Assisted Reproductive Technology Treatment Outcomes

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Abstract
Information on the outcomes of ART treatments in Ireland is not readily available to Irish practitioners. The data for hospital affiliated clinics has been made available for many years and is included in the hospital reports. We present a 10-year analysis of the Irish ART results voluntarily reported by six out of seven IVF clinics. The data was collected from published ESHRE reports and from results (2007-8) not yet published. Data collected included: number of clinics and ART cycles, female age, clinical and multiple pregnancy rates and treatment complications. The clinical pregnancy rate per embryo transfer was 31.7% for IVF and 29.8% for ICSI. The proportion of singleton, twin and triplet deliveries for IVF and ICSI combined was 75%, 23.35% and 1.64%. The rate of ovarian hyperstimulation was 0.8%. ART practice in Ireland is safe, effective and responsible. Financial and societal savings could result from the introduction of state funded IVF with compulsory eSET where recommended.

Introduction
Infertility is a World Health Organization (WHO) recognised disease. The International Committee Monitoring Assisted Reproductive Technologies (ICMART) and the WHO have recently agreed a glossary of Assisted Reproductive Technology (ART) terminology describing infertility as a disease of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse. The first organised service commenced in 1986 and is currently still in operation in Ireland. The data was initially reported through volunteer work, since 2005 the Irish Fertility Society (IFS) has been the scientific body empowered by its members to collect, summarise and forward the national cumulative results. To date, national ART outcomes have not been reported in Irish medical journals. This study aims to report ten years of cumulative ART results from the seven IFS ART centres in order to provide a reference range for practicing doctors in Ireland.

Methods
The data was collected from published ESHRE reports (1998 to 2006) and from results submitted to ESHRE (2007-8) but not yet published. The Irish data is anonymised and voluntarily originated from: Clane Fertility Clinic, Cork Fertility Centre, Galway Fertility Centre, HARI (Human Assisted Reproduction Ireland) Unit, Kilkenny Clinic, and Merrion Fertility Clinic. The following outcomes were measured: number of clinics and numbers of cycles of therapy commenced (overall activity), female age, clinical pregnancy rates after IVF, ICSI, FET and oocyte donations, multiple pregnancy rates, pregnancy rates after IUI with partner or donated sperm and treatment complications. A clinical pregnancy was defined as ultrasound visualisation of a gestational sac and includes ectopic pregnancy.

Results
Overall activity
The number of IVF clinics reporting their activity and outcomes has increased as services expanded (Table 1). Since 1999 a total of 24,378 cycles of ART were initiated. The size of the clinics varied from 200 to over 1000 cycles annually. In 1999 one clinic provided less than 100 cycles of therapy while 2 had between 500 and 1000 cycles. In 2008 one clinic performed 100-200 cycles, two clinics performed 200-500 cycles, one clinic performed 500-1000 cycles and one clinic more than 1,000 cycles. The number of treatment cycles has constantly increased in IVF (257%), ICSI (241%) and FET (385%), an overall increase of 265% between 1999 and 2008. Despite this, Ireland (762 cycles/ million population) is still well below the European average (2,539 deliveries). The 10-year average clinical pregnancy rates per cycle started, per aspirate and per transfer were 24.84%, 28.42% and 31.76%, respectively. Annual Irish rates compared favourably with the European average (Table 2). In the years where comparison was possible (1999 to 2006), Irish clinical pregnancy rates exceeded the European average in 5 of the 8 years.

Female age distribution
The largest group of patients in our study belonged to the 35 to 39 age group (44-47%), with no changes over the last 10 years. There was a decrease in the percentage of younger women (<35 years, 42% to 32%) and a rise in older women (>45 years, 15% to 21%), though this seems to have reversed in 2007-8. This reflects demographic changes occurring in the last decade when the average age at conception increased from 30 to 31.1 years old. Compared with other European countries, Ireland constantly had the lowest percentage (5%-9%) of women less than 29 years old undergoing ART.

Pregnancy Rates
IVF Treatments
The 12,242 IVF cycles commenced resulted in 10,597 oocyte aspirations, 9,738 embryo transfers, 3,097 pregnancies and 1,663 deliveries. The 10-year average clinical pregnancy rates per cycle started, per aspirate and per embryo transfer were 24.84%, 28.42% and 31.76%, respectively. Annual Irish rates compared favourably with the European average (Table 2). In the years where comparison was possible (1999 to 2006), Irish clinical pregnancy rates exceeded the European average in 5 of the 8 years.

ICSI Treatments
The 7,695 ICSI cycles commenced, 7,025 resulted in oocyte aspirations with 6,639 embryo transfers, 2,008 pregnancies and 1,863 deliveries. The 10-year average clinical pregnancy rates per cycle started, per aspirate and per embryo transfer were 25.42%, 28.14% and 29.81% respectively. Similarly, annual Irish rates compare favourably with the European average published to date (Table 2).

FET Treatments
For the 10-year period, a total of 4,248 FET cycles were initiated with 3,678 embryo transfers, 850 pregnancies and 603 deliveries. The 10-year clinical pregnancy rate per transfer was 22%, compared to the European average of 16-20% during the same period (Table 2).

Multiple Pregnancy
IVF/ICSI
In Ireland, the number of singleton deliveries from ART treatments has increased from 72.7% in 1999 to 77.9% in 2008. The incidence of twin deliveries has seen a significant decrease, particularly in the last two years of study (24.3% in 2007, 20.9% in 2008), triplet deliveries have reduced three fold from 3.5% in 1999 to 1.2% in 2008 (Table 3). European reports show that multiple pregnancy rates have seen a decrease for the last 3 years, however this was not the case in Ireland.
The number of singleton deliveries has significantly increased from 64.3% in 1999 to 87.5% in 2008 while the number of twin deliveries sharply reduced from 35.7% to 9.6%. In comparison, European average singleton (84.8% vs. 84.9%) and twin (14% vs. 13.4%) deliveries have not changed from 1999 to 2006.

IUI (H) and IUI (D)

Results of IUI therapy are an important tool in counselling patients prior to deciding between IVF and IUI. The treatment can be provided either with partner/husband or with donor sperm. IUI treatments are also practised in non-IVF clinics, the results of which are not available. Therefore, the data reported here includes only cases from the Irish IVF Clinics submitting results to IFS and ESHRE and commenced in 2001.

IUI husband

In women < 40 years of age, a total of 6,169 IUI treatments were commenced resulting in 664 pregnancies. Clinical pregnancy rates were 11.22% with 86.2% singleton, 9.2% twin and 0.6% triplet deliveries. The European clinical pregnancy rate for the same period was 11.7% with 87.6% singleton, 11% twins and 1.3% triplet deliveries.

> 40 years

A total of 737 IUI procedures and 43 clinical pregnancies were reported in this group. The clinical pregnancy rate was 5.6%, of which 88.9% were singleton and 9.9% twin deliveries. No triplet deliveries were recorded. The European clinical pregnancy rate for the same period was 8.16% with 82.7% singleton, 6.8% twins and 0.4% triplet deliveries.

IUI donor

< 40 years

Donor IUI results in women younger than 40 showed a total number of 895 cycles resulting in 205 clinical pregnancies. The clinical pregnancy rate was 25.5%. Of these 88.9% were singleton, 9.1% twin and 1% triplet deliveries. Of note, triplets were only recorded in 2007. The European clinical pregnancy rate for the same period was 14.3%, with singleton, twin and triplet delivery rates of 88.7%, 10.3% and 1% respectively.

> 40 years

A total number of 285 cycles and 46 clinical pregnancies were recorded. The vast majority of these were singleton pregnancies. The clinical pregnancy rate was 13.6%, higher than the European rate of 7.2%.

Complications

Of the 19,937 cycles of IVF and ICSI analysed we identified 160 cases of OHSS, corresponding to a risk of OHSS of 0.8% per cycle started, with one mortality. The European incidence of OHSS for the same period was 0.8%-1.2%, with three deaths occurring. Among other complications there were ten cases of peri-operative bleeding (0.05%) and four cases of infection (0.02%).

*PPA= clinical pregnancy per aspirate, *PPT= clinical pregnancy per transfer

Discussion

This ten year Irish data shows that Ireland lags far behind its European counterparts in terms of ART uptake. A potential reason is the lack of state funding of fertility therapy. Up to 2007, the percentage of patients over 40 years old attending for ART increased while the percentage of women less than 29 years old decreased. In 2007 and 2008 the trend reversed, possibly due to better patient education and the realisation that fertility declines with female age. Pregnancy rates in Ireland have consistently been above European averages despite the higher age of the female population treated. As female age is the best prognostic indicator for successful pregnancy following ART, such results reflect excellent patient care. ART treatments in Ireland appear to be very safe with complication rates well within European benchmarks. Unfortunately, like all medical treatments, tragic, fatal complications occur and remind us of the need to constantly audit and improve our practice.

In relation to donor oocyte treatments the small number of Irish cycles reported does not fully reflect reality. Numerous Irish patients undergo overseas therapy and satellite services are available in Ireland. Unfortunately, accurate data on the real number of oocyte donation treatments is lacking as many couples choose to keep it secret. As regards multiple pregnancy, with the exception of FET treatments, the twin pregnancy rates have not changed in the first 9 years of study. In 2008 a shift from two to single embryo transfers translated into an increase in singleton and significant decrease in twin pregnancies. An increase in elective single embryo transfers (eSET) is evident with a significant rise in 2007 and 2008, while three embryo transfers significantly declined since 2004. All these changes are in line with European practices with the exception of an orchestrated effort to promote (eSET) on a large scale.
This is an area of priority for the future requiring political commitment to support and publically fund ART.

Transferring more than one embryo results in higher pregnancy rates but increases the risk of multiple pregnancies. For this reason eSET is compulsory in some European countries, where the state understands the risk of couples to have financial access to advanced fertility treatment and the enormous social and fiscal burden of multiple pregnancies resulting from ART. Such European states freely finance IVF therapy while insisting that couples accept eSET. The health budget benefits could be significant as the costs of providing free IVF are far less than the cost of care for premature births related to ART multiple pregnancy. In Ireland, while patients cannot universally access free ART services money is spent unnecessarily on treating iatrogenic prematurity due to high order multiple pregnancy rates following IVF. The recent introduction of blastocyst culture in Ireland creates the possibility of pursuing eSET aggressively while maintaining excellent success rates and reducing multiple pregnancy.

Our paper reports a 10 years analysis of outcomes of ART therapy from all Irish IVF clinics that report annually. ART practice in Ireland is safe, effective and responsible with clinical pregnancy rates above the European average. The realisation that financial and societal savings could result from the introduction of a state funded IVF programme with compulsory eSET should come sooner rather than later.

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