

Natural-cycle/mild IVF: a science-based and patient-centered approach for the future

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Geeta Nargund

St George's Hospital, Blackshaw Road, London, SW17 0RE, UK
Tel.: +44 208 947 9600; Fax: +44 208 944 5800; E-mail: geetanargund@gmail.com

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In addition, global concerns about protection of human fertility, safety, regulation, accessibility and affordability of assisted reproduction technology dominated the debate and agenda at the congress.

Key presentations

Natural-cycle IVF is the term used when a single naturally selected oocyte (egg) is collected in a woman's own menstrual cycle without ovarian stimulation.

Mild IVF is the term used when small doses of ovarian stimulation tablets or injections are given in a woman's own menstrual cycle without the suppression of ovaries in order to obtain a small number of eggs (between two and seven) and embryos. The current widely used IVF treatment is termed conventional IVF where a woman's ovaries are suppressed for 10–14 days (making her menopausal) prior to stimulation of ovaries to produce high numbers of eggs and embryos.

The first day of the congress was dominated by the role of mild IVF, safety and regulation of assisted reproductive technology.

Professor Bart Fauser, University Medical Centre, Utrecht, The Netherlands, explained that over the years, ovarian stimulation protocols had become extremely complex, time consuming, expensive and associated with considerable patient discomfort and chances of complications, such as the ovarian hyperstimulation syndrome. Moreover, there was increasing evidence that such stimulation protocols can harm embryo quality, endometrial receptivity and implantation. In addition, distress associated with treatment causes significant patient dropouts (even under conditions where IVF treatment is reimbursed), denying couples additional pregnancy chances from repeated IVF. Since patients or health insurance companies pay per cycle and centers are usually compared on the basis of pregnancy rates per cycle, the high stimulation protocols used by most centers result in increased perinatal

morbidity and mortality, multiple pregnancy, fetal reduction, enormous cost and human suffering. Professor Fauser explained that the need for profound changes in the management of couples having IVF was being increasingly recognized. When referring to mild IVF, a distinction should be made between mild ovarian stimulation and mild embryo transfer. These two policies are not the same since the transfer of a single embryo can be performed following conventional stimulation and, similarly, multiple embryos may be transferred following mild stimulation. However, both approaches appear to go hand in hand and seem to reinforce one another. Mild approaches to ovarian stimulation promise to be more science-based and patient-friendly IVF, in addition to improved health of the offspring. Moreover, improvements in the cost-effectiveness of IVF will eventually augment social acceptance and access to IVF.

Esther Baart from the same medical center explained that chromosome abnormalities in embryos are considered the main cause of embryonic wastage and loss, and that this phenomenon may be primarily responsible for the relatively poor pregnancy rates reported after IVF. Her group recently completed a randomized, controlled trial comparing a mild-stimulation regimen with a conventional high-dose regimen. They employed preimplantation genetic screening to study the effect of the two stimulation approaches on the chromosomal constitution of the resulting embryos. They observed that mild stimulation reduced the number of embryos retrieved, but resulted in a significantly higher proportion of chromosomally normal embryos. Baart explained that during a woman's natural menstrual cycle, certain levels of hormones are released allowing the body to naturally

select the best-quality follicle to release an egg that will produce the best-quality embryo. With current aggressive IVF methods, a woman's hormones are suppressed for nearly 2 weeks (which gives unpleasant menopausal symptoms) followed by the introduction of high levels of hormones to stimulate multiple follicular growth, resulting in very high levels of estrogen in her body. Baart suggested that this can lead to a greater quantity of eggs but these eggs could be of lower quality. Mild IVF treatment is conducted in a woman's own natural cycle, which means there is no interference with the natural selection of her follicle/egg. This allows the body to select the better-quality follicles and reduce the proportion of low-quality follicles/eggs.

Carlos Simon from the University of Valencia, Spain, explained that endometrial receptivity in the human is a self-limited period in which the endometrial epithelium acquires a functional and transient ovarian steroid-dependent status. This window extends from day 1 to day 9 following the luteinizing hormone surge in a natural cycle, and from day 1 to day 9 following human chorionic gonadotropin administration in a stimulated cycle. When he compared gene-expression profiles in natural versus stimulated cycles using microarray technology, he found that ovarian stimulation induces morphological, biochemical and functional genomic modifications of the endometrium throughout this 'window of implantation'. This could potentially have an impact on how receptive the endometrium is to an embryo. Simon explained that this is an area that needs

further research in order to assess the extent to which these effects have an impact on implantation rates for the current aggressive IVF approach.

Geeta Nargund, St George's Hospital, London, UK, addressed concerns about the aging population and lower fertility and birth rates in the developed world. Some countries have robust family policies aimed at promoting fertility rates; however, Britain appears to have a reactive approach with limited state funding directed mainly towards problem cases rather than tackling the wider problems associated with declining fertility. A radical policy rethink is required to tackle this fertility crisis in the long term. She explained that liberal immigration policies and advances in fertility, such as egg freezing, were not primary long-term solutions to reverse the declining birth rates of an aging population. The central government should tackle this problem head on and consider creating a department dedicated to a multifaceted, proactive family policy with funds and resources from departments of education, social care, work and pensions, local government and also directly from the treasury. The main components of a long-term radical policy to tackle the fertility crisis should include a strong emphasis on protection of reproductive health in secondary-school curriculum, preconception care clinics specifically designed to educate men and women on factors affecting their fertility, an ongoing fertility-awareness program for communities funded by local government and the provision of affordable, high-quality childcare facilities with flexible part-time career posts for women. For those couples requiring assisted conception,

provision of safe, mild and cost-effective assisted-reproduction treatment with single-embryo transfer would help to provide more treatment cycles within the budget available. This would save costs associated with drugs, hospital admissions for ovarian hyperstimulation syndrome and multiple pregnancies. Nargund concluded that we need a coordinated, proactive approach to address the fertility crisis that will provide long-term solutions.

Future perspective

The scientific evidence provided at this congress indicates that mild approaches in IVF appear to be the way forward, with the introduction of single-embryo transfer. The need to take the welfare of the woman into account at the same time as the welfare of the child was emphasized. Mild IVF will also offer a cost-effective strategy for public health services.

Information resource

- The International Society for Mild Approaches in Assisted Reproduction (ISMAAR).
www.ismaar.org

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The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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