

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

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**CONCEPTIONS**  
REPRODUCTIVE ASSOCIATES  
OF COLORADO



**Subset : Coags, TSH, Prednisone**

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## Implantation efficiency and sustenance

### Coagulopathy and MTHFR defect

- Observational data suggests a relationship between elevated homocysteine levels and decreased folate levels with pregnancy loss as well as a benefit of folate, B6 and B12 supplementation (1).
- Panel cost (Colorado LabCorp 3/3/10):  
Factor V (\$263.50), Factor II (263.50), AT III (134.50),  
ACA (342.75), LAC (379.25)  
MTHFR (263.50), Protein C/S activity (143.50/146)

## Coagulopathy and MTHFR defect

- RPL and single C677T
  - Folgard 2.2 BID and 81 ASA QD
- RPL and C677T x2 or C677T/A129
  - Lovenox 40 QD at +hCG
- History of VTE, RPL and thrombophilia
  - Low risk (Factor V hetero, Factor II hetero, C/S deficiency)
    - Lovenox 30 BID, anti-Xa level (0.1 – 0.2) after 2 weeks
  - High risk (AT III, homozyg V or II, compound V/II, +APA)
    - Lovenox 1mg/kg BID, anti Xa (0.6 – 1.0)
- Monitor for heparin induced thrombocytopenia
- Unfractionated heparin: prophylaxis 5000 BID; therapeutic 5–10K q 8-12h with aPTT midway between doses 1.5 – 2.5x

## Implantation efficiency and sustenance

### Coagulopathy and MTHFR defect

- While controversial, frame of reference is not second and third trimester obstetrical outcomes but first trimester failure of nidation and early maternal interaction and perfusion of placenta.
- Lovenox potentiates AT III to foster increased flow through placental intervillous spaces (delivery of O<sub>2</sub> and nutrients) as well as a direct anti-inflammatory effect.
- Folgard 2.2 BID (or equivalent) delivers 4.4 mg folic acid, 50mg B6 and 1mg B12. Water soluble B vitamins that can decrease intensity of N/V and be prophylactic with regard to NTD.

# Maternal immune acceptance of placenta

- Thyroid function and TPO/TG
- Prednisone

## Thyroid function and TPO/TG

- Miscarriage rate in TPO positive women was significantly higher than in those with no antibody, 13.8 versus 2.4 %, (RR 4.95, CI 2.59-9.48) (1)
- Levothyroxine dose requirements can increase as much as 50% during pregnancy. With the importance in implantation, maintenance of pregnancy and fetal cognitive development, one group's approach is to increase levothyroxine dosing 30% at positive pregnancy test

(1) Negro R, et al. Levothyroxine treatment in euthyroid pregnant women with autoimmune thyroid disease: effects on obstetrical complications. J Clin Endocrinol Metab 2006; 91:2587.

(2) Alexander EK, et al. Timing and magnitude of increases in levothyroxine requirements during pregnancy in women with hypothyroidism. N Engl J Med 2004; 351:241.

## Prednisone

- Safety and efficacy of prednisone 10mg BID thru 12 weeks demonstrated with a livebirth rate of 77% in 80 women with therapy as opposed to a 35% pregnancy rate in 52 matched women without therapy. Concurrent use of 5mg folate QOD, 100mg ASA QD, 20mg PO progesterone QD; autoimmunity not tested (1).
- Reznikoff-Etievant et al, Human Reproduction 1999, Vol 14(8) p. 2106 also demonstrated safety of prednisone at 20mg/d in 277 women.
- Category B. Drugs in Pregnancy and Lactation, 5<sup>th</sup> ed, Briggs, Freeman, Yaffe. Williams & Wilkins, 1998, p. 884-5.

## Prednisone

- Women with recurrent loss had significantly more uNK than controls ( $p = 0.008$ ).
- Prednisone treatment (20 mg/d for 21 days) significantly reduced the number of CD56 cells in the endometrium, from a median of 14% before to 9% after treatment ( $p = 0.0004$ ).
- Demonstrated that high numbers of uterine natural killer cells in preimplantation endometrium of women with recurrent miscarriage can be reduced with the administration of prednisone.