The ABC of infertility management revisited

MIDDLE EAST FERTILITY SOCIETY EXCHANGE COURSE
Lisbon - Portugal, 14 June 2015
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THE ABC OF INFERTILITY MANAGEMENT REVISITED

Sunday, 14 June  | Organised by the Middle East Fertility Society

Course coordinators
Johnny Awwad (Lebanon) and Mohammad Aboulghar (Egypt)

Course type
Basic and advanced

Course description
While most advances in the field of human reproduction have focused on reproductive technologies, much less has been vested in the basic management of infertility. Many related practices remain as an old heritage of the past, without ever being revisited on the basis of emerging evidence.

The process of counselling any subfertile couple involves the following:
- A diagnostic assessment plan
- A pre-intervention conception prognosis estimate
- A proposed intervention with improved conception estimate

The final management of subfertility is subject to a shared patient-physician decision. The counseling process should therefore take into account the couple’s sense of urgency as it relates to personal choice, culture and/or beliefs. A clear knowledge of the conception prognosis estimates pre- and post-proposed intervention is therefore essential for proper decision-making on the basis of sound risk-benefit and cost-effectiveness analysis.

This pre-congress course will discuss some of these parameters from an evidence-based perspective for the purpose of establishing an updated platform for infertility management more reflective of the current status of the evidence.

Target audience
- Reproductive endocrinologists and fertility specialists
- Biologists involved in assisted reproductive technologies
- General gynaecologists
- Infertility nurses
- Policy regulators and representatives of third party stakeholders

Educational needs and expected outcomes
At the completion of this pre-congress course, participants should be able to:
- Re-define infertility in relation to women’s reproductive characteristics
- Re-explore the benefits of simple ovulation monitoring and timed intercourse in the context of subfertility
- Understand to what extent ovarian reserve testing may influence natural conception
- Critically assess whether laparoscopy, endometrial biopsy and semen mucus interaction testing should remain an essential component of every subfertility work-up
- Understand to what extent an abnormal semen analysis, the presence of anti-sperm antibodies and varicoceles may affect natural conception in a couple with subfertility
- Determine optimal ovulation protocols to improve outcome in subfertile couples
- Critically evaluate whether intrauterine insemination should remain the bridge between ovulation induction and assisted reproduction
- Design a fertility management algorithm and a fertility counselling platform for subfertile couples on the basis of the above
SCIENTIFIC PROGRAMME

Chairman: Mohamed A. Aboulghar (Egypt)
09:00 - 09:25  Re-defining infertility: Adjustment for ovarian and chronological age – Johnny Awwad (Lebanon)
09:25 - 09:50  The roles of ovulation documentation and timed intercourse in increasing the likelihood of pregnancy in women trying to conceive – Robert W. Rebar (U.S.A.)
09:50 - 10:15  How would ovarian reserve testing influence the probability of natural pregnancy in women with subfertility? – Thomas D’Hooghe (Belgium)
10:15 - 10:30  Discussion
10:30 - 11:00  Coffee break

Chairman: Michel Abou Abdallah (Lebanon)
11:00 - 11:25  Laparoscopy: Should it remain an essential component of the fertility work up – Cindy M. Farquhar (New Zealand)
11:25 - 11:50  Does measurements of sperm-mucus interaction (Post-coital Test) influence the chances of conception? – Thomas D’Hooghe (Belgium)
11:50 - 12:15  The value of endometrial biopsy in modern fertility management – Johnny Awwad (Lebanon)
12:15 - 12:30  Discussion
12:30 - 13:30  Lunch break

Chairman: Johnny Awwad (Lebanon)
13:30 - 13:55  The value of basic semen analysis in altering early fertility management – Craig Niederberger (U.S.A.)
14:20 - 14:45  Would the presence of varicocele alter fertility management of couples? – Craig Niederberger (U.S.A.)
14:45 - 15:00  Discussion
15:00 - 15:30  Coffee break

Chairman: Mohamed A. Aboulghar (Egypt)
15:30 - 15:55  Oral ovulation induction agents [clomiphene, letrozole]: when to start and for how long? – Johnny Awwad (Lebanon)
15:55 - 16:20  Intratuterine insemination: Is it still the bridge between ovarian stimulation and in vitro fertilization in unexplained subfertility – Richard Reindollar (U.S.A.)
16:20 - 16:45  How would a cost-effective fertility management algorithm look like? – Cindy M. Farquhar (New Zealand)
16:45 - 17:00  Discussion
Re-defining infertility: Adjustment for ovarian and chronological age
Johnny Awwad, MD
Professor of Obstetrics and Gynecology
American University of Beirut Medical Center

No Conflict of Interest

Objectives

- Review the various definitions of infertility in the medical literature
- Re-evaluate the definition of infertility while adjusting for
  - Ovarian age
  - Chronological age
Definition of "Infertility"

The Practice Committee of the American Society for Reproductive Medicine.

Infertility is a disease. The diagnosis of the disease must be made in a patient to rule out any other factors before an evaluation for infertility begins. In women, the disease is defined by the failure of the ovary to ovulate regularly and to develop normal follicles. A woman who fails to ovulate regularly is said to have ovulatory dysfunction. In men, the disease is defined by the failure of the testicles to produce sufficient numbers of sperm. Infertility is a condition that affects both men and women and is defined by the inability to achieve a pregnancy after 1 year of regular sexual intercourse without the use of any contraceptive method.

Infertility revisited: The state of the art today and tomorrow

TheESHRECaplWorkshop

Infertility

Definition:

Fertility: Based on the distribution of fecundity observed in a normal population, infertility was defined by the ESHRE group as achieving a pregnancy within 2 years by regular sexual intercourse. Infertility is defined as inability of a couple to achieve a pregnancy after 1 year of regular sexual intercourse.

Table 1: Published definitions of infertility

<table>
<thead>
<tr>
<th>Organization</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>National Institute for Health and Clinical Excellence guidelines 2005</td>
<td>Infertility should be defined as failure to conceive after regular unprotected sexual intercourse for 2 years in the absence of known reproductive pathology.</td>
</tr>
<tr>
<td>ASRM 2006</td>
<td>Infertility is defined as failure to achieve a successful pregnancy after 12 months of regular unprotected intercourse. Further evaluation and treatment may be indicated based on reproductive history and physical findings. It is diagnosed after 6 months for women over age 30 years.</td>
</tr>
<tr>
<td>International Committee for Monitoring Assisted Reproductive Technology (ICMART) and World Health Organization 2009</td>
<td>Infertility (clinical definition) is a disease of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months of regular unprotected sexual intercourse.</td>
</tr>
<tr>
<td>Demographic definition</td>
<td>Infertility is a non-conception of a woman who has had a live birth in a year of regular unprotected sexual intercourse.</td>
</tr>
</tbody>
</table>
• Re-defining infertility
  - Advanced chronological age
  - Irregular cycles
  - Shorter cycles
  - Prolonged unexplained infertility
  - Previous ovarian surgery

• Education and enhanced awareness of the effect of age on fertility is essential in counseling the patient who desires pregnancy.
  - Women older than 35 years should receive equalized evaluation and treatment after 6 months of failed attempts to conceive or earlier, if clinically indicated.
  - In women older than 40 years, immediate evaluation and treatment are warranted.

Female age-related fertility decline
• Juul et al., 1999, 2000 and Jensen et al., 2001 only recorded Time To Pregnancy TTP retrospectively among pregnant women using questionnaires to measure fertility, by assessing exposures related to semen quality, age or environment.
• Their study design does not estimate real fecundity, because infertile couples were excluded. Therefore, effects on the proportion of truly infertile couples cannot be assessed.

• Wang et al. (2003) prospectively observed 518 newly married Chinese textile workers (20–34 years of age) trying to conceive.
• They recorded vaginal bleeding, sexual intercourse and collected daily first-morning urine specimens for up to 1 year or until a clinical pregnancy was achieved.
• In their cohort of women, about 50% became clinically pregnant in the first two cycles and more than 90% in the first six cycles.
• They found that the monthly fecundity varied between 30 and 35%.

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**Research on infertility: which definition should we use?**

<table>
<thead>
<tr>
<th>Definition</th>
<th>Question</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary infertility</td>
<td>Have you ever had problems getting pregnant?</td>
<td>Respondents' unsuccessful attempts to become pregnant (Kase et al. 1981). Retaining one of the sperm donors will enable the partners to have a baby. The deceased donor's sperm should be stored for no more than 12 years. If there is no spouse, the patient needs to be under 35 years of age during the last menstrual period. If the sperm donor is under 35 years of age during the last menstrual period, the patient needs to be under 35 years of age during the last menstrual period. If the patient is under 35 years of age during the last menstrual period, the patient needs to be under 35 years of age during the last menstrual period. If the patient is under 35 years of age during the last menstrual period, the patient needs to be under 35 years of age during the last menstrual period.</td>
</tr>
<tr>
<td>Secondary infertility</td>
<td>Have you had had trouble getting pregnant in the last 2 years?</td>
<td>Respondents' unsuccessful attempts to become pregnant (Kase et al. 1981). Retaining one of the sperm donors will enable the partners to have a baby. The deceased donor's sperm should be stored for no more than 12 years. If there is no spouse, the patient needs to be under 35 years of age during the last menstrual period. If the sperm donor is under 35 years of age during the last menstrual period, the patient needs to be under 35 years of age during the last menstrual period. If the patient is under 35 years of age during the last menstrual period, the patient needs to be under 35 years of age during the last menstrual period. If the patient is under 35 years of age during the last menstrual period, the patient needs to be under 35 years of age during the last menstrual period.</td>
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<tr>
<td>Subsequent infertility</td>
<td>No children</td>
<td>Respondents' unsuccessful attempts to become pregnant (Kase et al. 1981). Retaining one of the sperm donors will enable the partners to have a baby. The deceased donor's sperm should be stored for no more than 12 years. If there is no spouse, the patient needs to be under 35 years of age during the last menstrual period. If the sperm donor is under 35 years of age during the last menstrual period, the patient needs to be under 35 years of age during the last menstrual period. If the patient is under 35 years of age during the last menstrual period, the patient needs to be under 35 years of age during the last menstrual period. If the patient is under 35 years of age during the last menstrual period, the patient needs to be under 35 years of age during the last menstrual period.</td>
</tr>
<tr>
<td>Subsequent infertility and wanting a child</td>
<td>No children or current children of any age</td>
<td>Respondents' unsuccessful attempts to become pregnant (Kase et al. 1981). Retaining one of the sperm donors will enable the partners to have a baby. The deceased donor's sperm should be stored for no more than 12 years. If there is no spouse, the patient needs to be under 35 years of age during the last menstrual period. If the sperm donor is under 35 years of age during the last menstrual period, the patient needs to be under 35 years of age during the last menstrual period. If the patient is under 35 years of age during the last menstrual period, the patient needs to be under 35 years of age during the last menstrual period. If the patient is under 35 years of age during the last menstrual period, the patient needs to be under 35 years of age during the last menstrual period.</td>
</tr>
<tr>
<td>Cessation of fertility</td>
<td>No children</td>
<td>Respondents' unsuccessful attempts to become pregnant (Kase et al. 1981). Retaining one of the sperm donors will enable the partners to have a baby. The deceased donor's sperm should be stored for no more than 12 years. If there is no spouse, the patient needs to be under 35 years of age during the last menstrual period. If the sperm donor is under 35 years of age during the last menstrual period, the patient needs to be under 35 years of age during the last menstrual period. If the patient is under 35 years of age during the last menstrual period, the patient needs to be under 35 years of age during the last menstrual period. If the patient is under 35 years of age during the last menstrual period, the patient needs to be under 35 years of age during the last menstrual period.</td>
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<table>
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<tr>
<th>Table 1: Prevalence of infertility by different definitions.</th>
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<tr>
<td>Definition of Infertility</td>
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Measuring infertility in populations: constructing a standard definition for use with demographic and reproductive health surveys.
Couples with a good prognosis (unexplained infertility, no tubal or male factor and no signs of reduced ovarian reserve) should be advised to wait as they have a reasonably good chance (>60%) of conceiving spontaneously during the next 36 months.
According to commonly accepted medical criteria for infertility, women are categorized as infertile if they experience a year of unprotected intercourse without conception. Using this definition, the National Survey of Family Growth (NSFG) estimates that 7.4 percent of married U.S. women were infertile in 2002. It makes no explicit reference to intent to conceive, but, given the availability of contraception, this definition implies that women meeting the criteria for infertility were trying to conceive.

Data from the National Study of Fertility Barriers (NSFB) reveal that there are a large number of women who at some point in their lives fit the NSFG definition of infertility but who do not describe themselves as having tried to become pregnant at that time.

Subfertility must be raised after six cycles of unprotected intercourse without conception—regardless of age because most of the women less than 30 years of age should have conceived...

For women after the age of 35 years—if treatment (e.g., IVF) will be necessary—the chance of a live birth will decrease rapidly.
Demographers tend to define infertility as childlessness in a population of women of reproductive age. Epidemiological definition is based on ‘trying for’ or ‘time to’ a pregnancy, generally in a population of women exposed to the risk of conception. There is considerable variation in terms of the duration of ‘trying for pregnancy’, the age of women sampled and their marital or cohabitation status. This leads to inconsistencies in determining the numerator and denominator used to calculate the prevalence of infertility.

**References**


**References**

The Roles of Ovulation Documentation and Timed Intercourse in Increasing the Likelihood of Pregnancy in Women Trying to Conceive

Robert W. Rebar, M.D.
Professor and Chair,
Department of Obstetrics and Gynecology
Western Michigan University Homer Stryker M.D. School of Medicine

Disclosures
• I serve on multiple Data Safety Monitoring Boards for randomized trials; write summaries for Journal Watch, a non-profit publication of the Massachusetts Medical Society; and am Deputy Editor of the journal Contraception.
• I receive no monies from any commercial source.
• Any opinions I express are mine alone and do not represent the views of any organization.

At the conclusion of this presentation, participants should be able to:
• Describe the biophysical and hormonal changes that typically occur during the normal menstrual cycle.
• Summarize the data from studies documenting the “fertile window” and presumptive ovulation.
• Discuss how the frequency of intercourse affects the pregnancy rate.
• Discuss advantages and disadvantages of using ovulation monitors and timed intercourse.
Single follicular development; a. D1; b. D10; c. D14; d. CL
Ovulation of the cumulus-oocyte complex through the stigma (Erickson GF. Semin Reprod Endocrinol 1986;4:233)

Mean Daily Estrogen Metabolites (Mersereau et al., Menopause 2008;15:482-6)
Mean Daily Progesterone Metabolites (Mersereau et al., Menopause 2008;15:482-6)

Urinary Metabolites (Averaged over cycle phases) (Mersereau et al., Menopause 2008;15:482-6)

<table>
<thead>
<tr>
<th></th>
<th>Younger (20-34 yrs) n=28</th>
<th>Older (35-50 yrs) n=78</th>
<th>p value**</th>
</tr>
</thead>
<tbody>
<tr>
<td>PdG</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total*</td>
<td>11.2 ± 4.5</td>
<td>6.6 ± 3.1</td>
<td>0.001</td>
</tr>
<tr>
<td>Follicular*</td>
<td>5.6 ± 2.2</td>
<td>2.7 ± 1.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Luteal*</td>
<td>18.1 ± 8.9</td>
<td>11.0 ± 5.2</td>
<td>0.090</td>
</tr>
<tr>
<td>E1G</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total*</td>
<td>97.2 ± 39.8</td>
<td>89.2 ± 32.7</td>
<td>0.469</td>
</tr>
<tr>
<td>Follicular*</td>
<td>81.7 ± 32.9</td>
<td>88.5 ± 37.3</td>
<td>0.431</td>
</tr>
<tr>
<td>Luteal*</td>
<td>115.4 ± 56.1</td>
<td>98.4 ± 33.6</td>
<td>0.876</td>
</tr>
</tbody>
</table>

*Mean values ± SD. Values are standardized by day of ovulation
**p value based on ranksum test

Documentation of Ovulation

- Ovulation only can be proven in any given menstrual cycle by a resulting pregnancy or by physically observing ovulation; even then there is no way to identify if the oocyte is normal.
- Virtually no study “documenting” ovulation has confirmed its occurrence.
- Surrogates for ovulation are typically used: measurement of progesterone or its metabolites (sometimes after an elevated LH or in association with measurement of estrogen or its metabolites), evidence of follicle collapse on ultrasound, endometrial biopsy, and changes in biophysical parameters such as BBT and cervical mucus.
Findings of one study of ovulation
(Blackwell et al., Hum Reprod 2013;28:3306)
• Prospective uncontrolled cohort study of 62 fertile women with apparently normal menstrual cycles
• Daily urine samples collected for 2 cycles and assessed for E1G and PdG
• Concluded that 80.5% of cycles were potentially fertile and that 19.5% had some luteal defect (LUF, deficient luteal phase, short luteal phase)
• The “luteal defects” were arbitrarily defined and were not proven to be associated with inability to become pregnant during that cycle.

Findings of another study of ovulation
(Hambrídge et al., Hum Reprod 2013;28:1687)
• Prospective uncontrolled cohort study of 250 regularly menstruating (21-35 d) women aged 18-44
• Serum LH, E2, & P were measured in blood samples obtained in up to 16 visits over 2 cycles.
• 87.6% of the women had 2 normal cycles with P > 5 ng/ml; 9.6% had 1 ovulatory cycle; 2.8% had two anovulatory cycles.
• The unproven presumption was that cycles with P ≤ 5 ng/ml were anovulatory.

Summary findings from 8 studies of ovulation
• Eight studies including 2411 subjects
• Presumptive anovulation rates in 3 studies ranged from 3.7-12.8%; one study found a 19.5% incidence of luteal phase defect.
• There was insufficient evidence to designate any gold standard; the presumed standard is serum Progesterone.
These newer data are consistent with reports from the 1960s and 1970s that approximately one in every 12 menstrual cycles appeared anovulatory on the basis of hormonal changes.

Despite the absence of definitive proof, it appears reasonable to conclude that ovulation occurs essentially monthly in regularly menstruating women with cycle length between 24 and 35 days. It would seem unlikely that documentation of ovulation, generally by measurement of serum progesterone in the luteal phase, would provide any additional assistance even though mid-luteal progesterone levels correlate with pregnancy by identifying those women who are anovulatory.

An Evidence-Based Assessment of Diagnostic Tests Used in Evaluating Infertility (A.Collins, 1999)

• Test results correlating with pregnancy
  • Semen analysis
  • Tubal patency testing by HSG or laparoscopy
  • Mid-luteal progesterone levels
The Probability of Pregnancy and the Frequency of Intercourse

- A retrospective study of almost 9500 semen specimens found that, in men with normal semen quality, sperm concentration, and motility, sperm concentration and motility remain normal even with daily ejaculation (Levitas et al., Fertil Steril 2005;83:1680).
- After abstinence intervals of ≥10 days, semen parameters begin to deteriorate (Check et al., Arch Androl 1995;27:93).
- In 221 presumably fertile couples attempting pregnancy, daily intercourse resulted in the highest cycle fecundability (37%), but the pregnancy rate was comparable with intercourse on alternate days (33%); the likelihood of pregnancy decreased to 15% with intercourse only weekly (Wilcox et al., NEJM 1995;333:1517).

These data imply that couples should be informed that the likelihood of pregnancy increases with the frequency of intercourse and is highest with intercourse at 1 to 2 day intervals; however, couples should be advised that the optimal frequency of intercourse during midcycle is best defined by their own preferences so as to reduce any stress.

1.2.2.1 People who are concerned about their fertility should be informed that vaginal sexual intercourse every 2 to 3 days optimises the chance of pregnancy. [NICE Fertility Guidelines, 2004, amended 2013]
1.3.4.1 Women who are concerned about their fertility should be asked about the frequency and regularity of their menstrual cycles. Women with regular monthly menstrual cycles should be informed that they are likely to be ovulating. [2004]

1.3.4.2 Women who are undergoing investigations for infertility should be offered a blood test to measure serum progesterone in the mid-luteal phase of their cycle (day 21 of a 28-day cycle) to confirm ovulation even if they have regular menstrual cycles. [2004, amended 2013]

1.3.4.4 The use of basal body temperature charts to confirm ovulation does not reliably predict ovulation and is not recommended. [2004]

**Additional NICE Fertility Guidelines**

**The “Fertile Window” and the Probability of Pregnancy**

• The so-called “fertile window” can be defined as the 6-day interval ending on the day of ovulation; pregnancy is most likely with intercourse during the 3 days prior to ovulation (Wilcox et al., NEJM 1995;333:1517; Brosens et al., Sex Reprod Menopause 2006;4:13).

• The likelihood of pregnancy decreases with increasing age.

• The likelihood of pregnancy can be maximized by increasing the frequency of intercourse from the end of menses through ovulation in midcycle.

Probability of pregnancy according to vaginal secretion observations on the day of intercourse. Data from Scarpa et al., Eur J Obstet Gynaecol Reprod Biol 2006;125:72.

Documentation of Ovulation

- Commercial approaches to determining when ovulation occurs include among others:
  - Basal Body Temperature (BBT)
  - Urine LH kits such as Ovuquick® and First Response™
  - Clearplan/Clearblue Easy Fertility Monitor® of urinary LH and estrogen metabolites
  - Duofertility™ monitor of temperature and heat flow
  - OvuSense™ Fertility Monitor of vaginal temperature
  - OvaCue™ Fertility Monitor of electrolyte changes in saliva and cervical mucus
- All tests have false positives and false negatives.
Documentation of Ovulation (cont.)
• It is also possible to document ovulation by:
  • Serial ultrasound (relatively precisely and expensively)
  • Fertility awareness based methods, including cervical mucus and BBT changes and calendars (imprecisely)
  • Menstrual cycle charting (very imprecisely)

Data indicate that stress associated with trying to become pregnant can reduce sexual esteem, satisfaction, and frequency of intercourse; moreover, stress can be further increased by utilizing ovulation predictor kits or following a strict schedule (Lenzi et al., J Endocrinol Invest 2003;26:72; Andrews et al., Fertil Steril 1992;57:1247).

Timed intercourse was found to be the most emotionally stressful activity in the initial infertility evaluation (Kopitzke et al., Fertil Steril 1991;55:1137).
Timing of Intercourse

- BBT is known to be a poor predictor of the day of ovulation (Templeton, Penney, & Leader, Br J Obstet Gynaecol 1982;89:985)
- While hormonal ovulation detection kits are better at predicting ovulation, they are expensive and there is no evidence their use improves pregnancy rates.
- In one study 105 couples with unexplained infertility and 45 couples with asthenozoospermia were randomized to timed intercourse with an LH detection kit or advice for timing intercourse, pregnancy rates were not significantly different (Leader, Russell, & Stenning, Aust N Z J Obstet Gynaecol 1992;32:158).

Timed Intercourse for Couples Trying to Conceive
(A New Cochrane Review)
(Manders et al., In Press)

- Conclusion: “There was insufficient evidence to draw definite conclusions on the effectiveness of timed intercourse for live births, adverse events or clinical pregnancy in couples trying to conceive.”
- There may be a higher pregnancy (including self-reported pregnancies, especially for women trying for <12 months, BUT “the overall quality of the evidence is low to very low” and “the size of the benefit is small.”

Ovulation detection kits may be of benefit to couples who have intercourse sporadically, perhaps because they travel extensively or work in different cities, and to those who wish to use them, but there are no data documenting that they increase the likelihood of pregnancy.
Might it be just as effective to ask couples to record menses and days when intercourse occurred retrospectively?

Summary and Conclusions

• Normal ovulation can only be documented by a resulting pregnancy.
• Surrogate markers for pregnancy involve measuring various biophysical and hormonal parameters.
• It appears that perhaps 3-12% of menstrual cycles of normal length may be anovulatory, but there is no evidence that women with regular menses are more than seldom anovulatory.
• Intercourse at intervals of 1-3 days from the end of menses through midcycle appears as effective as any monitoring in resulting in pregnancy.
• In today's complicated world ovulation monitors may be of assistance to some couples, but there is no evidence from controlled studies that they increase pregnancy rates.

Summary and Conclusions (cont.)

• Large scale randomized controlled trials are required to document any benefit for the different methods for timing intercourse versus spontaneous intercourse and versus each other.
• The economic impact of the different ovulation prediction methods— as well as the impact on the emotional health of the couple— should also be assessed, as this must be considered in recommending any method.
How would ovarian reserve testing influence the probability of natural pregnancy in women with subfertility

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Yale University (USA)³
Institute Primate Research (WHO CC), Nairobi, Kenya⁴

“ESHRE Pre-congress Course PCC14:
MEFS exchange course: the ABCs of infertility management revisited.”
June 14th, 2015, Lisbon, Portugal

Disclosure:

- Co-Chair WHO Infertility Guidelines Development Group Steering Committee
- Board Member European Endometriosis Liga (EEL)
- Council Member Society Gynecol Investigation (SGI)
- Research Associate and Chair International Advisory Board, Institute of Primate Research, Kenya (WHO-CC)
- Grants from Merck Serono, Ferring, MSD, Besins, WERF
- Consultancy/KOL for Merck Serono, Ferring, MSD, Bayer, Abbott, Abbvie, Preglem, Gedeon Richter, Pharmaplex, Ultron Pharma, Roche, Proteomika

Learning objectives

- What is the role of AMH as a test for ovarian reserve?
- Can ovarian reserve tests (AMH, FSH, AFC) predict the probability of natural pregnancy in an infertile population?
AMH (Anti-Mullerian Hormone)
Produced by small pre-antral, large pre-antral and antral follicles

Plasma concentration: 1-7ng/ml
dependent on type of test and lab

Reproductive age: 0.65 - 12.60 ng/ml
Postmenopausal phase: < 0.08 ng/ml
AMH and follicular recruitment profile across the human reproductive lifespan.

Reproductive lifespan
Reproductive lifespan

Serum AMH determination

- Parameter for ovarian reserve
  - One assessment is sufficient
  - Independent of cycle phase and consistent over several cycles
  - Independent of intake of oral contraception or GnRH agonists during short duration. (In case of long duration: reduction with 20%).

Geometric mean AMH across the menstrual cycle in eumenorrheic women by age category.
AMH determination
= parameter for ovarian reserve

- Lower in women who smoke
- Lower in women with increased BMI?
- Increased (2-3x) in women with PCOS

PCO

Can serum AMH predict

- Ovarian reserve and function (N)?
- Egg quality (Q)?
- Pregnancy (N&Q)?
- Menopause (N&Q)?
Can plasma-AMH predict time to pregnancy?

<table>
<thead>
<tr>
<th>Reference</th>
<th>N patients</th>
<th>Age patients</th>
<th>60% 80% in 6m</th>
<th>TTP</th>
<th>AMH</th>
<th>fecundability ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steiner 2011</td>
<td>100</td>
<td>30–44</td>
<td>Time to pregnancy</td>
<td></td>
<td></td>
<td>FR= 0.38 (95% CI 0.08–0.91)</td>
</tr>
<tr>
<td>Hagen 2012</td>
<td>186</td>
<td>26.6 (95% CI 21.4–31.8)</td>
<td>Quintile 1 vs Quintile 2–4: FR 0.81 (95% CI 0.44–1.40)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Streuli 2014</td>
<td>87</td>
<td>23–41</td>
<td>82% in 6m</td>
<td></td>
<td></td>
<td>AMH (r=−0.10)</td>
</tr>
</tbody>
</table>

Do tests of ovarian reserve predict the probability of pregnancy in infertile women?

In expectant management populations:
- AMH: Casadei 2013
- AFC: Casadei, Haadsma 2008,
- CCCT: Haadsma 2008

None of these studies found that any of the ORTs assessed had any clinically meaningful value for predicting pregnancy or live birth, either when used alone or when added to a prediction model.

Clinical value of AMH testing

- Parameter for ovarian reserve
- Good prediction of poor response and of exaggerated response in the context of ART treatment
- Potentially useful for ovarian stimulation protocols
  - Start dose
  - Adaptation dose
  - Predict ovarian response
Ovarian reserve testing before the first IVF cycle would permit to categorize patients as expected poor-, normal- or hyper-responders.

CONCLUSIONS

• AMH testing, FSH testing or AFC testing not useful to predict spontaneous conception in subfertile women during expectant management
• AMH testing useful for prediction of ovarian response during ART treatment
Laparoscopy: should it remain an essential component of the fertility work up?
Professor Cindy Farquhar
University of Auckland

Declarations
- Co-ordinating editor of the Cochrane Menstrual Disorders and Subfertility Group
- Co-Chair of the Diagnostic section of the WHO Fertility Guidelines 2014-2015
- No commercial conflicts to declare

Laparoscopy and fertility: learning objectives
- What information is provided by a laparoscopy that assists fertility?
- Does having the diagnosis improve outcomes?
- What are the alternatives to laparoscopy?
- Which women should we offer laparoscopy to?
WHO is developing guidelines for investigation and treatment of women with infertility

- Process – question development
  - Developing a PICO
  - P – patients
  - I – intervention
  - C – comparison
  - O – outcomes

Which women should be offered laparoscopy at the time of presenting with infertility?

- Women of reproductive age with infertility with and without the following clinical flags:
  - painful periods (endometriosis),
  - risk factors for tubal disease (past history of chlamydia/gonorrhea),
  - history of pelvic surgery (appendicitis/ovarian cystectomy/previous diagnosis of endometriosis),
  - abnormal clinical examination or imaging
- I – laparoscopy (diagnostic)
- C – no laparoscopy or imaging prior to laparoscopy
- O – Outcomes
  - adhesions (underlying infection/endometriosis/postsurgery) and endometriosis
  - change in previously planned management of women as a result of the findings on diagnostic laparoscopy
  - pregnancy/live birth (either naturally conceived or through fertility treatment)
  - cost

What information is provided by a laparoscopy that assists fertility?

- Tubal disease/adhesions secondary to infection, previous surgery, hydrosalpinges
- Endometriosis – peritoneal and ovarian, bowel disease
- Tubal patency
Harms and benefits of laparoscopy

**Benefits**
- Diagnosis leads to treatment of disease that may improve pregnancy rates and improve success of IVF

**Harms**
- Invasive
- Potential for injury
- Days off work
- Cost

Laparoscopy may lead to treatment

- Treatment of peritoneal or ovarian endometriosis
- Removal of hydrosalpinges in preparation for IVF
- Possibility of release of adhesions

Endometriosis

- Benefits of diagnosis
  - Surgical removal is associated with better outcomes
  - Pre IVF down regulation for 3 months
Cochrane review on surgical treatment of endometriosis Duffy et al 2014

- "There is moderate quality evidence that laparoscopic surgery to treat mild and moderate endometriosis ... increases live birth or ongoing pregnancy rates"

Pretreatment of women with endometriosis who are undergoing IVF

- Cochrane review: Long-term pituitary down-regulation before in vitro fertilization (IVF) for women with endometriosis Hassan et al 2006

- The administration of GnRH agonists for a period of three to six months prior to IVF or ICSI in women with endometriosis increases the odds of clinical pregnancy by fourfold

Tubal infertility

- Infertility – 15-20% of infertility is tubal adhesion related
- Post surgical adhesions are very common
- Incidence of adhesions forming after surgery varies from 55-100%

(Diamond 1991)
Tubal adhesions and fertility

- The incidence of tubal infertility following pelvic inflammatory disease (Westrom et al. 1980)
  - 12% after 1 episode of pelvic infection
  - 23% after 2 episodes
  - 54% after 3 episodes of pelvic infection

- Surgical treatment to restore patency (Techniques for pelvic surgery in subfertility Ahmad et al. 2006 and Surgery for tubal infertility Pandian et al. 2007)
  - But no RCTs and based on case series

- Adhesions may interfere with assisted reproduction
  - Distortion makes monitoring and ovum pick up more difficult

Removal of hydrosalpinges in preparation for IVF, Johnson et al. CIR 2010

- No evidence to support aspiration

What are the alternatives to laparoscopy for tubal infertility?

- Tubal Disease
- Ultrasound
- HSG/HyCoSY
- CAT

- 5 Systematic reviews
  - All moderate or good quality
Chlamydia Antibody Testing (CAT) vs laparoscopy: 2 SRs

- Prevalence of any tubal pathology was 29% (27 to 30%) and for bilateral tubal pathology was 13% (12 to 15%), as defined by laparoscopy.
- Sensitivity and specificity of CAT not pooled
  - For any tubal pathology, sensitivity was 12 to 91% and specificity was 35 to 100%.
- Broeze 2011: CAT - low sensitivities of CAT but high specificities
  - High specificities mean that CAT might avoid unnecessary testing in women without tubal pathology
  - Low sensitivities might be too low to accurately rule out tubal pathology.
- Mol 1997:
  - CAT is comparable to HSG in the diagnosis of tubal occlusion in the diagnosis of any tubal pathology.
  - No information on the anatomy of uterus and cervix.

Hysterosalpingogram vs Laparoscopy: SR Broeze 2011

- 7 primary studies with 7226 women
- Prevalence of any tubal pathology* was 30% (95% CI 29 to 32%)
  - Prevalence of bilateral tubal pathology was 15% (95% CI 14 to 17%)
- Pooled sensitivity and specificity of HSG were 53% and 87% for any tubal pathology and 46% and 95% for bilateral tubal pathology.
- Diagnostic accuracy of HSG in women with risk factors compared to women without risk factors:
  - In women without risk factors, the sensitivity of HSG was 38% for any tubal pathology compared with 61% in women with risk factors (p=0.005).
- “HSG can be considered equally useful in detecting tubal pathology for all groups of women. Although some women may still benefit from laparoscopy, HSG can be used as a screening test for all infertile couples.”
  - *as defined by diagnostic laparoscopy.

CAT and HSG

- In the comparison of CAT with HSG, the combination of patient history with CAT and HSG testing provided the best estimate of bilateral tubal pathology, compared to either test alone.
- Prevalence rates of chlamydia infection varies between countries.
**HSG vs HyCoSy**

- HyCoSy appears to be a well tolerated procedure when compared to HSG.
- No studies were identified which directly compared all diagnostic tests for tubal patency.
- Diagnostic accuracy of HSG and HyCoSy were similar.

**CAT/HSG/Laparoscopy and fertility outcomes**

- +ve CAT serology associated with reduced pregnancies.
  - Keltz 2013
    - 70/1279 (5.5%) had a positive chlamydia serology result.
    - + CTA more likely to have blocked tubes on HSG (37.5% vs 10.1%, p=0.001) and laparoscopically confirmed damage (62.7% vs 48.9%, p=0.002).
    - No spontaneous pregnancies in CAT positive patients with an abnormal HSG.
  - Verhoeve 2011
    - HSG and laparoscopy results were similar wrt spontaneous pregnancy.
      - unilateral tubal pathology on HSG and laparoscopy reduced chances of a spontaneous pregnancy and bilateral tubal pathology severely reduced preg.
  - Coppus 2011
    - Positive chlamydia IGC serology was associated with a statistically significant 33% lower probability of an ongoing pregnancy (adjusted fecundity rate ratio 0.66 (0.49 to 0.89)."

**Who should we offer laparoscopy to?**

- Why not everyone?
  - Expensive and invasive
  - Potential for harm
- Should we limit to women with possible underlying pathology
  - Those women with clinical flags?
- What are the clinical flags?
Clinical flags for pelvic disease

- **Endometriosis**
  - Painful periods – new onset of symptoms, requires pain relief >24 hours
  - Pain with sex, pain with bowel motions
  - Change in symptoms
- **Tubal Disease**
  - Risk factors for tubal disease (past history of chlamydia/gonorrhea)
  - History of pelvic surgery (appendicitis/ovarian cystectomy/previous diagnosis of endometriosis)
  - Abnormal clinical examination or imaging

Evidence for laparoscopy as part of the investigation of infertility

- 8 studies
  - One systematic review (Luttjeboer 2009)
  - 3 RCTs (Perquin 2006, Badawy 2010, Tanahatoe 2005)
  - One controlled cohort study (Berube 1998)
  - One prognostic cohort study (Mol 1999)
  - One cost study (Moayeri 2009)

Description of studies

- One systematic review was identified that provided indirect evidence on the role of laparoscopy
- The remaining studies were RCTs (n=3), cohort studies (n=2), one cross sectional study and a cost effectiveness study
- Four studies were undertaken in the Netherlands (n=4) and one each in Egypt, Canada, USA and Turkey
Diagnosis of tubal infertility at laparoscopy

Systematic review: Luttjboer 2009 included studies were

Cohort studies:
- History of complicated appendicitis (OR 7.2, 95% CI 2.2 to 22.8)
- Pelvic surgery (OR 3.6, 95% CI 1.4 to 9.0)
- PID (OR 3.2, 95% CI 1.6 to 6.6)

Case control studies:
- History of complicated appendicitis (OR 3.3, 95% CI 1.8 to 6.3)
- PID (OR 5.5, 95% CI 2.7 to 11.0)
- Ectopic pregnancy (OR 16.0, 95% CI 12.5 to 20.4)
- Endometriosis (OR 5.9, 95% CI 3.2 to 10.8)
- Sexually transmitted disease (OR 11.9, 95% CI 4.3 to 33.3)

"Subfertile women reporting a history of PID, complicated appendicitis, pelvic surgery, ectopic pregnancy and endometriosis are at increased risk of having tuboperitoneal pathology. In these women, diagnostic laparoscopy should be offered early in the fertility workup."

RCT of HSG then laparoscopy or immediate laparoscopy Perquin 2006

- Average length of infertility = 2 years
- Risk factors were equally distributed between the groups
  - 3% of each group had a history of PID, 2% and 3% respectively had a history of tubal surgery.
- Coagulation of endometriosis (grade I or II) was performed in 25% and 27% respectively.
- Laparoscopic adhesiolysis in 5% and 4% respectively and laparoscopic cystectomy in 1% of both groups
- 68% and 68% did not require therapeutic surgery

"Routine use of HSG at an early stage of fertility workup prior to laparoscopy does not influence cumulative pregnancy rate compared with routine use of laparoscopy with out HSG."

RCTs (2) laparoscopy then OI or IUI or treatment with OI or IUI first then laparoscopy

Badawy 2010: unexplained infertility (normal HSG)
- Adhesions were identified in 15% to 18% of women
- Endometriosis in 14% to 16% of women
- Pregnancy rate after 6 months – Lap + OS = 44.7% cf with OS: 41.7% (NS)
  - "laparoscopy could be postponed"

Tanahatoe 2005 unexplained
- Abnormalities were identified in 48% to 56% of the randomized women
- Endometriosis was found in 44% to 52% and adhesions in 0% to 4% respectively
- Pregnancy rates: lap + IUI = 44%, IUI + Lap = 49% (NS)
  - Authors questioned the value of routinely performing a laparoscopy prior to IUI
Prospective cohort study (Mol 1999)

- Compared the HSG and laparoscopy
- Consecutive subfertile couples (n=794) in 11 Canadian centres who underwent HSG and laparoscopy were included
- Patients with an abnormal HSG underwent laparoscopy without delay but in patients with a normal HSG, laparoscopy was only performed in cases where subfertility persisted for a longer period of time
- Of those having laparoscopy, 16% of tubal diagnoses showed "other tubal pathology" (included adhesions and phimosis) at laparoscopy and for endometriosis diagnoses, 78% had no endometriosis, 20% had grade 1 or 2 endometriosis and 2% had grade 3 or 4 endometriosis

Cross-sectional study Kahyaoglu 2009

- 191 unexplained infertile women in Turkey.
- Women had both primary and secondary infertility, with a mean age of 27 and 29 years respectively.
- All women had HSG and transvaginal ultrasound. Results were as follows:
  - 123/191 (64%) of patients had pelvic pathology. 16% had pelvic adhesions, 26% had endometriosis, 19% had tubal occlusion, 35% had normal pelvic anatomy.
  - Risk factors for infertility included: abnormal HSG, previous pelvic surgery, ectopic pregnancy (for secondary infertility), ovarian surgery and dysmenorrhea/pelvic pain.
  - There was no significant difference in the rate of pathology on diagnostic laparoscopy according to whether or not women had prior risk factors: 61% vs 59%.

Planning laparoscopy - conclusions

- Women with risk factors appear to have an elevated risk of tubal pathology, including PID and endometriosis
- Other studies found that in women with generally unexplained infertility, the risk of adhesions ranged from 0% to 24% and the risk of endometriosis ranged from 14% to 52%
- It is difficult to extrapolate from these figures, as the populations in the individual studies are likely to have differed, although generally they had either unexplained infertility or were candidates for IUI
Laparoscopy leading to change in management

- RCT Badawy 2010
  - randomized with unexplained fertility to laparoscopy plus treatment compared to treatment alone (with laparoscopy if it was unsuccessful)
  - 2.3% of patients had a change of management according to laparoscopy findings
  - 6/257 patients were found to have moderate and severe adhesions and were referred directly to the IVF/ICSI program
- X-sectional study Kahyaoglu 2009: association between lap and risk factors
  - A high rate of pelvic pathology was identified; only 35% of the whole group had normal pelvic anatomy. The authors reported:
    - Treatment strategies of 8% (primary) and 13% (secondary) of infertile women without risk factors were changed as a result of laparoscopy findings
    - Treatment strategies of 43% (primary) and 49% (secondary) of infertile women with risk factors changed after diagnostic laparoscopy

Conclusions

- There was moderate evidence that women with unexplained infertility and normal HSG findings could delay diagnostic laparoscopy for 6 to 10 months, without influencing their chances of a spontaneous pregnancy.
- There was low quality evidence that diagnostic laparoscopy findings in women with risk factors such as previous surgery, ectopic pregnancy, pelvic pain and abnormal HSG may result in change of their subfertility management in 43% to 49% of the women.
- Abnormal findings at laparoscopy may lead to an alteration in management including correction at surgery and treatment of endometriosis and decisions about fertility treatment

What do guidelines say?

- The 2013 NICE guideline recommends that:
  - Women who are thought to have comorbidities should be offered laparoscopy and dye so that tubal and other pathology can be assessed at the same time
Laparoscopy: should it remain an essential component of the fertility work up

- It is not an essential component for all women
- Women with clinical flags for tubal disease or endometriosis should be considered for laparoscopy
- Bilateral tubal disease detected by HSG may be so severe that laparoscopy not likely to improve changes of conceiving but removal of the tubes indicated prior to IVF
- Treatment of endometriosis a useful step in treatment

References

Does assessment of sperm-mucus interaction (postcoital test) influence the chances of conception?

Prof Dr TM D’Hooghe, MD, PhD
Prof Dr D. De Neubourg, MD, PhD
KU Leuven/University of Leuven (B) 1,2
Yale University (USA) 1
Institute Primate Research (WHO CC), Nairobi, Kenya 1

*ESHRE Pre-congress Course PCC14:
MEFS exchange course:
the ABCs of infertility management revisited.*
June 14th, 2015, Lisbon, Portugal

Disclosure:
- Co-Chair WHO Infertility Guidelines Development Group Steering Committee
- Board Member European Endometriosis Liga (EEL)
- Council Member Society Gynecol Investigation (SGI)
- Research Associate and Chair International Advisory Board, Institute of Primate Research, Kenya (WHO-CC)
- Grants from Merck Serono, Ferring, MSD, Besins, WERF
- Consultancy/KOL for Merck Serono, Ferring, MSD, Bayer, Abbott, Abbvie, Preglem, Gedeon Richter, Pharmaplex, Uteron Pharma, Roche, Proteomika

Learning objectives
- What is the postcoital test?
- What is the added value of the postcoital test?
Learning objectives

• What is the postcoital test?
• What is the added value of the postcoital test?

POSTCOITAL TEST (PCT)
1. MUCUS SCORE:
Timing:
very close to ovulation,
(cycle length, BTC, US dominant ovarian follicle)

Mucus aspiration:
- nonlubricated speculum, tuberculin syringe
- aspirate mucus 1 cm into endocervical canal
- put sample on slide
- assess phase contrast microscope
- scoring: volume, stretching/spinnbarkeit (10 cm), color,
  absence of WBCs, Ferning pattern

Before ovulation
Cervix
Cervix is closed

At ovulation
Mucus

After ovulation
Cervix
Cervix is fully open
POSTCOITAL TEST

Timing:
- close to ovulation (see mucus)
- abstinence of 2 -3 days
- coitus within 8-12 hours prior to PCT
(Speroff: 2-8 hours; WHO: 9 to 24 hours)

Collection (see mucus):
- non lubricated speculum
- aspirate 2 samples
  - from fluid pool in posterior vaginal fornix: microscopic sperms?
  - from endocervical canal (use different tube): endocervical fluid: -
- put 0.1 mL on 1 slide, cover with cover-slip and assess
- put remaining fluid on 2nd slide and let dry (assess Ferning)

POSTCOITAL TEST (PCT) ASSESSMENT

1. Report number of spermatozoa/HPF
2. Report motility (Rapidly, slowly progressive, non-progressive, immotile)

POSITIVE = 1 or more than 1 fast progressively motile sperm cell/HPF
in more than half or in at least 5 HPFs
Unsatisfactory: 1 or more with slow or irregular motility
NEGATIVE: 1 or more nonprogressive or immotile sperm cell

NEGATIVE TEST IS ONLY VALID IF
- A COITUS WITH EJACULATION TOOK PLACE (sperm cells in posterior vagina)
- MUCUS SCORE IS MORE THAN OR EQUAL TO 10 (repeat in same cycle if required)
- NEGATIVE RESULTS ARE FOUND IN 2 SEPARATE CYCLES
Learning objectives

• What is the postcoital test?
• **What is the added value of the postcoital test?**

Literature search

• PubMed 16 March 2016
• Key words: “postcoital test”, “cervical factor infertility”
• Reviews and clinical trials
• 14 papers: presented in 3 parts
  - Published before Cochrane 2005 SR
  - Cochrane 2005 SR
  - Original research after Cochrane 2005 SR

Papers before Cochrane 2005

Check et al, 1995 RCT
• Couples Unexpl Infert with nl semen analysis and abnl PCT
• Abnl PCT = no progressively forward moving sperm 8-12hrs after intercourse at time of mature follicle
• IUI natural cycle vs sexual intercourse
• Monthly fecundity rate after 1 month: higher after IUI (21%) dan after intercourse (4%)
Papers before Cochrane 2005
Oei et al, HR 1995. When is the PCT normal?
A critical appraisal
- Predictive value nl PCT: 0.37-0.92 and for abnormal PCT: 0.30-0.97
- Sensitivity 0.10-0.90; Specificity 0.30-0.97
- Likelihood ratio 0.77 (nl) and 1.85 (abnl)
- Overall poor discriminating ability
- Recommendation: < 1 sperm/HPF as cut-off point for high specificity and high LHR

Papers before Cochrane 2005
Oei et al, BJOG 1995. EU PCTs: opinion and practice
- Used in 92% of Ob Gyn Departments
- Large differences in timing of the test in relation to
  - menstrual cycle
  - coitus
  - method for analysis
  - cut-off level for normality
- Type of treatment offered for abnl test
Conclusion: Added value of PCT unclear

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  - menstrual cycle
  - coitus
  - method for analysis
  - cut-off level for normality
- Type of treatment offered for abnl test
Conclusion: Added value of PCT unclear, even though no negative effect on sexual relationship (Oei et al, 1996 and 1998)
Papers before Cochrane 2005
Oei et al, BMJ 1998

• RCT to investigate impact of PCT on PR among subfertile couples
• 736 consecutive new couples
• PCT standardized 6-18 hrs after intercourse, 14-16 days before menses, negative test (<1 fast moving sperm/HPF) only valid if good Q mucus, positive test always valid
• No difference in Cum PR, but more treatment offered in intervention group (54%) than in control group (41%). Over-treatment???

Cochrane 2010 (Helmerhorst et al)

• IUI vs Timed intercourse or expectant Mx for cervical hostility in subfertile couples
• Literature updated till Aug 2008
• 6 studies of variable quality ➔ pooling of results in SR not possible
• 5 studies with important flaws regarding method of randomization, failure to conceal upcoming assignment, losses after randomization
• One study (Steures et al, 2007): good Q according to CONSORT guidelines for RCTs
• Overall conclusion: no evidence that IUI is an effective treatment for cervical factor infertility

Expectant management: indications

- Only patients without ovulation disorder, tubal pathology, azospermia (Hunault et al, 2004) or severe sperm problem (< 3 million TMC, van der Steeg et al, 2007).
- These patients and their doctors may overestimate ART success and underestimate ART risks.
- Based on calibrated and validated Hunault score with good prognostic performance (Hunault et al, 2004; van der Steeg et al, 2007)
Definitions Hunault score

- **Duration of subfertility**: time interval from discontinuation of contraceptive activities until registration at the fertility centre (Hunault et al, 2004).

- **Primary and secondary subfertility**: subfertility without and with a previous clinical pregnancy (Zegers-Hochschild et al, 2009) in a current or previous relationship (Van der Steeg et al, 2007).

- **Progressive motility**: percentage motile spermatozoa of the first semen analysis (Van der Steeg et al, 2007).

  - Referral by gynaecologist/other medical specialist: tertiary-care (Hunault et al, 2004)
  - Self-referral: secondary-care, but tertiary care if couple has already been investigated or treated by another gynecologist or another medical specialist (andrologists, urologist, geneticist, …), even if couple was not specifically referred by this other gynecologist/medical specialist.

**SCORING TABLE**
(adapted from Hunault et al, 2004 – 3 sample model)

<table>
<thead>
<tr>
<th>Woman's age</th>
<th>21-25</th>
<th>26-31</th>
<th>32-35</th>
<th>36-37</th>
<th>38-39</th>
<th>40-41</th>
<th>Score</th>
</tr>
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<tbody>
<tr>
<td>Duration (Yrs) of Subfertility</td>
<td>0</td>
<td>3</td>
<td>7</td>
<td>10</td>
<td>13</td>
<td>15</td>
<td>8</td>
</tr>
<tr>
<td>Type of subfertility</td>
<td>Secondary</td>
<td>PRIMARY</td>
<td>8</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Sperm Progressive Motility (%): (A+B)</td>
<td>&gt;60</td>
<td>40-59</td>
<td>20-39</td>
<td>0-19</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Referral status</td>
<td>Secondary-care couple</td>
<td>Tertiary-care couple</td>
<td>8</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

**Prognostic index score (sum)**
Expectant management
Belgian consensus
Depends on predicted chances of spontaneous conception within 1 year:
- if > or = 40% (Hunault score 10 or less): Expt Mx for 1 yr, then treatment
- if 30-40% (Hunault score 10-15): choice between Expt Mx and medical/surgical treatment to be discussed with patient (probability, patient preference, and effectiveness/safety of treatment).
- if < 30%: (Hunault score > 15): active medical/surgical treatment recommended.

Steures et al, 2007a
- RCT 99 couples with isolated cervical factor infertility and good pregnancy prognosis >30% in next 12/12 (Hunault score)
- IUI natural cycle versus expect Mx for 6/12
- After 6/12: N ongoing pregnancies:
  22 (43%) in IUI group and
  13 (27%) in Expt Mx group
  (RR 1.6 (95% CI 0.91-2.8):
  not significant but interesting trend
Steures et al 2007b

- Added value of ovarian stimulation with IUI in couples with abnormal PCT and poor prognosis (<=30% spf pregnancy in next 12/12)
- IUI (n=132 with COH/n=133 without COH)
- Pregnancy rate after IUI:
  - 25% with COH (2/26 twins) and
  - 21% without COH (1/22 twins)

Scholten et al, 2013

- Long term outcome in subfertile couples with isolated cervical factor
- FU for 3 years after conclusion of RCT with 99 participants who had isolated cervical infertility (Steures et al, 2007)
- Local treatment up to 3 years
- Similar cumulative pregnancy rates in both groups
Overall conclusion

- PCT: not standardized, huge variability
- Diagnostic relevance unclear
- Prognostic relevance poor
- Value of treatment with IUI not proven
- Not recommended in clinical practice
- Potentially interesting in a research context (repeat RCT Steures et al, 2007)
The value of endometrial biopsy as a diagnostic tool in modern fertility management

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American University of Beirut Medical Center

No Conflict of Interest

Objectives

- Evaluate the clinical benefits of routine endometrial biopsy to enhance the reproductive outcome of couples with sub/fertility
  - Diagnostic value – luteal phase defect, endometrial pathology
  - Prognostic value – with and without intervention
Background

- The use of endometrial biopsy to assess luteal phase defects has been an essentially component of the routine infertility work-up of women.
- The practice has been largely introduced with little evidence as to its diagnostic and prognostic value.
- It has been partially abandoned in current fertility practice,
  - Because of the indiscriminate use of luteal supplementation, reducing the need to address its invasive nature and associated costs.
  - Because of the lack of consensus in diagnosing luteal phase defect
  - Because it fails to predict infertility

Incidence of detecting luteal phase defect

- Coutifaris et al
- RCT / mid and late luteal biopsies in fertile and infertile women; n=619
- Luteal phase defect in midluteal phase:
  - Fertile vs infertile couples: 49.4% vs 43.2%; P = NS
- Luteal phase defects in late phase:
  - Fertile vs infertile couples: 35.3% vs 23.0%; P <0.05

Given the high prevalence of luteal phase defect in fertile couples, it calls into question the diagnosis of luteal phase defect as a cause of infertility

<p>| Presence of luteal phase endometrial biopsy in fertile women and in women of infertile couples at either the midluteal or late luteal phase. |
|---|---|---|---|---|---|
| Presence of luteal phase endometrial biopsy in fertile women and in women of infertile couples at either the midluteal or late luteal phase. |</p>
<table>
<thead>
<tr>
<th>N</th>
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<th>N</th>
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<tbody>
<tr>
<td>Fertile</td>
<td>49.4%</td>
<td>43.2%</td>
<td>P = NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Infertile</td>
<td>35.3%</td>
<td>23.0%</td>
<td>P &lt;0.05</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

Table: Presence of luteal phase endometrial biopsy in fertile women and in women of infertile couples at either the midluteal or late luteal phase.

Coutifaris et al

Out of phase biopsy results diagnosing luteal phase defect poorly discriminates between women from fertile and infertile couples in either the midluteal or late luteal phase.
Incidence of detecting luteal phase defect

- Balasch et al
- Retrospective
- No significant difference in the incidence of luteal phase defect between infertile and fertile couples (30.6% vs 17.8%, P = NS)

Incidence of detecting endometrial pathology

- Tuberculous endometritis: 1.8 – 3.3% (Sahmay et al, Zawar et al, Coutifaris et al, Nisa et al)
- Chronic endometritis and endometrial polyps: 0.23-12% (Sahmay et al, Nisa et al)
- Endometrial hyperplasia (typical and atypical) and carcinoma: 0.06 – 4.68% (Sahmay et al, Zawar et al, Kurabayashi et al, Nisa et al)
- Early pregnancy tissue found inadvertently: 0.21% (Sahmay et al)

Value of improving pregnancy outcome

- NICE 2004
- Systematic review
- No significant benefit of treatment of luteal phase defect was found
- The relative risk of pregnancy in infertile couples who received treatment with progesterone versus no treatment was RR=1.9 (CI 0.4 to 8.1)
Value of improving pregnancy outcome

- Balasch et al. Case control cohort
- No significant difference of the absence or presence of luteal phase defect on: Term delivery and Spontaneous miscarriage

<table>
<thead>
<tr>
<th>Pregnancy outcome</th>
<th>Endometrial histology</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>In phase(b)</td>
</tr>
<tr>
<td>Term</td>
<td>15 (79%)</td>
</tr>
<tr>
<td>Spontaneous abortion</td>
<td>5 (72%)</td>
</tr>
</tbody>
</table>

\(\chi^2 = 0.69; P = NS\)

*One hydatidiform mole excluded (endometrial biopsy; in phase).

Value of improving pregnancy outcome

- Balasch et al. Case control cohort
- No significant difference in reproductive outcome between treatment and no treatment for luteal phase defect on: Term delivery and Spontaneous miscarriage

<table>
<thead>
<tr>
<th>Treatment for LPOD</th>
<th>Pregnancy outcome</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Term</td>
<td>Spontaneous abortion</td>
</tr>
<tr>
<td>Yes</td>
<td>14 (78%)</td>
<td>4 (27%)</td>
</tr>
<tr>
<td>No</td>
<td>27 (77%)</td>
<td>8 (23%)</td>
</tr>
</tbody>
</table>

\(\chi^2 = 0.69; P = NS\)

*One hydatidiform mole excluded.

*One ectopic pregnancy excluded.

Assessment of endometrial receptivity

Available biomarkers for the assessment of endometrial receptivity are increasing exponentially, but validation of these biomarkers has been limited.

There is a paucity of studies with adequate power and validity based on study design to help determine which biomarkers have the greatest value and consistency.
The accuracy and reproducibility of the endometrial receptivity array is superior to histology as a diagnostic method for endometrial receptivity.

### Training stage: predictor training parameters after the cross-validation testing of each machine-learning prediction.

<table>
<thead>
<tr>
<th>Algorithm</th>
<th>Correct</th>
<th>Uncorrect</th>
<th>Specificity</th>
<th>Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVM</td>
<td>73 (92.4%)</td>
<td>6 (7.6%)</td>
<td>0.83</td>
<td>1.00</td>
</tr>
<tr>
<td>KNN</td>
<td>69 (87.3%)</td>
<td>10 (12.7%)</td>
<td>0.90</td>
<td>0.86</td>
</tr>
<tr>
<td>RF</td>
<td>68 (86%)</td>
<td>11 (14%)</td>
<td>0.84</td>
<td>0.89</td>
</tr>
</tbody>
</table>

Note: KNN = K-nearest neighbor; RF = random forest; SVM = support vector machine.

Uterine–not peripheral–NK cell subsets, are good diagnostic markers of unexplained infertility.

Further analysis with larger sample size should be conducted to test this hypothesis and to determine the clinical importance of endometrial NK cells testing in improving pregnancy and take home baby rates.

### Conclusions

<table>
<thead>
<tr>
<th>Value proposition</th>
<th>Status of the evidence</th>
<th>Quality of the evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Value of routine endometrial biopsy in diagnosing luteal phase defects</td>
<td>Unfavorable</td>
<td>Low</td>
</tr>
<tr>
<td>Value of routine endometrial biopsy in detecting suspicious endometrial pathology</td>
<td>Favorable</td>
<td>Low</td>
</tr>
<tr>
<td>Value of routine endometrial biopsy in predicting pregnancy outcome</td>
<td>Unfavorable</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

### Recommendations

- The use of endometrial biopsy to detect luteal phase defects during the routine work-up of women presenting with sub/infertility, should be abandoned because of the lack of supportive evidence for an improvement if reproductive outcome with/without intervention
- The use of endometrial biopsy to detect endometrial pathology during the routine work-up of women presenting with sub/infertility, is associated with a low yield, and should be reserved to women at risk
References


References

The value of basic semen analysis in altering early fertility management

The ABC of infertility management revisited
June 14, 2015

Craig Niederberger MD FACSI
Chairman – Medical Practice and Fund, Department of Urology, UC College of Medicine
President, Department of Fertility, UI College of Engineering
Co-Chair in Clinical Fertility and Sterility

Disclosures

ASA – Journal Editor – Medical Communications
AUA – Journal Section Editor – Medical Communications
Ferring – Investigator – Scientific Study
BSIA – Investigator – Scientific Study
Nedland – Co-Founder – Medical Device Company

No relationship presents a conflict of interest with the material in this presentation.

Learning Objectives

At the conclusion of this presentation, the participant will be able to:

1. Summarize the limitations of the predictive value of bulk semen analysis parameters
2. Describe the natural variability of bulk semen parameters
3. Explain how the limitations and variability of semen parameters affect scientific studies
The most informative semen analysis outcome is azoospermia.
Everything else must be considered in terms of probabilities.

Except for azoospermia, there is no such thing as infertile. There is only likely infertile.

Above or below any number does not mean fertile or infertile.
TABLE 2. FERTILITY, INFECTIONS, AND SUBFERTILITY RANGES FOR VARIOUS MEASUREMENTS OF FERTILITY-AND-REGRESSION TREE ANALYSIS AND CLASSIFYING OVOX RESULTS FOR INFERTILITY.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Semen Measurement</th>
<th>Infertility Range</th>
<th>Representative Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Concentration</td>
<td>&gt;40.0</td>
<td>20.0</td>
</tr>
<tr>
<td></td>
<td>Motility</td>
<td>&gt;85</td>
<td>95.0</td>
</tr>
<tr>
<td></td>
<td>Sperm viability</td>
<td>&gt;82</td>
<td>58.0</td>
</tr>
<tr>
<td></td>
<td>Sperm motility</td>
<td>10.9-16.6</td>
<td>15.7-21.0</td>
</tr>
<tr>
<td></td>
<td>Sperm motility</td>
<td>0.1 (90-100)</td>
<td>1.5 (90-100)</td>
</tr>
<tr>
<td></td>
<td>Sperm motility</td>
<td>0.8-1.2 (90-100)</td>
<td>1.3 (10-2)</td>
</tr>
<tr>
<td></td>
<td>Sperm motility</td>
<td>0.1 (90-100)</td>
<td>1.5 (90-100)</td>
</tr>
<tr>
<td></td>
<td>Sperm motility</td>
<td>&gt;22</td>
<td>&gt;22</td>
</tr>
<tr>
<td></td>
<td>Sperm motility</td>
<td>12.5</td>
<td>22.0</td>
</tr>
<tr>
<td></td>
<td>Sperm motility</td>
<td>25.0</td>
<td>33.0</td>
</tr>
<tr>
<td></td>
<td>Sperm motility</td>
<td>34.0</td>
<td>39.0</td>
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<td></td>
<td>Sperm motility</td>
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</tr>
<tr>
<td></td>
<td>Sperm motility</td>
<td>34.0</td>
<td>39.0</td>
</tr>
</tbody>
</table>

*CI (95% confidence interval)

MacLeod vs Guzik

<table>
<thead>
<tr>
<th>Semen parameter</th>
<th>MacLeod ROC Area</th>
<th>Guzik ROC Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>Density</td>
<td>0.59</td>
<td>0.69</td>
</tr>
<tr>
<td>Motility</td>
<td>0.59</td>
<td>0.59</td>
</tr>
<tr>
<td>Morphology</td>
<td>0.59</td>
<td>0.66</td>
</tr>
</tbody>
</table>

World Health Organization reference values for human semen characteristics:

- Volume: Normal: 1.5-5.0 ml; Low: <1.5 ml; High: >5.0 ml
- Density: Normal: >15 million/ml; Low: <15 million/ml
- Motility: Normal: >50%; Low: <50%
- Morphology: Normal: >40%; Low: <40%
- pH: Normal: 7.2-8.0; Low: <7.2; High: >8.0

For more information, please refer to the World Health Organization guidelines on the evaluation and processing of human semen.
Above or below any number does not mean fertile or infertile.
Other than azoospermia, everything must be considered in terms of probabilities.
"Using the results of two semen analyses did not lead to a better goodness-of-fit. Discriminative capacity was rather poor, with an area under the ROC curve (AUC) ranging from 0.51 to 0.56."

For studies, as bulk parameters are highly variable, regression to the mean is the norm.
Other Current Metrics?
Clinical Relevance Unknown

- Computer-assisted semen analysis (CASA)
- Nuclear morphology (MSOME)
- Nuclear DNA structure (Comet, TUNEL, SCSA, Raman microspectroscopy)
- Metabolic activity
- Surrogate IVF outcomes (Hamster Ova)

What is the value of basic semen analysis in altering early fertility management?
For azoospermia, a great deal.

For everything else, we still have some work to do.

Thank you!
Anti-Sperm Antibodies (ASA): Any Role for Screening in Modern Fertility Management?

Robert W. Rebar, M.D.
Professor and Chair, Department of Obstetrics and Gynecology
Western Michigan University Homer Stryker M.D. School of Medicine
Kalamazoo, Michigan

Disclosures

• I serve on multiple Data Safety Monitoring Boards for randomized trials; write summaries for Journal Watch, a non-profit publication of the Massachusetts Medical Society; and am Deputy Editor of the journal Contraception.
• I receive no monies from any commercial source.
• Any opinions I express are mine alone and do not represent the views of any organization.

At the conclusion of this presentation, participants should be able to:

• Briefly discuss the antigenicity of the male and female reproductive tracts.
• List conditions associated with antisperm antibodies.
• Discuss current tests for antisperm antibodies – and their difficulties.
• Discuss current treatment for antisperm antibodies.
Can Immune Infertility Exist?

- The antigenicity of sperm and seminal plasma components has been recognized since the turn of the 20th century.
- Experimental evidence has documented the immune responsiveness of the female genital tract at all levels.
- Antibodies against a variety of antigens common to sperm, such as blood group and HLA antigens, are present in cervical mucus and may prevent recognizing sperm as “foreign”.

Can Immune Infertility Exist? (cont.)

- A “blood‐seminiferous tubule barrier” exists that prevents recognition of developing sperm as “foreign”; this barrier is needed because developing sperm acquire new surface antigens after puberty while immunological tolerance to self antigens arises during embryological development.
- Any breach of this barrier can lead to the development of sperm antibodies in the male.

Immune Infertility

- ASA have been found in both males and females.
  - Reported in up to 9.12.8% of infertile couples (Ayvaliotis et al., Fertil Steril 1985;43:393; Collins et al., Hum Reprod 1993;8:592)
  - Present as well in 1–2.5% of fertile men (Heidenreich et al., Am J Reprod Immunol 1994;31:69; Sinisi et al., Int J Androl 1993;16:311) and in 1.4% of fertile women (Clarke & Baker, Fertil Steril 1993;59:463)
- No available test identifies a specific antigen that may be associated with infertility.
Conditions Historically Associated with ASA in Males
(Adapted from Walsh & Turek, 2009)

- **Obstruction**
  - Vasectomy, CBAVD, idiopathic epididymal obstruction, ejaculatory duct obstruction
- **Inflammation**
  - Orchitis, venereal disease, prostatitis, cancer
- **Thermal**
  - Varicocele, cryptorchidism, hot baths
- **Trauma**
  - Torsion, coital, testis biopsy, oral or rectal trauma
- **Genetic**
  - Thymic maldevelopment, HLA-B28 haplotype

Some clinicians maintain that ASA should be sought when:

- **Semen Analysis (SA)** shows sperm agglutination or clumping in the absence of infection
- There is poor sperm motility and a history of testis injury or surgery
- There are increased leukocytes on SA
- There is unexplained infertility
- (There is poor penetration of mucus on postcoital testing)
- (Sperm “shaking” is observed on sperm-cervical mucus contact testing)

**ASA Testing: Immunobead Test**

- The direct immunobead test (IBT) has been used most frequently and uses polyacrylamide beads coated with antibodies against human immunoglobulin to bind antibody-coated sperm. A second antibody uses smaller beads and rabbit antibodies to human Ig to bind any sperm-bead complexes and result in agglutination of sperm and beads.
- IBT can identify the classes of ASA (IgG, IgA) and the sites on sperm affected.
- IgA are believed to be more detrimental than IgGs to sperm function; IgMs are not believed to have any significant role.
- Generally the IBT is first done with all classes of immunoglobulins; if more than 20% show binding, then each immunoglobulin class can be tested separately.
- If IgA are positive, then some clinicians suggest intrauterine insemination (IUI) to bypass cervical mucus.
Positive ASA with Immunobead Testing

ASA Testing: Mixed Agglutination Reaction Test
• The direct MAR test can use sperm from unwashed or washed ejaculates.
• Either IgG-coated latex particles or IgG-sensitized erythrocytes are placed on a microscope slide with antiserum against IgG and sperm and observed for agglutination.
• If ≥20% sperm are agglutinated, further testing, first with the better characterized IBT.

Intrauterine Insemination for ASA
• There are no controlled prospective studies of IUI for the treatment of ASA.
• The studies that have been done are largely retrospective and involve small numbers of patients.
Informal discussions with andrology laboratories in the United States indicates that almost no tests for ASA have been ordered in the last 15 years.

Immunoglobulin G antisperm antibodies do not predict spontaneous pregnancy (Leushuis et al., Fertil Steril 2009;92:1659)
- Dutch prospective cohort study involving 1794 consecutive ovulatory infertile couples, 16% of whom had a spontaneous pregnancy within one year
- 3% of couples had a positive mixed agglutination reaction (MAR) for IgG ASA
- In multivariable analysis, a positive MAR (≥50%) did not predict the likelihood of spontaneous pregnancy (hazard ratio 0.99; 95% CI, 0.4-2.4)

ASA Are Not Associated with Pregnancy Rates after IVF and ICSI: A Meta-Analysis (Zini et al., Hum Reprod 2011;26:1288)
- Included 16 studies with 4209 treatment cycles (1508 IVF; 2701 ICSI)
- The overall (IVF + ICSI) combined OR for failure to achieve a pregnancy was 1.08 (95% CI, 0.85-1.38).
- ASA cutoff values were heterogeneous
Summary and Conclusions

- Although it appears that some ASA cause or contribute to infertility, current diagnostic techniques fail to distinguish between antibodies that cause and those that do not cause infertility.
- None of the tests identify specific antigens: available tests are heterogeneous and more qualitative than quantitative.
- Experiments have generally been uncontrolled and poorly conducted.
- Because of the success of IVF + ICSI, there have been very few advances in the last two decades.

Summary and Conclusions (cont.)

- Because it appears unlikely that immune-mediated infertility is common and because of the inability to diagnose the disorder, let alone to treat it specifically, it would seem most prudent to rule out all other causes of infertility before considering immune infertility – and even then to treat the couple with IVF + ICSI.
Would the presence of varicocele alter fertility management of couples?

MEPB Exchange course

The ABC of infertility management revisited

June 14, 2015

Graig Niederberger MD FACS

Chairman, Section Professor and Head, Department of Urology, UBC College of Medicine

Professor, Department of Urology, UBC College of Engineering

Co-Editor, Infertility and Sterility

Disclosures

ASRM Journal Editor Medical Communications
AJU Journal Section Editor Medical Communications
Fertility Investigator Scientific study
IBSA Investigator Scientific study
Neuland Co-Founder Medical Device Company

No relationship presents a conflict of interest with the material in this presentation.

Learning Objectives

At the conclusion of this presentation, the participant will be able to:

1. Describe how a varicocele forms and adversely affects spermatogenesis

2. List what types of varicoceles are clinically significant, and how

3. Summarize the scientific evidence for varicocele diagnosis and treatment
Anatomy

L int spermatic v drains into L renal v ~ 6 - 10 cm superior to entry of R int spermatic vein.
Hydrostatic column of blood on L predisposes to venous incompetence > R.
L sided varicoceles are more common.
Consider renal pathology for isolated R varicocele, especially of sudden onset.
Counter-Current Heat Exchange

Testicular artery

Abdomen

Pampiniform plexus

Testis

How Heat Damages

DNA fragmentation
Apoptosis
Oxidative stress
Predisposition to aneuploidy
Intracellular metabolic and ionic changes

Grades

I: Non-palpable, non-visible; detected only on imaging
II: Palpable but not visible*
III: Visible through the surface of the skin*

*Clinically significant: do not image non-palpable varicoceles
Gonadal Toxicity

- 9,034 males
- Varicocele found in:
  - 25.4% of men with abnormal semen
  - 11.7% of men with normal semen
- Testicular volume correlated to grade
- Semen analysis correlated to grade

"Varicocele is clearly associated with impairment of testicular function and infertility."

Surgery

- Graph: Treatment success rates for different treatments:
  - Non-treated at 1 y: 30%
  - Treated at 1 y: 60%
  - Both after crossover: 70%

Micro-Doppler
Micro-varicocelectomy

Surgery or embolisation for varicoceles in subfertile men
(Review)


"Surgical or radiological treatment of varicoceles in men from couples with otherwise unexplained subfertility cannot be recommended."

Surgery on varicoceles for varicoceles in infertile men

**Problems**

- Studied only pregnancy as an outcome
- Included men with normal semen parameters
- Included subclinical varicoceles

---

**Vasectomy and Male Factor Infertility Treatment: A New Meta-analysis and Review of the Role of Varicocelectomy**


---

Vasectomy repair is clearly associated with a significant improvement in sperm concentration as well as total and progressive sperm motility. Vasectomy repair also appears to reduce seminal oxidative stress and sperm DNA damage and to improve sperm ultramorphology. However, there is insufficient evidence at present to demonstrate a beneficial effect of vasectomy repair on spontaneous pregnancy rates. Although the various methods of repair are all viable options, microsurgical repair appears to be associated with better outcomes and lower complication rates. Presently, the data suggest that subclinical varicocelectomy repair for male factor infertility is not beneficial.

---
Valvuloplasty repair: does it still have a role in severity treatment?

Pierro Neri,*,†, Cédric Michell,†, Daniel Chevalier,‡, Jean-Marc Arfert* and François Maroteaux*

*Department of Cardiology, Georges Pompidou University Hospital, Paris, France
†Department of Cardiology, Estimauville Private Hospital, Paris, France
‡Department of Cardiology, Montparnasse Private Hospital, Paris, France

Background and methods: The aim of the study was to evaluate the role of valvuloplasty repair in the treatment of severe aortic regurgitation. Aortic valve repair was performed in 10 patients with severe aortic regurgitation and a normal left ventricular function. The patients were divided into two groups based on the presence of aortic valve calcification. Group A consisted of 6 patients with severe aortic regurgitation and a normal left atrial size, while group B consisted of 4 patients with severe aortic regurgitation and a dilated left atrium.

Results: All patients in group A underwent successful valve repair with no complications. The mean mitral valve area was 2.5 cm² in group A and 1.8 cm² in group B. The mean left atrial diameter was 4.2 cm in group A and 5.0 cm in group B. There were no differences in terms of procedural success, hospital stay, and early and late mortality between the two groups.

Conclusions: Aortic valve repair is a feasible and effective option for the treatment of severe aortic regurgitation, especially in patients with a normal left atrial size. However, more studies are needed to further evaluate the long-term outcomes of this procedure.
Would the presence of varicocele alter fertility management of couples?
Would the presence of varicocele alter fertility management of couples?  

YES!

Thank you!
Oral ovulation induction agents: When to start and for how long?

Johnny Awwad, MD
Professor of Obstetrics and Gynecology
American University of Beirut Medical Center

No Conflict of Interest

Objectives

• Review the various recommendations for the use of oral ovulation induction agents in the context of infertility
• Review of algorithms for dose adjustments
• Evaluate the benefits of prediction models in clinical practice
• Evaluate cancer risks from prolonged use of some oral induction agents
Background

- Normogonadotropic anovulation
- Clomiphene citrate (CC) is first-line treatment, anti-estrogen MRL-41. (Greenblatt et al., 1961)
- NICE guidelines: CC should be used for up to twelve months. But, lacking evidence for this recommendation
- Gonadotropins? More expensive, higher risk of multiple pregnancies

Background

- CC is safe and convenient with limited chances for complications
- Multiple pregnancy
- Ovarian hyperstimulation syndrome
- About 60% to 85% of PCOS women starting ovulation induction with CC ovulate
- Life-table analysis indicates a conception rate of up to 22% per cycle in those ovulating on CC (Hammond 1983; Kousta 1997; Eijkemans 2003)
- The cumulative live birth rate within 12 months has been estimated to be 42%
The cumulative conception rate continues to rise after 6 months of treatment, reaching a plateau by treatment cycle 12 and approaches that of the normal population.
A fixed-dosage regimen of 50 mg clomiphene per day is likely to cause ovulation in only 46% of patients; subsequent increment in dosage increases the number of responders but at the expense of considerable delay in individualization of treatment.

- After receiving CC, 58 (38%) women conceived, leading to live birth. The cumulative live birth rate within 12 months was 42% for the total study population and 56% for the ovulatory women who had received CC.
- Factors predicting the chances for live birth included free androgen index (testosterone/sex hormone-binding globulin ratio), body mass index, cycle history (oligomenorrhea versus amenorrhea), and the woman’s age.
High singleton live birth rate confirmed after ovulation induction in women with anovulatory polycystic ovary syndrome: validation of a prediction model for clinical practice.
The M-OVIN study; does switching treatment to FSH and/or IUI lead to higher pregnancy rates in a subset of women with world health organization type II anovulation not conceiving after six ovulatory cycles with clomiphene citrate – a randomised controlled trial

- A multicentre RCT in the Netherlands
- Women with WHO type II anovulation
- Low risk of damaged Fallopian tubes
- Randomization after six ovulatory cycles with CC
- Outcome: live birth

\[ n = 680 \]

6 cycles CC 6 cycles CC + IUI 6 cycles FSH 6 cycles FSH + IUI

Letrozole appears to improve live birth and pregnancy rates in subfertile women with anovulatory PCOS, compared to clomiphene citrate. [The quality of this evidence is low]
Letrozole is as effective as clomiphene in women with unexplained infertility. A total of 36 women were included in the study out of which 16 women were diagnosed with primary unexplained infertility and the other 20 women with severe oligoasthenozoospermia/azoospermia male partners. Endometrial samples were collected on the seventh day post-ovulation and analyzed. In women with unexplained infertility treated with letrozole and CC, epithelial and stromal expression of αβ3 integrin, L-selectin, leukemia inhibitory factor (LIF), and pinopod formation was found to be significantly higher as compared to controls. Stimulation with letrozole and CC appears to enhance endometrial receptivity in women with unexplained infertility. However, letrozole and CC did not have any significant effect on the endometrial receptivity markers of women with severe male factor infertility.

- Fourteen potentially relevant trials were identified of which seven were included in this review.
- There was no evidence that clomiphene citrate was more effective than no treatment or placebo for live birth (odds ratio (OR) 0.79, 95% CI 0.45 to 1.38; P = 0.41) or for clinical pregnancy per woman randomised both with intrauterine insemination (IUI) (OR 2.40, 95% CI 0.70 to 8.19; P = 0.16), without IUI (OR 1.03, 95% CI 0.64 to 1.66; P = 0.91) and without IUI but using human chorionic gonadotropin (hCG) (OR 1.66, 95% CI 0.56 to 4.80; P = 0.35).

Ovulation and cancer risk

- Epithelial ovarian cancer is the most fatal gynecological malignancy. Its severity is essentially the result of delayed diagnosis at advanced stage in two-thirds of cases, which implies a poor prognosis with a survival rate lower than 20%.
- Cited risk factors for ovarian cancer include the hypothesis of incessant ovulation (Fathalla, 1971) with potential implications for ovarian stimulation.
- Such role of ovarian stimulation has been suggested (Harris et al., 1992; Whittemore et al., 1992), but not confirmed.
More ovarian histopathological abnormalities are found after stimulation, suggesting the responsibility of ovulation induction in the appearance of dysplastic lesions.

The presence of histopathological abnormalities seems to be linked to the intensity and number of hyperstimulations.
References


References

References

- Nikolaos P. Polyzos, Spyridon Tzioras, Davide Mauri, Maria Tsagpi, Ivan Cortinovis, Lamprini Tsali, and Giovanni Casazza. Treatment of Unexplained Infertility With Aromatase Inhibitors or Clomiphene Citrate A Systematic Review and Meta-Analysis. OBSTETRICAL AND GYNECOLOGICAL SURVEY Volume 63, Number 7, 2008
Intrauterine insemination: Is it still the bridge between ovarian stimulation and in vitro fertilization in unexplained subfertility

Richard H. Reindollar
Adjunct Professor, Departments of Obstetrics and Gynecology
Geisel School of Medicine at Dartmouth and UAB
Executive Director, ASRM

Disclosure statement:
Richard H. Reindollar, M.D. has no relevant financial relationships with any manufacturers of pharmaceuticals, laboratory supplies, or medical devices.

This presentation is my personal interpretation of the literature and not the opinion of American Society for Reproductive Medicine.

Learning Objectives
At the conclusion of this presentation the participant will consider the couple with unexplained infertility, the female partner ≤ 40 years, and be able to:
1. List the most important factors to be considered;
2. Describe key studies that provide evidence for and against the use of specific treatments;
3. Discuss whether IUI strategies are useful treatments.
4. Describe a treatment paradigm that is supported by the literature.
UI Rx: Factors for Consideration

1. The chance for pregnancy without and with Rx (evidence for improved success with Rx)
2. Access to treatment (availability, cost, etc.)
3. Safety/Adverse Events (e.g., multiples)
4. The need (and ability) for some couples to “have any treatment” and others to do “less invasive treatments.”

What is the Evidence?

U. S. Preventive Services Task Force

Levels of Evidence

• I: Properly powered and conducted randomized controlled trial (RCT); well-conducted systematic review or meta-analysis of homogeneous RCTs
• II-1: Well-designed controlled trial without randomization
• II-2: Well-designed cohort or case-control analytic study
• II-3: Multiple time series with or without the intervention; dramatic results from uncontrolled experiments
• III: Opinions of respected authorities, based on clinical experience; descriptive studies or case reports; reports of expert committees

What is the Evidence?

• Level of Evidence (Levels I, II, and III)
• RCT (Gold Standard)
  – Treatment Comparisons (Rx 1 vs. Rx 2)
  – Treatment Paradigm Comparisons (Strategy 1 vs. Strategy 2, may not address specific Rx)
• Absence of Evidence: “What is most appropriate treatment, if any?”
  – Cost, risks, gains
  – Accurate counseling
### Cycle-Specific Pregnancy Rates For 200 Couples Initiating Attempt at Conception

![Graph showing cycle-specific pregnancy rates](image)

### Unexplained Infertility Treatment Successes

( Mean Reported)

<table>
<thead>
<tr>
<th>No Rx</th>
<th>Before 1995*</th>
<th>1995</th>
<th>2004</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.5 – 4%</td>
<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td>Clomiphene/IUI</td>
<td>8.3%</td>
<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td>Gonadotropin/IUI</td>
<td>17.1%</td>
<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td>IVF</td>
<td>20.7%</td>
<td>24%</td>
<td>36.9%†</td>
</tr>
</tbody>
</table>

* Guzick et al, Fertil Steril 1998 70: 207; † 2004 CDC National Summary, females ≤ 35

### Rationale for UI Treatments:

“Upping the Ante”

- Expectant Management: Coitus (maximum 200 sperm) + Monofollicular ovulation (baseline aneuploidy)
- Upping the Ante
  - IUI alone (more sperm)
  - COS alone (more euploid oocytes)
  - IUI + COS
  - IVF (more euploid embryos)
Rationale for UI Treatments: “Upping the Ante”

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- Upping the Ante
  - IUI alone (more sperm)
  - COS alone (more euploid oocytes)
  - IUI + COS
  - IVF (more euploid embryos)

Studies Often Quoted

- NCRMN RCT (Guzick 1999): ICI vs. IUI vs. FSH/ICI vs. FSH/IUI;
- Bhattacharya, RCT Scotland (2008): Clomiphene (cc) vs. IUI vs. expectant management;
- Steures, RCT Lancet (2006): COH/IUI vs. expectant management;
- FASTT Trial (Reindollar 2010): Conventional Rx vs. Fast Track to IVF.
**Immediate IVF**

- US success rates clinically higher than for other Rx options, but: twins and HOM remain 20 – 30% and 0.7 – 1.1%, respectively.
- Number of Level II, paucity of Level I studies comparing IVF to other Rx.
  - Most of studies showing no difference, before 2000 (IVF 15 – 20% / cycle success).
- Cochrane Review of literature up to 2010: “Any effect of IVF relative to expectant management, CC, IUI with and without stimulation and GIFT in terms of live-birth rates for couples with unexplained subfertility remains unknown (Pandian 10).”
- FASTT computer simulation: conventional approach vs. immediate IVF, no difference cost-wise (because of IVF twin pregnancy rate at time).
- Mild stimulation IVF over 3 – 4 cycles = 1 US IVF cycle, but higher patient satisfaction (some parameters), lower cost, lower multiples.

**IVF will be a reasonable option for routine initial treatment of Unexplained Infertility when:**

- treatment is routinely available / accessible;
- costs are affordable to “all” couples;
- multiple pregnancy rates are appreciably lower by standard practice;

(except, for those couples seeking less invasive initial strategies).
Until then, the appropriate question is: “Which alternative treatment(s) meet sufficient criteria for efficacy and / or an acceptable multiple birth rate to warrant a place in a routine treatment paradigm?”

The Choices: How does IUI fare compared to the other options?

- IUI alone?
- Clomiphene (cc) COS alone?
- Gonadotropin (Gn) COS alone?
- CC COS + IUI?
- Letrozole COS + IUI?
- Gonadotropin COS + IUI?

IUI Alone

- 2012 Cochrane review, 14 RCTs: “there is evidence that IUI with OH increases the live birth rate compared to IUI alone (Veltman-Verhulst 2012).”
- NCRMN RCT (Guzick 1999): only 18% of 234 couples pregnant over 4 cycles of IUI alone (4.5% / cycle).
- Bhattacharya, RCT Scotland (2008), 23% of couples in IUI only arm pregnant over 6 cycles (3.8% / cycle)
The weight of the cumulative literature –no support for **IUI alone** as a routine Rx for UI.

Except, of course, for sexual dysfunction and neurological disorders.

---

**Clomiphene COS Alone**

- Cochrane review of 7 trials, 5 CC with coitus (Hughes 2010). Pregnancy rates not enhanced.
- Most noted study of Bhattacharya 2008 (cc, IUI, expectant management over 6 cycles): cc alone no better than expectant management but:
  - Only 56% of 167 couple not pregnant from cc received 6 Rx cycles;
  - 4% of cycles cancelled for “hyperstimulation;”
  - 2 couples IUI, not CC

Currently, studies in the literature do not demonstrate benefit from **clomiphene COS alone**---

but, the literature begs better RCTs (particularly using US Rx protocols).
Gonadotropin (Gn) COS Alone

- No studies that have compared Gn COS to expectant management for UI, except-
  - 2 of 4 arms of NCRMN Trial
    1. Gn with intracervical insemination (4% / cycle)
    2. Intracervical insemination alone (2% / cycle)
    – AND, Gn Rx associated with 1 set of quads, 1 set of triplets, ≥ 20% twins + OHSS

The use of **Gonadotropin COS alone** in couples with UI not justified by any literature.

Clomiphene COS + IUI

- Systematic review of literature, 8.3% / cycle compared to 4% / cycle untreated patients (Guzick 1998).
- Meta-analysis, 6 RCTs (cc/IUI vs. natural cycle/coitus), 4 – 5 X higher pregnancy rate for cc/IUI. "Clomiphen and IUI is an effective early treatment option (Costello 2004)."
- 2012 Cochrane Review, 14 RCTs: "there is evidence that IUI with OH increases the live birth rate compared to IUI alone (Veltman-Verhulst 2012)."
- FASTT Trial: all 503 couples cc/IUI, 1294 prospective cycles, sustained pregnancy rate 7.6% / cycle, 25% / 3 cycles (8% multiples, 1 triplet) (Reindollar, 2010).
NIH RMN AMIGOS RCT
Diamond, MP et al, Presented 2014 ASRM Annual Meeting

Gn/IUI vs. CC/IUI vs. Letrozole/IUI:
• Up to 4 cycles each for 300, 301, 299 couples with UI, the female partner 18 – 40 years;
• Live birth rates in 32%, 23%, 18.7%* of cycles;
• Multiple births in 31.8%* (24 twins, 10 triplets), 9.4% (twins), 13.4% (twins)

Live births for Letrozole lower and multiple births intermediate between Gn and CC/IUI.
CC/IUI remains first line Rx for UI.

Clomiphene COS + IUI remains a reasonable first line treatment option for couples with UI.

Letrozole COS + IUI
• Prior literature suggested that Letrozole cos / IUI had similar efficacy when compared to cc cos / IUI.
NIH RMN AMIGOS RCT
Diamond, MP et al, Presented 2014 ASRM Annual Meeting

Gn/IUI vs. CC/IUI vs. Letrozole/IUI:
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---

Gonadotropin COS + IUI

- Initial systematic review: 20.7% / cycle (Guzick 1998)
- Initial studies plagued with multiples
  - Gleicher (2000): 441 pregnancies, 88(20%) twins, 22(5%) triplets, 10(2.3%) quadruplets, 5(1.1%) quintuplets, 2(0.5%) sextuplets.
  - Dickey (2001): 294 pregnancies, 41(14%) twins, 20(68%) "higher order multiples" – at least 1 quintuplet.
- NCRMN RCT, Gn/IUI 9% / cycle: twins, triplets, quadruplets (Guzick 1999).
- FASTT RCT, Gn/IUI 10% / cycle (Reindollar 2010)

---

NCRMN Trial for FSH/IUI:
Only stimulation of FSH (150 IU) with IUI had a significantly improved success rate (but associated with HOM and high twin rate)

Success rates over 4 cycles:
- ICI 10%
- IUI 18%
- FSH/ICI 19% (1 quad, 1 triplet)
- FSH/IUI 33% * (2 quads, 3 triplets)
  * 9 % /cycle

FASTT: Pregnancy Rates Per Treatment Cycle Initiated (Reindollar 2010)

<table>
<thead>
<tr>
<th>Rx (N cycles)</th>
<th>Conventional</th>
<th>Fast Track</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td>95 (36.4)</td>
<td>73 (28.0)</td>
<td>145 (40.2)</td>
</tr>
</tbody>
</table>

Mild Stimulation Gn COS + IUI

- Steures (2006), COS (mostly Gn) /IUI: no difference than expected management.
- Dankert (2007), CC/IUI (10%/cycle and 28% couples) vs. Gn/IUI (8.2%/cycle and 27% couples).

COH/IUI vs. Expectant Management

Steures et al. Lancet, 2006
The Netherlands

RCT: 253 couples 6 mo, COH/ IUI vs. Exp. Manag.
Pregnant 42/127 (33%) 40/126 (32%)
Ongoing Preg 29/127 (23%) 34/126 (27%)

CONCLUSION: IN THIS STUDY, COH/IUI WAS NO DIFFERENT AS A TREATMENT THAN NO TREATMENT (Expectant Management).
COH/IUI vs. Expectant Management


RCT: 253 couples 6 mo, COH/IUI vs. Observation
- “Recommended” FSH (37 IU to 150 IU, average 75 IU)
- 127 COH/IUI cycles
- 126 Expectant Management cycles
- 14% Rx cycles cancelled (> 3 follicles ≥ 16 mm or > 5 follicles ≥ 16 mm)
- 58% of IUI cycles had only 1 mature follicle
- 20% of EM group received COH/IUI
- Table 2: PR for mono- and multi-follicular cycles were 4 and 5%/cycle

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<table>
<thead>
<tr>
<th>COH/ IUI</th>
<th>Expectant Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>72%</td>
<td>80%</td>
</tr>
</tbody>
</table>

The Fast Track and Standard Treatment (FASTT) Trial
NIH/NICHD R01 HD38561*

Study Characteristics

- Treatment Naive
- Met definition of unexplained infertility (FASTT, 1 year)
- Age
  - FASTT: < 40th birthday, (mean age 33 yrs);
- Normal ovarian reserve before and during trials: (FSH < 15 mIU/ml, E2 < 100 pg/ml);

Treatment Arms

<table>
<thead>
<tr>
<th>Conventional</th>
<th>Fast Track</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clomiphene</td>
<td>Clomiphene</td>
</tr>
<tr>
<td>100 mg x 5 days/1 IUI* x 3 cycles</td>
<td>100 mg x 5 days/1 IUI* x 3 cycles</td>
</tr>
<tr>
<td>↓ 150 FSH IU x 5 days/1 IUI each cycle x 3 cycles</td>
<td>↓</td>
</tr>
<tr>
<td>↓ IVF x 6 cycles (Maximum 4 fresh cycles)</td>
<td>IVF x 6 cycles (Maximum 4 fresh cycles)</td>
</tr>
</tbody>
</table>

*LH Kit, US backup

FASTT CONSORT Flow Diagram

Preliminary Screen for Eligibility, n = 10,188
Randomized, n = 503
9/2001 – 8/2005

Conventional Protocol, n = 247
Initiated Treatment Protocol, n = 243
Follow-up Per Protocol, n = 212
Analyzed, n = 247

Fast-track to IVF Protocol, n = 256
Initiated Treatment Protocol, n = 250
Follow-up Per Protocol, n = 236
Analyzed, n = 256
Cycle Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Conventional</th>
<th>Fast Track</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients Randomized</td>
<td>247</td>
<td>256</td>
<td>503</td>
</tr>
<tr>
<td>Patients With ≥1 Cycle</td>
<td>243 (98)</td>
<td>250 (98)</td>
<td>493 (98)</td>
</tr>
<tr>
<td>Total CC/IUI Cycles</td>
<td>646</td>
<td>648</td>
<td>1294</td>
</tr>
<tr>
<td>Total FSH/IUI Cycles</td>
<td>439</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total IVF Cycles</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Cycles</td>
<td>1346</td>
<td>1009</td>
<td>2355</td>
</tr>
</tbody>
</table>

* NOTE 337 (25%) FEWER CYCLES IN FAST TRACK COMPARED TO CONVENTIONAL ARM

Sustained Pregnancy Rates Per Couple

<table>
<thead>
<tr>
<th></th>
<th>Conventional</th>
<th>Fast Track</th>
<th>All N/total * (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
<td></td>
</tr>
<tr>
<td>CC</td>
<td>45 (19)</td>
<td>53 (22)</td>
<td>98/475 (21)</td>
</tr>
<tr>
<td>FSH</td>
<td>43 (25)</td>
<td>-</td>
<td>43/169 (25)</td>
</tr>
<tr>
<td>IVF</td>
<td>73 (66)</td>
<td>118 (69)</td>
<td>191/283 (68)</td>
</tr>
<tr>
<td>Subtotal</td>
<td>161 (68)</td>
<td>171 (68)</td>
<td>332/493 (67)</td>
</tr>
<tr>
<td>CIP†</td>
<td>24 (10)</td>
<td>28 (11)</td>
<td>52/503 (10)</td>
</tr>
<tr>
<td>Total</td>
<td>185 (75)</td>
<td>199 (78)</td>
<td>384/503 (76)</td>
</tr>
</tbody>
</table>

* Total couples undergoing treatment; † Cycle Independent Pregnancies

Pregnancy Rates Per Treatment Cycle Initiated

<table>
<thead>
<tr>
<th>Rx (N cycles)</th>
<th>Conventional</th>
<th>Fast Track</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All N (%)</td>
<td>Sustained N (%)</td>
<td></td>
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</tr>
</tbody>
</table>
Cumulative Incidence of Pregnancy

Conventional (n=247) median time to pregnancy 11 mo.
Fast Track (n=256) median time to pregnancy 8 mo.

HR=1.40 (95% CI 1.03-1.90) P=0.03
(Analysis using piecewise Cox proportional hazards model)

Total Charges Per Delivery

Includes outpatient, inpatient, ER, and medication charges for women, and infant inpatient charges obtained from Insurance Companies.

<table>
<thead>
<tr>
<th>Arm</th>
<th>Couples N*</th>
<th>Sum Total Charges</th>
<th>Couples with a live birth delivery N</th>
<th>Charge Per Delivery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional</td>
<td>215</td>
<td>$9,424,646</td>
<td>132</td>
<td>$71,399</td>
</tr>
<tr>
<td>Fast Track</td>
<td>233</td>
<td>$9,606,269</td>
<td>156</td>
<td>$61,553</td>
</tr>
</tbody>
</table>

* Insurance data available for 448 (89%) of 503 couples

Multiple Births of Sustained Pregnancies

<table>
<thead>
<tr>
<th></th>
<th>Conventional</th>
<th>Fast Track</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CC</td>
<td>FSH</td>
</tr>
<tr>
<td>Twins</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 (11)</td>
<td>7 (16)*</td>
<td>21 (29)</td>
</tr>
<tr>
<td>Triplets</td>
<td>0</td>
<td>1 (+1)*</td>
</tr>
<tr>
<td>&gt; 3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>5 (11)</td>
<td>8 (19)</td>
</tr>
</tbody>
</table>

* Includes 1 reduced from triplets; † includes cycle independent (CIP)
Unknown multiple status for 5 CIP and 1 IVF ongoing pregnancies
Conclusions

- Gonadotropin /IUI treatment does not add value to a contemporary treatment paradigm.
- An accelerated approach to IVF (that eliminates FSH/IUI but starts with CC/IUI) results in an equivalent percentage of pregnancies with:
  - a 40% increased rate of pregnancy (between 3 and 11 months of treatment) that is statistically significant;
  - fewer treatment cycles; and,
  - at an estimated lower cost.
- IVF would have to cost $17,749 for conventional treatment to have a lower cost per delivery than accelerated therapy.

NIH RMN AMIGOS RCT
Daimond, MP et al, Presented 2014 ASRM Annual Meeting

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- Up to 4 cycles each for 300, 301, 299 couples with UI, the female partner 18 – 40 years;
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Live births for Letrozole lower and multiple births intermediate between Gn and CC/IUI.
CC/IUI remains first line Rx for UI.

Weight of the evidence suggests that there is no role for Gonadotropin COS + IUI in the routine treatment of UI.
Treatment of UI Summary

- IVF is the most successful Rx, but costs, access, and multiple currently limit its use for initial routine Rx.
- Mild stimulation IVF is an acceptable alternative treatment with intermediate success and costs and improved patient satisfaction by some parameters.
- IUI alone, CC COS alone, or Gn COS alone do not improve outcome over no treatment.
- The literature supports CC COS + IUI but not Gn COS + IUI for an initial routine treatment.

Management of Unexplained Infertility: numerous studies world-wide.

Observation (4%/cycle)

Clomiphene/IUI (8%/cycle)

How to fill the gap?

IVF (40%/cycle)
References

- 2004 CDC National Summary, Sonera c 18.
- NORMA RCT (Guzick 1999): AI vs. AI+HMG vs. FSH/ICSI.
- FASTT Trial (Reindollar 2010): Carbohydrate Rx vs. Fast Track to IVF.
- Systematic review of literature: 8.3% / cycle compared to 4% / cycle untreated patients (Guzick 1998).
- FASTT Trial (Reindollar 2010): Carbohydrate Rx vs. Fast Track to IVF.
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- Systematic review of literature: 8.3% / cycle compared to 4% / cycle untreated patients (Guzick 1998).
What would a cost effective fertility management algorithm look like?

Professor Cindy Farquhar
University of Auckland

Declarations

- Coordinating editor of the Cochrane Menstrual Disorders and Subfertility Group
- Co-Chair of the Female Diagnostic section of the WHO Fertility Guidelines 2014-2015
- No commercial conflicts to declare

Learning objectives

- Cost effectiveness and fertility treatments – why?
- How to develop the costs of an algorithm?
- What does a cost effective algorithm look like for female investigation?
Costs and fertility

- The bottom line – can we afford it?
- High stakes – how can we not afford it?
- Time is short – want it now!

Who is paying?

- Third party
  - Government, insurance
- Self paying
- Co-payment

Cost effectiveness and fertility treatments – why?

- Evidence based medicine cannot be isolated from cost
- Economic approaches are central to informing advice and decisions by guideline developers and funders
- Safety needs to be taken into consideration
- To get the best from funding
  - We must be able to express results as a form of benefit and the cost to the population
  - Simple questions – what is the cost of one live birth from a fertility treatment
+ IVF is an expensive treatment

Connolly 2010

Cost and success rates in IVF

- Live birth rates after one initiated cycle and fresh transfer only around the globe usually vary from 20-35% per initiated cycle
- Little data on cumulative rates with fresh and frozen transfer
- Difficult to assess SET and DET if only use fresh transfers
- Should cost include the neonatal care
- If an IVF cycle costs $10,000 (fresh transfer only)
  - Optimistic: likelihood of a live birth is 33% per fresh transfer then the cost of one live birth is $30,000
  - Pessimistic: likelihood of live birth = 10%, then cost of live birth is $100,000

Health system payer

- There are never enough resource to meet all potential uses
- Decisions about what will be funded (and at what level) and what will not be funded need to be made
- Opportunity costs
  - Once the resource is used it can never be used for anything else
  - What else might that resource have been spent on
  - Allocating resources to one option incurs the cost that some benefit will be lost because resources were not allocated to another option...
  - Maximize benefits and minimise opportunity costs
- In order to do that you need data on resources (costs) and benefits (effectiveness)
Economic evaluation is important when:

- ...significant amounts of health care resources are at stake; and where trade-offs between costs and outcomes, or between different types of outcomes, are likely.
- Lowest cost and maximal effectiveness and safety also important for self funding couples.
- Rely on advice to make decisions.

Matrix linking “new treatment” effectiveness with cost:

<table>
<thead>
<tr>
<th>Decreasing effectiveness</th>
<th>Increasing costs</th>
<th>Cost savings</th>
<th>No difference in costs</th>
<th>Increased costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved effectiveness</td>
<td>□□□□□□□□□□□□□□□□□</td>
<td>□□□□□□□□□□□□□□□□□</td>
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<td>□□□□□□□□□□□□□□□□□</td>
</tr>
<tr>
<td>No difference in effectiveness</td>
<td>□□□□□□□□□□□□□□□□□</td>
<td>□□□□□□□□□□□□□□□□□</td>
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<td>□□□□□□□□□□□□□□□□□</td>
</tr>
<tr>
<td>Not enough evidence</td>
<td>□□□□□□□□□□□□□□□□□</td>
<td>□□□□□□□□□□□□□□□□□</td>
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</tbody>
</table>

Challenges in developing cost effective algorithms:

- Variation in health systems
- Who is paying?
- Access to treatment
- Variable drug costs
- Variable protocols
- Safety
Investigating the infertile woman and man

The work up – 4 questions?

- Does this woman ovulate?
  - Serum progesterone
  - or just take a history....

- Normal semen analysis?
  - WHO criteria
  - Role of post coital testing

- Is there a satisfactory passage for fertilisation and implantation to occur?
  - CAT or HSG or laparoscopy?

- Clinical flags for pelvic pathology?
  - Additional or alternative testing

Draft WHO pathway for investigation 2015
+ Confirming ovulation

- Mid luteal phase progesterone test or mid cycle urinary LH/estrone testing is usually recommended
- Low cost
- A clinical history of regular menstrual cycles is also sufficient

+ Ovarian reserve testing

- Evidence summary – 11 studies, 4 SRs + 7 prospective cohort studies
- SRs: low-moderate evidence that ORTs assessed had no clinically meaningful predictive value for pregnancy or live birth
  - Most studies were in women with regular cycles
  - Expectant management and IUI (mostly)
- There are studies reporting extremely low AMHs and pregnancies (Yarde 2013)
- Main role is in ovarian stimulation protocols

+ Tubal testing – CAT, HSG or laparoscopy?

- Two scenarios tested cost effectiveness:
  - Verhoeve 2013 - HSG followed by tailored treatment or diagnostic laparoscopy if HSG shows no tubal patency was also considered cost effective
  - Mol 1999 Chlamydia antibody titre (CAT) if they had good fertility prospects but should have immediate HSG if poor fertility prospects (clinical flags for pathology)
- Laparoscopy is indicated if there are clinical flags for tubal disease or endometriosis…. but
  - If HSG suggests severe tubal disease & no symptoms then IVF
  - Treatment of endometriosis is useful step
**Post coital testing**

- 5 studies (n=8709)
  - SR + 4 cohort studies
- PCT has a poor predictive value on pregnancy rate both naturally conceived and through fertility treatment (low quality evidence)
- PCT result correlates with semen quality
  - Positive PCT in the presence of severe male factor infertility results in a higher chance of spontaneous ongoing pregnancy (very low quality evidence)
- Total absence of visualized motile sperm in a PCT may help to detect those couples who are infertile secondary to significant male factor infertility, or due to coital technique (very low quality evidence)


**Post coital testing - recommendations**

- The PCT should not be offered in the investigation of the infertile/subfertile couple because it doesn't predict the likelihood of pregnancy
- For couples where the woman has a normal evaluation for infertility factors and the male refuses semen analysis, the PCT can be used to suggest that further evaluation of male factor infertility and/or coital technique is indicated.

**Keeping costs down in investigation pathway**

- Laparoscopy – can be avoided in many cases
  - Bilateral tubal blockage – IVF not tubal surgery unless very experienced surgeon or to clip tubes
  - Abnormal scan and pelvic pain main indication
- Tubal testing – chlamydial antibody test first, if negative continue trying, if positive, then HSG
  - The most cost-effective strategy for tubal pathology in couples whose 3 year chance of conception was >14%
  - If the chance of conception was < 14% then HSG first (Moi et al 1999)
- Low cost items – could be stopped eg. Post coital tests, ovarian reserve testing, ovulation testing, endometrial biopsy, others…
Can we ignore lifestyle factors?

- What about lifestyle factors that we encounter at the time of the first consultation?

Patient selection for IVF

- Maximize success rates and reduce drug costs
- Avoid high BMIs
- Non-smokers
- Age < 42

It's true.....

"Don't cry if I make you cry."
Role of BMI and success of an IVF cycle

- Maheshwari et al. 2007: Infertility women undergoing IVF
  - If BMI >25 then OR for pregnancy = 0.71 (CI 95% 0.62-0.81)
  - If BMI >30 then OR for pregnancy = 0.68 (CI 95% 0.55-0.83)

Resource usage increases

<table>
<thead>
<tr>
<th>Study</th>
<th>BMI</th>
<th>Resource issue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lewis 1990</td>
<td>&lt;25</td>
<td>Reduced oocytes recovered</td>
</tr>
<tr>
<td>Crosignani 1994</td>
<td>&gt;29</td>
<td>Greater use of gonadotrophins</td>
</tr>
<tr>
<td>Ramzy 1996</td>
<td>&gt;28</td>
<td>Greater use of gonadotrophins</td>
</tr>
<tr>
<td>Lashen 1999</td>
<td>&gt;28</td>
<td>No impact</td>
</tr>
<tr>
<td>Wittmer 2000</td>
<td>BMI &gt;26</td>
<td>Increased no. ampoules, ↓ oocytes</td>
</tr>
<tr>
<td>Spandorfer 2004</td>
<td>BMI &gt;27</td>
<td>Increased cycle cancellation</td>
</tr>
<tr>
<td>Dokras 2006</td>
<td>BMI &gt;39</td>
<td>Increased cycle cancellation</td>
</tr>
<tr>
<td>Engel 2003</td>
<td>&lt;25</td>
<td>Greater use of gonadotrophins</td>
</tr>
<tr>
<td>Fedorscak 2004</td>
<td>BMI &gt;30</td>
<td>Greater use of gonadotrophins</td>
</tr>
</tbody>
</table>

Gonadotrophin usage

Difference in total amount administered (IU) for obese versus non-obese women
Weight and Age

- Sneed et al found BMI did not appear to have a significant effect on IVF outcome (Hum Repro 2008;23:1835-1839)
- However compounded with combination of obesity and age
- At young age, sig BMI had a pronounced neg effect on fertility which reduced with age.
- After 36 yrs, BMI had minimal impact

Figure 1: The Effect of Age and BMI on clinical pregnancy rates. Lines illustrate the best-fit regression lines derived by multiple logistic regression for clinical pregnancy rates as a function of BMI and Age at 5-year intervals: 20, 25, 30, 35 and 40. Sneed et al HR2008;23:1835-1839

Role of maternal age and number of treatment attempts

- Australian cost–effectiveness analysis using ANZARD data from 2002 (Griffiths et al, 2010)
- A treatment program included one fresh cycle and a variable number of frozen cycles
- 30-33 yo
  - cost per LB – $27373 - $31986 on 1st and 3rd program
- 42-45 yo
  - cost per LB – $130951 - $187515 on 1st and 2nd program
- Overall these costs were not affected by the inclusion of costs of OHSS or multiple births (20% at 30-33 yo and 12% at 42-45 yo)

All costs Australian $
Women and Cigarette Smoking

  - Increased risk of infertility OR 1.60 (CI= 1.34-1.91)
  - Dose related
  - Earlier menopause by 1-4 yrs

Smoking and Fertility Treatment

- MA of 21 studies (Waylen et al, HRU, 2009)
  - OR livebirth/cycle if smoked =0.54 (CI= 0.30- 0.99)
  - Spontaneous misc OR= 2.65 (CI= 0.1,33-5.3)
  - Ectopic OR = 15.69 (CI= 0.2,87-85.76)
- Canadian Retrospective study (Neal et al HR 2005)
  - Passive smoking also important
  - preg rates smokers (19.4%)
  - passive smokers (20%)
  - non-smokers (48.3%)

Smoking Cessation

- Beneficial for chances of conception, healthy pregnancy and healthy environment for child to grow up in.
  - Observational data suggests negative effect reversed within 1 yr of cessation
Treatment choices for couples with unexplained infertility

- Continue trying
- Intrauterine insemination
- In vitro fertilisation

Calculate the probability of a spontaneous ongoing pregnancy within 1 year (leading to live birth).

IUI or IVF Pandian et al Cochrane review 2015

- 9 RCTs: compared IVF with expectant management
- 2 RCTs: compared IVF with unstimulated IUI
- 6 RCTs: compared IVF with stimulated IUI (FSH or CC)
- Moderate to very low – poor reporting, imprecision
IUI versus IVF: live birth rates

- IVF versus expectant management: Live birth rate per woman was significantly higher with IVF (45.8%) than EM (3.7%) (odds ratio (OR) 22.00, 95% confidence interval (CI) 2.56 to 189.37, 1 RCT, 51 women)
- IVF versus unstimulated IUI: significantly higher with IVF (OR 2.47, 95% CI 1.19 to 5.12, 2 RCTs, 156 women), 40.5% with IVF versus 18.3% with unstimulated IUI.
- IVF versus stimulated IUI: no evidence of a difference between the groups among treatment-naive women (OR 1.11, 95% CI 0.95 to 1.30, 4 RCTs, 745 women), 46.3% with IVF versus 41.7% with IUI+SO
- RCT of women undergoing IVF versus IVF with FSH who had been pretreated with IUI + clomiphene citrate (OR 2.66, 95% CI 1.94 to 3.63, 1 RCT, 341 women), 58.1% with IVF versus 21.8% with IUI+SO.
- RCT comparing IVF and IUI+CC: There was no evidence of a significant difference in live birth rate between IVF (31.3%) and IUI+CC (15.6%), (OR 2.46, 95% CI 0.94 to 6.41, 1 RCT,102 women).
- No evidence of difference between treatment groups for multiple pregnancy and OHSS

Pandian et al Cochrane review 2015

IUI versus expectant management

- Two RCTs:
  - Bhattacharya 2008: unstimulated IUI had similar rates of live birth to expectant management
  - Steures et al 2006: couples with prediction scores between 30 and 40% had similar live birth rates with IUI + FSH and expectant management


IUI stimulation protocols

- RCT of 900 women up to 4 cycles of IUI
  - outcomes of LBR, MPR
    - Clomiphene 23.3%, 1.3%
    - Letrozole 18.7%, 2.7%
    - FSH 32%, 10.3%
    - Letrozole was significantly lower than CC and FSH for LBR
    - No high order multiple in CC and Letrozole but 10 sets of triplets in the FSH group
    - CC and IUI remains first line therapy for couples with unexplained infertility
  - Diamond et al Abstract ASRM 2014
An assisted reproduction cycle is a series of individual steps….

- Complex with interactions between steps
- Benefits and harms can take place with each step
- Trade-offs may be necessary
- Two patients to consider – mother and baby

Steps in an ART cycle – where are the cost savings?

- Gonadotropins – urinary/recombinant/depot
- Oral stimulation protocols
- Antagonist cycles
- Modified natural cycle IVF
- Minimal monitoring - ultrasound
- Triggering
- Freeze all cycles
- Ovum pick up
- The transfer – SET, ultrasound guidance
- Length of embryo incubation
- Luteal phase support

Which gonadotrophin – urinary or recombinant?

- Cochrane review van Wely et al 2010:
  - Live birth rate: 28 trials, 7339 couples, OR 0.97, 95% CI 0.87 to 1.08
  - This suggests that for a group with a 25% live birth rate using urinary gonadotrophins the rate would be between 22.5% and 26.5% using rFSH
  - OHSS rate: 32 trials, 7740 couples, OR 1.18, 95% CI 0.86 to 1.61.
  - This means that for a group with 2% risk of OHSS using urinary gonadotrophins, the risk would be between 1.7% and 3.2% using rFSH.
  - “Clinical choice of gonadotrophin should depend on availability, convenience and costs”
  - Connolly 2008: cost difference per cycle €468 (1 fresh and 1 frozen transfer)
  - When effectiveness and safety is the same then make decision on cost
Long acting FSH

- No evidence of a difference between long acting and daily dose of FSH (Cochrane review: Pouwer et al 2012)
- If the long acting FSH is cheaper than the daily dose then cost savings

Which protocols? Antagonist or agonists

- Cochrane review: Al-Inany et al 2010 Live birth rate – all studies
- No evidence of difference between the different antagonists or minimal stimulation IVF
- Cochrane review: Gibreel et al 2010
- No difference in live birth rates
- Reduction in OHSS
- Reduction in ampoule usage

Authors conclusions: these findings based on a small number of underpowered studies. Recommended further studies.
Natural cycle or modified NC IVF

**Natural cycle-IVF (NC-IVF)**
- No drugs are administered
- When the follicle approaches maturity (10 mm), start monitoring
- Triggering with hCG when the follicle 15 to 20 mm or when the serum estradiol rises, or both

**Modified natural cycle-IVF (MNC-IVF)**
- Gonadotrophins for 2-6 days to stimulate follicular growth.
- After maximum six days of FSH or largest follicle is 14 mm, then GnRH antagonists
- When leading follicle is 15 to 20 mm, ovulation is triggered in the same manner as in COH-IVF but only one oocyte is fully grown and retrieved

Modified natural cycle CR Allersma et al 2013

**Mild stimulation**

Promising...

Time to pregnancy Bensdorp et al BMJ 2015

IVF+ SET: 8 months
IVF+MNC: 8.3 months
IUI+COH: 8.4 months
Cost of modified natural cycle

- MNC is cheaper per cycle than COH but also less effective in terms of live birth rate
- Groen et al 2013: tested different scenarios using observational data from the Netherlands
- “The comparison of simulated scenarios indicates that a strategy of three to six cycles of MNC with minimized medication is a cost-effective alternative for one cycle of COH with strict application of single embryo transfer (SET)”

Definitely promising…..

Cycle Monitoring: Cochrane review Kwan et al 2014

- No evidence of a difference between ultrasound and ultrasound plus estradiol levels for clinical pregnancy rate, number of oocytes, OHSS and cycle cancellation

Triggering – GnRH agonist or hCG?

- 17 RCTs
  - 9 report OHSS
  - 5 report live birth rate
- Risk of bias
  - Only 2/17 used blinding
  - 4/17 studies stopped prematurely for differing reasons
  - All studies were either funded by pharmaceutical companies or did not report their funding
Ovarian hyperstimulation rate is reduced with agonist trigger in high risk women only.

Youssef et al, updated 2013*4 studies no events in either arm

OR 0.06 (0.01, 0.34)

Live birth rates

<table>
<thead>
<tr>
<th>OHSS – low risk</th>
<th>OHSS – high risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCG trigger</td>
<td>34% 1% 3%</td>
</tr>
<tr>
<td>GnRH agonist</td>
<td>24% 0.01% .03%</td>
</tr>
</tbody>
</table>

Number need to treat* -10 113 38

* Number need to treat in order to have one less live birth or one less woman with OHSS (NNT) = 100/ARR

Live birth rate reduced with GnRHa triggering

Balancing the benefits and risks
As an Editor of this journal, I would whole-heartedly welcome a manuscript on the first sufficiently powered RCT of GnRHa triggering in one arm, and traditional hCG triggering in the other; with subsequent secondary randomization to a ‘freeze-all’ strategy or a ‘fresh transfer’ strategy in either of the two arms.

Price difference between hCG and GnRH agonist trigger
- $100
- Reduced OHSS costs with GnRHa
- But you need to factor in the freezing/thaw and any further stimulation used

Freezing protocols
- Thaw cycle stimulation protocols
- Unclear if there is a superior protocol
Fresh versus frozen Wong et al. 2015

<table>
<thead>
<tr>
<th>Study or Subheading</th>
<th>Outcome</th>
<th>Total</th>
<th>Control</th>
<th>Fresh</th>
<th>Total</th>
<th>Control</th>
<th>Fresh</th>
<th>Total</th>
<th>Control</th>
<th>Fresh</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probability of live birth</td>
<td>41%</td>
<td>27%</td>
<td>38%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probability of multiple pregnancies</td>
<td>29%</td>
<td>1.6%</td>
<td>&lt;1%</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

Trade off between better live birth rates from one fresh transfer and multiple pregnancy rates.

Need to take obstetric and neonatal costs into account - SET delivers considerable savings.

DET is the most expensive strategy and only more effective for fresh transfer.

Single embryo transfer CR Pandian et al. 2013

<table>
<thead>
<tr>
<th>Study or Subheading</th>
<th>Probability of live birth</th>
<th>Probability of multiple pregnancies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Double embryo transfer</td>
<td>41%</td>
<td>29%</td>
</tr>
<tr>
<td>Single embryo transfer</td>
<td>27%</td>
<td>1.6%</td>
</tr>
<tr>
<td>Single embryo transfer + FZET</td>
<td>38%</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

Single embryo transfer and cost

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Single embryo transfer</th>
<th>Twin transfer</th>
<th>Cost difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Connolly</td>
<td>UK (2002)</td>
<td>£416</td>
<td>£416.9</td>
<td>£416.5</td>
</tr>
<tr>
<td>Connolly</td>
<td>The Netherlands (2005)</td>
<td>£416</td>
<td>£416.9</td>
<td>£416.5</td>
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<tr>
<td>Connolly</td>
<td>Sweden (2006)</td>
<td>£416</td>
<td>£416.9</td>
<td>£416.5</td>
</tr>
<tr>
<td>Connolly</td>
<td>Italy (2006)</td>
<td>£416</td>
<td>£416.9</td>
<td>£416.5</td>
</tr>
</tbody>
</table>

Notes: Costs provided in sterling using exchange rates and converted to euro using average 2005 exchange rates. 10% accuracy.
**Flushing for follicles**

- Follicular flushing: CR by Wongtra-ngan 2010
- 3 studies, 164 patients
- No evidence that follicular aspiration and flushing is associated with improved clinical or ongoing pregnancy rates, nor an increase in oocyte yield
- The operative time is significantly longer and more opiate analgesia is required for pain relief

**Conscious sedation for pain relief**

- Cochrane review: Kwan et al 2012
- Better than other interventions such as acupuncture and cervical block
- No studies comparing general anaesthesia with sedation

**Blastocyst or cleavage stage**

- Day 5 – less embryos to transfer than CS so any rates difficult to compare unless per started cycle
- a higher implantation rate
- the opportunity to select the most viable embryo(s) for transfer
- the potential decrease in the number of embryos transferred and the need for transfer
- better temporal synchronization between embryo and endometrium at the time of embryo transfer
Cleavage stage versus blastocyst stage embryo transfer in ART: live birth after fresh transfer

- 2000: 10 RCTs - No evidence of a difference in pregnancy rate, live birth only reported in 1 trial.
- 2005: 16 RCTs - Still no difference in pregnancy rate.
- 2007: 18 RCTs - New conclusion that significant difference in live birth and pregnancy outcome in favour of blastocyst culture.
- 2012: 23 RCTs - Live birth reported in 11 studies (favour blastocyst culture) and first reporting cumulative pregnancy rates (favouring cleavage stage).

NNT = 1 in 12

31% LB rate in day 2/3 and 39% in day 5/6 = 8% difference
For every 12 women who have a blastocyst transfer there is one extra live birth

Cumulative pregnancy rate with cleavage stage versus blastocyst stage embryo transfer in ART after fresh and frozen embryos

- 45% in the day 5/6 group and 56% in the day 2/3 group = 11% difference
NNT = 9
For every 9 women who have all available fresh and frozen embryos transferred there is one additional pregnancy

Number of embryos transferred: live birth after fresh transfer
Costs – no clear answer re BL and CS

- Better pregnancy rate with fresh transfer
- Reduced cumulative pregnancy rates
- Reduced no. embryos to transfer
- Reduced embryos to freeze
- Laboratory cost of extended culture

Ultrasound guided embryo transfer  CR: Brown et al 2010

- Lower pregnancy rate with fresh transfer
- Better cumulative rate
- Greater number of transfers
- More embryos to freeze

Luteal phase support  van der Linden et al 2010

- Favours synthetic progesterone without any additions
- No specific route
- hCG associated with OHSS
Topics not covered today

- Laboratory techniques such as oxygen levels, adhesion molecules
- Culture media
- Time lapse systems
- New incubator techniques – the walking egg incubator

My version of a cost effective ART cycle

- Which gonadotropin? urinary
- Oral stimulation protocols – maybe, not yet
- Antagonist cycles – yes
- Modified natural cycle hCG – maybe
- Minimal monitoring – ultrasound only
- Which trigger? hCG, if no risk factors, GnRHα + freeze all policy if risk factors
- Single embryo transfer – yes.
- Length of embryo incubation – cleavage stage with transfer of frozen embryos?
- Ovum pick up – sedation, no flushing, adhesion molecules, oxygen concentrations
- Embryo transfer with ultrasound guidance
- Luteal phase support with progesterone

A minimalist pathway

[Diagram]

150
References for ovulation testing


Reference list for post coital tests


References for tubal patency testing


References for IVF

- Broeze KA, et al. Integration of patient characteristics and the results of Chlamydia antibody testing and hysterosalpingography in the prediction of tubal patency. Fertility and Sterility 2003; 80(1): 165-171.
Acknowledgements

- Cochrane Menstrual Disorders and Subfertility Group
Sexual functioning in women dealing with infertility and/or endometriosis

www.eshre.eu/leuven/endo

Leuven, Belgium
24-25 September 2015

Donor sperm banking: medical, socio-cultural, ethical and juridical considerations

www.eshre.eu/leuven/andro

Leuven, Belgium
10-11 December 2015

Endoscopy in reproductive medicine

www.eshre.eu/endoscopy/oct15

Leuven, Belgium
28-30 October 2015

The impact of reproductive surgery on cross-talk between the embryo and the endometrium

www.eshre.eu/milan

Milan, Italy
28-30 January 2016

When is surgery the answer to early pregnancy complications?

www.eshre.eu/coventry

Coventry, United Kingdom
21-22 January 2016

Oocyte maturation - from basics to clinics

www.eshre.eu/brussels

Brussels, Belgium
3-5 March 2016

For information and registration: www.eshre.eu/calendar
or contact us at info@eshre.eu
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