Clinical Trials of the Reproductive Medicine Network: How Cooling the Testis, Estrogen Inhibition in Women and a New Goal for Ovulation Induction Could Improve Fertility (One child at a time!)

Gregory M. Christman M.D.
Associate Professor
Reproductive Endocrinology and Infertility
UMHS Center for Reproductive Medicine

The Eunice Kennedy Shriver
National Institute of Child Health and Human Development
Reproductive Medicine Network
Sites of the Reproductive Medicine Network
The Reproductive Medicine Network - Expansion

- 7 clinical sites:
  - University of Michigan
  - Wayne State
  - Penn State
  - University of Pennsylvania
  - University of Vermont
  - University of Texas-San Antonio
  - University of Colorado at Denver

- Data coordinating center at Yale

- Ancillary sites: University of California – San Francisco, University of Connecticut, University of Wisconsin-Madison, SUNY-Syracuse

- 7 CREST Sites
RMN TRIAL Network – Why?
History of the Reproductive Medicine Network

- 5 year award for a trial network focusing on infertility and reproductive disorders in men and women
- Currently in the 4th funding cycle
- Application in September 2006 added a new requirement for expertise and experience in andrology or male factor infertility
The RMN and ARRA stimulus

- Extra 9 million over the next 2 years
- ARRA 2 year stimulus to RMN to focus on reducing the health burden of multiple gestation (AMIGOS trial)
To determine the safety and efficacy of letrozole, an aromatase inhibitor, compared to clomiphene citrate, a selective estrogen receptor modulator, in achieving live birth in infertile women with PCOS.

PREGNANCY IN POLYCYSTIC OVARY SYNDROME II

A 20-week double-blind randomized trial of clomiphene citrate and letrozole for the treatment of infertility in women with PCOS
After progestin withdrawal, women are randomized equally to either:

- clomiphene citrate 50 mg each day for 5 days (days 3-7 of cycle) or

- letrozole 2.5 mg each day for 5 days (days 3-7 of cycle)

Dosages will be increased in subsequent cycles in both treatment groups for non-response or poor ovulatory response up to a maximum of 150 mg of CC or 7.5 mg of letrozole each day for 5 days for 5 treatment cycles or until pregnancy results
PPCOS II inclusion criteria for screening

**Key Criteria**
- ovulatory dysfunction and either hyperandrogenism or PCO appearing ovaries on ultrasound

**Couple Criteria**
- no other major infertility factor
- agree to have intercourse 2-3x/week during the study
- no previous vasectomy, or tubal ligation reversal procedures
PPCOS II Exclusion Criteria

- poorly controlled Type 1 or 2 diabetes
- liver disease or dysfunction
- renal disease
- significant anemia
- history of DVT, pulmonary embolus, or CVA
- uncontrolled hypertension
- known symptomatic heart disease
- history of cervical, endometrial or breast carcinoma
- undiagnosed vaginal bleeding, and
- unable to stop using meds known to affect reproductive function or metabolism e.g., OCPs, GnRH agonists and antagonists, anti-androgens, obesity drugs, somatostatin, diazoxide, ACE inhibitors, calcium channel blockers*

*There is a 1-2 month washout period for listed med use
VIA Trial – University of Michigan

Designed to address men with impaired fertility, an abnormal semen analysis and a palpable varicocele, the Varicocele-IUI assessment trial will examine the effect of Microsurgical Varicocelectomy on conception and live birth outcome.

http://clinicaltrials.gov/ct2/show/NCT00767338
Microsurgical varicocelectomy will result in an increase in the live birth rate in infertile couples where the male partner has a palpable varicocele and an abnormal semen analysis.
Varicocele – Definition and Incidence

- Varicoceles are abnormally dilated testicular veins secondary to internal spermatic vein reflux
- Varicoceles are found in 15% of the population, 35% in couples with primary infertility, and 75% of men with secondary infertility
## Classification of a Varicocele

<table>
<thead>
<tr>
<th>Classification</th>
<th>Clinical Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade III (Large)</td>
<td>• Visible at rest</td>
</tr>
<tr>
<td>Grade II (Medium)</td>
<td>• Palpable with standing alone</td>
</tr>
<tr>
<td>Grade I (Small)</td>
<td>• Palpable with ValSalva Maneuver</td>
</tr>
<tr>
<td>Sub clinical</td>
<td>• Detected by ultrasound alone (not palpable)</td>
</tr>
</tbody>
</table>
Varicocele Treatment and Significance

- Varicoceles are associated with decreased testicular size, testosterone levels, and sperm abnormalities.
- Pathophysiology of varicoceles is poorly understood but is related to increased temperature, decreased intratesticular testosterone and stasis.
- Varicocele corrective surgery is recommended by the Practice Committee of the ASRM if the varicocele is palpable, the semen analysis is abnormal and female infertility factors are not present or corrected.
- Health outcome estimates suggest that the cost per delivery for varicocele surgery vs. IVF/ICSI is $12,700 vs. $89,000.
Advantages of Microsurgical Repair

- Preserves Testicular Artery
- < 1% Recurrence Risk
- Avoids hydrocele formation
- No Serious Morbidity
Varicoceles and Infertility: Three Key Steps In Management
Primary Aim I: To study the effect of varicocelectomy in men with infertility and an abnormal semen analysis and a palpable varicocele in a randomized controlled clinical trial on subsequent live birth rates.

Secondary Aim I: To study the effect of varicocelectomy in men with infertility and an abnormal semen analysis and a palpable varicocele on testicular semen analysis parameters.

Secondary Aim II: To study the effect of varicocelectomy in men with infertility and an abnormal semen analysis and a palpable varicocele on quality of life, and costs of care.
Couples will be selected for study after meeting the following entrance criteria:

- 6 months of infertility (primary or secondary – randomization will be stratified to allow equal numbers of primary and secondary infertility couples in the treatment vs. observation group) male partner > 18 years of age and ≤ 50 years of age
- female partner > 18 years of age and ≤ 40 years of age
- evidence of a hysterosalpingogram or SIS with one patent tube and regular ovulatory cycles ≥ 25 days and < 35 days in the female partner
- Evidence of a bilateral grade I or unilateral grade II-III varicocele on physical exam in the male partner
- abnormal semen analysis (WHO II) with sperm count > 5 X10^6 /ml or abnormal morphology (Kruger criteria)
The presence of retrograde ejaculation or uncorrectable ejaculatory dysfunction

Decreased ovarian reserve in the female partner as evidence by a day #3 FSH ≥ 12 mIU/ml
VIA-IUI Study Protocol

Varicocele

- Surgery
  - Timed IC/IUI
- No Surgery
  - Timed IC/IUI
VIA Secondary Outcome Measures

- testicular volume, testosterone, FSH, scrotal temperature, sperm concentration, motility and morphology
- novel assays of sperm function (micro RNA and mRNA, motility longevity, DNA integrity testing, acrosome reaction, mucus penetration)
- Quality of Life Indices (both partners)
- Costs and Health Outcome Measures
- Pregnancy Outcomes
Octomom, Research and Politics
For couples with unexplained infertility who undergo ovarian stimulation treatments, the RMN Ameliorating Multiple Gestation Ovarian Stimulation trial will seek to determine the optimal application of available ovulation induction medication to reduce the occurrence of multiple gestation pregnancies.
Gonadotrophins – Playing with Fire

FRENETIC WANDERINGS www.swensonfunnies.com

THE GOOD NEWS, FOLKS, IS THAT YOU ARE PREGNANT WITH TWIN DAUGHTERS. THE BAD NEWS IS THAT YOUR TWINS ARE PREGNANT TOO.

PROBLEMS WITH FERTILITY DRUGS.