

Reproductive Technology Outcomes in Australia: Analysing the Data

By Dr Nicholas Tonti-Filippini

Difficulties in Assessing Assisted Reproductive Technology (ART) Outcomes

Assessing the results of infertility treatments is a complex matter. A couple is considered infertile if they have an inability to achieve conception after a year of unprotected intercourse, or the inability to carry a pregnancy to live birth¹²³⁴. The recognition of infertility also depends on reporting. There is what is now being called "social infertility"⁵ in which women leave trying to become pregnant until they are of relatively advanced age when fertility in most women will have greatly declined. Fertility rates in women decline as they approach peri-menopause. In today's culture, there would seem to be more women in that group who then report difficulty with infertility, when in earlier generations they would have had their desired families by that age and would not consider infertility to be a problem.

In those who are reported as infertile, there is a natural conception rate which would appear to be of the order of 25-30 % per annum.⁶⁷⁸⁹ From a broad range of studies it would appear that between 50% and 70% of couples who are classified as having a problem with infertility will conceive a child within five years. There are several retrospective studies that indicate that in developed countries, the rate of absolute infertility may be as low as 3% where absolute infertility includes only those women who tried to have a child and had not done so by the time they had reached menopause.¹⁰¹¹

In the assessment of any infertility treatment intervention it is important to note that the pregnancy rate attributable to the intervention needs to take into account what the natural

¹ Ducot B, Spira A, Thonneau P, Toulemon L, Leridon H. Difficulties in conceiving. Discussion about methodology concerning the INED-INSERM survey carried out in France in 1988 on 3,181 women aged between 18 and 49. *Journal de Gynecologie, Obstetrique et Biologie de la Reproduction* 1991; 20(5):643-50, UI: 1955659.

² Gunnell DJ, Ewings P. Infertility prevalence, needs assessment and purchasing. *J Publ Health Med* 1994 Mar; 16(1):29-35, UI: 8037949.

³ Healy DL, Trounson AO, Anderson AN. Female Infertility: Causes and Treatment *The Lancet* 1994; 343:1539.

⁴ Crosignani PG, Rubin BL. Optimal use of infertility diagnostic tests and treatments. The ESHRE Capri Workshop Group. *Human Reproduction* 2000 Mar; 15(3):723-32, UI: 10686227.

⁵ Weston G, Vollenhoven B. Is IVF becoming a band-aid for social infertility? *Aust N Z J Obstet Gynaecol* 2002 Nov; 42(5):476-7.

⁶ Rousseau S, Lord J, Lepage Y, Van Campenhout J. The expectancy of pregnancy for "normal" infertile couples. *Fertil Steril* 1983;40:768-772.

⁷ Barnea ER, Holford TR, McInnes DRA. Long-term prognosis of infertile couples with normal basic investigations: a life-table analysis. *Obstet Gynecol* 1985;66:24-26.

⁸ Hull MGR, Glazener CMA, Kelly N, et al. Population study of causes, treatment, and outcome of infertility. *Brit Med J* 1985;291:1693-1697.

⁹ Templeton AA, Penney GC. The incidence, characteristics, and prognosis of patients whose infertility is unexplained. *Fertil Steril* 1982;37:175-182.

¹⁰ Gunnell DJ, Ewings P. Infertility prevalence, needs assessment and purchasing. *J Publ Health Med* 1994 Mar; 16(1):29-35.

¹¹ Webb, A. A Survey of Reproductive Disability. *Aust J Publ Health* 1992; 16(4): 376-381.

pregnancy rate would have been without intervention. In the application of reproductive technologies, natural pregnancies occur in women on IVF waiting lists, during treatment and after they have left the programmes.

The data available for reproductive technology (RT) is often limited. The data usually do not include:

- the number of pregnancies in women on RT programmes whose pregnancies are natural pregnancies rather than laboratory conceived;
- the live birth rate per woman while on an RT programme;
- the live birth rate per women entering an RT programme *that is attributable to the RT intervention*;
- the live birth rate per embryo produced;
- the live birth rate per embryo transferred.

It is a source of frustration that neither the State agencies nor the National Perinatal Statistic's unit publish data in a way that would assist infertile couples and those involved in policy formation to assess IVF in these crucial respects.

Intracytoplasmic Sperm Injection (ICSI) and IVF

There is a marked trend toward using ICSI in IVF. In the calendar year 2000, in Australia and New Zealand, ICSI with transfer of fresh or frozen embryos accounted for 51.4% of all embryo transfers.¹² Of the total of IVF cycles attempted, 54% (10,147) were ICSI cycles.¹³

Ovarian hyperstimulation rates

In the Australian State of Victoria, the Infertility Treatment Authority (ITA) reports that, for the 2000 calendar year, 5019 (86%) of 5,866 cycles of IVF and Gamete Intrafallopian Transfer (GIFT) were stimulated¹⁴. It is also important to note that what happens is hyperstimulation. This is different from ovarian stimulation in women who are not ovulating where the goal is to establish ovulation. The goal of hyperstimulation in IVF and ET is to increase the chances of pregnancy by increasing the numbers of eggs and then embryos produced. The goal is mild to moderate ovarian hyperstimulation. Occasionally that results in severe ovarian hyperstimulation which is a life threatening condition requiring extensive treatment and hospitalisation. In 1999, 2.4% of women who achieved pregnancy undergoing assisted conception in Australia and New Zealand required hospitalisation for ovarian hyperstimulation syndrome.¹⁵

¹² Hurst T, Lancaster P. *Assisted conception Australia and New Zealand 1999 and 2000*. AIHW Cat. No. PER 18. Sydney: Australian Institute of Health and Welfare National Perinatal Statistics Unit (Assisted Conception Series No. 6) 2001, 5.

¹³ *Ibid.*, 11-12.

¹⁴ Infertility Treatment Authority *Annual Report 2001*, (available from www.ita.org.au), 24.

¹⁵ Hurst *et al.*, *Op. Cit.*, 19.

In the 1980s, the drugs of choice for ovarian stimulation in IVF were Clomiphene and Human Menopausal Gonadotrophin (hMG) or Follicle Stimulating Hormone (FSH). These drugs were used in more than 90% of IVF procedures. Clomiphene has fallen out of favour. hMG was the subject of investigation following the scandals associated with Cruetzfeldt Jakob Disease (CJD) and the enquiry undertaken by Professor Margaret Allars for the Australian Commonwealth Minister for Health into the use of human cadaveric pituitary derived hormones in Australia¹⁶. In 2000, Clomiphene was used in only 2% of treatment cycles¹⁷.

Egg collection, insemination, fertilisation and embryo formation

In 1999, the Infertility Treatment Authority (ITA) records that Victorian IVF programmes undertook 4,363 egg retrieval procedures on women from which they collected 42,986 eggs, an average of 9.9 eggs per retrieval cycle. That compares to the mostly uni-ovular natural cycles in women. They inseminated 38,075 eggs, which resulted in 23,647 (62%) being fertilised. Of those, they transferred 7,466 fresh embryos and froze 9,377. 6,803 embryos were considered unsuitable for transfer or freezing.¹⁸ (Note: an embryo is defined in the statute as being formed if syngamy follows insemination of an ovum).

Embryo Wastage

The ITA Annual Report of 2001 contains final outcomes data for the treatment cycles of 1999 and was most recently updated on 28th March 2001. It records that from the IVF treatment cycles of 1999, there were 1006 babies born, including those from embryos who had been frozen and subsequently thawed¹⁹. 9.5% of embryos transferred fresh survived to be born alive. 3.1% of embryos transferred after freezing and thawing survived to be born alive. The latter figure does not account for those frozen embryos who were not transferred, either being withdrawn from storage without transfer or remaining in storage after March 2001.

From the ITA data it would appear that of the total of 23,647 embryos formed in Victoria by IVF in 1999,

- 28.7% were lost because not considered suitable for freezing or transfer;
- 28.5% were lost after having been transferred fresh;
- the rest were frozen and some of those were later thawed and transferred of whom 96.9% were lost after transfer.
- Some remained in storage and some were thawed and not transferred.

¹⁶ Margaret Allars Report of the inquiry into the use of pituitary derived hormones in Australia and Cruetzfeldt-Jakob Disease, AGPS June 1994.

¹⁷ Hurst *et al.*, *Op. Cit.*, 18 & 22.

¹⁸ Infertility Treatment Authority *Annual Report 2000*. p. 24 and the *Annual Report 2001* p. 20 (available from www.ita.org.au). The ITA data is the most complete data available publicly in Australia. The IVF teams have a statutory obligation to submit their data to ITA which is an independent statutory authority established by the Victorian Parliament and it is the only publicly available source of reliable data in relation to numbers of embryos produced. The Australian National Perinatal Statistics Unit also record ART data for Australian and New Zealand but does not collect embryo numbers.

¹⁹ Infertility Treatment Authority *Annual Report 2001*, www.ita.org.au, 20.

It is not possible from the available data to produce an absolute survival rate because some embryos from 1999 would have remained in frozen storage and might yet be transferred, and the data for those frozen embryos transferred in 1999 includes embryos formed in earlier years. If all those frozen embryos formed in 1999 were later thawed and transferred, and we know that that is not the case, then the live birth rate to embryos formed could not be more than 4.2%.

The above are IVF (and ICSI) data. We do not know how many embryos are formed by GIFT. The use of GIFT is declining even though it has higher success rates than IVF in select women (particularly those experiencing endometriosis or unexplained infertility). From the 1999 cohort, by 2001, the final outcomes for the 303 GIFT cycles in Victoria were 59 babies and 47 of those were from the Mercy GIFT programme (211 cycles)²⁰.

Spontaneous Abortion and Complications of Pregnancy

In 2000, spontaneous abortion (loss of an intra-uterine pregnancy detected clinically, and not including loss of pregnancies identified by bio-chemistry alone, and not including pre-implantation losses and losses after 20 weeks) occurred in 15.7% of assisted conception pregnancies in women less than 30 years and in 36.4% of women 40 years and over. The average rate of spontaneous abortion for ART was 19.6%.²¹ 25% of all ART pregnancies had significant complications.²²

Multiple Births and Caesarean Section

In 1999, 21.2% of IVF pregnancies, 21.8% of ICSI pregnancies and 26.8% of GIFT pregnancies were multiple pregnancies compared to 1.6% of all Australian births. In IVF 20.0% were twins, 1.1% were triplets, and there was only one pregnancy of quadruplets. In 1999, the caesarean section rates for singleton pregnancies was 39.7%, 63.5% for twins and 89.6 for triplets, the average rate for all ART pregnancies being 43%²³.

Perinatal Deaths

The perinatal death rate (stillbirths after 20 weeks and neonatal death within 28 days) for all Australian births in 1999 was 10.1 per 1000 births. The reported perinatal death rate for all ART births was 24.7 per 1000 births, 17.3 per 1000 in singletons, 32.3 per 1000 for twins, and 95.2 per 1,000 for triplets²⁴.

Congenital Malformation

The rate of major congenital malformation (in live births, stillbirths and those pregnancies terminated for foetal abnormality) in ART in 1999 in singletons was 1.2% in IVF, 2.4% in ICSI and 3.0% in GIFT. The overall major congenital malformation rate for ART was 2.0%.²⁵

²⁰ *Ibid.*

²¹ Hurst *et al. Op. Cit.*, 23-4.

²² *Ibid.*, 25.

²³ *Ibid.*, 28-30.

²⁴ *Ibid.*, 32.

²⁵ *Ibid.*, 33.

Ectopic Pregnancy

The ectopic pregnancy rate in IVF was 2.2% in 1999 and there were seven heterectopic pregnancies (in fallopian tube and in uterus).

IVF Failure

In 1999, 3,745 Victorian women underwent IVF. 2,088 women had frozen embryos transferred (some were 1999 IVF women returning, others were women returning for embryos formed in earlier years). By March 2001, 852 women who attended IVF clinics in Victoria delivered babies either from fresh embryo transfer or from frozen-thawed embryo transfer.²⁶ (Note that some of these women had multiple pregnancies). Because of the inclusion of women returning from previous years and because some women undergoing IVF in 1999 would still have had embryos frozen by March 2001, it is not possible, from the data, to give a definite figure for the likelihood of a woman entering an IVF programme in 1999 having a child while on the programme. The figure would appear to be of the order of one in five but this is based on the assumption that transfers of frozen embryos from previous years were approximately the same as those left in storage from the 1999 year. That data is not publicly available.

There does not appear to be any way of distinguishing natural conceptions from artificial conceptions in IVF patients. Nor is there any control group data available to indicate what the natural conception rate might have been for IVF patients without IVF. Of the one in five women in IVF programmes in 1999 who conceived, some could reasonably be expected to have conceived naturally. But without more detail about the cohort of women entering IVF in Victoria in 1999, it is not possible to estimate the proportion who may have conceived naturally.

Dr Robert Jansen recently published data on patients at a private IVF clinic in Sydney in which he analyses the resultant live birth rate to the number of retrievals performed in 1998²⁷. Jansen points to a significant decline in live birth to egg retrieval rates as patient age exceeds 33. In his study, involving 565 women and 648 egg retrievals, he reports that approximately 50% of egg retrievals resulted in a live birth in women aged 36 but this fell to approximately 25% for the peak age of utilisation at age 39, and declined further for older women on the programme. It is not clear how many of those pregnancies were naturally conceived rather than as a result of artificial fertilization. It is interesting that success rate for the women in the study showed the same decline that one sees in natural pregnancies in relation to the age of the women.

²⁶ Infertility Treatment Authority *Annual Report 2000*. p. 24 and the *Annual Report 2001* p. 20. (available from www.ita.org.au).

²⁷ Jansen RPS. The effect of female age on the likelihood of a live birth from one in-vitro fertilisation treatment. *Med J Aust* 17 March 2003;178:258-261.