Maternal-Fetal Conflict

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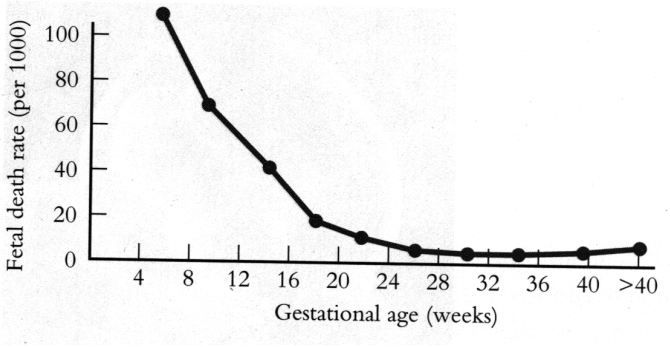
Outline

- There are lots of fetal deaths. Are these unavoidable accidents or strategic choices?
- Kin-selection theory predicts conflict between mother and fetus.
- Evidence of conflict
- The outcome
- Revisit kin-selection theory.

Fetal Deaths



There are lots of fetal deaths.

Pregnancy involves a trade-off

- Mother transfers resources to fetus during pregnancy.
- The more the better for the fetus.
- But there is a cost to the mother.
- If resources are scarce, pregnancy
  - impairs mother's health (maternal depletion)
  - reduces her longevity (Lycett et al 2000)

How much resource should go to each fetus?

- Too little: current fetus will suffer.
- Too much: mother will suffer; will have fewer future children.
- What would be favored by natural selection?
- The answer depends on whose body is expressing the gene.

Gene expressed (used to make protein) by mother

1. Equally likely to be present in each of mother's children.
2. Each child is equally "valuable."
3. Selection maximizes number of children.
4. No tendency to prefer one child to another.

Gene expressed (used to make protein) by fetus

1. Present in fetus's own body,
2. but in only half of siblings.
3. Gene might benefit by taking resource from sibling.

Reason for conflict between mother and fetus

- Gene expressed by mother "values" offspring equally.
- Gene expressed by fetus "values" self over siblings.

The two kinds of gene may "disagree" about how much resource the fetus should get.

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The battleground

1. blood supply to the placenta
2. blood sugar
3. progesterone
4. imprinted genes

Fetus increases the blood supply, increases blood sugar, and maintains the supply of progesterone. Mother opposes these actions.

Fetal efforts to increase blood supply

Mother supplies blood to fetus via the *spiral arteries*.

- Shortly after implantation, fetal cells attack the walls of these arteries so they cannot restrict blood supply.
- An unknown mechanism destroys the maternal nerves that cause spiral arteries to constrict.
- Mother then has no direct control over fetal blood supply

Maternal efforts to restrict fetal blood supply

Unable to constrict spiral arteries, mother's options are indirect:

- Opens arteries in the rest of her body, reducing pressure in spiral arteries (incidentally causing varicose veins).
- Lowers overall blood pressure during 1st and 2nd trimesters.
- Spiral shape of the arteries also functions to reduce blood supply to the fetus.

Placentation

The placenta is a fetal organ that attaches to the inside of the womb. In humans, the placenta establishes an unusually close connection to the maternal blood supply.

- The cells that separate maternal blood from fetal blood are all of fetal origin.
- The fetus is therefore in control of what passes through this membrane.
- Any hormones secreted by the mother must be filtered through fetal tissue before they can reach fetal blood.
- The fetus can secrete hormones directly into the mother's blood stream.

The battle over progesterone

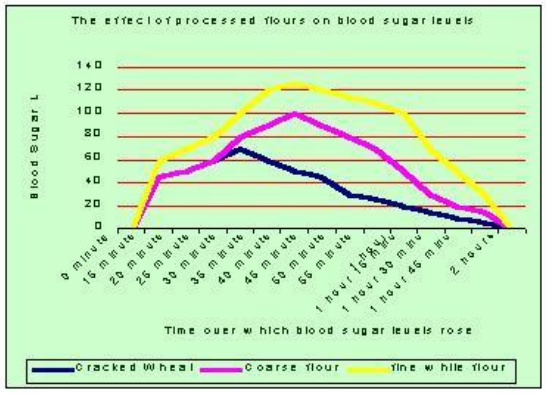
Progesterone is a hormone that maintains pregancy and is secreted by the mother's corpus luteum. In most mammals, pregnancy ends if the corpus luteum is removed. True of humans, but only up to the 8th week of pregnancy.

After week 8, the fetus makes progesterone itself and secretes this into the mother's blood. The pregnancy can therefore continue even if the mother shuts down the supply of progesterone.

The fetus protects the progesterone even before week 8

The corpus luteum produces progesterone in response to a signal (LH) from the anterior pituitary gland. The fetus mimics this signal by secreting yet another hormone into the mother's blood. This hormone, *human chorionic gonadotropin* (hCG), causes the mother's corpus luteum to continue producing progesterone even if the mother tries to stop it.

Blood sugar



- Blood sugar rises after meals.
- Then falls in response to insulin.
- (Pardon the blurry slide.)

The battle over blood sugar

1. Blood sugar falls during gestational weeks 1–12. (Not a consequence of fetal energy needs: falls when needs are small; stable when needs grow.)
2. Fetus secretes *human placental lactogen* (hPL), which binds to maternal prolactin receptors, increasing their resistance to insulin. This keeps sugar level high for a longer period after meals.
3. Placenta contains enzymes that degrade insulin—may act as a sink for maternal insulin.
4. Mother responds by increasing insulin production.
5. Gestational diabetes results when mom can't make enough insulin.

"Why should a mother restrict fetal access to glucose, and why should she increase her production of insulin at the same time as she is becoming resistant to its effects?" (Haig 1993: p. 510)

The battleground

- blood supply to the placenta
- blood sugar
- progesterone
- imprinted genes

Imprinted genes

Paternally imprinted genes active only if inherited from father

Maternally imprinted genes active only if inherited from mother

All imprinted genes are expressed in placenta.

Paternally imprinted genes tend to increase fetal growth

Maternally imprinted genes tend to reduce fetal growth

How do we know this?

Knockout experiments in mice

Knockout experiments disable specific genes.

Paternally active genes such as Igf2, Peg1, Peg3 and insulin:

- Fetal growth reduced in knockout mice

Maternally active genes such as H19 and Igf2r:

- Fetal growth accelerated in knockout mice

Genetic disease in humans

- Igf2 (Insulin-like growth factor 2) affects fetal growth
- Only paternal copy is active in normal humans
- But some get two active copies
  - Two copies from father
  - Active copy from mother
- Either way, gene is over-expressed
- Result: Beckwith-Weidemann syndrome (rapid fetal growth, cancers, & other problems)

Phylogenetic distribution of imprinting

Imprinting is

- present in most mammals with internal gestation
- absent from animals that lay eggs
  - fish
  - reptiles
  - birds
  - monotreme mammals (platypus)

Suggests that imprinting evolved in response to conflict between mother and fetus.

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Has the fetus won?

1. A newborn human may have enough fat to survive 3 to 4 weeks. Most other mammals are lean at birth.
2. We (usually) have litters of one.

Maternal-fetal conflict is an example of maladaptive evolution

- Conflict squanders resources: everyone would be better off without it.
- Recall farmers and thieves: selection may be maladaptive if fitnesses are frequency-dependent.
- Fitnesses are frequency-dependent here because optimal behavior of mother depends on fetus, and vice versa.
- Example: mother should make more insulin if fetus makes more hPL.
- Maladaptive evolution is no surprise.

Further reading

- Haig, David. 1993. Genetic conflicts in human pregnancy. *Quarterly Review of Biology*, 4:495-532.
- Reik, Wolf et al. 2003. Regulation of supply and demand for maternal nutrients in mammals by imprinted genes. *The Journal of Physiology*, 547:35-44.

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Lecture stops here. Remaining slides are optional.

Kin-selection theory predicts conflict between mother and fetus

Consider a mutation that benefits current fetus at expense of future fetuses. If expressed in mother, the mutant will be favored if

$$0.5 \times (\text{Benefit to current fetus}) > 0.5 \times \begin{pmatrix}\text{Reduction in \# of} \\ \text{future fetuses}\end{pmatrix}$$

If expressed in fetus, the gene will be favored if

$$1.0 \times (\text{Benefit to current fetus}) > 0.5 \times \begin{pmatrix}\text{Reduction in \# of} \\ \text{future fetuses}\end{pmatrix}$$

Conflict occurs when these conditions do not agree.

Hypothetical Example

Given the normal supply of blood, fetus A will survive with probability 0.7 and will have (on average) 3.3 younger brothers and sisters.
Given an increased supply of blood, Fetus A would survive with probability 0.8 and would have (on average) 3.15 younger brothers and sisters.
The proposed increase in blood supply would provide a direct benefit to fetus A:

$$B = 0.8 - 0.7 = 0.1$$

and an indirect cost (in fewer siblings):

$$C = 3.3 - 3.15 = 0.15$$

Would selection increase fetal blood supply?

If the increase in blood supply were caused by a gene expressed by the fetus, it would be favored if

$$B > C/2 \qquad \text{or} \qquad 0.1 > 0.075$$

Since this is true, fetal genes favor increased blood supply.
If the increase in blood supply were caused by a gene expressed by the mother, it would be favored if

$$B > C \qquad \text{or} \qquad 0.1 > 0.15$$

Since this is false, maternal genes oppose increased blood supply.
Maternally and fetally expressed genes are in conflict over blood supply.