Spontaneous abortion and fetal abnormality in subsequent pregnancy

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Summary and conclusions

In a prospective survey neural tube defects and other congenital abnormalities were studied in the babies born to 510 mothers ascertained during pregnancy. The women were divided into two groups according to the outcome of their immediately preceding pregnancy. Those whose preceding pregnancy had resulted in a spontaneous abortion (256 women) formed the index cases; those in whom the outcome had been a normal baby (254 women) served as controls.

There was a highly significant increased number of congenital abnormalities in the index cases. This may possibly be explained by the trophoblastic "rest" hypothesis and suggests that spontaneous abortions are more relevant to congenital abnormalities than has been thought.

Introduction

Knox[1] and Clarke *et al*[2] suggested that residual pathological[2] trophoblastic material from a spontaneous abortion or stillbirth might interact unfavourably with the fetus in an immediately succeeding pregnancy and cause anencephaly or spina bifida (ASB). Their hypothesis was supported by the results[2] of a study of mothers who had conceived both before and after giving birth to a baby with ASB (the "middle child"), which had shown that the incidence of miscarriages and stillbirths in the pregnancy immediately before one resulting in a child with ASB was about twice that in the pregnancy immediately after. This finding was confirmed by others[3 4] and by one of us (OMM, personal communication), though controversy remains about its interpretation.[3-5]

A method suggested[2] and used in this study to test the hypothesis was to examine for ASB the newborn babies of women from whom it had been ascertained at the antenatal clinic that their previous pregnancy had ended in a spontaneous abortion and compare the results with those in a control series, in which the mother's previous pregnancy had resulted in a normal baby. Since the incidence of ASB in Liverpool was about 6·5/1000 births[6] any such series would have to be large, but because only four months was available to one of us (AG) we first carried out a preliminary survey. The findings with respect to non-ASB abnormalities in the 510 cases studied were so unexpected, however, that we report them here in the hope that other centres will repeat the survey. We propose to carry out another investigation, in which the index cases will include not only women whose previous pregnancy ended in a spontaneous abortion but also those in whom the outcome was a stillbirth.

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Patients and methods

The case notes of women attending antenatal clinics in five Liverpool hospitals during four months in 1977 were scrutinised and the women divided into two groups—an index group of 290 women whose previous pregnancy had ended in a spontaneous abortion and a control group of 287 women whose previous pregnancy had resulted in a normal baby. The controls were matched closely with the index cases for age and gravidity—that is, number of pregnancies irrespective of outcome, except for the selected difference distinguishing index from control cases. Of these 577 women, two of the index cases and one of the controls aborted, one and three respectively were found not to be pregnant, and in 31 and 29 respectively there was no information on outcome. Most of the women on whom information was lacking had moved away. Of the remaining 510 women available for analysis, 256 were index cases and 254 controls.

The social-class distribution at the different maternity hospitals varied. In only one of them was the occupation of the husband given routinely in the case notes, and here the classes were similar in 64 index cases (mean class 3·4) and 71 controls (mean 3·8). Elsewhere the information was less accurate, but each index case was always paired with a control taken from the same unit.

In the index cases we recorded the interval between the expulsion of the abortus and the last menstrual period marking the beginning of the current pregnancy. In the controls the corresponding interval was between the birth of the last normal baby and the last menstrual period. During this interval the uterus is generally thought to be empty; we refer to the interval as the interpregnancy gap (IPG). When possible we also noted the gestational age of the abortus in the index cases and whether dilatation and curettage had been carried out.

Each baby was examined in the routine manner at birth and on discharge from hospital by paediatricians and obstetricians who were unaware of our study. Any malformations were recorded on the standard form. None of us saw or questioned the women during their pregnancy, any information being obtained solely from case notes. Some months later one of us (JC) followed up the abnormal babies to see if there had been any changes in the conditions diagnosed at birth. When doing this she was unaware of which were control and which index cases.

Results and comment

Tables I and II list the abnormalities that seemed to be of developmental origin and could be recorded objectively. Seventeen abnormalities occurred in the index cases and four in the control cases. This difference was highly significant ($\chi^2_1 = 8{\cdot}29$; $P < 0{\cdot}01$).

We excluded from the analysis babies with talipes and similar conditions (four in the index cases and one in the controls) because these were probably of the positional type and the result of moulding and therefore not developmental in origin. We also excluded babies with clicking hips and evanescent heart murmurs because such observations are highly subjective. Clicking hips are being studied as a research project in Liverpool, which may have introduced bias and accounted for the high number recorded. Nevertheless, all three of the excluded conditions occurred more often in the index cases than the controls, which might mean that some of the conditions omitted were less trivial than we thought. On the other hand, they may have been recorded because the cases in which the previous pregnancy had ended in an abortion were perhaps subjected to special scrutiny. We do not think, however, that this could have applied to the abnormalities in table I, which would have been recorded anyway. We have no information on whether there is a "middle-child" effect for any of the conditions other than ASB.

TABLE I—*Abnormalities noted among 256 index cases,* and details of previous spontaneous abortions and interpregnancy gaps*

Case No	Gestational age at previous spontaneous abortion (weeks)	Inter-pregnancy gap (months)	Dilatation and curettage	Abnormality (confirmed at follow-up)	Sex
1	10	45	NK	Hypospadias	M
2	8	10	NK	Cleft lip	M
3	8	1	Yes	Sacrococcygeal dimple	F
4†	26	30	No	Hypospadias	M
5†	26	30	No	Hypospadias	M
6	8	5	Yes	Anencephaly. NND	NK
7	12	24	Yes	Sacrococcygeal dimple, brisk knee and ankle jerks, epicanthic folds, clinodactyly	M
8	8	2	Yes	Sacrococcygeal dimple	F
9	11	24	Yes	Ventricular septal defect	M
10	10	10	Yes	Sacrococcygeal dimple with hairy patch above	M
11	11	2	Yes	Spina bifida (meningomyelocele). NND	F
12	10	12	Yes	Rectal stricture	F
13	14	24	Yes	Hirschsprung's disease	M
14	8	5	NK	Sacrococcygeal dimple	F
15	23	6	NK	Edward's syndrome and congenital heart disease. NND	F
16	7	12	Yes	Sacrococcygeal dimple	F
17	12	3	Yes	Congenital dislocation of hip	M

NK = Not known. NND = Neonatal death.
*In addition to those listed the following abnormalities were noted but not included in the analysis: clicking hips (19 cases); systolic murmur (5), later thought to be innocent; metatarsus varus (2; one with clicking hips); and positional talipes (2).
†Cases 4 and 5 were twins.

The IPG tended to be shorter in the index cases than in the controls, which is readily explicable. After the birth of a live baby there is a period of relative infertility during lactation; furthermore, the mother has to look after the baby and is not usually anxious to become pregnant again immediately. This contrasts with the attitude of many women who have just lost a baby. Table I shows that the IPG was less than 12 months in nine of the 17 cases, which may well have been relevant to the presence of the abnormality. Fedrick and Adelstein[7] showed that IPGs of less than six months were associated with a high neonatal death rate and thought that there might be other ways in which these infants were at special risk.

TABLE II—*Abnormalities noted among 254 control cases,* and interpregnancy gap*

Case No	Interpregnancy gap (years)	Abnormality (confirmed at follow-up)	Sex
18	10	Sacrococcygeal dimple	M
19	1	Hypospadias	M
20	1	Syndactyly	M
21	1	Congenital hemiplegia with bony abnormalities	F

*In addition to those listed the following abnormalities were noted but not included in the analysis: clicking hips (9 cases; innocent systolic murmur in one); innocent systolic murmur (1); and bilateral talipes (1).

The two babies with ASB and the one with the hairy patch were all index cases. Though this could have happened by chance, it was in the direction indicated by the "rest" hypothesis and supported by the excess of sacrococcygeal dimples in the index group (four girls and two boys). The exact interpretation of dimples is uncertain, but some cases at least are related to spinal dysrhaphia,[8 9] which may be classed as a neural tube defect.[10] The IPGs in the cases with ASB and in some of those with dimples were among the shortest recorded (see tables I and II), which is consistent with a short-lived factor such as a rest. Nevertheless, in all these cases dilatation and curettage had been carried out after the abortion (except case 14, in which the information was not available). Whether this eliminates all trophoblastic remnants and how soon after it the uterine endometrium is restored to normal remain uncertain, but scrutiny of all the index cases, irrespective of whether the subsequent baby had an abnormality, showed that in an overwhelming proportion dilatation and curettage had been carried out.

Discussion

The significant difference between the findings given in tables I and II is clearly an overall effect that cannot be shown for each individual condition; nor could this be expected in such a small series. There are several possible explanations for our results. The first is biased reporting, which has been mentioned but may be ruled out for the conditions listed in table I. Secondly, the spontaneous abortion may have occurred because the abortus itself was abnormal. Thus some miscarriages are fetuses with ASB,[11] and James,[5] analysing within families the data used in our earlier paper,[2] showed that the abortions tended to occur early rather than late in the sibships, which may explain our middle-child results. He did not, however, take account of our stillbirth information.[2] In that paper there was the same middle-child effect (also found by Field and Kerr[3]), and yet we know that the stillbirths were not affected by either spina bifida or anencephaly, because if they were it would have been recorded and the mothers would have been index cases. Furthermore, the abnormalities listed in table I are so varied that it seems unlikely that each baby was preceded by an abortion in which the fetus had a more serious degree of the same defect.

Another possibility is that there is a uterine factor that might lead to deficient implantation, particularly if the fertilised ovum were abnormal. Various types of abortus might result,[12] and there might be some residual effect that influences a subsequent fetus. In support of this uterine factor it has been shown[13] that in induced (as opposed to spontaneous) abortions in which the suction technique is used the subsequent pregnancy is not deleteriously affected. This is in contrast to both induced and spontaneous abortions dealt with by dilatation and curettage, after which there is an excess of stillbirths and premature births in the subsequent pregnancy compared with controls.[14] Pathological changes in either the abortus or the uterine environment thus seem to influence the implantation and survival of the subsequent ovum. The difficulty is how to test this hypothesis, but some information might be obtainable if it were known whether any particular type of abortus[12] created a special risk for the subsequent baby. There is also strong evidence that the uterine endometrium takes time to return to normal. Ascertaining through stillbirths and neonatal deaths, in some of which there were congenital abnormalities, Fedrick and Adelstein[15] found that the pregnancy before was much more likely to have ended in a stillbirth, abortion, or neonatal death than it was in a control series.

Finally, there is the rest hypothesis, which postulates the presence of residual pathological material. Villi may be found up to 10 weeks after an abortion,[16 17] and Stevenson (personal communication) therefore advised women to wait before becoming pregnant again after an abortion. If pathological rests lead to the formation of an antifusion factor this might account for the various defects, many of them midline, recorded in table I and provide a unifying concept.[18] Furthermore, the hypothesis would explain the randomness of ASB in relation to abortion. The rest would have to be in proximity to the succeeding trophoblast, otherwise there would be no interaction. The great advantage of this hypothesis is that it is testable, and with the help of Professor Stuart Campbell, of King's College Hospital, we are investigating whether trophoblastic remnants can be detected by ultrasound and whether the concentrations of human chorionic gonadotrophin (HCG) (measured by beta subunit assay), pregnancy-specific β_1-glycoprotein, and α-fetoprotein persist longer after some spontaneous abortions than after the birth of normal babies. Pastorfide *et al*[19] showed that HCG persists for about twice as long after therapeutic abortions as after normal vaginal delivery (22 days as opposed to 11) and attributed this to viable trophoblastic cells being left in the uterus after surgical intervention, since after term delivery there is a more complete removal of placental tissue.

Whatever the correct explanation our findings suggest that spontaneous abortions are more relevant to ASB and other abnormalities than has been thought. Because of the short IPG in many of the index cases it might be informative to determine whether the incidence of malformations is reduced when a subsequent pregnancy is delayed after a spontaneous abortion, especially if the HCG concentration is raised. There has been a pronounced fall in the birth rate, particularly in social classes IV and V, which is probably the result of family-planning campaigns. Additional advice could easily be given about procedure after a spontaneous abortion, and if this were done and our hypothesis is correct the incidence of ASB and probably other abnormalities would automatically fall.

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Creamatocrit: simple clinical technique for estimating fat concentration and energy value of human milk

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Summary and conclusions

A simple micromethod has been devised for estimating the fat and energy content of human milk based on the centrifugation of milk in a haematocrit centrifuge. The percentage of cream, or "creamatocrit," is read from the haematocrit capillary tube and is linearly related to the fat and energy content.

The technique, which is rapid and cheap, may be used in clinical practice, in research, and in epidemiological studies.

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Introduction

There has been increasing interest in human milk in the community, in special-care baby units, and in the Third World. Many of the methods for studying the composition of human milk, however, are lengthy, require technical skill, and often entail using special equipment or reagents. Such studies are therefore not practicable for many potential investigators.

An important variable in studies of breast milk is the fat concentration, which is the major determinant of the energy value. There is a need for a quick and simple micromethod for estimating milk fat and energy that may be used in the nursery, in the research laboratory, or in the field. Fleet and Linzell[1] described a method for estimating fat in goats' milk on very small samples by the microcentrifugation of milk in glass capillary tubes. Their preliminary data on other species suggested that this technique might be developed for use in man.

Materials and methods

For the present technique we used a haematocrit centrifuge (Hawksley, London), standard glass capillary tubes ($75 \times 1{\cdot}5$ mm outside diameter), and vernier callipers. From well-mixed samples of fresh untreated human milk approximately 75 µl was drawn by capillarity into the standard glass capillary tubes. These were then sealed at one end by means of a flame and centrifuged for 15 minutes at 12 000 *g*. To prevent the cream layer "setting" at an angle the