Infertility workup

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Inser
Curacao 2015

- Diagnosis
- Causes
- Diagnostic workup
  - Ovulatory function
  - Tubal function
  - Uterine cavity
  - Semen
- Controversies
  - Unexplained infertility
  - Varicocele
  - Fibroids

Infertility diagnosis

1yr

2yr

Clinical definition of infertility “failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse”


Time to pregnancy in humans

Barnea y Cols
ObstetGynecol 66: 24,1985
Infertility vs. Subfertility

Aging and fertility, forever enemies?

Fertility potential related to age

Infertility according to age groups

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Table III. Age of marriage and risk of childlessness

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Risk of childlessness (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20–24</td>
<td>5.7</td>
</tr>
<tr>
<td>25–29</td>
<td>9.3</td>
</tr>
<tr>
<td>30–34</td>
<td>15.5</td>
</tr>
<tr>
<td>35–39</td>
<td>20.6</td>
</tr>
<tr>
<td>40–44</td>
<td>63.5</td>
</tr>
</tbody>
</table>

From Menken et al. (1986); by permission from Science.
**A persistent misperception: assisted reproductive technology can reverse the “aged biological clock”**

SART 2003-2009: IVF cycles <35 years 47.6% LB 41.4%
IVF cycles in >42 years or older → 9.08% LB 4.2%

*Fertil Steril. 2012 May;97(5):1044-7*

**When to intervene?**

- **1 yr**
  - < 35 yrs
- **6 months**
  - ≥ 35 yrs
- **ASAP**
  - ≥ 40 yrs
  - Endometriosis
  - PCOS
  - Pelvic adhesions
  - Uterine anomalies
  - Testicular pathology
  - Impaired sexual intercourse

Human Reproduction Vol. 19, No. 8 pp. 1689-1692, 2004
ASRM. Practice committee report. Fert Steril. 90 (3), Nov 2008*

**Who’s to blame?**

**Causes**

- **Ovulatory**
- **Tubal**
- **Male**
- **Unexplained**
- **Other**

**Causes**

- **Single**
- **Combined**

Human Reproduction Vol. 19, No. 8 pp. 1689-1692, 2004
ASRM. Practice committee report. Fert Steril. 90 (3), Nov 2008*
Infertility is a couple thing

How intense must we be in the infertility diagnostic workup?

ASRM expert committee

Subsequent evaluation should be conducted in a systematic, expeditious, and cost-effective manner so as to identify all relevant factors, with initial emphasis on the least invasive methods for detection of the most common causes of infertility.

The pace and extent of evaluation should take into account the couple’s preferences, patient age, the duration of infertility, and unique features of the medical history and physical examination.

The couple must be studied concurrently.


What are the main points in infertility workup?

Mission: Go to Gap, Buy a Pair of Pants

Investigation of the infertile couple: when is the appropriate time to explore female infertility?


How to study the ovulatory function?

Ovulatory disfunction

- Progesterone vs. endometrial biopsy
- LH ovulation kit.
- Ultrasound.
- Basal FSH / Estradiol
- AMH
- AFC
- TSH – free T4
- Prolactin
- PCOS labs


AMH, Inhibin B and AFC Prediction of poor reponse y COH

Prospective cohort study.

135 patients

Outcomes is the poor response and no conception

AFC and AMH were the best. AUC of 0.935 and 0.905,

AFC (limit 10) : Sens de 93%, Esp de 88%

AMH (limit 0.99 ng/ml): Sens 100%, Esp 72%

• The AFC and AMH are the most significant predictors of poor response to ovarian stimulation during ART.
How to study Fallopian tube function?

HSG, SHG (SIS) or Laparoscopy?

Optimal use of infertility diagnostic tests and treatments
The ESHRE Capri Workshop Group

- **Hysterosalpingography**
  - Pros
    - Tubal fx & uterine cavity
    - Low cost
    - Less invasive
  - Cons
    - Screening: no definitive Dx
    - Endometriosis?
    - Low therapeutic effect
    - Pain

- **Laparoscopy**
  - Indications:
    - Suspected endometriosis.
    - Pelvic adhesions.
    - Tubal disease.
  - Pros
    - Definitive diagnosis
    - Endometriosis
    - Therapeutic options
  - Cons
    - Cost
    - Invasive

- **Sonohysterography (SIS)**
  - Endometrial cavity
  - Tubal function with high operator dependance.


Advantages and Disadvantages of Hysterosalpingography (HSG), Hysterosalpingo-contrast sonography (HyCoSy), and laparoscopy with intravital dye instillation (L&D):

<table>
<thead>
<tr>
<th>Study</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
</table>
| HSG   | Potential visualization of entire length of fallopian tubes  
Polyvinyl alcohol (PVA) to diagnose certain tubal pathologies (e.g., SPH, hydrosalpinx)  
Therapeutic agents with documented improvement in pregnancy rates (e.g., PVA) | |
| HyCoSy | Visualization of ovaries, uterine and fallopian tubes in one study | |
| L&D   | Visualization of salpingo-oophoritis, adenomyosis, and scar tissue with appropriate equipment & facilities  
Therapeutic agents improve pregnancy rates not documented | |

Chlamydia antibodies

Women without risk factors for tubal disease:

A negative test does not require further tubal assessment: ≤15% of tubal pathology.

If the test is positive, further tubal function evaluation must be considered.

Women with high risk of tubal disease should be screened with HSG/Lx/SHG.

Chlamydia antibodies

Prediction of normal tubes with CAT compared to laparoscopy:

- Sensitivity 40-50%
- PPV 50-60%
- NPV 80-90%

Uterine cavity evaluation

- Exploration of the uterine cavity is actually one of the basic explorations in infertility workup
- Hysteroscopy – Gold Standard

**Options**

- **Sonohysterography (SIS)**
  - Pros
    - Tubal fx & uterine cavity
    - Low cost
    - Less invasive
  - Cons
    - Less invasive
  - 3D ultrasound
    - Less invasive
    - Mullerian anomalies

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**SIS for uterine cavity evaluation**

- Sens 0.88 (95% CI 0.85 – 0.90)
- Spec 0.94 (95% CI 0.93 – 0.96)
- Highly sensitive investigative modality and comparable to the gold standard tool

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**SIS vs HSG for uterine cavity evaluation**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Sensitivity</th>
<th>Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIS</td>
<td>80.4%</td>
<td>95% CI 0.66 – 0.97</td>
</tr>
<tr>
<td>HSG</td>
<td>37%</td>
<td>95% CI 0.24 – 0.51</td>
</tr>
</tbody>
</table>

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**Male factor evaluation**

**Semen Analysis**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normal Values for SA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume</td>
<td>1.5 – 5 ml</td>
</tr>
<tr>
<td>Sperm Concentration</td>
<td>&gt; 15 mill</td>
</tr>
<tr>
<td>Motility</td>
<td>&gt; 32% of sperm (A+B)</td>
</tr>
<tr>
<td>Morphology</td>
<td>&gt; 4% motile (A+B+C)</td>
</tr>
<tr>
<td>Vitality</td>
<td>≥ 58%</td>
</tr>
</tbody>
</table>

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**Male factor**

- Obtained by masturbation
- Abstinence 2 to 7 days
- Analyze within 1 hour
- A normal semen analysis excludes male factor 90% of the time

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Cooper TG, et al. World Health Organization reference values for human semen characteristics.  *Hum Reprod*. 16(3); 231. 2010

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Cooper TG. et al. *World Health Organization reference values for human semen characteristics*.  *Hum Reprod*. 16(3); 231. 2010
Evaluation of abnormal semen analysis

- Repeat semen analysis in 30 days
- Physical examination
  - Testicular size
  - Varicocele
- Laboratory tests
  - Testosterone
  - FSH (spermatogenesis: Sertoli cells)
  - LH (testosterone: Leydig cells)
- Referral to urology


Endometriosis

Severe:
- Adhesions
- Tubal obstruction
- Ovarian reserve

Mild:
- Hostile biochemical pelvic environment.


Unexplained infertility

- Normal semen analysis
- Patent tubes
- Normal uterine cavity
- Ovulatory

MSCOCO by British Medical Journal Publishing Group

Unexplained infertility

Endometriosis?
- Pelvic adhesions?
- Luteal phase deficiency?
- Sperm function tests.
- Antisperm antibodies.
- Genetic analysis?
- Postcoital test.

Time to pregnancy leading to live birth in groups allocated to clomifene citrate, expectant management, or unstimulated intrauterine insemination.

S Bhattacharya et al. BMJ 2008;337:bmj.a716

©2008 by British Medical Journal Publishing Group
Unexplained infertility

Expectant management for 6 months is justified.

Varicocele

- Varicocele is a common abnormality with the following andrologic implications:
  1. Failure of ipsilateral testicular growth and development
  2. Symptoms of pain and discomfort
  3. Reduced fertility: only in clinically palpable varicocele.

Infertility and Varicocele

- Poor venous drainage: interrupted heat exchange in spermatic cord.
- Increased scrotal temperature.
- Altered spermatogenesis.

Varicocele is the most common cause of male infertility: in 40% of infertile men.

Indications for varicocele repair

- Abnormal semen analysis.
  - Not in isolated teratozoospermia.
- Infertility or desire for future fertility.
- Female partner with normal fertility or treatable cause.
  - Time to conception is not a concern.
- Varicocele is clinically palpable.
- Testicular atrophy.

Not all varicocele is worthwhile to treat.
Although a varicocelectomy should always be performed before ART is pursued, this surgery does not increase pregnancy rates or decrease miscarriage rates following ICSI.

Can avoid need for testicular biopsy in men with nonobstructive azoospermia.


Fibroids and reproduction

Reduced implantation and clinical pregnancy in IVF for IM and SM

Increased pregnancy complications

Increased miscarriage rate for IM and SM
Reduced clinical pregnancy in IVF in IM fibroids vs controls

No change clinical pregnancy after myomectomy in IM

Increased clinical pregnancy after myomectomy in SM

Fibroids and reproduction

- SS fibroids don’t affect reproductive potential.
- SM fibroids affect reproductive potential.
  - Myomectomy of SM increase pregnancy and live birth rates.
  - IM fibroids seem to diminish pregnancy and live birth rates.
    - Evidence is poor quality and non conclusive
    - In most reports the uterine cavity evaluation was poor.
    - Even if IM fibroids do indeed decrease fertility, it is not a given that their removal will reverse the process and normalize fertility or even be beneficial to the patient.
  - IM fibroids seem to be detrimental especially over 5 cms.

Conclusions

1. Infertility diagnostic workup should be done on couples with at least 1 year of periodical unprotected sexual intercourse without reaching pregnancy. This period should be 6 months if the women is 35 years or older.
2. It should be done right away in couples with conditions associated with infertility, such as endometriosis, PCOS, PID or testicular anomalies.
Conclusions

3. Diagnostic workup should include both members of the couple and must be complete.
4. Most couples with infertility have a diminished, but not abolished, possibility of a spontaneous pregnancy.
5. Infertility diagnostic workup must include semen analysis, ovulatory function analysis, Fallopian tube function analysis and the uterine cavity condition evaluation. Have endometriosis in mind.

Summary

- Semen analysis
- FSH - TSH
- TV ultrasound
- Day 21 serum progesterone
- BSG, SIS, LhRs, Chlamydia

- Reproductive Medicine
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  - Paula Vanegas
  - Marcela Pantoja
  - Carolina Zapata
  - Teresa Ortega

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  - Angela Trujillo, MD

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