

# Follow-up studies of children born after frozen sperm donation

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The need to assess the health of children born after assisted reproductive technologies (ART) using frozen donor spermatozoa has been a major concern for the last decade. Most available published studies are confusing (since they are retrospective) and refer to small numbers of cases or involve a bias. Two prospective and large population-based studies have been published, one in France and the other in Australia. The general characteristics of children born after ART using frozen spermatozoa was unchanged in comparison with the general population (weight, prematurity, stillbirths, sex ratio). However, the rate of multiple pregnancy was increased, first in artificial insemination with donor semen (AID), where the use of hormonal treatment may be too heavily prescribed, and second in IVF with donor semen (IVF/D) where both the ovulation induction treatments and embryo transfer policy increase the rate of multiple pregnancies. As far as birth defects or chromosomal abnormalities are concerned, no difference has been observed from the general population. Finally, the use of frozen spermatozoa does not seem to affect the health of children conceived by AID or IVF/D. The psychosocial development of such infants is not as well known because of the confidentiality in many countries concerning sperm donation. However, the available information on the psychosocial development of these children up to the age of 8–10 years appears to be reassuring. Larger and longer studies are needed to answer such questions, particularly with regard to adulthood.

*Key words:* ART with donor semen/health of children/IVF with donor semen/pregnancy/psychosocial development

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## Introduction

Artificial insemination with donor semen (AID) is used worldwide to treat couples with azoospermia or severe male factor infertility in families carrying genetic diseases which may be transmitted by the husband's spermatozoa and, in some countries, to treat single women. In 1987, more than 170 000 women were treated in the USA (Critser, 1998) ~3000 couples are treated each year in the UK (Human Fertilisation and Embryology Authority, 1994) and since 1973 nearly 50 000 children have been born after AID in France (Hennebicq and Thépot, 2000).

The need to assess the health of children born after assisted reproductive technologies (ART) using frozen donor spermatozoa has been a major concern for the last decade. Several points

needed to be answered with large population studies: (i) using frozen spermatozoa might have some adverse effects on the children; (ii) the choice of assisted reproductive technology (AID or IVF with donor spermatozoa) needs to take into account the respective risks of each procedure; (iii) if pregnancy is achieved, it is necessary to be aware of all the possible problems (including psychological development), so that correct care may be taken to prevent or to screen low risk couples and donors for any eventual complications; and (iv) before employing these techniques, the risks to the child must be evaluated and these risks should be explained to the couples requesting AID.

Most published studies are confusing, since they are retrospective and refer to small numbers of cases or involve a bias (Swaab, 1974; Matsuoka *et al.*, 1979; Kovacs and Lording, 1980; Weller, 1980; Fédération CECOS *et al.*, 1983; Lansac *et al.*, 1983, 1984; Virro *et al.*, 1984; Forse *et al.*, 1985; Varma and Patel, 1987; Amuzu *et al.*, 1990; Grefenstette *et al.*, 1990; Melzer, 1991). Only two prospective and large population-based studies have been published. The first by the French Sperm Bank network, which covers 22 centres of sperm cryopreservation working under the same rules: CECOS (Mayaux *et al.*, 1990; Thépot *et al.*, 1996; Lansac *et al.*, 1997). In this prospective study, 24 978 pregnancies achieved after AID (21 597 pregnancies) or IVF with frozen

**Table I.** Children born after artificial insemination with donor semen (AID): comparison with the French national register 1995

	Children after AID <sup>a</sup> (Thépot <i>et al.</i> , 1996)	French national register 1995 (Blondel <i>et al.</i> , 1997)
Number of children	8943	13 631
Mean weight (g ± SD)	3281 ± 491	3300 ± 600
Weight <2500 g	4.7%	6.2%
Prematurity <37 weeks	4.8%	5.9%
Still births	1%	0.83%

<sup>a</sup>Single pregnancies

donor spermatozoa (IVF/D) (3689 pregnancies) were followed to term and reported to the central CECOS office between 1987 and 1994. Only 2% of the pregnancies were lost to follow-up. The second large series (Hoy *et al.*, 1999) 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.

For this review, we will use many of the findings from these studies. As far as ART procedures are concerned, AID and IVF/D provide some specific questions requiring answers: (i) the effects of the ages of the biological father and mother who should not be related, as should be the case in other conditions; (ii) date of insemination with reference to the cycle should be taken in account; (iii) influence of duration of sperm cryostorage on the children's health; and (iv) the psychosocial development of children born after frozen semen donation. This has not been fully established and is partly related to the maintenance of secrecy by donor insemination recipients in many countries and to the current age of people conceived by AID. So far, few AID children have reached adulthood.

### Children born after AID

#### Infant weights

Lower infant weights than normal have been reported (Mochimaru, 1979) but this levels out after the age of 5 years. Many studies have reported normal mean weights for single pregnancies (Lansac *et al.*, 1983, 1984). In the prospective CECOS study, the mean infant weight at birth for single pregnancies was 3281 ± 491 g and the incidence of children born weighing <2500 g was 4.7%. The prematurity rate (<37 weeks) was 4.8%, and the rate of stillborn children 1%. These figures are similar to those supplied by the French perinatal inquiry for 1995 covering 13 631 pregnancies (Table I) (Blondel *et al.*, 1995; Lansac *et al.*, 1997). Other studies (Schoysman *et al.*, 1981; Hoy *et al.*, 1999) showed that, compared with the general population, AID is not associated with any significant difference in the incidence of preterm birth, low birth weight or perinatal mortality.

#### Multiple pregnancies

The multiple pregnancy rate (MPR) varies from 2.5 to 7.5% (Lansac *et al.*, 1997; Hoy *et al.*, 1999). Such results suggest a relationship with the use of ovulation induction treatments. This was confirmed in the CECOS report by the use of anti-oestrogens

and/or gonadotrophins in 77.4% of pregnant women after AID. In the Australian report, ovulation induction was used in 23.8% of AID cycles and was associated with a six-fold significant increase of multiple births compared with AID pregnancies conceived without ovulation induction (Hoy *et al.*, 1999). This MPR was far lower than that of IVF/D during the same period (3313 pregnancies; twins 24.8%, triplets 4.1%, higher rank 0.1%). Such results explain the need to perform an ultrasound scan at 8–10 weeks of pregnancy after AID.

#### Sex ratio

Until recently, the reports of the sex ratio from AID-conceived children appeared to be conflicting; some reports mentioned an increase in the frequency of male offspring (Mochimaru, 1979; Weller, 1980; Katzorke *et al.*, 1981), whereas other reports indicated an increase in the frequency of female offspring (Chong and Taymor, 1975; Newill *et al.*, 1976; Aiman, 1982). To explain these discrepancies, some authors proposed timing insemination at the last low point of the Basal Body Temperature (BBT) chart to induce an increase in the male offspring rate (Harlap, 1979; Virro and Shewchuck, 1984). Others suggested the use of ovulation induction treatments to induce an increase in the female offspring rate (Adashi *et al.*, 1979; James, 1984). In view of the sample size of all published series, it remains difficult to draw any conclusions about gender distribution. The French CECOS prospective study reported the results of 8943 single pregnancies (Thépot *et al.*, 1996). The male/female offspring ratio was 1.04:1, compared with the ratio of 1.09:1 reported by the French National Registry (Blondel *et al.*, 1996). Such results are very similar and were confirmed by the Australian report (Hoy *et al.*, 1999)

#### Malformations

The reported incidence of fetal malformations is summarized in Table II. The results range from 0.9 to 5.2%, with high variations in the sample size. The CECOS study (Thépot *et al.*, 1996) covered 9794 births and took into account abnormalities which were detected by prenatal diagnosis followed by medically indicated abortion. The total incidence was 1.7%. The rate for singleton birth defects was 1.5% compared with 1.4% for multiple deliveries. Overall, single abnormalities were observed in 1.2% of cases, compared with multiple abnormalities in 0.2%. The different fetal malformations are reported in Table III. Such results are similar to those reported in the French National Registry (Blondel *et al.*, 1997). Comparing women with or

**Table II.** Infant malformation rate following artificial insemination with donor semen (AID)

Author	Year	Pregnancies (n)	Malformations (%)	Sperm quality
Steinberger and Smith	1973	71	1.4	Fresh + Frozen
Newill	1976	58	5.2	Fresh
Katzorke <i>et al.</i>	1981	210	0.9	Fresh
Schoysman <i>et al.</i>	1981	744	1.6	Fresh + Frozen
Amuzu <i>et al.</i>	1990	487	2.9	Fresh + Frozen
CECOS	1993	9794	1.7 <sup>a</sup>	Frozen
Hoy <i>et al.</i>	1999	1552	3.6	Frozen

<sup>a</sup>This rate includes terminated pregnancies.

without malformed children, no difference was observed in maternal age at menarche, average cycle length, hormonal treatment, date of insemination, donor age at time of sperm collection or duration of sperm cryopreservation, except for maternal age at delivery which was greater for women with malformed children (31.9 versus 31.1 years). In the Australian report, the overall prevalence of birth defects did not differ significantly between AID (3.6%) and control births (3.2%). The odds ratio (adjusted for maternal age) for autosomal trisomies, which can be readily ascertained at birth, was 2.7% (Hoy *et al.*, 1999).

In the CECOS series (Thépot *et al.*, 1996), 3.7% chromosomal anomalies were reported among 9794 births and 35 fetuses. Down's syndrome accounted for 0.25% of the incidence in this population. Among the factors evaluated for malformations, two parameters were significantly associated with trisomy 21: maternal age at delivery was higher (which is a commonly accepted fact), and trisomy 21 was associated with higher donor age (35.2 versus 34.5 years,  $P < 0.005$ ) regardless of maternal age. Paternal age as a risk factor for Down's syndrome has already been debated (for: Stene *et al.*, 1987; against: Croos and Hook, 1987; Hook *et al.*, 1990; both contested by de Michelena *et al.*, 1993). However, the high frequency (>95%) with which Down's syndrome might be associated with maternal non-disjunction does not support the hypothesis of a predominant role for paternal age (Antonarakis, 1991). These conflicting findings have led to recommending some age limitation for sperm donors in some countries.

### Children born after IVF/D

The results reported for IVF/D do not drastically differ from those reported for AID, except for the multiple pregnancy rate (Lansac *et al.*, 1997). Although a higher abortion rate (21.5 versus 18.1%) and higher ectopic pregnancy rate (1.7 versus 0.9%) were observed in IVF/D pregnancies compared with AID pregnancies, the major discrepancy concerned the three to four times higher twin pregnancy rate, and the six to seven times higher triplet pregnancy rate, despite a five-fold increase in embryo reduction.

The incidence of birth defects following pregnancies after IVF/D tended to be higher than after AID (2.7 versus 1.9% for IVF/D [ $n = 2665$ ] and for AID [ $n = 16926$ ] respectively; Table III; Lansac *et al.*, 1997), although no difference was observed after IVF with fresh husband spermatozoa (2.6%; FIVNAT, 1993).

This increase could not be explained by the increase in the multiple pregnancy rate, as birth defects are mainly observed in monozygotic pregnancies which are quite uncommon in IVF.

The main guideline that could be drawn from these results concerns the cautious use of ART procedures for using donor spermatozoa, seeking equilibrium between efficacy and safety. This means that well-conducted AID before deciding to use IVF/D may achieve good results with low multiple pregnancy rates. The choice of IVF/D might be indicated for either tubal lesions or the failure of prior AID cycles, and in all cases thoroughly discussed with the couples involved.

### Infant development

The psychological development of children born after AID has been assessed in short series from 122 (Seikowski *et al.*, 1990) to 261 families (Bendvold *et al.*, 1990). The answers (only 55% response to questionnaires sent) suggested that there were no differences in terms of behaviour towards pregnancy and children, between wife and husband, and in the degree of neurosis of the parents and children when compared with control groups (Seikowski and Glander, 1990).

A follow-up study of 108 children up to the age of 6 years was reported following births after AID (Clement, 1991). Based on questionnaires and interviews with GPs and paediatricians, both psychomotor and educational development appeared unaltered. In contrast, an increased rate of consultations for pulmonary, skin disorders and oto-rhino-laryngology disorders was observed. This might be interpreted as indicative of over-protection of a 'precious' child rather than an actual increase in health disorders.

A controlled quantitative assessment of psychosocial development was reported, comparing children conceived by donor insemination ( $n = 22$ ) with adoptees and naturally-conceived children who were matched for age and sex ( $n = 20$ ) (Kovacs *et al.*, 1993). No differences were observed between the groups.

Such findings are reassuring, as they reported no increase in psychopathology or developmental problems. It was also reassuring that both parents were actively involved in the questionnaire, suggesting a sharing of parenting. The divorce rate reported among AID families is 2.2% in Norway (Bendvold *et al.*, 1990) and 7.2% in the USA (Amuzu *et al.*, 1990), which is lower than the divorce rate in the general population. This might

**Table III.** Types of malformation observed in fetuses or children born after artificial insemination with donor semen (AID) or IVF with donor semen (IVF/D) (termination of pregnancies included) (Lansac *et al.*, 1997). Values in parentheses are percentages

	AID (n = 16926 fetuses)	IVF/D (n = 2665 fetuses)
Single malformation	216	36
Cardiovascular	52	7
Limbs	37	7
Urinary	30	3
Genital	14	1
Gastro-intestinal	28	5
Nervous system	30	10
Respiratory	6	1
Face	19	1
Others	–	1
Associated malformations	22	7
Chromosomal abnormalities	67	11
Trisomy 21	42	6
Others	25	5
Other malformations	21	18
Total	325/16926 (1.9)	72/2665 (2.7)

be interpreted as a sign of stability for infertile couples conceiving with AID, compared with the general population.

### Secrecy

The secrecy question still remains a matter of debate. One group (David *et al.*, 1988) questioned 850 couples and reviewed the literature concerning this subject. Overall, <10% of couples intended to inform the child of the way in which he/she was conceived. The rate was 27% in a prospective study in the USA (Klock *et al.*, 1994). The parents considered the disclosure to be ‘unnecessary’, and creating ‘problems’ for the child, particularly to protect them from negative reactions from society, family and friends, as well as to protect the child from being looked upon as different from others, while having no positive effect. ‘The father is the one that loves the child and who wanted the child and who is prepared to bring him/her up’. Similar findings were confirmed in recent reports (Brewaeys *et al.*, 1997). In some countries, e.g. Victoria State in Australia and Sweden, secrecy is considered to be unhealthy, and laws have provided the opportunity for the child to know his/her biological father when reaching adulthood. Long-term studies are required to examine the possible psychological impact on children informed about the means of their conception. A psychosocial evaluation is currently in progress among 15 adults (men and women) conceived by AID (J.L.Clement, personal communication). Subjects were recruited for interview after an advertisement in national newspapers. The results have not yet been published.

### Conclusions

The general characteristics of children born after ART using donated frozen semen are not different to the general

population (weight, prematurity, stillbirths, sex ratio). However, the rate of multiple pregnancy is increased, first in AID conception where the use of hormonal treatment may be too heavily prescribed, second in IVF/D conception where both ovulation induction treatments and embryo transfer policy increase the rate of multiple pregnancies. In terms of birth defects and chromosomal abnormalities, no difference has been observed from the general population. Finally, the use of frozen spermatozoa does not seem to affect the health of children conceived by AID or IVFD.

The psychosocial development of such infants is not as well understood because of confidentiality offered in many countries concerning sperm donation. However, the results available on the psychosocial development of children look reassuring up to the age of 8–10 years. Larger and longer studies are needed to answer such questions, particularly in regard to adulthood.

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