

Commentary

Towards a more physiological approach to IVF

Geeta Nargund^{1,3}, René Frydman²

¹Department of Obstetrics & Gynaecology, St George's Hospital Medical School, Cranmer Terrace, London, SW17 0RE, UK; ²Department of Obstetrics and Gynecology and Reproductive Medicine, Hôpital Antoine Bécère, 157, rue de la Porte de Trivaux, 92141, Clamart, France

³Correspondence: geetanargund@googlemail.com

Abstract

The International Society for Mild Approaches in Assisted Reproduction (ISMAAR) is founded to promote a more physiological, less drug-oriented, lower risk, less expensive and more patient friendly approach to Assisted Reproduction embracing not only natural cycle treatment but also gentle stimulation protocols and in-vitro maturation of oocytes. Recent research suggests that IVF in modified natural cycle/mild stimulation with antagonist is likely to replace the current conventional approach in down-regulated cycles. The Society will focus both on the basic science and clinical aspects of assisted reproduction. It will be committed to promoting international multi-centre scientific research, regular practical workshops for training and also seminars for educating assisted reproduction technology professionals. ISMAAR aims to establish a direct dialogue with the voluntary sector and politicians to campaign for IVF to be a safer, softer and affordable treatment globally.

Keywords: *affordable IVF, ISMAAR, IVM, minimal stimulation IVF, natural cycle IVF, ovarian stimulation*

The International Society for Mild Approaches in Assisted Reproduction (ISMAAR) is, we believe, much needed because not only are we, as reproductive medicine clinicians, entering an era of single embryo transfer but also we are increasingly aware of the need to put the welfare of the woman right at the top of the agenda when it comes to assisted reproduction technology (ART). Therefore the Society is founded to promote a more physiological, less drug-oriented, lower risk, less expensive and more patient-friendly approach to assisted reproduction embracing not only natural cycle treatment but also gentle stimulation protocols and in-vitro maturation (IVM) of oocytes.

We feel that advances in embryology, ultrasound technology and endocrinology will make the natural cycle/minimal stimulation IVF and in-vitro maturation of oocytes more successful and increasingly relevant to everyday practice. The Society will focus both on the basic science and clinical aspects of assisted reproduction. It will be committed to promoting international multi-centre scientific research, regular practical workshops for training and also seminars for educating ART professionals. IVF is not easily accessible in the public sector in most countries. It is necessary to make this treatment affordable and accessible to all. ISMAAR aims to establish a direct dialogue with the voluntary sector and politicians to campaign for IVF to be a safer, softer and affordable treatment globally.

The conventional approach to ovarian stimulation in IVF treatment is aimed at maximizing the number of oocytes available for fertilization, in order to generate several embryos for selection and transfer. The short term and serious clinical problems associated with ovulation induction are well known to all clinicians involved in fertility management. Multiple births remain a significant problem with current IVF treatment protocols. Pinborg *et al.* (2004a) in a large Danish study reported

that 40% of children born as a result of IVF/intracytoplasmic sperm injection (ICSI) are twins. These babies had a 7.4-fold increase in delivery before 32 weeks compared to singletons and also significant increases in stillbirth, Caesarean section and admission to the Neonatal Intensive Care Unit. The same group in another report (Pinborg *et al.*, 2004b) found that maternal well being in IVF/ICSI twin pregnancies was compromised with a significant increase in sick leave and hospitalization compared with singleton IVF/ICSI pregnancies. The cost to the national healthcare budget of multiple births is considerable. Current data indicates that the average hospital cost per multiple gestation delivery is greater than the average cost of IVF and ICSI cycles (European Society for Human Reproduction and Embryology Capri Workshop, 2000).

The prevalence of severe ovarian hyperstimulation syndrome (OHSS) ranges from 0.5–5% of cycles and is potentially fatal (Devigne and Rozenberg, 2002). Furthermore the impact of such side effects can influence many patients to say 'never again'. The long-term effects of conventionally stimulated cycles have thrown up the possibility of an increased risk of endometrial cancer but not of ovarian cancer (Brinton, 2004; Althuis *et al.*, 2005). Most of these studies however are based on the effects of clomiphene citrate treatment and detailed long-term analyses of the effects of gonadotrophins related to dosage are not available and are urgently needed.

Less well known are the effects of ovarian stimulation and the resultant supra-physiological oestradiol concentrations on the reproductive process. There is now substantial evidence that endometrial receptivity may be adversely affected by ovulation induction therapy (Basir *et al.*, 2001; Devroey *et al.*, 2004). This may be due to advanced endometrial maturation and dysfunctional progesterone receptor activity. Elevated oestrogen concentrations in ovulation induction cycles compared to

control cycles are characterized by higher progesterone concentrations at the time of oocyte collection, and advanced histological dating with reduced pinopode formation at the time of embryo implantation (Kolb and Paulson, 1997). This accentuated maturation of the endometrium may lead to embryo–endometrial asynchrony and reduced implantation rates in IVF cycles (Tavaniotu *et al.*, 2002). Other mechanisms may also be involved. A greater degree of endometrial gene expression disturbances have been reported in long down-regulation protocols using gonadotrophins for ovarian stimulation (Horcajadas, 2005). Macklon and Fauser (2000) believe that alterations in the oestradiol/progesterone ratio, growth factor concentrations and cell adhesion molecule profiles may occur after ovarian stimulation, potentially affecting endometrial implantation.

There is also increasing evidence that ovulation induction induces oocyte abnormalities. The reduced viability of in-vitro matured oocytes from stimulated cycles could be related to a significantly higher proportion of chromosomal abnormalities (Magli *et al.*, 2006). Baart *et al.* (2007), in a large prospective study used preimplantation genetic screening to study the effects of mild versus conventional stimulation on chromosome segregation behaviour during meiosis. The study was terminated prematurely when interim analysis found a significantly lower embryo aneuploidy rate following mild stimulation. They conclude that future ovarian stimulation strategies should avoid maximizing oocyte yield but concentrate on generating chromosomally normal embryos through reduced interference with ovarian physiology.

Finally there is a potential detrimental effect to the patient of conventional ovarian stimulation protocols both financially, and emotionally. In the UK, the National Formulary for drugs provides no recommended upper limit for the dosage for FSH/human menopausal gonadotrophin (HMG) per day (surprisingly the only drug without such a limit) and many clinics take advantage of this to prescribe high dosages of FSH/HMG (we are talking about doses of ~600–800 IU daily), which double the cost of treatment and cause significant side effects without any evidence that they are of any benefit and indeed with substantial evidence to the contrary.

Fortunately the tide is now turning. Better understanding of ovarian physiology in relation to ovarian follicular growth and maturation, advances in ultrasound technology and clinical availability of gonadotrophin-releasing hormone antagonist, have allowed ovarian stimulation to be started in a natural menstrual cycle (i.e. without forced follicular recruitment) and have given us the opportunity to develop novel, gentler approaches to ovarian stimulation (Macklon *et al.*, 2006). In some clinics natural or minimal stimulation IVF has been restricted to women with poor ovarian reserve where results have been found to be equally good and in some studies better than conventional management (Morgia *et al.*, 2004; Ubaldi *et al.*, 2005). However Pellinck *et al.* (2006) showed that minimal stimulation IVF seems to be suitable for all indications with a cumulative ongoing pregnancy rate after up to three cycles was 20.8% per patient.

Thus the case for treating all couples requiring IVF treatment with minimal stimulation regimens has been convincingly made. Over the next few years the role of IVM of oocytes will

be defined. At the present time over 400 babies have been born following this procedure. It appears to be suitable for younger women with polycystic or multifollicular ovaries who are at high risk of developing severe OHSS (Mikkelsen *et al.*, 2001). The combination of IVM with natural cycle IVF could be the way forward in certain patient groups in the future (Chian *et al.*, 2004).

More than 50 peer-reviewed papers have been published in the last 5 years addressing natural, semi-natural and milder approaches to ovarian stimulation. Nargund *et al.* (2001) showed that after four cycles, the cumulative probability of pregnancy with natural cycle IVF was 46% with an associated live birth rate of 32%. They also calculated that natural cycle IVF could be offered at approximately 23% of the cost of a stimulated cycle. A recent randomized study of all patients less than 38 years of age attending a major fertility centre (Heijnen *et al.*, 2007) found that cumulative live birth rates over 1 year of treatment were similar when patients were randomized to have mild ovarian stimulation with single embryo transferred (43.4%) and standard stimulation with two embryos transferred (44.7%). Furthermore the mild stimulation group has less discomfort and the cost of treatment was significantly reduced. Most of the leading centres in this movement were represented at the London Congress in December 2006 and are included in the pages of the special Compendium issue associated with it. Currently these centres are producing some of the most scientific work on clinical reproductive medicine at present for it is only by studying women who have not had forcible recruitment of follicles and excessively high oestradiol concentrations that we will be able to make advances in this area. In truth the universal adoption of high stimulation ovulation induction regimens by IVF clinics has set reproductive medical research back several decades. There is an urgent need to address this. Natural cycle IVF has specific applications in poor responders and in those where stimulating drugs are to be avoided. The role of IVM is limited and needs further trials. Modified natural cycle/mild stimulation with antagonist seems to be the future. The papers contained in this issue represent a significant step forward.

References

- Althuis MD, Moghissi KS, Westhoff CL *et al.* 2005 Uterine cancer after the use of clomiphene citrate to induce ovulation. *American Journal of Epidemiology* **161**, 607–615.
- Baart EB, Martini E, Eijkemans J *et al.* 2007 Milder ovarian stimulation for in-vitro fertilization reduces aneuploidy in the human preimplantation embryo: a randomized controlled trial. *Human Reproduction*, in press.
- Basir GS, WS O, Ng EH, Ho PC 2001 Morphometric analysis of peri-implantation endometrium in patients having excessively high-oestradiol concentrations after ovarian stimulation. *Human Reproduction* **16**, 435–440.
- Brinton LA, Lamb EJ, Moghissi KS *et al.* 2004 Ovarian cancer risk after the use of ovulation stimulating drugs. *Obstetrics and Gynecology* **103**, 1194–1203.
- Chian RC, Buckett WM, Abdul Jalil AK *et al.* 2004 Natural cycle in vitro fertilization combined with in vitro maturation of immature oocytes is a potential approach in infertility treatment. *Fertility and Sterility* **82**, 1675–1678.
- Devigne A, Rozenberg S 2002 Epidemiology and prevention of ovarian hyperstimulation syndrome (OHSS): a review. *Human Reproduction Update* **8**, 559–577.
- Devroey P, Bourgain C, Macklon NS, Fauser BCJM 2004 Reproductive biology and IVF: ovarian stimulation and

- endometrial receptivity. *Trends in Endocrinology and Metabolism* **15**, 84–90.
- ESHRE Capri Workshop Group 2000 Multiple gestation pregnancy. *Human Reproduction* **15**, 1856–1864.
- Heijnen E, Marinus JC, De Klerk C *et al.* 2007 A mild treatment strategy for in-vitro fertilisation: a randomised non-inferiority trial. *Lancet* **369**, 743–749.
- Horcajadas JA, Riesewijk A, Polman J *et al.* 2005 Effect of controlled ovarian hyperstimulation in IVF on endometrial gene expression profiles *Molecular Human Reproduction* **11**, 195–205.
- Kolb BA, Paulson RJ 1997 The luteal phase of cycles utilising controlled ovarian hyperstimulation and the possible impact of this hyperstimulation on embryo implantation. *American Journal of Obstetrics and Gynecology* **176**, 1262–1269.
- Macklon NS, Fauser BC 2000 Impact of ovarian hyperstimulation on the luteal phase. *Journal of Reproduction and Fertility* **55**, 101–108.
- Macklon NS, Stouffer RL, Guidice LC, Fauser BC 2006 The science behind 25 years of ovarian stimulation for in vitro fertilisation. *Endocrine Reviews* **27**, 170–207.
- Magli MC, Ferraretti AP, Crippa A *et al.* 2006 First meiosis errors in immature oocytes generated by stimulated cycles. *Fertility and Sterility* **86**, 629–635.
- Mikkelsen AL, Lindenberg S 2001 Benefit of FSH priming of women with PCOS to the in vitro maturation procedure and the outcome: a randomized prospective study. *Reproduction* **122**, 587–592.
- Morgia F, Sbracia M, Schimberni M *et al.* 2004 A controlled trial of natural cycle versus microdose gonadotrophin-releasing hormone analog flare cycles in poor responders undergoing in vitro fertilization. *Fertility and Sterility* **81**, 1542–1547.
- Nargund G, Waterstone J, Bland J *et al.* 2001 Cumulative conception and live birth rates in natural (unstimulated) IVF cycles. *Human Reproduction* **16**, 259–262.
- Pellinck MJ, Vogel NE, Hoek A *et al.* 2006 Cumulative pregnancy rates after three cycles of minimal stimulation IVF and result according to subfertility diagnosis: a multicentre cohort study. *Human Reproduction* **21**, 2375–2383.
- Pinborg A, Loft A, Nyboe Andersen A 2004a Neonatal outcome in a Danish national cohort of 8602 children born after in vitro fertilization or intracytoplasmic sperm injection: the role of twin pregnancy. *Acta Obstetrica et Gynecologica Scandinavica* **83**, 1009–1011.
- Pinborg A, Loft A, Schmidt L *et al.* 2004b Maternal risk and perinatal outcome in a Danish national cohort of 1005 twin pregnancies: the role of in-vitro fertilization. *Acta Obstetrica et Gynecologica Scandinavica* **83**, 75–84.
- Tavaniotu A, Albano C, Smitz J, Devroey P 2002 Impact of ovarian stimulation on corpus luteum function and embryonic implantation. *Reproductive Immunology* **55**, 123–130.
- Ubaldi FM, Rienzi L, Ferrero S *et al.* 2005 Management of poor responders in IVF. *Reproductive BioMedicine Online* **10**, 235–246.

Paper based on a contribution presented at the First World Congress on Natural Cycle/Minimal Stimulation IVF in London, UK, December 15–16, 2006.

Received 20 February 2007; refereed and accepted 26 February 2007.