PRECONCEPTION COUNSELING: IS GESTATIONAL SURROGACY PART OF YOUR CONVERSATION?

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I have no conflicts of interest to disclose in presenting this information.
THE KIWIS ARE PRETTY LAID BACK AFTER 7.5 EARTHQUAKE 11/2016 SOUTH ISLAND
Aspens changing during typical autumn day, Steamboat Springs 2016
Preeclampsia: The Role of Angiogenic Factors in Its Pathogenesis

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Abnormal placentation in preeclampsia

In normal placental development, invasive cytotrophoblasts of fetal origin invade the maternal spiral arteries, transforming them from small-caliber resistance vessels to high-caliber capacitance vessels capable of providing placental perfusion adequate to sustain the growing fetus. During the process of vascular invasion, the cytotrophoblasts differentiate from an epithelial phenotype to an endothelial phenotype, a process referred to as "pseudovasculogenesis" or "vascular mimicry" (top). In preeclampsia, cytotrophoblasts fail to adopt an invasive endothelial phenotype. Instead, invasion of the spiral arteries is shallow, and they remain small caliber, resistance vessels (bottom). Figure adapted from Ref. 50.
WHY?

• What leads to this altered physiology?

• We are still one step away from the genesis of this pregnancy-specific disease

• Are there clues available in the ART era?
Immunogenesis of Pre-Eclampsia

Theory:
- Immune maladaptation causes shallow endovascular trophoblast invasion
  - Placental ischemia
  - Endothelial cell dysfunction

Mechanism?
- Cytokine release, proteolytic enzymes that disrupt trophoblastic invasion and maternal endothelium

Genetic Theories Intact
- Th$_1$, Th$_2$ balance affects maternal response
# IMMUNOGENESIS OF PREECLAMPSIA 2.0: LESSONS FROM DONOR GAMETES

**CO OBX data 2010-2014**

<table>
<thead>
<tr>
<th></th>
<th>Native Gametes</th>
<th>Donor Gametes</th>
<th>Two sided p value (test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age, yrs</td>
<td>41.4 (n=176; SD=1.57)</td>
<td>44.6 (n=69; SD=2.85)</td>
<td>&lt;.0001 (t-test/Wilcoxon)</td>
</tr>
<tr>
<td>PE/GH</td>
<td>35/176 = 19.89%</td>
<td>28/69 = 40.58%</td>
<td>0.0018 (Fisher’s exact)</td>
</tr>
<tr>
<td>Para 0</td>
<td>14/56 = 25.00%</td>
<td>19/44 = 43.18%</td>
<td>0.086 (Fisher’s exact)</td>
</tr>
<tr>
<td>Multiples</td>
<td>10/27 = 37.04%</td>
<td>21/41 = 51.22%</td>
<td>0.32 (Fisher’s exact)</td>
</tr>
<tr>
<td>Gestational age at birth, wks</td>
<td>36.3 (n=176; SD=3.17)</td>
<td>34.7 (n=69; SD=3.46)</td>
<td>0.0007 (t-test)</td>
</tr>
</tbody>
</table>
Immunogenesis of Pre-Eclampsia

Conclusions

1. Primipaternity probably a real phenomenon, although harder to study than it appears on paper

2. Sperm (not semen) exposure is protective

3. AID, donor ovum, donor/donor increase risk of PE/E and/or hypertensive disorders in most studies (1)
Immunogenesis of Pre-Eclampsia

Speculation

1. “Naïve Hosting” immunologically foreign tissue derived from donor gametes provokes in some as yet undefined way a cascade of pathological events that eventually manifests in a clinical presentation of pre eclampsia/eclampsia syndrome.
Gestational Surrogacy

• If DO/DS pregnancies do indeed carry an increased risk of PE/GH due to immunogenesis reasons—hosting two foreign gametes with no exposure to the male gamete—as suggested by our practice data

• Wouldn’t gestational carrier “see” the same immunogenesis burden?

• I can find no information of this type to inform our thinking about this!

• So I did a retrospective study of our practice to see how the clinical outcomes compared
But let’s first talk about gestational surrogacy more generally and see if you all agree with some of the more onerous ethical/legal issues.
Gestational Surrogacy

ACOG Committee Opinion (2)

Gestational surrogacy is a form of family building

Gestational carrier (agrees to bear a genetically unrelated child) and intended parents (legal and rearing parents)

Embryos are derived from gametes from one or both intended parents, or can be from donated ova or sperm or both

Traditional surrogacy where the gestational carrier uses her own ovum and is inseminated with sperm from the intended parent or donor sperm. Legally and ethically complex and no longer offered by surrogacy programs
Gestational Surrogacy

Benefits

Individual or couple to become a parent(s) of a genetically related child when pregnancy is biologically impossible or medically contraindicated

Single men and men in same-sex relationships can parent a genetically related child

Gestational carriers derive altruistic benefits as well as monetary benefits (state laws may determine appropriate amounts)
Gestational Surrogacy

Complexities

Ethical issues derive from socioeconomic disparities between gestational carriers and intended parents—compensation could be a coercive inducement in some settings.

Ethics of trivializing reproductive capacities and turns infants into commodities.

Independent legal counsel (GC)

Independent care and autonomous decision making after careful medical counseling regarding risks and benefits (GC)
Gestational Surrogacy

Medical Risks

- antenatal diagnosis of fetal disease requiring invasive treatments
- how many embryos to transfer
- high order multiple pregnancy
- serious fetal anomaly
- how each party would respond to an unexpected newborn defect
Gestational Surrogacy

Legal Risks

As many as 5 parties could be involved if donor gametes are utilized.

Laws surrounding surrogate parenting relationships and responsibilities reside at the state level in the US (CO has no gestational surrogacy law on the books).

Qualified legal counsel, preferably independent for the gestational carrier and the intended parents.
Gestational Surrogacy

Legal Risks

- prebirth orders, postbirth orders, adoption proceedings
- disputes resolved by courts
  - intent of the parties to the contract
  - genetic linkage to intended parents
  - rights of the gestational carrier
  - best interests of the child
- signed written contract by qualified legal counsel clarifying what medical information can be shared with intended parents and what is confidential
Gestational Surrogacy

Psychosocial Issues

offspring reassuring adjustment in limited studies

gestational carriers have claimed parental rights over offspring and intended parents have refused to accept parental rights

counseling to both the gestational carrier and intended parents both from mental health professionals and legal counsel may be able to prepare and/or anticipate for unplanned outcomes
Gestational Surrogacy

**OBGYN’s Responsibilities** to pregnant gestational carriers

- **primacy of her right** to autonomous decisions regarding her health and the pregnancy, including privacy of selected information

- **intended parents have no a priori rights** to input into these decisions, including labor and delivery

Potential gestational carriers and intended parents should discuss as many foreseeable decision scenarios as possible and documented in the contract.
Gestational Surrogacy

**OBGYN’s Responsibilities to pregnant GCs**

Examples include prenatal genetic screening and response to abnormal findings on laboratory tests and ultrasounds.

- CVS
- Amnio
- MFPR
- Fetal surgery
- Delivery timing and location—all reside with the gestational carrier—although they may constitute contract breaches.

It is common for intended parents to make decisions regarding the newborn(s), although transfer to another hospital may complicate this until formal parentage is established.
Dichorionic triamniotic triplets after single embryo transfer
Dichorionic tetra-amniotic quadruplets, spontaneous
Dichorionic tetra-amniotic quadruplets, spontaneous
Gestational Surrogacy

Cross-border surrogacy arrangements

ART sought outside domicile country

Applies to gestational surrogacy arrangements—Americans seeking GCs abroad and foreign nationals seeking GCs in the US

affordability, legal restrictions, quality, privacy, same-sex relationships

No internationally acceptable framework to deal with a myriad of potential difficulties, both legal, medical and political
Late blooming
Columbine
September, 2016
Gestational Surrogacy

- Retrospective review of OBX Colorado ongoing private patients, both singleton and multiples
- 2010 to 2015, inclusive
- Determination from the EHR whether the patient is a surrogate gestational carrier, generally noted in the HPI at time of the new OB visit
- Exempt status prospectively granted from HealthONE IRB as long as the CRFs and Xcel spreadsheets are de-identified
## Gestational Surrogacy

### Overall Comparisons

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Surrogates (%)</th>
<th>DO/DS (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=38</td>
<td>n=18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal Age, mean yrs</td>
<td>33.0</td>
<td>44.7</td>
<td>&lt; .0001 (t-t)</td>
</tr>
<tr>
<td>Gestational Age, mean wks</td>
<td>35.7</td>
<td>34.9</td>
<td>0.37 (t-tst)</td>
</tr>
<tr>
<td>Nulliparity</td>
<td>4 (10.5)</td>
<td>13 (72.2)</td>
<td>&lt;.0001 (Xsq)</td>
</tr>
<tr>
<td>Multiple gestation</td>
<td>30(78.9)</td>
<td>10 (55.6)</td>
<td>0.07 (X-sq)</td>
</tr>
<tr>
<td>PE/GH</td>
<td>12(31.6)</td>
<td>10(55.6)</td>
<td>0.086 (Xsq)</td>
</tr>
</tbody>
</table>

Confounders!
## Gestational Surrogacy

### Plurality - Singletons

<table>
<thead>
<tr>
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<th>Surrogates (%)</th>
<th>DO/DS (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=8</td>
<td>n=8</td>
<td></td>
</tr>
<tr>
<td>Maternal Age, mean yrs</td>
<td>31.1</td>
<td>45.6</td>
<td>&lt; .0001 (t-t)</td>
</tr>
<tr>
<td>Gestational Age, mean wks</td>
<td>36.9</td>
<td>36.6</td>
<td>0.88 (t-t)</td>
</tr>
<tr>
<td>Nulliparity</td>
<td>0 (0.0)</td>
<td>7 (87.5)</td>
<td>&lt;0.0014 (F)</td>
</tr>
<tr>
<td>PE/GH</td>
<td>1(12.5)</td>
<td>3 (37.5)</td>
<td>0.57 (F)</td>
</tr>
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Confounders!
### Gestational Surrogacy

#### Plurality - Multiples

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<td></td>
<td>n=30</td>
<td>n=10</td>
<td></td>
</tr>
<tr>
<td>Maternal Age, mean yrs</td>
<td>33.5</td>
<td>43.9</td>
<td>&lt; .0001 (t-t)</td>
</tr>
<tr>
<td>Gestational Age, mean wks</td>
<td>35.3</td>
<td>33.5</td>
<td>0.067 (t-test)</td>
</tr>
<tr>
<td>Nulliparity</td>
<td>4 (13.3)</td>
<td>6 (60.0)</td>
<td>0.0074 (Fsh)</td>
</tr>
<tr>
<td>PE/GH</td>
<td>11(36.7)</td>
<td>7 (70.0)</td>
<td>0.14 (Fsh)</td>
</tr>
</tbody>
</table>

**Confounders!**
Gestational Surrogacy

Summary

1. Surrogates younger and with higher parity than donor egg/donor sperm (DO/DS) counterparts.

2. Prevalence rate of multiples higher among surrogates; prevalence rate of PE/GH higher among DO/DS pregnancies, irrespective of plurality (NS – very small numbers).

3. Gestational age at delivery seems unaffected by surrogate or DO/DS status, with possible exception of multiples – lower among DO/DS patients (?related to very high prevalence of PE/GH in this group).
In 2017 as patients who have significant co-morbidity (markedly advanced maternal age), the use of gestational carriers should be discussed in any comprehensive counseling session. The threshold for accepting risk will drop as gestational surrogacy becomes commonplace. The next controversy will be when is "elective" gestational surrogacy acceptable to the professional community.
TOP OF RABBIT EARS PASS LOOKING WEST
WILDFIRES CREATING SPECTACULAR SUNSETS
SUGGESTED READING


