Genetic Conflicts in Human Pregnancy

David Haig
Harvard University

Maternal provisioning of a fetus is associated with an opportunity cost.

The opportunity cost translates into lower expected fitness through other offspring.

If extra resources are transferred to an embryo:

- The embryo’s expected fitness increases
- The mother’s expected fitness from other offspring decreases
Genetic Conflicts in Human Pregnancy
Prof. David Haig

**Figure 4**

- Benefit to fetus
- Cost to siblings
- Maternal investment in fetus
- Minimizes (benefit to sibling)

**Figure 5**

- Mother
- Maternal (Non-inherited)
- Maternal (inherited)
- Paternal (inherited)
- Fetus

**Figure 6**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Benefit (to fetus)</th>
<th>Cost (to sibs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal (Non-inherited)</td>
<td>0</td>
<td>1/2</td>
</tr>
<tr>
<td>Maternal (Inherited)</td>
<td>1</td>
<td>1/2</td>
</tr>
<tr>
<td>Paternal (Inherited)</td>
<td>1</td>
<td>$\frac{p}{2}$</td>
</tr>
</tbody>
</table>

$p = \text{probability of shared paternity}$
A non-inherited maternal gene gains no benefit from the survival and reproduction of a fetus

Worse than that!

Non-inherited maternal genes will benefit from the early demise of the fetus

How is pregnancy possible?

Rarity of genetic self-recognition

“The parliament of the genes” (mutual policing)

Paternally-derived genes in fetuses favor greater demands on mothers than maternally-derived genes
Genetic Conflicts in Human Pregnancy
Prof. David Haig

Human chromosome 11p15.5

Beckwith-Wiedemann syndrome (fetal overgrowth)

Paternal uniparental disomy

The screen versions of these slides have full details of copyright and acknowledgements
Genetic Conflicts in Human Pregnancy
Prof. David Haig

**Paternal duplication 11p15.5**

- **Mat**
- **Pat**
- **Pat**

- **CDKN1C** 1
- **IGF2** 2

**Reactivation of paternal IGF2**

- **Mat**
- **Pat**

- **CDKN1C** 1
- **IGF2** 2

**Loss-of-methylation at maternal ICR2**

- **Mat**
- **Pat**

- **CDKN1C** 0
- **IGF2** 1

The screen versions of these slides have full details of copyright and acknowledgements.
Genetic Conflicts in Human Pregnancy
Prof. David Haig

Inactivating mutation of maternal CDKN1C

Silver-Russell syndrome (intrauterine growth retardation)

Loss-of-methylation at maternal ICR1
Genetic Conflicts in Human Pregnancy
Prof. David Haig

Maternal duplication 11p15.5

Mother

Maternal (Non-inherited)  Maternal (Inherited)  Paternal (Inherited)

Fetus

Incomplete information

<table>
<thead>
<tr>
<th></th>
<th>Benefit (to fetus)</th>
<th>Cost (to sibs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mother</td>
<td>1/2</td>
<td>1/2</td>
</tr>
<tr>
<td>Fetus</td>
<td>1</td>
<td>(1+p)/4</td>
</tr>
</tbody>
</table>

\[ p = \text{probability of shared paternity} \]
Genetic Conflicts
in Human Pregnancy
Prof. David Haig

Conflict can exist over

- Whether or not to miscarry
- The nutrient quality of maternal blood
- The volume of blood reaching the placenta

The screen versions of these slides have full details of copyright and acknowledgements
Genetic Conflicts in Human Pregnancy
Prof. David Haig

Women attempting to conceive

- Number of cycles: 707
- Chemical pregnancies: 198
- Clinical pregnancies: 155
- Term pregnancies: 136

Data from Wilcox et al., (1988)

Anterior pituitary
- Luteinizing hormone
  - Corpus luteum
  - Progesterone
  - Uterus

Corpus luteum
- Progesterone

Placenta
- Chorionic gonadotropin
- Placental lactogen

Placental hormones

- hCG
- Progesterone
- Estradiol
- hPL

Gestational age

The screen versions of these slides have full details of copyright and acknowledgements
Concentrations in maternal serum

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Non-pregnant</th>
<th>Pregnant</th>
</tr>
</thead>
<tbody>
<tr>
<td>hLH/hCG</td>
<td>100 mIU/ml</td>
<td>50,000 mIU/ml</td>
</tr>
<tr>
<td>hGH/hPL</td>
<td>5 ng/ml</td>
<td>10,000 ng/ml</td>
</tr>
<tr>
<td>Progesterone</td>
<td>10 ng/ml</td>
<td>200 ng/ml</td>
</tr>
<tr>
<td>Estradiol</td>
<td>0.4 ng/ml</td>
<td>20 ng/ml</td>
</tr>
</tbody>
</table>

Placental hormones; Why shout?

Placental hormones originate as fetal attempts to manipulate maternal physiology for fetal benefit
Placental hormones may evolve to become little more than endocrine SPAM

Maternal carbohydrate metabolism

- Fasting blood glucose falls in first trimester
- Maternal sensitivity to insulin decreases as pregnancy progresses
- Maternal insulin production increases in parallel with reduced sensitivity

Maternal circulation during pregnancy
Genetic Conflicts in Human Pregnancy
Prof. David Haig

Fetal share of mother’s systemic blood supply
\[ \frac{R_m}{R_m + R_p} \]

- \( R_p \) = resistance of uteroplacental circulation
- \( R_m \) = resistance of non-placental circulation

34

<table>
<thead>
<tr>
<th>Placental factors</th>
<th>Uteroplacental resistance</th>
<th>Non-placental resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Decrease</td>
<td>Increase</td>
</tr>
<tr>
<td>Maternal factors</td>
<td>Increase</td>
<td>Decrease</td>
</tr>
</tbody>
</table>

35

Arteries of the endometrium

36

The screen versions of these slides have full details of copyright and acknowledgements
Genetic Conflicts in Human Pregnancy
Prof. David Haig

Maternal blood pressure in pregnancy

- Blood pressure reduced during most pregnancies; rises toward term
- ≈ 10% women develop hypertension = pregnancy-induced hypertension (PIH)
- Preeclampsia (PIH + proteinuria) affects ≈ 3% pregnancies

Preeclampsia

- Major cause of maternal mortality
- Endothelial damage in multiple maternal organs
- Most effective treatment is delivery
- Sflt1 and endoglin implicated as placental factors responsible for the disease

Maternal-fetal relations lack important feedback controls because signals are not evolutionarily credible

The screen versions of these slides have full details of copyright and acknowledgements
Genetic Conflicts in Human Pregnancy
Prof. David Haig