Factors Affecting Success in Intrauterine Insemination

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Kadın Hastalıkları ve Doğum A.D., ÜYTE Merkezi
Overview of Infertility

• involves a couple, rather than a single individual

• in women < 35 years of age; inability of a couple to conceive after 12 months

• in women > 35 years and older; after 6 months of regular intercourse without use of contraception

Practice Committee of American Society for Reproductive Medicine; Fertil Steril; 2008
Normal Fertility

- **Fecundability**, the probability of achieving a pregnancy in one menstrual cycle (20-25%)

- **80 to 90%** of apparently normal couples will conceive **within the first year** of attempted conception

- The fecundability of the cohort **decreases** over time and with **increasing age of the female partner**

- **5 to 15%** of apparently normal couples will conceive **in the second 12 months** of attempted conception

So that 95% percent of couples will have conceived after 24 months

*Habbema JD, Fertil Steril; 2004
Zinaman MJ, Fertil Steril, 1996*
Figure 11.1  Probability of a spontaneous live birth without treatment in a woman with either primary (no previous pregnancies) or secondary (previous pregnancies) infertility of 2 years duration, who is having regular intercourse and where she has normal ovulation, patent fallopian tubes and a partner with normal sperm motility (40%) (Hunault et al., 2004)
Worldwide Prevalence of Infertility

- Involuntary childlessness affects more than 70 million couples worldwide.
- In 2010,
  - 1.9% of women aged 20 to 44 years who wanted to have children were unable to have their first live birth.
  - 10.5% of women with a previous live birth were unable to have an additional live birth.

Mascarenhas MN, PLoS Med; 2012
Causes of Infertility

- **Male factor** (hypogonadism, post-testicular defects, seminiferous tubule dysfunction) 26%
- **Ovulatory dysfunction** 21%
- Tubal damage 14%
- Endometriosis 6%
- Coital problems 6%
- Cervical factor 3%
- **Unexplained** 28%

_Bhattacharya S., Hum Reprod; 2009_
Evaluation of Infertile Couple

- Semen analysis
- Menstrual history, documentation of normal ovulatory function
- Assessment of LH surge in urine, D21-24 P4
- HSG or Sonohysterogram with a test of tubal patency
- D3 serum FSH, E2 levels, AMH, and/or AFC
- TSH
- Pelvic ultrasound; uterine myomas and ovarian cysts
- In select couples; Hysteroscopy and/or L/S

Practice Committee of American Society for Reproductive Medicine, Fertil Steril; 2012
Treatment Options

• **Lifestyle modifications** to improve fertility,
  – **Losing weight**, smoking cessation, reducing excessive caffeine and alcohol consumption, and appropriate timing and frequency of coitus

• **Therapeutic interventions** for treatment of male and female infertility
  • Drug therapy
  • Surgery

• **IUI or IVF**
The rationale of IUI

• **Only 0.1%** of spermatozoa placed in the upper vagina were also present in the cervical canal, 1 h after insemination.

• More strikingly **only 1 in every 14 million motile sperm** deposited in the vagina reaches the site of fertilization in the oviduct.

*Setlage DS., Fertil Steril; 1973*
Intrauterine Insemination

• **Hypothesis:** is to increase the gamete density at the site of the fertilization even when sperm or cervical mucus abnormalities are present.

• **The minimum requirements are:**
  – ovulation in the IUI cycle,
  – patency of at least one fallopian tube,
  – adequate number of motile sperm,
  – absence of documented or suspected active cervical, intrauterine, or pelvic infection
IUI in a historical perspective

- **1678**, first description of spermatozoa by Antoni van Leeuwenhoek
- **1770**, John Hunter described the first case of human intravaginal insemination because of severe hypospadias.
- **1784**, the first IUI was reported by Lazzaro Spallanzani in canine
- **mid-1800s** J. Marion Sims reported on 55 intravaginal inseminations, only one pregnancy reported
- The first reports on human IUI originated from Guttmacher (**1943**) and Kohlberg (**1953**)

*Cohlen B., Hum Reprod Update; 2018*
IUI in a historical perspective

- **1953**, Dr Jerome K. Sherman frozen sperm
- **1964**, birth of the first DI by Dr Sherman
- **1978**, one of the most important milestones in the history of IUI was the **sperm washing procedures** (Steptoe and Edwards)
- **1988**, Sunde et al. 127 births in 20 clinics as a result of IUI with pretreated sperm

*Cohlen B., Hum Reprod Update; 2018*
Insemination of Semen in humans....

- Originally developed to help heterosexual couples to become pregnant in case of **severe male factor infertility** of a physical or psychological nature,

- Nowadays insemination with homologous semen is most commonly used for **unexplained and mild male factor infertility**.
Indications of IUI

- mild male infertility
- minimal or mild endometriosis
- while waiting for IVF
- when IVF is not affordable in women with patent tubes
- unexplained subfertility
- DI is commonly used for individual women who desire a pregnancy
### Changes in WHO semen variable criteria

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<tbody>
<tr>
<td>Volume (mL)</td>
<td></td>
<td>≥ 2.0</td>
<td>≥ 2.0</td>
<td>≥ 2.0</td>
<td>≥ 1.5</td>
</tr>
<tr>
<td>Concentration (×10^6/mL)</td>
<td>20–200</td>
<td>≥ 20</td>
<td>≥ 20</td>
<td>≥ 20</td>
<td>≥ 15</td>
</tr>
<tr>
<td>Total sperm number (10^6/ejaculate)</td>
<td>≥ 40</td>
<td>≥ 40</td>
<td>≥ 40</td>
<td>≥ 40</td>
<td>≥ 39</td>
</tr>
<tr>
<td>Motility (motile, %)</td>
<td>≥ 60</td>
<td>≥ 50  (a + b)</td>
<td>≥ 50  (a + b)</td>
<td>≥ 50  (a + b)</td>
<td>≥ 50  (a + b + c)</td>
</tr>
<tr>
<td>Morphology (normal, %)</td>
<td>80.5</td>
<td>≥ 50</td>
<td>≥ 30</td>
<td>≥ 14</td>
<td>≥ 4</td>
</tr>
<tr>
<td>Viability/vitality (live, %)</td>
<td>≥ 50</td>
<td>≥ 75</td>
<td>≥ 75</td>
<td>≥ 75</td>
<td>≥ 58</td>
</tr>
<tr>
<td>White blood cells (10^6/mL)</td>
<td>&lt; 4.7</td>
<td>&lt; 1.0</td>
<td>&lt; 1.0</td>
<td>&lt; 1.0</td>
<td>&lt; 1.0</td>
</tr>
</tbody>
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**Evaluation of sperm concentration, motility, morphology and vitality**

*Cooper TG, Hum Reprod Update; 2010  
Kim YJ., Semin Reprod Med; 2014  
Murray KS., Fertil Steril; 2012*
### Table I  Cut-off values of sperm parameters according to the WHO 1999 and 2010 criteria and nomenclature.

<table>
<thead>
<tr>
<th></th>
<th>WHO 1999</th>
<th>WHO 2010</th>
<th>Nomenclature if below cut-off value</th>
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<tbody>
<tr>
<td>Volume</td>
<td>2 ml</td>
<td>1.5 ml</td>
<td>Hypospermia*</td>
</tr>
<tr>
<td>Sperm concentration</td>
<td>$20 \times 10^6$ spermatozoa/ml</td>
<td>$15 \times 10^6$ spermatozoa/ml</td>
<td>Oligozoospermia**</td>
</tr>
<tr>
<td>Motility (A + B)***</td>
<td>50%</td>
<td>32%</td>
<td>Asthenozoospermia</td>
</tr>
<tr>
<td>Morphology</td>
<td>30% normally formed</td>
<td>4% normally formed***</td>
<td>Teratozoospermia</td>
</tr>
</tbody>
</table>

**TMSC** = \[
\frac{\text{Sample volume} \times \text{Density} \times \text{Motility}(A+B)\%}{100}\]

**SUMMARY ANSWER:** The prewash TMSC shows a better correlation with the spontaneous ongoing pregnancy rate (SOPR) than the WHO 2010 classification system.

- In daily practice,
  - TMSC; 5×10^6, 5 to 20×10^6 and > 20×10^6 spermatozoa (normospermia)
  - No differences in SOPR whether the TMSC was, 1×10^6, 1–3×10^6 or 3–5×10^6

*Hamilton JAM, Hum Reprod; 2015*
Should We Continue Performing Intrauterine Inseminations in the Year 2004?

B.J. Cohlen

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- The evidence-based value of IUI as a treatment for cervical hostility, male factor and unexplained infertility was first described in 2004.

- IUI in cycles with mild ovarian hyperstimulation should be the treatment of choice in couples with mild male subfertility (average TMSC > 10 million) and unexplained subfertility.

- MOH/IUI is more cost-effective compared with IVF and ET.
For people with unexplained infertility, mild endometriosis or ‘mild male factor infertility’, who are having regular unprotected sexual intercourse:

- do not routinely offer intrauterine insemination, either with or without ovarian stimulation (exceptional circumstances include, for example, when people have social, cultural or religious objections to IVF)
- advise them to try to conceive for a total of 2 years (this can include up to 1 year before their fertility investigations) before IVF will be considered. [new 2013].
The revival of intrauterine insemination: evidence-based data have changed the picture

W. Ombelet¹,²,³

• The limited value of IUI in infertility treatment as mentioned in the 2013 NICE guidelines was surely a premature statement and should be adapted to the actual literature.
• NICE guidelines were partly based on a study in which mathematical modelling

• The data used in their calculations were not based on prospective RCTs but derived from the published peer-reviewed literature as well as activity data of local infertility units

• The methods used were criticized and according to Bahadur et al. (2016) the evidence strongly favours IUI over IVF in selected couples and therefore national funding strategies should include IUI treatment options before IVF is recommended (Bahadur et al., 2016).

• The results of the multi-centre RCT reported by Bensdorp et al. (2015), clearly shows that from a cost-benefit point of view IUI–OS is the best first choice treatment in patients with moderate male infertility and poor prognosis unexplained infertility.
In women with unexplained infertility and an unfavourable prognosis for natural conception, three cycles of IUI with OS were associated with a three-fold improved CLBR compared with three cycles of EM.

- 6% multiple PR. (Two sets of twins)
## What Are Good Prognosticators?

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<tr>
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<th><strong>Good</strong></th>
<th><strong>Bad</strong></th>
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<tbody>
<tr>
<td>Cause of infertility</td>
<td>Anovulatory</td>
<td>Endometriosis or Male factor</td>
</tr>
<tr>
<td>Age</td>
<td>&lt;25-35 y old</td>
<td>&gt;35-40 y old</td>
</tr>
<tr>
<td>TMSC</td>
<td>&gt;10-30 x 10⁶</td>
<td>&lt;1.0-5.0 x 10⁶</td>
</tr>
<tr>
<td>Duration of Infertility</td>
<td>&lt;3-4 y</td>
<td></td>
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</table>

Freour T., *Int J Androl*; 2009  
Clinical pregnancy rates following homologous intrauterine insemination are significantly influenced by female age, male smoking, primary/secondary infertility and inseminating motile count.
Is Ovarian Stimulation Beneficial?

- The aim of OS is to increase the number of oocytes available for fertilization and to enhance accurate timing.

- The “ideal” stimulation cycle may be deemed as the recruitment of two follicles measuring > 16 mm, with an E2 concentration > 500 pg/mL on the day of hCG administration.

*Van Rumste MM., Hum Reprod Update; 2008*
When to perform?  
Once or twice?

- Insemination at 36 hours after hCG administration has been the preferred time for IUI.
- No difference in PRs when compared with double 12- and 36-hour inseminations.

Kim Yong J., Semin Reprod Med; 2014
Tonguc E., Fertil Steril; 2010
Flexible versus rigid intrauterine insemination catheters: A prospective, randomized, controlled study


**Objective:** To prospectively compare pregnancy rates for couples undergoing IUI by a single healthcare provider with random assignment to either rigid (Tomcat; Kendall Sovereign, Mansfield, MA) or flexible (Soft Pass; Cook, Spencer, IN) catheters.

**Conclusion(s):** There is no statistically significant difference between flexible and rigid catheters for IUI. (Fertil Steril® 2005;83:1544–6. ©2005 by American Society for Reproductive Medicine.)
Which Semen Preparation Technique?

- Swim-up procedure
- Migration-sedimentation
- Density gradient centrifugation
- Glass wool filtration
- Sephadex columns
- Transmembrane migration

Advantages and disadvantages of density gradient centrifugation.

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
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<tr>
<td>- usually clean fraction of highly motile spermatozoa</td>
<td>- production of good interphases between the different media is a bit more time-consuming</td>
</tr>
<tr>
<td>- spermatozoa from ejaculates with a very low sperm density can be separated</td>
<td>- a bit more expensive</td>
</tr>
<tr>
<td>- good yield</td>
<td>- potential risk of endotoxins</td>
</tr>
<tr>
<td>- leukocytes are eliminated to a large extent</td>
<td>- Percoll® may no longer be used in IVF/ICSI</td>
</tr>
<tr>
<td>- reactive oxygen species are significantly reduced</td>
<td></td>
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</table>

Henkel RR., Reprod Biol Endocrinol; 2003
Luteal Phase Supplementation

• Routine LPS using vaginal progesterone does not seem to improve PRs in normally ovulating women when stimulated with CC for IUI.

  Kyrou D., Hum Reprod ;2010

• an increase in PRs of IUI cycles was observed with LPS using vaginal suppositories in women with unexplained infertility.

  Erdem A., Fertil Steril; 2009
• Progesterone LPS is beneficial to patients undergoing OI with gonadotropins in IUI cycles. The NNT is 11 patients to have one additional live birth.

• Progesterone support did not benefit patients undergoing OI with CC or CC + gonadotropins.
Alternative Protocol for LPS

• Not to give LPS routinely

• If 7 days after insemination, the progesterone level is less than 20 pmol/L, vaginal P4 pessaries 200 mg x 2-3/day may be prescribed.

• Till to serum β-hCG analysis on day 14 after the insemination

Fatguhar CM., Lancet; 2018
Couples with unexplained subfertility and unfavorable prognosis: a randomized pilot trial comparing the effectiveness of in vitro fertilization with elective single embryo transfer versus intrauterine insemination with controlled ovarian stimulation

Fertility and Sterility® Vol. 96, No. 5, November 2011

Inge M. Custers, M.D., a Tamar E. König, M.D., b Frank J. Broekmans, M.D., Ph.D., c Peter G. A. Hompes, Prof. b

**Conclusion(s):** In patients with unexplained or mild male subfertility and a poor prognosis for natural conception, one cycle of IVF-eSET might be as effective as three cycles of IUI-COS as primary treatment. Elective single embryo transfer does not seem an effective strategy in preventing multiple pregnancies in this particular population. In the future a strict SET policy (i.e., compulsory SET) might be an option. Our trial provides evidence for the feasibility and highlights the importance of a large definitive trial to determine the effectiveness and side effects of both strategies. (Fertil Steril® 2011;96:1107–11. ©2011 by American Society for Reproductive Medicine.)

- As a primary treatment in **unexplained or mild male subfertility couples**

  **1 cycle of IVF = 3 IUI+COH**
My concluding remarks will be through the questions and algorithm of a recent publication...
IUI: review and systematic assessment of the evidence that supports global recommendations

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Submitted on November 6, 2017; resubmitted on November 6, 2017; editorial decision on December 4, 2017; accepted on December 19, 2017
1. What are the indications for IUI versus intercourse or expectant management in infertile couples and when should treatment be initiated

In couples with unexplained infertility with a prognosis of becoming pregnant without assistance within the next 12 months (estimate >30%), IUI could be postponed for at least 6 months. In couples with unexplained infertility and men with a total motile sperm count (TMSC) >10 million and a prognosis of spontaneous pregnancy <30% within a year, it is recommended that IUI plus ovarian stimulation (OS) is the treatment of first choice.
2. When is OS required in an IUI cycle?

In couples with unexplained infertility and men with a TMSC above 10 million, IUI should be combined with OS to improve live birth rates.

Cohlen B., Human Reprod Update, 2018
3. What is the influence of sperm quality on IUI outcome? Can we define threshold levels for successful IUI?

It is not possible to define clear lower cut-off levels of pre- or post-wash sperm parameters below which IUI should be withheld.

Cohlen B., Human Reprod Update, 2018
4. When is the best timing of insemination in an IUI cycle? What is the optimal method of timing in natural or stimulated IUI cycles?

Providers can determine the method of triggering in IUI stimulated with gonadotrophins as there is no evidence to recommend for or against a method. Moderate

Providers can determine the method of timing IUI in natural cycles (no OS) as there is no evidence to recommend for or against a method. Moderate

If a HCG injection is used, single IUI can be performed any time between 24 and 40 hours after HCG injection without compromising pregnancy rates. Moderate

IUI in a natural (not ovarian stimulated) cycle should be performed 1 day after LH rise. Moderate

Cohlen B., Human Reprod Update, 2018
6. What is optimal number of inseminations per cycle?

In both unexplained and male infertility there is insufficient evidence that the intervention, a double IUI, within the same cycle will lead to better pregnancy rates than a single IUI within a cycle. Women undergoing IUI should be offered a single insemination per cycle.

Cohlen B., Human Reprod Update, 2018
7 Is there a benefit of bed rest after IUI?

Women undergoing IUI, should have 10 to 15 minutes of bed rest after an insemination. Moderate

Cohlen B., Human Reprod Update, 2018
8. What is the ultimate number of consecutive IUI cycles per couple/woman in which pregnancy rates still increase significantly?

In couples with an indication for IUI at least three consecutive IUI cycles should be performed. There is insufficient evidence to recommend a maximum number of IUI treatment cycles.
9. Which semen preparation technique used yields the best results (in terms of pregnancy rates) for IUI?

According to the available evidence, it is not possible to recommend any semen preparation technique over another (swim-up, gradient, wash and centrifugation).

Cohlen B., Human Reprod Update, 2018
10. What is the cost-effectiveness of IUI versus IVF/ICSI

In couples with unexplained infertility and men with a TMSC of >10 High million and a prognosis of a pregnancy without assistance <30% within a year, at least three cycles of IUI–OS is the most effective option.
12. How can you prevent multiple pregnancies and ovarian hyperstimulation syndrome in an IUI programme?

In order to prevent high rates of multiple gestation pregnancies in IUI–OS, IUI should be withheld when more than two dominant follicles >15 mm or more than five follicles >10 mm at the time of HCG injection or LH surge are present. When gonadotrophins are used in IUI, regimens with 75 IU or lower should be used because higher doses have similar pregnancy rates but increase multiple pregnancy rates. Clomiphene citrate or tamoxifen are acceptable alternatives to low dose gonadotrophins for low multiple pregnancy and birth rates and with lesser costs, although at a lower live birth rate than with gonadotrophins. Addition of GnRH agonist to gonadotrophins in IUI–OS is not recommended because there is no increase in pregnancy rate despite increased multiple pregnancy rates and increased costs. Good practice point: As an alternative to cycle cancelation, aspiration of excess follicles at the time of HCG injection or LH surge might be additional options for reducing the risk of multiple pregnancy in IUI–OS.
• duration of subfertility,
• women’s age,
• primary or secondary infertility,
• percentage of motile sperm,
• referral status (general practitioner or gynaecologist).
Thank you for your patience...