The First World Congress on Natural Cycle/Minimal Stimulation IVF
London, December 15th and 16th 2006

At the Royal College of Obstetricians and Gynaecologists, London, UK

www.naturalcycle.org
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The Congress Committee
Geeta Nargund  Stuart Campbell
René Frydman  Robert Edwards
Krinos Trokoudes  Rex Scaramuzzi

ISNAR
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ORGANISED BY
HER Trust – Women’s Health Foundation (Reg. Charity No: 1082195) www.hertrust.org
in collaboration with
The French Society of Reproductive Medicine

Serono Symposia International Foundation (www.seronosymposia.org) has submitted this program ‘The First World Congress on Natural Cycle/Minimal Stimulation IVF’ (London - UK - December, 15-16) for accreditation by the European Accreditation Council for Continuing Medical Education (EACCME) and The Royal College of Physicians (UK).
A special conference edition of RBM Online will be published in 2007.

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
The First World Congress on Natural Cycle/Minimal Stimulation IVF

We are delighted to welcome you to the First World Congress on Natural Cycle IVF at the Royal College of Obstetricians and Gynaecologists, London.

This new Society, we believe, is much needed because not only are we entering an era of single embryo transfer but also we are increasingly aware of the need to put the welfare of the woman right at the top of the agenda when it comes to assisted reproduction.

This Society is founded to promote a more physiological approach to assisted reproduction. It embraces not only Natural Cycle Assisted Reproduction but also minimal stimulation protocols and in vitro maturation of oocytes. We feel that advances in embryology, ultrasound technology and endocrinology will make the natural cycle / low stimulation approach more successful and increasingly relevant to everyday practice. The Congress will focus on both basic science and clinical aspects of assisted reproduction. We have organised workshops to address the practical aspects of natural cycle, minimal stimulation IVF treatment, in vitro maturation of oocytes and advanced ultrasound technology in reproductive medicine.

We hope you enjoy your the congress!

Mrs Geeta Nargund
President

Prof. René Frydman
Chairman

Dr Krinos Trokoudes
Secretary
Invited Faculty Speakers

Nelly Achour-Frydman (France)  
Louise A Brinton (USA)  
Clare Brown (UK)  
Carine Camby (France)  
Stuart Campbell (UK)  
Jean Cohen (France)  
Ian Cooke (UK)  
Salim Daya (Canada)  
Dominique De Ziegler (Switzerland)  
Jehoshua Dor (Israel)  
Robert Edwards (UK)  
Renato Fanchin (France)  
Bart Fauser (Netherlands)  
René Frydman (France)  
Ian Gibson MP (UK)  
Mark Hamilton (UK)  
André Hazout (France)  
Tim Hedgeley (UK)  
Stephen Hillier (UK)  
Stephen Killick (UK)  
Michèle Lachowsky (France)  
Nathalie Lédée (France)  
Elizabeth Lenton (UK)  
Svend Lindenberg (Denmark)  
Angela McNab (UK)  
Daniel Méndez Lozano (Mexico)  
Antonis Makrigiannakis (Greece)  
Geeta Nargund (UK)  
Karl Nygren (Sweden)  
François Olivennes (France)  
Willem Ombelet (Belgium)  
Evangelos Papanikolaou (Belgium)  
Antonio Pellicer (Spain)  
Helen Picton (UK)  
Chantal Ramogida (France)  
Hassan Sallam (Egypt)  
Rex Scaramuzzi (UK)  
Adrian Shulman (Israel)  
Allan Templeton (UK)  
Shokichi Teramoto (Japan)  
François Thepot (France)  
Krinos Trokoudes (Cyprus)  
Jonathan Van Blerkom (USA)  
Willem Verpoest (Belgium)  
Veljko Vlaisavljevic (Slovenia)

Contributors to Workshops:

Wilfried Feichtinger (Austria)  
Sudarshan Ghosh-Dastidar (India)  
Davor Jurkovic (UK)  
Milton Leong (Hong Kong)  
Luciano Nardo (UK)  
Povilas Sladkevicius (Sweden)  
Juan García Velasco (Spain)
All lectures will take place in the Lecture Theatre and Collegiate Room

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<thead>
<tr>
<th>Time</th>
<th>Event</th>
<th>Speaker/Chair</th>
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<tbody>
<tr>
<td>08:00</td>
<td>Registration &amp; Coffee in <strong>Nuffield Hall</strong></td>
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<tr>
<td>08:50</td>
<td>Welcome</td>
<td>Allan Templeton</td>
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<tr>
<td>09:00</td>
<td>Plenary Lecture - IVF Strategy – Time for a Re-Think</td>
<td>Robert Edwards</td>
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<td>09:20</td>
<td><strong>Round Table 1 - The Ovary - Lessons from a Natural Cycle</strong></td>
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<td><strong>Chair</strong> Bart Fauser (Netherlands) Stephen Hillier (UK) Rex Scaramuzzi (UK)</td>
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<tr>
<td>09:20</td>
<td>Follicular Recruitment and Selection of the Dominant Follicle</td>
<td>Helen Picton</td>
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<td>09:35</td>
<td>The Role of Gonadotrophins in Oocyte Maturation</td>
<td>Dominique de Ziegler</td>
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<td>09:50</td>
<td>The Chromosomal Complement of the Embryo in a Natural Cycle</td>
<td>Willem Verpoest</td>
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<td>10:05</td>
<td>Follicular Vascularisation and Oocyte Quality</td>
<td>Geeta Nargund</td>
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<td>10:20</td>
<td>AMH in Follicular Fluid and in Serum</td>
<td>Renato Fanchin</td>
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<td>10:35</td>
<td>The Cumulus and Oocyte Quality</td>
<td>Jonathan Van Blerkom</td>
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<td>10:55</td>
<td>DISCUSSION</td>
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<td>11:15</td>
<td>Coffee in <strong>Nuffield Hall</strong></td>
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<td>11:35</td>
<td><strong>Round Table 2 - The Uterus and the Endometrium</strong></td>
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<td><strong>Chair</strong> André Hazout (France) Stuart Campbell (UK) Antonis Makrigiannakis (Greece)</td>
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<tr>
<td>11:35</td>
<td>Ultrasound and the Endometrium and the Myometrial Zone</td>
<td>Stephen Killick</td>
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<td>11:50</td>
<td>Uterine Markers in Natural versus Stimulated IVF</td>
<td>Nathalie Lédee</td>
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<td>12:05</td>
<td>Is Ovarian Stimulation Detrimental to the Endometrium and to the Embryo?</td>
<td>Antonio Pellicer</td>
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<tr>
<td>12:25</td>
<td>DISCUSSION</td>
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<td>12:40</td>
<td><strong>FREE COMMUNICATIONS</strong></td>
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<tr>
<td>12:40</td>
<td>1. Embryo Quality of Modified Natural Cycle IVF</td>
<td>EG Arts et al</td>
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<td>12:50</td>
<td>2. Age, E2 Levels and Blastocyst Development for Prediction of Success</td>
<td>Tomaž Tomaževic et al</td>
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<tr>
<td>13:00</td>
<td>Lunch in <strong>Nuffield Hall</strong></td>
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### Timetable of Events

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
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<tbody>
<tr>
<td>14:00</td>
<td><strong>Round Table 3 - Indications and Results</strong></td>
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<td><strong>Chair</strong> Jean Cohen (France) Hassan Sallam (Egypt) Adrian Shulman (Israel)</td>
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<tr>
<td>14:00</td>
<td>For Routine Use in Ovulatory Women                                   François Olivennes</td>
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<tr>
<td>14:15</td>
<td>Poor Responders and Failed Implantation                              René Frydmam</td>
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<td>14:30</td>
<td>Alternatives to Ovarian Stimulation when it Poses a Risk             Jehoshua Dor</td>
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<tr>
<td>14:45</td>
<td>DISCUSSION</td>
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<tr>
<td>15:00</td>
<td><strong>FREE COMMUNICATIONS</strong></td>
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<tr>
<td>15:00</td>
<td>3. Low Dose hCG for prevention of OHSS                               Geeta Nargund</td>
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<tr>
<td>15:10</td>
<td>4. Cumulative Pregnancy Rates                                        MJ Pelinick et al</td>
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<tr>
<td>15:20</td>
<td>5. Larger Birth Weight Infants Born After Minimal Stimulation IVF    Annemieke Hoek</td>
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<td>15:30</td>
<td>Coffee in <strong>Nuffield Hall</strong></td>
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<td>15:50</td>
<td><strong>Round Table 4 - ‘How to Do’ Natural/Minimal Stimulation Cycle</strong></td>
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<td><strong>Chair</strong> René Frydmam (France) Geeta Nargund (UK)</td>
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<tr>
<td>15:50</td>
<td>Natural Cycle IVF with and without hCG                               Elizabeth Lenton</td>
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<tr>
<td>16:05</td>
<td>Natural Cycle IVF with LH Surge Control                              Krinos Trokoudes</td>
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<td>16:20</td>
<td>Minimal Stimulation IVF                                              Shokichi Teramoto</td>
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<td>16:35</td>
<td>Follicular Aspiration and Follicular Flushing                        Daniel Mendez Lozano</td>
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<tr>
<td>16:50</td>
<td>Embryo Transfer and Luteal Support                                   Veljko Vlaisavljevic</td>
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<tr>
<td>17:05</td>
<td>The Biological Point of View: Advantages and Disadvantages of Natural Cycle Nelly Achour-Frydmam</td>
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<tr>
<td>17:20</td>
<td>DISCUSSION</td>
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<td>17:50</td>
<td>Closing Speech                                                       René Frydmam</td>
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**19:30 - 23:00 Congress Dinner at The Houses of Parliament**
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<thead>
<tr>
<th>Time</th>
<th>Event</th>
<th>Speaker(s)</th>
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<tbody>
<tr>
<td>08:00</td>
<td><strong>Isnar Foundation Meeting: Your Opportunity to Join</strong> in the Lecture Theatre</td>
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<td>08:30</td>
<td>Coffee in <strong>Nuffield Hall</strong></td>
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<tr>
<td>09:00</td>
<td><strong>Plenary Session</strong>&lt;br&gt;Chair: Ian Cooke (UK) Jonathan Van Blerkom (USA)</td>
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<tr>
<td>09:00</td>
<td>Mild Ovarian Stimulation for IVF: Enough is enough</td>
<td>Bart Fauser</td>
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<td>09:20</td>
<td>Long-term Physical Effects of Ovarian Stimulation</td>
<td>Louise Brinton</td>
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<td>09:50</td>
<td><strong>Round Table 5 - The Friendly Approach to IVF</strong>&lt;br&gt;Chair: René Frydman (France) Dominique de Ziegler (Switzerland) Mark Hamilton (UK)</td>
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<tr>
<td>09:50</td>
<td>Affordable IVF for Third World countries</td>
<td>Willem Ombelet</td>
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<td>10:05</td>
<td>In Vitro Maturation as the Future</td>
<td>Svend Lindenburg</td>
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<td>10:20</td>
<td>The Effect of Multi-Follicular Ovarian Stimulation on the Outcome: More May Not Be Better</td>
<td>Evangelos Papanikolaou</td>
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<tr>
<td>10:35</td>
<td>Single Embryo Transfer: The Role of Natural Cycle/Minimal Stimulation IVF in the Future</td>
<td>Karl Nygren</td>
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<td>10:50</td>
<td>Cost Effectiveness of Natural versus Stimulated IVF</td>
<td>Salim Daya</td>
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<td>11:05</td>
<td>DISCUSSION</td>
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<td>11:20</td>
<td><strong>FREE COMMUNICATIONS</strong></td>
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<tr>
<td>11:20</td>
<td>6. Cost Effectiveness of Natural versus Stimulated IVF</td>
<td>H Groen et al</td>
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<td>11:30</td>
<td>7. Natural Cycle IVF in Developing Countries</td>
<td>Ahmed Shahin</td>
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<td>11:40</td>
<td>Coffee in <strong>Nuffield Halls</strong></td>
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<td>11:55</td>
<td><strong>Round Table 6 - The Patient’s Perspective</strong>&lt;br&gt;Chair: Ian Gibson (UK) Geeta Nargund (UK) Krinos Trokoudes (Cyprus)</td>
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<td>11:55</td>
<td>The Patient’s Perspective</td>
<td>Tim Hedgeley / Clare Brown</td>
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<td>12:10</td>
<td>The Patient’s Choice and the Informed Patient</td>
<td>Angela McNab / Chantal Ramogida</td>
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<td>12:25</td>
<td>Psychological Aspects of IVF with Natural/Stimulated Cycle</td>
<td>Michèle Lachowsky</td>
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<td>12:40</td>
<td>Fertility &amp; Public Health</td>
<td>Carine Camby / François Thepot</td>
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<td>12:55</td>
<td>Closing Speech</td>
<td>Geeta Nargund</td>
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<td>13:05</td>
<td>CLOSE OF DAY 2 (LECTURES ONLY)</td>
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<td>13:05</td>
<td>Lunch in <strong>Nuffield Hall</strong></td>
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<td>14:05</td>
<td><strong>WORKSHOP</strong> Natural Cycle IVF and In-Vitro Maturation</td>
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<td>14:30</td>
<td>Coffee in <strong>Nuffield Hall</strong></td>
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<tr>
<td>15:30</td>
<td><strong>WORKSHOP</strong> Advanced Ultrasound in Reproductive Medicine</td>
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<td>18:00</td>
<td>CLOSE OF DAY 2</td>
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Natural Cycle and Minimal Stimulation IVF
Moderators:
René Frydman, Krinos Trokoudes, Geeta Nargund,
Adrian Shulman, Veljko Vlaisavljevic,
Juan García Velásco
14.00 Indications and Patient selection
Natural cycle: René Frydman,
Veljko Vlaisavljevic, Adrian Shulman (10 minutes)
Minimal stimulation: Wilfried Feichtinger (10 minutes)
14.20 Protocol
Pre-cycle preparation & Cycle monitoring: Adrian
Shulman & Geeta Nargund
Follicular phase supplementation: Veljko Vlaisavljevic
Ovulation triggering: Veljko Vlaisavljevic
Follicle aspiration: Flushing/No flushing: René Frydman
Embryo transfer: Day of ET: Krinos Trokoudes
Luteal phase supplementation: Juan García Velásco
14.50 Video Clip by Veljko Vlaisavljevic
In-vitro Maturation of oocytes
Moderators:
Milton Leong, Renato Fanchin, René Frydman, Svend Lindenberg,
Nelly Achour-Frydman
15.00 In-Vitro Maturation of Oocytes
Indications: M Leong
Management of cycles: Renato Fanchin
Biological aspects of IVM: Nelly Achour-Frydman
3:30 Coffee Break in Nuffield Hall

Advanced Ultrasound in Reproductive Medicine
Moderators:
Stuart Campbell; Davor Jurkovic; Stephen Killick;
Povilas Sladkevicius; Luciano Nardo;
Geeta Nargund; Sudarshan Ghosh-Dastidar
15.50 Stuart Campbell: Ultrasound Techniques; 2D; Doppler; 3D.
16.00 Davor Jurkovic: Uterine anomalies and cavity assessment
16.10 Discussion
16.20 Stephen Killick: Endometrial receptivity
16.30 Discussion
16.40 Geeta Nargund: Fertility Scan and Ovarian Reserve
16.50 Discussion
17.0 Povilas Sladkevicius: HyCoSy and Hydrosonography
17.10 Discussion
17.20 Luciano Nardo: Endometriosis
17.30 Discussion
17.40 Sudarshan Ghosh-Dastidar: Ultrasound Guided Procedures in IVF
17.50 Stuart Campbell: Closing Remarks
18.00 Close

Nuffield Hall
• Coffee Breaks and Lunches
• Posters

Exhibitors
- Serono
- Diagnostic Sonar and Medison Company Limited
- The Women’s Clinic
- GE Healthcare
- Siemens Medical Solutions
- Phillips
- Prodimed
- CCD Laboratories
- Shire Pharmaceuticals
- RBM Online
A Brief History of the Houses of Parliament
Where Parliament now stands has been a centre of authority for over a thousand years. Once the home of the royal family, and still officially a royal palace, the buildings that now make up the modern Houses of Parliament have developed through design, accident and attack.

A Royal Palace
The first known royal palace to occupy Parliament’s site was Edward the Confessor’s (c1065). Parliament officially remains a royal palace and is still referred to as the ‘Palace of Westminster’. The site was used as a royal residence until Henry VIII moved the royal family out in 1512 following a fire.

Westminster Hall
Westminster Hall is the oldest part of Parliament. The walls were built in 1097 and the hall is one Europe’s largest medieval halls with an unsupported roof. It was extensively rebuilt during the 14th century.

Once used as a law court, the hall has held several notable trials, including that of Sir William Wallace Braveheart (1305), the Gunpowder Plot conspirators Guy Fawkes (1606) and King Charles I (1649).

Today the hall is often used for important State occasions such as the Queen’s Golden Jubilee and the lying-in-State of the late Queen Elizabeth the Queen Mother, both in 2002.

The 1834 fire and rebuilding
The Palace almost completely burnt down in a fire on 16 October 1834, which destroyed everything except Westminster Hall, the crypt of St Stephen’s Chapel and the Jewel Tower.

The Houses of Parliament, as we know them today, were rebuilt after the fire. The process, which incorporated Westminster Hall and the remains of St Stephen’s Chapel, took just over 30 years. The rebuilding was completely finished by 1870.

Architect Charles Barry won an open competition for a new design with his gothic vision. Barry was assisted by Augustus Welby Pugin, especially in the details, fittings and furniture.

The bombing of 1941
During the Second World War, on 10 May 1941, a bombing raid destroyed the House of Commons chamber.

Architect Sir Giles Gilbert Scott designed a new, five-floor block (with two floors occupied by the chamber). It was used for the first time on 26 October 1950.

From www.parliament.uk, please visit the website for more information
Concepts on the maturation of mammalian oocytes began with the work of Pincus in the 1930’s. He discovered that rabbit oocytes matured spontaneously in 11 hours from the germinal vesicle stage to metaphase 2 and an extruded polar body when they were released from their follicles into culture media. Later, he attempted a similar achievement with the human oocyte. Unfortunately, a lack of chromosomal genetics led to mistiming the maturity of the human oocytes in vitro, and this led to failures at introducing human IVF by him and other workers. Only in the 1960s was it discovered that human oocytes released into media required 37 hours to fully mature. Uncertainty about the viability of the human oocytes that Edwards and Steptoe had matured in vitro led them to stimulate patients with HMG and HCG to obtain several follicles and sufficient mature oocytes to fertilise in vitro. With the later additions of clomiphene, GnRH agonists and antagonists, and recombinant gonadotrophins, ovarian stimulation has become very expensive, its costs perhaps being as high as 50% of the total price of IVF today. Nevertheless, endocrine problems with HMG and HCG, especially weak luteal phases and biochemical pregnancies led Edwards and Steptoe reverting to natural cycle IVF when they developed an LH assay that could detect the onset of the urinary LH surge, and so time the exact moment to aspirate the single maturing oocyte just before it ovulated. Its fertilization in vitro led to the first IVF baby. Even so, almost every IVF clinic still decided to use gonadotrophins rather than natural cycle IVF or oocyte maturation in vitro.

The clock has reversed as groups of investigators returned to human oocyte maturation in vitro for IVF. This subject struggled for a decade or more until some pioneers improved the method to make it acceptable for routine IVF. Indeed, some reports gave implantation and birth rates as being close to those attained with routine IVF. This field is thus now wide open, with clinics worldwide improving their methods of maturation in vitro as happened with the introduction of new forms of endocrine stimulation in the earlier days of IVF. Some preliminary data on results with IVM will be presented as it becomes obvious that research must now be concentrated on different topics than arise with ovarian stimulation. It is impossible to discuss them all in a 20 minute Introduction, so I will choose two or three examples. In vitro maturation makes certain aspects of oocyte development available for research. One of the most significant concerns the origin of monosomy and trisomy which are so frequent with normal IVF. These errors could arise in the early meiotic stages occurring soon after the onset of oocyte activation and they may arise on an immense scale. This leads to 50% of human oocytes and embryos being chromosomally abnormal. More will have to be learnt about the progress of meiosis at the critical stages of diplotene and diakinesis and the control of the final stages of meiosis since these will occur as the aspirated oocytes are placed in vitro. Can we therefore look forward to controlling the meiotic disasters that lead to monosomy and trisomy?

Another unusual aspect is that more oocytes may be aspirated after maturation in vitro than after routine IVF since many small follicles fail to respond to gonadotrophins so they are never aspirated in current endocrine-dominated IVF cycles. The need for any endocrine stimulation during IVM needs clarifying since some clinics practising maturation in vitro administer small amounts of HMG and HCG. Improvements will also be needed in the aspiration of smaller follicles which may contain a viable oocyte which is capable of development to full term. What are the smallest follicles that can be aspirated? And at the practical level, will more oocytes be aspirated for maturation in vitro than is achieved by current endocrine methods of stimulation? But will small follicles bleed more freely than mature follicles? And finally, will it be possible to do successful natural cycle IVF and simultaneously aspirate small follicles for maturation in vitro? IVF might be very different in a year or so.
Follicular Recruitment and Selection of the Dominant Follicle

Dr. HM Picton and Prof. BK Campbell. ‘Reproduction and Early Development Research Group, Leeds Institute of Genetics and Health Therapeutics, University of Leeds, UK; ‘Department of Obstetrics and Gynaecology, School of Human Development, Queens Medical Centre, University of Nottingham, UK

Extensive research has established that the main physiological stimulant for the growth of preovulatory follicles is FSH, while the trigger for follicle selection, resumption of meiosis and ovulation of a fertile oocyte is provided by the preovulatory LH surge. Critically, during the selection of an ovulatory follicle in monovular species the follicle transfers its gonadotrophic dependence from FSH to LH as the LH pulse frequency increases during the latter part of the follicular phase of the natural cycle. This results in a marked increase in intra-follicular oestradiol levels. A direct consequence of this changing gonadotrophin milieu is the resumption of meiotic maturation in the oocyte, and the transition of the steroid environment from predominately oestrogen dominated synthetic pathways to progesterone dominated production by the luteinizing granulosa cells as they undergo remodelling into the corpus luteum. The LH driven changes within the follicle are therefore associated with: (i) a decrease in intracellular cyclic AMP in the oocyte; and (ii) the production of hyaluronic acid, which leads to the mucification and expansion of the cumulus cells. The loss of junctional contacts and cross talk between the cumulus cells and oocyte leads to deactivation of cAMP dependent protein kinase A and reduces the inhibitory influences of purines on the maintenance of meiotic arrest in the oocyte.

Contingent with gonadotrophic stimulation of growth in natural cycle is the moderation of gonadotrophin action by paracrine and autocrine factors derived from the oocyte and somatic compartment of the follicles. Acknowledged local regulators of the gonadotrophins include: the IGF family (including the inhibin/activin systems) and their binding proteins which modulate the sensitivity of cells to FSH and LH; the BMPs and their interactions with endogenous antagonists which act as intrafollicular signalling molecules during early and late follicle and oocyte development; and members of the TGFβ superfamily of growth factors including GDF-9 and Anti Müllerian Hormone which promote primordial follicle recruitment and/or regulate oocyte maturation and cumulus cell expansion and mucification.

In humans during any natural cycle, only one or perhaps two follicles attain dominance and are selected to ovulate. The greater majority regress. In contrast, virtually all assisted reproduction cycles induce premature maturation of a population of less developmentally advanced antral follicles via protracted elevation of the circulating FSH concentrations. This aggressive strategy produces oocytes of variable developmental competence because both the gametes and their supporting granulosa cells have not been exposed to the normal physiological array of endocrine and follicular factors over the required time frame. A further deficiency of long ovarian stimulation protocols is that the normal shift from FSH to LH dependence in the ovulatory follicles has not been allowed to occur. While this difference may have little or no effect on the magnitude of the ovarian response to stimulation, it may have a profound influence on oocyte quality. In light of this evidence it is high time we used the insight gained from physiological studies of follicle recruitment and selection in animals to support natural cycle assisted conception in humans.
The Role of Gonadotropins in Oocyte Maturation

D. de Ziegler, T. Fraisse, G. de Candolle, N Vulliamoz. Reproductive Endocrinology and Infertility, University Hospitals Geneva and Lausanne, Switzerland

Introduction: In the natural cycle, follicular recruitment, selection and maturation, the 3 primary steps of the follicular phase, are controlled by gonadotropins. Classically, the earlier step, follicular recruitment, takes place under FSH dominance whereas, the last step, follicular maturation, occurs under LH dominance. In this process, the switch from FSH to LH dominance takes place during the intermediary or selection step of the follicular phase, whereby the dominant follicle bound for ovulation is selected.

In natural cycle-IVF, there are 2 uncertainties inherent to follicular phase physiology that may complicate oocyte retrieval from the single dominant follicle:

First, follicular recruitment in response to FSH elevation, which initiates the whole follicular phase, occurs at a poorly specified time during the inter-cycle interval. Hence, timing the advancement of the follicular phase to the 1st day of menses, a phenomenon that is not inherently linked to the inter-cycle FSH signal, is incorrect and possibly misleading. By references to menses, follicular maturation may be slightly ahead or behind without anyone being aware of it. This inherent uncertainty as to when the functional onset of the follicular phase takes place affects all our efforts to assess the degree of advancement of the whole follicular phase.

Second, the exact timing of the LH surge leading to ovulation cannot be prospectively predicted in the natural cycle. This latter uncertainty regarding the timing of the LH surge is often circumvented by deliberately triggering ovulation with exogenous hCG (>5,000IU). This practice, however sound on practical standpoint, may shorten the last stage of the follicular phase, resulting in hampering follicular maturation when exogenous hCG is used to induce ovulation. To palliate this problem, certain teams block endogenous LH with timely administration of a GnRH antagonist for the last 1-3 days of the follicular phase thus, allowing to delay hCG administration. This practice however leads to falling E2 levels, which in turn calls for exogenous gonadotropin administration to sustain E2 levels and follicular maturation. In the end result, all these corrective measures result in a not-so-natural hormone support that is often deployed in so called natural-cycle IVF.

It is the purpose of this presentation to review how these 2 variables affecting the onset and the end of the follicular phase, the uncertainty about the timing of the inter-cycle FSH signal and LH surge, could be better controlled in order to optimize natural cycle IVF.

Timing the inter-cycle FSH signal. In previous work we have demonstrated that it is the decrease in E2 levels at the demise of the corpus luteum that generates the inter-cycle increase in FSH.

Contrasting with this process, menses result from the drop in progesterone also occurring at the end of the luteal phase through a process identified as withdrawal bleeding (1). While these 2 phenomena are often concomitant, it is not necessarily so all the time in every woman. In contrast some degree of staggering between the decreases in E2 and P levels may exist, which will lead to dissociate the inter-cycle FSH signal from the onset of menses. This actually constitutes the primary factor that accounts for the inherent variability of follicular phase length, with early and late drops in E2 resulting in short and long follicular phases, respectively.

Drawing from our understanding of the instrumental role played by E2 on the inter-cycle FSH signal (1), we designed an original system for controlling its timing based on exogenous E2 administration (2). In this model, administration of exogenous E2 (2mg PO BID or 0.1mg transdermally) starting on day 25 of the previous menstrual cycle (or approximately 3 days prior to menses) delays FSH elevation until after E2 treatment is discontinued (2). FSH, which starts to rise when E2 treatment is discontinued, reaches an acme on the 3rd day after E2 was stopped. In a prospective trial, we showed that LH surge leading to ovulation occurred on the 13th following the interruption of E2 treatment. Hence, this approach allows scheduling E2 treatment so that the LH surge and ovulation will take place on a week (and/or desired) day.

Timing the LH surge. The preovulatory LH surge is triggered by rising E2 levels, which are produced by the maturing follicle. When a threshold level of circulating E2 is reached, a positive feedback mechanism takes over whereby, further E2 elevations stimulate gonadotropins and trigger the LH surge. Yet, E2 is not the only player acting on LH at the time of the preovulatory surge. It has now been amply documented that a non-steroid factor of ovarian origin, the gonadotropin surge attenuating factor (GnSAF), also participates in controlling LH by antagonizing the surge promoting properties of E2 (3-5). Practically speaking therefore, the actual timing of the LH surge is given by the moment when the surge triggering effects of rising E2 levels exceed the
anti surge properties of GnSAF. Hence, an advancement of LH surge may result from decreased GnSAF production as this is feared to take place in women whose ovaries have undergone age related changes. As of now, it has not been clearly defined whether GnSAF is produced by the cohort of small not-growing follicles present in the ovary or by the maturing follicle(s). In support of the latter hypothesis we know that GnSAF is produced in increasing amounts in COH where higher levels of E2 are needed for triggering an LH surge. The exact nature of GnSAF is unknown in spite of over 20 years of active research in the field (3). In the future, a better understanding of GnSAF production by the ovary carrying the dominant follicle might help modulate this production by adding the proper gonadotropin regimen in the later stages of the follicular phase.

**Conclusion.** Two unknown factors affecting the follicular phase of the menstrual cycle are still hampering our attempts to tame natural-cycle IVF. Current regimens are the best available options. We believe however that a better understanding of the respective roles of FSH and LH on the inter-cycle FSH signal and the dualistic relationship that oppose the surge promoting and inhibiting properties of E2 and GnSAF, respectively might improved our mastering of natural-cycle IVF:

**References**

Le Néstour E, Marrouj I, Lahbou N, Roger M, de Ziegler D, Bouchard P. Role of estradiol in the rise in follicle-stimulating hormone levels during the luteal-follicular transition. J Clin Endocrinol Metab. 1993;77:439-42.


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**The Chromosomal Complement of Natural Cycle Embryos.**

Dr W Verpoest on behalf of the Centre for Reproductive Medicine and the Centre for Medical Genetics and Preimplantation Genetic Diagnosis at the Vrije Universiteit Brussels, Belgium

Ovarian hyperstimulation for IVF and ICSI may theoretically induce chromosome abnormalities (Boué et al, 1973; Kola 1988; Gras et al, 1992). Previous studies have already illustrated that the proportion of chromosomal abnormalities may be reduced as a result of lower ovarian stimulation (Baart et al, 2005). Other studies however have not been able to establish this (Gras et al, 1992). Preimplantation genetic screening for aneuploidy (PGS) is a technique allowing chromosomal aneuploidy analysis in pre-transfer embryos following IVF or ICSI, and can be considered as an early form of prenatal screening for chromosomal abnormalities. The clinical benefit of PGS in improving live birth rate may be under scrutiny (Shahine et al, 2006; Twisk et al, 2006), but this technique may appear to be useful in improving selection of euploid embryos, thereby reducing implantation failure and miscarriage rates. Some data demonstrate that even in young patients, the rate of numerical chromosomal abnormalities in embryos is remarkably high, after ovarian stimulation for IVF/ICSI (Munné et al, 2004; Baart et al, 2006), and some authors argue that PGS may be useful for this group of patients as well (Munné et al, 2004). We report the results of a study designed to investigate the chromosomal abnormality rate in embryos obtained after intracytoplasmic sperm injection (ICSI) in unstimulated (natural) cycle embryos in young women under 36, and establish proof of concept of natural cycle ICSI associated with PGS.
Follicular vascularisation and oocyte quality

Geeta Nargund. Head of Reproductive Medicine, St George’s Hospital, London

The female reproductive tract provides an outstanding model for the study of physiological neo-angiogenesis. Follicular angiogenesis is crucial for folliculogenesis. Ovarian follicles and corpora lutea have been shown to contain and produce angiogenic factors. Vessels in the corpus luteum have the highest blood velocities in human body.

During the immediate pre-ovulatory period, increased follicular angiogenic activity mediated by elevated levels of VEGF is observed in peri-follicular vessels. This vasculature shows increased capillary sprouting and vascular permeability. Following ovulation, rapid growth and infiltration of capillaries within the follicular wall contributes to luteal vasculature. This is essential for corpus luteal formation and function.

Study of follicular angiogenesis and factors affecting vascularisation is fundamental in understanding follicular recruitment, atresia, growth, development, selection, ovulation and formation of the corpus luteum.

Advances in high resolution and 3D ultrasound with the use of colour and power Doppler have provided us with a non-invasive method and a unique opportunity to study follicular vascular changes from an early antral stage to ovulatory stage and later the luteal vasculature. Longitudinal observations in spontaneous and stimulated cycles could provide answers to questions relating to altered folliculogenesis in fertile and subfertile women. Studies have suggested strong positive correlations between follicular blood velocity and oocyte quality. High flow is closely related with follicular oxygenation, better quality oocytes and normal ploidy (oocyte health). Gonadotrophins seem to have an effect on production of angiogenic factors from follicular/luteal cells. It has been shown that increased vascularity is associated with ovarian hyperstimulation syndrome (OHSS) and reduced vascularity is associated with poor ovarian response to FSH.

Assessment and monitoring of follicular vascularity in conjunction with endometrial changes in spontaneous cycles is useful in making natural cycle IVF treatment more successful. Similarly, measurement and monitoring of follicular and stromal blood flow could prove to be an essential tool to estimate ovarian sensitivity to gonadotrophins and to make minimal stimulation IVF more effective. The effect of follicular aspiration on the formation and health of corpus luteum could be studied with the use of advanced ultrasound Doppler examination. In the era of ‘Single Embryo Transfer (SET)’, we are constantly seeking markers to select the best embryo for transfer in order to reduce multiple pregnancies. ‘Follicles with the highest vascularity and blood velocities’ could give the ‘Best Embryos’ needed to improve success with Single Embryo Transfer (SET).

Further research is required to investigate what factors affect follicular blood flow and whether we can manipulate it in order to achieve improved methods of fertility regulation in humans.

References:
1. Redmer DA & Reynolds LP. Angiogenesis in the ovary, Rev Reprod, 1996; 1 (3) 82-92
AMH in Follicular Fluid and in Serum
Renato Fanchin, MD, PhD

Anti-Müllerian hormone (AMH), a glycoprotein that is exclusively produced by the granulosal cells of ovarian follicles in the adult female (Vigier et al., 1984), is new and maybe unique biomarker of the ovarian follicular status. Indeed, in contrast with inhibin B and E2, AMH is produced, presumably FSH-independently (Bath et al., 2003; Eldar-Geva et al., 2005), in a wide range of follicles that goes from the primary to the early antral stages of folliculogenesis (Baarends et al., 1995; Durlinger et al., 2002b; Weenen et al., 2004), and with little susceptibility to disorders of antral follicle growth during the luteal-follicular transition.

Our presentation will essentially 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 lose 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 granulosal cell activity and health. In addition, unpublished data on the striking relationship between FF AMH production and the quality of the ensuing oocyte/embryo as well as on the profile of serum AMH levels during the menstrual cycle will be presented and discussed.

Cumulus and Oocyte Quality
Jonathan Van Blerkom Department of Molecular, Cellular and Developmental Biology University of Colorado, Boulder, Colorado; Colorado Reproductive Endocrinology Rose Medical Center, Denver, Colorado.

The female germ cell is surrounded by a somatic cell component that in the preovulatory follicle, exists as an outer network of interconnected cumulus oophorus cells embedded in a matrix of hyaluronic acid, and inner layer of corona radiata cells that reside on the surface of the zona pellucida; the latter cells elaborate cellular extensions, termed transzonal processes, that communicate with the oocyte by means of gap junctions. These compartments form the so-called cumulus oocyte complex of the ovarian follicle and their developmental relationship is most often described in terms of a ‘dialogue,’ in which specific molecules produced by the oocyte regulate somatic cell function and activity, and factors secreted by the somatic cells control certain aspects of oocyte growth and development, including preovulatory nuclear and cytoplasmic maturation. In clinical treatments of infertility, the word ‘quality,’ as applied to this complex, pertains to the contribution of each element in the establishment embryo developmental competence. This is especially important in clinical IVF, where a considerable body of evidence demonstrates the significant extent to which embryo competence (i.e., embryo quality) is established in the oocyte. This presentation will describe the structural basis of interactions between germ and somatic cell compartments that that extend well into the ooplasm and regulate the molecular dialogue. In particular, the association between germ and somatic cell compartments will be discussed with respect to the activity of a spatially unique population of high-polarized mitochondria that reside in the subplasmallemmal cytoplasm of the oocyte and are currently though to participate in the establishment of developmental competence.
Ultrasound appearances of the endometrium and junctional zone
Stephen Killick
Time-lapse images of the uterus have shown rhythmical contractions, which vary in frequency and intensity throughout the ovarian cycle. They are most frequent at mid cycle when they assist sperm in their journey from the cervix to the fallopian tube, and least frequent at the time in the menstrual cycle when embryos would normally implant. The chance of successful embryo implantation is reduced in cycles in which these uterine contractions are increased.

During an IVF treatment cycle embryos are transferred to the uterine cavity much earlier than in a natural cycle, at a time when uterine contractions are more frequent. IVF cycles with more contractions not only have a lower chance of pregnancy, but even if pregnancy does occur it is more likely to be ectopic. Uterine contractions have been shown to be capable of pushing embryos from the uterine cavity into the fallopian tube and the first IVF pregnancy, before the birth of Louise Brown, was indeed ectopic. Less aggressive ovarian stimulation and lower hormone levels would be expected to reduce this problem and hence a move towards minimal stimulation or natural cycle IVF is logical.

Uterine markers in natural versus stimulated IVF
Nathalie Lédée
The purpose of the study is to document the impact of supra-physiological concentrations of ovarian steroids on the endometrium, and more precisely on the endometrial angiogenesis.

We therefore compared for 17 patients the mRNA expression of vascular related growth factors ad cytokines (VEGF, VEGF r, angiopoietin-1, angiopoietin-2, Tie-1, Tie-2, interleukine-15, interleukin-18) quantified by real-time PCR using the Light Cycler system. We also compared the protein expression of the IL-18 system and the CD56+ count by immunochemistry.

The results suggest the ovarian steroids decrease the expression of some vascular factor as IL-18, VEGF and angiopoietin-2 and could therefore decrease the physiological angiogenesis and remodelling of spiral arteries that should occur during the implantation window.

Based on a possible impact on angiogenesis, we will present the preliminary results of the ongoing pilot study including patients in implantation failure after conventional IVF/ICSI and a documented depletion of vascular cytokines. The outcome is the ongoing pregnancy rate after the first embryo transfer in minimal ovarian stimulation.

Is ovarian stimulation detrimental to endometrium and the embryo?
Prof. Antonio Pellicer. Fundación IVI (FIVI)-Instituto Valenciano de Infertilidad Foundation
Controlled ovarian hyperstimulation (COH) used in IVF produces lower implantation rates per embryo transferred compared to natural cycles when the oocyte donation method is carefully analyzed, suggesting a suboptimal endometrial development. Classical methods of evaluation of the endometrium are based on work done in the 50’s employing regular histological methods.

Today, however, we can look at the expression of different genes in a particular tissue, which give us a more detailed approach of the events occurring during COH. After the publication of several studies about the endometrial receptivity in the natural cycles using microarray technology (gene expression), we have investigated the impact of COH in the gene expression pattern of the endometrium employing microarrays which allow more than 22,000 genes to be tested simultaneously. Our main target has been day hCG +7, in other words, the day of theoretical implantation in humans. We have found that a high number of genes are dys-regulated showing a differential expression during the natural cycle and the stimulated cycles and, moreover, that these changes depend on the different medications employed. The large degree of gene expression changes found is surprising and highlights the need for further efforts to optimize COH protocols.

In parallel, we surprisingly found a high rate of chromosomal abnormalities in embryos derived from young oocyte donors. These patients displayed >50% aneuploidy rates in their embryos despite of havin an average age of 25 yrs. Thus, we wanted to investigate whether COH was responsible for this abnormal finding, as it has been described in animal. To investigate this further, we are undergoing a study in which we treat the same donor in different COH cycles with different amount of gonadotrophins: in the frist cycle she receives a certain amount required to sustain a reasonable response; in the second they receive half the dose employed in the first attempt. By halving the dose of gonadotrophins, the initial data show a reduction in the rate of aneuploidies from 50% to 33%. Thus, we firmly believe that excessive ovarian stimulation is detrimental for both, the endometrium and the oocyte, the latter resulting in a higher incidence of chromosomally abnormal embryos.
In Vitro Fertilisation And Embryo Transfer In Seminatural Cycles for patients with ovarian aging
René Frydman, M.D. Department of Obstetrics and Gynecology and Reproductive Medicine, Hôpital Antoine Béclère, Clamart, France

To investigate whether seminatural cycle is a reasonable management for ovarian aging patients. We investigate a prospective study in ART Unit, Clamart, France.

Seventy-five women, 158 cycles were considered.

Only Infertile women who presented with ovarian aging (defined as low ovarian reserve and characterized by cycle day 3 high FSH, high E2, and/or low inhibin B and/or previous cycle cancellations due to poor ovarian response to COH) were studied. Patients were offered up to three cycles. Treatment was scheduled as follows. From cycle day 8 onward the selection of the dominant follicle was monitored by ultrasound and hormonal measurements. When the dominant follicle appeared, patients received GnRH antagonist and, thereafter, hMG to support further follicular development.

Twenty-eight of 158 cycles were cancelled (17.7%). Oocyte pickups were performed in 119 (75.3%) cycles, 91 (57.6%) mature oocytes were retrieved, and 67 (42.4%) embryos transferred.

Nineteen clinical pregnancies were obtained; the cumulative pregnancy rate per patient, after 3 cycles, was 35.2%.

Conclusion: Use of a seminatural cycle is a reasonable management for patients with ovarian aging who have ovulatory menstrual cycles. It achieves a high implantation rate (28.3%).

Controlled Natural Cycle IVF With Antagonist Use and Blastocyst Transfer

Dr Krinos Trokoudes KM Trokoudes1, MB Minbattiwalla, L Kalogirou, K Pantelides, P Mitsingas, A Sokratous, A Chrysanthou, Sj Fasouliotis

A method of controlled natural cycle IVF (CONCIVF) was sought to provide simpler and shorter treatment without the risks of ovarian hyperstimulation syndrome and multiple pregnancies. A total of 138 couples with normal ovulation and normal sperm parameters, in whom the women were <40 years old, were the candidates for this study. Gonadotrophin-releasing hormone antagonist was used before human chorionic gonadotrophin (HCG) administration if LH increased to a concentration of 10 mIU/ml before HCG injection. Treatment was initiated at ≥16 mm follicular growth and at oestradiol concentrations ≥400 pmol/l with 5000 IU HCG induction. All the embryos were cultured to the blastocyst stage and transferred only if they reached early or advanced blastulation. A total of 126 patients underwent oocyte retrieval. In 102 cases, one oocyte was retrieved; 95% of the oocytes fertilized, 99% cleaved and 47.9% achieved the blastocyst stage. The implantation rate per blastocyst transfer was 53.3% and the live-birth rate per embryo transfer was 40%. Therefore, CONCIVF with blastocyst transfer gives acceptable blastocyst development and implantation rates without the long- or short-term side effects of ovulation induction.
Minimal Stimulation IVF
Shokichi Teramoto, Keiichi Kato, Masashige Kuwahara, Osamu Kato KATO Ladies 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. Our minimal ovarian stimulation protocol takes full advantage of these characteristics of clomiphene citrate (Fig. 1). Administration of 50mg clomiphene citrate is initiated on Cycle d3, which is defined as the 7th day after the end of birth control pill administration. From d8, patients receive 150 UI/L of FSH 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 (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. Table 1 shows the outcome of this protocol between 2001 to 2005.

Table 1: Outcome of the minimal stimulation protocol

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>27-29</th>
<th>30-32</th>
<th>33-35</th>
<th>36-38</th>
<th>39-41</th>
<th>42-44</th>
<th>45-47</th>
<th>Total</th>
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</thead>
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<tr>
<td>No. of initiated cycles</td>
<td>928</td>
<td>2881</td>
<td>5289</td>
<td>6943</td>
<td>8410</td>
<td>7478</td>
<td>3825</td>
<td>35754</td>
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<td>No. of cycles in which oocytes were retrieved</td>
<td>901</td>
<td>2803</td>
<td>5120</td>
<td>6729</td>
<td>8093</td>
<td>7202</td>
<td>3649</td>
<td>34497</td>
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<tr>
<td>No. of cycles in which ovulation had occurred before oocyte retrieval</td>
<td>23</td>
<td>58</td>
<td>125</td>
<td>158</td>
<td>194</td>
<td>211</td>
<td>128</td>
<td>897</td>
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<td>Rate of ovulation cycles in which ovulation had occurred before oocyte retrieval (%)</td>
<td>2.5</td>
<td>2.0</td>
<td>2.4</td>
<td>2.3</td>
<td>2.3</td>
<td>2.8</td>
<td>3.4</td>
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<td>No. of cycles in which oocyte(s) were obtained</td>
<td>814</td>
<td>2482</td>
<td>4434</td>
<td>5353</td>
<td>6225</td>
<td>5009</td>
<td>2263</td>
<td>26760</td>
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<tr>
<td>Mean no. of oocytes retrieved*</td>
<td>3.30</td>
<td>2.83</td>
<td>2.45</td>
<td>2.00</td>
<td>1.63</td>
<td>1.23</td>
<td>0.92</td>
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<tr>
<td>No. of cycles in which oocyte(s) were fertilized</td>
<td>713</td>
<td>2134</td>
<td>3811</td>
<td>4633</td>
<td>5007</td>
<td>3823</td>
<td>1581</td>
<td>21702</td>
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<tr>
<td>Mean no. of oocytes fertilized*</td>
<td>2.21</td>
<td>1.92</td>
<td>1.72</td>
<td>1.41</td>
<td>1.13</td>
<td>0.83</td>
<td>0.60</td>
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<tr>
<td>No. of cycles in which embryo(s) were divided</td>
<td>586</td>
<td>1815</td>
<td>3230</td>
<td>3910</td>
<td>4042</td>
<td>3002</td>
<td>1161</td>
<td>17746</td>
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<td>Mean no. of embryos divided*</td>
<td>1.46</td>
<td>1.37</td>
<td>1.28</td>
<td>1.08</td>
<td>0.84</td>
<td>0.62</td>
<td>0.43</td>
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<tr>
<td>Rate of Veeck grade 1 embryos (%)</td>
<td>73</td>
<td>72</td>
<td>73</td>
<td>70</td>
<td>69</td>
<td>63</td>
<td>60</td>
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<tr>
<td>No. of cycles in which 4 cell-stage embryo(s) were cryopreserved</td>
<td>31</td>
<td>101</td>
<td>186</td>
<td>221</td>
<td>220</td>
<td>122</td>
<td>36</td>
<td>917</td>
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<tr>
<td>Mean no. of embryos cryopreserved</td>
<td>2.06</td>
<td>1.61</td>
<td>1.52</td>
<td>1.34</td>
<td>1.41</td>
<td>1.35</td>
<td>1.42</td>
<td>-</td>
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<tr>
<td>No. of cycles in which blastocyst(s) were cultured</td>
<td>196</td>
<td>595</td>
<td>1064</td>
<td>1116</td>
<td>908</td>
<td>573</td>
<td>184</td>
<td>4636</td>
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<td>Blastocyst formation rate (%)</td>
<td>65</td>
<td>61</td>
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<td>52</td>
<td>38</td>
<td>15</td>
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<tr>
<td>Mean no. of blastocysts cryopreserved</td>
<td>1.19</td>
<td>1.17</td>
<td>1.06</td>
<td>0.84</td>
<td>0.54</td>
<td>0.18</td>
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<td>No. of cycles in which d2 embryo transfer was carried out</td>
<td>558</td>
<td>1703</td>
<td>3052</td>
<td>3646</td>
<td>3698</td>
<td>2682</td>
<td>1028</td>
<td>16367</td>
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<tr>
<td>Mean no. of embryos transferred</td>
<td>1.54</td>
<td>1.45</td>
<td>1.42</td>
<td>1.42</td>
<td>1.44</td>
<td>1.42</td>
<td>1.37</td>
<td></td>
</tr>
<tr>
<td>Rate of Veeck grade 1 embryos (%)</td>
<td>73.7</td>
<td>70.2</td>
<td>64.7</td>
<td>58.1</td>
<td>33.3</td>
<td>33.9</td>
<td>7.4</td>
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<tr>
<td>d12 βhCG (mIU/mL)</td>
<td>26.2</td>
<td>24.0</td>
<td>20.5</td>
<td>15.7</td>
<td>8.5</td>
<td>3.2</td>
<td>0.8</td>
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</tr>
<tr>
<td>LBR (%)*</td>
<td>19.3</td>
<td>20.5</td>
<td>24.4</td>
<td>31.0</td>
<td>44.5</td>
<td>54.7</td>
<td>84.4</td>
<td></td>
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<tr>
<td>Miscarriages (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>
* in relation to the number of initiated cycles

Follicular Aspiration and Follicular Flushing
*Departments of Obstetrics and Gynecology and Reproductive Medicine and, ** Biology and Genetics of Reproduction, Hôpital Antoine Béclère (AP-HP)

Background and objective: Follicular flushing has been quickly abandoned and considered as useless after the studies that showed the same oocyte collection with or without flushing, with a longer anesthesia and more expensive procedure (Tan et al., 1992; Kingsland et al., 1991). In addition, it was observed a reduced performance from oocytes obtained by follicular flushing (el Hussein et al., 1992) which was described as superfluous (Knight et al., 2001) and is not longer utilized on COH protocols. However, the higher incidence of oocyte retrieval failure on the natural/ seminatural cycle IVF has awakened the interest on the practice of follicular flushing and the unknown reproductive competence of the oocytes obtained by this protocol. As this, the objective of this study was to evaluate the importance of follicular flushing on semi natural cycle IVF.

Material and Methods: We have compared prospectively the reproductive competence of oocytes obtained from follicular fluid (Group A, n=79) to those obtained from follicular flushing (Group B, n=47) on 146 oocyte retrievals.

Results: The group A and B were similar on the fertilization rate (79.7% versus 88.1%, respectively), percentage of superior grade embryos (28.8% versus 37.8%) and the implantation rate (24.1% versus 44.1%). 53.6% of total clinical pregnancies were obtained from group B.

Conclusion: The practice of follicular flushing on IVF semi natural cycle duplicates the pregnancy rate. The oocytes obtained by follicular flushing had the same reproductive potential than those obtained on follicular fluid.
What Did We Learn From Review of 1000 Natural Cycles for IVF/ICSI?
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A retrospective chart review of 1024 cycles in patients undergoing IVF and ICSI in unstimulated cycle at our institution was performed. IVF and ICSI for oocyte pick up were performed using four different approaches for cycle monitoring. Unstimulated cycles monitored with ultrasound and combination of serum E2 and urinary LH can produce an acceptable pregnancy rate after IVF and ICSI.

In cases when hCG was applied in smaller follicles (at least 15 mm in diameter) and lower serum E2 values (> 0.49 nmol/L), the pregnancy rate per transfer was higher in the IVF group (23.8%) and in ICSI group (including TESA) (26.4%) than in protocol where E2 values were higher and mean follicle diameter were bigger.

The collection of a mature oocyte from naturally selected follicle followed by IVF or ICSI is an alternative to conventional controlled ovarian hyperstimulation protocols. Monitoring of follicle growth is simple and oocyte pick-up from single follicle extremely quick procedure performed with no sedation or anaesthesia. A higher pregnancy rate and lower cancellation rate was obtained when hCG was applied in lower values of serum E2 and smaller follicle diameter.

The implantation rate per transferred embryo was higher when the blastocyst was transferred (42.8%) instead day 2 embryo transfer (23.5%) in same monitoring protocol.

Mild Ovarian Stimulation for IVF: Enough is Enough
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Milder forms of ovarian hyperstimulation will undoubtedly result in a minor reduction of pregnancy rate per cycle. This also holds true for the transfer of a single rather than multiple embryos. However, it can be seriously questioned whether pregnancy rate per cycle should still be used as the gold standard for success in IVF. Major patient discomfort, increased chances for complications, complex and time consuming stimulation regimens and very high cost are associated with conventional hyperstimulation, and distinctly increased perinatal morbidity and mortality results from multiple pregnancies. Successful IVF could also be viewed in terms of chances for health children born over a given period of time (which may include multiple IVF cycles) in the context of side effects, patient discomfort, risks and cost. Novel approaches in IVF can only prosper in the framework of such a paradigm shift with major implications for health care providers, health insurance companies and society.

Long-term Physical Effects of Ovarian Stimulation
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The role of ovulation in the etiology of breast and gynecologic malignancies is well recognized. As a result, there has been increasing attention focused on whether the use of ovulation-stimulating drugs might influence the risk of developing these cancers. Of particular concern has been the effect on ovarian cancer risk, given evidence that lifetime ovulatory activity is a strong predictor of risk. In addition, two early epidemiologic studies indicated strong relationships of risk with use of infertility drugs in general or more specifically of clomiphene citrate. However, these as well as most subsequent studies, which for the most part have not confirmed the findings, have had methodologic shortcomings which have led to continued confusion regarding the nature of the relationships.

This presentation will review existing studies which have addressed the effects of ovulation-stimulating drugs on cancer risk. In addition to ovarian cancer, there have been concerns regarding potential effects on breast and endometrial cancers, two sites that have strong hormonal components. Albeit based on a limited number of studies, there are little data to support strong effects of ovulation-stimulating drugs on breast cancer risk. However, there are several studies which suggest that use of clomiphene citrate may increase the risk of endometrial cancer. This finding is of interest given that clomiphene is a selective estrogen receptor modulator which is structurally similar to tamoxifen, a drug that has been extensively linked with increases in endometrial cancer risk.

Approaches which have been utilized to assess cancer risks associated with different infertility treatments will be discussed, along with their strengths and limitations. Retrospective studies have
been hindered by potential inclusion and recall biases, while prospective studies have usually been limited by small sample sizes, short follow-up periods, or absence of information on other cancer risk predictors. In order to account for latency effects usually associated with chemical carcinogens, most studies have focused on exposures that are no longer relevant to clinical practice today, with scant information available on effects of in vitro fertilization.

Directions for needed future research will be outlined, taking into account the types of data that would be most relevant to collect to clarify further the long-term effects on cancer risk of different fertility treatment regimens. The importance of understanding relationships in terms of possible biologic mechanisms will be stressed.

Affordable IVF in Third World Countries
Willem Ombelet

Worldwide more than 80 million couples suffer from infertility, the majority of this population are residents of developing countries. New reproductive technologies are either unavailable or very costly in so far that the large majority of the population cannot afford infertility treatment at all. Bilateral tubal occlusion due to sexually transmitted diseases, illegal abortions and complications during and after delivery is the most important reason for infertility in developing countries, a condition that is potentially treatable by assisted reproductive technologies (ART).

Moreover, the negative consequences of childlessness are much stronger in developing countries compared to Western societies. In many cultures, childless women are stigmatised which may lead to isolation, neglect, domestic violence and suicide. The problem of overpopulation in developing cannot be used as a reason to disguise the problems of millions of infertile couples.

Symplifying the diagnostic procedures in the infertility work-up, symplifying ART methods, minimising the complication rate of ART, organising training-courses for medical and paramedical personnel and incorporating the infertility treatment programme in the family-planning-programme will be the keystones for its success.

Considering diagnosis: hysterosalpingography, hystero-salpingo-contrast-sonography and vaginal ultrasound are simple and reliable techniques that can easily be performed without major costs. Combining these techniques with an accurate anamnesis and a simple semen analysis will identify the majority of infertility causes such as ovulatory disorders, male subfertility and tubal factor infertility. Even office mini-hysteroscopy can be done without major costs and risks, provided a good training is guaranteed and the risk of infection can be controlled.

Our other main objective is to organise simplified inexpensive assisted conception techniques that can be adapted for conditions in the developing world.

Concerning the preparation of the oocytes, a low-dose clomiphene citrate (CC) regimen could be used with acceptable results and minimal complication rates. The use of CC-stimulation seems to be superior to natural (unstimulated) IVF cycles. Monitoring the IVF cycle and timing of the hCG administration can easily be done solely on sonographic criteria (basic inexpensive ultrasound equipment).

Considering the laboratory procedures: an expensive laminar flow hood can be replaced by a simple plastic box commonly used for keeping newborns snug. A portable and near sterile environment can be created in which embryos can be handled at a very low price. ‘Submarine incubators’ have been used for cow embryos for more than a decade: a bag containing the Petri dish with the embryos is dropped into a warm water bath, instead of using carbon dioxide which is much more expensive and complicated. Pilot studies will be needed to assess the efficacy and safety of such low-cost IVF protocols.

Complications such as multiple gestation and ovarian hyperstimulation syndrome have been avoided as much as possible. Prevention, education and treatment of infertility should be incorporated in existing family-planning centres.

For those couples where prevention failed, the introduction of simplified methods might convince local politicians of the need to formulate a policy concerning infertility treatment in their country. Therefore, support from the government and International Organisations is mandatory.
In Vitro Maturation in the Future.
Svend Lindenberg, Professor dr. med. Nordica Fertility Clinic Copenhagen, Denmark. Nordica Fertility Clinic, Lygten 2c DK-2300, Denmark

In vitro maturation technique to be used in human fertility treatment has now gained a successful platform for further development. More than 400 children have been born from this technique. The obvious advantages of this technique is avoidance of ovarian hyperstimulation syndrome, it is cheap, and easy for the patient with out serious adverse effects. At the present carefully selection of patient, standardized laboratory protocols are the basis for success. Patient to be chosen for IVM should be less than 35 yrs of age, PCO or having multifollicular ovaries i.e. more than 10 small antral follicles at day 3 in their cycle. Using such criteria and light ovarian stimulation with FSH for 3 days provide pregnancy rates per transfer of 30%. Specifically, women with prior hyper stimulation syndrome have the highest pregnancy rate among IVM patients. Among the factors now alleviating the start problems in IVM is the increasing number of oocyte retrieved per cycle, the temperature control in the laboratories and assisted hatching of the embryos and finally shorter culture in vivo.

The Effect of Multi-Follicular Ovarian Stimulation on the Outcome: More May Not be Better
Evangelos Papanikolaou

The goal for many follicles has dominated ART practice for many years. Among other drawbacks, it has been observed that in ovarian stimulation for IVF a preovulatory modest increase in serum progesterone levels is associated with lower pregnancy rates and higher pregnancy loss. Two mechanisms have been proposed; either a poor oocyte quality plus a reduction in their fertilizability, or a detrimental effect on endometrial receptivity.

In a cohort study, 628 infertile patients aged <36 years and with FSH <12mIU/ml, who were undergoing their first or second IVF treatment under the new Belgian law (elective single embryo transfer), initiated multifollicular ovarian stimulation with a GnRH-antagonist/recFSH protocol (detailed description elsewhere). The day of the embryo transfer (Day-3 group, SET; or single blastocyst transfer, Day-5 group, SBET) had been predefined by the treating physician at consultation. Premature luteinization was defined as progesterone elevation above 1.5ng/ml on the day of HCG triggering.

The incidence of premature luteinization was 18.2% (n=88). Patients with a progesterone rise were high responders (15.0± 0.8 oocytes retrieved vs. 11.6± 0.3 respectively, p=0.001) and consequently, had significantly (p=0.001) more 2PN embryos and embryos cryopreserved than patients with normal progesterone. In the day-3 SET subgroup, patients with progesterone above 1.5ng/ml had significantly lower probability of clinical pregnancy compared with the patients whose progesterone was normal [odds ratio (OR): 0.39, 95% confidence interval (CI): 0.18-0.88]; On the contrary, premature luteinization in the Day-5 SBET subgroup had no effect on the pregnancy outcome (OR:1.10, 95%CI: 0.53-2.27).

The present study provides sufficient evidence that even modest rises of progesterone in the follicular phase have a detrimental effect on the implantation potential of a good quality cleavage stage embryo. Mild ovarian stimulation protocols have to be implemented in current practice, thereby diminishing the chances of a normal-responder to be turned into high responder iatrogenically dampening her likelihood for pregnancy achievement.
Single Embryo Transfer: The Role of Natural Cycle / Minimal Stimulation IVF in the future.
Karl Nygren, IVF Sophiahemmet, Stockholm

There are good reasons to assume that single embryo transfer, SET, eventually, will become the norm in IVF treatments, internationally. Medical, psycho-social, economical data and indeed recent national data on maintained clinical efficacy with SET as the norm, all speak the same language. The pace at which SET has been introduced in countries so far, has not been uniform, but the tendency is visible internationally, also in the latest IVF World Report. The Nordic countries, and Belgium, have been leading the way, and countries like the UK, Holland and others now follow.

Sweden, since a couple of years back, performs, on a national basis, 70% SET, with 5% twins and a pregnancy rate per transfer remaining at about 30%. Preliminary data shows a drastic reduction of the risk of pre-maturity and therefore of child morbidity and perinatal mortality. These recent developments, with a drastic revision of clinical policies in IVF have not, yet, at least in Sweden, led to any revision or even much discussion of the current practice of heavy ovarian stimulation. On the contrary, heavy stimulation is still the norm with and increasing emphasis on freezing and thawing procedures, which even have been described as a prerequisite for a functional SET policy.

It is now time to discuss alternatives to heavy ovarian stimulation in settings where SET is the norm. When and at what proportion could natural cycle/soft stimulation be used? What group of patients would benefit? What will the consequences be in terms of efficacy, safety, cost, time and quality-of-life? How should we best look at outcomes in terms of efficacy, safety, and quality and how should we report it?

This conference is looking into most of these questions.

The availability, perhaps in the near future, of much more efficient methods for selecting a viable and healthy embryo, through ‘metabolomics’ and similar techniques, together with the advent of new methodologies to quantify ‘quality-of-life’ in a meaningful way, may lead to a rapid transition to SET as the norm. Selection of the most beneficial treatment for the individual couples, by clinicians and by couples, may well include a much wider use of natural cycle / soft stimulation in IVF, in the future.

Psychological aspects of IVF: Natural/Stimulated Cycle
Michèle LACHOWSKY, gynecologist Consultant in Psychosomatic Obs/Gyn. University Hospital Bichat Paris

Infertility has in itself a psychological dimension, not always dependent on the etiology or the medical context. In our society, where having a child is not only a wish but is considered as a ’right’, a woman or a couple has first to cope with the concept, then with the reality, and finally with the treatments. Again, their idea of IVF is somewhat different from the actual facts, but usually accepted as a mean and feared as a time-consuming painful medical ordeal…which is not so far from the truth!

Natural versus stimulated cycle, it does seem simpler and easier to the patient, it makes much less demands on their ability to bear with injections and medical devices. Perhaps even more important is the feeling that pregnancy may be attained with a lesser technical approach and a more ‘natural’ one. For the woman, suffering from what she feels is her body’s incapacity to give home and birth to her child, an IVF based on her own body responses may well help to restore her self-esteem, as well as make the whole process easier to understand, and less unpleasant. With sperm problems, the man also might be glad to impose a lesser strain on his partner, and thus cope better with his frequent guilt feeling.

Of course, to some patients, fearful of not getting the ‘best’ treatment with the higher percentages of chances, natural cycle may not seem sophisticated enough or not scientifically proved after their nightly reading of the last developments on the Web. They feel deprived of what the others seem to be offered, again of their ‘rights’.

Nevertheless, natural cycle is an extremely interesting approach of a non-natural process, a process which has changed our infertile men and women into mothers and fathers but is still very much feared by the new candidates.
1. Embryo Quality of Modified Natural Cycle IVF


Introduction Since 2001 part of our IVF cycles are carried out in modified natural cycle IVF (MNC). In MNC-IVF, the oocyte from the one follicle that spontaneously develops to dominance is used for IVF, whereas a GnRH-antagonist is administered to prevent untimely ovulations and loss of the oocyte. Because of the presence of one oocyte it offers the unique opportunity to study the direct relationship between embryo quality and implantation after natural selection of the dominant follicle, without selection of embryos before transfer.

Material and methods All patients were younger than 38 years with conventional IVF indication. When the natural cycle resulted in a follicle diameter of ≥ 14 mm, GnRH-antagonist and FSH were given until the follicle had a diameter of 18 mm, followed by one gift of hCG. After isolation the oocyte was insem inated and cultured in a droplet of about 50 μl HTF supplemented with plasma solution and antibiotics under mineral oil at 37°C, 5% CO2. All oocytes were scored at day 1 (18-20 h after insem ination) for the presence of pronuclei (PN) and at days 2 and 3 for number of blastomeres, percentage of anucleated fragments and the presence of multinucleated blastomeres (MNB). All embryos were transferred on day 3 without further selection except those who showed ≥ 3PN, ≥ 50% fragmentation or no cleavage. Only cycles in which actually one embryo was transferred were used to relate embryo quality with implantation rate.

Results Between February 2001 and July 2004, a single oocyte was obtained in 623 IVF oocyte retrievals. Fertilization was observed in 442 (71%) oocytes, from which 383 had normal (2PN) and 59 had abnormal (3PN, 1PN and 0PN with cleavage) fertilization. Embryos developed predominantly via 2-4 cells on day 2 to 4-8 cells on day 3 (79%) of which 73% had ≤ 10% fragmentation. A total of 375 embryo transfers were performed which resulted in 95 implantations (25%). Implantation rates for day 3 embryos of ≤ 3, 4, 5, 6, 7, 8 and >8 blastomeres were respectively: 9%, 23%, 32%, 23%, 27%, 33% and 0%. The implantation rate of the theoretically expected embryo (2PN day 1, 4 cells day 2, 8 cells day 3 and ≤10% fragmentation) was 39%. In 54 embryos MNB were present, which showed an implantation rate of 15%.

Conclusions The dominant follicle yielded oocytes which predominantly developed to embryos with 4-8 blastomeres and ≤ 10% fragmentation on day 3. Furthermore, these embryos showed the highest implantation rates. Embryos with MNB were capable of implantation, however, the implantation rates were clearly diminished (15% with MNB versus 27% without). Since in our study all embryos were transferred, except those with ≥ 3PN, ≥ 50% fragmentation or no cleavage, we were able to calculate the implantation potential per embryo, regarding number of blastomeres, % fragmentation and the development from day 2 to day 3. In our series the highest implantation rate was found for embryos with 2 PN at day 1, 4 cells at day 2, 8 cells at day 3 and ≤ 10% fragmentation. These findings can be helpful for embryo selection in stimulated cycles.

2. Age, estradiol levels and blastocyst development to predict the success of IVF in the natural cycle with ET on the day five

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Study objective. To evaluate the influence of the woman age, of the estradiol levels on the day of hCG on the blastocyst development and the pregnancy rates of IVF in unstimulated cycle.

Methods Data on follicular growth monitoring, laboratory data and clinical results in 435 classical IVF attempts with ET on the day five for female and moderate male infertility in unstimulated cycles triggered with HCG – in patients who failed to conceive in 4-6 stimulated IVF cycles - were retrospectively evaluated. According to the age, the cycles were divided in two groups : <39 years and ≥ = 39 years. According to the estradiol levels on the day of hCG, the younger age group was divided into two subgroups : low E2 0,4 - 06 nmol/l and high E2 0,6 -1,25 nmol /l on the day of hCG. The age, the estradiol levels on the day of hCG, blastocyst developmpent and clinical pregnancy rates were the main study parameters. Results

The puncture was positive in 321out of 435 (74%) cycles. The 229 ETs were performed on day 5. Pregnancy rates was 36% after 109 transfers in blastocyst stage, 9% after 95 transfers in morula stage and 0% after 25 transfers of lower stage embryos. The pregnancy rate was 11% per cycle, 15 % per positive puncture and 21% per ET.
Positive puncture rate was 74% out of 309 cycles in younger group and 72% out of 126 cycles in older group. The ET rate was 54% in younger group and 68% in older group. The pregnancy rate/cycle was significantly higher in younger group 14% vs. 4% (P<0.005).

In younger group significantly more embryos developed to the blastocyst stage 54% vs 31%. (P<0.005) The pregnancy rate after 90 blastocyst ETs in younger group was higher compared to 19 blastocyst ETs in older group 39% vs. 21%. The pregnancy rate after 62 morula ETs in younger group was higher compared to 32 ETs in the older group 13% vs. 3%.

There were no differences comparing pregnancy rates between low estradiol and high estradiol subgroup 25% vs 24% per ET and 17% vs 15% per cycle. The blastocyst development rate in the low estradiol subgroup was insignificantly higher compared to the blastocyst development rate in the higher estradiol subgroup 58% vs. 56%. The pregnancy rate after blastocyst transfer did not differ between the two subgrups 36% vs 40%, There were no differences after transfer of morulas on the day 5 between the two subgrups 12% vs 14%.

Conclusion. Unstimulated cycle with the ET on day five is a serious treatment option in younger women with no severe male infertility problem. In contrast with the age of woman the low estradiol levels on the the of hCG do not unfavourably influence the blastocyst development and the clinical pregnancy rates in unstimulated IVF cycle.

3. Low-dose hCG may be useful in preventing the occurrence of OHSS without adversely affecting the outcome of IVF cycles

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Introduction: The timing and administration of an adequate dose of hCG is integral to the success of IVF cycles. The use of hCG as a natural analogue of LH to induce ovulation takes advantage of particular pharmacokinetic properties that give hCG a longer circulating half-life than LH. The longer half-life of hCG means it persists in the circulation longer which should be favourable to the development of fully competent corpus luteum (CL). However, the amount and persistence of hCG in the circulation are associated with the development of ovarian hyperstimulation syndrome (OHSS). The Vascular endothelial growth factor (VEGF) or Vascular permeability factor (VPF) is elevated in women with OHSS and the enlarged ovaries with increased vascularity are likely to be the cause of the rise in VEGF/VPF secretion. The expression of VEGF mRNA by luteinised granulosa cells is hCG dose and time dependent. Therefore hCG is essential for CL function but, high amounts of hCG could lead to OHSS in high-responders. Based on this information about angiogenesis and OHSS, we decided to reduce the dose of hCG in women at risk of OHSS with informed verbal consent.

Design: Prospective Observational study in women at high risk of developing severe OHSS.

Patients and Protocol: Women at high risk of severe OHSS were included. They received a daily dose of 100/112.5 (first attempt) or 150 IU FSH (second attempt) in a long pituitary down regulation protocol. The hCG was administered when the mean diameter of the leading follicle was 18mm. In all cases, at the time of hCG administration;

1: There were 4-5 follicles greater than 14mm and more than 20 total follicles in each ovary.
2: Serum oestradiol levels (E2) were greater than 8,000pmols/l.
3: High ovarian volume and vascularity as assessed subjectively by power Doppler.

Women exhibiting the above three criteria were given 2500IU hCG and follicle aspiration was planned 34-36 hours after hCG administration.

Embryo transfer (ET) was performed either on day 3 or 5 depending on the available embryos as per the protocol of the laboratory.

Progesterone supplements in the form of cyclogest pessaries (400mg twice daily) were given for luteal support. All women were followed up with telephone calls during luteal phase regarding their well-being and serum beta hCG was carried out 2 weeks after ET to check for pregnancy.

Results: 21 women (aged between 28 and 36 years) at risk of developing severe OHSS received 2500IU hCG. Six of them had developed severe OHSS in a previous IVF attempt including one woman who had a pulmonary embolus with an ovulatory dose of 5000IU hCG. The mean duration of stimulation was 9.4 days. The mean number of total follicles was 38 and follicles greater than 14 mm was 10 (two ovaries combined). The mean ovarian volume prior to hCG was 92ml. Assessment of power Doppler showed a high vascularity with colour signals around all follicles greater than 12mm. The total dose of FSH used per cycle ranged between 750 IU and
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1650IU per woman. The range for serum E2 was between 8449 and 27,669 pmol/l on the day of hCG. Three women whose E2 levels were greater than 30,000pmol/l were coasted for 3 days prior to hCG administration. The mean number of oocytes collected was 24 (range 11-32) and fertilisation rate per collected oocyte was 46.4%. Eleven women had two blastocysts and ten had two day 3 embryos transferred. Ten women had spare embryos frozen for future use. Only one woman developed symptoms of mild OHSS. None developed moderate or severe OHSS. Thirteen women conceived (61.9%) of those three had twin pregnancies.

Conclusion: Severe OHSS is rare but potentially fatal. In anovulatory women with PCO/PCOS, low-dose stimulation is recommended but it can still lead to hyperstimulation associated with high serum oestradiol levels by the time leading follicles suggest maturity. Several methods are used to prevent OHSS. Abandoning cycles and freezing all embryos is a waste of a treatment cycle. Coasting can reduce the risk of OHSS but it is associated with follicular compromise and the response of E2 levels following coasting is unpredictable. Unilateral ovarian aspiration is associated with increased morbidity with no apparent reduction in OHSS. The use of GnRH agonists instead of hCG has been tried but it is not suitable in all cycles and the administration of hCG is the universally accepted method for induction of ovulation in IVF cycles. The current minimum dose used in IVF cycles is 5000IU.

The evidence from this observational study is that in women at high risk of OHSS a reduction of the current “minimum” dose of hCG appears to prevent the development of OHSS without compromising success rates.

We need further randomised studies to establish a minimal ovulatory dose of hCG/LH required in the management of IVF cycles.

4. Cumulative Pregnancy Rates After a Maximum of Nine Cycles of Minimal Stimulation IVF And Analysis Of Patient Dropo**: A Cohort

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BACKGROUND: In minimal stimulation IVF, treatment is aimed at using the one follicle that spontaneously develops to dominance. A GnRH-antagonist is used to prevent untimely ovulations together with gonadotrophins for substitution.

Due to the lack of ovarian stimulation, minimal stimulation IVF has a low-risk and patient-friendly profile. Duration of a treatment cycle is short and treatment is easily repeated in consecutive cycles.

METHODS: In this single-centre cohort study, nine cycles of minimal stimulation IVF were offered to 243 patients. Cumulative pregnancy rates were calculated.

RESULTS: A total of 231 patients completed 1001 cycles (4.3 per patient). Cumulative pregnancy rates found were 39.0% (actual observed pregnancy rate) and 58.0% (life table analysis). Dropout rates were high. The pregnancy rate per started cycle remained stable in higher cycle numbers, possibly caused by selective dropout of poor prognosis patients.

CONCLUSIONS: Despite high dropout rates, the cumulative pregnancy rate after nine cycles of minimal stimulation IVF is favourable. Considering its advantages, the very low multiple pregnancy rate and negligible risk of OHSS in particular, it is our opinion that minimal stimulation IVF forms a valuable treatment modality for patients requiring IVF.
5. Larger Birth Weight in Singletons Born After Minimal Stimulation IVF Compared to Singletons Born After COH-IVF

A. Hoek, M. Pelinck M. Keizer, K. Schelling, A. Simons and M. Heineman University Medical Center Groningen, Groningen, Netherlands

Objective Singletons born after controlled ovarian hyperstimulation IVF (COH-IVF), have a lower birth weight than singletons resulting from spontaneous conceptions. This difference could be due to ovarian hyperstimulation, IVF laboratory procedures or patient characteristics. In the present study a comparison was made of pregnancy outcome of singletons resulting from either minimal stimulation (MS)- IVF or COH-IVF. The difference between MS-IVF and COH-IVF is that for MS-IVF, no COH is performed and the (one) dominant follicle that naturally develops is used for IVF, while laboratory procedures are identical in both treatments.

Design A group of 80 singleton pregnancies resulting from MS-IVF was compared to a group of 106 pregnancies resulting from COH-IVF. IVF treatments in both groups were performed between February 2001 and July 2004. Pregnancy outcome was compared between groups, after registration of patient age, parity, duration of subfertility, BMI, smoking habits and alcohol consumption and ethnicity.

Materials and methods For MS-IVF, the GnRH-antagonist cetrorelix was started at a follicle size of 14mm, to prevent untimely LH-surges and cancellation of oocyte retrieval, together with 150 IU r-FSH daily to prevent a fall in E2 levels. For COH-IVF, a flare-up or downregulation protocol was used. Ovulation was triggered at a follicle size of 18mm. Oocyte retrieval and laboratory procedures were performed according to standard procedures. Only conventional IVF was performed. Details on patient characteristics and life style habits, as well as pregnancy outcome were obtained from chart review and additionally by patient questionnaires. For statistical analysis, Chi-square and Student-t test were used where applicable.

Results Results are shown in the table. A difference in mean birth weight of 273 g was found, while gestational age, fetal gender, and mothers age and parity were not statistically different. Duration of subfertility was longer in the group with COH-IVF. BMI, alcohol consumption, ethnicity and length of father were not significantly different between groups, while smoking was more frequent in COH-IVF (p = 0.03; data not shown). To investigate the relation between birthweight and mode of treatment, correcting for known confounders that influence neonatal birthweight such as length of parents, smoking, parity, neonatal sex and duration of pregnancy we did a regression analysis. After correction for these known confounders there still is a significant difference in birthweight. After regression analysis, there remains a difference in birthweight in favour of singletons born after MS IVF. After correction for known confounding factors MS IVF singletons have a birthweight that is 139 grams higher than the birthweight of the singletons born after conventional IVF.

Conclusion The difference in birth weight between MS-IVF and COH-IVF singletons we found in this study is remarkable. Since IVF laboratory procedures are the same for both groups, and differences in patient characteristics are minimal, we hypothesize that this difference is attributable to the lack of ovarian hyperstimulation in MS-IVF, leading to a better implantational environment compared to COH-IVF.
6. Cost-Effectiveness of In Vitro Fertilisation (IVF) in the Manipulated Natural Cycle Versus Conventional IVF

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Introduction: In vitro fertilisation (IVF) is an effective technique for assisted reproduction. A major complication of IVF lies in the large number of multiple pregnancies (25-30%) which is associated with considerable costs. Alternatively, IVF can also be performed in the manipulated natural cycle (MNC-IVF), where one oocyte is harvested per cycle using minimal hormonal manipulation. The aim of this study was to compare the effects and costs of conventional IVF to MNC-IVF.

Methods: In a multi-centre study funded by the Dutch ZonMw Health Care Efficiency Research Programme 330 patients less than 37 years of age with ovulatory menstrual cycles were included. All patients underwent up to three cycles of MNC-IVF. Costs per individual treatment cycle of MNC-IVF were assessed on the basis of Dutch tariffs. Costs of conventional IVF were derived from the literature. Medication costs were calculated on the basis of actually prescribed medication in our clinic.

Results: Full treatment costs of MNC-IVF, including costs of pregnancy and delivery, ranged from 1,329 to 1,465 Euro per cycle, depending on the treatment phases completed and the number of pregnancies achieved. Medication costs ranged between 265 and 275 Euro per cycle versus 885 Euro for conventional IVF. The costs per live birth after three cycles of MNC-IVF was 17,197 Euro, which is comparable to the costs per live birth after a single cycle of conventional IVF.

Conclusion: Three cycles of MNC-IVF achieve similar pregnancy rates as conventional IVF but with much lower twin pregnancy rates. Therefore, MNC-IVF may be a cost-effective alternative for conventional IVF.

7. Has Natural Cycle IVF a Place in Developing Countries?

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Materials and methods: The cost of IVF in developing countries exceeds, beyond any doubt, the financial resources of health systems and represents a challenge for policy makers. The average income in Egypt, as an example for the developing world countries, ranges between 200 and 1000 USD. The cost of one IVF cycle ranges between 10,000 and 12,000 LE, that’s 2000 USD in average. This difference makes IVF a difficult choice, that is associated with resorting to short protocols of ovarian stimulation, day 2 transfer and a weak regimen of luteal support. All these measures aiming at cutting short the cost of stimulation. Most of the Egyptian couples (75%) seeking treatment for infertility, are young copules within the range of 20-32 years of age. Natural cycle IVF is used in Egypt mostly among patients who are undergoing embryo transfer of thawed embryos.

Results and Conclusions Natural cycle IVF, especially among young patients, is a promising strategy that should be encouraged among third world countries, especially in repeated failure IVF patients, and especially among a young target population in order to offer more trials and bypass the financial obstacles which, mostly, restricts these couples from seeking medical help.
**Results from natural IVF cycles in unselected group of patients**

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Study design: Retrospective study comprising all natural IVF cycles performed in the period of 2002-2005y. (cycles that were followed but without aspiration are not included). The data are collected from the medical documentation of the Assisted Reproduction Department from our hospital.

**Material and methods:** A total of 203 aspirations in natural cycles were performed between 2002 and 2005 and in 131 (64%) cycles oocytes were retrieved. Embryotransfer was carried out in 80 (61%) patients.

**Results:** Clinical pregnancy was confirmed in 19 (24%) patients. All of the pregnancies terminated successfully except for one (the patient miscarried in the middle of the pregnancy). Nineteen healthy babies were born (one two-zygote twin pregnancy).

**Conclusion:** In selected group of young, ovulating women with good husband semen quality, IVF treatment in natural cycles is an opportunity to achieve successful pregnancy.

**Statistical Characteristics and Modeling of Important Factors in Natural Cycles of Poor Responders Women**

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**INTRODUCTION** Since the first tube baby was born in 1978, in vitro fertilization (IVF) treatment offered high pregnancy rates due to improvements in oocyte puncture and culture techniques, sperm preparation and oocyte retrieval methods and production of new recombinant stimulating hormones of the ovarian production. However, different disadvantages such as ovarian hyperstimulation, multiple pregnancies, premature birth, expensive and not without risk stimulating protocols, are often involved in IVF cycles.

Our purpose was to assess the efficacy of IVF in natural cycles, as an alternative treatment in women with a poor ovarian response in gonadotropin stimulation and to explore the relationship between the important factors that control the natural cycle of women and the positive or negative β-human chorionic gonadotropin (β-hCG).

**MATERIALS AND METHODS** Twenty six women with regular menstrual cycles were offered a total of 37 natural cycles of treatment. One woman had four natural cycles, two women had 3 natural cycles each and 4 women had 2.

The women were treated from 29 to 46 years old and their mean age was 37,6±4,2 years old. LH surge was observed in 14 cycles (37,8%). In 20 cycles (54%) one oocyte was retrieved and in 2 cycles (5,4%) two oocytes were retrieved. The mean follicle diameter was 17,4±0,8mm and the mean endometrial thickness was 8,5±1,2mm of the day of hCG injection. From the 24 oocytes retrieved, 20 of them were in metaphase II stage (83,3%) and the fertilization rate after ICSI was 70% (14/20). All the embryos resulted from the fertilized oocytes were transferred after 2 or 3 days of incubation. The Body Mass Index (BMI) values and the smoking were also estimated as parameters that influence the chance of pregnancy.

Our purpose was to assess the efficacy of IVF in natural cycles, as an alternative treatment in women with a poor ovarian response in gonadotropin stimulation and to explore the relationship between the important factors that control the natural cycle of women and the positive or negative β-human chorionic gonadotropin (β-hCG).

**RESULTS** Embryo transfer was performed in 14 patients (37,8% per cycle, 70% per MII oocytes). Three patients were pregnant (8,1% per oocyte retrieval and 21,4% per embryo transfer). The quality of embryos transferred was grade 1 (no fragmentation) in 3 cases (21,4% per total number of embryos), grade 2 (≤15% fragmentation) in 9 cases (64,3%) and grade 3 (>15% fragmentation) in 2 cases (14,3%). The three pregnancies resulted from grade 1 four-cell embryo; one resulted from grade 2 five-cell embryo and one from a grade 3 six-cell embryo.

The comparison between the βhCG and the other variables suggests that important factors are the thickness of the endometrium (p=0.028) and the follicle diameter (p=0.049), for 95% significant level. In our experimental work, the investigation of the variables after using the logistic regression modeling, suggests that the important factors which were estimated satisfactory for the positive or negative βhCG, are the endometrium thickness (18,74 times) and the embryo grade (5,48 times) with estimated parameter values.

**CONCLUSIONS** The natural cycle is a simple and effective method in the field of the assisted reproduction, especially for poor-responder women in gonadotropin stimulation. Furthermore, the final proposed statistical model explains satisfactory the 89.2% of the original data of our study.

**Interruption of Vaginal Injection of Gonadotrophins is an Efficient and Economic Method for Ovarian Hyperstimulation in IVF Treatment**

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**BACKGROUND:** Daily injection of gonadotrophins causes significant distress in patients receiving fertility treatment. As an alternative treatment in women with a poor ovarian response in gonadotropin stimulation and to explore the relationship between the important factors that control the natural cycle of women and the positive or negative β-human chorionic gonadotropin (β-hCG).

**MATERIALS AND METHODS:** Twelve poor responder patients having at least three previous IVF failure (range 3-8), underwent 20 unstimulated IVF cycles between 1.1.2005-30.9.2006. Poor responder was defined as a patient developing in previous stimulated cycles < 4 follicles and estradiol (E2) levels < 500 pg/ml on the day of hCG administration. Their age was 35.5±5 years. All patients were nuliparous except three and had regular menses every 27-34 days. Basal FSH levels were 9.25±4.2 IU/ml.

Study design: Each patient underwent vaginal ultrasound examination at the beginning of menses to exclude pelvic pathology and to observe existence of antral follicle. Serial ultrasound examination followed every 5 days or until a 14 mm diameter follicle developed, then LH, estradiol and progesterone levels were measured and ultrasound follow up continued every 2 days until the follicle reached 18 mm. diameter. Human chorionic gonadotropin (hCG), 5000 IU (Pregnyl, Organon, Holland), was administered, unless hormonal levels indicated that spontaneous ovulation occurred. In this case the cycle was canceled and the patient was rescheduled for the following menstrual cycle. Routine egg collection was performed 34 hours after hCG administration using a double lumen 17 G needle (Cook, Australia) facilitating aspiration and flushing the follicle if an egg was not obtained in the first aspirate. The egg was fertilized mostly by ICSI, and cultured in ISM1 medium. Embryo quality and development was observed routinely. Embryo transfer was performed 2-3 days after egg collection.

**RESULTS:** In 16 out of 20 natural IVF cycles performed (80%), at least one oocyte was obtained (total-20 eggs). Fertilization rate of these oocytes was 50%. Cleavage rate was 100%. All embryos were of good quality (grade II-III), except one that was not transferred.

Four pregnancies were obtained.

**Conclusions:** Natural IVF cycle is a simple, not expensive and highly tolerable procedure for the patients. It seems that this procedure should be offered to poor responder patients with repeated failure in IVF before considering egg donation.
We began the procedure on May 2005. The first check up was on the day 8 of the cycle including ultrasound, E2 and LH serum level. We repeated that every (or every second) day. On the day 13 there were two follicles: 16mm on the left and 15mm on the right ovary; serum E2 was 256 pg/ml and LH was 7.9 mIU/ml. The patient received 250mcg rec. HCG (Ovidrel – Serono), and follicle aspiration was performed 31th and 30min after. We got two MII oocytes, both successfully fertilized and we transferred two blastocysts on the day 5. We saw two gestational sacs 3 weeks after. Pregnancy was going very well; preventive cerclage was performed in 19-th week and fetal lung maturation in 29-th week (3 doses of 24mg Dexamethason). When 36-th g.w. was completed, we did amniocenteses from both amniotic fluids for L/S test. As we confirmed fetal maturation (L/S=3.1 and 2.9; respectively); elective S/C was performed on January, 18, 2006. The first baby was 2850g, 49cm, Apagar 8/9; the second was 3310g, 51cm, Apagar 9/10. Both are girls.

According to our results (including this case) we can conclude that ART in spontaneous cycle is method of choice in patients: (1) up to 37 years old; (2) with tubular and peritoneal factor of infertility; (3) with normal hysteroscopy or ultrasound of uterus; (4) with regular ovulating cycles and (5) normal semen quality.

**Assisted Hatching and Natural Cycle: A Retrospective Study**

**Pappa H., Liarmakopoulou S., Argyriou A., Yuxdas G. Diagnosis-IVF Department, Athens, Greece**

**INTRODUCTION** The first successful birth after in vitro fertilization (IVF) was achieved in a natural unstimulated cycle. Since then, pregnancy rates have improved with the use of ovulation induction techniques, mainly as a result of transferring several embryos. However, certain disadvantages such as ovarian hyperstimulation, multiple pregnancies, premature birth, expensive and risky stimulating protocols are often involved in IVF cycles. Natural cycles have been proposed as an alternative to simplify IVF treatment procedures and reduce their costs and complications. Furthermore, several procedures such as assisted hatching have been involved in order to optimize implantation rates and thus, pregnancy rates in natural cycles.

Our objective was to assess the efficacy of assisted hatching (AH) in women with poor ovarian response enrolled in a natural cycle.

**MATERIALS AND METHODS** Patients were divided into two groups, group I where assisted hatching was performed in the embryos and group II where assisted hatching was not performed. Both groups were monitored daily or every two days ultrasound follicular measurements and whenever a follicle diameter 15±1mm was scanned, daily assessment of E2 and LH levels occurred. When LH measurement was 7-12IU/l and the follicle diameter 17mm, 6500IU of hCG were administered the same evening and oocyte retrieval was performed 35 hours later. ICSI was performed in all cases. A quarter partial assisted hatching was performed using a Laser (Saturn-R) for the drilling. A chi-square test was used to compare clinical pregnancy between the groups.

**RESULTS** 56 single embryo transfers were performed, 32 with AH (group I) and 24 without AH (group II). Mean age of women at treatment was comparative (36.94 ±4.812 and 37.04±4.298 for groups I and II respectively). The percentage of high quality embryos transferred was 71.9% in group I and 50% in group II. The clinical pregnancy rate per transfer was 25% in group I and 33.3% in group II.

**CONCLUSIONS** Many studies have been published concerning the beneficial role of assisted hatching in IVF. Most of them suggest that the use of a laser may be better than the chemical way (acide tyrosides). However, data from the present study show that assisted hatching may not be beneficial in natural cycles in poor responder women. On the contrary, we observed a better pregnancy rate in the group where we did not perform assisted hatching. Chi-square analysis failed to show a statistically significant difference between our results, thus, we suggest that more cases should be done in order to obtain a safer conclusion.

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**Synchronization of Antral Follicles: A Step Further Towards a Friendly IVF Program**

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**Ashraf Ramadan, M.D.**
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**Background:** luteal E2 administration was found to reduce size discrepancies of early antral follicles during the early follicular phase.

**Objective:** to evaluate the value of synchronization of follicles using luteal phase estradiol for a friendly IVF program.

**Materials & Methods:** A total of 108 infertile couples were included in a pragmatic trial. Group I (n=48) received Progynova 4mg/day for 10 days in the luteal phase preceding the ICSI cycle. Clomiphene citrate was started on the 2nd day of the cycle for five days, and hMG was administered on day 6 for 5 days. Group II (n=60) received the standard long protocol. The dose of hMG was then adjusted according to the ovarian response.

**Results:** There was no significant difference between both groups regarding age, duration of infertility and body mass index. Group I showed a statistically significant reduction in duration of stimulation, dose of hMG (16.4 ± 4.7 vs. 40.9 ± 7.9), and number of oocytes retrieved (4.8 ± 2.6 vs. 16.2 ± 7.5), but it also showed a significant increase in cycle cancellation (8.3%). Even so, there was no significant difference in clinical pregnancy rate transfert (33.3% vs 40%) between the two groups.

**Conclusion:** this approach is both simple and effective and it may prove to be an attractive alternative to the standard GnRH agonist long protocol.

**Rate of Increase in Estradiol Levels Midway of Cycle, in Predicting Ovarian Response in Art Cycle**

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**OBJECTIVES:** Although, earlier studies have evaluated the significance of various estradiol patterns during controlled ovarian hyperstimulation (COH), their prognostic significance remains unclear. The objective of this study is to investigate the rate of increase in estradiol (ROE2) during COH and evaluate it as a predictor of ovarian response. METHODS: In this retrospective study, 130 patients undergoing COH for IVF/ICSI cycles were reviewed. The E2 level during COH was evaluated on day 1, 5, 6, 7 & 8 and the ROE2 was determined. Age, basal FSH, number of mature follicles, number and maturity of oocytes, and incidence of ovarian hyperstimulation syndrome (OHSS) were recorded and their relationship with ROE2 was determined. RESULTS: Patients with elevated basal FSH have shown poor ROE2 on day six and a significant negative correlation was observed. Similarly, patients with advanced age group demonstrated poor ROE2 on day six. The average ROE2 on day six was significantly higher in patients who developed OHSS than non-OHSS group. The number of follicles, oocytes and maturity of the oocytes were maximum among the patients with higher ROE2 on day six. CONCLUSION: In a COH cycle, there is significant predictive association between ROE2 on day six and good ovarian response and hyper response.

**Successful Two-Zygote Twin Pregnancy in Natural IVF Cycle: Case Report**

**Slobodan Lazarevski, Snezana Adamoska; Mihailo Popovich; Mitko Ivanovski; Aneta Anevска; Ana Marija Stefanovska Special hospital of gynecology and obstetrics ‘Mala Bogorodica - Sistina’**

Natural cycle is part of our routine IVF practice (about 10-15%). My colleague will announced our results here, but last year we had very unusual case and, finding nothing in literature so far, we decided to report it.

We selected the patients for ART in spontaneous cycle according to sperm quality; age, menstrual cycle; hysteroscopy or ultrasound of the uterus and HSG and/or laparoscopy. The crucial conditions for HCG administration are: diameter of follicle over 15mm; serum level of estradiol over 130 pg/ml and LH up to 10mlU/ml. We do follicle aspiration 31-32 hours after the HCG administration and, if there is successful fertilization, embriotransfer after 5 days (blastocyst or morula).

**The case:** young couple from Skopje, he was 30 years old and she was 29. Her grandmother and her aunt had borne twins. First visit in our clinic was on 10.04.2005. They where married one year and she had history of ectopic pregnancy on the right side treated with 3 doses 50mg methotrexat i.m. Five months after (September 2004) HSG showed bilateral proximal tube obstruction. Two months after (November 2004) laparoscopic examination confirmed the diagnosis and hysteroscopy showed normal cavum uteri.
Introduction

The spontaneous cycle in such a situation has the advantage not to interfere with natural ovarian recruitment and selection. Therefore it could yield better quality oocytes, and subsequently better embryos in young patients with a diminished ovarian reserve. The purpose of this study was to evaluate the use of a modified natural cycle (MNC) for IVF in poor responders aged under 38 years old compared to a mild stimulated antagonist protocol.

Materials and methods:

Fourteen patients with a regular menstrual cycle and one or more failed IVF cycles, with five or fewer cumulus-oocyte complexes (COCs) retrieved, were included in this prospective study. They were randomised in two groups, and were offered four cycles from the start.

Study design and details:

MNC group (A): Recombinant FSH 150 IU and GnRH antagonist 0.5 mg/day were started concomitantly when a follicle with a mean diameter of 14 mm was present at ultrasound.

Mild stimulated group (B): Recombinant FSH 150 IU was started upon day five and GnRH antagonist 0.25 mg/day was started when a follicle with a mean diameter of 14 mm was present at ultrasound.

HCG 10 000 IU was administered as soon as the mean follicular diameter was INCLUDEDPICTURE "http://humrep.oxfordjournals.org/math/ge.gif" MERGEFORMAT 18 mm in both groups. Oocyte pick up was performed under local anesthesia and intra venous sedation. Follicular flushing was systematic at the time of retrieval and ICSI was systematically performed.

Results:

The baseline characteristics of the two groups were equivalent.

Group A Eight patients underwent 14 cycles in. Four cycles were cancelled due to a lack of recruitment or premature LH surge. In two cycles, no COC was retrieved. There was one pregnancy out of 3 transfers in group A, it was followed by a miscarriage.

Group B Six patients underwent 15 cycles. Two cycles were cancelled due to a lack of recruitment or premature LH surge. The 13 retrievals were all successful. Pregnancy rate was 3 out of 10 transfers in group B. There was an ongoing pregnancy with a live birth and two miscarriages.

The patients in group B used statistically more gonadotropins and antagonist, and yielded more oocytes and more embryos without reaching statistical significance.

Conclusions: MNC and mild stimulated cycles offer chances of pregnancy in patients with previous poor response to ovarian stimulation, when selected upon their age. Mild stimulated cycle seems a more pragmatic approach reducing the risk of cancellation and failed retrieval. The use of recombinant FSH seems adequate to sustain folliculogenesis in this type of protocols.

Multiple pregnancy rate development after introduction of monofollicular cycle IVF


Introduction
To prevent multiple pregnancies and other complications, make IVF cheaper and more patient-friendly, the usefulness of the monofollicular cycle in IVF was explored in consecutive projects since 2000 in our clinic. The introduction of GnRH-antagonists was the starting point. From that moment on natural cycles could be controlled better than before by preventing LH-surges and getting a higher probability that ovum pick-up could be performed in time. To prevent stagnation of folliclegrowth by decreased FSH-levels caused by the GnRH-antagonist, exogeneous FSH is given simultaneously, not for stimulation but only for replenishment. This supported (manipulated) natural cycle (sn-cycle) has a total different intention (keep monofollicular growth) than hyperstimulation or minimal stimulation cycles in which a (sub)maximal or limited number of ova is the aim. Naming and defining different kinds of treatments is of vital importance to compare the different strategies fairly.

Method
From 2000 sn-cycle treatment was offered to IVF patients younger than 37 years with regular menstrual cycles, from 2002 it was offered to such ICSI-patients. The first of normally offered three hyperstimulation (COH) treatments was replaced by six sn-cycles. At a follicle diameter of 14 mm cetrorelix (0,25 mg/d sc) and rec-FSH (150 IU/d sc) was started; at a follicle diameter of 18 mm 10.000 IU HCG was given, 34 hours later ovum pickup (OPU) was performed, mostly without anaesthesia. After three days the embryotransfer (ET) took place. Luteal support consisted of three times 1500 IU HCG at 5,8 and 11 days after the pickup. In 2003 our policy changed definitively to transfer maximal one embryo despite the fact sometimes more than one could be transferred.

Results
In 2000-2005 444 patients started 1792 sn-IVF-cycles resulting in 1471 OPU’s (82%), 647 ET’s (36%), 179 pregnancies (10%) and 138 ongoing pregnancies (7%); 4 twins after transfer of 2 embryo’s. In 2002-2005 195 women started 740 sn-ICSI-cycles resulting in 586 OPU’s (79%), 273 ET’s (37%), 73 pregnancies (10%) and 39 ongoing pregnancies (8%;1 twin). Cumulative pregnancy rate after six sn-cycles-IVF was 35% and after ICSI 33%.

In the same years 18-28% of the pregnancies from COH-IVF/ICSI, all or not preceded by sn-cycles, was a multiple. In the years 2000-2005 the multiple birth rate overall diminishes gradually (26-19-12-21-18-12%) (37% ), 73 pregnancies (10% ) and 5 9 ongoing pregnancies (8%;1 twin).

Conclusions
One in three patients who started sn-IVF/ICSI got a child, nearly all singletons. One in three pregnancies in our clinic results from monofollicular cycle IVF/ICSI. The decreasing trend of multiples seems to be interrupted by some years with high numbers of twin pregnancies, especially produced by COH-ICSI. Starting IVF/ICSI with six sn-cycles prevents a lot of twin pregnancies, but further decrease of the multiple pregnancy rate is necessary and can be obtained by carry on longer time with sn-cycles and/or perform (elective) single embryo transfer in COH-cycles. However, perhaps even more important is to stimulate research in monofollicular cycle IVF to be able to use that natural instrument routinely in assisted human reproduction.

Methionine is Important for Blastocyst Development and Implantation in a Natural Cycle

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Materials and methods:

In this prospective study 54 human embryos after in vitro fertilization of oocytes from a natural cycle were cultured to the blastocyst stage in Blast Assist System sequential media M1 and M2 (MediCult, Denmark). Each embryo was cultured in 4 μl droplet of medium under mineral oil near the same treated control droplet of medium without embryo. Each embryo was daily transferred into the fresh medium and former droplet was analyzed on 13 different amino acids, including methionine by gas chromatography (GC). Embryo uptake and release of amino acids into medium was calculated from the difference in amino acid concentrations between droplets with embryo and without embryo.

Study design and details:

Blastocyst development was correlated with amino acid concentrations in medium. During embryo development, amino acid turnover was compared between blastocysts and embryos who did not reach the stage of blastocyst - arrested embryos, and between implanted blastocysts and non-implanted blastocysts.

Results and Conclusions

There were negative correlations between the concentrations of methionine and asparagine in culture medium and blastocyst development (r = -0.235, P < 0.05 and r = -0.285, P < 0.05, respectively). Arrested embryos had a significantly higher amino acid turnover than blastocysts. Asparagine was amino acid, which was most intensively metabolized on day 3 of development in embryos developing to blastocysts, whereas lysine was most intensively metabolized in arresting embryos. Among blastocysts, implanted blastocysts had a significantly higher amino acid turnover than non-implanted blastocysts; they had intensive metabolism of methionine, whereas non-implanted blastocysts metabolized most intensively lysine. Methionine seems to be important for development of human embryos to the blastocyst stage and for blastocyst implantation in a natural cycle. This might be related to enhanced cell proliferation and establishment of epigenetic information by methionine, as known from studies in animals. Natural cycle is a good model to study human embryo metabolism to exclude the effect of hormonional stimulation.
INTRODUCTION

The first pregnancy in assisted reproduction was achieved in a natural (unstimulated) cycle (NC), many IVF units have abandoned this method because it has been judged as inefficient therapy. Efficacy of NC IVF is hampered by high cancellation rates because of premature luteinizing hormone (LH) rise and premature ovulations. Furthermore, NC has many difficulties in programming oocyte retrievals. However, the advantages might overcome these problems, so scientists are motivated to find solutions.

GnRH-antagonist induce a reversible medical hypophysectomy which prevents the occurrence of premature LH surges and allows the programming of treatment cycles as mentioned in other studies.

DESIGN

The aim of this study was to compare the results of NCs with and without the use of a single dose of GnRH-A. Thus, group I patients underwent 143 IVF NCs (control group) and group II patients performed 22 IVF NCs supported with GnRH-a.

MATERIAL AND METHODS

Both groups were monitored daily or every two days ultrasound follicular measurements and whenever a follicle diameter ≥1.1 mm was scanned, daily assessment of E2 and LH levels occurred. In group I, when LH measurement was 7-12IU/l and the follicle diameter ≥17mm, 6500IU of hCG were administered the same evening and oocyte retrieval was performed 36 hours later. In group II, when LH measurement was 7-12IU/l but the follicle diameter was <16mm, then a single injection of 0.25mg Cetrorelix was administered. The next evening 6500IU of hCG were administered and the oocyte retrieval was performed 36 hours later. ICSI was performed in all cases.

RESULTS

84 patients underwent 143 cycles in group I. 13 patients underwent 22 cycles in group II. Mean age at treatment was 37.59±4.29 and 38.77±1.82 for groups I and II respectively. The main cause of infertility was poor responding in gonadotropin’s stimulation (95.8% and 95.5% respectively). Lower rate of cancellation was observed in group II. Successful oocyte retrievals were achieved in 71.3% in group I and 86.4% in group II. Retrieval of mature oocytes was accomplished in 79.05% in group I and 89.5% in group II. Fertilization rate was 75.90% in group I and 82.40% in group II. Normal fertilization resulting in embryo transfer occurred in 54.90% in group I and 68.42% in group II. Pregnancy rates per starting cycle and per embryo transfer were also higher in group II (11.12% vs 18.18% and 28.60% vs 30.80% respectively).

CONCLUSIONS

Poor responders may benefit from NCs because it is associated with a close to zero multiple pregnancy rate, no risk of ovarian hyperstimulation syndrome. Furthermore, NC is less time consuming, physically and emotionally less demanding for patients and cheaper than stimulated IVF. Our study showed better results with the administration of GnRH-a, however none of these observations has shown statistically significant difference. Thus, more cases must be done in order to lead us to a conclusion. It is really important though that the use of GnRH-a in NCs is effective in order to have a better control of LH surge and a better schedule of oocyte retrieval.

Single Embryo Transfer: Oligonucleotides Modified Medium Advantages

Zaeva, V.

Introduction: The success of in-vitro fertilization (IVF) largely depends on the causes of infertility, the patient’s age, the quantity and quality of embryos produced and transferred into the uterus. The rate of success of this method is often low in elderly patients and women with inadequately low ovarian response to hormonal stimulation, which may lead to decreased numbers of oocytes and poor quality of embryos. Improvement of embryo viability in vitro is one of the principal goals of modern reproductive technologies. A considerable part of the research in this area focuses on various modifications of the culture medium and other conditions that could improve the quality of oocytes and embryos. In the present study, we assessed the therapeutic value of non-modified oligonucleotides (ODNs) for culture medium modification.

Materials and methods: 173 patients of 19 to 44 years old undergoing treatment of infertility using IVF were included in this study. Infertility was caused by tubal-peritoneal factor, polycystic ovary syndrome, endometriosis, etc. or a combination of two or more of these factors. Patients whose partner had pathospermia were excluded from the study. The included patients were then randomly divided into two groups (ODNs treatment or control). Superoxolulation was induced beginning from day 2-3 of the cycle, usually according to the short protocol, using gonadotrophic agents, recombinant FSH, hCG, menopausal gonadotropins. The mean initial dose of gonadotropins was 150-225 IU, mean total dose – 1425 IU. Transvaginal puncture was performed on day 12-14 of the cycle. Standard insemination procedure was used for in vitro fertilization.

From the moment oocytes were obtained to 24 hours after in vitro insemination, oocytes and embryos were cultured in medium containing ODNs (ODNs treatment group), after which the embryos were cultured without ODNs until they were transferred to the uterus. Oocytes in the control group were cultured without ODNs from the moment oocytes were obtained. Embryos were cultured under standard conditions: t 37°C, 5% CO2 in the air.

Results: On Day 2 there were significantly fewer embryos with >25% fragmentation in the treatment group (p=0.009). On Days 2 and 3 the percentage of high-quality embryos was higher in the treatment group compared to the control group (p=0.048 vs. p=0.005, respectively). A total of 36 out of 87 women (41.38%) in the ODNs treatment group became pregnant, compared to 27 out of 85 women (31.40%) in the control group. In most cases 2 embryos were transferred to each patient, and pregnancy rate in such patients was (32/71; 45.07%) in the ODNs treatment group vs. (27/70; 38.57%) in the control group. This higher pregnancy rate in the AsODNs treatment group can only be explained by significant improvement of embryo quality with the addition of AsODNs to culture medium. It is worth noting that among 30 patients (15 in active treatment and 15 in control group), the transfer of a single embryo (no embryo selection) led to 4 pregnancies in the ODNs treatment group and no pregnancies in the control group (p<0.01).

Conclusion: The results demonstrate the improved pregnancy rate in single embryo transfer connected with the addition of ODNs to the culture medium. It may be caused by improved quality of culture embryo and reduced fragmentation of blastomeres.
Clomid IVF (Mini-IVF) or conventional IVF: A Comparative Study
John Zhang, M.D., Ph.D., New Hope Fertility Center, New York, NY and Osamu Kato, M.D., Kato Ladies clinic, Tokyo, Japan

In the United States, the average pregnancy rates for conventional IVF have continued to improve, due to strict selection of candidates for IVF, controlled ovarian stimulation, and improved IVF laboratory techniques. However, the high cost of drugs as well as the discomfort and inconvenience of daily injections, has not changed. 40% of patients who dropped out of IVF treatment report that their reasons for doing so are the issues surrounding daily injection protocols. In promoting single embryo transfer, we have primarily been performing in vitro fertilization with Clomiphene citrate (50 mg) initiation orally each day, beginning on Day 3. Subcutaneous administration of 75–150 IU of hMG every 48 hours was begun on Day 8. A gonadotropin releasing hormone agonist (GnRHa) nasal spray (Synarel) was administered to trigger an endogenous LH surge for final maturation of oocytes. Oocyte retrieval was performed 34–36 hours after the administration of nasal spray. A fresh embryo transfer was performed between the third and fifth day after oocyte retrieval. Supernumerary embryos were cryopreserved if they reached the blastocyst stage. The frozen embryos were to be thawed and transferred in subsequent natural menstrual cycles if no pregnancy had been achieved from the fresh IVF cycles. In the conventional IVF cycles, 70% of the cases were stimulated with long-term GnRH analog protocol, and the remaining 30% were stimulated with either short term GnRH analog protocol, or GnRH antagonist protocol.

In conventional IVF, 3600 IU gonadotropins were given in each cycle as compared with less than 475 IU in Mini-IVF. While high clinical pregnancy rates were obtained from conventional IVF, more frozen embryo transfer cycles were performed with Mini-IVF with comparable clinical pregnancy rates. The mean number of oocytes retrieved with conventional IVF was +/- 12, and the mean number of oocytes retrieved with Mini-IVF was +/- 3. The efficacy of Mini-IVF and the cumulative clinical pregnancies between Mini-IVF and conventional IVF will be discussed in this presentation.

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<td>7</td>
</tr>
<tr>
<td>% live births</td>
<td>38.8</td>
<td>30.0</td>
<td>3/16</td>
<td>2/11</td>
<td>1/7</td>
</tr>
<tr>
<td># embryos transfer</td>
<td>1.6</td>
<td>1.5</td>
<td>1.7</td>
<td>2</td>
<td>2.4</td>
</tr>
</tbody>
</table>

Pregnancies from Mini – IVF

<table>
<thead>
<tr>
<th>Age</th>
<th>&lt;35</th>
<th>36-37</th>
<th>38-40</th>
<th>41-42</th>
<th>43-44</th>
</tr>
</thead>
<tbody>
<tr>
<td># cycles</td>
<td>101</td>
<td>73</td>
<td>65</td>
<td>43</td>
<td>21</td>
</tr>
<tr>
<td>% cancellations</td>
<td>4.0</td>
<td>0</td>
<td>4.6</td>
<td>7</td>
<td>9.5</td>
</tr>
<tr>
<td>Mean # oocytes/ER</td>
<td>17</td>
<td>15.5</td>
<td>12</td>
<td>7.8</td>
<td>6.6</td>
</tr>
<tr>
<td>% embryos transfer</td>
<td>2.3</td>
<td>3</td>
<td>3.2</td>
<td>3.7</td>
<td>2.9</td>
</tr>
<tr>
<td>% birth per ER</td>
<td>58.8</td>
<td>47.9</td>
<td>35.5</td>
<td>17.5</td>
<td>1/19</td>
</tr>
<tr>
<td>% birth per ET</td>
<td>59.4</td>
<td>49.3</td>
<td>36.7</td>
<td>17.9</td>
<td>1/16</td>
</tr>
<tr>
<td># Thawed embryo ET</td>
<td>13</td>
<td>2</td>
<td>4</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>% live births</td>
<td>2/13</td>
<td>1/2</td>
<td>1/4</td>
<td>0/1</td>
<td>-</td>
</tr>
<tr>
<td># embryos transfer</td>
<td>2.6</td>
<td>3.5</td>
<td>3.8</td>
<td>3</td>
<td>-</td>
</tr>
</tbody>
</table>
C.C.D. International manufactures Ob/Gyn medical devices and biological media for assisted reproductive technologies, cancer screening, antenatal detection and gynaecological imaging.

Our gold-standards are available worldwide: Frydman® catheters, Ultrasoft Embryoview® transfer catheter, HSC Tubal Access, B2 Upgraded Inra Medium, B9 Upgraded Medium, Icsimed®, Ovorinse®, Spermacare®, Pipelle® by Dr Cornier, Pipelle® Mark II, H Pipelle®, S.I.S. Rudigoz catheter, and many other devices specifically dedicated to Ob/Gyn practice.

GE Healthcare provides transformational medical technologies that are shaping a new age of patient care. Our expertise in medical imaging and information technologies, medical diagnostics, patient monitoring systems, drug discovery, and biopharmaceutical manufacturing technologies is helping clinicians around the world reimagine new ways to predict, diagnose, inform and treat disease, so their patients can live their lives to the fullest.

GE Healthcare’s broad range of products and services enable healthcare providers to better diagnose and treat cancer, heart disease, neurological diseases, and other conditions earlier. Our vision for the future is to enable a new ‘early health’ model of care focused on earlier diagnosis, pre-symptomatic disease detection and disease prevention. Headquartered in the United Kingdom, GE Healthcare is a $15 billion unit of General Electric Company (NYSE: GE). Worldwide, GE Healthcare employs more than 43,000 people committed to serving healthcare professionals and their patients in more than 100 countries.

Philips is a leading supplier of medical equipment and related services, providing a complete range of medical imaging, monitoring and clinical IT.

Philips offers a comprehensive portfolio of ultrasound equipment including Philips’ iU22 with intelligent control and advanced ergonomic design, providing a wide range of high performance features to increase workflow and reduce RSI. The new ‘Vision 2007’ features bring cutting-edge workflow assistance, expanded volumetric capabilities, new clinical application areas and additional quantification tools. With volumetric imaging, it is only necessary to acquire a few volumes to produce more clinical information and in less time, with less repetitive motion for the operator and less discomfort for the patient.

The iU22 was cited in an independent review of six high-end ultrasound systems as the only system that ‘met Industry Standards’ recommendation for independent height adjustment of the monitor and control panel and for the full range of viewing distances.’
Our Company Serono is a unique Biotech company, with a global presence and fully integrated from discovery to market. We are a world leader in the field of biotechnology. We compete for leadership in all the markets in which we operate. Our competitive advantage is derived from achieving superior performance above and beyond the sum of our parts. In achieving our goals we maximize the return on investment of our shareholders. Our overall aim is to develop innovative products to address unmet medical needs and improve the quality of life of our patients.

Our people Serono creates an environment in which individuals add value and participate in the growth and development of our company. We attract, develop and retain the best talent in the industry by promoting their leadership spirit. Our leaders are responsible for achieving success by managing, developing and coaching our people and leading integrated teams to reach peak performance. We strive to understand the needs of our stakeholders and continuously challenge the efficiency of our key processes to serve them better. We are considered to be a superior company to work for and one that has consistently performed beyond expectations.

Our products Serono’s future is built on its investment in R&D both internally and in collaboration with our partners. Biology is at the heart of all we do. We develop products with the highest standards of quality, safety and efficacy for the benefit of our patients. We are recognized industry wide for our speed to market in research and development. We create global brands and communicate the value of our science, technology and medicine. Respecting ethical principles, we will continue to create, to promote and to nurture life.
Diagnostic Sonar Ltd was formed in 1975 with the specific aim to build Britain’s first real-time ultrasound scanner. This was then displayed 1 year later at the British Medical Ultrasound Society’s annual meeting in Dundee. Many hundreds were produced but in the end we had to cease production when the economies of scale started to favour major overseas competitors.

From the start we pursued our own ideas and as a result we introduced a number of unique products. Electronic measuring systems are now built into scanners but we were first to introduce a self contained microprocessor controlled lightpen-based measuring station (Echo Computer). We also introduced Ultrasound Couplant and have since become one of the largest producers.

At about the time when we displayed our first major medical system the company started to trade in industrial ultrasonics, manufacturing and supplying a variety of imported and in-house designed products. The Industrial Division has enjoyed steady growth over the years and currently produces a unique phased array A, B and C-scanning system that has found favour in a number of industries but is particularly popular with aerospace companies.

During the last 10 years in particular DSL has been instrumental in getting the medical profession to accept 3D (and more recently 4D) ultrasound scanning. This has led to a close cooperation with Medison, one of the world’s largest ultrasound companies and a pioneer in 3D. Please contact us for more information.

Medison’s innovations in digital imaging technology are making a difference in hospitals, clinics, and private practices around the world. Through its global network, extending to more than 80 countries, the company provides a comprehensive range of state-of-the-art ultrasound products from portable devices to multi-specialty real-time 3D systems that is meeting the demands of healthcare professionals for greater functionality, reliability, and diagnostic accuracy.

A dedicated ultrasound solutions provider, Medison’s commitment to research and development is unmatched. Our scientists and engineers are not only continually developing leading-edge ultrasound devices, but are also setting standards that position Medison as the first and often the only company to offer innovative solutions in 3D imaging technology.

The development of automatic volume data acquisition, multi-beam technology, and Live 3D are just a few of the company’s technological breakthroughs. Unique to Medison, automatic acquisition enables users to acquire an entire volume of data in a single, static action rather than separate slices of information in several movements, resulting in more exact spatial relationships and more lifelike images. Using Medison’s automatic data acquisition and Live 3D technology, which provides image display in real time, physicians worldwide are performing a greater number of clinical applications with greater diagnostic confidence than ever before.

The Women’s Clinic has been caring for the obstetrical and gynecological needs of women in Hong Kong over 15 years and was instrumental for making the first IVF baby in Hong Kong 1986. The Clinic is headed by Dr. Milton Leong.

The Women’s Clinic provides a full range of obstetrical and gynecological services. It is designed to provide all necessary investigations and laboratory testing within a single location.

The Clinic also offers two unique diagnostic programmes. Fertility Diagnosis, designed to complete investigation into the causes of infertility; and a comprehensive Down’s Syndrome screening which includes first trimester Nuchal Translucency scanning and second trimester blood tests.
HER Trust is an innovative charity which aims to change the lives of women across the world. The charity has been specifically founded to focus on women’s reproductive health from puberty to menopause. The HER Trust approach to women’s health is empowering, proactive and holistic. The charity aims to support educational programmes and research projects which are essential for the continuous improvement in women’s health and healthcare.