IVF Protocols: Hyper & Hypo-Responders, Implantation

Midwest Reproductive Symposium
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Subset: Implantation efficiency & sustenance

Mark R. Bush, MD, FACOG, FACS
Implantation efficiency and sustenance

Myomectomy

• Size and location
• Prospective cohort unexplained infertility, 11% conceived with myomas v. 25% without myomas v. 42% laparoscopic myomectomy (1)
• IVF rates lower with intramural myomas (2), with mean diameter 2.4 cm (3), when larger than 5 cm (4)
• 23 studies examined, fibroids with a submucosal component led to decreased clinical pregnancy and implantation rates with removal likely to improve pregnancy rates (5)

Implantation efficiency and sustenance
Myomectomy
### Table 6-4.

**Outcomes After Hysteroscopic metroplasty for Septate Uterus**

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Preoperative</th>
<th>Postoperative</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Spontaneous Abortion (%)</td>
<td>Preterm Delivery (%)</td>
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<tr>
<td>DeCherney, 1986*</td>
<td>103</td>
<td>100</td>
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<tr>
<td>Israel, 1984b</td>
<td>15</td>
<td>80</td>
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<tr>
<td>Valle, 1986</td>
<td>12</td>
<td>93</td>
<td>—</td>
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<tr>
<td>Fayez, 1986c</td>
<td>33</td>
<td>—</td>
<td>—</td>
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<tr>
<td>Daly, 1989</td>
<td>55</td>
<td>86</td>
<td>5</td>
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<tr>
<td>Choe, 1992d</td>
<td>19</td>
<td>80</td>
<td>7</td>
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<td>Zhioua, 1993</td>
<td>23</td>
<td>72</td>
<td>10</td>
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<td>Gaucherand, 1994</td>
<td>78</td>
<td>47</td>
<td>17</td>
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<tr>
<td>Goldenberg, 1995b</td>
<td>47</td>
<td>87</td>
<td>—</td>
</tr>
</tbody>
</table>

*a Patients with two or more first-trimester losses and otherwise normal evaluation.

b Also includes infertility patients.

c History of habitual abortion, preterm labor, or infertility.

d Nd:YAG laser.
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Septolysis

- Hysteroscopic resection with laparoscopic follow
- 5mL intrauterine stent x10 days with doxy 50mg BID
- Estrace 2mg BID for 21 days followed by Prometrium 200 qHS x 7d (2 courses) starting day after surgery
- Office hysteroscopy test of cure
- 15% fundal coaptation rate requiring H/S resection
Implantation efficiency and sustenance
Septolysis
Implantation efficiency and sustenance
Septolysis
Implantation efficiency and sustenance
Salpingectomy for hydrosalpinx

- 116 randomized to salpingectomy before IVF, 88 control
- Delivery rates 28.6% v. 16.3% (p < .05) (1)
- Subgroup of hydros visible on ultrasound: 40% v. 17.5% (1)
- Direct embryotoxic effect (2), decreased endometrial receptivity, mechanical disruption of implantation by fluid
- Based on the results from 3 trials, ongoing pregnancy rate after salpingectomy or proximal occlusion is two-fold higher than controls, 34% v. 17% (3)

3) ASRM Practice Committee, Salpingectomy for hydrosalpinx 2008; 90(3) S66-8.
Implantation efficiency and sustenance
Salpingectomy for hydrosalpinx
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 O2 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
Controversial

- Thyroid function and TPO/TG
- Prednisone
- Intralipids
- IVIG
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

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).


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.

• 79 patients with elevated NK-cell activity (> 10%) treated with 2-4 mL IV of 20% intralipid.

• 68 with implantation failure (cumulative total of 8 cleaved or 4 blasts without + hCG) – 27/68 (40% PR) following intralipid with IVF. Four patients > 40 did not conceive making the ≤ 40 group 27/64 (42% PR).

• 11 with RPL ( > 2) – 10/11 (91%) had a LB with treatment.

Intralipid Infusion

• Intralipids suppress Nka for approx 40 days possibly through NK-cell nuclear PPARs.

• First dose during stimulation. Needs to be on board ≥7 days prior to implantation/ET. Second dose at + hCG. Some give monthly to 20 weeks.

• 4 mL 20% solution, 250 mL, 50 cc/hr, then 125 cc/hr. Approx $ 600. Contraindicated if hyperlipidemia, increased LFTs, allergy to egg or soy.

• Adverse reactions <1% - allergic, brown pigment deposition in RE system, hypercoagulability, overloading syndrome, thrombocytopenia.
IVIG

- Human IgG derived from pooled plasma.
- Treatment cost significant at $7 – 14,000 per single course of therapy (1).
- Severe reactions in IgA deficient patients including nephrotoxicity, alopecia, aseptic meningitis, retinal necrosis; unknown infective risk.

IVIG

• Five RCTs of patients with RPL reported on 121 treated vs. 125 placebo controlled.

• Live birth rate was 62% (95% CI 53% - 71) vs 54% (95% CI 45% - 62).

• IVIG is not effective for primary recurrent pregnancy loss with likelihood of live birth 0.98 (95% CI 0.45 – 2.13).

• In secondary RPL (with at least one LB), likelihood 2.19 (however 95% CI crosses 1 at 0.65 – 7.39 denoting that patient number insufficient to rule out a chance finding).

• History of pregnancy of at least 20 weeks followed by 3 consecutive first trimester losses.

• 38 randomized to treatment with 39 normal saline controls. Gamimune or Gamunex 500 mg/kg prior to ovulation and continued q4 weeks until 81-20 wks gestation.

• No significant difference in live birth rate at 70% for treated vs. 63% controls. 94% live birth rate in each group if pregnancy achieved 6 weeks. This phase III multi-center trial ended early on interim A-B analysis (designed to enroll 178).

• Findings may be influenced by not selecting out patients that had prior aneuploid losses (only 18% had placental karyotype) and the beneficial effect of frequent ultrasounds and supportive care.

Refractory Endometrium
Including POF, longstanding hypothalamic dysfunction, Kallmann’s, empty sella syndrome, DE recipients nearing menopause with fibroatrophic 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

- 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 ≥ 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
Endometrial activation

- 134 euresponders 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
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.
Endometrial activation

  - 2 pipelle biopsies total on d21 and 26 during luteal lupron application.

  - Single biopsy in the luteal phase in the cycle preceding stimulation.

  - 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