Obstetric and neonatal outcome in women with a history of recurrent miscarriage: a cohort study

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Obstetric and neonatal outcomes of women who had a history of recurrent miscarriage were compared with a control population from 1 January 1992 to 30 June 1998. Amongst a total of 162 pregnancies which progressed beyond 24 weeks gestation in women with a history of recurrent miscarriage, there were four perinatal deaths and 16 babies were admitted to the special care baby unit. The rates of preterm delivery (13%), small-for-gestational-age (13%), perinatal loss (2.5%) and Caesarean section (36%) were significantly ($P < 0.05$) higher than those of the control group (3.9, 2.1, 1 and 16.7% respectively). The ratio of male to female babies was equal. There was no significant difference in the incidence of hypertension or diabetes between the two groups. Patients with recurrent miscarriage represent a population at high risk of obstetric problems and close surveillance in the antenatal period is therefore required.

Key words: growth retardation/perinatal outcome/pre-eclampsia/recurrent miscarriage

Introduction

Recurrent miscarriage is generally defined as the loss of three or more consecutive pregnancies. It occurs in 0.5–3% of women (Daya, 1993; Tulppala et al., 1993; Katz and Kuller, 1994). Whilst the risk of miscarriage in a subsequent pregnancy has now been well documented (Quenby and Farquharson, 1993; Clifford et al., 1997), the obstetric and neonatal outcomes of pregnancy which progressed beyond 24 weeks in this group of women are still far from clear.

Reginald et al. (1987) examined 97 women who had had three or more miscarriages, and who had at least a singleton birth that had reached 28 weeks gestation. They found that the small-for-gestational-age rate (30%), preterm delivery rate (28%) and perinatal mortality rate (1.6%) were higher than expected. However, the underlying causes of recurrent miscarriage and the treatment, if any, of this group of women were not documented, and the results were not compared with a local obstetric population (control group).

In contrast, Hughes et al. (1991), who examined the obstetric outcome in 88 women with a past history of three or more consecutive pregnancy losses and compared the results with their local obstetric population (control group), found that rates for small-for-gestational-age infants (3.4%), preterm delivery (12.5%) and perinatal mortality (0%) were no different to the control group. As in the study of Reginald et al. (1987), the investigation and treatment of these subjects with recurrent miscarriage appeared incomplete, e.g. there was no mention of antiphospholipid syndrome and its treatment at all.

In a more recent study, Tulppala et al. (1993) conducted a prospective study of 63 women with a history of recurrent (≥3) spontaneous miscarriage, and presented the results of a detailed investigative protocol, including antiphospholipid syndrome, in the population studies. The obstetric outcomes of 32 deliveries were analysed. The authors found that the rates for growth retardation (20%), preterm delivery (9.7%) and impaired glucose tolerance (22.8%) appeared to be increased. Unfortunately, the results were not compared with any control population, partly because the small number of deliveries in the study did not leave much room for formal statistical analysis.

It seems, therefore, that the currently available literature on the obstetrics and neonatal outcome of pregnancies from women with a history of recurrent miscarriage shows inconsistent results, partly because of small numbers in the studies reported, and partly because of a lack of an appropriately chosen controlled population. In this study we compared the obstetric and neonatal outcome of 162 pregnancies which progressed to beyond 24 weeks in a group of women with a history of recurrent (≥3) miscarriages who completed a thorough investigative protocol, with that of a local control population over the same period.

Materials and methods

Patients attending the recurrent miscarriage clinic at the Jessop Hospital for Women between 1 January 1992 and 30 June 1998 were included in the study. The hospital numbers of these patients were identified and the hospital computer system was then checked to see if there had been an antenatal or labour ward admission after 24 weeks gestation from the hospital register. If there had been an admission, the case notes were retrieved and information obtained. The following data were collected: the diagnostic category of recurrent miscarriage (≥3), obstetric outcomes, including small-for-gestational-age rate, preterm delivery rate and perinatal mortality rate, were compared with those of the local obstetric population (control group).
miscarriage (if known), maternal age, occurrence of hypertension, diabetes, gestational age at delivery, mode of delivery, sex of the baby, birth weight and admission to the special care baby unit. If there was an admission to the special care baby unit, the paediatric notes were obtained to determine the reason for admission and subsequent events.

These women underwent investigations according to an established protocol (Li, 1998) including chromosomal analysis of both partners, pelvic ultrasonography, hysterosalpingogram, thyroid function test, prolactin, day 5 follicle stimulating hormone and luteinizing hormone (LH), day 21 progesterone, autoantibody screen, and a comprehensive coagulation study. The latter included lupus anticoagulant, antiphospholipid antibodies (IgG and IgM), and screening for prothrombotic states including antithrombin III deficiency, activated protein C (APC) resistance, thrombocytopenia, protein C and protein S deficiency. The coagulation study was performed in the Haematology Laboratory at the Royal Hallamshire Hospital under the direction of Professor E. Preston. Many of the subjects also had an endometrial biopsy obtained in the mid-luteal phase, timed according to the LH surge, for histological dating according to the criteria of Noyes et al. (1950).

Twenty two women who had a prothrombotic state or fulfilled the criteria for antiphospholipid syndrome were treated with low dose (75 mg/day) aspirin and subcutaneous heparin or clexane. Uterine septum and adhesions were present in five subjects and were removed hysteroscopically. One patient who had a bi-cornuate uterus had Straussman’s metroplasty. Fifteen women with oligomenorrhoea prior to conception had luteal support in the form of i.m. HCG injections (Quenby and Farquharson, 1993) at a dose of 10 000 IU per week as soon as pregnancy was confirmed up to 12 weeks gestation. Three patients had laparoscopic ovarian drilling for polycystic ovarian disease. One patient received thyroxine treatment. Eight women had ovarian stimulation by HMG for luteal phase defect. None of the subjects received immunotherapy or steroid treatment prior to 24 weeks gestation.

The control population consisted of all deliveries in this hospital between 1 January 1992 and 30 June 1998. Information about the control population was obtained from the hospital database. For each woman in the control group, the following outcome data were collected: occurrence of hypertension, diabetes, gestational age at delivery, mode of delivery, birth weight and perinatal mortality rate. Comparison between the study and the control group was made using the χ²-test.

A diagnostic category of ‘unknown’ implied that the patient did not complete her investigations before becoming pregnant. Unexplained recurrent miscarriage was diagnosed when all investigations were normal and no associated factor for the condition was found. Polycystic ovarian disease was defined when transvaginal ultrasonography showed typical features of the condition, i.e. multiple (>10) small (6–8 mm) follicles arranged in the periphery of the ovary with evidence of stromal hypertrophy, in addition to elevated LH:FSH ratio (>2) in the early follicular phase (days 2–5 of the menstrual cycle). Prothrombotic state was defined as persistently raised levels of antiphospholipid antibodies, or testing positive for lupus anticoagulant on at least two occasions, or deficiency of protein C, protein S or antithrombin III. Small-for-gestational-age was defined as birth weight less than 2 standard deviations below the mean for that particular gestation according to growth and development record charts (Keen and Pearse, 1988). Hypertension was defined as a diastolic blood pressure of >90 mmHg on two consecutive occasions taken at least 4 h apart. Diabetes was defined according the World Health Organization criteria of fasting venous plasma glucose level >9 mmol/l or a 2 h level of >11 mmol/l after ingestion of 75 g of oral glucose. Preterm delivery was defined as the number of babies born before 37 completed weeks of gestation. Neonatal death was defined as the death of a baby within 28 days following birth. Stillbirth was defined as the number of babies born after 24 completed weeks of gestation without signs of life. Perinatal death rate was defined as the number of stillbirths and neonatal deaths expressed as a percentage of all deliveries.

### Results

Between 1 January 1992 and 30 June 1998, 290 patients with recurrent (≥3) miscarriage attended our miscarriage clinic, of whom 256 (88.3%) conceived again. Among the 256 subjects who conceived 178 (69.5%) had at least one singleton pregnancy which progressed to beyond 24 weeks gestation and delivered during the study period. For the purpose of this study, only the first singleton pregnancy which progressed to beyond 24 weeks among these 178 subjects was included. A total of 162 (91%) case notes were successfully retrieved. All these patients had their deliveries at the Jessop Hospital for Women. There were only 16 patients whose obstetric case notes were not retrieved. All these patients had their deliveries at surrounding district general hospitals from which they were originally referred. Table I shows the diagnostic categories of recurrent miscarriage in the study population.

The mean (+SD) age at conception was 32.0 (+ 5.4) years. The mean number of miscarriages was 3.4 (range 3–10). Ninety-five (59%) women had never had a live birth (primary miscarriage); whereas the remaining 67 (41%) women had had at least one live birth (secondary miscarriage). The mean (+SD) parity was 0.6 (+0.8). The incidence of diabetes was 1.7% and the incidence of hypertensive-related disorders was 7.3% (0.6% essential hypertension, 6.7% pregnancy-induced hypertension or pre-eclampsia). The preterm delivery rate was 13.3%. A total of 49% of the babies was female whereas 51% of the babies were male. Sixteen (9.9%) babies were admitted to the special care baby unit, of which 10 were due to complications related to prematurity. There were four perinatal deaths. Two babies died at 25 weeks and 26 weeks respectively due to prematurity and there were two intrauterine deaths at 25 weeks and 28 weeks respectively. The perinatal death rate was 2.5%.

Sixty subjects (36%) had a delivery by Caesarean section; half of these patients had an emergency Caesarean section. The indications for the emergency and elective Caesarean

| Table 1. The diagnostic categories of recurrent miscarriage in the study population (n = 162) |
|---------------------------------|---------|-------|
| Diagnosis                      | n       | %     |
| Unknown                        | 45      | 28    |
| Unexplained                    | 61      | 38    |
| Prothrombotic state            | 22      | 13.5  |
| Structural uterine abnormality | 12      | 7     |
| Endocrine factors¹             | 22      | 13.5  |
| Chromosomal anomalies          | 0       | 0     |

¹Endocrine factors include abnormal thyroid function, luteal phase insufficiency resulting in suboptimal endometrial development, polycystic ovarian syndrome and hypersecretion of LH.
sections are shown in Table II. Eight out of the 30 patients in the emergency Caesarean section group delivered preterm (28–36 weeks) whereas in the elective Caesarean section group, two babies were delivered at 35 weeks and one baby was delivered at 36 weeks, both related to growth retardation. The rest were delivered at term. Eighty-one women (50%) had a normal vaginal delivery whereas 23 (14%) had an instrumental delivery.

**Control population**

Between 1 January 1992 and 30 June 1998, there were a total of 24 699 deliveries from singleton pregnancies (multiple pregnancies were excluded from the analysis). The mean (±SD) age of the control population was 28.3 ± 5.4 years. The mean (±SD) parity was 0.8 ± 1.1 years. The incidence of hypertensive-related problems in these women was 2643 (10.7%) and that of diabetes was 198 (0.8%). The perinatal mortality rate for the control population was 1.0%. The overall Caesarean section rate was 16.7%. The total Caesarean section rate increased steadily from 12.4% in 1992 to 22.9% in 1998. In addition, the normal vaginal delivery rate decreased steadily from 72.0% in 1992 to 60.8% in 1998.

The obstetric and neonatal outcomes in women with a history of recurrent miscarriage are compared with the control population in Table III. There was a significantly higher rate of preterm delivery, small-for-gestational-age babies, perinatal mortality and Caesarean section and a significantly lower rate of normal vaginal delivery rate in the recurrent miscarriage group. The rates of diabetes and hypertension were not significantly different between the recurrent miscarriage and the control populations.

Further analysis of the results of subgroups of women with recurrent miscarriage, including: (i) primary miscarriage group, i.e. women who never had a live birth; (ii) secondary miscarriage group, i.e. women who had at least one live birth; and (iii) unexplained miscarriage group, i.e. women in whom all investigations according to our investigative protocol appeared normal, are also shown in Table III. Whilst the numbers in each group were relatively small to permit meaningful statistical analysis, the results appear to be similar to the whole group (n = 162), except that the primary miscarriage group appeared to have a higher preterm delivery rate (18%) than the secondary miscarriage group (7.7%).

**Discussion**

In this study, we examined the obstetric and neonatal outcome of 162 pregnancies which progressed to beyond 24 weeks in a cohort of women with recurrent (≥3) miscarriages, and compared the results to a local, control obstetric population who had deliveries during the study period. We found that the preterm delivery, small-for-gestational-age, Caesarean section and perinatal mortality rates in women with recurrent miscarriages were higher than those of the control population, although there were no differences in the rates of hypertensive disorders and diabetes between the two groups.

Whilst two previous studies reported an increased incidence of impaired glucose tolerance (17.0%, Hughes et al., 1991; 22.8%, Tulpala et al., 1993), we were unable to confirm such a finding in our study. Although impaired glucose tolerance may be associated with polycystic ovarian disease (Barbieri et al., 1988) which in turn is associated with recurrent pregnancy loss, another possible explanation put forward by Hughes et al. (1991) of the increased incidence of impaired glucose intolerance is simply a result of observational bias, i.e. with increased surveillance of women with a history of repeated pregnancy loss.

In a previous study, Hughes et al. (1991) found that the incidence of chronic hypertension among women with a history of recurrent miscarriage (3.4%) was higher than the control group (0.4%), whereas the incidence of pre-eclampsia appeared to be similar in both groups (2.3 and 2.6% respectively). In our study, we found no difference in the incidence of chronic hypertension and pre-eclampsia between the two groups. Seidman et al. (1989) found that whilst an abortion reduced the incidence of pre-eclampsia in a subsequent pregnancy, spontaneous miscarriage did not appear to offer any protection against pre-eclampsia in a subsequent pregnancy.

While our study suggested that women with recurrent miscarriage had an increased risk of preterm delivery, small-for-gestational-age, Caesarean section and perinatal mortality, it should be recognised that recurrent miscarriage is a heterogeneous condition with several underlying causes. It would be of interest to analyse the results according to different causes of recurrent miscarriage to determine if the outcomes differ according to different subgroups. However, the number in our current study is too small to permit analysis according to these subgroups, with the exception of a subgroup of women with apparently unexplained recurrent miscarriages (n = 61). The results appeared very similar to the whole group, except that the perinatal mortality was lower (1.6%), but the number is too small for any formal statistical analysis or firm conclusion to be made.

The association between low birth weight and the number of previous miscarriage(s) was examined by Alberman et al. (1980). The authors conducted a survey of pregnancies among 3502 women doctors and found that the mean birth weights of babies following two or three spontaneous miscarriages (3114 g and 3031 g respectively) were significantly lower than those following one miscarriage (3398 g) or a successful first pregnancy not preceded by any miscarriage (3324 g). They concluded that, in the subgroup of women with repeated early
A potential bias in our study is the inclusion of only 162 of 178 (91%) pregnancies identified. The remaining 16 (9%) of pregnancies were delivered in adjacent district general hospitals. We had considered the inclusion of these 16 subjects, but as the control group consisted of the local obstetric population, we felt it more appropriate not to include this small number of subjects so that both the study and control population were based on the local obstetric population. These 16 pregnancies are expected to exhibit a low rate of preterm delivery and small-for-gestational-age delivery since the women had been admitted for delivery in district general hospitals. As this subset constitutes only a small proportion of the total number of deliveries examined, the overall results are not expected to change.

Another potential bias in our study relates to the effect of age and parity on the results of obstetric and neonatal outcome. Whilst we compared the results of women with recurrent miscarriage to a local, obstetric population, we have not corrected for the potential impact of age and parity on the outcome. In our study, women with a history of recurrent pregnancy loss were slightly older (mean age 32.0 years) and of lower parity (mean 0.6) than the control population (mean age 28.3 years and mean parity 0.8), although the differences were small. It seems, therefore, that the bias in this respect is unlikely to be significant. On the other hand, to analyse the impact of parity on the results, we divided women with recurrent miscarriage into two groups: primary, i.e. nulliparous, and secondary, i.e. parous subjects. As expected, women with primary recurrent miscarriage appeared to have a higher incidence of pregnancy-induced hypertension (8.4%) than those with secondary miscarriage (6.6%), and the preterm delivery rate (18%) in the primary miscarriage group was more than double that of the secondary miscarriage group (7.7%). There were no other significant differences between the two groups. However, in future studies, the control population should ideally consist of subjects’ age and parity matched for the study population.

In a previous analysis of 160 women with recurrent miscarriage from our centre, the prevalence of abnormal paternal karyotype was 2.5% (Li, 1998). In this report, it appeared none of the pregnancies which progressed to beyond 24 weeks gestation belonged to this group of subjects, although there were at least four pregnancies in the group which miscarried in the first trimester. It is well recognized that pregnancy failure associated with abnormal karyotypes very often occurs early on in the first trimester.

To conclude, the pregnancy of women with a history of recurrent miscarriage is not associated with an increased risk of hypertension or diabetes. However, it is associated with a higher incidence of small-for-gestational-age babies, preterm delivery, Caesarean section rate and perinatal loss. Therefore, patients with recurrent miscarriage represent a population at high risk of obstetric problems and close surveillance during the antenatal period is required.

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