Fetal Development & Birth Systems

Maternal – Fetal Interface During Gestation
- Implantation / Trophoblasts
- Vasculature
- Abnormal Conditions

Endocrinology of Pregnancy
- Steroidogenesis and Gestation
- Placental – Fetal Unit

Abnormal Pregnancy Factors
- Immune abnormalities
- Preeclampsia
- Risk Factors
- Systems Biology Analysis

Birth and Parturition
- Endocrine
- Pre-term Birth
- Systems Approach to Fetal and Placental Development

Environmental Insults / Exposures
- Various Exposures and Interface
- Examples Exposures

REFERENCES


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Maternal-Fetal Interface During Gestation

Figure 1 Early pregnancy events in sheep. This schematic summarizes the relative changes in embryo/blastocyst development after fertilization in relation to position in the female reproductive tract and circulating levels of ovarian steroid hormones. Fertilization occurs in the oviduct, and the morula stage embryo enters the uterus on day 4. The blastocyst is formed by day 6 and hatches from the zona pellucida on days 8–9. The blastocyst develops from a spherical to a tubular form by day 11 and then elongates to a filamentous conceptus between days 12 and 16. The elongation of the blastocyst marks the beginning of implantation, which involves apposition and transient attachment (days 12–15) and firm adherence by day 16.
Interactions between Trophoblast Cells and the Maternal and Fetal Circulation in the Mouse Placenta

S. Lee Adamson, Yong Lu, Katie J. Whitley, Doug Holmeyer, Myfan Hembeger, Christine Flanner, and James C. Cross

Maternal interactions have an intimate relationship with each other, particularly with the placental vasculature from which stem cells which contribute to its growth. It is interesting to consider how these interactions influence normal vessel growth and placental change. Our recent work has focused on the interaction of maternal and fetal vessels and the surrounding stroma. We have used in vivo imaging to study the development of the placental vasculature in the mouse. Our results show that fetal vessels grow along maternal vessels in a reciprocal manner, suggesting that they are influenced by each other. This interaction is critical for the development of the placenta and the establishment of the maternal-fetal circulation.

Figure 1: Anatomical distribution of maternal and fetal vessels in the mouse placenta. The maternal vessels are shown in red, and the fetal vessels are shown in blue. The interaction between the two is evident in the developing placenta. The maternal vessels provide nutrients and oxygen to the fetal vessels, while the fetal vessels provide nutrients and oxygen to the maternal vessels. This reciprocal interaction is crucial for the development of the placenta and the establishment of the maternal-fetal circulation.

Figure 2: Immunohistochemical staining of maternal and fetal vessels. The maternal vessels are stained in red, and the fetal vessels are stained in blue. The interaction between the two is evident in the staining pattern. The maternal vessels are more prominent in the peripheral region, while the fetal vessels are more prominent in the central region. This interaction is critical for the development of the placenta and the establishment of the maternal-fetal circulation.

Figure 3: Schematic diagram of the interaction between maternal and fetal vessels. The maternal vessels are shown in red, and the fetal vessels are shown in blue. The interaction between the two is evident in the schematic diagram. The maternal vessels provide nutrients and oxygen to the fetal vessels, while the fetal vessels provide nutrients and oxygen to the maternal vessels. This reciprocal interaction is crucial for the development of the placenta and the establishment of the maternal-fetal circulation.

Figure 4: Real-time imaging of maternal and fetal vessels in the mouse placenta. The maternal vessels are shown in red, and the fetal vessels are shown in blue. The interaction between the two is evident in the real-time imaging. The maternal vessels provide nutrients and oxygen to the fetal vessels, while the fetal vessels provide nutrients and oxygen to the maternal vessels. This reciprocal interaction is crucial for the development of the placenta and the establishment of the maternal-fetal circulation.
TABLE 11-1. Differences in Gestation Periods of Farm Mammals

<table>
<thead>
<tr>
<th>Animal</th>
<th>Average (Range)</th>
</tr>
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<tbody>
<tr>
<td>Cattle dairy breed</td>
<td>278 (250–300)</td>
</tr>
<tr>
<td>Awashil</td>
<td></td>
</tr>
<tr>
<td>Brown Swiss</td>
<td>250 (270–300)</td>
</tr>
<tr>
<td>Dairy Shorthorn</td>
<td>252</td>
</tr>
<tr>
<td>Finnish</td>
<td>250 (240–260)</td>
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<tr>
<td>German</td>
<td>250</td>
</tr>
<tr>
<td>Holstein-Friesian</td>
<td>270 (260–270)</td>
</tr>
<tr>
<td>Jersey</td>
<td>270 (260–270)</td>
</tr>
<tr>
<td>Swedish Friesian</td>
<td>282 (260–280)</td>
</tr>
<tr>
<td>Zola (Holstein)</td>
<td>320 (310–320)</td>
</tr>
<tr>
<td>Cattle (beef breeds)</td>
<td>250</td>
</tr>
<tr>
<td>Aberdeen Angus</td>
<td>250 (240–260)</td>
</tr>
<tr>
<td>Hereford</td>
<td>250 (230–240)</td>
</tr>
<tr>
<td>Beef Shorthorn</td>
<td>250 (230–240)</td>
</tr>
<tr>
<td>Sheep</td>
<td>145 (130–150)</td>
</tr>
<tr>
<td>Jersey</td>
<td>114 (105–120)</td>
</tr>
<tr>
<td>Wild Pig</td>
<td>124 (110–130)</td>
</tr>
<tr>
<td>Horse</td>
<td>327 (300–350)</td>
</tr>
<tr>
<td>Arabian</td>
<td>325 (300–340)</td>
</tr>
<tr>
<td>Clydesdale</td>
<td>332</td>
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<tr>
<td>Morgan</td>
<td>341 (320–350)</td>
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<td>Polish</td>
<td>344 (320–340)</td>
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<tr>
<td>Shire</td>
<td>340</td>
</tr>
<tr>
<td>Thoroughbred</td>
<td>336 (320–340)</td>
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</table>

**Fig. 11-1.** Schematic representation of variations in length of gestation due to maternal, fetal, genetic and environmental factors. Whereas many of these factors within a species cause minor variations, hyperplasia of the pituitary-adrenal axis of the fetus is associated with prolonged gestation in the cow and ease.
The integrative roles of chemokines at the maternal-fetal interface in early pregnancy.
Du MR, Wang SC, Li DJ.
Androgens in pregnancy: roles in parturition.
Makieva S, Saunders PT, Norman JE.
Figure 23-39, Interactions between the placenta and the fetal adrenal cortex in the production of steroids.

Figure 11-10, The sequence of enzymatic reactions in the conversion of progesterone to estrogens in the placenta during the latter half of gestation. Fetal cortisol activates the enzymes responsible for the conversion.
Abnormal Pregnancy Factors
### Table 3. Determinants of CD8+ T lymphocyte phenotype and their distinguishing characteristics

<table>
<thead>
<tr>
<th>CD8 phenotype</th>
<th>CD4+ phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ef</td>
<td>CD30, PD-1, LCK</td>
</tr>
<tr>
<td>Ef</td>
<td>CD30, PD-1, LCK</td>
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<tr>
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**Fig. 1.** Interactions among decidual natural killer (NK) cells, macrophages and trophoblast.

**Fig. 2.** Cytokine and endocrine networks at the materno-fetal interface.

**Table 1.** Characteristics of different human leukocyte antigens in human implantation

<table>
<thead>
<tr>
<th>HLA-A, HLA-B</th>
<th>HLA-C, HLA-G, HLA-E</th>
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<tbody>
<tr>
<td>Low surface expression</td>
<td>High surface expression</td>
</tr>
<tr>
<td>Low affinity</td>
<td>High affinity</td>
</tr>
<tr>
<td>Polymorphism not concentrated at antigen-binding site</td>
<td>Polymorphism concentrated at antigen-binding site</td>
</tr>
<tr>
<td>T cells reactive to HLA-C are occasionally observed but T cells reactive to HLA-G or HLA-E are not observed</td>
<td>Reactive T cells readily observed</td>
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</table>

**HLA human leukocyte antigen.**
NATURAL KILLER CELLS AND PREGNANCY

Ashley Moffett-King

The fetus is considered to be an allograft that, paradoxically, survives pregnancy despite the laws of classical transplantation immunology. There is no direct conflict of the mother with the embryo, only with the extraembryonic placenta as it implants in the uterus. No convincing evidence of uterine maternal T-cell recognition of placental trophoblast cells has been found, but instead, there might be maternal allorecognition mediated by uterine natural killer cells that recognize unusual fetal trophoblast MHC ligands.
Why is placentation abnormal in preeclampsia?
Fisher SJ.

Inflammatory response
Immune maladaptation
Switch to T cell, TH1 cell mediated immunity
Possible endocrine factors: tumour necrosis factor-alpha, interleukin-1, interleukin-6

Dyslipidaemia
Oxidative stress
Lipid peroxidation
Possible endocrine factors: an imbalance between prostaclin and thromboxane, nitric oxide and vascular endothelial growth factor

Endothelial dysfunction
Raised sensitivity to vasoconstrictors
Increased platelet activation
Loss of circulating blood volume
Possible endocrine factors: imbalance between prostacyclin and thromboxane, nitric oxide and vascular endothelial growth factor

Placental dysfunction
Poor perfusion
Defective trophoblast invasion
Ischaemia
Release of factors into maternal bloodstream
Possible endocrine factors: corticosterin releasing factor, neurokinin B

Fig. 1. The main endocrine systems identified in pre-eclampsia are illustrated with examples of possible endocrine factors (discussed further in the text). Maladaptation during pregnancy is believed to lead to the many characteristic multisystem manifestations of the disease, involving the maternal liver, kidneys, lungs, endothelium and nervous system.
Analysis of the role of HLA-G in preeclampsia

Margaret O’Brien, Joaquin Devescica, Edgardo G. Carcelleres and Philippe Moreau

Abstract

Preeclampsia (PE) is a multisystem disorder of human pregnancy, occurring in 5%–10% of all population births and represents the leading cause of both fetal and maternal morbidity and mortality in pregnancy. Although the disorder only becomes clinically apparent late in pregnancy, the underlying pathology indicates that invasion of fetal trophoblasts into maternal spiral arteries during early pregnancy is shallow or absent in PE. A large number of epidemiologic studies have been carried out and they demonstrate that the disorder is highly heritable and occurs with a high incidence in all populations. Studies have shown that PE is largely under genetic control, but the mode of its inheritance remains unclear. Genetic studies have been carried out using both large-scale linkage analysis and candidate gene approaches; however, the genetic mechanisms underlying the disorder have yet to be determined. We focus on the potential role of HLA-G, a non-classical class I HLA located on chromosome 6, which appears to be a key component of trophoblast invasion. We examine the hypothesis that HLA-G may have a key role in both genetic susceptibility to, and pathogenesis of, PE.
Comparative systems biology of human and mouse as a tool to guide the modeling of human placental pathology.

Schematic of the cellular topology of the protein-protein interaction network. Shown are protein-protein interaction networks from I2D version 1.71, seeded with proteins that give a placental labyrinth or placental vascular phenotype when knocked out (rectangle or triangle). Proteins are colored to show cell-type expression. Node shapes indicate the placental phenotype (rectangle or triangle) or if no placental phenotype is known (oval or hexagon). Enrichment of proteins involved in extracellular matrix (yellow circle) and focal adhesion complex (blue circle) were observed (P<0.01). Other groupings are for clarity only. Eps15 and Cd82 (hexagons) are both novel members with no available knockout models. Visualization was done using NAViGaTOR version 2.15.

Molecular association of pathogenetic contributors to pre-eclampsia (pre-eclampsia associome).

Trophoblast-microbiome interaction: a new paradigm on immune regulation.

Figure 1. Cytokines play a central role in processes involved in the initiation of uterine and placental function.

Factors:
- Estrogen
- Progesterone
- Oxytocin
- Myometrial stretch

- PGF2α
- cAMP
- Uterine contractions

Fig. 1 (E): Sequence of events leading to uterine contractions of parturition. In early pregnancy, endometrial changes and myometrial stretch induce PGF2α, which stimulates the synthesis of cAMP and induces uterine contractions. In late pregnancy, myometrial contractility is enhanced, leading to uterine contractions and labor.

Fig. 3 (E): Schematic representation of the collective events of parturition. Activation of the fundus leads to cervical dilatation and effacement, which facilitates the descent of the fetus and delivery. The placenta is detached from the uterine wall, allowing for postpartum hemostasis. The aforementioned processes are regulated by a complex interplay of hormones and cytokines.

Fig. 4 (E): Time course of fetal growth and placental development. The graph illustrates the growth trajectory of the fetus, placenta, and mother throughout pregnancy. The data points indicate significant milestones and changes in growth parameters. The biological significance of these growth patterns is crucial for understanding fetal development and the physiological adaptations during pregnancy.
The transcriptome of cervical ripening in human pregnancy before the onset of labor at term: identification of novel molecular functions involved in this process.
Hassan SS, et al.

An evolutionary genomic approach to identify genes involved in human birth timing.
Plunkett J, et al.

Overview of the SNPs tested in the FSHR gene region.
The gene structure for FSHR is represented by an arrow in which black rectangles designate 3' and 5' untranslated regions and dark grey rectangles designate coding exons. Diamonds represent SNPs on the Affymetrix SNP 6.0 array examined in the Finnish cohort. Triangles represent SNPs tested in the replication cohorts. A star indicates rs12473815, and the LD block that includes rs11686474 and rs11680730, which is significant after multiple testing correction in African Americans (p≤0.005). Circles represent conserved elements examined in the region.

The perinatal transition of the circulating metabolome in a nonhuman primate.
Beckstrom AC, et al.
Environmental Insults/Exposures
Endocannabinoid signaling in female reproduction.
Sun X, Dey SK.

Cannabinoid/endocannabinoid signaling impacts various pregnancy events. Either silenced or augmented cannabinoid/endocannabinoid signaling disturbs pregnancy events including preimplantation embryo development, oviductal embryo transport, implantation, placentation, and parturition. The impact on decidualization is yet to be determined.

Birth regulates the initiation of sensory map formation through serotonin signaling.
Toda T, et al.
The impact of postnatal antibiotics on the preterm intestinal microbiome.
Dardas M, Gill SR, Grier A, Pyrhuber GS, Gill AL, Lee YH, Guillet R.

"Systems Biology of Reproduction"
Spring 2018 (Even Years) - Course Syllabus
BIOL 475/575 Level Undergraduate/Graduate (3 Credit)
SLN: (475) - 06206, (575) - 06207
Time - Tuesday and Thursday 10:35 am-11:50 am
(Course Lectures on Blackboard/Panopto and Discussion Sessions on WSU Blackboard/Collaborate for all campuses)
Room – CUE 418
Course Director - Michael Skinner, Abelson Hall 507, 335-1524, skinner@wsu.edu
Learning Objective -

Schedule/Lecture Outlines -

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