“Mild stimulation strategies in IVF”

SPECIAL INTEREST GROUPS
REPRODUCTIVE ENDOCRINOLOGY &
SAFETY AND QUALITY IN ART

28 June 2009
Amsterdam
The Netherlands
# Table of contents

**Program overview**

<table>
<thead>
<tr>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
</tr>
</tbody>
</table>

**Speakers’ contributions**

<table>
<thead>
<tr>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild ovarian stimulation for IVF: theory and practice</td>
<td>4</td>
</tr>
<tr>
<td><em>Bart Fauser (The Netherlands)</em></td>
<td></td>
</tr>
<tr>
<td>Ovarian stimulation and embryo quality: less is more?</td>
<td>14</td>
</tr>
<tr>
<td><em>Esther Baart (The Netherlands)</em></td>
<td></td>
</tr>
<tr>
<td>Natural cycle IVF - Is it effective and cost-effective</td>
<td>24</td>
</tr>
<tr>
<td><em>Geeta Nargund (United Kingdom)</em></td>
<td></td>
</tr>
<tr>
<td>Individualising ovarian stimulation for IVF</td>
<td>39</td>
</tr>
<tr>
<td><em>Anders Nyboe Andersen (Sweden)</em></td>
<td></td>
</tr>
<tr>
<td>Single embryo transfer: where are we?</td>
<td>62</td>
</tr>
<tr>
<td><em>Petra de Sutter (Belgium)</em></td>
<td></td>
</tr>
<tr>
<td>How can we reduce the burden of treatment?</td>
<td>79</td>
</tr>
<tr>
<td><em>Jacky Boivin (United Kingdom)</em></td>
<td></td>
</tr>
<tr>
<td>Panel discussion: The impact of milder stimulation upon indicators of benefit (efficacy, safety, time and costs, quality)</td>
<td>94</td>
</tr>
<tr>
<td>• Is there an optimal balance?</td>
<td></td>
</tr>
<tr>
<td><em>Christina Bergh (Sweden)</em></td>
<td></td>
</tr>
<tr>
<td>• Which patients benefit?</td>
<td>98</td>
</tr>
<tr>
<td><em>Karl Nygren (Sweden)</em></td>
<td></td>
</tr>
</tbody>
</table>

**Notes**

<table>
<thead>
<tr>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>101</td>
</tr>
</tbody>
</table>
Mild stimulation strategies in IVF

Organised by the Special Interest Groups Reproductive Endocrinology, Safety and Quality in ART and Task Force on Mild Approaches in Assisted Reproduction

Course co-ordinators: Nicholas Macklon (NL), Christina Bergh (Sweden) and Geeta Nargund (UK)

Course description: Milder strategies for ovarian stimulation in IVF are being increasingly advocated as a means of achieving satisfactory live birth rates while minimizing severe side effects such as multiple pregnancy, ovarian hyperstimulation syndrome and patient drop out from treatment. But is this hype or hope? This course, which is provided jointly by the SIGs Safety and Quality in ART and Reproductive Endocrinology, will provide participants with a state of the art overview of these new approaches, and by critically examining their risk and benefits compared with conventional stimulation strategies, will clarify their appropriate use in clinical practice. An update in single embryo transfer outcomes will be provided, and a panel discussion will engage speakers and delegates in the contentious issues around mild strategies in IVF.

Target audience: Clinicians, midwives/nurses, biologists/embryologists working with reproductive medicine

08:45 - 09:00  Introduction - Nicholas Macklon (The Netherlands)

09:00 - 09:30  Mild ovarian stimulation for IVF: theory and practice - Bart Fauser (The Netherlands)

09:30 - 09:45  Discussion

09:45 - 10:15  Ovarian stimulation and embryo quality: less is more? - Esther Baart (The Netherlands)

10:15 - 10:30  Discussion
10:30 - 11:00 Coffee break

11:00 - 11:30 Natural cycle IVF - Is it effective and cost-effective - Geeta Nargund (United Kingdom)

11:30 - 11:45 Discussion

11:45 - 12:15 Individualising ovarian stimulation for IVF - Anders Nyboe Andersen (Sweden)

12:15 - 12:30 Discussion

12:30 - 13:30 Lunch

13:30 - 14:00 Single embryo transfer: where are we? - Petra de Sutter (Belgium)

14:00 - 14:15 Discussion

14:15 - 14:45 How can we reduce the burden of treatment? - Jacky Boivin (United Kingdom)

14:45 - 15:00 Discussion

15:00 - 15:30 Coffee break

15:30 - 16:30 Panel discussion: The impact of milder stimulation upon indicators of benefit (efficacy, safety, time and costs, quality)

The following topics will be presented (5 minutes followed by panel discussion):

- Defining success in IVF - Bart Fauser (The Netherlands)
- Cost-effectivity - Petra de Sutter (Belgium)
- Is there an optimal balance? - Christina Bergh (Sweden)
- Which patients benefit? - Karl Nygren (Sweden)

16:30 - 16:45 Summary and conclusions - Nicholas Macklon (The Netherlands)

16:45 - 17:00 Discussion
Mild ovarian stimulation for IVF;  
- theory and practice

Prof. Dr. Bart CJM Fauser
University Medical Center, Utrecht, The Netherlands

Fauser Conflict of interest statement

Grant support and fees from the following companies

- Andromed,
- Ardana,
- Ferring,
- Genovum,
- Glycotope,
- Merck Serono,
- Organon,
- Pantharei Bioscience,
- Philips,
- PregLem,
- Schering,
- Schering Plough,
- Serono,
- Wyeth.

Learning objectives

- To appreciate why understanding ovarian physiology is important for improving ovarian stimulation protocols
- To appreciate that GnRH antagonist co-treatment enables the development of simpler stimulation protocols closer to physiology
- To appreciate that failed implantation is still the major cause of failed IVF
- To appreciate that what we do today should be viewed in the context of future health of IVF children (Barker hypothesis)
- To understand that the current measure to define success in IVF has major shortcomings
- To appreciate that access to IVF is insufficient in the overwhelming majority of countries worldwide
Left:

- Lecture outline
  - Background
  - Own data
  - Conclusions

How successful is IVF?
(isolated focus on outcomes per cycle)

![Graph showing IVF success rates](image)

How to define successful IVF
- Towards a more holistic approach -

**The issues**
- Live births? (20 wks)
- Patients treated (age, indic., smoking)
- Multiples/fetal reduction?
- Complications? (OHSS)
- Side effects / long-term risks?
- Cryo results?
- Definition started cycle?
- Duration of cycle?
- Cost?
- Drop outs? (cumulative results)

---

Gleicher, HR 2006
The IVF paradox

Insufficient access to treatment
- Expensive
- No health insurance coverage

Tendency Over-treatment in Western societies
- Varying indications for treatment
- Commercial environment / consumer behaviour

> 70% of failed IVF = failed implantation

Superovulation strategy for in vitro fertilization

Consequences for
- Luteal phase endocrinology
- Endometrial receptivity
- Embryo aneuploidy
The need of more patient tailored ovarian stimulation for IVF

Individualization:
- female age
- BMI
- smoking
- AMH / AFC
- genetic markers

Hyporesponse = poor outcome

Hyperresponse = danger

Ovarian response

Ovarian stimulation

Clinical pregnancy rate (Sterrenburg, unpublished)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Sterrenburg, 1983</td>
<td>100</td>
<td>101</td>
<td>102</td>
<td>103</td>
<td>104</td>
<td>105</td>
<td>106</td>
<td>107</td>
<td>108</td>
<td>109</td>
<td>110</td>
<td>111</td>
<td>112</td>
<td>113</td>
<td>114</td>
<td>115</td>
<td>116</td>
</tr>
<tr>
<td>Sterrenburg, 1984</td>
<td>117</td>
<td>118</td>
<td>119</td>
<td>120</td>
<td>121</td>
<td>122</td>
<td>123</td>
<td>124</td>
<td>125</td>
<td>126</td>
<td>127</td>
<td>128</td>
<td>129</td>
<td>130</td>
<td>131</td>
<td>132</td>
<td>133</td>
</tr>
<tr>
<td>Sterrenburg, 1985</td>
<td>134</td>
<td>135</td>
<td>136</td>
<td>137</td>
<td>138</td>
<td>139</td>
<td>140</td>
<td>141</td>
<td>142</td>
<td>143</td>
<td>144</td>
<td>145</td>
<td>146</td>
<td>147</td>
<td>148</td>
<td>149</td>
<td>150</td>
</tr>
<tr>
<td>Sterrenburg, 1986</td>
<td>151</td>
<td>152</td>
<td>153</td>
<td>154</td>
<td>155</td>
<td>156</td>
<td>157</td>
<td>158</td>
<td>159</td>
<td>160</td>
<td>161</td>
<td>162</td>
<td>163</td>
<td>164</td>
<td>165</td>
<td>166</td>
<td>167</td>
</tr>
<tr>
<td>Sterrenburg, 1987</td>
<td>168</td>
<td>169</td>
<td>170</td>
<td>171</td>
<td>172</td>
<td>173</td>
<td>174</td>
<td>175</td>
<td>176</td>
<td>177</td>
<td>178</td>
<td>179</td>
<td>180</td>
<td>181</td>
<td>182</td>
<td>183</td>
<td>184</td>
</tr>
<tr>
<td>Sterrenburg, 1988</td>
<td>185</td>
<td>186</td>
<td>187</td>
<td>188</td>
<td>189</td>
<td>190</td>
<td>191</td>
<td>192</td>
<td>193</td>
<td>194</td>
<td>195</td>
<td>196</td>
<td>197</td>
<td>198</td>
<td>199</td>
<td>200</td>
<td>201</td>
</tr>
<tr>
<td>Sterrenburg, 1989</td>
<td>202</td>
<td>203</td>
<td>204</td>
<td>205</td>
<td>206</td>
<td>207</td>
<td>208</td>
<td>209</td>
<td>210</td>
<td>211</td>
<td>212</td>
<td>213</td>
<td>214</td>
<td>215</td>
<td>216</td>
<td>217</td>
<td>218</td>
</tr>
</tbody>
</table>

Native GnRH vs GnRH analogues
Meta-analysis GnRH agonist vs antagonist - ongoing pregnancy rates

Kolibianakis, HRU 2006

Improving the patient’s experience of IVF/ICSI: a proposal for an ovarian stimulation protocol with GnRH antagonist co-treatment

2009

2007

No GnRH antagonist/ Clomid    FSH add-back    arom inhibitors    low-dose    early start FSH/HMG    combinations    late start FSH    GnRH analogues

Mono-follicle development

Multi-follicle development
Mild Hyperstimulation for IVF: Study design

**Study design**

- **A** (n=38)
  - GnRH agonist (long prt)
  - hCG
  - (n = 48)
  - Progestan (intravag)

- **B** (n=35)
  - GnRH antag
  - FSH (150 IU/d)
  - (n = 40)
  - Progestan (intravag)

- **C** (n=41)
  - GnRH antag
  - FSH (150 IU)
  - (n = 41)
  - Progestan (intravag)

Decrease in pituitary responsiveness

Cycle day 2
5 foll > 14 mm

Hohmann, JCBM 2003
**IVF study design issues**

- **Pregnancy rates** vs. Health babies as primary outcome
- Outcomes per cycle vs. Per stared treatment
- Isolated focus on outcomes vs. Holistic approach (outcomes vs discomfort, complications, cost)

**Lancet 2007**

- Mean cycle No: 2.3 mild
- 1.7 conventional

![Graph showing cumulative pregnancies over cycle number](image)
Cycle specific characteristics

Pregnancy outcomes

Patient distress and IVF
- conclusions own studies -

Conclusions:

Little perceived need for counselling
No difference 3 counselling sessions

More physical and depressive symptoms during down regulation in conventional IVF

Failed IVF results in less depressive symptoms after mild IVF

Complex relationship between initial psychol. parameters and IVF outcomes
Optimal oocyte number for IVF - how to balance risks vs benefits -

- Mild vs maximal stimulation
- % of patients
- Oocyte number
- Risks / Side effects
- Benefits

(Adapted from Nyboe Andersen)

In vitro fertilization - the true balance -

- Substitute outcome parameters
  - Oocyte number
  - Follicle number
  - Embryo number
  - Implantation rate
  - Pregnancy rate/cycle
  - Healthy term live birth per treatment

Healthy term live birth per treatment

Risks / complications

Patient discomfort

Costs

Heijnen, HR 04

Collaborators in mild IVF studies

- Rotterdam
  - de Jong
  - Hohmann
  - Beckers
  - Eijkemans

- Utrecht
  - Heijnen
  - Baart
  - Verberg
  - Boomsma
  - Teklenburg
  - Sterrenburg
Ovarian stimulation and embryo quality: less is more?

Esther Baart, PhD

Department of Reproductive Medicine and Gynaecology, University Medical Center, Utrecht and Division of Reproductive Medicine, Department of Obstetrics and Gynaecology, Erasmus Medical Center, Rotterdam, The Netherlands

Conflict of interest

I have no conflict of interest to report

Learning Objectives

- Differences in oocyte quality exist in a cohort of oocytes retrieved after ovarian stimulation
- Embryo quality is not completely reflected by embryo morphology
- The ability of an oocyte/embryo to correctly segregate chromosomes is a quality indicator
- Mild stimulation may allow only the most mature follicles to develop, resulting in the retrieval of only the most competent oocytes
- Mild stimulation lowers the proportion of aneuploid embryos
- Further development of mild stimulation strategies is needed to optimize oocyte quality
What is a good oocyte/embryo?

- Competent to undergo fertilization
  - Chromatin remodeling
  - DNA repair
- Supports timely completion of cleavage divisions
- Reliably segregates chromosomes
  - Spindle formation
  - Checkpoint functions
- Activates the embryonic genome (8 cell stage)
  - Chromatin remodeling
  - Establishment of genomic imprinting

Oocyte growth and maturation

Cumulus cells ‘feed’ the oocyte

- Transzonal projections connect oocyte and cumulus cell
- TZP mediates transport of nutrients and small molecules (mRNAs?)
- Density is regulated by the oocyte
- Highly sensitive to FSH

Hutt and Albertini, RBM online, 2007

Follicle and oocyte development are interlinked

Intra-follicular signaling between:
- Oocyte
- Cumulus granulosa cells
- Mural granulosa cells
- Theca cells

Russell and Robker, HRU, 2007
How to assess embryo quality?
- The classical approach -

- Morphology and development:
  - Assessment of pronucleate embryos
  - Timing of cleavage
  - Assessment on day 3 after fertilization
  - Development to the blastocyst stage
  - Implantation potential, ongoing PR and live birth

The perfect embryo
(based on morphology and development)

Successful implantation after SET in 49% of patients ≤36 yrs

At least 50% of embryos are chromosomally abnormal

Day 3: cleavage stage and chromosome abnormalities

- 662 patients, 916 cycles
- Poor prognosis patients
- PGS on day 3
- XY, 13, 14, 15, 16, 18, 21, 22
- Cleavage stage assessment

Papanikolaou et al., NEJM, 2006
Magli et al., Fertil Steril, 2007
Day 3: fragmentation and cell number

Magli et al., Fertil Steril 2007

Development to the blastocyst stage and chromosomal abnormalities

- 148 patients, 148 cycles
- patients ≥37 years
- IVF and ICSI
- PGS on day 3, two cells
- XY, 13, 16, 18, 21, 22
- Assessment of blastocyst development

Staessen et al., Hum Reprod, 2004

FISH diagnosis on day 3 and development on day 5

Staessen et al., Hum Reprod, 2004
Randomized comparison of two ovarian stimulation approaches

- Determine the incidence of aneuploidy and mosaicism in embryos from younger IVF patients
- Study the effect of ovarian stimulation on embryo aneuploidy
- Can PGS be used as an extra parameter to assess embryo quality?
Preimplantation genetic screening

Fertilization

Day 3: embryo biopsy

FISH analysis

Diagnosis on one or two blastomeres

Transfer of chromosomally normal embryos

Fixation and analysis of blastomeres

Method using HCl/Tween and Methanol/Acetic acid

First round of FISH: chromosomes 1, 7, 15, X & Y

Second round of FISH: chromosomes 13, 16, 18, 21, 22

PGS Diagnosis in young IVF patients

Analysis of 265 embryos:

Diagnosis based on:

- one blastomere
- two blastomeres

- Abnormal
- Mosaic
- Normal

- 34%
- 36%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
- 40%
**PGS Diagnosis for statistical analysis**

Analysis of 265 embryos:

- Abnormal: 44%
- Normal: 56%

Diagnosis based on: first blastomere biopsied

**Lower aneuploidy rate after mild stimulation**

- Stimulation protocol: Conventional vs. Mild
- % abnormal embryos / diagnosed:
  - Conventional: 60%
  - Mild: 40%
- $P = 0.016$
- Good quality embryo rate per patient:
  - Conventional: 35%
  - Mild: 51%
- $P = 0.04$

**Average number per patient**

- Conventional vs. Mild
  - Oocytes: 20
  - Embryos: 18
  - Normal embryos: 16

- Average number:
  - Oocytes: 10
  - Embryos: 8
  - Normal embryos: 6
  - Abnormal embryos: 2
What could it mean to the embryologist?

Conventional ovarian stimulation:

Mild ovarian stimulation:

Chromosomal mosaicism after analysis of two cells

Conventional stimulation (98 embryos)  Mild stimulation (98 embryos)

Rate of mosaic embryos per patient:

65%  37%  P= 0.004
Mild stimulation and ovarian response

Conclusions

• Follicle development is correlated to oocyte quality
• The chromosome constitution provides an additional marker for oocyte/embryo quality
• Ovarian stimulation has an impact on embryo aneuploidy rates (chromosomal mosaicism)
• Ovarian stimulation should not aim at maximizing oocyte yield but optimizing oocyte quality

BIBLIOGRAPHY

• Magli MC, Gianaroli L, Ferrareti AP et al. 2007 Embryo morphology and development are dependent on the chromosomal complement. Fertility and Sterility 87, 534-541.

Natural cycle IVF: Is it Effective and Cost-effective?

Geeta Nargund FRCOG
Head of Reproductive Medicine
St George's Hospital London
Chair, ESHRE Task Force "Mild ART"

Disclosures

None

BIRTH OF LOUISE BROWN:
25th July 1978
Learning Objectives

- Definition of Natural cycle IVF
- Terminology for Effectiveness & Cost-effectiveness
- Different forms of ovarian stimulation for IVF
- Indications for Natural cycle IVF
- Clinical management of Natural cycle IVF
- Methods used for modified Natural cycle IVF
- Relevant studies published on Natural cycle IVF
- Results & Cost-effectiveness of Natural cycle IVF
- Critical analysis and future indications for Natural cycle IVF

Natural cycle IVF

- Spontaneous cycle
- Single mature oocyte
- No medication used at any stage of cycle
- Monitoring with USS and or Hormone assay


Effectiveness: The Definition

- Efficiency: doing things in the most economical way (good input to output ratio)
- Efficacy: getting things done, i.e. meeting targets
- Effectiveness: doing "right" things, i.e. setting right targets to achieve an overall goal (the effect)
Cost-Effectiveness

Cost-Effectiveness Analysis (CEA)
Is a form of economic analysis that compares the relative expenditure (costs) and outcomes (effects) of two or more courses of action.

Natural /Modified natural cycle IVF

- Cohort studies
- Cumulative data
- In selected population
  1. Poor responders
  2. Failed implantation
  3. Older women
  4. Cancer risk group

The ISMAAR proposal on Terminology for Ovarian Stimulation for IVF

Rotterdam consensus group on Terminology for ovarian stimulation for IVF

Nargund G, Fauser BCJM, Macklon NS, Ombelet W, Nygren K and Frydman R


For the ISMAAR Consensus Group on Terminology for Ovarian Stimulation for IVF
Consensus on Terminology

Consistency is needed
- For clinical practice
- For research publications
- Patient understanding & communication
- For policy makers
- For public information

Terminology is focused on the meaning & conveyance of concepts

Definitions

<table>
<thead>
<tr>
<th>Terminology</th>
<th>Aim</th>
<th>Methodology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natural cycle IVF</td>
<td>Single oocyte</td>
<td>No medication</td>
</tr>
<tr>
<td>Modified Natural cycle IVF</td>
<td>Single oocyte</td>
<td>hCG only Antagonist &amp; FSH/HMG add-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>back</td>
</tr>
<tr>
<td>Mild IVF</td>
<td>2-7 oocytes</td>
<td>Low dose FSH/HMG, oral</td>
</tr>
<tr>
<td></td>
<td></td>
<td>compounds &amp; antagonist</td>
</tr>
<tr>
<td>Conventional IVF</td>
<td>≥8 oocytes</td>
<td>Agonist or antagonist</td>
</tr>
<tr>
<td></td>
<td></td>
<td>conventional FSH/HMG dose</td>
</tr>
</tbody>
</table>

Terminology

<table>
<thead>
<tr>
<th>Recommended</th>
<th>To replace</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natural cycle IVF</td>
<td>Unstimulated, Spontaneous cycle IVF</td>
</tr>
<tr>
<td>Modified Natural cycle IVF</td>
<td>Semi-natural, Controlled natural cycle IVF</td>
</tr>
<tr>
<td>Mild IVF</td>
<td>Soft, Minimal stimulation, 'Friendly' IVF</td>
</tr>
<tr>
<td>Conventional IVF</td>
<td>Standard, Routine IVF, Controlled Ovarian Hyperstimulation (COH) IVF</td>
</tr>
</tbody>
</table>
Modified Natural cycle IVF

- Spontaneous cycle
- Exogenous hormones used

Scenarios:
1. hCG only
2. GnRH antagonist ±FSH add-back & hCG
3. Luteal support
   - Low risk of cancellation
   - Commonly used method of natural cycle IVF

Nargund & Frydman: RBM Online, 2007;14:550-552

Modified Natural cycle IVF

- More physiological
  *Follows the path of follicular growth*
- Minimal cost
- Fits into a spontaneous cycle
- Less stressful
- No cancellation/LH surge with antagonist
- Effective alternative

Time for a re-think?

- Revival of natural cycle IVF
- Concept of modified natural cycle IVF
- Development of protocols for Mild IVF
- Concerns about conventional stimulation IVF
Conventional stimulation (downregulation & high stimulation) approaches:

- Complex /unphysiological/unnecessary/unpleasant
- Time consuming (up to 4-5 weeks)
- High costs (direct and indirect)
- Patient discomfort (prolonged injections)
- Menopausal symptoms, Headaches
- Supra-physiological steroid levels
- OHSS
- Thrombo-embolism
- Increase in chromosome abnormalities in oocytes & embryos
- Adverse endometrial conditions
- Long-term health consequences
- High drop-out rates (psychological burden)

Development of Superovulation IVF protocols

- To block premature LH surge
- To avoid cancellation of cycles
- To plan weekly schedules in clinics
- Due to relative inefficiency of single embryo transfer
- To allow multiple fresh embryo transfer

Why Now?

- Single Embryo Transfer
- Clinical availability of antagonists
- Advances in Endocrinology
- Latest Ultrasound Technology
- Improved Embryology
- Concerns about embryo & endometrial quality
- Cancer survivors requiring ART
- “Cost” of conventional IVF
- Increased demand in public health service
Natural/Modified natural cycle IVF:

**Patient selection - Current practice**
- In cancer patients & those with family H/O cancer
- Poor responders
- Older women
- Failed implantation
- With severe endometriosis
- For those who want to avoid drugs

**Monitoring & Optimisation of cycles**
- Normal cycle length
- Follicular-Endometrial synchronisation
- Alternate ovulation
- Single ovary

Synchronising Follicular & Endometrial growth & maturity

- Growth of follicle & Thickness of endometrium (early scan)

- Volume & follicular blood flow and Endometrial morphology & blood flow

- Peri-ovulatory follicle, Endometrial morphology & cervical mucus
Revival of Natural cycle IVF

- 44 cycles
- 33 women (26-36 years)
- Single dose Cetrorelix & HMG (4.7±1.4 amps)
- 4 cycles cancelled
- 40 oocyte collections
- 10 cycles with no oocytes
- 22 embryo transfers
- 7 clinical pregnancies
- 32% clinical pregnancy per ET
- 17.5% clinical pregnancy per oocyte collection

Rongieres-Bertrand C et al Human Repro 1999;14 (3): 683-8

Natural Cycle IVF

Cumulative Conception & Live birth Rates:
Nargund et al Human Reprod 2001
-52 women &181 cycles (3.49 cycles/patient)
-Life table analysis
After 4 successive cycles of treatment
Cumulative probability of pregnancy -46%
Cumulative probability of Live birth -32%
Natural Cycle IVF


Conclusions:
1. For maximum effectiveness, must be offered as a series of treatment cycles
2. Safer, less stressful and can be offered over consecutive cycles
3. Can be offered at ~23% of the cost of stimulated cycle

Natural cycle IVF: Cost Effectiveness Analysis

  240 cycles: 12% clinical pregnancy/cycle
  Despite the high failure rate at each step in the process, natural cycles are more cost-effective than stimulated cycles which incur an incremental cost per live birth of $48,000. Natural cycles offer a low-cost alternative that may be more accessible to patients
  181 cycles: Cumulative LBR -32% (4 cycles)
  Natural cycle IVF can be offered at 23% cost of stimulated cycle

Modified Natural Cycle IVF

- Feldman B et al: Gynae Endo 2001
- Ubaldi FM : RBM online 2005
  - Favourable in poor responders & failed implantation
  - The use of antagonists did not change intrafollicular VEGF/Inhibin A levels
Natural cycle IVF: In Poor Responders

- Prospective study
- 22 poor responders over 1 year
- 44 NCIVF and 55 SIVF cycles
- 82% had one oocyte collected
- 41% had at least 1 cycle with ET
- 9% had a live birth

Results of NCIVF & SIVF comparable
Feldman et al: Gynae Endocrinology 2001

Semi-Natural IVF: In Poor prognosis patients

- Prospective study - 133 cycles
- Altered ovarian status & Implantation failure
- 66 patients (AOS - 47; IF - 19)
- OPU rate (81.2%; 61.1%)
- Clinical pregnancy rate/OPU (15.4%; 16.6%)


Modified Natural cycle IVF: In Poor Responders

- 540 cycles
- Retrospective evaluation
- MNIVF vs Antagonist SIVF vs LongSIVF
- 52 vs 200 vs 288 cycles
- 1.4 vs 2.3 vs 2.5 oocytes
- 10% vs 14.3% vs 6.75% implantation
- 10.2% vs 7.4% vs 10.6% pregnancies

Elizur et al: Assist Reprod Genetics 2005
**Natural cycle IVF: In Poor Responders**

- 294 patients & 500 consecutive cycles
- ≤ 35: 36-39: ≥40 years old
- 18.1%: 11.7%: 5.8% pregnancy/cycle
- 29.2%: 20.6%: 10.5% pregnancy/ET
- 31.7%: 20.3%: 10.5% pregnancy/pt

NCIVF is an effective treatment.

*Schimberni et al: Fertil Steril 2008*

---

**Semi-Natural Cycle IVF**

*Pelinck MJ (Netherlands): Human Reprod 2005*

- Late follicular start FSH/Antagonist
- 50 patients/119 cycles (2.4 cycles/pt)
- 52 Embryo Transfers
- 17 ongoing pregnancies
- PR = 32.7%/ET
- Cumulative ongoing pregnancy rate
- After 3 cycles: 34%
- Live Birth Rate per patient: 32%

---

**Modified Natural cycle IVF: Cumulative pregnancy rates**

- 268 patients with sequential treatment
- MNC IVF followed by COS IVF
- Time to pregnancy - 28.8 weeks
- 9 cycles of MNC followed by COSIVF
- Cumulative ongoing pregnancy 56.7%
- Cumulative LBR 50% per patient

*Sequential treatment is patient-friendly, low-risk & has low twin pregnancy rate*

*Pelinck et al: Hum Reprod 2008*
Natural /Modified Natural cycle IVF/ICSI: In cancer risk women

- In BRCA1 & BRCA2 carriers
- H/O breast tumours
- Other oestrogen dependent tumours
- Prior to chemotherapy in other cancers

An effective & safe option
Dor J: NCIVF abstracts:2006

Natural cycle IVF with IVM: A New approach?

- In ovulatory Normal & PCO women
- hCG 10,000 IU
- 3 women
- 3 pregnancies
- 2 live births
Chain RC et al : Fertil Steril 2004
- 350 cycles
- 262 women
- 15.2% ongoing pregnancy rate
Benkhalifa M et al:RBM Online 2009

Natural/Modified Natural cycle IVF: Patient opinions

Despite cancellations & lower success rates per cycle, women prefer:
- Natural selection
- Simplicity & short duration
- Treatment fitted in their spontaneous menstrual cycles
- No/Low hormone strategy
- No/Few injections
- No/Few side effects
- Fewer visits/blood tests
- No/less interference with professional/social life

Hojaard et al,Hum Reprod 2001
Norman A & Nargund G (MSc Thesis) 2004
Pistorius EF et al ,Hum Fertil 2006
Seddan E et al, RBM Online 2006 (French data)
De clerck C et al ,Hum Reprod 2007
Verberg MF et al,Hum Reprod 2008
What are the priorities for “results” of IVF?

For the Patient
- No side effects
- No OHSS
- Less interference
- Low cost
- No long-term concerns
- Healthy mother & Child

For the Service & State
- Low Cost/Economic loss
- Social responsibility
- No multiple pregnancy
- No OHSS & future risks
- Healthy mother & child
- Suitable for developing & developed world

Safety and Comfort

Quality NOT Quantity

Mild Vs Standard Strategy

Mild Strategy
- 444 cycles
- SET
- Term live birth rate 43.4%
- OHSS -1.4%
- Mean cycle -2.3

Standard Strategy
- 325 cycles
- DET
- Term live birth rate 44.7%
- OHSS – 3.7%
- Mean cycle – 1.7

Natural cycle IVF:
Is it effective & cost-effective?

- Yes. For selected groups of patients

For a wider application using public purse:
Well designed, large scale, randomised, controlled trials are required using different methods of stimulation.

- Mild IVF would be an acceptable future strategy for wider application
References


References (continued)


References (continued)

References (Continued)

14. Dor J: Abstract Book 2006; ISMAAR Congress (www.ismaar.org)

References (continued)

Individualising ovarian stimulation for IVF

Anders Nyboe Andersen, Professor
The Fertility Clinic, Copenhagen University Hospital, Righospitalet, Denmark

Disclosure of conflicts of interest.
Have done RCT w/ Merck Serono, Organon, Ferring, MediCult
Have received educational grants for ph.d students from Merck Serono, Organon and Ferring

Learning objectives

• That a number of variables can be used to calculate/construct gonadotropin dosage nomograms

• That we may do controlled ovarian stimulation with a "conventional", "mild" or "appropriate" (individual) approach

• That individually based dosage regiments do give a significantly more favourable oocyte distribution which may have clinical benefits.

Ovarian stimulation with gonadotrophins

What are our key concerns?

• Ovulation induction in anovulatory patients
  – Defining threshold dose that induces maturation of a single dominant follicle

• Controlled ovarian stimulation for IUI in ovulatory patients
  – Defining a dose that is just above the threshold in order to induce growth of two (or three) follicles

• Controlled ovarian stimulation for IVF
  – Defining the appropriate dose well above the threshold according to your target
    • Conventional IVF – long and short
    • Mild IVF
What is our key concern?

What are our key concerns?

Li, 23/01/2008
The FSH dose and recruitable follicles

What determines the ovarian follicular response

The number of recruitable follicles
Their sensitivity to FSH
The dose of FSH
The bioavailability of FSH

The ovary holds the key to stimulation strategies

- **THE OVARY**
  - AFC
  - Volume
- **Clinical**
  - Age, reflects AF
  - Cycle length, reflects AF
- **Endocrine**
  - FSH, reflects AF and
  - AMH reflects preantral and small AF
  - (FSH receptor polymorphism)
- **BODY WEIGHT**
  - BMI - Bioavailability
Slide 4

P5  The FSH dose and the recruitable follicles to The FSH dose and recruitable follicles
Li; 23/01/2008

Slide 5

P7  What does ++++ refer to?
Li; 23/01/2008

Slide 6

P7  What does ++++ refer to?
Li; 23/01/2008
Controlled ovarian stimulation for IVF/ICSI

• The concept of a standard dose for a standard patient
    • ‘Standard’ patient
      – Below 40 years of age
      – Regular menstrual cycle between 21–35 days
      – Two ovaries
      – Normal basal FSH level
    • ‘Standard’ dose
      – Range from 100–250 IU/day

Controlled ovarian stimulation for IVF/ICSI

• Defining the appropriate dose well above the threshold according to your target
  • Conventional IVF – long and short
  • Mild IVF

In brief….

• What is the optimal starting FSH dose?
• Predictive factors and models
• Personalizing the FSH dose?
• Personalizing the protocol and the FSH dose?
• Future prospects
### Prospective studies – agonists

<table>
<thead>
<tr>
<th>Ref</th>
<th>Age</th>
<th>Dose / IU</th>
<th>Nr. cycles</th>
<th>Oocytes (mean)</th>
<th>Pregnancy rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Out 2001</td>
<td>18-37</td>
<td>100 vs. 200</td>
<td>91 vs. 66</td>
<td>6.7 vs 12</td>
<td>NS</td>
</tr>
<tr>
<td>Out 2000</td>
<td>18-39</td>
<td>150 vs. 250</td>
<td>67 vs. 73</td>
<td>9.1 vs. 10.6</td>
<td>NS</td>
</tr>
<tr>
<td>Out 2000</td>
<td>18-39</td>
<td>100 vs. 200</td>
<td>141 vs. 94</td>
<td>6.2 vs. 10.6</td>
<td>NS</td>
</tr>
<tr>
<td>Lat Am 2000</td>
<td>30-39</td>
<td>100 vs. 200</td>
<td>201 vs. 203</td>
<td>9.9 vs. 10.2</td>
<td>NS</td>
</tr>
<tr>
<td>Yong 2003</td>
<td>23-41</td>
<td>150 vs. 225</td>
<td>60 vs. 43</td>
<td>6.3 vs 8.3</td>
<td>NS</td>
</tr>
</tbody>
</table>

### Prospective studies – antagonists

<table>
<thead>
<tr>
<th>Ref</th>
<th>Age</th>
<th>Dose / IU</th>
<th>Nr. cycles</th>
<th>Oocytes (mean)</th>
<th>Pregnancy rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wikland 2001</td>
<td>20-39</td>
<td>150 vs. 225</td>
<td>60 vs. 60</td>
<td>9.0 vs 11*</td>
<td>NS</td>
</tr>
<tr>
<td>Out 2004</td>
<td>18-39</td>
<td>150 vs. 200</td>
<td>131 vs. 126</td>
<td>10.8 vs 11.9</td>
<td>NS</td>
</tr>
</tbody>
</table>

* p < 0.05

### Why individual stimulation?

"Unexpected" low response  "Unexpected excessive response"
### Variability of ovarian response

<table>
<thead>
<tr>
<th>IU</th>
<th>100 IU Range</th>
<th>200 IU Range</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oocytes range</td>
<td>1-29</td>
<td>3-30</td>
<td>Out 1999</td>
</tr>
<tr>
<td></td>
<td>1-30</td>
<td>1-40</td>
<td>Out 2001</td>
</tr>
</tbody>
</table>

### Variability of ovarian response

<table>
<thead>
<tr>
<th>IU</th>
<th>150 IU Range</th>
<th>250 IU Range</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oocytes range</td>
<td>1-24</td>
<td>1-60</td>
<td>Out 2000</td>
</tr>
<tr>
<td></td>
<td>1-31</td>
<td>1-35</td>
<td>Out 2001</td>
</tr>
</tbody>
</table>

Let’s be honest: ‘Controlled ovarian stimulation’ is quite often rather ‘uncontrolled’
The concept

The number of retrieved oocytes in relation to pregnancy rate per started

Harrison et al. 2001

- First RCT attempting to individualize the dose according to the basal FSH level (n=345)
- Basal FSH < 8.5 IU/l randomized to receive 150 or 200 IU/day (146 vs. 151)
- Basal FSH > 8.5 IU/l randomized to receive 300 or 400 IU/day (24 vs. 24)
- Outcome measures – efficacy of gonadotropin therapy
  - Doses adjustments on day 5 of stimulation
  - Duration of stimulation
  - Total dosage of FSH
Harrison et al. 2001 - results

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starting dose</td>
<td>150 IU</td>
<td>200 IU</td>
</tr>
<tr>
<td>Starting number</td>
<td>n=126</td>
<td>n=200</td>
</tr>
<tr>
<td>Oocytes retrieved</td>
<td>Median 10, Range 3-27</td>
<td>Median 11, Range 3-32</td>
</tr>
<tr>
<td>% of pregnancies per transfer (%)</td>
<td>29(26)</td>
<td>31(27)</td>
</tr>
</tbody>
</table>

Response prediction study - suggestion of a FSH dosage nomogram

- 145 1st IVF/ICSI cycle “standard” patients
- Down regulation with long protocol
- Starting dose of rFSH of 150 IU/day during the first week of treatment

Predictive factors
- Age
- Weight
- BMI
- Smoking habits
- Cycle length
- AFC
- Total ovarian volume
- Power Doppler (score allocation)
- Endocrine markers: FSH, LH, estradiol, testosterone and inhibin B

Significant predictors of number of retrieved oocytes in bivariate linear regression

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Regression coefficient</th>
<th>Adjusted R²</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.182</td>
<td>0.026</td>
<td>0.030</td>
</tr>
<tr>
<td>Cycle length</td>
<td>0.244</td>
<td>0.053</td>
<td>0.003</td>
</tr>
<tr>
<td>Smoking status</td>
<td>0.226</td>
<td>0.044</td>
<td>0.007</td>
</tr>
<tr>
<td>Serum FSH</td>
<td>0.188</td>
<td>0.029</td>
<td>0.024</td>
</tr>
<tr>
<td>Serum LH</td>
<td>0.174</td>
<td>0.023</td>
<td>0.038</td>
</tr>
<tr>
<td>Inhibin B</td>
<td>0.195</td>
<td>0.031</td>
<td>0.020</td>
</tr>
<tr>
<td>Ovarian volume</td>
<td>0.376</td>
<td>0.136</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AFC</td>
<td>0.554</td>
<td>0.302</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total Doppler score</td>
<td>0.476</td>
<td>0.221</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Popovic-Todorovic et al. 2003
Significant predictors of number of retrieved oocytes in backward stepwise regression analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Standardised coefficient B</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total antral follicles</td>
<td>0.424</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total Doppler score</td>
<td>0.247</td>
<td>0.001</td>
</tr>
<tr>
<td>Smoking status</td>
<td>0.163</td>
<td>0.015</td>
</tr>
</tbody>
</table>

Model accounts for 38% variability of the number of retrieved oocytes


rFSH dosage nomogram (1)

<table>
<thead>
<tr>
<th>Total number of antral follicles 10mm</th>
<th>rFSH score IU/day</th>
<th>rFSH starting dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;15</td>
<td>0</td>
<td>50</td>
</tr>
<tr>
<td>15-25</td>
<td>0</td>
<td>60</td>
</tr>
<tr>
<td>&gt;25</td>
<td>0</td>
<td>60</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total ovarian volume 2-5</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;9 ml</td>
<td>0</td>
</tr>
<tr>
<td>9-13 ml</td>
<td>60</td>
</tr>
<tr>
<td>&gt;13 ml</td>
<td>60</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total Doppler score 2-5</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>30</td>
</tr>
<tr>
<td>3-4</td>
<td>20</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>6</td>
<td>0</td>
</tr>
</tbody>
</table>

rFSH dosage nomogram (2)

<table>
<thead>
<tr>
<th>Age</th>
<th>rFSH score IU/day</th>
<th>rFSH starting dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;35</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>30-35</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Smoking habits/ cigarettes per day</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non smoker</td>
<td>0</td>
</tr>
<tr>
<td>≤10</td>
<td>10</td>
</tr>
<tr>
<td>&gt;10</td>
<td>20</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total rFSH score (sum of scores) same as dose IU/day</th>
<th>Score</th>
</tr>
</thead>
</table>
Individual vs. standard rFSH dose RCT

- 232 1st IVF/ICSI treatment cycle standard patients
- Long agonist protocol
- Individual rFSH dose based on nomogram range 100-250 IU/day vs. standard dose of 150 IU/day
- Study end-points
  - To test whether rFSH dosage nomogram predicts the ovarian response
  - To test whether use of the nomogram to dose the patients gives clinical benefits in relation to a more appropriate ovarian response, defined as retrieval of between 5-14 oocytes

Does the model predict the response?

Conclusions on RCT

- The use of the dosage nomogram predicted the ovarian response
- Individual dosage regimen in a well-defined ‘standard’ patient population increased the proportion of appropriate ovarian responses
- A higher ongoing pregnancy rate was observed in the individual dose group

Risk charts to identify low and excessive responders among first cycle IVF/ICSI standard patients

Could it be that the parameters we use to identify the clinically relevant patient groups – low vs high responders – are different

A "risk chart" may be another possibility to identify those patients where you decide to modify the "standard dose" in your clinic.
Normogram to Nomogram
Li; 23/01/2008
Material and Methods

- "Standard" patients (n=276)
- 150 IU rFSH/day
- Low responders:
  - < 8 follicles ≥11 mm
- Excessive responders:
  - > 20 follicles ≥11 mm

Ovarian response in 276 standard patients
150 iu/day - follicles

<table>
<thead>
<tr>
<th>Follicles</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>33 (12)</td>
</tr>
<tr>
<td>Appropriate</td>
<td>160 (58)</td>
</tr>
<tr>
<td>Excessive</td>
<td>83 (30)</td>
</tr>
</tbody>
</table>

 Freiesleben et al, submitted

Risk - low response

- Logistic regression analysis
- 1000 bootstrap cross-validations
Risk – excessive response

Risk charts

- Risk charts allows clinicians to be guided on the percentage risk of either low or excessive response and may be used as a guide to increase or decrease the standard dose used in the clinic

The Serono database study (CONSORT)

- Predictive factors and a corresponding treatment algorithm for COS in patients with rFSH during ART procedures
- An analysis of 1378 patients (<35 years)
- Pooling of 11 trials
- Four factors remained significant during backward stepwise regression:
  - Basal FSH
  - BMI
  - Age
  - AFC

The Serono database study

- A dosing nomogram was developed, based on a weighed use of these four factors
- A computer model was developed to suggest FSH doses, based on clinical decisions and a target of stimulation of 11 oocytes
- In an uncontrolled clinical study the following distribution was found:

<table>
<thead>
<tr>
<th>Dose (IU/day)</th>
<th>75</th>
<th>112</th>
<th>150</th>
<th>187</th>
<th>225</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>48</td>
<td>45</td>
<td>34</td>
<td>24</td>
<td>10</td>
</tr>
<tr>
<td>Oocytes</td>
<td>8.3</td>
<td>9.6</td>
<td>12.1</td>
<td>12.7</td>
<td>8.3</td>
</tr>
</tbody>
</table>

Olivennes et al., RBMONline, 2009, 18, 195-204

FSH dosing based on AMH
(Nelson et al., 2007 and 2009)

Determination of pragmatic clinical cut-offs of AMH levels
- <1.0 pmol/l
- 1 to <5.0 pmol/l
- 5.0 to <15 pmol/l
- 15 to <25 pmol/l

Table 1: Deployment of GnRH analogues and doses of follicle stimulating hormone in the groups categorized by anti-Müllerian hormone in the two centres

<table>
<thead>
<tr>
<th>AMH group (pmol/l)</th>
<th>Centre 1</th>
<th>GnRH analogues</th>
<th>Centre 2</th>
<th>GnRH analogues</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1.0</td>
<td>375</td>
<td>[Inhibit]</td>
<td>375</td>
<td>[Inhibit]</td>
</tr>
<tr>
<td>1 to &lt;5.0</td>
<td>35</td>
<td>[Inhibit]</td>
<td>35</td>
<td>[Inhibit]</td>
</tr>
<tr>
<td>5.0 to &lt;15</td>
<td>35</td>
<td>[Inhibit]</td>
<td>35</td>
<td>[Inhibit]</td>
</tr>
<tr>
<td>≥15</td>
<td>35</td>
<td>[Inhibit]</td>
<td>35</td>
<td>[Inhibit]</td>
</tr>
</tbody>
</table>

AMH, anti-Müllerian hormone; GnRH, gonadotropin-releasing hormone.
AMH – as a single dosing parameter

- This was a non-controlled non-randomised study

1. It seems safe to dose aggressively with AMH < 5 pmol/l
2. Dosing with 150 iu/day in patients with AMH > 15 pmol/l lead to 20/148 (14%) patients who were hospitalised due to OHSS

Nelson et al., 2009 - dosing and treatment strategies

<table>
<thead>
<tr>
<th>AMH group (pmol/l)</th>
<th>Centre 1</th>
<th>Centre 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FSH daily</td>
<td>GnRH analogue</td>
</tr>
<tr>
<td>&lt; 1.0</td>
<td>375</td>
<td>Antagonist</td>
</tr>
<tr>
<td>1.0 to &lt;5</td>
<td>375</td>
<td>Agonist</td>
</tr>
<tr>
<td>5.0 to &lt;15</td>
<td>225</td>
<td>Agonist</td>
</tr>
<tr>
<td>≥ 15.0</td>
<td>150</td>
<td>Agonist</td>
</tr>
</tbody>
</table>

Nelson et al., 2009 AMH category : 1-<5 pmol/l

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Centre 1</th>
<th>Centre 2</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protocol</td>
<td>N=370</td>
<td>N=168</td>
<td></td>
</tr>
<tr>
<td>Patients</td>
<td>74 (20%)</td>
<td>61 (36.3%)</td>
<td></td>
</tr>
<tr>
<td>Age (mean)</td>
<td>37.3</td>
<td>39.0</td>
<td>0.005</td>
</tr>
<tr>
<td>AMH (median)</td>
<td>2.6</td>
<td>3</td>
<td>0.4</td>
</tr>
<tr>
<td>No of oocytes</td>
<td>5 (3-7)</td>
<td>5 (4-8)</td>
<td>0.001</td>
</tr>
<tr>
<td>Low oocyte yield (%)</td>
<td>7/55 (12.7%)</td>
<td>20/58 (35.7%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Frozen all (%)</td>
<td>1 (1.4%)</td>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>Cancelled cycles (%)</td>
<td>19 (25.7%)</td>
<td>5 (6.2%)</td>
<td>0.005</td>
</tr>
<tr>
<td>Clinical pregnancy rate per cycle (%)</td>
<td>6 (8.1%)</td>
<td>9 (14.7%)</td>
<td>0.27</td>
</tr>
</tbody>
</table>
Nelson et al., 2009 AMH category : 5 - <15 pmol/l

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Centre 1 (N=370)</th>
<th>Centre 2 (N=168)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>120 (34.8%)</td>
<td>73 (44.4%)</td>
<td>&gt;0.0001</td>
</tr>
<tr>
<td>Age (mean)</td>
<td>35.1</td>
<td>37</td>
<td>0.001</td>
</tr>
<tr>
<td>AMH (median)</td>
<td>9.2</td>
<td>6.7</td>
<td>0.001</td>
</tr>
<tr>
<td>No of oocytes</td>
<td>10 (7-15)</td>
<td>8 (4-10)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Low oocyte yield n (%)</td>
<td>1 (10.1%)</td>
<td>0 (4.4%)</td>
<td>0.66</td>
</tr>
<tr>
<td>Freeze all n (%)</td>
<td>1 (1.4%)</td>
<td>0</td>
<td>0.004</td>
</tr>
<tr>
<td>Hospitalised for OHSS</td>
<td>0 (0%)</td>
<td>1 (0.6%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Cancellation cycle n (%)</td>
<td>3 (2.3%)</td>
<td>0 (0.2%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Clinical pregnancy rate per cycle n (%)</td>
<td>20 (13.2%)</td>
<td>24 (15.8%)</td>
<td>0.13</td>
</tr>
</tbody>
</table>

Nelson et al., 2009 AMH category : ≥15 pmol/l

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Centre 1 (N=370)</th>
<th>Centre 2 (N=168)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>148 (40.1%)</td>
<td>34 (20.2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age (mean)</td>
<td>32.8</td>
<td>32</td>
<td>0.94</td>
</tr>
<tr>
<td>AMH (median)</td>
<td>22.4</td>
<td>25.8</td>
<td>0.018</td>
</tr>
<tr>
<td>No of oocytes</td>
<td>14 (10-19)</td>
<td>10 (8.5-13.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Low oocyte yield n (%)</td>
<td>4/144 (2.8%)</td>
<td>1/33 (3.0%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Freeze all n (%)</td>
<td>27 (18.2%)</td>
<td>0 (0%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Hospitalised for OHSS</td>
<td>20 (13.9%)</td>
<td>0 (0%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Cancellation cycle n (%)</td>
<td>4 (2.7%)</td>
<td>1 (0.6%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Clinical pregnancy rate per cycle n (%)</td>
<td>47 (31.8%)</td>
<td>21 (61.7%)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Prediction of an optimal ovarian response in ovulatory patients stimulated with low-dose rFSH and GnRH antagonist protocol

An integrated low-dose approach for IUI / IVF

Freiesleben et al.Reprod Biomed Online. 2008
Treatment regimen

Day 2 or 3 of menses

Flexible starting day antagonist

At least one follicle of 14 mm

rFSH 75 IU/day, cd 3–8

After Day 8, 50–150 IU/day

IUI

IVF

Number of follicles

Number of follicles ≥15 mm on the day of hCG

Predictors of the number of mature follicles (>15 mm)

- Simple linear regression:
  - Body weight p<0.005
  - BMI p<0.03
  - Ovarian volume p=0.04
  - AFC p=0.01

- Multiple linear regressions identified two independent predictors:
  - Body weight p=0.001
  - AFC p=0.004

**Converted to IVF**
Third bullet point amended (previously 9<sup>1</sup>)
Li; 23/01/2008
A RFSH dosing nomogram for IUI based on the 2 independent variables: Body weight and AFC

![Nomogram for rFSH starting dose in ovulatory IUI patients](image)

- 40
- 45
- 50
- 50IU
- 30% risk >3 foll.
- 60% risk 1. follicle
- 0
- 5
- 10
- 15
- 20
- 25
- 30
- 35
- 45 55 65 75 85 95 105
- Weight (kg)

A RCT with and FSH dosing in an antagonist protocol for IUI/IVF

- 258 Couples with unexplained, mild male factor, mild endometriosis
- Indication for IUI – first FSH cycle
- Randomised to
  1) Standard FSH (75 iu/day), n=113
  2) Individual (50 -100iu/day) according to nomogram, n=115

Freiesleben et al, Submitted

A RCT with and FSH dosing in an antagonist protocol for IUI/IVF

- Follicles > 14 mm
  - Individual
    - 1: 23%
    - 2-3: 70%*
    - > 3: 7%
  - Standard
    - 1: 33%
    - 2-3: 56%*
    - > 3: 11%

*difference 14.3 CI 2-26, P<0.05)

Ongoing preg/cycle Indiv: 20.4% vs Stand: 18.4%
Multiples: Indiv: 4.3 vs Stand: 23.8%

Freiesleben et al, Submitted
An integrated low-dose approach for IUI / IVF

What can be achieved with a low-dose "integrated" IUI / IVF Protocol?

<table>
<thead>
<tr>
<th></th>
<th>Cycles</th>
<th>Live Preg/cycle</th>
<th>Twins</th>
<th>Triplets</th>
</tr>
</thead>
<tbody>
<tr>
<td>IUI</td>
<td>344 (92%)</td>
<td>75/344 (22%)</td>
<td>9 (12%)</td>
<td>2 (2.7%)</td>
</tr>
<tr>
<td>IVF</td>
<td>31 (8%)</td>
<td>10/31 (32%)</td>
<td>1 (10%)</td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>375</td>
<td>85/375 (23%)</td>
<td>10 (12%)</td>
<td>2 (2.3%)</td>
</tr>
</tbody>
</table>

Final conclusion

- An estimated 50% of the world’s COS for ART are first cycles with uncertain responses.
- Considering the number of published papers on COS for IVF/ICSI, it is amazing that the knowledge we have on response predictive factors has only sporadically been developed into clinically useful models to guide us on the key issue of appropriate gonadotrophin dosing.
- Dosing models based on simple clinical, sonographic and endocrine tests should be tested in RCTs.
- We need these models for long and short protocols, and for conventional and mild stimulation – different targets.
References

Olivennes et al. RBMOnline 2009: 16; 195-204.
Single embryo transfer: where are we?

Prof. Dr. Petra De Sutter
Div. Reproductive Medicine, Dept Ob/Gyn
University Hospital Ghent / University Ghent

ESHRE PCC - Mild stimulation strategies in IVF

Disclosure

Institutional research and/or traveling grants have been received in 2009 by the following companies:

- Merck-Serono
- Ferring
- Cook

Learning objectives

After this lecture, participants should be able to

- Understand the risks and complications of multiple pregnancies
- Describe the patients who are twin prone and candidates for elective SET
- Understand the conclusions from randomized trials comparing SET with DET
- Have an idea of the worldwide application of the SET strategy to date
- Compare SET with DET from a health-economic perspective
Multiple embryo transfer to increase the chance for a (successful?) pregnancy

<table>
<thead>
<tr>
<th>No. of embryos transferred</th>
<th>Pone (%)</th>
<th>Pmult (%)</th>
<th>Pnone (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>0</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>27.5</td>
<td>2.5</td>
<td>34</td>
</tr>
</tbody>
</table>

Trade-off of the probability of no pregnancy versus a multiple pregnancy as the number of embryos transferred increases, assuming a 10% implantation rate

1 embryo transferred:
* Pone = 10%
* Pmult = 0%
* Pnone = 90%

3 embryos transferred:
* Pone = 27.5%
* Pmult = 2.5%
* Pnone = 70%

Trade-off of the probability of no pregnancy versus a multiple pregnancy as the number of embryos transferred increases, assuming a 30% implantation rate

1 embryo transferred:
* Pone = 30%
* Pmult = 0%
* Pnone = 70%

3 embryos transferred:
* Pone = 44%
* Pmult = 22%
* Pnone = 34%

Martin and Welch, FS 1998
Trade-off of the probability of no pregnancy versus a multiple pregnancy as the number of embryos transferred increases, assuming a 50% implantation rate.

1 embryo transferred:
* \( P_{\text{one}} = 50\% \)
* \( P_{\text{mult}} = 0\% \)
* \( P_{\text{none}} = 50\% \)

2 embryos transferred:
* \( P_{\text{one}} = 50\% \)
* \( P_{\text{mult}} = 25\% \)
* \( P_{\text{none}} = 25\% \)

Martin and Welch, FS 1998

<table>
<thead>
<tr>
<th>IR(%)</th>
<th>n embr</th>
<th>( P_{\text{one}} )</th>
<th>( P_{\text{mult}} )</th>
<th>( P_{\text{none}} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>19</td>
<td>0.38</td>
<td>0.25</td>
<td>0.38</td>
</tr>
<tr>
<td>10</td>
<td>9</td>
<td>0.39</td>
<td>0.23</td>
<td>0.39</td>
</tr>
<tr>
<td>15</td>
<td>6</td>
<td>0.40</td>
<td>0.22</td>
<td>0.38</td>
</tr>
<tr>
<td>20</td>
<td>4</td>
<td>0.41</td>
<td>0.18</td>
<td>0.41</td>
</tr>
<tr>
<td>25</td>
<td>3</td>
<td>0.42</td>
<td>0.16</td>
<td>0.42</td>
</tr>
<tr>
<td>30</td>
<td>3</td>
<td>0.44</td>
<td>0.22</td>
<td>0.34</td>
</tr>
<tr>
<td>35</td>
<td>2</td>
<td>0.46</td>
<td>0.12</td>
<td>0.42</td>
</tr>
<tr>
<td>40</td>
<td>2</td>
<td>0.48</td>
<td>0.16</td>
<td>0.36</td>
</tr>
<tr>
<td><strong>40</strong></td>
<td><strong>1</strong></td>
<td><strong>0.40</strong></td>
<td><strong>0.00</strong></td>
<td><strong>0.60</strong></td>
</tr>
<tr>
<td>45</td>
<td>2</td>
<td>0.50</td>
<td>0.20</td>
<td>0.30</td>
</tr>
<tr>
<td>50</td>
<td>1</td>
<td>0.50</td>
<td>0.00</td>
<td>0.50</td>
</tr>
</tbody>
</table>

Pregnancy outcomes at various implantation rates if the number of embryos transferred is selected to maximize the \( P \) (singl. preg.).

The problem of multiple pregnancies.

Twins


Triplets

Cumulative singleton gestation weeks for IVF & ICSI <= 42 weeks

Gestation weeks


Cumulative twin gestation weeks for IVF & ICSI <=42 weeks

Gestation weeks

Cumulative twin gestation weeks: 45, 58, 107, 118, 219, 235, 331, 451, 683, 883, 1368, 1843, 2928, 3906, 3985, 1159, 402, 52, 17

Cumulative triplet gestation weeks <= 42 weeks

Gestation weeks

Attractive triplet gestation weeks: 5, 5, 14, 18, 31, 65, 84, 96, 158, 234, 283, 209, 128, 29, 15, 4, 3, 0, 2

Maternal Morbidity

Multiple (n=44,674) vs singleton pregnancy (n=165,188)

RR (95% CI)

<table>
<thead>
<tr>
<th>Condition</th>
<th>RR 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-eclampsia</td>
<td>2.8 (2.7-2.9)</td>
</tr>
<tr>
<td>Gestational diabetes</td>
<td>1.1 (1.9-1.2)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>3.7 (2.3-5.8)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>12.9 (2.7-62.3)</td>
</tr>
<tr>
<td>Venous thromboembolism</td>
<td>2.7 (2.0-3.5)</td>
</tr>
<tr>
<td>Pulmonary oedema</td>
<td>7.1 (4.5-11.3)</td>
</tr>
<tr>
<td>Post partum haemorrhage</td>
<td>1.9 (1.8-1.9)</td>
</tr>
<tr>
<td>Caesarean delivery</td>
<td>2.2 (2.1-2.2)</td>
</tr>
<tr>
<td>Hysterectomy</td>
<td>2.3 (1.7-3.2)</td>
</tr>
</tbody>
</table>

Walker et al, BJOG, 2004
Elective single embryo transfer

Reducing the number of twin births

Single embryo transfer in selected cases

Twin-prone patient selection
Embryo selection

The pioneers


- In women with medical contraindications for MP (hemi-uterus, isthmic insufficiency, IDDM,...) The first clinical data

Pregnancy rate
- 74 elective SET 29.7% + FER = 47.3%
- 94 non-elective SET 20.2%
- 742 two-embryo transfers 29.4% 24% twins
Patient Selection

- Female age < 35-37 years of age
- IVF cycle number 1st and 2nd
- No. of good quality embryos available ≥ 2
- Tubal factor infertility (absent)

Univariate and multivariate analysis of 661 cycles

+ - IVF as method of fertilization
  - No of 4-cell embryos on day 2
  - FSH per oocyte retrieved

RCT: SET versus DET
in pts. <34y, 1st trial, at least two TQEs

<table>
<thead>
<tr>
<th>Group</th>
<th>SET</th>
<th>DET</th>
</tr>
</thead>
<tbody>
<tr>
<td>N cycles (transfers)</td>
<td>28</td>
<td>28</td>
</tr>
<tr>
<td>N positive HCG</td>
<td>14</td>
<td>15</td>
</tr>
<tr>
<td>N clinical pregnancies</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>N ongoing pregnancies</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>N multiple pregnancies</td>
<td>1 MZ</td>
<td>6</td>
</tr>
<tr>
<td>Conception rate (%)</td>
<td>18/29 (62.1%)</td>
<td>28/36 (77.8%)</td>
</tr>
<tr>
<td>CPR (%)</td>
<td>14/29 (48.3%)</td>
<td>26/36 (72.2%)</td>
</tr>
<tr>
<td>GPR (%)</td>
<td>11/29 (37.9%)</td>
<td>24/36 (66.7%)</td>
</tr>
<tr>
<td>MPR (%)</td>
<td>11/29 (37.9%)</td>
<td>6/24</td>
</tr>
<tr>
<td>OPR (%)</td>
<td>26/36 (72.2%)</td>
<td>14/29 (48.3%)</td>
</tr>
<tr>
<td>CPR (%)</td>
<td>26/36 (72.2%)</td>
<td>14/29 (48.3%)</td>
</tr>
</tbody>
</table>

Clinical results and the Belgian model

**BELENG FUNDING REGULATION**

- Six IVF/ICSI cycles (= oocyte harvests) funded in a lifetime
- 1250 € per cycle for laboratory costs (gamete procurement and handling)
- Including cryocycles
- Up to the age of 43 years

Linked to a rational transfer strategy

<table>
<thead>
<tr>
<th>≤ 36 years</th>
<th>&gt;36 – ≤ 39 years</th>
<th>&gt;39 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st attempt ever or 1st trial after previous IVF/ICSI-delivery: always one embryo; 2nd attempt: one embryo if of sufficient quality; two if of insufficient quality; 3rd attempt: max 2 embryos.</td>
<td>1st and 2nd attempt: maximum 2 embryos; 3rd attempt: max 3 embryos.</td>
<td>No maximum number of embryos to transfer is dictated</td>
</tr>
</tbody>
</table>

CRYOCYCLLES: 1 or 2 embryos
Hum Reprod 21; 1907-11, 2006

| Table II. Outcome parameters of SET vs DET singleton pregnancies (gestational age, birthweight, preterm births and ongoing pregnancies) |
|---|---|
| SET (n = 404) | DET (n = 404) |
| Mean gestational age | 39.6 | 39.1 |
| Birthweight (grams) | 3240(1500) | 3238(1507) |
| NICU admission | 4.2% | 11.4% |
| Low birthweight | 1.8% | 11.4% |
| 1.77 (1.06-2.94) | 2.29 (1.44-3.77) |

<table>
<thead>
<tr>
<th>Obstetric and neonatal outcome after single embryo transfer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients 253 1179 with bleeding without bleeding</td>
</tr>
<tr>
<td>Database IVF/ICSI 1993 – 2002 ongoing pregnancies</td>
</tr>
<tr>
<td>Singleton pregnancies</td>
</tr>
<tr>
<td>Preterm contractions</td>
</tr>
<tr>
<td>IUGR</td>
</tr>
<tr>
<td>Intrauterine death</td>
</tr>
<tr>
<td>Cesarean section</td>
</tr>
<tr>
<td>Duration of pregnancy</td>
</tr>
<tr>
<td>Birth weight (g)</td>
</tr>
<tr>
<td>Low birth weight</td>
</tr>
<tr>
<td>2.4%</td>
</tr>
<tr>
<td>&lt;7 1 min Apgar score</td>
</tr>
<tr>
<td>&lt;7 5 min Apgar score</td>
</tr>
<tr>
<td>NICU admission</td>
</tr>
<tr>
<td>Perinatal deaths</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>First-trimester bleeding and pregnancy outcome in singletons after assisted reproduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients 253 1179 with bleeding without bleeding</td>
</tr>
<tr>
<td>% 2 nd T bleeding</td>
</tr>
<tr>
<td>% P-RDOM</td>
</tr>
<tr>
<td>% Preembryo contractions</td>
</tr>
<tr>
<td>% IUGR</td>
</tr>
<tr>
<td>% Intrauterine death</td>
</tr>
<tr>
<td>% Cesarean section</td>
</tr>
<tr>
<td>Birth weight (g)</td>
</tr>
<tr>
<td>% low birthweight</td>
</tr>
<tr>
<td>% very low birth weight</td>
</tr>
<tr>
<td>% 1 min Apgar score &lt;7</td>
</tr>
<tr>
<td>% 5 min Apgar score &lt;7</td>
</tr>
<tr>
<td>% NICU admission</td>
</tr>
<tr>
<td>% perinatal deaths</td>
</tr>
</tbody>
</table>
Not only does eSET cause less twin-related morbidity and mortality but also healthier singletons.

<table>
<thead>
<tr>
<th>Embryos</th>
<th>Total Pregnant</th>
<th>1st trim. bleeding</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>208</td>
<td>26 (12.5%)</td>
<td>182 (87.5%)</td>
</tr>
<tr>
<td>2</td>
<td>795</td>
<td>129 (18.2%)</td>
<td>666 (83.8%)</td>
</tr>
<tr>
<td>3</td>
<td>347</td>
<td>75 (21.6%)</td>
<td>272 (78.4%)</td>
</tr>
<tr>
<td>&gt; 3</td>
<td>82</td>
<td>23 (28.0%)</td>
<td>59 (72%)</td>
</tr>
</tbody>
</table>

Linear correlation between incidence of 1st trimester bleeding and number of embryos transferred.

Results of SET versus DET - Finland

<table>
<thead>
<tr>
<th>Type of transfer</th>
<th>Transfers</th>
<th>CPR/ET</th>
<th>DR/ET</th>
<th>TPR/D</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>2 embryos</td>
<td>517</td>
<td>203 (40.0)</td>
<td>160 (30.9)</td>
<td>42/160 (26.2)</td>
</tr>
<tr>
<td>compulsory SET</td>
<td>94</td>
<td>17 (18.1)</td>
<td>13 (13.8)</td>
<td>1/13 (7.7)</td>
</tr>
<tr>
<td>elective SET</td>
<td>127</td>
<td>49 (38.6)</td>
<td>34 (26.8)</td>
<td>1/34 (2.9)</td>
</tr>
</tbody>
</table>

Cryo-augmentation effect after eSET

<table>
<thead>
<tr>
<th>Type of ET</th>
<th>Transfers</th>
<th>PR</th>
<th>DR</th>
<th>Twins</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>Fresh ET</td>
<td>127</td>
<td>49 (38.6)</td>
<td>34 (26.8)</td>
<td>1 (2.9)</td>
</tr>
<tr>
<td>Frozen ET</td>
<td>129</td>
<td>39 (30.2)</td>
<td>32 (24.8)</td>
<td>4 (12.5)</td>
</tr>
<tr>
<td>1 embryo</td>
<td>46</td>
<td>8 (17.4)</td>
<td>5 (10.9)</td>
<td>0</td>
</tr>
<tr>
<td>2 embryos</td>
<td>83</td>
<td>31 (37.3)</td>
<td>27 (32.5)</td>
<td>4 (14.8)</td>
</tr>
<tr>
<td>CPR/patient</td>
<td>78</td>
<td>62.4</td>
<td>56.2</td>
<td>4 (7.6)</td>
</tr>
</tbody>
</table>

ET=embryo transfer; PR=pregnancy rate; DR=delivery rate; CPR=cumulative pregnancy rate.
Cryopreservation

• When more eSET is performed, more embryos are available for cryopreservation
• Optimal standard of success = the cumulative OPR per oocyte harvest = fresh + frozen/thawed attempts
• The more eSET the better a centre
• The more cryocycles the better the centre

Swedish Experience: 1 + 1 cryo = 2
Thurin et al., N Engl J Med 2004; 351: 2440-2442
Academic Hospital Göteborg and 10 other Scandinavian centres: RCT

Fresh DET:
* 42.9% live birth rate
* 33% twins

Fresh SET + 1 cryo-SET:
* 38.5%
* + cryo: 38.8%

Dutch experience: 2 x 1 = 1 x 2
Lukassen et al., Hum Reprod 2005; 20: 702-708 - UMC Nijmegen

<table>
<thead>
<tr>
<th>Variable</th>
<th>SET (n = 54)</th>
<th>DET (n = 55)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st cycle</td>
<td>2nd cycle</td>
<td>Cumulative</td>
</tr>
<tr>
<td>No. of subjects</td>
<td>54</td>
<td>40</td>
</tr>
<tr>
<td>Live birth (n (%))</td>
<td>44 (21)</td>
<td>30 (25)</td>
</tr>
<tr>
<td>Miscarriage (n (%))</td>
<td>6 (11)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Clinical pregnancy (n (%))</td>
<td>14 (26)</td>
<td>9 (28)</td>
</tr>
<tr>
<td>Twin birth (n (%))</td>
<td>14 (26)</td>
<td>8 (15)</td>
</tr>
<tr>
<td>Birth weight &lt; 2500 g (n (%))</td>
<td>2 (4)</td>
<td>0</td>
</tr>
<tr>
<td>Low birthweight infants (&lt;2500g) (n (%))</td>
<td>1 (2)</td>
<td>0</td>
</tr>
</tbody>
</table>
sSET irrespective of the availability of a good-quality embryo in the first cycle only is not effective in reducing overall twin pregnancy rates

INTRODUCTION: In several cases, elective single-embryo transfer (eSET) is applied to a selected group of patients based on age and the availability of a good-quality embryo. Whether or not eSET can be applied irrespective of the presence of a good-quality embryo in the first cycle to further reduce the twin pregnancy rate, remains to be elucidated.

METHODS: In patients > 38 years, two transfer strategies were compared, which differed in the first cycle only: group A (n = 140) received eSET irrespective of the availability of a good-quality embryo, and group B (n = 170) received eSET when a good-quality embryo was available, otherwise they received double embryo transfer (DET, referred to as SET/DET transfer policy). In any subsequent cycle, in both groups the SET/DET transfer policy was applied. RESULTS: After completion of their IVF treatment (including a maximum of three fresh cycles and the transfer of frozen-thawed embryos), comparable cumulative live birth rates (62.4% in group A and 68.8% in group B) and twin pregnancy rates (11% versus 3.6%) were found. However, patients in group A required significantly more fresh (25 versus 18) and frozen (0.8 versus 0.3) cycles. CONCLUSIONS: The transfer of one embryo in the first cycle, irrespective of the availability of a good-quality embryo, in all patients > 38 years, is no more effective transfer policy for reducing the overall twin pregnancy rate.
Elective single blastocyst transfer reduces twin rates without compromising pregnancy rates

**Table 1**

<table>
<thead>
<tr>
<th>Immediate clinical results from the fresh blastocyst transfers, comparing eET with elective two-embryo transfer.</th>
</tr>
</thead>
<tbody>
<tr>
<td>**</td>
</tr>
<tr>
<td><strong>Transfer procedures</strong></td>
</tr>
<tr>
<td>Gestational sac-positive pregnancies</td>
</tr>
<tr>
<td>Clinical pregnancy (60%)</td>
</tr>
<tr>
<td>Clinical pregnancy (60%)</td>
</tr>
<tr>
<td>Clinical pregnancy (60%)</td>
</tr>
<tr>
<td>Clinical pregnancy (60%)</td>
</tr>
<tr>
<td>Clinical pregnancy (60%)</td>
</tr>
<tr>
<td>Clinical pregnancy (60%)</td>
</tr>
<tr>
<td>Clinical pregnancy (60%)</td>
</tr>
</tbody>
</table>

Statistical analysis: *P* = significant. **P** = non-significant.
Introduction of SET policy

UK: Braude et al., 2007

Prerequisites for a particular centre to implement eSET

• 1. Excellent results (the better the centre, the higher % of eSET)
• 2. Willingness to decrease a very high MP rate
• 3. Willingness to invest in optimization of a freeze/thaw programme
• 4. eSET must be compatible with specific societal circumstances in which the centre works

A real-life prospective health economic study of elective single embryo transfer versus two-embryo transfer in first IVF/ICSI cycles

*Prospective non-randomized multicenter study, comparing SET with DET in good prognosis patients*

<table>
<thead>
<tr>
<th>N of transfers</th>
<th>eSET (56%)</th>
<th>DET</th>
</tr>
</thead>
<tbody>
<tr>
<td>N of transfers</td>
<td>201 (56%)</td>
<td>158</td>
</tr>
<tr>
<td>Clinical preg rate</td>
<td>83/206 (40.3%)</td>
<td>65/161 (40.4%)</td>
</tr>
<tr>
<td>Live births</td>
<td>77/206 (37.4%)</td>
<td>59/161 (36.6%)</td>
</tr>
<tr>
<td>Singletons</td>
<td>77 (100%)</td>
<td>39 (66%)</td>
</tr>
<tr>
<td>Twins</td>
<td>-</td>
<td>20 (34%)</td>
</tr>
</tbody>
</table>
This prospective health economic study shows that eSET is equally effective as but ~50% cheaper than double embryo transfer in first IVF/ICSI cycles.

Health economic comparison SET/DET and singletons/twins in DET

![Bar charts showing cost comparison between SET and DET for singletons and twins in DET.](image)

Only cases with complete data included.


A health-economic decision-analytic model comparing double with single embryo transfer in IVF/ICSI: a sensitivity analysis.

![Graph showing cost comparison between SET and DET.](image)
It can be concluded that DET is the most expensive strategy. DET is also most effective if performed in one fresh cycle. eSET is only preferred from a cost-effectiveness point of view when performed in good prognosis patients and when frozen/thawed cycles are included. If frozen/thawed cycles are excluded, the choice between eSET and DET depends on how much society is willing to pay for one extra successful pregnancy.

Conclusion: SET in whom and when?
References


16: van Montfoort AP, Fiddelers AA, Janssen JM, Derhaegh JS, Dirksen CD, Dunselman GA, Lind JA, Gerris J, Evers JL, Dumoulin JC. In unselected patients, elective single embryo transfer prevents all multiples, but results in significantly lower pregnancy rates compared with double-embryo transfer: a randomized controlled trial. Hum Reprod. 2008 Sep;23(9):2389-91.


How can we reduce the burden of treatment?

Jacky Boivin, Ph.D.
School of Psychology
Cardiff University

Disclosure

• ASRM, ESHRE and Merck-Serono jointly sponsored the FertiQoL project

Learning objectives

• Identify sources of burden in fertility treatment
• Describe psychosocial reactions during treatment and their impact on treatment outcome
• Learn general and treatment specific techniques to minimise the burden of treatment
  – Techniques for patients
  – Techniques for staff
• Gain knowledge on the effectiveness of general and treatment specific interventions on wellbeing and pregnancy rates
Causes of burden: physical and behavioral consequences

Boivin et al. Hum Reprod 1996

Causes of burden: uncertainty and harm

Boivin & Walker, ESRC, 1997

Partner distress during IVF

Boivin et al. Hum Reprod 1998
Causes of burden: Staff feedback & monitoring during IVF/ICSI

Causes of burden: Negative feedback from staff

Impact of staff feedback on emotional distress during IVF
Causes of burden: Stressful organisational care

Investigation & Initial treatment IVF/ICSI % ending treatment

5.3% - 40%
Diagnosis, IUI, DI

12.2% to 62%
IVF, ICSI, etc

Malcolm & Cummings, 2004: 16.9 - 39%
Gleicher et al. 1999: 21 - 40%
Goverde et al. 2000: 15 - 16%
Guerif et al. 2003: 5.5-25%

Olivius et al. 2004: 53.8%
Goverde et al. 2000: 42%
Osmanagaglu et al. 1999: 25-40%
Smeenk et al. 2004: 12.2-18.3%
Schroder et al. 2004: 39-62%

Psychological burden

Reason Percentage
Emotional distress & coping failure 64.3%
• Assembly-line treatment
• Never the same staff
• Clinic disorganised

Poor patient-centered care 48%
• Insufficient care of the man
• Lack of empathy
• Poor listening skills
• Unkind treatment by staff

Other “psychological” reasons:
• balancing treatment & work commitment (Osmanagaglu et al. 1999)
• distance from clinic (Malcolm et al. 2004)
• undergone agreed number of cycles (deVries et al. 1999)

Other psychological variables must be involved

• “Psychologically too stressful” (Osmanagaglu et al. 1999)
• “Psychological burden” (Olivius et al. 2004)
• “Psychological reasons” (Smeenk et al. 2004)
• “Emotional costs” (Hammarberg et al. 2001)
• “Reached limit” (Brew et al. 2001)
• “Emotional exhaustion” (Daniluk, 2001)
How can we reduce the burden of treatment?

Targets to reduce the burden of treatment

Boivin & Duff, in prep
Most important reason for not using counselling

![Bar chart showing reasons for not using counselling]

Prospective versus retrospective accounts of distress during IVF

![Graph showing prospective versus retrospective distress]

Capitalise on spontaneous coping efforts

![Graph showing capitalisation on spontaneous coping efforts]

Boivin et al. Hum Reprod, 1999

Boivin & Takefman, Fertil Steril, 1995

Boivin & Walker, Proceedings, 1997
Brief coping interventions for the waiting period: The Positive Reappraisal Intervention Card

- Ten statements
  - Rationale explained to women
  - "prime" positive redefinition associated with positive adjustment
  - Instruction to read once in the morning, once in the evening and any other time needed

During this experience I will:

- Try to do something that makes me feel good
- See things positively
- Look on the bright side of things
- Make the best of the situation
- Discover what is important in life
- Focus on the positive aspects of the situation
- Find something good in what is happening
- Try to do something meaningful
- Focus on the benefits and not just the difficulties
- Learn from the experience

Randomised Controlled (Pilot) Trial of Positive Reappraisal Coping Intervention

<table>
<thead>
<tr>
<th>Week 1</th>
<th>Week 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.4</td>
<td>0.6</td>
</tr>
<tr>
<td>0.8</td>
<td>1.0</td>
</tr>
<tr>
<td>PRCI group</td>
<td>PMI group</td>
</tr>
</tbody>
</table>

PRCI = positive reappraisal coping intervention; PMI = Control mood intervention; ET = embryo transfer.

Use minimal stimulation protocols to reduce physical symptoms

Hjegard et al. Hum Reprod 2003
Role for complementary (CAM) interventions in reducing physical burden of treatment?


Humaidan, 2004
Gejervall, 2004

Study Used CAM n=223, 30.6% No CAM use n=505, 69.4%

T1 815 couples
# treatments 1.95±1.24 2.49±1.31
Pregnancy rate* 42.2% 61.4%

Reduce burden by giving patients control over monitoring

Boivin & Schmidt, Humn Reprod, in press, N=728 women
Prospective 12-month observational cohort study

Copyright restrictions may apply.

Copyright restrictions may apply.

Online viewing behaviour

Online support intervention

Optimizing IVF

- Make IVF easier for patients
- Stress Reduction
- Invest in nurses
- Focus on customer satisfaction
- Improve communication
- Develop IVF leadership
- Improve documentation
- Continual improvement
- Data collection

Experiences of sonography nurses

Table 2. Factors causing difficulty when giving bad news: mean scores (M) and standard deviations (SD)

<table>
<thead>
<tr>
<th>Factor</th>
<th>M</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>The patient is not expecting to hear bad news</td>
<td>5.65</td>
<td>1.07</td>
</tr>
<tr>
<td>Inadequate time to support the patient adequately</td>
<td>3.38</td>
<td>1.06</td>
</tr>
<tr>
<td>Pressure of being behind schedule for subsequent patients</td>
<td>3.41</td>
<td>1.18</td>
</tr>
<tr>
<td>Not knowing how the patient will react</td>
<td>3.52</td>
<td>1.13</td>
</tr>
<tr>
<td>Difficulty contacting the doctor to refer the patient to</td>
<td>3.98</td>
<td>1.28</td>
</tr>
<tr>
<td>There is no chance to play how to tell the patient</td>
<td>2.83</td>
<td>1.11</td>
</tr>
<tr>
<td>People accompanying the patient how different reactions which also</td>
<td>2.77</td>
<td>1.21</td>
</tr>
<tr>
<td>have to be coped with</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colleagues are too busy to help with other appointments</td>
<td>2.76</td>
<td>1.22</td>
</tr>
</tbody>
</table>

Simpson & Bos, 2003+ 
Interventions available to manage distressed patients

- Outburst (This is catastrophe!)
  - Don’t take it personally, be patient, stay calm, listen & express empathy
- Freeze (“…”)
  - Ask questions (what are you thinking?), share the silence, give them space and an opportunity to speak later
- Denial (“This isn’t happening”)
  - Empathise, report the facts, reinforce identity
- Folly (“just give me another chance”)
  - Confirm the decision is final, focus on positive consequences
- Self-blamer (“I’m useless”, “a failure”)
  - Reinforce their identity, explain what else has contributed
- Attack (“It’s your fault, your incompetent”)
  - Don’t take it personally, remain calm, listen, don’t answer back, empathise with the anger & disappointment

Emotional care can become a priority even in busy clinics

- Identify challenging situations
  - Administration, nursing, laboratory, physicians, etc
- Discuss different approaches to handling specific challenging situations
  - Identify strengths and limitations
  - Work out situational factors that impact on realistic implementation of different approaches
- Practice using different approaches and implement those best for you and the context

Impact of reducing burden
Improved quality of life during treatment

FertiQoL

The first internationally validated instrument to measure quality of life in individuals experiencing fertility problems

Professionals can download FertiQoL
FREE OF CHARGE
www.fertiqol.org

Available in 17 languages

FertiQoL, International
Optional Treatment Module

FertiQoL Core
N=1230; FertiQoL treatment
N =1050
FertiQoL validation sample

Scope to improve quality of life during fertility treatment

FertiQoL Core N=1230; FertiQoL treatment N =1050
FertiQoL validation sample
Increased treatment persistence

Reduced effect of distress on treatment outcome

Couples may require fewer treatment cycles to conceive

Note: Cycle by marital stress interaction on live birth (B=.182 ± .08, Wald(1)=4.76, P < .05, OR=1.20; Model χ²(F(3, 817)=27.63, p < .001).
Effect of psychosocial interventions on pregnancy rates

<table>
<thead>
<tr>
<th>Study or original</th>
<th>Type</th>
<th>Need</th>
<th>Help</th>
<th>Risk factors</th>
<th>Risk Ratios</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovulation Induction</td>
<td>9.11</td>
<td>7.12</td>
<td>6.13</td>
<td>4.56</td>
<td>0.98</td>
</tr>
<tr>
<td>In vitro fertilisation</td>
<td>9.12</td>
<td>7.13</td>
<td>6.14</td>
<td>4.57</td>
<td>0.99</td>
</tr>
<tr>
<td>Intracytoplasmic sperm injection</td>
<td>9.13</td>
<td>7.14</td>
<td>6.15</td>
<td>4.58</td>
<td>0.99</td>
</tr>
<tr>
<td>Surrogacy</td>
<td>9.14</td>
<td>7.15</td>
<td>6.16</td>
<td>4.59</td>
<td>0.99</td>
</tr>
</tbody>
</table>

Learning objectives

• Identify sources of burden in fertility treatment
• Describe reactions during treatment and their impact on treatment outcome
• Learn general and treatment specific techniques to minimise the burden of treatment
  – Techniques for patients
  – Techniques for staff
• Gain knowledge on the effectiveness of general and treatment specific interventions on wellbeing and pregnancy rates

Conclusion

• Psychosocial factors have an impact on ART
• Need to expand and diversify psychological services to meet needs of patients and staff
How can we reduce the burden of treatment?

Jacky Boivin, Ph.D.
School of Psychology
Cardiff University
Boivin@cardiff.ac.uk

ESHRE, Amsterdam, 2009
Mild stimulation strategies in IVF
Is there an optimal balance?

*Christina Bergh*

ESHRE Amsterdam 2009

Is there an optimal balance? (In the number of oocytes retrieved)

Benefits: Singleton live births
Risks: Complications (OHSS)

Is there an optimal balance? (In the number of embryos replaced)

Benefits: Singleton live births
Risks: Complications (multiple births)
Delivery rate, multiple birth rate and single embryo transfer rate in Sweden 2000-2006

Karlström and Bergh, 2008

Birth per embryo transfer (%) and MBR in Sweden and USA


Reprinted from Van der Gast et al, RBMonline 2006;13:476-80, with permission from Reproductive Healthcare Ltc.
Pregnancy rate

Live birth after 1st, 2nd or > 3rd cryopreservation SET from the same egg retrieval

Reprinted from Olivius C et al 2008 RBMonline 2008;17:676-83, with permission from Reproductive Healthcare Ltc.
Is there an optimal balance?
(In the number of oocytes retrieved)

10 oocytes!? We don’t know!
RCT-ESHRE Task force on Mild stimulation
Which patients benefit?

Karl Nygren M.D., Ph.D.
EIM Past Chair
ICMART Chair
SQUART and TFMS member
(PCC 3, Amsterdam, 2009)

Conflict of interest

• None to declare, July 2009.

Karl Nygren

Benefit?

• Benefit equals success?
• Success rate equals pregnancy rate?
• No + No!

Benefit is the balance between efficacy, safety, quality, cost and time.
What patients benefit, differs in different settings:
- Policy on the number of embryos/ET (SET)
- Patient characteristics (e.g. age)
- Clinic capacity
- Clinics financial arrangements
- Re-imbursement policies
- Patient’s attitudes
- Doctor’s attitudes
- Efficacy reporting
- Safety reporting
- Quality reporting

Patient selection:
- Self selection
- Doctor’s selection

Patient self selection
- Avoidance of “hormones”
- Natural
- Complications
- Cost
- Risk
- Previous experience
Doctor’s selection

- Matching SET
- Risk awareness, risk factors
- Cost awareness
- Patient’s individual prognosis on efficacy

Who can best decide on patient benefit?

Probably the well informed couple
(in agreement with their doctor)

So, which patients benefit?

- Younger rather than older
- High rather than low ovarian capacity
- IVF rather than ICSI
- Patients at increased risk for complications
- At clinics with a pro-SET policy
- At clinics where "benefit" is understood
- The well informed patient