either test, may not have selected their patients on the basis of these values. Therefore, the patients we studied might not be comparable with those examined by these authors. In addition, we measured VIIIWF using formalin-treated and not freshly prepared washed platelets, although in the few cases in which VIIIWF was also assayed on platelets obtained as described by Kazatchkine *et al.*⁷ the values obtained did not differ from those reported in the table. Our data do not rule out the possibility that a low plasma VIIIWF level, if present, might contribute to the bleeding tendency of some patients with CRF. They do, however, also imply that a selective defect of VIIIWF is probably an uncommon finding in patients with CRF and abnormal bleeding time and platelet retention.

The practical implication of the results of Kazatchkine *et al.*,⁷ though not mentioned by them, is that factor VIII-rich preparations could be used in the management of the bleeding diathesis of patients with CRF undergoing haemodialysis. On the basis of our data, we would caution against any hasty generalising of such a therapeutic approach. Indeed, the cause of the bleeding tendency found in many patients with CRF is still to be established.

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Spina bifida and anencephaly: Are miscarriages a possible cause?

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Summary

The marriage-to-conception interval in 151 pregnancies producing infants with anencephaly or spina bifida was not significantly different from that in 218 pregnancies resulting in normal infants. Significantly more miscarriages occurred before than after the birth of 285 infants with anencephaly or spina bifida, but in 133 controls no before-after difference was observed.

These observations seem to favour the idea that miscarriages are a manifestation rather than a cause of anencephaly and spina bifida.

Introduction

The hypothesis that anencephaly and spina bifida (ASB) might be due to an interaction between twin fetuses or between a fetus and residual trophoblastic material from a previous normal

pregnancy was put forward by Clarke *et al.*¹ among others. They suggested that information from miscarriages might support such a hypothesis, and, combining the information from several investigations, including a large family study from South Wales,² they found more miscarriages before than after an ASB pregnancy, but the interval between miscarriage and the next pregnancy was no higher in cases of ASB than in other pregnancies. They thought that the former finding supported their hypothesis while the latter did not.

We examined the information on miscarriages in a large number of women not included in the analyses of Clarke *et al.* in the hope that it might throw further light on the subject.

Patients and methods

The obstetric histories of two series of women were reviewed. The first series consisted of 1087 women who attended the genetic advisory service in Cardiff between 1967 and 1976 for various problems. An accurate obstetric history was taken, which included details of all miscarriages. In respect of pregnancies resulting in either stillbirths or live births, the length of gestation or the date of the last menstrual period, the date of delivery, and any malformations present were recorded.

The second series comprised 867 women living in Glamorgan and Gwent who had a pregnancy resulting in an offspring with a major ASB malformation from January 1962 to December 1972 and who were subsequently visited and interviewed in their homes in 1968-74 as part of an investigation into possible causal factors. They included the mothers of all infants with ASB born within an area of about 20

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miles around Swansea and Caerphilly, these being the home bases of the two interviewers. Only a randomly selected proportion of those who were living further afield were visited and therefore included in this investigation. These patients had an accurate obstetric history taken including details of all their miscarriages. In respect of pregnancies resulting in stillbirths and live births, the length of gestation or the date of the last menstrual period, the date of delivery, and any malformations present were recorded.

The study of the interval between miscarriage and the beginning of the next pregnancy was carried out only when the interval could be estimated accurately to the nearest month by knowing the date of the miscarriage and the probable date of conception. Missed abortions were not included. In all, 100 suitable miscarriages where the subsequent pregnancy had resulted in a fetus with a major neural tube malformation and 110 where the subsequent pregnancy had ended in a normal fetus (as a control group) were extracted from the 867 obstetric histories of the women included in the spina bifida investigations. The corresponding numbers from the 1087 women who attended for genetic advice were 51 and 108. Fifty-nine miscarriages had to be excluded because of uncertainty about the time interval or the possibility of a "missed abortion."

To compare the number of miscarriages occurring immediately before and after a pregnancy which resulted in an infant with ASB and those occurring in control pregnancies only those obstetric histories where there was at least one recognised pregnancy before and one pregnancy after the index case were included. A total of 285 suitable pregnancies which ended in an infant with ASB were found among the patients who were part of the spina bifida aetiology investigation. A control group was selected from the 1087 who attended for genetic advice; only those who attended for counselling about a single gene defect, chromosome anomaly, multiple malformation, or some acquired condition were included. Those who attended for advice about ASB, repeated abortion, and infertility were specifically excluded. A total of 133 suitable pregnancies that satisfied these criteria were found.

Results

In both series there was no significant difference in the miscarriage-to-conception interval between the index cases and controls. The mean interval for all groups was 10 to 13 months (table I).

There were significantly more miscarriages before a pregnancy resulting in an infant with ASB (26%) than after (14%) ($P < 0.05$).

TABLE I—Miscarriage-to-conception interval in ASB and control pregnancies

Interval (months)	Cumulative frequency (%)	
	ASB pregnancies	Control pregnancies
<i>First series</i>		
	(n = 51)	(n = 108)
<3	12	10
<6	32	33
<12	62	65
<24	79	82
<36	100	100
Mean $\pm$ SD	12.7 $\pm$ 10.10	11.8 $\pm$ 9.8
<i>Second series</i>		
	(n = 100)	(n = 110)
<3	13	20
<6	38	44
<12	62	66
<24	87	89
<36	100	100
Mean $\pm$ SD	10.8 $\pm$ 8.9	11.9 $\pm$ 9.1

TABLE II—Miscarriages immediately before and after index pregnancies

Type of pregnancy	No of pregnancies	Miscarriages in relation to index pregnancy	
		No (%) before	No (%) after
ASB	285*	74 (26)	41 (14)
Control	133†	24 (18)	30 (22)

*From 867 obstetric histories. †From 393 obstetric histories.

There was no significant difference in the proportion of miscarriages before and after a normal pregnancy in the control group (table II).

Discussion

Our results confirm those of Clarke *et al*¹ that there are more miscarriages before than after a pregnancy that results in an infant with ASB. Our additional finding that this difference was not present among women giving birth to normal babies can be regarded as supporting the hypothesis that ASB might arise from an interaction between a fetus and residual trophoblastic material from a previous pregnancy. It might, however, also be regarded as a logical expectation of the hypothesis that the frequency of ASB is much higher than is usually supposed, the prevalence at birth tending to be much lower than the true incidence in early pregnancy because of a very high early mortality of affected embryos.³ In this case the observation of an increased abortion rate antedating the birth of infants with ASB (table II) may simply reflect the loss of malformed fetuses who also had an ASB. This explanation is simpler than the interactive hypothesis, and, unlike the latter, it is consonant with a growing body of evidence from human and animal studies. Ideally, however, both the hypotheses proffered would expect a higher frequency of miscarriages in the index group than in the control group, and this was not observed by Clarke *et al*¹ or by ourselves.

But the confirmation of the latter expectation is complicated by the fact that the number of miscarriages reported will be related to the number of conceptions that occur. Women who have given birth to an infant with ASB are more likely, as a group, to take steps to prevent further conceptions, in which case the after-pregnancy frequency of miscarriage among the index group may not be a fair reflection of the miscarriage pattern that would emerge from a completely unprotected post-coital series. On balance therefore, the results seem to give slight support to both hypotheses but do not help to discriminate between them.

The confirmation in our study that the interval between miscarriage and the next pregnancy was no greater in the case of pregnancies resulting in an infant with ASB than in the control series does not support the interaction hypothesis. This inference is based on the not unreasonable assumption that the process of interaction requires some time to develop and is not instantaneous. The observation that the interval was no greater—first reported by Clarke *et al* and now confirmed in two separate series by us—suggests that the processes of miscarriage or its sequelae, or both, are not directly implicated in causing ASB.

Considered jointly, the observation of a greater frequency of miscarriages before than after an ASB pregnancy and the fact that the miscarriage to next conception interval appears to be unrelated to outcome seem to favour the notion that miscarriages are a manifestation rather than a cause of ASB. This being so, our findings and those of Clarke *et al* are perhaps more likely to reflect a high incidence of ASB followed by high embryonic mortality rate in such cases, as suggested by Roberts and Lowe,³ than an interaction between residual trophoblastic and normal fetal material leading to ASB, as proposed by Clarke *et al*¹.

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