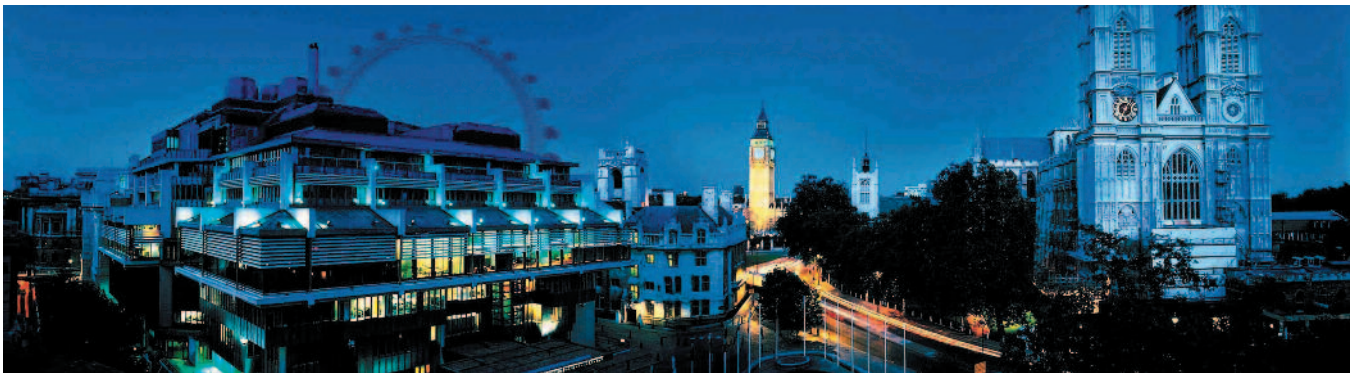
Final Programme
and Abstract Book



The Second World Congress on Mild Approaches in Assisted Reproduction

Embracing Mild IVF and IVM

London, 10th, 11th and 12th April 2008

At the Queen Elizabeth II Conference Centre, Westminster, London, UK

ISMAAR
International Society
for Mild Approaches
in Assisted Reproduction

www.ismaar.org

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ISMAAR has submitted this programme 'The Second World Congress on Mild Approaches in Assisted Reproduction Embracing Mild IVF and IVM' (London - UK - April 2008) for accreditation by the European Accreditation Council for Continuing Medical Education (EACCME).

HER Trust

This congress is organised by Health Education Research (HER) Trust, a charity devoted to the promotion of an evidence-based, holistic and supportive approach to women's reproductive health through education and research. HER Trust aims to be the most comprehensive, enlightened women's reproductive health charity across the world.

Helping women help themselves to better health

Welcome

The Second World Congress on Mild Approaches in Assisted Reproduction Embracing Mild IVF and IVM

We are delighted to welcome you to the Second World Congress on Mild Approaches in Assisted Reproduction to be held at the prestigious Queen Elizabeth II Conference Centre, Westminster London on April 10th, 11th, 12th 2008.

The Congress will focus on the objectives of ISMAAR to raise scientific and public awareness about mild, safe, more physiological and affordable approaches in assisted reproduction as its key topics. The Faculty will dedicate their time and efforts in promoting practical aspects of Mild IVF and IVM.

In addition, global concerns about protection of human fertility, safety, regulation, accessibility and affordability of ART will dominate the debate and agenda at the congress.

Best regards

Geeta Nargund
President

Rene Frydman
Chairman

Bart Fauser
Head of Scientific Committee

Contents

Invited Faculty

Mohamed Aboulghar (Egypt)
Nelly Achour-Frydman (France)
Esther Baart (Netherlands)
David Baird (UK)
Stuart Campbell (UK)
Marco Conti (USA)
Ian Cooke (UK)
Juana Crespo (Spain)
Alan Doran (UK)
Robert Edwards (UK)
Marinus JC Eijkemans (Netherlands)
Adrian Ellenbogen (Israel)
Renato Fanchin (France)
Bart Fauser (Netherlands)
René Frydman (France)
Stephen Hillier (UK)
Ilpo Huhtaniemi (UK)
Jacques Kadoch (Canada)
Osamu Kato (Japan)
Svend Lindenberg (Denmark)
Nick Macklon (Netherlands)
Raj Mathur (UK)
Philippe Monget (France)
Geeta Nargund (UK)
Karl Nygren (Sweden)
François Olivennes (France)
Willem Ombelet (Belgium)
Antonio Pellicer (Spain)
Nick Raine-Fenning (UK)
Hassan Sallam (Egypt)
Povilas Sladkevicius (Sweden)
Carlos Simón (Spain)
Shokichi Teramoto (Japan)
Basil Tarlatzis (Greece)
Dirk Timmerman (Belgium)
Krinos Trokoudes (Cyprus)
Filipo Maria Ubaldi (Italy)
Menon Usha (UK)
Sheryl Vanderpoel (Switzerland)
Zephne van der Spuy (South Africa)
Juan García Velásco (Spain)
Theresa K Woodruff (USA)
John Zhang (USA)

Thursday 10 April

Timetable of Events

Time	Churchill Auditorium	Speaker
	MILD IVF: *Chair: Bart Fauser and Geeta Nargund*	
09:00	Welcome	**Geeta Nargund**
09:10	Mild IVF-should it become the norm?	**Bart Fauser**
09:40	New developments in GnRH antagonist co-treatment	**Basil Tarlatzis**
10:00	Ovarian stimulation & embryo quality	**Esther Baart**
10:20	COFFEE	
10:40	Implications of ovarian stimulation for endometrial receptivity	**Nick Macklon**
11:00	The use of clomiphene citrate in mild IVF cycles	**Shokichi Teramoto**
11.20	Are steroids, IVIg, Viagra, heparin, etc. safe and necessary to improve implantation?	**Antonio Pellicer**
11:40	DISCUSSION	
12:00	**Lunch Reception at the House of Lords**	
	SAFETY, AFFORDABILITY, REGULATION: *Chair: Mohamed Aboulgar and Sheryl Vanderpoel*	
14:00	Affordability and access to ART	**Ian Cooke**
14:20	Improving safety and reducing complications	**Karl Nygren**
14:40	How should IVF success rates be measured and presented to the public?	**Alan Doran**
14:50	PANEL DISCUSSION Karl Nygren, René Frydman, Willem Ombelet, Svend Lindenburg, Jacques Kadoch, Filipo Maria Ubaldi, Geeta Nargund, Juan Garcia Velasco	
15:30	COFFEE	
15:50	Future healthcare policies	**Willem Ombelet**
16:10	Fertility needs in Africa and the impact of the HIV/AIDS	**Zephne van der Spuy**
16:30	Fertility crisis; Requires a radical policy rethink	**Geeta Nargund**
16:50	DISCUSSION	
17:10	Company-sponsored lecture: Science-based & Patient-centred Commitment to Fertility Care By Schering-Plough	**Hans Vermer**
17:20	Closing Remarks	**René Frydman**
17:30	Close of Day 1	

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Timetable of Events

Friday 11 April

Time	Churchill Auditorium	Speaker
08.30	**ISMAAR GENERAL ASSEMBLY**	
	PHYSIOLOGY & MODIFIED NATURAL CYCLE IVF: *Chair: David Baird and René Frydman*	
09:00	Control of ovulation rate	**Phillipe Monget**
09:20	Gonadotrophin and gonadotrophin receptor structure and function	**Ilpo Huhtaniemi**
09:40	The new biology of LH and ovulation	**Marco Conti**
10:00	Indications for modified natural cycle IVF	**René Frydman**
10:20	COFFEE	
10:40	*Free Communication: Modified Natural Cycle IVF and Mild IVF: A 10 years Swedish material*	***Arthur Aanesen***
10:55	*Free Communication: Oestradiol-priming improves oocyte-retrieval in natural-cycle IVF*	***Mikael Tang-Pedersen***
11:10	Endometrium & embryo quality in modified natural cycle IVF	**Juana Crespo**
11:30	Fading follicles – the essence of ovarian ageing	**Stephen Hillier**
11:50	*Free Communication: IVF lite: Modified natural cycle IVF/ICSI as standard care*	***Christian Hammer***
12:15	*Free Communication: Invocell: A New device that allows IVF in an office setting*	***Claude Ranoux***
12:30	**30 Years of IVF**	**Robert Edwards**
13:00	LUNCH	
	Natural Cycle/Modified Natural Cycle IVF Workshop: *Panel: René Frydman, Osamu Kato, Filipo Maria Ubaldi, Juan Garcia Velasco, Jacques Kadoch, Geeta Nargund, Krinos Trokoudes*	
14:00	Indications and the Role of Natural/Modified Natural cycle IVFPCO/PCOS	**Filipo Maria Ubaldi**
14:15	Pre-cycle preparation & Cycle monitoring	**Adrian Ellenbogen**
14:35	Prevention of LH surge & Ovulation triggering	**Jacques Kadoch**
14:50	Follicle aspiration and Day of ET	**Krinos Troukodes**
15:05	Luteal phase supplementation	**Juan García Velásco**
15:20	DISCUSSION "Lessons from Natural/Modified Natural cycle IVF"	
15:35	COFFEE	
15:50	**MILD IVF – WORKSHOP Indications and the Role of Mild IVF**	**Nick Macklon**
16:05	Health Economics Aspects of Mild IVF	**Marinus JC Eijkemans**
16:20	Embryological aspects and the day of embryo transfer	**Esther Baart**
16:35	The role of clomiphene citrate in Mild IVF	**J Zhang**
16:50	Panel discussion on practical aspects of Mild IVF	
17:00	Closing remarks	**Geeta Nargund**
17:30	Close of Day 2	

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Friday 11 April

Timetable of Events

Time	Westminster Suite	Speaker
IVM: CLINICAL AND BIOLOGICAL CONSIDERATIONS *Chair: Robert Edwards and François Olivennes*		
14:00	Does IVM improve success rates of IVF in women with PCO/PCOS	**Svend Lindenberg**
14:20	Essential requirements for oocyte maturation	**Theresa K Woodruff**
14:40	Is the oocyte safe after IVM?	**Nelly Frydman**
15:00	The impact of induction of ovulation on endometrial receptivity	**Carlos Simón**
15:20	IVM makes Natural Cycle IVF an acceptable treatment for certain couples	**Renato Fanchin**
15:40	COFFEE	
16:00	Panel discussion on practical aspects of IVM	
17:00	End of Programme in the Westminster Suite	

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Saturday 12 April

Timetable of Events

Time	Westminster Suite	Speaker
ADVANCED ULTRASOUND IN GYNAECOLOGY AND REPRODUCTIVE MEDICINE DIPLOMA COURSE Chair: Stuart Campbell		
08.30	REGISTRATION AND COFFEE	
08.50	Welcome and Introduction	**Stuart Campbell**
09.10	Principles and Safety of Clinical Ultrasound Including Doppler and 3D Ultrasound	**Stuart Campbell**
09.30	Normal Morphology of Uterus	**Stuart Campbell**
09.50	Normal and Abnormal Morphology of Ovaries including PCO/PCOS	**Nick Raine-Fenning**
10.10	COFFEE AND DISCUSSION	
10.30	One-stop fertility assessment	**Geeta Nargund**
11.00	Assessment of ovarian reserve & implications in ART	**Renato Fanchin**
11.20	Hystero-Contrast Sonography: Set Up and Technique	**Povilas Sladkevicius**
11.40	3D Ultrasound in Gynaecology & Reproductive Medicine	**Nick Raine-Fenning**
12.00	Panel Discussion	
12.30	LUNCH	
13.30	Management and prevention of OHSS	**Raj Mathur**
13.50	Abnormal morphology of uterus and factors affecting implantation	**Stuart Campbell**
14.10	Ultrasound - guided embryo transfer	**Hassan Sallam**
14.30	Coffee	
14.50	Diagnosis and Management of ovarian cysts	**Dirk Timmerman**
15.10	Screening for ovarian and Endometrial cancer	**Usha Menon**
15.30	Early Pregnancy Assessment and Ectopic Pregnancy	**Dirk Timmerman**
15.50	**Case Discussions and Video Demonstrations:** Baseline Scan in Infertility/Assisted Conception Management • Management of fibroids, adenomyosis & Endometriomas in infertity care • Markers of Implantation • Early Pregnancy Scanning Including Complications	
17.00	END OF COURSE	

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Mild IVF – should it become the norm?

Prof. Bart CJM Fauser

Department of Reproductive Medicine and Gynecology, University Medical Center, Utrecht, The Netherlands

Currently, over 1 million cycles of IVF are performed globally each year and an estimated 3 million IVF children have been born so far. In some Western countries up to 1 in 20 children born is from IVF, whereas in other countries virtually no IVF is available. The majority of IVF children are from multiple pregnancies, and cost associated with pregnancy complications outweigh the cost of IVF itself. Overall efficacy of IVF treatment remains modest, with a 25% pregnancy rate per treatment cycle. Coverage of IVF cost by health insurance is rare (even in developed countries) and therefore access to IVF remains insufficient. These conditions create the paradox of risk for overtreatment in commercial settings and extensive undertreatment in less privileged societies.

The clinical development of IVF is characterized by profound ovarian stimulation, in an attempt to maximize pregnancy rates per cycle. These approaches aim at obtaining many oocytes to counterbalance shortcomings in in vitro oocyte fertilisation and subsequent embryo development, as well as embryo selection for transfer. Over the years ovarian stimulation protocols have become extremely complex, time consuming, expensive, and are associated with considerable patient discomfort and chances for complications. Moreover, there is increasing evidence that such stimulation protocols may harm embryo quality, endometrial receptivity and implantation. In addition, distress associated with treatment causes significant patient drop out (even under conditions where IVF is reimbursed), denying the couple additional pregnancy chances from repeated IVF.

The need for profound changes in IVF is increasingly recognized. When referring to 'mild IVF', a distinction should be made between mild ovarian stimulation and 'mild' embryo transfer (preferably one). 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 seem to go hand in hand and reinforce one another.

Undoubtedly, both mild ovarian stimulation and the transfer of fewer embryos will result in somewhat reduced pregnancy rates per cycle. Because mild stimulation cycles are shorter en cheaper more IVF cycles can be performed in a given period of time at similar cost and patient discomfort. The aim of mild approaches is NOT maximizing pregnancy rates per cycle at all cost, but rather to optimize the balance of chances for true success in terms of healthy babies born per initiated IVF treatment (which may include multiple cycles) and patient discomfort, complications and cost of treatment. Resistance to the further development of these mild strategies for IVF may be explained by the focus of patients on rapid results, and insufficient awareness of the significance of optimal periconceptional and perinatal conditions for health of off-spring during adult life. Moreover, patients or health insurance companies pay per cycle and centers are usually compared on the basis of pregnancy rate per cycle. The consequence of the current paradigm is much prenatal morbidity and mortality, fetal reduction, enormous cost and human suffering.

The assessment of the quality of IVF programs away from the isolated focus on surrogate outcomes per cycle is a prerequisite for the further advancement of IVF. Novel approaches hold the promise of more patient friendly IVF treatments and improved health of off-spring. Moreover, improved cost-effectiveness of IVF will eventually augment social acceptance and access to IVF.

New Developments in GnRH antagonist Co-Treatment

Basil C. Tarlatzis, MD, PhD

Professor of Obstetrics – Gynecology and Reproductive Medicine, Aristotle University of Thessaloniki, Greece

GnRH antagonists have been introduced in clinical practice during recent years and are characterised by a similar probability of pregnancy to GnRH agonists. However, GnRH antagonists, are much more patient friendly and safer in terms of OHSS occurrence. Optimization of GnRH antagonists protocols is still an ongoing process. Currently, available data suggest that prolongation of follicular phase significantly decreases the probability of pregnancy. Moreover, patients with elevated progesterone at initiation of stimulation have significantly fewer chances of achieving an ongoing pregnancy. Luteal support remains mandatory, while the replacement of hCG by GnRH agonist does not appear to be feasible. Although not conclusive, existing data are not in favor of increasing the starting dose of gonadotrophins, of luteinizing hormone (LH) supplementation or of using a flexible antagonist protocol.

Ovarian stimulation and embryo quality: less is more?

Esther Baart

By limiting the number of embryos transferred to the uterus to only a single embryo, the risk for multiple gestations can be reduced. In order to improve the effectiveness of single embryo transfer, the ability to select the embryo with the highest potential to develop into a healthy child is of vital importance. While embryos rated as high quality by standardized morphological assessment are associated with higher implantation and pregnancy rates, it is still not possible to predict with certainty which embryo will implant and has the highest potential to develop into a healthy child. An increasing body of evidence suggests that the incidence of chromosomal abnormalities in embryos is extremely high and good embryo morphology does not necessarily exclude an abnormal chromosomal constitution. Since aneuploidies are considered the main cause of embryonic wastage and loss, this phenomenon may be primarily responsible for the relatively poor pregnancy rates reported after IVF.

Our group recently completed a randomised controlled trial comparing a mild stimulation regimen and gonadotrophin-releasing hormone (GnRH) antagonist co-treatment with a conventional high-dose exogenous gonadotrophin regimen and GnRH agonist co-treatment1. We employed preimplantation genetic screening (PGS) to study the effect of the two stimulation approaches on the chromosomal constitution of the resulting embryos. We observed that mild stimulation reduced the number of oocytes retrieved but resulted in a significantly higher proportion of chromosomally normal embryos. Consequently, the absolute number of chromosomally competent embryos obtained per woman was similar in both stimulation groups, while no differences in overall embryo morphology were detected between the groups. In addition, analysis of two cells per embryo demonstrated that the increase in chromosomal abnormalities observed after conventional stimulation, was mainly due to an increased incidence of chromosomal mosaicism.

The observed differences between the two stimulation protocols maybe due to a different impact on both follicle recruitment and selection. In the natural cycle, a synchronous cohort of follicles gains gonadotrophin dependence due to the intercycle rise in endogenous FSH and are thus recruited to continue development. The dominant follicle is selected around the mid-follicular phase from this pool of 20-30 antral follicles. Decreasing FSH concentrations are crucial for this selection process. In mild stimulation, interference with decreasing FSH allows the development of multiple follicles, whereas follicle recruitment and the initial stages of selection remain unaffected. In contrast, during conventional ovarian stimulation complete pituitary down regulation by GnRH agonist cotreatment is achieved, thereby completely overruling natural follicle recruitment and selection and allowing the non-discriminate growth of many follicles at different developmental stages.

Our findings show for the first time a direct relationship between ovarian stimulation and the chromosomal competence of embryos. They furthermore suggest that selection of better quality embryos may be achieved by applying milder stimulation approaches.

Baart EB, Martini E, Eijkemans MJ, Van Opstal D, Beckers NG, Verhoeff A, Macklon NS, Fauser BC. Milder ovarian stimulation for in-vitro fertilization reduces aneuploidy in the human preimplantation embryo: a randomized controlled trial. Hum Reprod. 2007; 22 (4): 980–988

Implications of Ovarian Stimulation for Endometrial Receptivity

Prof. Nick S. Macklon
UMC Utrecht, The Netherlands

Ovarian stimulation is employed in in-vitro fertilization (IVF) programs in order to produce multiple embryos per cycle of treatment. While this enables selection of higher quality embryos for transfer, ovarian stimulation also results in supraphysiological levels of progesterone and estradiol. These high sex steroid concentrations and a disrupted luteal phase are considered to be responsible for an impaired endometrial receptivity in IVF. The clinical effect of ovarian stimulation on endometrial receptivity is illustrated by the oocyte donation model, in which embryos equally divided among donors and recipients result in higher implantation rates in the recipients who have not undergone ovarian stimulation. In addition, high responders to ovarian stimulation show increased implantation rates when milder stimulation, resulting in lower estradiol levels, is applied.

Further evidence for sex steroid mediated disruption of endometrial receptivity comes from histological, histochemical and gene expression studies. Estrogen and progesterone act through endometrial nuclear receptors, which are usually down-regulated in response to physiological increases in estrogen and progesterone in the early luteal phase. Ovarian stimulation has been shown to advance this down-regulation of steroid receptors. The histological changes throughout the menstrual cycle were first described by Noyes. Next to an advancement in nuclear receptor down-regulation in stimulated cycles, a peri-ovulatory endometrial advancement of 2-4 days according to the Noyes criteria is observed. Elevated estrogen concentrations may increase sensitivity to progesterone action and thus lead to secretory advancement. Immunocytochemically, studies have indicated a disruptive effect on molecular processes in implantation by ovarian stimulation. A number of proteins, which are considered to be key regulators in the implantation process, such as integrins, L-selectin, and glycodelin-A were shown to be differentially expressed in stimulated compared to natural cycles. In recent years, the emergence of micro array technology allows the study of the entire gene expression

pattern of the endometrium and several studies have reported gene dysregulation following ovarian stimulation. Although gene expression studies offer a powerful tool for the study of implantation, it is uncertain to what extent dysregulated gene expression is translated into altered levels of secreted proteins.

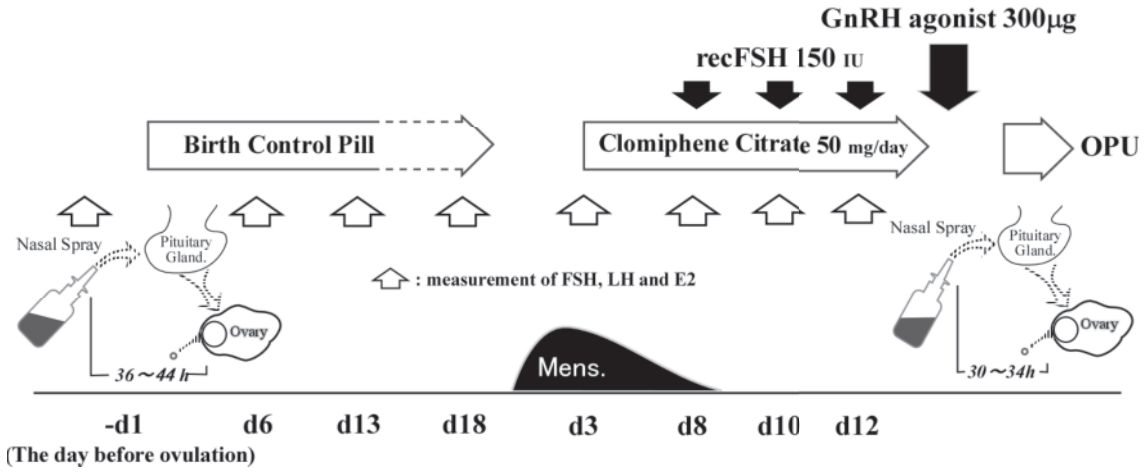
Understanding the molecular events underlying the development and continuation of a receptive endometrium is fundamental if we are to further improve the success of embryo implantation during IVF therapy. Our group has developed a novel means of assessing the intra-uterine milieu by endometrial secretion analysis which is objective, non-invasive and represents the in-vivo milieu encountered by the embryo. This approach may help to elucidate the impact of ovarian stimulation on the expression of key regulatory cytokines, chemokines and growth factors in endometrial secretion and the uterine blood flow, at the time of embryo transfer.

Clomiphene Cycle

Shokichi Teramoto
Shimbashi Yume Clinic

Enclomiphene, an isomeric component of clomiphene citrate, acts antagonistically to estradiol (E2) receptor at the level of the hypothalamus, inhibiting both negative and positive feedback, resulting in the induction of ovarian stimulation and suppression of ovulation. This ovarian stimulation protocol takes full advantage of these characteristics of clomiphene citrate (Fig. 1). Administration of 50mg clomiphene citrate (Serophene; Serono, Japan) is initiated on Cycle d3, which is defined as the 7th day after the end of oral contraceptive administration. From d8, patients receive 150 IU of FSH (Follistim; Organon, Japan every other day. When the size of the dominant follicle and the E2 level reach the predefined values, GnRHa is administered to induce follicle maturation. Oocytes are then retrieved 32-34 hours later. Because the short half-life of enclomiphene (less than 24 hours) is of critical importance in this protocol, it is necessary to continue oral administration of clomiphene citrate until the day before the maturation is triggered (Teramoto, 2007). Every patient's menstrual cycle is regulated by the use of oral contraceptives (Marvelon; Organon, Japan) prior to the oocyte-retrieval cycle in order to homogenize the growth of antral follicles (Fig. 1). The point of this is to inhibit the level of the FSH and to reduce the follicular size by adjusting the dose and the duration of the oral contraceptives, the target levels for these being less than 1.0 IU/l for 5 days or longer and less than 3 mm in diameter, respectively. Table 1 shows the outcome of this protocol between May 2007 and February 2008. All the embryos were cultured to the blastocyst stage and cryopreserved. After thawing, single embryo transfer was carried out in the Natural cycle or Hormone Replacement cycle. The success rates for blastocyst cryopreservation and pregnancy were 67% and 33% in the 27-39 year-old group, and 31% and 9% in the 40-47 year-old group respectively. The dosage of FSH per cycle was 474 IU. This mild stimulation protocol renders the use of HCG unnecessary and eliminates the occurrence of complications, including OHSS, thus giving least damage to the ovarian functions. Furthermore, the total cost of the medication and various examinations is approximately 200, making the protocol an extremely economical one.

Fig. 1 Clomiphehe Cycle Protocol



Age range Mean (SD)	BMI SD	No. of initiated cycles No. of cancelled cycles †	No. of oocyte cycles in which oocytes were retrieved Mean number of oocytes retrieved	No. of cycles in which oocytes were cleaved Mean number of oocytes cleaved	No. of cycles in which oocytes were cryopreserved Mean number of oocytes cryopreserved	No. of cycles in which oocytes were thawed/transferred No. of cycles in which pregnancy was achieved Rate of pregnancy (%)‡
27-39	20.6	446	428	399	299	317
35.3 (2.8)	(2.4)	18	4.3	3.4	2.4	146 32.7
40-48	20.8	344	301	265	106	113
42.5 (1.8)	(2.4)	43	2.5	2.4	1.6	31 9.0

† Cancelled cycles: Cycles where the oocyte could not be inseminated due to premature or spontaneous ovulation, or the oocyte's defectiveness.

‡Rate of pregnancy: The rate of pregnancy cycles in relation to initiated cycles.

Table 1: Outcome of the clomiphene cycle protocol

Are Viagra, aspirin, heparin, IVIG and steroids safe and necessary to improve implantation?

Antonio Pellicer, Marco Melo and Carlos Simón
Instituto Valenciano de Infertilidad (IVI), University of Valencia, Spain

Successful implantation is dependent of a close interaction between a receptive endometrium and a normal embryo. When the model of oocyte donation, in which endometrial preparation has not changed, is observed over the years, a clear trend towards increased implantation and pregnancy rates is seen (Remohi et al., 1997; Budak et al. 2007), providing evidence that our laboratory methods have substantially improved the quality of the embryos and therefore ART success rates. Thus, the first message is to check carefully to the quality of the embryos produced by a given couple, although methods and approaches to do so are out of the scope of this presentation.

During the last few years, considerable progress has been made towards a better understanding of the process of implantation. It is clear that the preparation of the endometrium for implantation is probably achieved by the coordinate actions of different mediators. Steroids and paracrine mediators, such as cytokines and growth factors, are necessary for an appropriate decidualization. In an effort to improve IVF outcome, numerous pharmacologic interventions have been studied as adjuvant therapy over the years.

Sildenafil citrate (Viagra) is a type 5-specific phosphodiesterase inhibitor that prevents the breakdown of cGMG and potentiates the effects of nitric oxide on vascular smooth muscle leading to vasodilatation. In the last years, Viagra has been studied in patients with implantation failure, showing to improve the endometrial thickness and uterine blood flow (Sher and Fisch, 2000, 2002). However, a significant improvement in implantation in well randomized-controlled trials is lacking.

Low-dose aspirin is a widely used vasoactive substance that exerts its effects by inhibiting the synthesis of thromboxane A2 (a vasoconstrictor and promoter of platelet aggregation) more than that of prostacyclin (a vasodilator). Due to these antithrombotic and vasodilatory effects, aspirin has been one of the agents studied in several trials to evaluate its potential role in increasing IVF success rate. The report of two recent metaanalysis containing each 6 to 7 clinical trials show that low dose aspirin does not improve implantation, pregnancy or miscarriage rates; similarly, aspirin is not effective in reducing the incidence of ectopic pregnancies (Gelbaya et al., 2007; Khairy et al., 2007). Regimens with heparin, usually added to aspirin, have also been evaluated in patients with implantation failure with similar outcome (Fiedler and and Würfel, 2004). On the top of that, the use of ancoagulants without indication can potentially originate complications in some patients that need to be discussed in depth.

Immunotherapy such as with intravenous immunoglobulin (IVIG) has been introduced into IVF programs with the hope of improving ART success. It appears that IVIG may have several mechanisms of action, including modulation of cytokine production and/or release, alterations of lymphocyte proliferation and function and inhibition of natural killer cytolytic activity. A prospective-randomized study failed to show any improvement in ART outcome with this medication (Stephenson and Fluker, 2000). Also, glucocorticoids have been used to improve embryo implantation acting as an immunomodulatory agent. A Cochrane Database analysis of this topic has shown that there is no clear evidence that administration of peri-implantation glucocorticoids in ART cycles significantly improves clinical outcome (Boomsma et al., 2007).

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Sher G, Fisch JD. Vaginal sildenafil (Viagra): a preliminary report of a novel method to improve uterine artery blood flow and endometrial development in patients undergoing IVF. Hum Reprod 2000; 15(4):806-9.

Sher G, Fisch JD. Effect of vaginal sildenafil on the outcome of in vitro fertilization (IVF) after multiple IVF failures attributed to poor endometrial development. Fertil Steril 2002; 78(5):1073-6.

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Khairy M, Banerjee K, El-Toukhy T, Coomarasamy A, Khalaf Y. Aspirin in women undergoing in vitro fertilization treatment: a systematic review and meta-analysis. Fertil Steril 2007; 88(4):822-31.

Stephenson MD, Fluker MR. Treatment of repeated unexplained in vitro fertilization failure with intravenous immunoglobulin: a randomized, placebo-controlled Canadian trial. Fertil Steril 2000; 74(6):1108-13.

Boomsma CM, Keay SD, Macklon NS. Peri-implantation glucocorticoid administration for assisted reproductive technology cycles.Cochrane Database Syst Rev 2007; (1):CD005996.

Affordability and access to ART

Ian Cooke
Emeritus Professor , University of Sheffield, Director of Education, IFFS, i.d.cooke@sheffield.ac.uk

Affordability and access are two important elements often not considered by health care professionals. The former is country dependent and is influenced by whether care is available in the private sector or whether there is provision within a national health service. Access is related, but there are very different aspects in the developed and in the developing world. Although access in the developed world may seem to be economically determined, there is a major element of political will involved in the creation of any ART component of a national health service. Although this is also true in the developing world the economic pressures are much greater. The quality of existing health services, of staff, and the organisation and governance of service provision are crucial in determining the level of provision and hence access. Private sector care is minimal and generally unaffordable.

The stimulus of the Millennium Development Goals has lead to the creation of clear programmes to achieve improved coverage of care in areas such as maternal and neonatal mortality, malaria management and the provision of contraceptive and abortion services. as well as the recognition and prevention of intimate partner violence. These details of these regimes can act as a spur to create realistic programmes for coverage by appropriate assisted reproductive technologies (ART). Elements will be highlighted to help build regimens providing affordable and accessible ART in both the developed and developing worlds.

Improving safety and reducing complications.

Karl Nygren
IVF-clinic, Queen Sophia Hospital, Stockholm, Sweden

The safety of ART treatment is crucial for its acceptance by couples, professions and society. Indicators of benefit include, in addition, efficacy, quality, cost and access, but safety is the major concern. Safety relates to the children born, the mothers of these children, the women unsuccessfully treated – and the men.

Factors possibly responsible for an increased medical risk include different clinical and laboratory ART techniques per se, clinical and laboratory policies in current use, and also parental characteristics, be they inherited or acquired from disease or from life-style. Also, pre- and postnatal care is of importance, e.g. medication during pregnancy and modes of delivery. Most of these factors show a variation over time and also geographically.

Country specific and time specific differences make a continuing, national surveillance of safety a high priority. However, there is at present a paucity of national ART safety data.

ART, as practiced today, carries with it well documented (albeit from a limited number of countries) increased risks for the children and their mothers and much less well documented risks for the women who are unsuccessfully treated – and possibly the men.

Can the safety on ART be improved?
Yes, it can and it must.

There are three obvious steps to be considered:

- Hasten the transition to single embryo transfer, SET, as the norm. This had already been successfully done in a number of countries with a dramatic reduction of medical risks related to pre-maturity (not yet documented in all details). A reduction of risk, but not a complete elimination of the risk increase will follow. A small increase in birth defects will remain
- Use milder forms of controlled ovarian hyper-stimulation, COH. This is what this congress is all about. Different clinical protocols have been designed and are currently being tested and documented. Short term complications, some of a potentially very serious nature, such as ovarian hyper stimulation syndrome, OHSS, will be substantially reduced, as well as long term medical risks.
- Invest in national safety surveillance systems to assure acute alarm systems and the monitor of long term risk trends. If a national system is out of reach, use data from nearby countries but note country specific factors.

In summary, it is within reach now, to substantially improve safety and reduce complications in ART treatments.

Future healthcare policies

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Introduction

The current practice in medically assisted reproduction is still too exclusively focused on effectiveness and success rates. To increase the effectiveness of IVF remains the major objective of infertility specialists. It is well known that the psychological, physical and emotional stress experienced by both women and men during assisted conception treatment is high and underestimated. The final result is that many potential ART-couples never go to the fertility clinic and a high drop out during ART treatment, even if the treatment is reimbursed !

To convince healthcare policy makers and/or health insurance providers to reimburse ART and to convince couples to come to the fertility clinics, we have to change our strategy. Couple-friendly ART should be standard-practice.

Cost-effectiveness

Infertility treatment can be performed in a less costly way, but even if enough studies have proven the value of such methods, most fertility specialists are not interested: (1) An efficient first line approach of infertility can be realised through fertility awareness programs but the interest is minimal. (2) When ovarian stimulation is needed in IUI treatment cycles, clomiphene citrate (CC) can be used as a first line stimulation drug instead of the more expensive gonadotrophins and/or recombinant FSH, but most fertility specialists still opt for the more expensive medication. (3) A third example is the recommendation to offer up to four cycles of intrauterine insemination (IUI) to couples with mild male factor fertility problems, unexplained infertility or minimal to mild endometriosis before IVF is started. Data from Australia and New Zealand clearly show that almost 80 % of centers are convinced of the cost-effectiveness of IUI, but nearly a third of centers still promote IVF as a first-line treatment even with patent tubes and normal semen. The fear for a diminished success rate and other more material benefits all contribute to non-optimal procedures. The influence of drug companies on the way assisted reproduction is practiced should not be underestimated either.

Access to treatment

ART is a relatively expensive treatment in most countries. This is especially true in countries in which infertility is primarily private treatment without (private of public) insurance coverage. The costs of IVF/ICSI to individual couples range from 10 % of annual household expenditures in European countries to 25 % in Canada and the USA. Even when couples are paying for the ART procedures out-of-pocket, the care for their offspring remains a burden on the community if neonatal, paediatric, social and educational services are financed by public funds. The Belgian project in which reimbursement of ART-related laboratory activities is linked to a transfer policy aiming at substantial multiple pregnancy reduction, is a good example of cost-effective health care through responsabilisation. Some couples will always opt for the treatment that costs them personally the least even if that option means a more aggressive technique for themselves and a much more expensive option for society. The reimbursement system should avoid such pitfalls.

Risk minimisation

A number of cost reducing measures involve the rejection of the 'aggressive' standard hormonal stimulation. This movement has been given several labels: 'soft', 'natural cycle', 'minimal stimulation' IVF etc. A major advantage of these procedures is the lower risk of ovarian hyperstimulation syndrome (OHSS). The reduction or even elimination of health risks for women would deprive the opponents of IVF of a very strong argument. The second main advantage is the significantly lower risk of multiple pregnancies. Single embryo transfer (SET) was a consequence of the realisation that the ultimate goal of assisted reproduction was not to create as many children as possible but to offer the parents a healthy singleton, a twin pregnancy being regarded as an adverse outcome. It's obvious that in non-IVF assisted reproduction, minimal ovarian stimulation also reduces the risk for multiple pregnancies and OHSS.

Burden minimisation
The psychological, physical and emotional stress for couples treated with ART is high and underestimated and is the main reason for the high drop-out rate. Mild stimulation in combination with SET represent a patient-friendly alternative for conventional IVF. Milder stimulation protocols have fewer side effects, and are also less stressful for the patients. Although it has become standard practice to stress patient's rights and to allow patients to participate in treatment decision making, patient preferences are only rarely studied in the field of reproductive medicine. Recent studies have shown that patients counterbalance the disadvantages of low stimulation (less efficiency per cycle, more cancellations) by the advantages on other aspects (few side effects, short duration, simplicity).

Conclusion
The current practice in ART too exclusively focused on effectiveness and success rates. Couple-friendly ART is composed of a mix of four criteria: all four components have a strong normative ethical basis. Cost-effectiveness relies on the optimal use of community resources to maximise well-being; access should be equitable and fair; minimal risk is founded on the fundamental 'do-not-harm' rule and minimal burden is largely based on the autonomy principle. It is high time to rethink and change our strategy in clinical practice. Affordable and couple-friendly ART are also important when dealing with the problem of infertility in developing countries.

Fertility Needs and the HIV/AIDS Pandemic: An African Perspective

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Fertility is highly valued in Africa for many reasons. Children are important for social status and long-term security and, as a consequence, failure to conceive or unsuccessful pregnancy outcomes may have very negative psycho-social consequences. Women lose status, support and are potentially very disadvantaged if they do not have children. Men also are similarly affected, although to a lesser degree. Even though Africa has the highest rate of disease-induced infertility in the world, little emphasis has been placed on fertility needs in sub-Saharan Africa. The main cause of infertility is tubal disease but unfortunately tubal surgery is often not possible and assisted reproductive technologies are usually not available. There is a reluctance among funders to spend resources on infertility programmes and the needs of couples with unmet fertility aspirations are often ignored.

The HIV/AIDS pandemic has presented many challenges and arguably resulted in more tragedy than any other medical condition in the past century. It is undoubtedly a condition which predominantly affects sub-Saharan Africa and the impact of AIDS on fertility aspirations and the outcome of pregnancy is often insufficiently recognized. HIV infection presents a profound clash with fertility and patients are often advised to practice safe sex and their fertility needs are not appropriately addressed. It is also evident that in Africa, until recently, AIDS was regarded as a universally fatal condition. It affects adults during their most productive years and is presently the leading cause of death in Africa. While the AIDS pandemic has attracted considerable international funding, unfortunately this has often been at the cost of other reproductive health requirements including contraceptive services and infertility care.

HIV infection reduces fertility both through biological and psychosocial mechanisms. While there may be a reduction in fecundity secondary to AIDS, there remains an ongoing desire for fertility. It is a particular challenge in resource-poor areas to address the needs of HIV+ individuals, offer them appropriate treatment for HIV and also for infertility. There is also a debate as to how we counsel the fertile HIV+ couple and what treatment we offer the discordant couples. Unfortunately at present healthcare facilities are overwhelmed by the impact of the pandemic.

While we may stress the need for adequate reproductive health care for all women in Africa, it must also be recognized that offering fertility therapy to couples without providing appropriate obstetric care is irresponsible. Undoubtedly the need in Africa is to provide infertility services, adequate treatment of HIV infection and to ensure that maternity services are in place to care for the pregnant mother and her infant and ensure that maternal to child transmission is prevented. In the final analysis we have to be advocates for the unborn child and ensure that he/she is born unaffected and into an environment that will offer long-term care and protection.

The Fertility Crisis: requires a radical policy rethink

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There are concerns about ageing population and lower fertility and birth rates in the developed world. Across Europe, United States, Canada and Japan, governments are using a range of policies to try and tackle this problem. Some countries have robust family policies aimed at promoting fertility rates. Others are trying to implement family-friendly policies. At the same time, there has been an ongoing political debate about the conflict between gender equality, independence of individuals and promoting family values. The government needs to create conditions that help women to have children while continuing to succeed in their chosen careers.

Lower levels of fertility are due to social changes such as delayed entry into parenthood and decline in marriage as

well as economic uncertainty due to lack of affordable housing, free child care and flexible, part-time career opportunities for women.Furthermore,there are environmental and life-style factors contributing to reduced fertility.

Subfertility is a multidimensional problem with a negative impact on family life, society and national economies. Therefore, long-term population based policies are required to achieve stable and high fertility rates.

Britain seems to have a reactive approach with limited state funding directed towards "problem cases" rather than tackling the wider problems associated with declining fertility.

This lecture will demonstrate that a radical policy rethink is required to tackle this "fertility crisis" in the long-term.

The management of fertility problems should not just fall at the door of the Department of Health. Freezing eggs or immigration not primary long-term solutions to reverse declining birth rates or ageing population. Central government should tackle this problem head on and consider creating a department or a unit dedicated to a multi-faceted, proactive family policy with funds and resources from departments of education, social care, work and pensions, local governments and directly from the treasury.

The main components of a long-term radical policy to tackle the fertility crisis should be as follows:

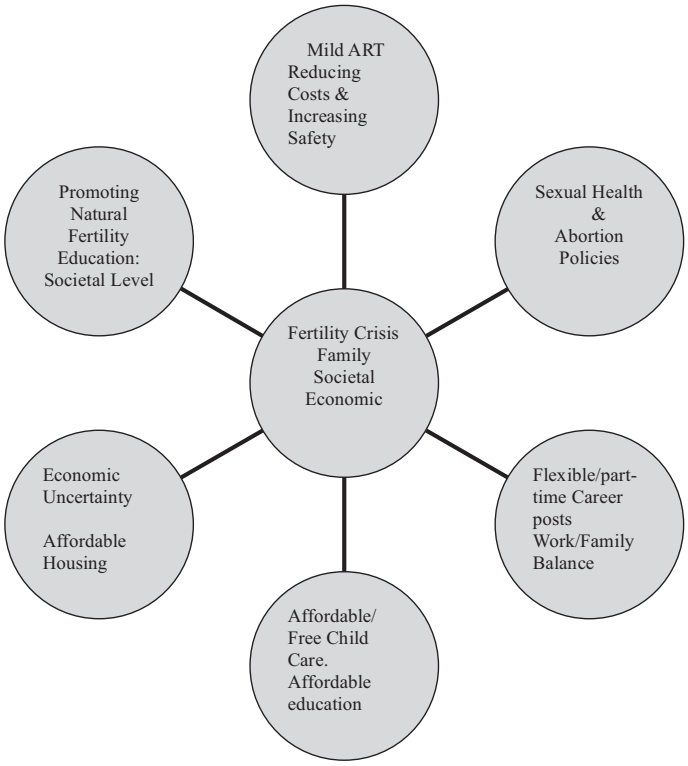
- A strong emphasis on protection of reproductive health in secondary school curriculum, based on "Prevention is better than Cure" approach
- "Pre-conception care" clinics must be established within the National Health Service specifically designed to educate men and women on factors affecting their fertility and to help them help themselves to natural conception
- An ongoing fertility awareness programme for communities funded by local governments in conjunction with the local voluntary sector. A tailored and sensitive programme would enhance the effect in a multicultural population
- A long-term plan for affordable housing for young couples should be continued. This could help couples plan an early parenthood

Provision of affordable and high quality chid care facilities should be available

Flexible, part-time career posts for women should be a priority

Provision of safe, mild and cost-effective assisted reproduction treatments (ART) with single embryo transfer (SET) would help to offer more treatment cycles within the budget available. This would save costs associated with drugs, hospital admissions for OHSS and multiple pregnancies.

In summary, we need a coordinated proactive approach to address the fertility crisis with long-term solutions. This is something our government needs to consider now.



A long-term, multi-dimensional solution to the fertility crisis.

The control of ovulation rate

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In mammalian ovary, the mechanisms that underlie the regulation of ovulation rate were enigmatic until the identification of the fecundity genes affecting ovulation rate in sheep, bone morphogenetic protein-15 (BMP-15), growth and differentiation factor-9 (GDF-9) and BMP receptor-1B (BMPR-1B), all these three genes belonging to the BMP super-family. Since 2000, a total of five complete loss of function mutations affecting oocyte-specific BMP-15 gene and one mutation affecting GDF-9 gene have been shown to be responsible for an increase of ovulation rate in heterozygous sheep, and sterility in homozygous sheep, with a blockage of ovarian folliculogenesis in primary follicles. One partial loss of function mutation in BMPR-IB gene has also been discovered in 2001, leading to an additive increase of ovulation rate in both hetero- and homozygous ewes. Several other genes or genomic loci affecting ovulation rate are suspected or studied in sheep as well as in cattle, the more advanced being a gene located on ovine chromosome 11. Interestingly, the genomic region does not seem to contain a gene of BMP family, suggesting another original way of regulation of ovulation rate.

Gonadotrophin and Gonadotrophin Receptor Structure and Function

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The structures and physiological functions of the two gonadotrophins, FSH and LH, are now well delineated. However, novel information about the pathophysiology of gonadotrophin action is accumulating both from novel human mutations of the gonadotrophin and gonadotrophin receptor genes and from genetically modified mice with enhanced (transgenic) or inhibited (knockout) gonadotrophin action. The purpose of this presentation is the review first the recent findings on human mutations in FSH, LH and their receptors in humans. The second topic covers the phenotypes detected in genetically modified mice, including the tumorigenic phenotype of transgenic mice producing high levels of hCG, the ovarian phenotypes of mice with knockout of LH receptor, and activating mutation of FSH receptor. The findings in mice are usually very close phenocopies of a similar mutation in humans, and therefore they make it possible to address the molecular pathogenesis of human genetic diseases in experimental in vivo conditions. Furthermore, the mouse models serve as useful hypothesis generating tools for future translational and clinical research.

The EGF network, ovulation and oocyte quality

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We have recently proposed that the LH-dependent activation of EGFR signaling is a critical event in ovulation. In support of this hypothesis, in vitro exposure of mouse ovulatory follicles to EGF-like growth factors recapitulates many of the LH effects at the time of ovulation. In vitro pharmacological data as well as in vivo observations using models of progressive disruption of the EGF network have further confirmed the intermediate role of this network at this critical stage of ovarian function. In addition to rodents, a role for these growth factors in humans is suggested by the accumulation of large amounts of bioactive EGF-like growth factors in the follicular fluid of human ovulatory follicles. Collectively, these data indicate that EGF-like growth factors are necessary and sufficient to induce oocyte maturation, cumulus expansion and ovulation in mammals. In order to define whether EGF-like growth factor production affects oocyte developmental competence, the properties of oocytes produced in the presence of a defective EGF network was investigated. To this aim, oocytes from Areg-/- mice were used for in vitro fertilization and preimplantation embryo development. Denuded oocytes or cumulus oocyte complexes derived from these mice were fertilized at a reduced rate compared to wild type controls. Moreover, the efficiency of in vitro embryo development to the blastocyst stage was significantly reduced in the Areg-/- embryos. Counting of the number of cells in morulae indicated the rate of cell division is reduced in the Areg-/- embryos. This phenotype could be partially rescued by exposure of the cumulus oocyte complex to recombinant AREG. This growth factor is not produced by the oocyte or the embryo but its mRNA is present in cumulus cells. Although Egfr mRNA is present throughout oocyte maturation up to the two-cell embryo, the translation of this mRNA is likely regulated since translation is minimal in GV oocytes, and increases in MII oocytes and zygotes. Thus, we propose that embryos at the early stage of development express functional EGFRs and therefore can potentially respond to growth factors produced by somatic cells. These data suggest that AREG plays a role in defining the developmental competence of the oocytes. Supported by NIH-HD052909.

Indications for Modified Natural Cycle IVF

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In-vitro fertilization without stimulation, in natural or modified natural cycles IVF ("FIV-NAT") offers an interesting alternative to controlled ovarian hyperstimulation (COH) for some patients.

This protocol may be proposed to patients suffering from altered ovarian status (AOS) with encouraging results. A second indication might be patients presenting with repeated implantation failure (IMF). FIV-NAT allows avoiding possible adverse effects of COH on the endometrium. Results are respectively 15.4% and 16.6% clinical pregnancy rate per oocyte retrieval for AOS and IMF. FIV-NAT can also be particularly interesting when COH is contra-indicated because of cancerologic reasons, as a history of hormono-dependant cancer or cryopreservation program before surgery for ovarian tumor.

Newer indications of modified natural cycles could emerge in the future.

Free Communication: Modified Natural Cycle IVF and Mild IVF: A 10 years Swedish material

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Introduction: The efficacy and safety of IVF in Sweden is well documented. 3% of all babies are born after IVF treatments. The transition to now 70% single embryo transfer (SET) has put focus on natural cycle IVF and mild treatment strategies as valid clinical policy alternatives.

Material and Methods: Modified natural cycle IVF or Mild IVF was offered to selected patients based on both medical criteria and the woman's desire for a "low interference" treatment. Between 1996 and 2007, 43 patients during 129 cycles were treated with modified natural cycle IVF. Monitoring of the natural cycle included one baseline ultrasound examination between cd 1-4 and additional ultrasound examinations in combination with analyses of serum estradiol levels starting on cd 9. Ovulation induction was given, as 5000 IE of HCG, when the leading follicle reached 17-19 mm and with estradiol levels between 500-750 pmol/l. Oocyte retrieval (OR) was performed approximately 37 h. later.

Between 1997 and 2007, 145 couples during 250 cycles were treated with mild IVF. Ovarian stimulation was performed with clomiphene citrate, 100 mg daily cd 3-7. Ovulation induction with 5000 IE HCG was given when the leading follicle was ≥18 mm. Oocyte retrieval (OR) was performed approximately 37 h. later

Results: Patients characteristics are described in Table I. Women's age, type of infertility and treatments indication were similar. In both groups (Modified natural cycle IVF and Mild IVF) tubal infertility was the major cause of infertility; 28% and 33% respectively. Treatment results are presented in Table II. Whereas 53,5% and 39,6% of started cycles, respectively, never reached ET, the pregnancy rate per ET were 26,7% for modified natural cycle IVF and 27.2 % for mild IVF. By comparison, mean rates for Europe 2004 was 30.6 % for standard IVF treatments.

Conclusion: Effectiveness of these treatment modalities cannot compete with conventional IVF in terms of pregnancy rate per started treatment cycle, but pregnancy rates per ET are comparable to mean European national rates.
In addition, cost of medication is less, risk for complications such as OHSS is dramatically reduced, and the treatments may be more psychologically acceptable to the patients.

These treatment modalities should be considered for selected patient groups.

Table I. Baseline demographics and clinical characteristics of patients			
		Modified natural cycle IVF (n=43)	Mild IVF (n=145)
Age of women at the time of OR		34,2 +/- 3,3	34,8 +/- 4,6
Duration of infertility (years)		2,0 +/- 2,1	2,6 +/- 1,8
Primary infertility (n) (% of all patients)		30 (69,8)	102 (70,3)
Previous child (n) (% of all patients)		13 (30,2)	43 (29,7)
Cause of infertility (%)	Male	16	15
	Tubal	28	33
	Unexplained	21	21
	Other	35	31
Values are mean±SD or number (%)			

Table II. Cycle-specific characteristics of the IVF cycles				
	Modified natural cycle		Mild IVF	
No of patients	43		145	
No of cycles started (n)	129		250	
Cancelled cycles before OR (n) (% of all cycles)	40 (31,0)		34 (13,6)	
	Due to ovulation	Other reasons	Due to ovulation	Other reasons
	17 (13,2)	23 (17,8)	17 (6,8)	17 (6,8)
OR (n)	89		217	
No of oocytes (oocytes/OR)	0,9 +/-0,4		1,9 +/-1,4	
ICSI (n)(% of ET)	19 (31,7)		45 (29,8)	
Embryo transfer (n)(%/cycle)	60 (46,5)		151 (60,4)	
Embryo transfer per OR (%)	67,4		74,4	
Implantation rate (%/transferred embryo)	26,7		22,5	
Ongoing PR (n) (%/cycle; %/ET)	16 (12,4; 26,7)		41 (16,4; 27,2)	
Multiple PR (n) (%/pregnancy; %/delivery)	0		4(9,8; 2,7)	
Values are mean±SD or number (%) OR= oocyte retrieval; PR=pregnancy rate; ET=embryo transfer; ICSI=intra cytoplasmatic sperm injecton.				

Free Communication: Oestradiol-priming improves oocyte-retrieval in natural-cycle IVF

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Background:
Lately a trend towards milder treatments has begun in ART. In natural cycle IVF a major problem is the relatively high cancellation-rate due to premature LH-rise, ovulation or "empty" or atretic dominant follicle. A summary of natural-cycle IVF shows approx. 29% cancellation before oocyte pick-up (OPU) in more than 1500 cycles (ref. 1.) Prevention of premature LH peak / ovulation by use of GnRH-antagonist or NSAID still leave a number of cancelled OPU; according to recent publications 24%-36% (ref. 2.) Oestradiol therapy in late luteal phase in order to predict most likely time for LH-peak and avoid premature ovulation is described in earlier work (ref. 3.) Delaying intermenstrual FSH-rise until a pre-defined day is the mechanism behind this option.

Aim :
In this study we compare the effect of oestradiol priming vs. no-priming in luteal-phase before unstimulated IVF-cycles.

Methods:
Retrospective analysis of 56 regularly cycling (26-34 days) women < 37 years, FSH< 15 IU/L, referred to IVF-treatment. 22 of the 56 women received oestradiol-priming, 2 mg twice daily (Femanest®, Sandoz), in 4-10 days. The remainder 34 women did not. Both groups had ultrasound (US) examination and blood samples on cycle days 3 and 8, 9 or 10 , and thereafter daily until the appearance of a dominant follicle > 16 mm, with a corresponding endometrium > 8 mm. An hCG-injection of 6500 IU is administered 34 hours prior to OPU. The mature oocyte is fertilized and transferred 2 days after aspiration. Serum samples and follicular fluids are stored frozen at -60 ºC for later analysis.

Results:
In 36/56 (64%) cases a mature oocyte was retrieved. In 10/56 (18%) cases premature ovulation was observed. Another 10/56 (18%) cases had an "empty" large follicle, with no oocyte recovered. Oestradiol priming significantly reduced frequency of premature ovulation, 1/22 (4,5%) vs. 9/34 (26,5%) (p=0,032 by Fisher´s exact test). In the primed group 17/22 (77%) had mature oocytes retrieved vs. 19/34 (56%) with no priming. (p=0,062 by Fisher´s exact test). Empty follicle in 4/22 (18%) vs. 6/34 (18%). Serum LH on the day of OPU was significantly higher in cases with oocytes retrieved (p=0,0022 by non-parametric test).

Conclusion:
Oestradiol priming in natural cycle IVF significantly reduces the incidence of premature ovulation. Further investigations with larger number of patients are needed to corroborate this finding.

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Endometrium and embryo quality in modified natural cycle IVF

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In the past, the endometrial receptivity had been studied from different view points:
- Morphological markers
- Biochemical markers
- Gene expression pattern

Critical analysis of traditional morphological criteria shows that the histological dating is not a valid method for the diagnosis of luteal phase deficiency or to guide clinical management in infertility. Single-molecule approach is not enougth to evaluate the implantation capable.

Functional genomic studies in human endometrium in natural cycles have demonstrated that endometrial receptivity is an active process involving up- and down-regulation of hundreds of genes. The gene expression pattern of endometrium in controlled ovarian stimulated cycles (COH) has been addressed specifically at the time of implantation at day LH+7.In our last work, we have expanded these studies by comparing the gene expression profile of the human endometrium troughout the early-mid secretory phase in natural versus COH cycles.

We have analyzed endometrial samples collected from healthy fertile cycling ovum donors (aged 23-39), that underwent either natural cycles (n=25) at days LH+1, LH+3, LH+5, LH +7 and LH+9 or a COH cycle (n=25) at days hCG+1, hCG+3, hCG+5,hCG +7 and hCG+9 (n=5 per time point). COH treatment consisted of a long protocol with leuprolide acetate and FSH/HP, hMG and hCG as described elsewhere. In natural cycles, no progesterone (P) supplementation was administered.

Results show that the endometrium from natural and COH cycles without P supplementation followed similar genomic patterns at days LH+1 versus hCG+1, LH+3 versus hCG+3, and LH+5 versus hCG+5. However, in COH cycles the stimulation protocol induced differences in the pattern expression of hCG+7 versus LH+7, the day of maximal endometrial receptivity and adhesion of the blastocysts to the maternal endometrium.

The endometrium from both natural and COH cycles recovered their similar genomic profile thereafter at LH+9 and hCG+9. These results indicate that gene expression profiling of the endometrium at the time of implantation is different between natural cycles specifically at LH+7 and COH cycles at hCG+7 and similarities are recovered thereafter. The functional relevance of this finding deserves further attention considering that the natural cycle is our gold standard for endometrial receptivity. Genomic profile of the endometrium under proper bioinformatic analysis could be an objective tool for the objective description of human endometrial receptivity.

By the other side we know several factors affecting gametes and embryos have been found to be related to an increase in chromosome abnormalities, such as changes in temperature during oocyte culture and handling, ageing of gametes or use of a 20% oxygen tension instead of 5%.

In 1990 our group published that in patients with high response to gonadotrophins there was an increased incidence of diploid oocytes, by the other side high levels of E2, which can be considered equivalent to high response to gonadotrophins, have been related to chromosomal abnormalities.

Several studies have been published that: In porcine oocytes, the addition of E2 inhibits maturation to metaphase II; in bovine oocytes, the addition of E2 to the culture media showed abnormalities such as multipolar spindles and persistence of chromosomes in the central region of late anaphase/telophase.

In 2001 our group published a study that showed that the culture of mouse embryos with increasing E2 levels decreases blastocyst rates; high levels of FSH have also been related to the alteration of oocyte maturation

Another study have shown that in Vitro Maturation experiments with higher concentrations of FSH in the culture media increased aneuploidies in MII oocytes.

All these data suggest that superovulation protocols in IVF might increase the risk of aneuploidies in the resulting embryos.

Then, Is high response to ovarian stimulation really related to the increase in the percentage of aneuploidies ? or Can the percentage of aneuplodies be reduced by lowering the dosages of gonadotrophins in order to lower the high ovarian response?

In 2007 Baart et al and Heijnen et al this year published two works in response to this question. After a year of analyzing the accumulated pregnancy rate, there were no significant differences between high or normal ovarian responses groups.

We are currently studying this question: One of our studies includes 10 donors; all of them were between the ages: 18-35 years, BMI: 18-25 kg/m2, no history of recurrent miscarriage or implantation failure, and no PCO. We performed a stimulation using a conventional dose, we then made a PGD from the resulting embryos. Later we performed a second

stimulation using a mild stimulation of half a dose and we made a PGD from those resulting embryos

The results of the high responders show that we significantly reduced the number of oocytes by almost half by lowering the doses.

The conclusions for this study indicate that high responders react differently than normal responders when doses are lowered.

In another study along these lines we compared the alterations in the embryos PGD resulting from 15 donors without stimulation (natural cycle) versus the same donnors group with ovarian stimulation.

The conclusions of this study show that, the current trend in IVF treatments is to stimulate ovulation as mildly as possible and the natural cycle is considered to be the most physiological.

However, our clinical results for the natural cycle oblige us to use ovarian stimulation, but also to keep in mind that high responders may benefit from milder doses.

Now a days we have in course a study in not response patient that is called VAIO " Vitrificación Acumulada Intermitente de Ovocitos" that means Cumulative Oocytes Vitrification in Natural Cycle..

Our preliminar results: Total started cases: 29 (middle age 41,5)
Total finished cases: 5 (middle age 36,6) with 4 oocytes by patient.

Until this moment the fecundation rate is 81,7%, the implantation rate is 40% and pregnancy rate 25%. The study steal in course in order to demonstrated if we can increase the results in this group.

Fading follicles: the essence of ovarian ageing

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A woman's fecundity declines with age, partly due to a progressive loss of oocytes in growing follicles from her ovaries but also to an associated reduction in the quality of those remaining. The size of the initial oocyte stock and the rate at which it diminishes varies from person to person, controlled by multiple genetic and environmental factors. Several years before menstrual cycles cease, usually during the late thirties, the initiation of follicular growth leading to loss of oocytes begins to accelerate. This alteration is associated with a gradual increase in circulating plasma FSH levels. The rise in FSH appears mainly due to reduced secretion of follicular growth and differentiation factors related to transforming growth factor-beta (TGFbeta) that negatively regulate pituitary FSH release. In particular the clinical application of assays for inhibins (INHA, INHB) and Anti-Müllerian Hormone (AMH) has helped clarify the roles of these substances in ovarian physiology and permitted their use as potential biomarkers of ovarian ageing. It seems that as the number of (immature) INHB and AMH secreting follicles declines with age, negative feedback regulation of pituitary FSH secretion is relaxed. Basal circulating FSH levels rise accordingly, promoting inappropriate maturation of granulosa cells in residual preantral (INHB-secreting) follicles containing eggs that have not completed their gonadotrophin-independent growth phase. Presumably due to the asynchronous maturation of the germinal and somatic components of such follicles, they eventually become atretic. As FSH levels continue to rise the process is amplified, until in the late perimenopause oestradiol and INHA levels also fall and menstrual cycles cease. Thereby FSH orchestrates the termination of oogenesis and folliculogenesis in the human ovary.

Free Communication: IVF lite: Modified natural cycle IVF/ICSI as standard care

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Introduction:

There is growing interest in a mild approach to IVF/ICSI.

A form of "IVF-lite" is modified natural cycle IVF/ICSI (MNC-IVF/ICSI).1

In MNC-IVF/ICSI, treatment is aimed at using the one follicle that spontaneously develops to dominance in a menstrual cycle. To prevent ovulation a GnRH antagonist is applied together with gonadotrophins in the late follicular phase to warrant growth of the follicle.

In The Netherlands three cycles of controlled ovarian hyperstimulation IVF (COS-IVF) are reimbursed. Since 2004 we implemented MNC-IVF/ICSI as part of standard IVF care in our centre. All patients aged 18-36 years with a regular and proven cycle and an indication for IVF or ICSI receive MNC-IVF/ICSI. A maximum of six cycles MNC-IVF/ICSI is offered instead of the first COS cycle, before eventually continuing with COS cycles.

We analysed the cumulative ongoing pregnancy rate (COPR) and searched for predictive factors for pregnancy in order to optimise patient selection for MNC-IVF/ICSI.

Materials and methods:

From July 2004 until October 2007, 373 patients started MNC-IVF/ICSI. Age, indication, primary or secoundary subfertility, day of embryo transfer (ET) and cycle events as cancellation of oocyte retrieval (OR), failed OR, fertilisation failure and failure to reach ET were analysed.

Data were analysed with SPSS 14.0, using Chi-Square test, Student's T-test or logistic regression where appropriate. A P-value <0,05 was considered statistically significant.

Results:

373 patients completed 1606 cycles (mean: 4,3 per patient). MMean age was 31,8 years. An OR was performed in 85,1% of all started cycles, an oocyte was obtained in 71,6% of all OR's. The embryo transfer (ET) rate was 35,1% per started cycle. Ongoing pregnancy rate was 7,9% per started cycle and 22,5% per ET.

The COPR was 33,0% after a maximum of six cycles. The cumulative drop out rate was 24,1%.

Age, indication and primary or secondary subfertility in an univariate and multivariate analysis did not correlate with pregnancy rate.

We found that an ET between cycle day 8-14 gave a significantly lower pregnancy rate per started cycle than an ET on cycle day 15 or later (5,7% vs 9,4%). Cancellation of OR, fertiliszation failure and failure to reach ET wereare repeating phenomena in subsequent cycles. These events also predisposed for drop-out, but did not decrease COPR. A failed OR was not a repeating phenomenon. It did however predispose for drop-out, but did not decrease COPR.

Conclusion:

The COPR after six cycles of MNC-IVF/ICSI is 33,0%.

Patient selection based on characteristics such as age, indication and primary or secoundary subfertility will not improve COPR. Cycle events such as a cancellation of OR, failed OR, fertiliszation failure and failure to reach ET predispose for drop-out, but did not decrease COPR.

ET between cycle day 8-14 gives a significantly lower pregnancy rate per cycle than an ET on cycle day 15 or later (5,7% vs 9,4%).

MNC-IVF as standard care can be a worthy alternative for COS-IVF for patients aged 18-36 years with a regular and proven ovulatory cycle and an indication for IVF or ICSI.

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Free Communication: INVOCELL: A NEW DEVICE THAT ALLOWS IVF IN AN OFFICE SETTING

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Introduction: INVO is a simplified alternative to In Vitro fertilization (IVF) that will revolutionize the treatment of infertility. The INVO procedure does not need complex laboratory equipment and can be performed in the office of an infertility specialist or Ob/Gyn. Initial prototypes of the INVOcell were difficult to use even for trained operators, explaining the low diffusion of the INVO technology. BioXcell has developed a new device, the INVOcell, specifically designed for the INVO procedure which is the subject of this presentation.

Materials and Methods: No or mild ovarian stimulation is used when performing the INVO cycle. Fewer than 10 follicles are usually punctured under ultrasound guidance using patient pre-medication with or without local anesthesia. Then the INVO procedure took place. One to 7 eggs are placed within the inner chamber of the device with washed motile spermatozoa (30,000 per ml) and 1 ml of culture medium. The inner chamber is closed and placed into the rigid cover which protects the inner chamber from the vaginal secretions and keeps the orifice of the valve of the inner chamber sterile. The INVOcell is then placed in the vaginal cavity for 2 to 3 days of incubation. During vaginal incubation, the pH of the culture medium will be kept using the p CO2 of the vaginal cavity. The INVOcell device comes with a retention system which prevents expulsion of the INVOcell from the vaginal cavity. After incubation, the device is removed and placed vertically in an incubator. By gravity embryos naturally denuded settle in the microchamber at the bottom of the inner chamber where they can be directly observed under microscope and loaded into the embryo transfer catheter. INVO does not require expensive equipment, air filtration, CO2 supplementation and alarm system as embryos are not stored in the office. INVO does not require the same experience from the operator as IVF or ICSI. All these factors allow for a lower cost of 1/3 to 1/2 of an IVF or ICSI cycle.
Study design:

-INVOcell device has been tested to assess toxicity and biocompatibility
-Clinical tests have been performed to evaluate comfort and retention of INVOcell
-A clinical trial of 84 cycles has been performed for FDA 510k clearance using INVOcell.
-BioXcell received certification for ISO 13485
-CE Marking expected in January 2008
Results: Over 800 cases have been published in scientific reviews using INVO prototypes. The average clinical pregnancy rate was 19.7% per cycle; comparable to the IVF clinical pregnancy rate of 20% reported in US at this time. Preliminary results of the FDA clinical trial using the INVOcell will be discussed; births of normal babies have been obtained.

Conclusions:
INVO is a simple, less expensive alternative to IVF performed by specialists in infertility or Ob/Gyn.

INVO can be performed almost everywhere in:
- Countries where infertile populations cannot access IVF for economic or geographic reasons
- IVF Centers as an alternative treatment for infertile couples they could not reach before
- Ob/Gyn groups where IVF centers are not present.

This presentation was sponsored by BioXcell Inc.

Indications and the role of natural/modified natural cycles IVF PCO/PCOS

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Over the last two decades different stimulation protocols have been proposed. Easier and less expensive stimulation treatments have been largely replaced by more complex and more demanding protocols during the years. Since the mid nineties the long term GnRH-agonist stimulation protocols are widely used in the world. Besides many advantages such lengthy expensive regimens are not free from short and long-term risks and complications.

With mild stimulation protocols the mean number of days of stimulation, the total amount of gonadotropins used and the mean number of oocytes retrieved is reduced, but the proportion of high quality and euploid embryos is higher compared with conventional stimulation protocols whereas the pregnancy rate per embryo transfer is comparable between the two approaches. Moreover, the reduced costs, the better tolerability for patients, the less time needed to complete an IVF make mild approaches clinical and cost effective over a given period of time.

According to these observations it might be possible that the lower is the stimulation the better oocyte quality can be obtained. Natural IVF cycle should then represent the most valid method to retrieve the best quality oocyte. Moreover, several important advantages as reduced costs, less physical (no side effects, no anaesthesia and hospital stay) and emotional burdens (less anxiety and stress as the patient does not have to worry about the ovarian response to the stimulation) are offered to the patients. This very mild approach have been recently proposed as an alternative to conventional stimulation protocols in poor-responders (Ubaldi et al., 2007) whereas conflicting data come from the literature regarding the efficacy of natural IVF cycles in normo-responder patients and large prospective randomized studies are needed to better evaluate the efficacy of these minimal regimens compared with conventional stimulation approaches.

Polycystic ovary syndrome (PCOS) is the commonest endocrine disorder in women of reproductive age, affecting 5–10% of premenopausal women. Women with this syndrome may present with menstrual irregularities, chronic anovulation, infertility, obesity and hyperandrogenism (The Rotterdam ESHRE/ASRM-sponsored PCOS consensus workshop group). Clomiphene citrate (CC) is usually used as the first-line drug to induce ovulation in women with PCOS. Successful ovulation is achieved in ~70–85% of women and 40–50% will conceive (The ESHRE Capri workshop, 1997, Laven et al 2002). Gonadotrophin treatment can be offered when these anovulatory women fail to respond to CC. The use of gonadotrophin is more expensive and associated with a much higher risk of multiple pregnancy and developing ovarian hyperstimulation syndrome. Recent reports revealed that the use of aromatase inhibitors (AIs) may significantly increase the ovulation and pregnancy rates from CC treatment in anovulatory women with CC-resistant PCOS.

Atay et al. Letrozole with clomiphene citrate (CC) as a first-line treatment for up ovulation induction in women with polycystic ovaries, concluding that letrozole is associated with a higher pregnancy rate than CC in PCO patients and may have a role as a first-line treatment for anovulatory patients with PCOs. Mitwally and Casper first postulated that blocking E production by inhibiting aromatization would release the hypothalamic–pituitary axis from estrogenic negative feedback. As a result, FSH secretion increases, stimulating the development of ovarian follicles. Because aromatase inhibitors block high levels of E from androgen conversion, the effects in PCOs are more prominent. In addition, androgens that are normally converted to estrogens accumulate in the ovary, and these androgens increase follicular sensitivity to FSH. Unlike CC, aromatase inhibitor does not deplete E receptors or produce a negative effect on the endometrium. Clomiphene citrate, on the other hand, has a longer half-life (2 weeks) that results in prolonged central E receptor depletion. The use of aromatase inhibitors for ovarian stimulation and controlled ovarian hyperstimulation (superovulation) is indeed promising. These studies suggest that the addition of letrozole to gonadotropins decreases gonadotropin requirements, increases the number of preovulatory follicles, and decreases endometrial thickness without a negative effect on pregnancy rates.

Conclusions: Preliminary evidence suggests that AIs may replace CC in the future because of similar efficacy with a reduced side effect profile. This could be even more important in PCOS CC resistant patients, who are often hyper responsive to gonadotropins.

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Natural cycle - Pre-cycle preparation & Cycle monitoring

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Over the last two decades, different, complex, demanding and expensive stimulation protocols have been developed in order to improve the success rate of IVF treatments. However, such ovarian stimulation protocols have posed significant risk of side-effects including physical and psychological complications. Considering the tremendous development and improvements that have occurred since the delivery of the first IVF child, it seems that natural cycle IVF may represent an easy, short, well-tolerated and inexpensive alternative approach to treatment, despite relatively low pregnancy rates per cycle. In order to improve the success rate, it seems obvious that proper pre-cycle preparation and cycle monitoring should be thoroughly performed.

One of the first steps in pre-cycle preparation should be an accurate selection of patients and to have them undergo counseling. The benefit of IVF natural cycle in women under 35 is more evident than in older patients where the opportunity to transfer multiple embryos seems to be advantageous (Phillips et al, 2007). Another distinctive group of patients which could benefit from natural cycle IVF before being referred to egg donation are the poor responders (Ellenbogen et al, 2007). Counseling the patients about the simplicity of the method, reduced discomfort during the procedure, avoidance of multiple pregnancies and OHSS and the possibility of repeating the procedure for more IVF cycles during a year may diminish patients' stress and concerns about failure of treatment.

Programming ovulation/oocyte retrieval in a natural cycle IVF by administration of estradiol valerate from the day 25 of the previous cycle until 1-15 days after the onset of menses (de Ziegler et al, 1999) or by identification of the intercycle FSH signal in urine sample (Schwarz et al, 2006), is suggested.

Cycle monitoring should be simple and comprehensive. It should include basic vaginal ultrasound examination at beginning of menses followed by serial ultrasound in combination of serum estradiol, progesterone and LH (both measured after the follicle is ≥ 14mm). The final LH surge is the most common problem in monitoring natural cycle. However, administration of hCG should be the solution when dominant follicle measures 16.5-19mm with corresponding estradiol level and low serum LH. In a recent group of 26 poor responder patients treated in our unit, no oocytes or fertilization were obtained when the dominant follicle was<16.5mm or>19mm, despite suitable hormonal levels for hCG administration.

In an effort to reduce cancellation rates, administration of indomethacin was described. There was a statistically significant association between premature ovulation and indomethacin with an odds ratio of 3.8 (95% CI, 1.2-12.3) (Kadoch et al,2008).

Follicular aspiration and flushing using a double lumen needle is advisable.

Conclusions: IVF in natural cycle should be viewed in terms of pregnancy and delivery rates over a period of time (that may include multiple IVF attempts) in the context of reduced discomfort, side effects, risks and cost. Proper pre-cycle preparation and cycle monitoring are expected to increase the success rate.

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Modified nIVF: Prevention of LH surge & Ovulation triggering

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The search for ways to reduce multiple pregnancies resulting from ART has renewed the interest in nIVF. In nIVF, the selection of the dominant follicle is natural and devoid of any stimulation, so only one oocyte is retrieved and fertilised to produce a single embryo. One of the main disadvantages of nIVF, causing it to fall out of favour, is the associated high rate of premature ovulations and the associated cycle cancellations, which leads to many consequences including time wastage and costs.

There have been several attempts to prevent the premature ovulation associated with nIVF: human chorionic gonadotrophin (hCG) in an effort to preempt the LH surge and gonadotrophin-releasing hormone (GnRH) anatagonist administered in the late follicular phase. GnRH antagonists may allow better control of the natural cycle but did not eliminate the problem of premature ovulation.

The use of Indomethacin may play an important role in overcoming one of the major obstacles in nIVF. In addition, the safety profile and the low cost of this medication make it more attractive to use. The use of Indomethacin in nIVF reduces premature ovulation from 16% without Indomethacin to 6 % with the use of Indomethacin. Patients who did not receive Indomethacin had four times the odds of premature ovulation than those who had received Indomethacin during the nIVF cycle. This led to a significant increase in oocyte retrieval rate per started cycle as a result of a reduction in cycle cancellation due to premature ovulation ($P<0.04$). These findings support the hypothesis that Indomethacin reduces premature ovulation before oocyte retrieval and cycle cancellation in modified nIVF, therefore, improving the efficacy of nIVF. Also, the oocyte retrieval rate per procedure was not affected significantly by the use of Indomethacin. In conclusion, the impact of using GnRH antagonist along side Indomethacin. We believe that this is an interesting and potentially useful finding that demands further investigation.

Follicle aspiration and Day of ET

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Many factors influence the retrieval of the Natural Cycle (unstimulated / Minimal stimulation cycle) oocyte(s) during follicular aspiration (FA). Premature follicular rupture and "empty follicle " phenomenon can cause cancellation of 1/3 of all the natural cycles. Follicular flushing is recommended during aspiration of the natural cycle follicle. The oocyte can be found in the first or second flushing in up to 20% of follicles in the Natural Cycle. Flushing does not seem to affect the oocyte quality. Furthermore clinical pregnancy rates were not different between flushed and non-flushed aspirated oocytes. Vacuum pressure during aspiration in common clinical practice does not seem to affect the integrity of the aspirated oocyte.

The optimal day of transfer in natural cycle (Modified or not) patients has not been studied extensively. Day-5 ET (embryo transfer) vs. Day 2-3 in controlled ovarian stimulation (COS) of "good prognosis" patients yields higher live birth rates, but not cumulative live birth rates; Furthermore blastocyst transfer in "poor prognosis" patients does not increase or may even decrease live birth rates compared to day 2-3.

In at least on study, day-2 ET produced the same pregnancy rates per day-2 embryo and per aspirated oocyte when compared to day-5 transfer. At present, therefore, one data exist that favor one transfer policy (day 2-3) versus the other (day-5).

Luteal phase support

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Controlled ovarian hyperstimulation (COH) is required to promote the development of multiple follicles in order to perform IVF. The number of follicles required for an optimal outcome has been decreasing in the last few years as the quality of the IVF laboratories has increased as well as the physicians have been aware of the deleterious effect of COH on the endometrium. In the current presentation we will first analyze the impact of COH on endometrial gene expression, focussing on the window of implantation and how different protocols impact differently on the expression of certain specific genes that are believed to be crucial for embryo implantation. Secondly, we will review the current evidence regarding luteal phase support, trying to overcome the deleterious effect of COH on the endometrium, with specific emphasis on estradiol supplementation during the luteal phase.

Cost effectiveness of a mild compared to a standard strategy for In Vitro Fertilisation: a randomised comparison using cumulative term live birth as the primary endpoint

Marinus JC Eijkemans

BACKGROUND: Conventional ovarian stimulation and the transfer of two embryos in IVF exhibits an inherent high probability of multiple pregnancies, resulting in high costs. We evaluated the cost-effectiveness of a mild compared with a conventional strategy for IVF. METHODS: Four hundred and four patients were randomly assigned to undergo either mild ovarian stimulation/GnRH antagonist co-treatment combined with single embryo transfer, or standard stimulation/GnRH agonist long protocol and the transfer of two embryos. The main outcome measures are total costs of treatment within a 12 months period after randomization, and the relationship between total costs and proportion of cumulative pregnancies resulting in term live birth within 1 year of randomization. RESULTS: Despite a significantly increased average number of IVF cycles (2.3 versus 1.7; P < 0.001), about equal costs of the treatment period over a 12-month period (¤5,407 versus ¤5,044, P = 0.26) were observed, while total costs over a 12-month period were lower (¤8333 versus ¤10,745; P = 0.006) using the mild strategy. This was mainly due to higher costs of the obstetric and post-natal period for the standard strategy, related to multiple pregnancies. The costs per pregnancy leading to term live birth were ¤19,156 in the mild strategy and ¤24,038 in the standard. The incremental cost-effectiveness ratio of the standard strategy compared with the mild strategy was ¤185,000 per extra pregnancy leading to term live birth. Uncertainty analysis revealed that there is only a 20% probability that the standard treatment strategy is cost effective up till a range of society's willingness-to-pay of ¤50,000 per extra pregnancy leading to term live birth. CONCLUSIONS: Despite an increased mean number of IVF cycles within 1 year, from an economic perspective, the mild treatment strategy is more advantageous per term live birth. It is unlikely, over a wide range of society's willingness-to-pay, that the standard treatment strategy is cost-effective, compared with the mild strategy.

Clomiphene citrate and minimal ovarian stimulation for in vitro fertilization

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Clomiphene citrate is an isomeric component of enclomiphene. It binds to the estrogen receptors at the hypothalamus level, thereby blocking both negative and positive feedback effects of estrogens. Ovarian

stimulation with Clomiphene citrate can take the full advantage of increase endogenous FSH production and suppression of LH. With promotion of single embryo transfer less number of oocytes are normally needed in each IVF cycle. Minimal stimulation with clomiphene citrate is, therefore, an idea approach for production of a less number of eggs.

While it is generally believed that minimal stimulation may work well for younger patients our finding shows that the implantation rate in clomiphene citrate stimulation IVF cycles did not differ from those in conventional IVF. Indeed, data from the clomiphene citrate challenge test clearly demonstrates that endogenous FSH levels can reached to the same levels as produced through daily gonadotropin injection in the old patient populations.

In this presentation we will analyze clinical outcomes in 1289 Clomid IVF cycles to assess their efficacy between younger and older patient populations.

Does IVM improve success rates of IVF in women with PCO/PCOS

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Only very few studies with limited number of patients have been published comparing regular IVF and IVM in comparative populations of PCO patients. These studies describes a lower pregnancy rate in the IVM groups, mainly due to a lower implantation rate per embryo transferred. However in a significant number of publications a 10-15% of PCO patients treated with regular IVF will experience moderate to severe ovarian hyper stimulation compared to IVM treated PCO patient, which had none.

Taking a survey of recent publication on IVM there is a consistent lower pregnancy rate (app. 28% in IVM compared to 38% in IVF) when PCO patients are treated. However other benefits to the IVM, have to be considered as well:

This is the lower cost for treatment, less time-consuming for the patient with the new programmed protocols for IVM and even more, the easiness to perform the IVM today excluding ICSI when not necessary. And finally the fact that more and more data confirm the safety for the IVM procedure in humans both for the patients and their offspring's.

Conclusion: Despite the fact that IVM does have a lower clinical pregnancy rate several benefits specific for the patient makes the IVM a very attractive new ART modality for PCO patients in need for ART.

Tissue Engineered Approaches to Ovarian Follicle Development

Dr. Theresa Woodruff

In vitro ovarian follicle culture provides a tool to investigate folliculogenesis, and may one day provide women with fertility-preservation options. The application of tissue engineering principles to ovarian follicle maturation may enable the creation of microenvironments that will coordinate the growth of the multiple cellular compartments within the follicle. Three-dimensional culture systems can preserve follicle architecture, thereby maintaining critical cell-cell and cell-matrix signaling lost in traditional two-dimensional attached follicle culture systems. Maintaining the follicular structure while manipulating the biochemical and mechanical environment will enable the development of controllable systems to investigate the fundamental biological principles underlying follicle maturation. Recent advances the tissue engineering principles of ex vivo ovarian follicle culture will be described. The ultimate goal of this work is to provide fertility preserving options for young women and girls facing premature infertility due to medical intervention such as chemotherapy or radiation or genetic or cell based premature lose of ovarian follicles.

Endometrial receptivity in natural vs controlled ovarian stimulation cycles

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The endometrium is a specialized hormonally regulated tissue that is non-adhesive for embryos throughout most of the menstrual cycle in humans and other primates. Thus, endometrial receptivity is a self-limited period in which the endometrial epithelium (EE) acquires a functional and transient ovarian steroid-dependent status. The luminal EE acquires the ability to adhere to the developing human blastocyst (receptivity) during this period, mainly due to the presence of progesterone (P) after appropriate 17b-estradiol (E2) priming. Controlled ovarian stimulation (COS) induces morphological, biochemical and functional genomic modifications of the human endometrium throughout the development of the window of implantation.

The objective of this presentation is to compare the gene expression profile of the human endometrium in natural versus COS throughout the early-mid secretory phase using microarray technology. Data obtained from 49 endometrial biopsies from LH+1 to LH+9 in natural cycle and from hCG+1 to hCG+9 in COS cycles were analyzed using different methods such as clustering, profiling of biological processes or selection of differentially expressed genes, as implemented in GEPAS and Babelomics programs.

Results: Endometrium from natural and COS cycles followed different genomic patterns in the transition from the pre-receptive to the receptive phase. Specifically, a two-day delay in the activation/repression of specific cluster of genes has been identified on day hCG+7 versus LH+7.

Conclusions: These results demonstrate that gene expression profiling of the endometrium is different between natural and COS cycles at hCG+7, and demonstrate the existence of genes that can be use as targets to "normalize" the endometrium during COS treatment to maximize uterine receptivity.

Assessment of ovarian reserve & implications in ART

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The progressive loss of female fertility potential with age essentially is due to the quantitative and qualitative attrition of ovarian follicles, a process that accelerates during the forth decade of life. Indeed, from the early 30s to the early 40s, women are expected to exhaust 3/4 of their follicular reserve. This issue assumes a pivotal importance in Reproductive Medicine since ovarian aging is the single most important factor in determining the effectiveness of treatments, in particular for women who delay the age of first childbearing.

The untimely and/or accelerated antral follicle growth during the luteal-follicular transition, a phenomenon that is frequent in ovarian-aged women and that is characterized by the presence of at least one overdeveloped antral follicle during the first days of the follicular phase, is likely to modify the expected relationship between hormonal parameters and the number of antral follicles. Since, by definition, outsized antral follicles contain more granulosa cells, their ability to produce inhibin B, and in some severe cases E2, is possibly increased as compared with timely-selected, small follicles. This, in turn, significantly attenuates FSH secretion and dissociates the profile of these hormones from the underlying ovarian reserve of antral follicles. Our results indicated that the presence of an overdeveloped antral follicle on cycle day 3 alters the strength of the relationship between antral follicle count and serum inhibin B and FSH levels. This phenomenon discourages the use of serum inhibin B and FSH measurements as exclusive indicators of the ovarian follicular status. Hence, to improve the reliability and interpretation of these hormonal markers, careful ultrasonographic evaluation not only of follicle counts but also follicle sizes should be routinely performed. Clinical measures aiming at preventing the occurrence of premature follicle selection during the luteal-follicular transition as luteal E2 or premenstrual GnRH antagonist administration may be useful to improve the relationship between inhibin B and FSH and the ovarian follicle status, in the case of unavailability of ovarian ultrasound scans. Finally, anti-Müllerian hormone, a glycoprotein that is produced, presumably FSH-independently, by the granulosa cells of both cyclic and non cyclic follicles may be less influenced by such disorders of the antral follicle development during the luteal-follicular transition. Yet, further clinical investigation is necessary to address these points.

Our presentation will also focus on our clinical research on the role of AMH as a marker of the ovarian functioning. It will address the fact that the relationship between antral follicle counts and serum AMH levels is stronger than that observed with FSH, inhibin B and E2 on day 3 (Fanchin et al., 2003a), and that intercycle reproducibility of AMH measurements is better than the latter parameters (Fanchin et al., 2005a). Also, it will provide data indicating that peripheral AMH levels decline during controlled ovarian hyperstimulation (COH), thus confirming that maturing follicles loose progressively their ability to produce AMH (Fanchin et al., 2003b), and data illustrating that follicular fluid (FF) AMH concentrations in small antral follicles are 3-fold as high AMH as in preovulatory follicles (Fanchin et al., 2005b). Further, we will show that hCG-driven luteinization additionally curtails follicular AMH production (Fanchin et al., 2005c). Finally, AMH production measured in FF from individual follicles is increased in women having normal follicular counts and responsiveness to COH (Fanchin et al., 2005b). Together, these data reinforce the soundness of AMH measurements as a quantitative and maybe qualitative marker of granulosa cell activity and health. In addition, unpublished data on the striking relationship between FF AMH production and the quality of the ensuing oocyte/embryo (Fanchin et al., 2007) as well as on the profile of serum AMH levels during the menstrual cycle will be presented and discussed.

Follicular phase oral phytoestrogen supplementation improves clomiphene induction cycle outcomes and pregnancy rates in unexplained infertility

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May it be the psychological pressure of the couple to conceive, or the clinical decision, patients with unexplained infertility usually find themselves after repeated failure of induction cycles on the verge of an IVF trial. Medical professionals should foccus on raising the success rates among these couples, using mild stimulation methods, to spare them an expensive and potentially risky IVF trial. Cost effectiveness studies support the use of CC over advanced ART management protocols. Although having an acceptable ovulation rate, the antiestrogenic effect of CC has been associated with a lower pregnancy rate than expected.

Objective: We investigated the role of oral phytoestrogen supplementation at a dose of 120 mg daily, starting from day one of the cycle till day 12 in improving pregnancy rate and cycle outcomes of CC.

Patients and methods: Patients with unexplained infertility, younger than 35 years of age, with a basal (day 3) serum level of Follicle Stimulating Hormone (FSH) lower than 10 IU/ml and having previous 5 unsuccessful CC induction cycles were randomly divided into two groups: group I (n=60) and II (n=59). Both groups received ovulation induction by CC 150 mg per day from day 3 to 7. Group I received additional oral phytoestrogen 120 mg/day starting before CC, from day 1 to day 12. Patients were followed by transvaginal folliculometric measurement till a follicle >17mm was seen, followed by human chorionic gonadotrophin (hCG) injection (10.000 IU I.M.) and timed intercourse. Serum estradiol (E2), luteinizing hormone (LH) and endometrial thickness were measured on the day of hCG injection. Serum progesterone was measured on day 21-23. A serum hCG level was determined 14 days after hCG injection if menses had not yet occurred.

Results: there was a non significant shortening of induction cycles (13.0 +/- 1.1 vs. 14.2 +/- 1.3) upon using phytoestrogens. E2 and LH levels were higher among group I compared to group II (274.5 +/- 48.5 vs. 254.6 +/- 20.6; 8.0 +/-0.9 vs. 7.0+/-0.4), P>0.01. Endometrial thickness, serum progesterone level and clinical pregnancy rate were significantly higher among patients receiving phytoestrogen (8.9 +/- 1.4 vs. 7.5 +/- 1.3mm, P<0.001; 13.3 +/- 3.1 vs. 9.3 +/- 2.0ng/mL, p<0.01; (36.7 % vs. 13.6 %, p<0.01 respectively). Pregnancies were followed up only till establishment of a diagnosis of a clinical pregnancy, with a miscarriage rate of (15.4%), among group I compared to (26.7%) among group II.

Conclusions: We conclude that follicular phase phytoestrogens, namely CR rhizomes dry extract, at the given dose and duration, can revert the antiestrogenic activity of CC, and consequently improve the pregnancy rate and cycle outcomes in unexplained infertility patients who are managed by CC induction and timed intercourse, and who received multiple unsuccessful CC induction cycles. This novel regimen could help to save these couples an expensive IVF trial.

In Vitro Maturation Following Vitrification Of Mouse Immature Oocyte

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Introduction: The storage of oocytes is important for advances in reproductive biology and infertility treatment. Although successful procedures for cryopreservation of human metaphase II oocytes have been reported, their results have been shown to be unsatisfactory, and they appear to require still development. The microtubular spindle of MII oocytes is sensitive to temperature changes. Germinal vesicle (GV) stage oocytes do not have microtubular spindle, so its cryopreservation may be an alternative approach to the storage of gametes. In this study we examined the viability and subsequent developmental ability of murine GV oocytes by ultra rapid vitrification.

Material and Methods: mouse ovaries were removed 48 hours after injection of 7.5 IU PMSG intraperitonealy, then oocytes were collected in GV stage. The collected oocytes vitrified and thawed ultra rapidly using different concentration and different kind of cryopretectant, such as DMSO , ethylene glycol and threhalos

In vitro maturation (IVM), and in vitro fertilization (IVF) and subsequent developmental ability of embryos were assayed.

RESULTS: The GV stage oocytes had good morphology and viability after vitrification and warming and most of them matured to the metaphase II (MII) stage. The fertilization rate of these oocytes and developmental capacity of embryos had no significant differences as compared with non-vitrified oocytes.

CONCLUSION: Vitrification is an effective method for cryopreservation of GV oocytes and may it can be used in human oocytes.

Key Words: Vitrification, In vitro Maturation, Oocyte

Initial Experiences With The Ivm Program In Colombia

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Introduction
Exogenous stimulation of the ovary is the option of choice for patients requiring in vitro fertilization. However, that form of treatment has adverse effects, including the risk of ovarian hyperstimulation syndrome (OHSS), especially in patients with polycystic ovary (PCO), or in polycystic ovary syndrome (PCOS) as a cause for infertility. In these patients there are high estrogen levels that have a deleterious effect on the maturation of the oocyte inside the ovary. For this reason, in vitro maturation of oocytes (IVM) recovered from non-stimulated ovaries is of great benefit for these patients. This new assisted reproduction technique has several advantages over conventional IVF, such as not having to use drugs for stimulation, simpler protocols and lower cost of treatment. Moreover, the endometrium is not subjected to the adverse effects of high estrogen concentrations associated with ovarian stimulation.

We started our IVM program in January 2006 and we would like to show our experience and our first results obtained so far.

Material & methods
We have, to this, 14 IVM cases, 12 of them with PCOS. Transvaginal ultrasound was performed on the first day of menstruation in order to determine the number and size of the follicles and to rule out the presence of ovarian cysts. Follicular follow-up with transvaginal ultrasound was started on day 5 until the dominant follicle reached a size of approximately 14 mm, with endometrial thickness greater than 6 mm. At that point, 10,000 UI of hCG were given and follicular aspiration was performed 36 hours later using the CooKÒ Australia, 19 g, 35 cm aspiration needle and a pressure of 120 mm Hg under transvaginal ultrasound guidance with a Hitachi (EUB-405) ultrasound machine and a 6.5 MHz. transducer.

In vitro maturation: The Sage BiopharmaÒ maturation kit was used. The kit comprised, 1) flushing medium for the recognition and flushing of the aspirated oocytes; 2) maturation medium supplemented with HMG, MassoneÒ (Argentina), at a final concentration of 7.5 mUI/ml of FSH and LH; and 3) development medium for post-ICSI oocyte culture up to 72 hours. Oocytes were collected in Falcon tubes containing 2-3 ml of 0.9% saline solution and 2 UI/ml of heparine at 37 °C. Immature oocytes were incubated in maturation medium at 37°C and 5% CO2, for 24 to 48 hours. After 24 h of maturation, the oocytes with an expanded cumulus were denuded, microinjected by ICSI and placed in the development medium.

Results
Fourteen cases (12 PCO) with 56% of maturation and 72% of fertilization, resulting in 3 more pregnancies (22%), 1 miscarried and the other 2 are ongoing fine.

Conclusions
Although we know that in vitro maturation of oocytes obtained without exogenous hormonal stimulation is still in its development phase, and that fertilization, cleavage and pregnancy rates vary among groups, we believe it holds great promise of significant patient benefit, in particular in those cases diagnosed with PCOS and PCO

Vitrification of human cleavage stage embryos: High survival rate and pregnancy outcome.

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Introduction: Vitrification, an ultra-rapid cooling technique is shown to be a better viable alternative to slow cryopreservation. This technique completely avoids intracellular process, thereby enhancing the survival rates of embryos. Vitrification has been reported in blastocysts using several combinations of cryoprotectants and carrier systems. There is limited information on vitrification of cleavage stage embryos. We have evaluated retrospectively survival rate of vitrified cleavage stage embryos and pregnancy outcome after frozen embryo transfer cycles.

Material and Methods: Since March 2006 patients who had their surplus embryos vitrified and had subsequent frozen embryo transfer cycles were identified from our database as the study group. Cleavage stage embryos graded as grade I (equal sized blastomeres without fragments) and grade II (equal sized blastomeres with less than 20% fragments were vitrified using the protocol published by Kuwayama et al. on cryotops. Embryos were first incubated in equilibration solution (Kitazato Vitrification kit) for 5-7 minutes at room temperature. After an initial shrinkage and recovery they were aspirated into virtification solution (Kitazato virtification kit) for less than 60 seconds at room temperature and loaded on to the tip of the cryotops (Kitazato, Japan) and plunged into liquid nitrogen. A maximum of four embryos were loaded on each cryotop. Thawing of embryos was done by placing the cryotop in thawing solution (Kitazato vitrification kit) for less than 60 seconds at 370c and then into dilution solution I and dilution solution 2 for 3 minutes each respectively. Endometrial preparation for embryo transfer was done by GnRH-A administration on D21 of previous cycle, estradiol valerate (Schering, Germany) on D2 of the next cycle and progesterone (naturogest, cadila,

India) 48 hours before embryo transfer. An endometrial thickness of 9 mm was considered optimal for embryo transfer.

Results: Out of 606 embryos thawed, 560 survived giving a survival rate of 92%. Out of 156 patients who had embryo transfer, 71 had positive b.hcg value greater than 10 mIU/ml resulting in a biochemical pregnancy rate of 46%. Clinical pregnancy rate was 33%.

Conclusion: Vitrification, an inexpensive and easy technique offers a new perspective in the cryopreservation of cleavage stage embryos. Since the survival rate is high after thawing, more embryos are available for embryo transfer. Results in terms of implantation rate and delivery rate will be confirmed in larger group of samples.

Cycle characteristics of minimal stimulation IVF: Preliminary results.

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Introduction: Controlled ovarian stimulation followed by IVF and ICSI is currently the most popular practice in infertility treatment. Though this procedure is convenient in programming the cycle, it has several side effects such as OHSS, multiple pregnancies, piling up of cryopreserved embryos and high cost. Few clinics world wide are now trying to simplify the stimulation protocol resulting in single embryo transfer. We have tried using clomiphene citrate and pure FSH for few patients and assessed the cycle characteristics in terms of oocytes retrieved, fertilization and cleavage rates.

Material and Methods: Retrospective analysis of 58 cycles of CC+ rFSH in our center between November 2007 and February 2008. Patients with poor response in the previous attempts and poor antral follicular count in the present attempts were chosen for this minimal stimulation protocol after informed consent. Clomiphene citrate 50 mg was initiated orally each day from D2. 150-200 IU of rFSH was given subcutaneously every 48 hours starting from D7 of the cycle. Final Oocytes maturation was triggered by 10,000 IU of HCG. oocyte pick up was scheduled at 33 hours post HCG injection. All patients underwent ICSI and subsequent vitrification of embryos.

Results: Out of 58 patients initiated, 3 patients had spontaneous ovulation ahead of pick up time and hence no oocytes were retrieved. 3 patients had immature oocytes on retrieval, which did not mature in culture and hence the cycle was cancelled. A total of 263 oocytes were retrieved, out which 80 %(211/263) were in metaphase II stage. Fertilisation rate was 77 % (162/211) and cleavage rate was 91 %(147/ 162). 140 embryos were vitrified. In patients less than 30 years old, average oocytes retrieved was 4.22, percentage of matured Oocytes was 74% (28/38), fertilization rate was 79% (22/28) and cleavage rate was 91%(20/22). In 30-34 age group of patients average oocytes retrieved was 4.6, percentage of MII oocytes was 84 % (77/92), fertilization rate was 71% (55/77) and cleavage rate was 95% (52/55). In 35-40 age group of patients average oocytes retrieved was 5.3,percentage of MII oocytes was 80% (90/113), fertilization and cleavage rates were 82%(74/90) and 88% (65/74) respectively. In patients above 40 years average oocytes retrieved was 2.5, percentage of MII, oocytes was 80% (16/20), fertilization rate was 69%(11/16) and cleavage rate was 91%. In patients below 30 years, an average of 500 IU of rFSH was used per patient. 550 IU of rFSH was used per patient in the 30-34 age group. In 35-40 and above 40 age group 700 IU and 675 IU of rFSH was used on an average for stimulation.

Conclusion: Preliminary results indicate that there were enough good quality embryos for vitrification after minimal stimulation. Fertilisation and embryo cleavage rates are indicative of the fact that few oocytes obtained after mild stimulation are likely to represent a homogeneous cohort of good quality Oocytes. Results will be further confirmed and updated in terms of pregnancy rate after frozen embryo transfer in these patients.

REFERRAL FOR ASSISTED REPRODUCTIVE TECHNOLOGY: INDICATIONS AND OUTCOME IN LOW RESOURCE SETTING.

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Background: In Nigeria, introduction of assisted reproductive technology (ART) has tremendously modified the outlook of infertility management. However, affordability and accessibility remains a major concern.

Objective: Indications for referral and outcome of ART created pregnancies.

Materials and Methods: A review of 23 infertile patients/couples that consented to referral for ART after knowing the cost implication.

Result: Twenty three infertile patients/couples agreed to be referred for ART following knowledge of the cost implication. Indication for referral were male factor in 5(21.7%) patients, female factor in 7(30.4%) patients and both male and female factors in 11(47.8%) cases. Of the 16 patients with male factors, 4(25%) were due to azoospermia and 12(75%) were on account of asthenospermia. In 18 patients with female factor, 11(61.1%) and 3(16.7%) cases were due to solely tubo- peritoneal factor and ovulatory disorder respectively, while the remaining 4 (22.2%) cases were on account of both tubo peritoneal factor and ovulatory disorder.Out of the 23 referred cases, 9(39.1%) had treatment (7 in Nigeria and 2 in the U.K), 1(4.3%) was denied treatment in Nigeria on account of her desire to use donor sperm and become a single parent, the remaining 13(56.2%) patients could not afford the treatment cost. Nine ART created pregnancies were recorded in 7(77.8%) of the 9 patients that had treatment, the remaining 2(22.2%) had failed treatment following 1 and 3 treatment cycles respectively. Of the 9 ART created pregnancies were 5(55.6%) singleton, 3(33.3%) twins and 1(11.1%) triplets. Outcome of the 9 pregnancies were 13 live births following 7 (77.8%) term caesarean deliveries and 2(22.2%) term vaginal deliveries. One congenital umbilical hernia and one mortality due to complications of exchange blood transfusion were recorded.

Conclusion: Provision of low cost ART will improve accessibility in resource poor countries. Regulation of ART practice is a necessary step to be taken in our setting.

The role of of three-dimensional ultrasonography in assisted reproduction

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Study design and details:
A prospective pilot study of 17 women in IVF/ICSI stimulation related to kind of stimulated protocol and cause of sterility to determine ovarian and dominant follicle blood flow characteristics using three dimensional power Doppler ultrasound , grading system of perifollicular vascularity /Chui D.K.C.et al. 1997/ and power doppler inde PI and RI of dominant follicle.

Materials and methods:
17 the patients were stimulated in a long protocol (GNrh agonist-Zoladex, Decapeptyl) on 22-th day of their period and subsequently with rekombianat FSH (puregon /gonal pen) 15 days after downregulation / no follicles more than 10 mm, endometrium thickness less than 5 mm and level of Estradiol E2 less than 50 pg/ml. We exluded the women, who didn ' t agree with the examination on the day of ovum pick up futher

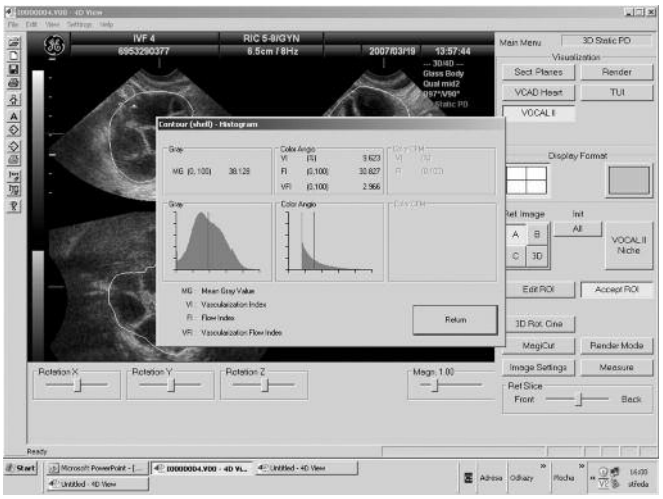
such women , whose stimulation was stopped for the risk of OHSS, women with the operation of right or left ovary, women with ovarectomy , women with uterine malformation , women with FSH level more than 10 mIU/l in early follicular period or women with ovarian cysts. On the basis of male faktor sterility exlusion we provided always ICSI Method. The 3D ultrasound examinations and power doppler sonography of the ovary and dominant follicle we provided on the day HCG (pregnyl) before ovum pick up. The volume of the ovary and dominant follicle, vascularization index /VI/, flow index /FI/, vascularization flow index / VFI / , mean grayness , perifolicular vascularity and PI a RI of the dominant follicle was determined for each ovary separately. The oocyte of the dominant follicle from both ovaries was fertilized by ICSI and observed his embryogeny. On the day of ovum pick up we have collected the samples of follicular fluid of dominanat follicle without of blood contamination. After the collecting of samples of follicular fluid of dominant follicle and serum we provided their centrifugate and stored at -40 C until their planned biochemical analysis after the completed collection of the samples at all intended 80 patients.

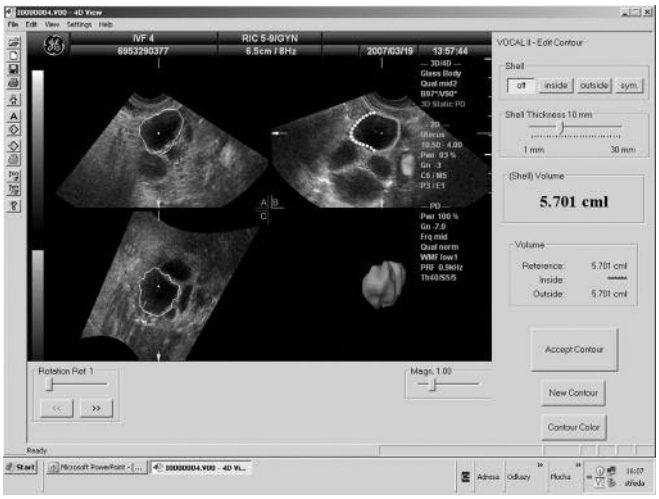
Results and conclusions:

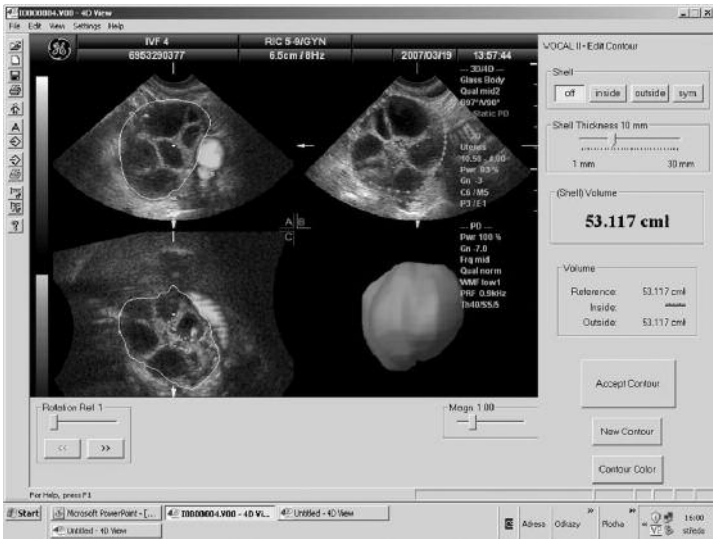
The IVF/ICSI cycle was evaluated in 17 women, among which 5 were pregnant (29.4 %) and 12 non-pregnant (70.6 %). The median age of the women was 32 (range 26-36). The causes of the infertility were male in 12 cases (70.6 %), tubal in 2 cases (11.8 %) and mixed in 3 cases (17.6 %). There were 11 cases (64.7 %) of primary and 6 cases (35.3 %) of secondary infertility.Statistical analysis of the data was performed with R programming language (http://cran.r-project.org), version 2.4.1. We have computed descriptive statistics and p-values of hypothesis tests for comparing the group of pregnant and non-pregnant patients. For continuous data the normality is not assumed because of small sample sizes and asymmetry of the data distribution. The following tables give the median and range (minimum and maximum) of each continuous variable together with the p-value of the two-sample Wilcoxon test. For categorical data we list the tables of counts with percentages of cases. To compare the two groups, the p-value of Fisher's exact test is computed (also for tables larger 2 by 2). Ultrasonography and Doppler angiography parameters measured on both ovaries are analyzed for each ovary separately.There is no significant difference between groups in the age of patients, type and causes of infertility and other general and clinical characteristics. In the group of pregnant women, there is a significantly larger number of grade 1 embryos on transfer day, a significantly larger flow index dx and there is a significant difference in the degree of morphological preimplantation quality of the 1. and 2. transferred embryos and in the degree of perifollicular vascularity of the right follicle dx. Other variables yield a non-significant difference between the pregnant and non-pregnant group because of small sizes of the data samples; however the p-values are near the 5%-level for the vascularization index and vascularization flow index, for which the observed values have the tendency to be larger for pregnant women and a future research with a larger number of patients is intended to attain significant results.

tables 1 (/note: Degree. of perifollicular vascularity grading system used to assess follicular vascularity. (a) shows 25% circumferential flow (grade F1); (b) 26–50% flow (F2); (c) 51–75% flow and (d) .75% flow (F4).

Chui D.K.C. , et al. 1997) and tables 2 /data are presented as mean +/- standart deviation / and images 1-3







total ovarian volume OV (ml) dx	43.96 (41.69-130.12)	42.65 (19.52-109.80)	0.279
total ovarian volume OV (ml) sin	45.06 (43.06-116.96)	42.06 (11.32-102.30)	0.316
Volume of the dominant follicle FV (ml) l dx	5.08 (5.26-8.43)	5.38 (3.35-7.05)	0.154
Volume of the dominant follicle FV (ml) l sin	5.09 (4.08-5.65)	4.98 (3.26-9.63)	0.57
Vascularization index VI l dx	12.47 (8.66-20.06)	8.22 (2.91-19.06)	0.068
Vascularization index VI l sin	10.38 (5.02-25.43)	6.54 (6.30-11.72)	0.169
Flow index FI l dx	47.66 (42.78-52.26)	40.45 (32.31-57.56)	0.044
Flow index FI l sin	46.90 (35.23-48.90)	41.91 (28.83-51.47)	0.099
Vascularization flow index VFI l dx	4.95 (2.05-8.46)	4.00 (0.90-10.06)	0.065
Vascularization flow index VFI l sin	4.84 (2.30-10.06)	3.91 (2.62-4.62)	0.067
Resistance index Doppler of the dominant follicle l dx	0.58 (0.55-0.62)	0.63 (0.42-0.67)	0.061
Resistance index Doppler of the dominant follicle l sin	0.58 (0.50-0.62)	0.65 (0.38-0.71)	0.581
Pulsatility index Doppler of the dominant follicle l dx	0.88 (0.83-1.00)	0.82 (0.65-1.24)	0.224
Pulsatility index Doppler of the dominant follicle l sin	0.93 (0.65-1.09)	0.65 (0.49-1.63)	0.461
Degree of perifollicular vascularity of the dominant follicle dx			0.029
1	1 (11.1)	8 (88.9)	
2	1 (20.0)	4 (80.0)	
3	3 (100.0)	0 (0.0)	
Degree of perifollicular vascularity of the dominant follicle sin			0.090
1	1 (12.5)	7 (87.5)	
2	2 (33.3)	4 (66.7)	
3	2 (100.0)	0 (0.0)	
not obtained	0 (0.0)	1 (100.0)	

Live birth following in-vitro maturation of oocytes and vitrification. Further strategies in fertility preservation.

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Background: With improved life expectancy for cancer survivors, preserving reproductive capability has become of paramount importance and developing technologies to achieve this is crucial. Two such technologies are in-vitro maturation of oocytes (IVM) and oocyte freezing. To date, pregnancies reported have resulted from vitrification of matured oocytes collected after traditional ovarian stimulation, with only one group claiming a live birth following IVM and oocyte vitrification. In this communication we support the idea that IVM followed by vitrification of oocytes is an option towards fertility preservation as we report a live birth following in-vitro maturation of oocytes and subsequent vitrification.

Methods: A 25 year old woman diagnosed with primary infertility and polycystic ovaries was recruited to our IVM programme. Collected oocytes were matured as described by Chian. Due to personal reasons matured oocytes had to be cryopreserved. After one year, oocytes were warmed and fertilized with ICSI. Embryo transfer was performed on day two.

Results: Nine immature oocytes were retrieved, from which six reached metaphase II (MII) status at 24 hours (82% maturation rate), undergoing vitrification. Four oocytes survived thaw (67% survival rate) and fertilised following intracytoplasmic sperm injection (ICSI) (100% fertilization rate). Four embryos were transferred on day two. A single intrauterine pregnancy was identified at seven gestational weeks (25% implantation rate). A healthy baby girl was delivered at 38 gestational weeks.

Conclusions: IVM followed by oocyte cryopreservation is, according to our results, a viable alternative to preserve fertility in those patients in whom conventional controlled ovarian stimulation is contraindicated

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