

RES MEDICA

Journal of the Royal Medical Society



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Abstract

Pregnancy is a truly remarkable process. While a single fertilised cell is developing into a complete individual, the mother usually tolerates this rapidly growing "transplant", her enlarging uterus and the accompanying dramatic hormonal changes with equanimity. Perhaps it is hardly surprising that such a complex process sometimes fails.

Changing times have influenced the degree of importance society attaches to fetal and perinatal loss. It is not very long since recurrent pregnancy, high infant mortality and stillbirth were accepted with resignation, as normal hazards of living. However with effective contraception, careful obstetric supervision and the improvements in nutrition, hygiene and health which have come to affluent western societies, the present expectation is of a chosen number of pregnancies, precisely timed and with perfect outcome. Yet about one in ten couples is infertile; nearly one in five recognised pregnancies ends in spontaneous abortion (1) and an even greater number of unrecognised early pregnancies are aborted (2). Fetal loss is still a common problem.

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ISSN: 2051-7580 (Online) ISSN: 0482-3206 (Print)

Res Medica is published by the Royal Medical Society, 5/5 Bristo Square, Edinburgh, EH8 9AL

Res Medica, New Series No.2, 1980: 33-38

doi:[10.2218/resmedica.v0i2.928](https://doi.org/10.2218/resmedica.v0i2.928)

FETAL PATHOLOGY IN SPONTANEOUS ABORTION

by

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Pregnancy is a truly remarkable process. While a single fertilised cell is developing into a complete individual, the mother usually tolerates this rapidly growing "transplant", her enlarging uterus and the accompanying dramatic hormonal changes with equanimity. Perhaps it is hardly surprising that such a complex process sometimes fails.

Changing times have influenced the degree of importance society attaches to fetal and perinatal loss. It is not very long since recurrent pregnancy, high infant mortality and stillbirth were accepted with resignation, as normal hazards of living. However with effective contraception, careful obstetric supervision and the improvements in nutrition, hygiene and health which have come to affluent western societies, the present expectation is of a chosen number of pregnancies, precisely timed and with perfect outcome. Yet about one in ten couples is infertile; nearly one in five recognised pregnancies ends in spontaneous abortion¹ and an even greater number of unrecognised early pregnancies are aborted². Fetal loss is still a common problem.

A major breakthrough in the study of human reproductive wastage resulted from successful cytogenetic studies of aborted material. The normal diploid human chromosome number is 46 with an XX (female) and XY (male) mechanism determining sex. At least half of all *early* spontaneous abortions have detectable chromosome abnormalities incompatible with the

normal development of the embryo¹. Abnormalities commonly detected in these abortuses include trisomy (with a single extra chromosome), monosomy (in which one homologue of a pair is missing) and polyploidy, particularly triploidy, with one additional haploid set of chromosomes, and tetraploidy with two sets. Monosomy appears to be almost exclusively restricted to loss of an X chromosome whereas trisomy has been reported for every autosome. Mosaic individuals, with more than one cell population, can be found.

The classical descriptions of human abortuses were made without the benefit of this knowledge^{2,3}. Even today, the way in which a chromosome abnormality exerts its phenotypic effect or contributes to abortion at a particular stage of pregnancy is not understood and remains a challenge jointly to cytogeneticists and pathologists.

The pathology of spontaneous abortion is also interesting. Complete "products of conception" comprise both fetal and maternal tissues, particularly decidua. Most of the tissue expelled in early spontaneous abortion is actually maternal in origin. In pregnancies ending at about 12 weeks of gestation, it is quite usual to find that fetal development has failed almost totally. In these cases the intact gestational sac is very much smaller than normal and contains only fluid or a small embryonic knob (Fig. 1). The general term,

“blighted ovum”, is sometimes used to describe sacs which do not contain an organised embryo. These sacs are usually accompanied by a large quantity of decidua or by a complete decidual cast of the uterine cavity (Fig. 1). Unfortunately, many spontaneous abortions commence in the mother’s own home and the tissue received for pathological examination is only the retained decidua which has been removed by curettage. This presents problems for the cytogeneticist since the accurate separation of fetal from maternal tissues is essential if chromosome analysis is to be of clinical value.

Apart from the small sacs just described, there are many other cases of spontaneous abortion in which the fetus is not of a size appropriate to the reputed length of gestation. These unduly small embryos and fetuses often show varying degrees of maceration, indicating that fetal death occurred some time before the onset of labour (Fig. 2). Maceration takes place at body temperature and usually in a sterile environment, so that body form is often retained sufficiently well to allow recognition of major structural abnormalities. The investigation of smaller (or particularly interesting) embryos is best achieved using a dissecting microscope and sometimes even serial sections.

Both fresh and macerated aborted fetuses include some individuals with no apparent structural abnormality, some with minor and some with major abnormality. Examples of clearly defined defects, compatible with post-natal life and identified in spontaneous abortuses, are hypospadias, cleft lip, Meckel’s diverticulum, polydactyly, double ureter (Fig. 3) and bicornuate uterus. More severe abnormalities include facial cleft, diaphragmatic hernia, coarctation of the aorta (Fig. 4), cardiac septal defects, pulmonary hypoplasia (Fig. 4), polycystic kidneys, anal atresia, and central nervous system malformations of all kinds. Of special interest are the cases where patterns or associations of abnormalities occur. Less easy to classify are those abortions in which the fetus has an odd appearance but is apparently morphologically and chromosomally normal. These may have subtle anatomical and metabolic abnormalities that elude us at present.

Table 1 summarises the pathological classification of more than 1,300 spontaneous abortions examined in Edinburgh over a period of five years.

<i>Twelve weeks of gestation and less</i> (62% of total)	Percentage of Total
Decidua and ruptured sacs	28
Intact empty sacs	9
Intact sac with embryonic knob	9
Fresh normal embryo	1
Fresh abnormal embryo	7
Macerated embryo	8
<i>Greater than twelve weeks of gestation</i> (35% of total)	
Fresh apparently normal fetus	6
Fresh abnormal fetus	17
Macerated apparently normal fetus	6
Macerated abnormal fetus	6
<i>Others</i> (e.g. Placenta only)	3
	100

Why do so many pregnancies end in spontaneous abortion? To suggest that this is simply nature’s way of eliminating developmental errors discounts both the apparently normal aborted fetus and on the other hand, the many babies surviving to term with major defects. If a screening mechanism for fetal defects does exist, whereby the mother rejects abnormal pregnancies, then it is probably most efficient in detecting the chromosomal abnormalities which are present in so many early abortions

The study of central nervous system (CNS) malformations shows that if selective spontaneous abortion does occur, then it is far from perfect. Before the antenatal detection of CNS defects became possible, with the accompanying option of termination of affected pregnancies, the birth incidence of spina bifida and anencephaly in Britain was about 0.4%. These severe structural abnormalities had not triggered an abortion mechanism in spite of being present from an early stage of gestation. However, CNS defects are found with an incidence of 4% in spontaneous abortuses (personal observation) especially among the small embryos where they may escape detection on a cursory glance (Fig. 5). This is a tenfold increase over the incidence at birth prior to antenatal diagnosis. If comparable figures apply for other congenital defects, this would suggest that despite the number of such defects seen in babies at term, spontaneous abortion does serve

a useful purpose in eliminating a majority of the abnormal conceptions.

The identification of a CNS defect (Fig. 5) in a spontaneously aborted embryo gives rise to a problem. Is the mother of that embryo at the same increased risk of recurrent defect as the mother of a baby born at term with a CNS abnormality? In fact, we know remarkably little about the implications for the subsequent pregnancy, after a spontaneously aborted abnormal fetus, except where the abnormality originates from a cytogenetic error. We are involved at present in a prospective study of pregnancies subsequent to spontaneous abortion. Meanwhile, it seems unwise to regard a spontaneous abortion as a negligible obstetric event. However, the findings in aborted material may well prompt appropriate investigation or counselling or simply reassurance of the parents. For example, ultrasound examination and alphafetoprotein estimation should be recommended at present in any pregnancy subsequent to the abortion of a CNS defective embryo.

Apart from the possible benefits to the mother and her future children, is anything else to be gained from a study of spontaneous abortion? It does provide opportunities to investigate the pathogenesis of defects in early human development, when the original pathology is not obscured by infection, by attempts at regeneration or by surgical intervention. Unfortunately maceration sometimes interferes with histological assessment. Because the time interval is shorter than in a full term pregnancy, maternal recall may well be more accurate in respect of illness, drugs, X-irradiation and other factors operating early in pregnancy, making retrospective epidemiological enquiry more profitable.

How is progress to be made in the understanding and prevention of fetal disease? I have neglected many important factors which may cause problems for the developing fetus. Since the fetus is totally dependent on its mother, some aspects of fetal pathology are clearly a reflection of maternal pathology, (as in maternal diabetes) or of the interaction between mother and fetus (as in rhesus incompatibility). I have concentrated on the congenital malformations because we have

made little headway in their understanding or prevention, while perinatal mortality from other causes has declined.

Animal experiments have contributed greatly to the study of abnormal fetal development. The most important conclusion, confirmed by numerous studies, is that it is the timing rather than the nature of the experimental insult which results in a particular defect. Totally unrelated agents administered separately at a given time in gestation may produce the same defect. Conversely, one given agent may produce different defects if administered at different stages of gestation. This may have important implications for the aetiology of human malformation but caution is needed when animal development is compared directly with that of man.

Undoubtedly the possible antenatal detection of inborn errors, chromosomal abnormality and morphological defects has revolutionised the care of high risk patients and enabled many couples to achieve a successful pregnancy after repeated failures, while the birth of individuals who would have been an almost intolerable burden on the family and society has been reduced.

However, these advances generate problems. The methods of antenatal diagnosis must be perfected to avoid elimination of normal fetuses. It is a drastic step to "kill the patient to cure his disease" as Warkany⁴ has put it. If the relation between spontaneous abortion and fetal defect were better understood, we might be able to increase the efficiency of early spontaneous elimination thus avoiding active intervention later in pregnancy. Even if we accept that there may not be an early alternative to antenatal detection and selective abortion, let us continue to strive for understanding of congenital defects and to make the best use of the knowledge we have. While drugs, nicotine and excess alcohol are all viewed with suspicion, we still have difficulty in protecting pregnant women from those agents, such as rubella virus, which are known to be teratogenic.

We should also be alert for the less obvious forms of fetal pathology. Until recently, the fetal alcohol syndrome may have been missed precisely because the abnormality in the affected fetus is only slight (until mental deficiency becomes

obvious in post natal life). Intrauterine growth retardation, resulting in small-for-dates babies, may be another preventable handicap which impairs many individuals. Responsibility falls heavily on all those caring for the pregnant woman and her fetus and on those engaged in the related research fields.

It is encouraging that we now have signals, such as protein and enzyme levels in maternal serum,

which indicate the possibility of fetal maldevelopment or distress even when the pregnancy appears to be progressing normally. I hope it is not unrealistic to believe that more of these will be discovered thus allowing active intervention to prevent further fetal deterioration in progressive disease, or to correct abnormality already present, while conserving the pregnancy. ●●

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LEGENDS

Fig. 1 — Decidual cast with opened gestational sac containing opaque knob of embryonic tissue.

x1



Fig. 2 — Macerated fetus, C.R. length 7cm., attached to placenta. There is an amniotic connection between the cord and the left hand.

x1



Fig. 3 — Dissection of posterior abdominal wall shows left double ureter. Meconium is spilling from the cut end of the colon. Normal fetal lobulation of the kidneys is shown.

x2.3

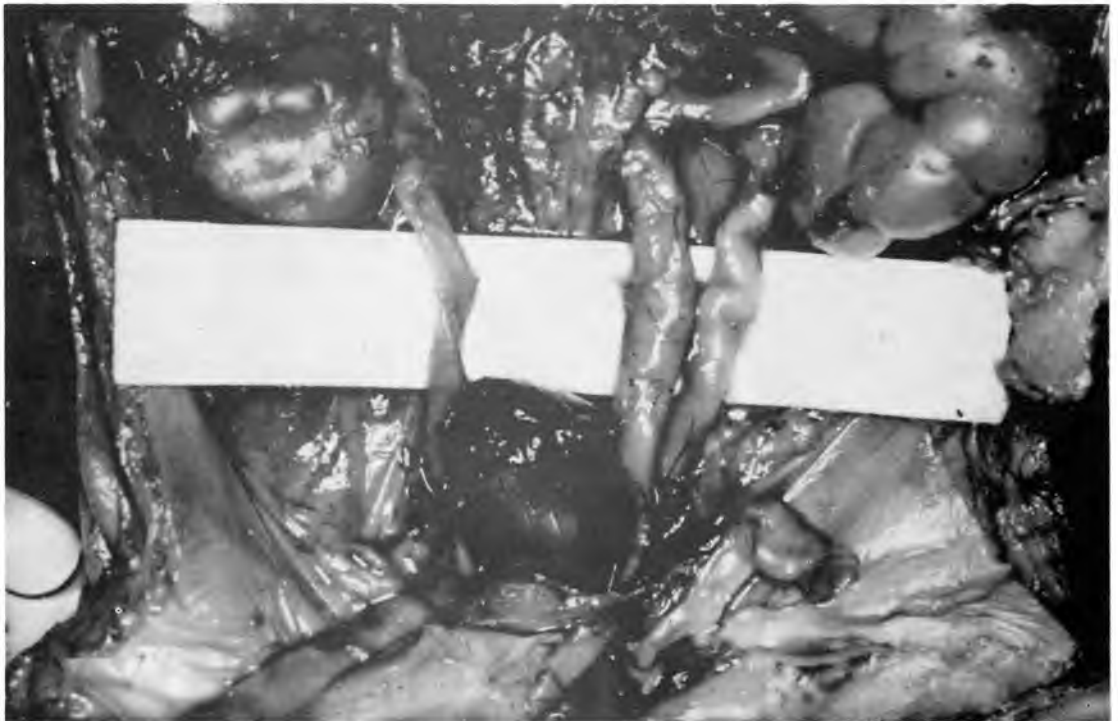


Fig. 4 — Dissection of thorax in a macerated fetus showing pulmonary hypoplasia (marked by pins) and coarctation of the transverse aorta.
x2

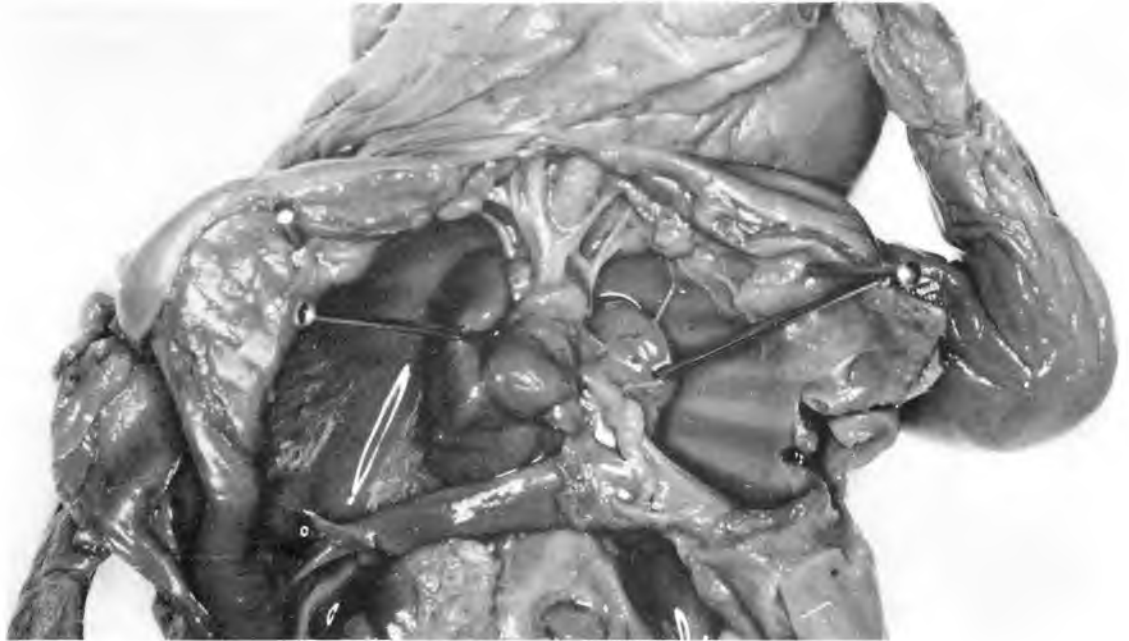


Fig. 5 — Slightly macerated embryo with lumbo-sacral spina fibida. The only other visible abnormality is polydactyly (extra digit attached to the ulnar side of the hand).
x4

