institutions total urinary oestrogen) excretion. The production of oestriol is dependant on the normal functioning of the fetal adrenals and liver as well as the placenta. The metabolic pathways concerned have been established by perfusion experiments using placentae and mid-trimester abortions (Fig. 6.)

Estimations of urinary oestriol levels in serial or weekly 24-hour urine specimens adequately collected are particularly valuable in the detection of retarded intrauterine growth and monitoring the at-risk pregnancy—particularly those complicated by hypertension. Since the normal levels vary with the techniques of estimations it is customary to produce a standard

Fig. 6—Interrelationship of fetus, placenta, and mother in oestrogen metabolism in pregnancy.

Fig. 7—Urinary oestriol levels: (a) normal, (b) small for dates, (c) intrauterine death.

chart for the laboratory and the results are recorded graphically (Fig. 7). A failure to rise progressively during pregnancy or a decrease in levels requires accurate clinical assessment and frequently premature delivery of the affected fetus.

Low results may occur in fetal disorders where the adrenals are abnormal. Adrenal hypoplasia occurs in anencephaly and in a congenital form and in both instances urinary oestriol levels are reduced. Maternal steroid therapy may also be associated with reduced oestriol excretion.

TRANSPORT FUNCTION

Estimates of placental transport depend on correlating maternal and fetal blood levels of various metabolites. In practice maternal blood levels are not widely used since arterial sampling is required to determine the appropriate concentrations in the intervillous space. Arterial sampling is, however, of value as a research technique. The most significant metabolite clinically is oxygen since intrauterine and intrapartum asphyxia are still major causes of fetal death and neonatal morbidity.

The fetus is readily accessible in utero only after the onset of labour and partial dilatation of the cervix have occurred. Blood may then be obtained from the presenting part, which in most instances is the scalp. The sample of blood obtained is used to determine the pH and acid-base values. Clinically the pH of the sample is considered the most valuable measurement and most

investigators accept pH 7.2 as being critical in that it indicates a dangerous degree of fetal acidosis and hypoxia. Nevertheless, since the pH of the fetal blood is not determined by fetal metabolic processes alone the biochemical data must be interpreted in the light of the clinical status of the mother and fetus and not acted on in isolation.

Clearly this technique is appropriate only during labour but it is an important aid in the diagnosis of fetal distress and the monitoring of "at risk" babies. The cause of hypoxia in most instances is decreased placental perfusion. If there is reduced perfusion in the maternal circulation this may be the result of mechanical effects of labour, vena caval compression, or partial placental separation. Reduced perfusion is particularly important when the placental reserve is reduced at the onset of labour as the result of some of the factors discussed above. The fetal circulation may be reduced by cord complications (such as nuchal cord, prolapsed cord, cord compression, and occasionally thrombosis of an umbilical vessel.)

Conclusion

The understanding of the role of the placenta in clinical obstetrics requires knowledge of the normal development and anatomy of the fetal and maternal circulations. In most instances where placental disease can be closely correlated morphologically or physiologically with fetal disease disturbances of the maternal component of the placental circulation play a major part. This is particularly true in the one disease specific to pregnancy—pre-eclampsia and eclampsia, where severe changes

may be found in the vessels supplying the intervillous space.

Modern obstetrics must therefore direct more research in the direction of the maternal side of the placenta—and in particular to the placental bed—since an understanding of the aetiology of the vascular lesions will probably clarify the aetiology of pre-eclampsia and also indicate ways in which these lesions may be prevented. If this were possible there would undoubtedly be an appreciable reduction in the perinatal mortality rate, and probably also in the maternal mortality rate. Like the natural environment, the placental environment must be improved.

This article is based on a lecture given in the Birmingham course under the title "The Scientific Basis of Clinical Practice" (see B.M.J., 27 November 1971, p. 510).

References

- ¹ Wigglesworth, J. S., *Journal of Obstetrics and Gynaecology of the British Commonwealth*, 1969, 76, 979.

Further Reading

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Any Questions?

We publish below a selection of questions and answers of general interest

Long-term Chlorpromazine Hazards

A woman of 93 with senile agitation and confusion has taken 5 ml of chlorpromazine daily for nearly 4 years. Are there any hazards in such long-term treatment?

The hazards of prolonged therapy with such a small dose of chlorpromazine (5 ml contains 25 mg of the active drug) are not great but they do exist.¹ So it would certainly be worth seeing whether the patient really needs continuous medication.

Hypersensitivity effects such as jaundice, blood dyscrasia, and dermatitis are unlikely after so long but long-term administration of chlorpromazine syrup carries a continuing risk of contact dermatitis in nursing staff. Sugar coated tablets should reduce this risk. Certain neurological effects may also occur. The commonest is Parkinsonism, while the second is akathisia, an uncontrollable restlessness and the third is dystonia, in which the patient assumes grotesque postures. More likely than these last two is dyskinesia tardiva, characterized by smacking and licking of the lips, sucking and chewing movements, rolling and protrusion of the tongue, and blinking and grimacing, possibly accompanied by choreoathetoid movements of the limbs. If these side effects occur it is important to recognize that they may be drug-induced and are not simply a result of degenerative changes in the nervous system associated with advanced age.

Chlorpromazine may cause postural hypotension because of its effect on the autonomic nervous system. This may occur at any stage in treatment as can anticholinergic side effects including blurred vision, dryness of the mouth, urinary retention, constipation, and paralytic ileus. Sudden death, possibly

due to ventricular fibrillation has also been reported in patients on phenothiazines. However, none of these problems is particularly likely to occur though they are all possible. If the patient is in a kindly and reassuring environment chlorpromazine may well be unnecessary.

- ¹ Shepherd, M., Lader, M., and Rodnight, R., *Clinical Psychopharmacology*, London, English Universities Press, 1968.

Gluten-free Diet and Vitamins for Schizophrenia

Is a gluten-free diet with added vitamins of any value in the treatment of schizophrenia?

Claims for a gluten-free diet and megavitamin therapy in the treatment of schizophrenia have not been established, but they have not yet been refuted. "Schizophrenia" is a diagnosis which may include a number of conditions with quite different aetiology. It seems possible that certain cases might respond to the treatments described. Only further research will show. In our present state of ignorance it would be wrong to be dogmatic. Ban and his colleagues^{1,2} have carried out a double-blind controlled trial of megavitamin therapy on a mixed population of schizophrenics and failed to find any significant benefit. However, they specifically said that their research design would not detect whether a small number of patients was showing particular benefit.

- ¹ Ban, T. A., *Psychopharmacological Bulletin*, 1969, 5, 5.

- ² Ban, T. A., and Lehman, H. E., *Canadian Psychiatric Association Journal*, 1970, 15, 499.