

# **IVF Protocols: Hyper & Hypo-Responders, Implantation**

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**CONCEPTIONS**

REPRODUCTIVE ASSOCIATES  
OF COLORADO



**Subset : Refractory Endometrium**

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## Refractory Endometrium

Including POF, longstanding hypothalamic dysfunction, Kallmann's, empty sella syndrome, DE recipients nearing menopause with fibrotrophic endometrium

- Oral/vaginal estrace with patch to increase E2 driven proliferation
- Viagra 25mg QID PV to increase vascularity/flow
- 81 ASA QD
- Acupuncture
- 800 mgs pentoxyifylline (PTX)(Pentoxil ER 400 mg x2/d or Trental CR 400 mg x2/d) with 1000 IU tocopherol (Vit E)
  - PTX (and metabolites) improve blood flow properties by decreasing viscosity; vit E as anti-oxidant

## Refractory Endometrium

- Successful pregnancies after combined pentoxifylline-tocopherol treatment in women with POF who are resistant to hormone therapy  
Letur-Kornisch et al, *Fertil Steril* 2003;79:439-411.
- Case report of 3 women with echogenic endometrium mean 4.9mm despite high serum E2 levels on ERT
- PTX 800mg with Vit E 1000mg qday for  $\geq$  9 months
- Improvement to mean 7.4mm triple layer
- 2 embryo FET in two of the patients resulted in pregnancy
- Fibroatrophic changes ameliorated
- Initial report of 6 women with radiation induced fibroatrophic changes responded to 12 months of therapy with increase in endometrial thickness from 3 to 6mm, 1.5 fold increase in myometrial volume, and restoration of diastolic uterine artery flow  
Letur-Kornisch et al, *Fertil Steril* 2002;77:1219-26.

## Endometrial activation

Barash et al, *Fertil Steril* 2003; 79: 1317-22.

- 134 eusers who failed to conceive to one or more prior ETs (4.0 +/- 2.0 v. 3.9 +/- 2.1).
- 45 randomly selected to undergo biopsy in subsequent attempt; same stimulation protocol.
- 4 pipelle biopsies total on days 8, 12, 21 and 26 in the natural cycle preceding the start of lupron. After natural cycle menses, they started lupron d2 thru 17, when hypo-E2 confirmed, they began gonadotropins.
- Embryos (3.4 +/- 1.0 and 3.1 +/- 0.9), implantation rate (27.7% vs. 14.2%  $P = .00011$ ), clinical PR (66.7% vs. 30.3%  $P = .00009$ ), live birth/ET (48.9% vs. 22.5%  $P = .016$ ).

## Endometrial activation

Barash et al, *Fertil Steril* 2003; 79: 1317-22.

### Potential modes of action

- Scratching of the progestational guinea pig uterus provokes rapid growth of endometrial cells identical to decidua cells.
- Intraperitoneal injection of the histamine releasing compound pyrathiazine in rats induced decidual response.
- Scratching induced decidualization in rats reversed by anti-histamine.
- Involves events that accompany wound healing to include secretion of cytokines and growth factors known to be involved in implantation.
  - Sharkey. *Rev Reprod* 1998;3: 52-61.
  - Basak et al, *Am J Reprod Immunol* 2002; 47: 2-11.

## Endometrial activation

- Raziel et al, *Fertil Steril* 2007; 87: 198-201.
  - 2 pipelle biopsies total on d21 and 26 during luteal lupron application.
- Esfandiari et al, *Fertil Steril*, 2004, Vol 82, Suppl 2, S152.
  - Single biopsy in the luteal phase in the cycle preceding stimulation.
- Kalma et al, *Fertil Steril*, 2008, in press.
  - Biopsy induced gene modulation/factor expression validation with biopsies d11-13 and 21-24.

## Endometrial activation

### Variations on a theme

- Pre-IVF cold loop polypectomy, gentle curettage of the functionalis, oral estrace 2mg x 5 – 10 days while on OCP prior to cycle start
- Endometrial biopsy in the luteal phase prior to IVF cycle start
- Set up non-infectious inflammatory/repair response to potentially enhance implantation