



## REPORT ON THE BERTARELLI FIRST GLOBAL CONFERENCE, Washington, November 1999

# Improving the treatment of infertility: towards avoiding high order multiple gestation

The Bertarelli Foundation, established in Tréflex in the canton of Vaud, Switzerland, in April 1999, is the first international foundation to provide a global forum addressing the broad issues surrounding infertility and IVF. It was established to humanise the social and scientific faces of infertility and its treatment. It recognises infertility as a disease that can be treated in an ethically acceptable manner with safe and effective medical procedures that are essentially an 'extension of nature'.

World leaders in infertility treatment direct the Foundation. These include Dr Eli Adashi (USA), Dr Jean Cohen (France), Dr Lars Hamberger (Sweden), Dr Howard Jones (USA), Dr David De Krester (Australia), Dr Bruno Lunenfeld (Israel), Dr Zev Rosenwaks (USA), Dr Yuji Taketanti (Japan) and Dr André Van Steirteghem (Belgium).

As part of its international achievements in 1999, the Foundation undertook a number of groundbreaking initiatives, eg

- It funded a multi-centre study on the health status of children conceived by IVF and ICSI;
- It joined with the United States National Institutes of Health (NIH) in sponsoring a global consensus conference in November on approaches to reducing multiple births in IVF.

All aspects of iatrogenic multiple pregnancies were covered by 25 speakers. Some 200 practitioners from 30 countries concerned with the care of the subfertile patient were invited to the conference held in Washington. Its task was to review and discuss the latest techniques to prevent high order multiple gestation, to develop recommendations for clinicians and to provide the media and public with objective information on the potential risks of multiple births. This report is limited to topics that are of major interest to twin researchers.

The delegates came from countries with widely differing practices in ART, which was reflected in the difference in their multiple birth rates. It became clear that the influences on gynaecological practice,

for instance the number of embryos transferred, varied from economics to competition and the couples themselves often had a powerful effect particularly in countries where infertility treatment practices are as yet unregulated.

The scene was set by a review of the data from the international working group for registers on assisted reproduction (IWGROAR). This group has been collecting data from 40 countries since 1991. A number of speakers described the implications of the dramatic rise in the number of higher multiple births worldwide, including the greatly increased risk of prematurity and low birthweight.

Micheline Garel, a psychologist from Paris (INSERM U149, Epidemiological Research Unit on Women and Children's Health), who had followed families with triplets through the first seven years of their lives, emphasised the heavy emotional strain on the mothers. She reported that, despite having healthy children and a good socio-economic status, several admitted to regretting they had triplets. A sadly revealing observation was that triplets often failed to fulfil the mother's desire for a child (one of whom she could give her undivided attention and love). Inevitably, the children had less individual stimulation and all mothers felt guilty about not being able to respond fully to the demands of their children. Several were being treated for depression some years after the birth.

John Collins, from Canada (McMaster University, Hamilton, Ontario), described the financial burden on governments imposed by the increasing number of multiple birth families with their much higher pregnancy and neonatal costs, due to the complications of low birthweight and prematurity. This was before even considering the long-term costs of a child with a disability – much more common amongst triplets than single children. Since 1998 the cost of multiple gestation pregnancies has been greater than all the IVF and ICSI programmes. This cost would be almost halved if triplets and quadruplets were avoided by the introduction of a two-embryo transfer policy. It would be reduced much

further still if unstimulated IVF cycles or single embryo transfer became more common practice.

Many people felt that practitioners were now aware of the risks and implications of a multiple birth but had difficulty in resisting the pressures to maintain a high pregnancy rate with the inevitable risk of higher multiple pregnancies. These pressures are economic for both practitioner and patient and the driving force will frequently come from the clients themselves, particularly in countries which do not yet have statutory regulations. Competition between clinics is inevitably another factor and there was considerable criticism of the clinic 'league tables' published by some countries.

Lynn Wilcox, from the US Centers for Disease Control and Prevention, has analysed with her co-workers a one-year (1996) population-based dataset of IVF-assisted reproduction technology (ART) cycles. The large sample afforded them an opportunity to explore more fully associations between embryo number and pregnancy, live births and multiple-birth rates. The data were collected in a standardised format from each of the 900 medical centres performing IVF or related ARTs, stratified by maternal age and whether extra embryos were available (ie cryopreserved). Aspects of the methodology included:

- each live-birth delivery was considered as a single live birth, eg a live-birth delivery of triplets was counted as 1;
- a live-birth delivery was classified as a multiple birth if there were two or more foetuses, at least one of whom was liveborn;
- embryo quality was not classified by any specific laboratory data but extra embryos available for cryopreservation were used as indicators of quality;
- only fresh, non-donor IVF cycles were included in the analyses.

A total number of 9873 live births were reported. The number of embryos needed to achieve maximum live-birth rates varied according to the age of the mother and whether extra embryos were cryopreserved. Among women 20–29 and 30–34 years of age, maximum live-birth rates (43% and 36%, respectively) were achieved when two embryos were transferred and extra embryos were cryopreserved. Among women 35 years of age and older, live-birth

rates were lower overall, and regardless of whether embryos were cryopreserved, live-birth rates increased if more than two embryos were transferred. Multiple-birth rates varied according to age of the mother and the number of embryos transferred, but not whether embryos were cryopreserved. With two embryos transferred, multiple-birth rates were 22.7%, 19.7%, 11.6%, and 10.8% for women aged 20 to 29, 30 to 34, 35 to 39, and 40 to 44 years, respectively. Multiple-birth rates increased to 45.7% for women aged 20 to 29 years and 39.8% for women aged 30 to 34 years if three embryos were transferred. Among women 40–44 years of age, the multiple-birth rate was less than 25% even if five embryos were transferred.

Alan Trounson, Director of the Centre for Early Human Development of the Monash Medical Centre in Clayton, Australia, discussed the indications for implanting blastocysts and its advantages and disadvantages. Indications and advantages are:

- (1) patients with repeated implantation failure, suspected of defects in oocyte quality, needing embryo biopsy for genetic selection, or undergoing replacement of supernumerary embryos at the blastocyst stage;
- (2) selection of the most developmentally competent embryos for transfer;
- (3) synchronisation of the embryo with the female tract, leading to increased implantation rates;
- (4) selection by culture as an additional benefit of cryostorage of embryos, since only the most competent will be saved, resulting in fewer vials stored and fewer problems with disposal of unwanted, long-term stored embryos; and
- (5) the use of sequential, physiologically based culture media that can be used to produce highly viable human blastocysts.

Disadvantages are:

- (1) loss of embryos that failed to develop to the blastocyst stages *in vitro*;
- (2) consideration of cost/benefit ratios – *in vitro* procedure takes more time, more expensive materials and more man-hours; and
- (3) potential risk of transmitting infective agents to the embryos from the possible use of feeder cell lines.

Lord Robert Winston, Reproductive Services and Medicine, Hammersmith Hospital, London, UK, reported on the UK national policy for prevention of high order multiple gestation. In 1990, the Human Fertilisation and Embryology Act became law. The Human Fertilisation and Embryology Authority (HFEA), the government regulatory body, was then empowered to grant licences to treatment and research centres and to register and oversee all human treatments involving in vitro fertilisation and gamete donation. The directive set up previously by a voluntary licensing authority to transfer a maximum of three embryos was written into their Code of Conduct. There are, however, loopholes in the British law. Most infertility procedures are not regulated. Superovulation with follicle stimulating hormone does not require a licence and is not subject to restrictions. Gamete intrafallopian transfer (GIFT) is also unregulated. Some practitioners refer a few patients to clinics outside the UK, in countries where there is no restriction.

The painful subject of multifoetal reduction was faced frankly by Richard Berkowitz whose unit has performed over 1100 such procedures. Despite the medical advantages of reduction to the mother and surviving children, in a series of 400 cases, his personal abhorrence of the procedure was clear, as was his concern for the couples who not uncommonly feel anger, guilt and sadness in a situation, which they should never be asked to face. Berkowitz made a strong plea for the need for the procedure to be minimised by more caution in the practise of embryo transfer and ovulation stimulation.

The conference ended with a lively discussion. The intention had been to reach a consensus on a global statement on the prevention of high order multiple gestation. Although there was general agreement that higher order births were not a desirable outcome of treatment for subfertility, it became clear that national practices and the views of the participants varied so much that no consensus could be reached on how preventive measures should be implemented. The following conclusions are provisional; Dr Adashi and Dr Cohen are preparing majority opinions from the discussion.

#### Premise

- The ultimate goal of infertility therapy, is the delivery of a healthy child.

- High order multifetal gestation (MG) must be viewed as a serious complication of infertility therapy directly correlating with the order of multiples.
- Optimal infertility therapy must be judged not only by overall delivery rate but also by ability to maintain the lowest possible MG.

#### Background

- Globally, a substantial proportion of MG is associated with ovulation induction in an ovulatory woman, controlled ovarian hyperstimulation (COH), or IVF.
- There are good data from which the relative contribution IVF to MG can be determined.
- It is essential to obtain data to identify the contribution of COH to MG.

#### Therapy

- A small reduction in the overall pregnancy rate is a price worth paying for the reduction in MG.
- Prevention of iatrogenic high order (> 3) gestation should be an immediate universally agreed target.
- Minimising iatrogenic twin gestation should be the eventual goal.
- In women up to 35 years old generating > 4 good quality embryos, the pregnancy rate when replacing two embryos is comparable to the rate of replacing  $\geq 3$  embryos.
- To the question whether the ultimate goal in the patient population was the transfer of one embryo, half the audience answered yes, the other half thought more data were needed.
- For women up to 35 years old, there is currently a controversy between those who favour replacing up to two embryos (and freezing the rest) to avoid completely the possibility of higher order gestation, and those who favour accepting the risk of triplets in order to increase the overall pregnancy rate.
- There is currently insufficient data to consider that blastocyst transfer will give better

implantation chances than transfer and cryo-preservation at earlier stages.

- There are insufficient data to think that in future blastocyst transfer technology will be a solution to avoiding MG.

#### International call to action

- Establish and maintain a campaign to ensure equity of access and insurance coverage for all patients seeking infertility therapy, including IVF.
- Continue intensive research to identify dependable embryo selection markers for the optimisation of subsequent implantation.
- Develop new and improved protocols for ovulation induction and COH.
- Research to better understand implantation.
- In view of the rejection of law or official guidelines by the conference, agree that one must accept and undertake self regulation.

- To minimise ambiguity, consider a better indicator of programme success to be the age-related or total singleton delivery rates, including fresh plus frozen transfers – a projection that can be made according to the probability of pregnancy with frozen embryos in clinic.
- Add and specify in the results the implantation rate, the % of twins, triplets, and higher order MG and also the % of foetal reduction.
- Educate the medical profession, patients, the general public, including the media, on the risks and consequences of MG.

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