

Perinatal and obstetric outcomes of donor insemination using cryopreserved semen in Victoria, Australia

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This study compared the perinatal and obstetric outcomes of 1552 donor insemination pregnancies in Victoria, Australia, with a control group of 7717 normally conceived pregnancies from the general population. Data on the outcomes of pregnancies of at least 20 weeks gestation, for both groups, were obtained from the same population-based birth registry. The study showed that there were no significant differences between the donor insemination and control groups in the incidence of preterm birth, low birthweight, multiple birth, perinatal death and birth defects, or in the sex ratio. Pregnancies conceived by donor insemination were significantly more likely than controls to have an induced labour (OR = 1.6, 95% CI 1.4–1.8), a forceps delivery (OR = 1.5, 95% CI 1.3–1.8) and/or a Caesarean section (OR = 1.6, 95% CI 1.4–1.9) and to develop pre-eclampsia (OR = 1.4, 95% CI 1.2–1.8) after adjusting for maternal age, multiple birth, parity and presentation. Reasons for the higher rate of induced and operative deliveries are not clear. Overall, the study's findings are reassuring for couples considering infertility treatment with donor insemination. The study illustrates the importance of complete follow-up in studies of pregnancy outcomes after assisted conception and the use of appropriate population-based control groups with comparable ascertainment of outcomes.

Key words: birth defects/donor insemination/follow-up/pregnancy outcomes

Introduction

Donor insemination (DI) has been widely used as a treatment for couples with a diagnosis of male infertility. It has been in longer use than any other assisted reproduction technique (Critser, 1995). Until recently, most studies describing the pregnancy outcomes of DI have been based on descriptive analyses of relatively small series of DI pregnancies (Chong and Taylor, 1975; Dixon and Buttram, 1976; Glezerman, 1981; Clayton and Kovacs, 1982; Amuzu and Shapiro, 1993).

Common problems and potential sources of bias in studies of pregnancy outcomes after DI and other assisted conception treatments include incomplete follow-up of pregnancies, a lack of statistical power with small study populations, reliance on self-reported data without medical record validation, and a lack of appropriate comparison groups. Factors contributing to the inadequacy of follow-up may include the perception that families who have children resulting from DI will be reluctant to participate in such studies and the difficulties in achieving follow-up when clinics providing DI treatment do not provide the patients' obstetric care (Amuzu *et al.*, 1990).

Only a few studies have compared the perinatal or obstetric outcomes of DI with a control group. The outcomes of 470 DI pregnancies have been compared with a series of hospital controls matched for parity and maternal age and with national births survey data (Grefenstette *et al.*, 1990). Higher rates of multiple pregnancy, preterm birth and delivery by Caesarean section were found after DI. Data on the outcomes of an increasingly large series of DI pregnancies have been collected prospectively by the French CECOS Federation for >10 years (Mattei and Le Marec, 1983; Thepot *et al.*, 1996; Lansac *et al.*, 1997). In the most recent publication (Lansac *et al.*, 1997), 21 132 DI pregnancies with known outcomes were reported. A sub-sample of 8943 single pregnancies were compared with data from a sample of 13 631 births from a French national register. The authors concluded that DI singleton births were no more likely to be low birthweight, preterm or stillborn than births in the general population. The high multiple birth rate of 8.0% reflected the use of ovulation induction in the treatment of 77.4% of those women who became pregnant with DI. The selection criteria for the sub-sample of DI births were not described. It is not clear how representative the French national registry data were of all births in the regions covered or whether adverse pregnancy outcomes, including congenital abnormalities, were ascertained equally in the DI and control populations.

Studies describing the prevalence of birth defects after DI have given variable results (Dixon and Buttram, 1976; Mattei and Le Marec, 1983; Virro and Shewchuk, 1984; Forse *et al.*, 1985; Amuzu *et al.*, 1990). The problems of small study populations, the lack of appropriate comparison groups and, in some instances, a failure to adjust for maternal age have made interpretation of these findings on relatively rare outcomes particularly difficult. The CECOS group has accrued data on the largest number of DI pregnancies with good follow-up. The prevalence of congenital abnormalities was 1.7% in 18 128 children at birth and 90 pregnancies terminated because of the presence of an abnormality (Lansac *et al.*, 1997). The authors concluded that the prevalence was no different from that in

the general population. The main difficulty in interpreting these findings comes from the comparison with regional birth registries where the quality of data and ascertainment of birth defects for the general population was likely to have been poorer than for the DI births (Thepot *et al.*, 1996).

Two studies have described a higher than expected incidence of pre-eclampsia in pregnancies conceived by donor insemination. In a large study of 584 Australian DI pregnancies (Need *et al.*, 1983), pre-eclampsia was found to be more common than expected from general population estimates, especially in multiparous women. Differences in the way pre-eclampsia was defined and measured in the DI group compared with the general population made the size of the effect difficult to assess. Pre-eclampsia was significantly more common in a small group of 37 DI patients than in 44 patients who had artificial insemination with partner spermatozoa (Smith *et al.*, 1997). The findings from these studies were interpreted as consistent with an immunological basis of pre-eclampsia: the idea that repeated exposure to sperm antigens prior to a pregnancy with that partner offers protection against pre-eclampsia.

Our study was prompted by an apparent increase in the incidence of perinatal death in the DI pregnancies conceived at two clinics in Victoria, Australia. Prior to this study, the clinics relied on women to report their pregnancy outcomes or data were collected by clinic staff who contacted women after the expected delivery date. Follow-up was known to be incomplete for women who were hard to trace and adverse perinatal outcomes were not usually verified with medical records. This study aimed to provide a more complete follow-up of DI pregnancies using data from the State's population-based births register and to compare DI outcomes with an appropriate comparison group selected from the same register.

Materials and methods

Study population

DI pregnancies from two major infertility clinics in Victoria, Australia, were identified from clinic records. The pregnancies were selected from all DI conceptions achieved from 1982 to 1995. Pregnancies known to have resulted in a loss prior to 20 weeks gestation were excluded. The outcomes of pregnancies of at least 20 weeks gestation were determined by record-linkage with the State's population-based births registry held at the Perinatal Data Collection Unit (PDCU).

Five normally conceived controls were randomly selected for each DI birth from the PDCU database and matched on year of birth of the infant. Multiple births were identified and all babies of twin and triplet pregnancies were included in the controls, as they were for the DI births. DI births that appeared in the random selection of controls were identified and excluded. The ratio of one DI to five control births was maintained after these inclusions and exclusions.

Data sources

The Health Act in Victoria mandates that all births must be reported to the PDCU. The PDCU was established in 1982 to collect, analyse and monitor the information contained in these reports. The information collected is maintained in two databases, the first contains data reported by the midwife attending the birth and includes a large number of variables relating to the mother and the obstetric

Table I. Donor insemination (DI) and control groups

	DI		Controls	
	<i>n</i>	%	<i>n</i>	%
Number of pregnancies	1552		7717	
Number of births	1602		7923	
Singletons	1503	96.84	7516	97.40
Twins (sets)	47	3.03	197	2.55
Triplets (sets)	2	0.13	4	0.05

and perinatal outcomes. The second database is the Congenital Malformations Register (CMR), which contains reports of congenital malformations apparent at birth or later in childhood from a voluntary network of laboratories and health professionals and is continually updated. Validation studies have shown that ascertainment of chromosomal anomalies was very high in the period covered by this study: >90% in 1982–1985 (Lumley *et al.*, 1988) and 100% in 1989–1992 (Kilkenny *et al.*, 1995). Ascertainment of other groups of birth defects was less complete but was not expected to differ between the DI and control groups.

Record linkage

Record linkage of DI pregnancies with the PDCU was carried out manually. A successful match was based on a match of three or more of the following data items: surname and first name of the mother, maternal date of birth, infant date of birth, sex of infant and expected date of delivery (with matched gestation). Additional data items could be used to confirm a match when one of these variables was missing, including birthweight, gestation, hospital of birth or residential postcode. For each successful match, data were abstracted from the birth notification data and the CMR. All data were de-identified following record linkage.

Statistical analysis

Power calculations using EpiInfo 6.0 indicated that the sample size available gave the study 80% power (with 0.05 level of significance) to detect the following increases in relative risk (RR): low birthweight RR = 1.4, preterm birth RR = 1.4, total birth defects RR = 1.5, perinatal mortality RR = 2.0, and Caesarean section RR = 1.2.

Analyses were performed using the statistical package SPSS for Windows (version 6.1, 1994, SPSS Inc., Chicago, Illinois). Where univariate analyses showed a difference between DI births and controls, logistic regression was used to derive an adjusted odds ratio (OR) and 95% confidence interval (95% CI) to account for the contribution of relevant independent variables that were probable predictors of the outcome.

Calculations for perinatal outcomes included all infants, while those for obstetric factors and demographic information included records for all singleton births and the first born infant in multiple births.

Results

The analyses were based on 1552 DI pregnancies where the outcome was identified in the PDCU data (96.9% of the identified pregnancies) and 7717 controls. The proportions of multiple births are shown in Table I. Ovulation induction was used in 23.8% of the DI cycles and was associated with a six-fold significant increase in the incidence of multiple births compared with DI pregnancies conceived without ovulation induction (RR = 6.0, 95% CI 3.4–10.7).

Table II. Maternal characteristics

	DI cohort		Controls		RR	95% CI
	<i>n</i>	%	<i>n</i>	%		
Married/de facto	1537	99.0	6956	90.1	1.1	1.09–1.11
≥35 years	248	16.0	777	10.0	1.6	1.4–1.8
First pregnancy	685	44.1	2451	31.8	1.4	1.3–1.5
First birth	828	53.4	3127	40.5	1.3	1.3–1.4
Previous perinatal death	45	2.9	197	2.6	1.1	0.8–1.6

RR = relative risk, CI = confidence interval, DI = donor insemination.

Table III. Perinatal outcomes

	DI cohort		Controls		RR	95% CI
	<i>n</i>	%	<i>n</i>	%		
Male infant	846	52.8	4060	51.2	1.1	1.0–1.2
Multiple birth	49	3.1	201	2.7	1.2	0.9–1.7
Preterm (<37 weeks)	103	6.4	527	6.6	1.0	0.8–1.2
Low birthweight (<2500 g)	117	7.3	537	6.8	1.1	0.9–1.3
Birth defect	57	3.6	253	3.2	1.1	0.8–1.5
Perinatal death	20	1.2	84	1.1	1.4	0.8–2.0
Stillborn	14	0.9	46	0.6	1.5	0.9–2.3
Neonatal death	6	0.4	38	0.5	0.8	0.3–1.8

Characteristics of the DI and control groups relating to the mother and the infant are compared in Tables II and III with crude relative risk estimates.

Maternal characteristics

Women giving birth following DI treatment were significantly older and more likely to be married or in a de-facto (living as married) relationship than women in the control group. There were more first pregnancies and births in the DI group than in the control group. There was no significant difference between the two groups in maternal history of prior perinatal death.

Perinatal outcomes

There was no significant difference in the sex ratio between DI and control births, nor did the overall prevalence of multiple births differ significantly between the two groups. DI births did not differ from controls in their incidence of preterm birth, low birthweight and perinatal deaths.

The overall prevalence of birth defects did not differ significantly between the DI and control births (Table III). The observation of a higher number of chromosomal abnormalities in the group of DI births, however, prompted further analysis of this sub-group of birth defects. The chromosomal abnormalities identified in each group are listed in Table IV. For the DI births, all the chromosomal abnormalities were aneuploidies (additional or deleted chromosomes). Two were sex chromosome aneuploidies, not usually detected at birth or in early childhood, that had been detected by prenatal diagnosis. For the controls, 11 were chromosomal aneuploidies and three were other chromosomal abnormalities with no additional genetic material. The odds ratio for the autosomal trisomies, which can be ascertained at birth quite readily, was 2.7 (95%

Table IV. Chromosomal abnormalities

	DI births	Control births
Trisomy 13	1	
Trisomy 18	1	
Trisomy 21	3	9
47XXY	1 ^a	
45XO		1
47XYY	1 ^b	
De-novo unbalanced translocation		3 ^c
Total (%) ^d	7 (0.4)	13 (0.2)

^aAscertained by prenatal diagnosis (mother 42 years) and pregnancy terminated at 20 weeks.

^bAscertained by prenatal diagnosis (mother 36 years) – baby born at term.

^cTwo ascertained by prenatal diagnosis (one advanced maternal age and one fetal abnormality on ultrasound) and one baby tested because of dysmorphic features in first year of life.

^dPercentage calculated from total number of births.

CI 0.9–8.2), adjusted for maternal age. All other observed differences were not statistically significant.

Obstetric outcomes

Univariate analyses showed no significant differences between the groups except for type of labour, method of delivery and the incidence of pre-eclampsia. Women who were pregnant as a result of DI treatment were significantly more likely to have an operative delivery or induced labour than women in the control group. The risk was significantly increased after adjusting for maternal age, parity, multiple birth and presentation (Table V). Although Caesarean section was more common in DI births, the proportion of Caesarean sections that were elective was similar to that in the control group (54.1% of DI Caesarean sections compared to 55.5% of the controls).

Pre-eclampsia was defined by the ICD-9 codes for severe

Table V. Obstetric outcomes

	DI cohort		Controls		Adjusted OR ^a	95% CI
	<i>n</i>	%	<i>n</i>	%		
Induced labour	447	28.8	1642	21.3	1.6	1.4–1.8
Forceps delivery	322	20.7	1110	14.4	1.5	1.3–1.8
Caesarean section	355	22.9	1268	16.4	1.6	1.4–1.9
Pre-eclampsia	131	8.4	399	5.2	1.4 ^b	1.2–1.8

^aAdjusted for maternal age, parity, multiple birth and presentation.^bAdjusted for maternal age and parity.

OR = odds ratio.

and unspecified pre-eclampsia and excluded those cases where pre-eclampsia was recorded as transient or due to pre-existing causes. Women in the DI group were significantly more likely to suffer from pre-eclampsia than women in the control group. The difference remained after adjusting for maternal age and parity (Table V).

Discussion

This study has described the obstetric and perinatal outcomes of pregnancies resulting from donor insemination. The strength of the study lies in the completeness of follow-up, size of the study population and comparison with appropriate population-based control data. Only 3% of DI births to women believed to be resident in Victoria, and whose births were expected to be notified to the State's perinatal data collection, were lost to follow-up. Reasons for loss to follow-up could have included change of residence to another State, notification of the birth under a different last name than that used by the woman when attending the DI clinic, or a pregnancy loss before 20 weeks gestation that was not notified to the clinic.

The method of record-linkage with the State's population-based births register gave more complete outcomes data than the clinics had been able to obtain by making contact with patients and care providers directly. However, there were discrepancies between clinic records and PDCU data in the recording of perinatal deaths that showed that the clinic had more complete information. Six perinatal deaths at 20–22 weeks gestation were notified to the clinic but did not appear in the PDCU database. Although it is a legal requirement for all births in Victoria of at least 20 weeks gestation or 400 g birthweight to be registered, the inclusion of births into the PDCU database is known to be incomplete for births at 20–22 weeks during some of the study period, and we would expect similarly incomplete data for both the control group and the DI group.

Women who conceived as a result of DI were significantly older than women in the control group. This was to be expected, because women tend not to commence treatment until after diagnosis of infertility following unsuccessful attempts to become pregnant. During the 1980s there was also a waiting list for treatment of up to 12 months duration. Women in the DI group were also significantly more likely to be married than the controls, a reflection of the legal requirement in Victoria for couples undergoing DI to be married.

The study showed that DI was not associated with any significant difference in the incidence of preterm birth, low birthweight and perinatal mortality compared with the general population. These findings are reassuring. The sex ratio of DI births did not differ significantly from the controls. Reports (Alfredson, 1984; Amuzu *et al.*, 1990) that DI is associated with a reduced proportion of male infants were not supported in this study. Multiple pregnancy was more common in the DI group than in the controls, though not significantly so, and reflected the restricted use of ovulation induction only for the treatment of women who had irregular cycles.

There were no significant differences between the DI and control groups in the overall prevalence of birth defects. The study does not, however, include malformation data from pregnancies lost prior to 20 weeks gestation for DI births or controls. Although the overall prevalence of birth defects was no different between the two groups, the higher prevalence of chromosomal aneuploidies in the DI group warrants further investigation and needs confirmation in other large studies. Validation of the CMR has shown that the reporting rate of chromosomal anomalies is very high. Differences in the reporting of birth defects between the DI and control groups is therefore unlikely to account for the increased prevalence of chromosomal aneuploidies in the DI births. This finding has to be interpreted cautiously, however, because of the very small number of affected pregnancies and the possibility that a greater use of prenatal testing in the DI group might explain the finding, since the sex chromosome aneuploidies found in the DI group were detected through prenatal testing. The importance of using the same definitions of birth defects and the same methods of ascertainment when comparing pregnancy outcomes after assisted conception with a control group have been highlighted recently in the controversy about the incidence of abnormalities in children conceived by intracytoplasmic sperm injection (Bonduelle *et al.*, 1997; Kurinczuk and Bower, 1997).

This study found significant differences between the amount of obstetric intervention in both labour and delivery for DI births. Adjusted odds ratios demonstrated this for Caesarean section, forceps delivery and induced labour. An increase in the proportion of deliveries by Caesarean section has been reported previously (Grefenstette *et al.*, 1990). The reasons for these differences are unclear. A possible explanation is the difference between obstetric practice in the private and public sector but data on health insurance status are not collected by

the PDCU. It is also possible that pregnancies conceived following assisted conception are perceived to be more 'precious'. This may result in the belief by some women and/or their obstetricians that a lower threshold for intervention is appropriate. We do not know in what percentage of cases did the obstetrician know that the conception was following DI. Several studies (Tan *et al.*, 1992; Venn and Lumley, 1993; Reubinoff *et al.*, 1997) have shown that Caesarean section is significantly more common in pregnancies following a period of infertility or IVF treatment. The increased rate has not been readily explained by maternal characteristics or obstetric complications. Women's views of the method of delivery, and those of their caregivers, have not yet been explored in studies of pregnancy outcomes after assisted conception.

The amount of obstetric intervention may, in part, reflect the increased incidence of pre-eclampsia found in the DI pregnancies. Misclassification of pre-eclampsia and eclampsia reported to the PDCU has been described (Riley and Halliday, 1998) but is likely to have occurred to a similar extent in the DI and control pregnancies.

Pre-eclampsia is a common and serious complication of pregnancy that has been shown to be more common in first than in subsequent pregnancies. Subsequent pregnancies with a change in paternity, however, have a similar risk to first pregnancies. The duration of exposure to sperm antigens has been associated with the risk of pre-eclampsia in some studies (Clark, 1994; Robillard *et al.*, 1994); repeated exposure having a protective effect. Protection appears to be reduced when barrier methods of contraception are used. This immunological model of the relationship between exposure to sperm antigens and the risk of pre-eclampsia predicts that DI patients would be at an increased risk. Further studies of pre-eclampsia in pregnancies conceived by DI or oocyte donation may contribute to our understanding of the mechanisms underlying this condition.

The results of this study will be reassuring to the many couples considering DI as an option for their infertility, to the clinics offering DI and to those who provide antenatal care to women who have conceived as a result of DI. Thorough follow-up of the outcomes of pregnancies conceived by reproductive technologies is an ongoing responsibility of those offering infertility treatment. To obtain meaningful outcomes data, studies should be mindful of the importance of size of the study population, completeness of follow-up, comparison with appropriate control groups and appropriate statistical analyses to account for differences in maternal characteristics.

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