Spring 2024 – Systems Biology of Reproduction
Lecture Outline – Fetal Development & Birth Systems
Michael K. Skinner – Biol 475/575
CUE 418, 10:35-11:50 am, Tuesday & Thursday
April 16, 2024
Week 15

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

Required Reading

Bazer FW and Fields MJ (2018) Pregnancy and Parturition, Mammals. in: Encyclopedia of Reproduction 2nd Edition, Ed: MK Skinner. Elsevier. Vol. 6, Pages 450-457.

Forhead AJ and Fowden AL (2018) Formation and Growth of the Fetus. in: Encyclopedia of Reproduction 2nd Edition, Ed: MK Skinner. Elsevier. Vol. 3, Pages 370-379.

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Pregnancy and Parturition, Mammals

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Glossary

Adrenal gland The cortex or outer layer secretes steroid hormones, particularly cortisol, in response to ACTH secreted by the anterior pituitary gland.

Anterior pituitary Structure at the base of the hypothalamus that secretes luteinizing hormone (LH), follicle stimulating hormone (FSH), prolactin (PRL), adrenocorticotrophic hormone (ACTH), thyroid stimulating hormone (TSH) and growth hormone (GH) hormones in response to releasing hormones secreted by the hypothalamus, but PRL secretion is regulated by prolactin inhibitory factor which is dopamine.

Cervix A thick cartilaginous structure between the vagina and uterus that serves as a barrier protecting the developing conceptus within the uterus during pregnancy. During the periparturient period the cervix dilates and forms a birth canal through which the fetus and placenta pass to reach the external environment.

Conceptus The embryo/fetus and associated membranes.

Corpus luteum The endocrine gland(s) formed by the granulosa and theca cells of the ovarian follicle after ovulation that secretes progesterone which is necessary for the establishment and maintenance of pregnancy.

Ferguson reflex A neural response from stimulation of the vagina resulting in the release of oxytocin from the hypothalamus/posterior pituitary into maternal blood.

Hypothalamus The structure at the base of the brain that regulates many physiological functions through secretion of hormones.

Labor The process in which the mother's uterine contractions physically force the offspring out of the reproductive tract via the cervix and vagina into the external environment.

Luteolytic hormone Hormone, particularly prostaglandin $F_{2\alpha}$ that causes functional and structural demise of the corpus luteum.

Luteotrophic hormone A hormone such as luteinizing hormone from the anterior pituitary gland or chorionic gonadotropin from placenta that stimulates secretion of progesterone by the corpus luteum.

Parturition The process of giving birth to offspring.

Periparturient The time immediately preceding, during, and immediately following parturition.

Placenta Fetal membranes that include the chorion, allantois and amnion. The chorion and allantois fuse to form the chorioallantois which transfers nutrients, waste products and gases between maternal blood and the fetal blood. In many species, the chorion secretes progesterone.

Posterior pituitary Structure at the base of the hypothalamus that secretes oxytocin and vasopressin in response to neurological signals.

Progesterone block During pregnancy, progesterone from the corpus luteum and/or placenta sustains the pregnancy by inhibiting uterine contractions and other activities that would lead to premature delivery of the fetus and placenta.

Prostaglandin $F_{2\alpha}$ The luteolytic hormone that causes functional and structural demise of the corpus luteum.

Uterus The major component of the female reproductive tract in which the conceptus (embryo/fetus and placenta) develop. It has an outer muscular layer known as the myometrium and an inner secretory layer known as the endometrium.

Introduction

Pregnancy is established and maintained in subprimate mammals in response to a series of interactions between the conceptus (embryo/fetus and associated membranes), uterus and/or ovarian corpus luteum (CL) (Bazer and First, 1983; Bazer and Spencer, 2009; Bazer *et al.*, 2008; Bazer, 2015). These interactions prevent functional and structural regression of the CL, or luteolysis. During the peri-implantation period of pregnancy, pregnancy recognition signals from the conceptus to the maternal system are either antiluteolytic or luteotrophic. The functional life span of the CL is controlled by release of prostaglandin $F_{2\alpha}$ (PGF) from either the uterus (subprimate mammals) and/or ovaries (primates, including humans). Pregnancy recognition signals from the trophoblast act in a paracrine or endocrine manner to interrupt either uterine or intra-ovarian production of luteolytic PGF (antiluteolytic) or the hormone may act directly on the CL (luteotropic).

Mammals have a placenta that surrounds the embryo/fetus and it is through these placental membranes that nutrients and other molecules from the maternal vascular system are transported to the vascular system of the conceptus to support its

growth and development. At some point in fetal development, depending on the species, there is maturation of the hypothalamic-pituitary-adrenal axis that is sufficient to induce parturition which involves expulsion of the fetus and its placenta from the uterus. Each species has a paradigm for producing live offspring so that the species is able to adapt to the external environment with maximum chances for survival of the neonate. This process of giving birth to offspring is called parturition (Latin, parturio, to be in labor). There are variations regarding factors controlling parturition; however, there is a common theme across species based on the roles of the fetal hypothalamic-pituitary-adrenal axis in inducing parturition. Parturition in sheep is the "classical" model because it has provided the preponderance of information that has advanced understanding of the endocrinology and physiology of parturition in subprimate mammals.

Pregnancy Maintenance in Ruminants

In ruminants, such as sheep and cows, an ovulatory surge of LH coincident with onset of estrus (Day 0) initiates events that culminate in ovulation about 30 h later. The antiluteolytic signal for pregnancy recognition in ruminants is interferon tau (IFNT) produced by mononuclear cells of conceptus trophectoderm. IFNT exerts a paracrine, antiluteolytic effect on the endometrium to inhibit uterine secretion of luteolytic pulses of PGF. Other conceptus and/or uterine products secreted during early pregnancy, for example, prostaglandin E2 (PGE) and platelet activating factor (PAF) may exert secondary luteal protective effects. The mechanism for pregnancy recognition is similar for sheep, cattle and goats.

Luteolysis is initiated as progesterone down-regulates expression of receptors for progesterone (PGR) in uterine epithelia 12–13 days after onset of estrus. With down-regulation of PGR there is an increase in expression of estrogen receptor alpha (ESR1) and then oxytocin receptors (OXTR) by the uterine epithelia. Oxytocin secreted by the corpus luteum (CL) and posterior pituitary binds OXTR and stimulates pulsatile secretion of PGF by uterine epithelia. IFNT inhibits expression of ESR1 and OTR mRNAs in endometrial epithelia to abrogate oxytocin-induced release of luteolytic pulses of PGF that ensures maintenance of the CL and its production of progesterone, the hormone of pregnancy. Nevertheless, inter-estrous intervals of 30–35 days result when sheep conceptuses are removed from uteri of ewes on Day 16 or after intrauterine infusions of either highly purified native ovine IFNT or recombinant IFNT (roIFNT) between Days 11 and 15 after onset of estrus. Thus, a secondary endometrial luteolytic mechanism activated between 25 and 30 days post-estrus must be abrogated by the conceptus to allow maintenance of pregnancy. The secondary mechanism for maintenance of CL function has not been established, but neither placental lactogen (CSH1) nor placental growth hormone (GH1) were found to be the secondary "signal" from the conceptus that reinforces the antiluteolytic effects of IFNT.

Binucleated trophectoderm cells in sheep conceptuses appear by Day 16 and secrete placental lactogen (CSH1). Placentae of other ruminant species secrete hormones structurally related to pituitary growth hormone (GH) and prolactin (PRL) and they are members of the CSH1 family. Both ovine GH and CSH1 have similar somatogenic activities; however, their circulating levels are regulated differently during the pregnancy. CSH1 is detected in blood of ewes by Day 50 of pregnancy and concentrations peak between 120 and 130 days of the 147 day period of gestation. Concentrations of CSH1 in fetal blood are less than in maternal blood and peak at mid-gestation after which time they may remain unchanged or decrease gradually to term. Concentrations of oGH1 are low in maternal serum throughout pregnancy and are not correlated with gestational age. Concentrations of oGH are greater in fetal than in maternal serum and greatest during mid-gestation. CSH1 may be critical to maintenance of pregnancy in sheep since lactogenic hormones influence steroidogenesis in CL and transport of water and other nutrients by placental membranes. Lactogenic hormones also stimulate proliferation of cells, expression of PGR, protein synthesis, exocrine secretion of PGF (pigs) by uterine epithelia, mammary growth and lactation. Ovine placental GH1 may have multiple roles in pregnancy.

Pregnancy Maintenance in Rodents

Gestation in rodents lasts 20–22 days, and functional CL must be maintained until Day 17. The transition in rodents, (i.e., rats, mice and hamsters) from recurring estrous cycles to pregnancy is dependent on maintenance of progesterone production by the CL, the main source of progesterone throughout pregnancy (Ben-Jonathan *et al.*, 2008; Soares *et al.*, 2007). Progesterone replacement alone is sufficient to maintain pregnancy in ovariectomized rats. In addition to lacking a true luteal phase during the estrous cycle, rodents do not exhibit a change in source of progesterone from the CL to the placenta. Thus, maternal recognition of pregnancy in rodents involves activation of nonfunctional CL of the cycle into functional CL of pregnancy.

Mating of rodents during estrus results in pseudopregnancy or pregnancy, and the activated CL secrete progesterone for 12–14 days. Extension of CL lifespan past Day 12 after onset of estrus depends on the presence of viable conceptuses within the uterus. A successful pregnancy in rats requires active secretion of progesterone from CL until at least Days 17–18. Therefore, establishment and maintenance of pregnancy in rodents requires two separate endocrine events. The first endocrine event initiated by mating results in diurnal and nocturnal surges of prolactin during the first 12 days of pregnancy or pseudopregnancy in rats. The prolactin is necessary for formation and maintenance of active CL and their secretion of progesterone. Therefore, the luteotrophic effects of PRL during early pregnancy are required to convert a nonfunctional CL of the estrous cycle into a functional CL of pregnancy or pseudopregnancy.

The second endocrine event required for the maintenance of pregnancy in rodents is dependent on implantation and development of normal conceptuses. In pregnant rodents, the placenta and stromal cells that differentiate to form the uterine decidua produce PRL-like hormones that have luteotrophic effects on the CL to ensure production of progesterone during the middle and late stages of pregnancy. The antimesometrial uterine decidual cells secrete numerous hormones, including PRL-like protein B (PLP-B) and decidual PRL-like protein (dPRP). The main luteotropic hormone of the decidua is a PRL-like protein, although uterine decidual cells also secreted PLP-B. Placental lactogens (CSHs) are found in a variety of subprimate mammals, including rodents. However, the only established physiological roles for CSH1s are in rodents. In rats, seven members of the PRL gene family are expressed by trophoblast cells of the placenta: placental lactogen-I (CSH-I), CSH1-I variant (CSH1-Iv), CSH1-I mosaic (CSH1-Im), CSH1-II, PRL-like protein A (PLP-A), PLP-B and PLP-C. CSH1-I and CSH1-II have biological activities similar to those of pituitary PRL, including CL maintenance and growth of the mammary glands.

Factors regulating production of CSH1s by trophoblast cells are not well known. The ontogeny of CSH1-I expression appears to be linked to differentiation of trophoblast cells during the peri-implantation period. In mice, expression of the CSH1-I gene appears to be regulated by the number of conceptuses and by the pituitary gland. Similarly, factors affecting expression of the CSH1-II gene include the number of conceptuses, genotype of the conceptuses, pituitary via growth hormone (GH), ovarian steroids and nutritional status of the mother. The shift from CSH1-I to CSH1-II is associated temporally with degeneration of the choriovitelline placenta between Days 13 and 14 of gestation.

In rats, PRL is essential for maintenance of progesterone secretion by CL throughout pseudopregnancy. However, in the pregnant rat, removal of the anterior pituitary after mid-gestation does not affect luteal function and pregnancy is maintained. Thus, pituitary PRL is not necessary after Day 6 of gestation in rodents. Given their PRL-like activity and their ontogeny during pregnancy, CSH1s are likely luteotrophic factors from the placentae during mid- to late-pregnancy in rodents.

Pregnancy Maintenance in Swine

Estrogens produced by conceptuses between Days 11 and 12 of gestation provide the initial signal for maternal recognition of pregnancy in swine (Bazer, 2015). This signal results in a switch in the direction of secretion of PGF by uterine epithelia from an endocrine direction (i.e., into maternal blood) to an exocrine direction (i.e., into the uterine lumen). A second period of estrogen production occurs between Days 15 and 25–30 of pregnancy in pigs. Injection of exogenous estrogen (estradiol valerate, 5 mg/day) on Days 11 through 15 of the estrous cycle results in CL maintenance for a period equivalent to or slightly longer than pregnancy. This condition of estrogen-induced CL maintenance in non-pregnant pigs is known as pseudopregnancy and it persists for about 120 days. Thus, two phases of exogenous estradiol, similar to that produced by conceptuses on Days 11–13 and Days 15–25–30, are necessary for prolonged secretion of PGF into the uterine lumen. Estradiol may induce receptors for maternal hormones, for example, prolactin, or conceptus secretory proteins, which influence exocrine (into the uterine lumen) secretion of PGF. The first estrogen signal may induce receptors for PRL and the second estrogen signal may be required to replenish those receptors. Administration of estradiol on Day 9 advances the uterine secretory response in pregnant gilts, but leads to conceptus death by Day 16 due to degeneration of the extracellular matrix on the uterine luminal epithelium. An explanation for this "induced" conceptus death is not available, but it may result from asynchrony between the developing conceptus and uterine environment that adversely affects maintenance of the extracellular matrix.

Estrogen induces endometrial receptors for prolactin (PRLR) in pigs, and PRL acts on the endometrium to induce calcium cycling across the epithelium. In pigs, PRL interacts with estrogen and progesterone to increase total recoverable uteroferrin, glucose and PGF in uterine flushings. Available results strongly indicate that prolactin enhances uterine responsiveness to progesterone during periods critical for maintenance of pregnancy.

Pregnancy Maintenance in Horses

The uterine luteolytic hormone in mares is PGF and the conceptus produces an unidentifried factor that inhibits uterine secretion of luteolytic pulses of PGF (see Bazer, 2015). In cycling mares, concentrations of PGF in uterine venous plasma and uterine flushings increase between Days 14 and 16 when luteolysis occurs and concentrations of progesterone decline in blood. The amount of PGF bound by luteal receptors is maximal on Day 14 of the estrous cycle and Day 18 of pregnancy. Since CL of mares can respond to circulating PGF during pregnancy, the conceptus must evoke an antiluteolytic mechanism. Pregnant mares have little PGF in uterine fluids, low concentrations of PGF in uterine venous plasma, and no pattern of pulsatile release of PGF (measured as the metabolite of PGF, PGFM) in peripheral plasma. In the presence of the conceptus, endometrial production of PGF in response to cervical stimulation and exogenous oxytocin is markedly reduced, indicating the absence or significant reduction in endometrial receptors for oxytocin in mares during early pregnancy.

The pregnancy recognition signal in mares is not known, but estradiol and/or proteins from the conceptus are likely candidates. There is also some evidence that PGE may play a role in pregnancy recognition signaling in mares. The equine conceptus migrates between the two uterine horns 12–14 times per day between Days 12–18 of pregnancy presumably to inhibit endometrial production of luteolytic PGF and protect the CL for production of P4. The equine conceptus also produces increasing amounts of estradiol

between Days 8 and 20 of gestation. A similar trend, but of greater magnitude, was found for estrone. Attempts to prolong CL lifespan in mares by injection of estrogens have been inconsistent.

Horse conceptuses secrete three major proteins between Days 12 and 14 of pregnancy with molecular weights of greater than 400,000, 50,000, and 65,000. However, the role(s) of those proteins is not known. Estrogens and/or conceptus secretory proteins may provide the maternal recognition of pregnancy signal in the mare by directly or indirectly inhibiting uterine production of luteolytic pulses of PGF.

Pregnancy Maintenance in Rabbits

Rabbits are induced ovulators and multiple ova are ovulated from each ovary approximately 10 h after mating. The oocytes remain fertilizable for about 6 h (Marcinkiewicz and Bahr, 1993). The fertilized ova arrive in the uterus 3 days post-ovulation and implantation occurs on Day 7 at the blastocyst stage of conceptus development. The rabbit placenta is not a significant source of progesterone and the CL are required for pregnancy to go to term. Following a sterile mating, CL form and persist for 14–16 days without support from conceptus products. For both pseudopregnant and pregnant does, progesterone begins to increase 2 days after mating to maximal levels of 12–20 ng/mL between Days 6–8 post-coitum. Between Days 8 and 10 post-mating progesterone profiles of pregnant and pseudopregnant does begin to diverge with concentrations of progesterone in blood declining rapidly after Day 12 to basal levels between Days 16 and 18 of pseudopregnancy. For pregnant does, concentrations of progesterone in blood do not begin to decline until 3–4 days prior to parturition (kindling).

Maternal recognition of pregnancy occurs after implantation between Days 10 and 12 of gestation. Estrogen and a placental luteotropin interact to maintain progesterone production by the corpora lutea until term (28–35 days). Estrogen from developing follicles is required to stimulate progesterone production by CL for the first 10–12 days of pregnancy, but not to term. Luteal cells of corpora lutea of rabbits express LH receptors; however, LH does not stimulate progesterone production *in vivo*.

Production of a placental luteotrophin is necessary for production of progesterone by corpora lutea to term, but exogenous estrogen does not support progesterone production by corpora lutea of hysterectomized does during late pregnancy. Placentae of rabbits secrete a molecule having immunoreactive GnRH-like activity, but there is no evidence for it being transported from the uterus to the corpora lutea. A putative placental luteotrophic factor with a molecular weight greater than 6–8 kDa does enhance progesterone production by cultured luteal cells. Placental giant cells in rabbits also contain immunoreactive chorionic gonadotropin, and cytotrophoblast cells contain immunoreactive CSH1/PRL. However, the function(s) of those proteins has not been determined.

Pregnancy Maintenance in Cats

The cat, also an induced ovulator, ovulates 25–50 h post-mating (about 24–36 h after the LH peak) with frequent matings reducing the time to ovulation (Verstegen *et al.*, 1993; Brown, 2006). Fertilization takes place in the oviduct up to 48 h after ovulation. Feline embryos enter the uterus at the blastocyst stage, 4–6 days post-ovulation, blastocysts hatch from the zona pellucida on Day 11 and begin implanting by Days 12–13 of pregnancy. Following mating, concentrations of progesterone in plasma increase from about Day 3 to maximal levels (15–90 ng/mL) between Days 10 and 40 of pregnancy, or Days 13 and 30 of pseudopregnancy. Pseudopregnancy typically lasts 40 days and gestation ranges between 56 and 71 days, averaging 63–65 days. By Day 30, circulating levels of progesterone are significantly higher in pregnant than in pseudopregnant queens. The corpora lutea of queens are resistant to luteolytic effects of PGF until after Day 40 of pregnancy.

The placenta does not appear to be a significant source of progesterone during gestation in cats. Concentrations of prolactin in maternal blood increase after Day 40 of gestation in queens and it is considered the be luteotrophic. Inhibition of secretion of PRL in the last trimester of gestation causes abortion. Concentrations of PRL are greatest just prior to parturition 5–10 ng/mL) and remain elevated during lactation in response to suckling. Relaxin is produced by the fetal-placental unit, corpora lutea and uterus during pregnancy. Relaxin likely works in concert with progesterone to keep the uterus quiescent and to facilitate parturition by softening the connective tissues of the pelvis and cervix (Sherwood, 2004). Following parturition, queens experience a period of lactational anestrus and resume cycling 2–3 weeks after weaning kittens.

Pregnancy Maintenance in Dogs

Dogs are spontaneous ovulators and fertilization of oocytes occurs 2–5 days after ovulation in the bitch and embryos enter the uterus at the blastocyst stage around Day 10 (Concannon, 1993; Verstegen-Onclin and Verstegen, 2008). Embryos remain free-floating in the uterus until hatching and implantation around Day 16. The ovary is the primary source of progesterone and ovariectomy or hypophysectomy at any stage of pregnancy results in abortion. Since the lifespan of corpora lutea of pregnancy 64–66 days) and pseudopregnancy 60–63 days) are similar, there is no known requirement for signaling between the conceptus and maternal system for CL maintenance, pregnancy recognition or maintenance of pregnancy.

The corpora lutea of bitches are resistant to luteolytic effects of PGF until after Day 40 of pregnancy or pseudopregnancy. The secretion of prolactin increases after Days 30–40 of gestation and it is considered to be luteotrophic. Inhibition of secretion of PRL after about Day 30 of gestation causes abortion. The ovaries and pregnant uterus produce relaxin for uterine quiescence during pregnancy, as well as relaxation of the cervix and pelvic ligaments. Interestingly, it remains detectable in blood of bitches for up to 60 days after parturition.

Endocrine Cascade Leading to Parturition

Subprimate mammals have placentae that include the amnion and amniotic fluid therein that provides support for the embryo/fetus to exist somewhat like a marine mammal and develop symmetrically in a liquid environment. The other two membranes, chorion and allantois, fuse to form the chorioallantois that transports nutrients from the blood of the mother to the blood of the conceptus and allows for the exchange of gases (O_2 and CO_2) between blood of mother and conceptus. At some point in development of the conceptus, varying with species, the fetus and its placental membranes are expelled from the uterus into the external world. Each species has a unique paradigm for producing live offspring that includes development of the fetus in utero, the birth process, and adaptation of the newborn to the external environment so that survival of the offspring is maximized for propagation of the species. The physiological events leading to birth of subprimate mammals is known as parturition (Latin, parturio, to be in labor), is the focus of this section of this chapter (see Thorburn and Challis, 1979; Liggins, 1988; Currie *et al.*, 1988; Wood and Cudd, 1997; Challis *et al.*, 2005).

One of the oldest records depicting birth is a stone relief in the tomb of Ti (2450-2320 BCE) showing assistance being given to a cow by applying traction to the limbs of a partially protruding calf and another showing removal of fetal membranes. Around 2000 years later the Greek philosopher Hippocrates proposed that the baby determines the timing of birth. In the 1930s, Joseph Barcroft found that restriction of oxygen and other nutrients to the fetus due to the mother's inability to meet the increasing demands of a developing fetus for nutrients lead to birth (see Liggins, 1988). However, Liggins (1988) published seminal findings establishing that maturation of the fetal hypothalamic-pituitary-adrenal gland axis provides for endocrine regulation of parturition. From the first record over 4400 years ago through to today, the paradigm of pregnancy leading to parturition is that the fetus and placenta signal their presence to the mother, secrete hormones that establish and maintain the pregnancy, prepare the mother's mammary glands for lactation and determine the time of birth.

There are a mulitude of variations on the theme of regulatory factors controlling reproduction in mammals and they are likely continuing to undergo evolutionary changes. Each species is exploring to find the "best fit" for maximizing survival of the species. The process of parturition also involves a mulitude of variations in factors controlling parturition. However, there is a common theme across species in regulating the major events of reproduction including parturition. Most is known about the physiology and endocrinology of parturition in the ewe, which is the "classical" model that has provided the preponderance of information toward our understanding of parturition in subprimate mammals.

Parturition, once initiated, leads to rapid expulsion of the young from the reproductive tract of the mother to the external environment. The mother prepares for this throughout pregnancy with a gradual change in her endocrine environment to accommodate changes that range from alterations in cardiac function and respiratory functions to mammogenesis and lactogenesis. The placental membranes and the hypothalamic-pituitary-adrenal axis of the fetus mature with advancing gestation and once that maturation process reaches a critical point events leading to parturition are initiated. The key events leading to parturition were established based largely on results from research by Liggins and co-workers with sheep (see **Fig. 1**).

In fetal lambs the hypothalamus at the base of the brain begins to secrete corticotropin releasing hormone (CRH) into the local portal circulation around Day 100 of gestation. The CRH enters the hypothalamic portal system supplying the anterior pituitary gland. On about Day 125 of pregnancy, the fetal anterior pituitary gland begins to respond to CRH by producing and secreting adrenocorticotropin hormone (ACTH) into the systemic circulation where it can stimulate the adrenal cortex to release cortisol. Arginine vasopressin (AVP) secreted by the hypothalamus may also play a role in parturition by stimulating the secretion of ACTH from the anterior pituitary gland. Beginning around Day 135 of gestation the adrenal cortex of the fetus has matured sufficiently to begin responding to ACTH and secreting cortisol in increasing amounts so that concentrations in fetal blood are maximum 24–48 h prior to the onset of parturition in ewes on Day 147 of gestation. In sheep and in many other species including goats, cows, and pigs, the endocrine events in the fetus leading to production of cortisol and culminating in parturition and birth of the offspring are very similar.

The critical role of the fetal hypothalamic-pituitary-adrenal axis was revealed in an elegant series of studies by Liggins and co-workers. They removed the fetal anterior pituitary gland at the end of the second trimester of pregnancy and found that parturition was delayed significantly. But, when ACTH was administered to the fetus at the end of the second trimester of pregnancy parturition was induced. Likewise removal of the fetal adrenal gland and cortisol prevented parturition while administration of cortisol to the fetus induced parturition. In sheep and cows with deformities in the fetal brain resulting in the absence of hypothalamic secretion of CRH, parturition does not occur normally and fetuses must be removed by Caesarean section. This is because the fetus will continue to grow to an extremely large size and eventually compress the gastrointestinal system of the ewe or cow leading to her death. A similar result was reported for fetal calves with an abnormality of the adrenal gland that prevented secretion of cortisol.

During the last 3–5 days prior to parturition there are significant changes in the endocrinology of the pregnant female (see **Table 1**). First, concentrations of progesterone in maternal blood decrease rapidly. This is because the placenta stops producing

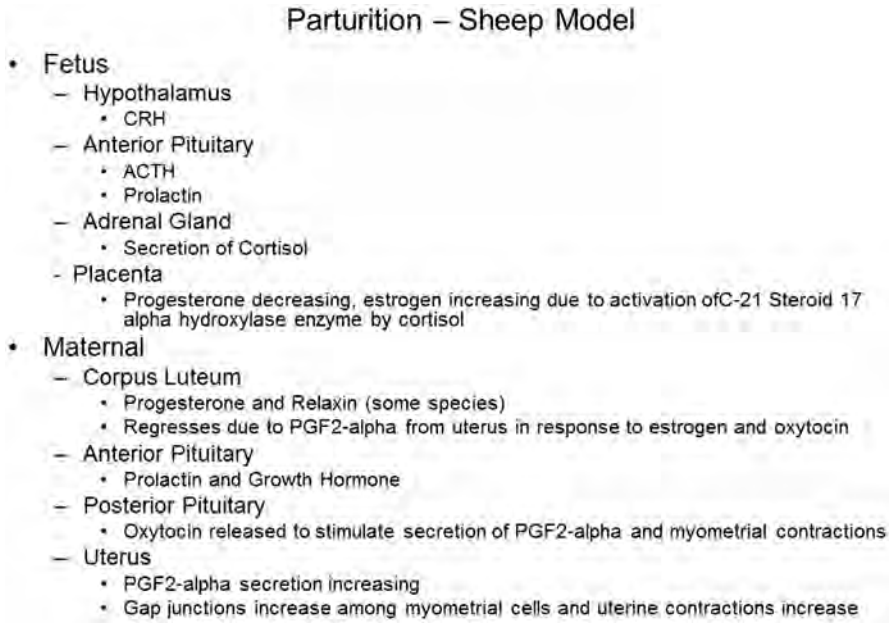

Fig. 1 Parturition: The sheep model. The periparturient endocrine events that occur in the mature fetus initiate the endocrine cascade that leads to parturition. The fetal hypothalamus secretes corticotropin releasing hormone (CRH) that acts on the fetal anterior pituitary gland to induce production and secretion of adrenocorticotropin hormone (ACTH) into the general circulation of the fetus. The fetal adrenal gland responds to ACTH with secretion of cortisol primarily. Cortisol acts on cells of the placenta to activate C21-steroid 17α-hydroxylase which allows progesterone to be metabolized to estrogens which are key to the initiation of parturition. The shift from progesterone dominance for maintaining pregnancy to estrogen dominance is integral to the cascade that leads to parturition. For example, estrogen activates enzymes that lead to synthesis of prostaglandin $F_{2\alpha}$ (PGF2-alpha) that plays a major role in parturition, and estrogen increases in expression of receptors for oxytocin on uterine epithelial cells and smooth muscle cells of the uterine myometrium. The mother's hypothalamus secretes oxytocin which acts via its receptors on uterine epithelial cells induce pulsatile secretion of PGF2-alpha and both oxytocin and PGF2-alpha act on the myometrium to induce contractions of the myometrium. In addition to PGF2-alpha causing regression of the corpus luteum to further decrease circulating concentrations of progesterone, it also release relaxin (e.g., pigs) from the corpus luteum which is responsible for dilation of the cervix and relaxation of pelvic ligaments. In other species the placenta is the source of the relaxin (Sherwood, 2004). The decrease in concentrations of progesterone and increasing concentrations of estrogen also induce formation of gap junctions among smooth muscle cells of the uterine myometrium which is necessary for the coordination of contractions among smooth muscle cells to expel the fetus and placenta to complete the process of parturition.

progesterone and starts secreting estradiol and there is regression of the corpus luteum to eliminate that source of progesterone. The sheep placenta produces progesterone; however, cortisol activates the enzyme C21-steroid 17-alpha hydroxylase which converts progesterone to 17-alpha hydroxyprogesterone that can be metabolized further to androgens and estrogens. The fetal gonads in mares provide androgens for synthesis of estrogens by the placenta. The estradiol produced by the placenta increases phospholipase A2 activity and expression of oxytocin receptors in uterine epithelia and uterine myometrium. Phospholipase A liberates arachidonic acid from phospholipids in uterine epithelia for conversion by prostaglandin synthase 2 and prostaglandin F synthase to PGF. Oxytocin from the posterior pituitary gland is released in pulses as the fetal head pushes on the cervix during parturition

Table 1 Characteristics of periparturient endocrine events

Species	*Days of gestation*	*Source of progesterone*	*Placental C21 Steroid 17α- hydroxylase*	*Fetal adrenal hormone*	*Source of relaxin*
Sheep	144–152	CL and Placenta	Yes	Cortisol	?
Goat	146–154	CL	Yes	Cortisol	?
Cow	270–300	CL and Placenta	Yes	Cortisol	CL
Pig	112–115	CL	Yes	Cortisol	CL
Horse	315–360	Placenta	No	Cortisol	Placenta
Dog	64–66	CL	Unknown	Unknown	CL and Placenta
Cat	64–66	Placenta	Unknown	Unknown	CL, Placenta and Uterus
Rat		CL	No	–	CL
Rabbit		CL	No	–	Placenta and Uterus
Primate		Placenta	No	Cortisol DHEA SO_4	CL+Uterus

Abbreviations: CL, corpus luteum; DHEA-SO_4, dehydroepiandrosterone sulfate.

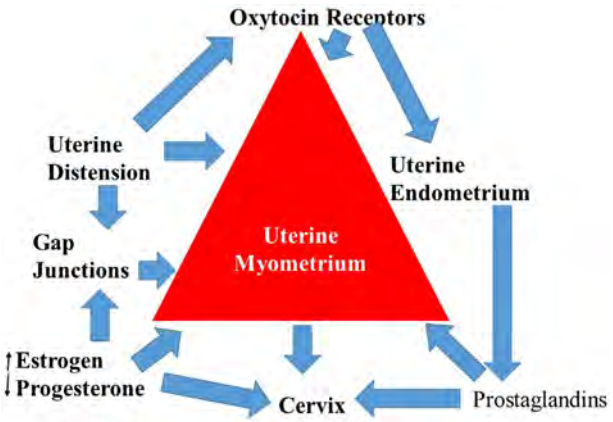

Fig. 2 The myometrium is composed of smooth muscle cells that are critical to providing the forces of contractions necessary for delivery of the fetus and placenta. A prerequisite for development of strong myometrial contractions is the increase in production of estrogens by the placenta and the decreased in progesterone which leads to the formation of gap junctions among myometrial cells that allows them to contract in unison and with increasing force as oxytocin and prostaglandin $F_{2\alpha}$ act via their respective receptors to stimulate uterine contractions. Distension of the uterus and pressure of the fetus on the cervix induce release of oxytocin from the posterior pituitary gland of the mother in a pulsatile manner. The uterine endometrium is the primary source of the prostaglandin F2α that acts on the myometrium and cervix to stimulate contractions. As noted in **Fig. 1**, relaxin softens and increases the distensibility of the pelvic ligaments and dilation of the cervix forming a passageway sufficient for delivery of the fetus. An increase in concentrations of oxytocin and prostaglandins in maternal blood, along with formation of gap junctions between smooth muscle cells of the uterine myometrium induce increasingly powerful contractions of the uterine myometrium that expel the fetus and placenta into the extra-uterine environment.

(Ferguson reflex) which causes pulsatile release of PGF from the uterine epithelia that is luteolytic and causes regression of the CL and their secretion of P4. So, cortisol changes the sex hormone ratio from high progesterone and low estradiol during pregnancy to high estradiol and low progesterone during parturition.

The decreasing concentrations of progesterone and increasing concentrations of estradiol in the ewe leads to the formation of gap junctions (known as connexin 43) between smooth muscle cells of the uterine myometrium (see **Fig. 2**). The gap junctions allow the smooth muscle cells to communicate with each other to contract and relax in unison. Visualize that early in parturition there are few gap junctions so contractions are weak and infrequent, but progressive increases in numbers of gap junctions allow strengthening of contractions at more frequent intervals as more and more smooth muscle cells contract and relax in unison. During this time in the peri-parturient period, oxytocin is being released in greater amounts with strength and frequency of contractions because the fetus is putting more pressure on the cervix (Ferguson reflex) at increasingly frequent intervals. Finally, uterine myometrial contractions are sufficient to expel the fetus and then the placenta from the uterus, through the cervix and vagina to the external environment. PGF is also acting with oxytocin to stimulate contractions of the uterine myometrium.

Relaxin is a hormone produced by large luteal cells of the corpus luteum of pigs, the placenta and corpus luteum of cow and placenta of the mare. Relaxin interacts with other hormones including estradiol, PGF and oxytocin to cause relaxation and dilation of the cervix and pelvic ligaments. Relaxin increases keratin sulfate and decreases dematin sulfate in cervical collagen. With loss of dermatin sulfate there is a decrease in cross-linking of collagen fibers which increases distensibility of the cervical collagen and the diameter of the lumen of the cervix.

Epinephrine stimulates synthesis and cortisol induces secretion of surfactant by epithelial cells of the fetal lungs which is critical for maturation and function of the lungs to ensure respiration and survival of the offspring.

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FETAL DEVELOPMENT

Formation and Growth of the Fetus

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The conceptus develops from a single fertilized egg into a complex multicellular organism by processes of cell proliferation, growth, and differentiation within the uterus. After organogenesis, the major period of body growth occurs in fetal life, during the second and third trimesters of human pregnancy. Fetal growth follows an orderly and coordinated increase in body weight and length, which is coupled with a proportionate increase in organ weights and their functional development. Normal fetal growth and maturation is essential for both the survival of the offspring at birth and for longer term health in adult life.

Measurement of Fetal Growth

Fetal growth can be assessed by a range of clinical and experimental methods. End-point measurements, such as body weight, length, and adiposity at the time of delivery, are simple indicators of intrauterine growth. It is also possible measure growth rate while the fetus is developing within the uterus. Ultrasound scanning can be used to make a variety of measurements of growth at different gestational ages. In clinical practice, the most common biometric measurements include biparietal diameter (diameter of a cross-section of the head or skull), femur bone length and abdominal circumference, and these values are combined to estimate the body weight of the fetus.

Using ultrasound data from many individuals, a series of growth charts can be generated to estimate the percentile and the growth trajectory of the fetus. These growth charts have recently been updated by the World Health Organization using data obtained in a multinational study. Longitudinal measurements were made from 14 to 40 weeks in singleton fetuses, where the pregnant women were recruited from middle to high income backgrounds to ensure good nutritional status (Kiserud et al., 2017; **Fig. 1**). Fetal growth charts can be used to diagnose abnormalities in intrauterine growth, particularly if fetal growth deviates from its previous trajectory. Estimated fetal body weight less than the 10th centile or greater than the 90th centile indicates a fetus that is small- or large-for-gestational age (SGA and LGA), respectively.

Experimentally, fetal growth has been monitored in large animal models, such as sheep, using both end-point and continuous intrauterine measurements. In the sheep fetus, indwelling growth devices measure the crown-rump length and abdominal circumference over a period of late gestation and incremental growth rates have been demonstrated in well-fed ewes with stable maternal plasma glucose concentrations (Mellor and Matheson, 1979; **Fig. 2**). Collectively, the ultrasound and experimental techniques have shown, in many species including the human, that fetal growth is greatest in absolute terms in the later stages of gestation. Close to term, however, the growth rate of the fetus slows as the developing tissues switch from cell proliferation to differentiation and functional maturation, in preparation for birth.

Control of Fetal Growth

The growth of the fetus is driven primarily by the genetic potential of the individual inherited at conception. Intrauterine growth and development, however, can be modified by a variety of factors including physiological, nutritional, environmental, and clinical conditions with consequences for size at birth. Many of these factors interact with each other to generate a wider range of birth weights in the human and animal population than predicted by genotype alone. These factors can be divided into those that originate in (1) the mother, (2) the placenta, and (3) the fetus itself (**Fig. 3**).

Maternal Factors

Maternal size

The size of the mother influences the growth rate of the fetus. This may be due to (i) the inherited genetic potential for fetal growth, as paternal height also correlates with birth weight, (ii) the size of the uterus and/or (iii) the body composition and energy reserves of the mother before and during pregnancy. The relative contributions of the genetic and uterine environment in determining fetal growth, however, are difficult to separate. In human populations, both maternal height and body mass index, and paternal height, correlate with offspring birth weight; further analysis shows that neonatal adiposity and head circumference are predicted by maternal height and body mass index, while limb lengths are more strongly associated with paternal height (Pomeroy et al., 2015). In assisted pregnancies where egg donation was used, the birth weight of the infant correlated with the weight and height

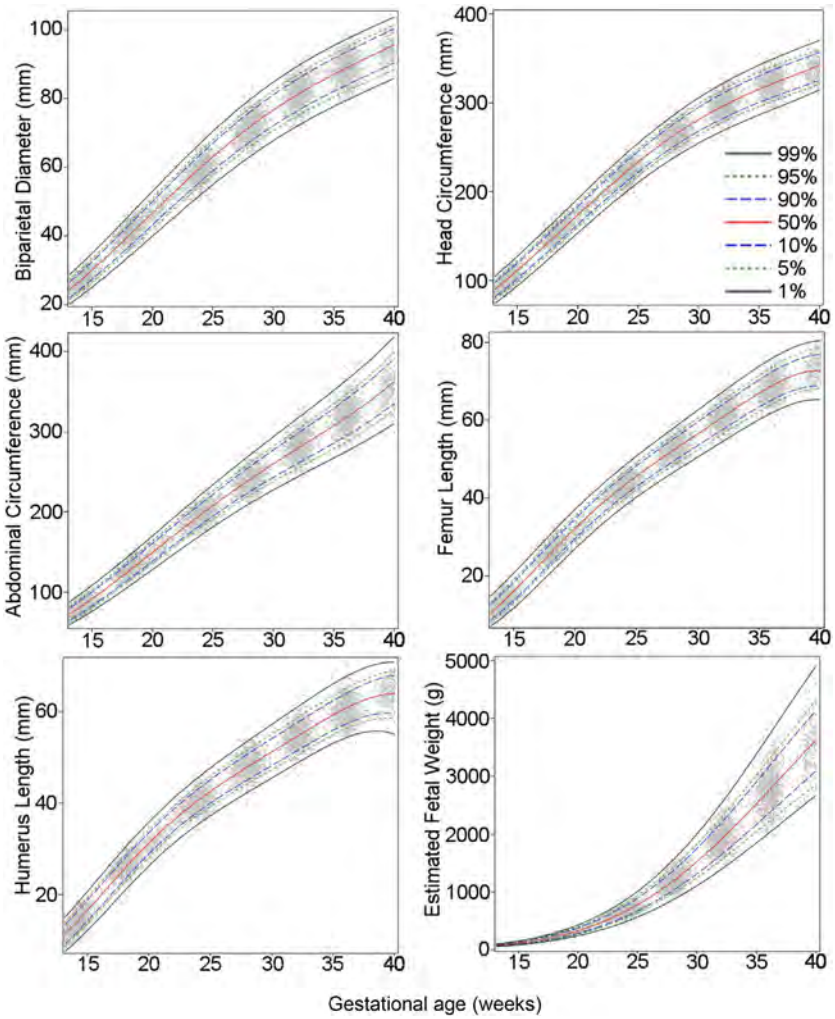

Fig. 1 Growth charts and percentiles for biparietal (*outer–inner*) diameter, head circumference, abdominal circumference, femur length, humerus length, and estimated body weight in human fetuses from 14 to 40 weeks of gestation. Taken from Kiserud, T., Piaggio, G., Carroli, G., Widmer, M., Carvalho, J., Neerup Jensen, L., Giordano, D., Cecatti, J.G., Abdel Aleem, H., Talegawkar, S.A., Benachi, A., Diemert, A., Tshefu Kitoto, A., Thinkhamrop, J., Lumbiganon, P., Tabor, A., Kriplani, A., Gonzalez Perez, R., Hecher, K., Hanson, M.A., Gülmezoglu, A.M. and Platt, L.D. (2017). Correction: The World Health Organization fetal growth charts: A multinational longitudinal study of ultrasound biometric measurements and estimated fetal weight. *PLoS Medicine* **14**(*3*), e1002284.

of the recipient, but not with measurements from the biological donor mother (Brooks et al., 1995). This suggests that the intrauterine environment may have a greater role in mediating the effect of maternal size on offspring birth weight than the genetic influence of the mother.

The larger the uterus, the more space is available for growth of both the placenta and fetus and equally, a small uterus can limit the ability of the placenta and fetus to grow to their genetic potential. The effect of uterine size on fetal growth was demonstrated in classical experiments by Walton and Hammond (1938). They developed the technique of artificial insemination to cross breed Shire horses and Shetland ponies. When a Shetland pony mare was inseminated by a Shire horse stallion, the foal produced was three times smaller than the foal conceived by a Shire horse mother and Shetland pony father (Walton and Hammond, 1938; **Fig. 4**). These studies showed that the size of the uterus can determine the size of the newborn foal, such that the birth weight of the offspring is a function of maternal body weight, around 8% in these experiments. Furthermore, the differences in foal size and body composition at birth persisted into later life.

Maternal nutrition

Maternal nutrition is a key regulator of fetal growth as the mother provides the macro- and micronutrients that both the fetus and placenta require to grow. Several experimental and epidemiological studies have shown that under-nutrition of the mother impairs fetal growth (Sferruzzi-Perri et al., 2013).

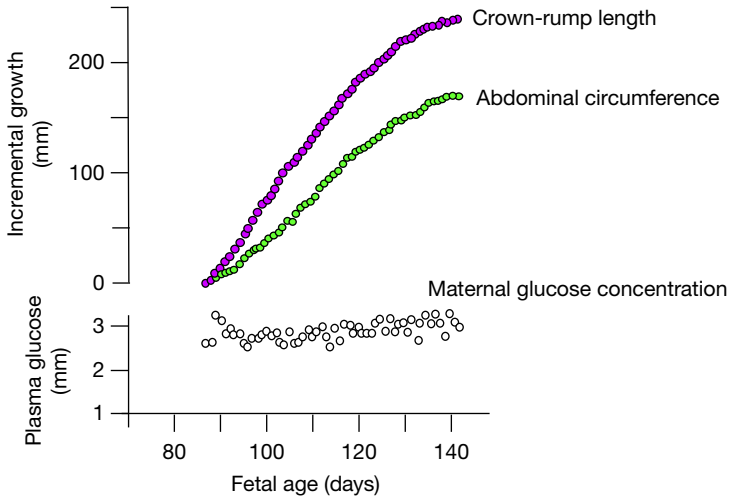

Fig. 2 Growth rates for crown-rump length and abdominal circumference using indwelling growth measuring devices in a sheep fetus during late gestation (term ~145 days). Redrawn from Mellor, D.J. and Matheson, I.C. (1979). Daily changes in the curved crown rump length of individual sheep foetuses during the last 60 days of pregnancy and the effects of different levels of maternal nutrition. *Quarterly Journal of Experimental Physiology* **64**, 119–131.

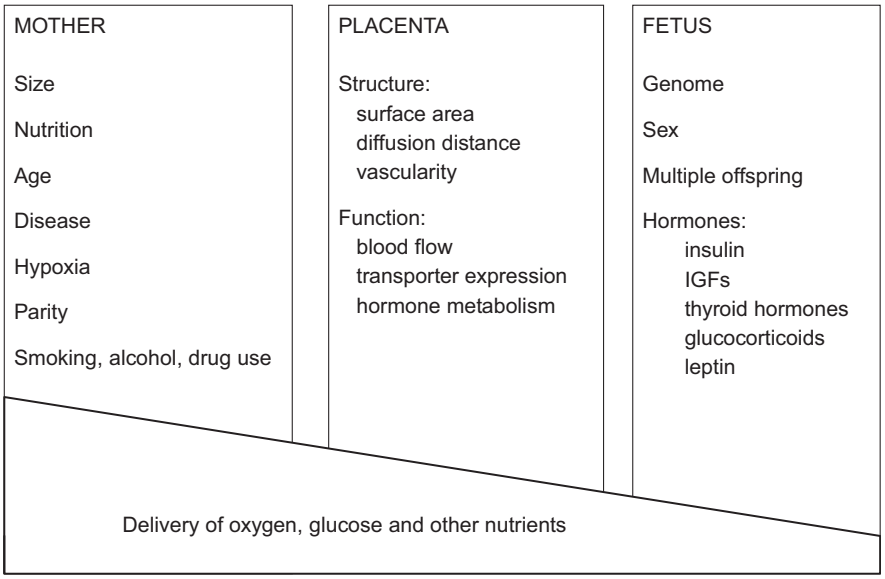

Fig. 3 Factors that influence the growth of the fetus.

Using growth-measuring devices in sheep fetuses, the growth rates of the axial skeleton and abdominal circumference were monitored before, during and after a 10-day period of maternal under-nutrition (Mellor and Murray, 1982; **Fig. 5**). Maternal plasma glucose levels fell when the mother was under-nourished and the growth rates measured in the fetus were suppressed. When the mother was re-fed to normal levels, maternal plasma glucose concentration returned to normal and the growth of the fetus was restored to the rate observed before the period of under-nutrition.

The Dutch Winter Hunger study is a unique opportunity to examine the effects of maternal under-nutrition on fetal growth in the human population. During World War II, parts of occupied Netherlands were severely rationed by the German army such that, for the last 6 months of the war, the food intake of the people of Western Netherlands, which included Amsterdam, Rotterdam, and The Hague, was reduced to <1000 calories per day. Pregnant women in the third trimester during this time did not show normal weight gain and their babies were around 200–300 g lighter in birth weight (Smith, 1947; Lumey, 1998; **Table 1**).

Other maternal factors

Fetal growth is also affected by a variety of interacting maternal factors. Parity influences growth of the fetus, whereby first-born offspring are usually smaller than subsequent siblings, in part, as a consequence of changes in uterine size. Extreme ends of maternal

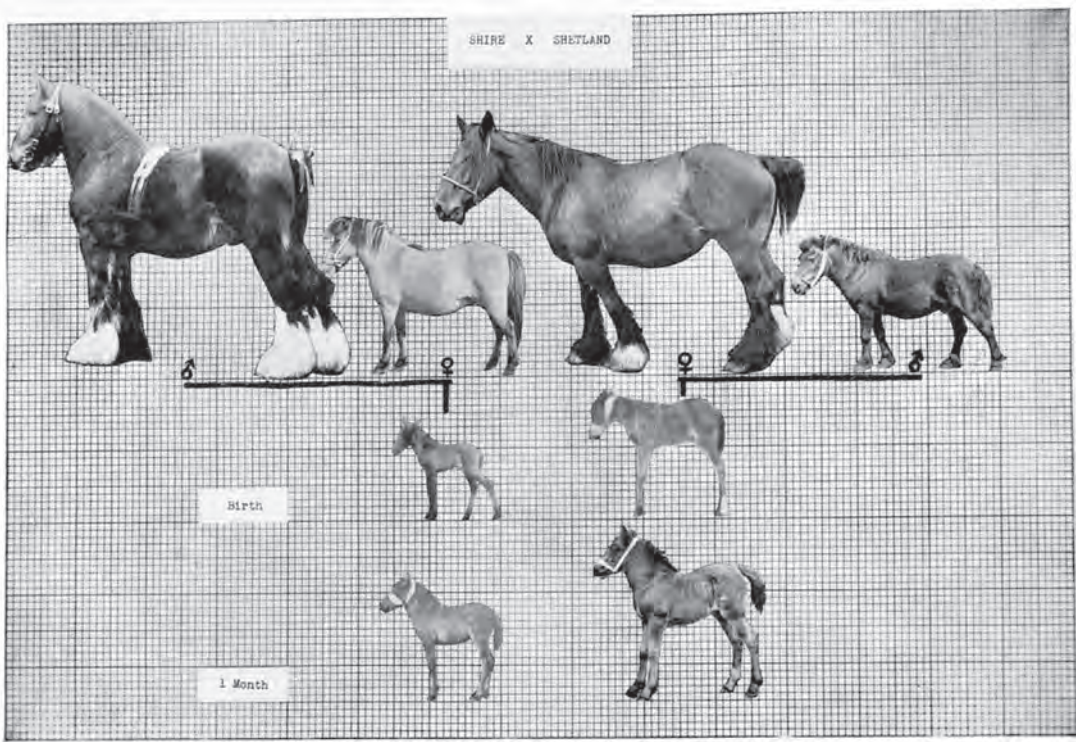

Fig. 4 Parents and offspring of reciprocal Shetland–Shire crosses to show consequences of maternal size for fetal growth. Taken from Walton, A. and Hammond, J. (1938). The maternal effects on growth and conformation in Shire horse-Shetland pony crosses. *Proceedings of the Royal Society London B* **125**, 311–335.

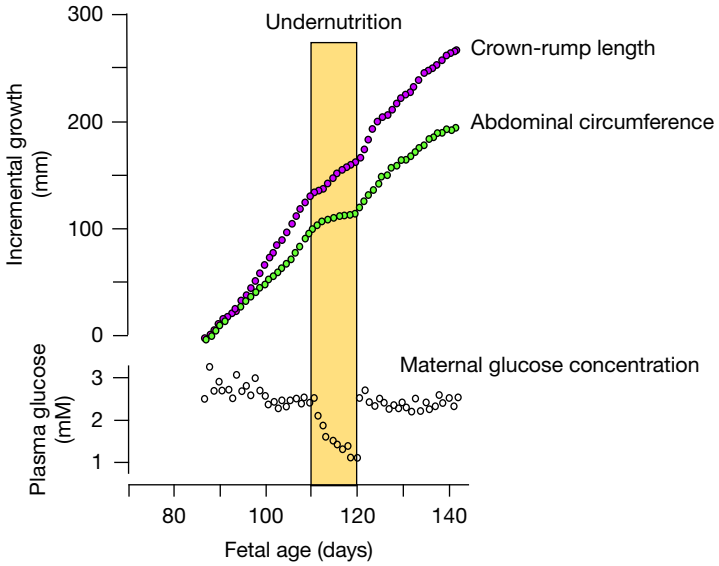

Fig. 5 Effect of maternal nutrition on growth rate of crown-rump length and abdominal circumference in a sheep fetus during late gestation. Redrawn from Mellor, D.J. and Murray, L. (1982). Effects of rate of increase in fetal girth of refeeding ewes after short periods of severe undernutrition during late gestation. *Research in Veterinary Science* **32**, 377–382.

age have been linked to impaired fetal growth, with both teenage and older (>35 years) mothers more likely to give birth to SGA offspring (Restrepo-Méndez et al., 2015). Low birth weight associated with young maternal age may be a result of suboptimal partitioning of resources between the fetus and mother that is still growing herself. In older mothers, preexisting disease may impair placental and fetal growth. These observations, however, are confounded by other factors linked with young and older pregnant women, such as socioeconomic class and nutritional status.

Table 1 Mean placental and birth weights, and placental efficiency, in the Dutch Hunger Winter study

		Trimester of famine exposure		
	Control	*1st*	*2nd*	*3rd*
Placental weight (g)	636	647	611	547
Birth weight (g)	3379	3361	3435	3130
Placental efficiency (g/g)	5.31	5.19	5.62	5.72

Data taken from Lumey, L.H. (1998). Compensatory placental growth after restricted maternal nutrition in early pregnancy. *Placenta* **19**, 105–111.

Low birth weight offspring are commonly associated with maternal smoking, chronic stress, alcohol, and drug use, lower socio-economic class and medical conditions such as preeclampsia, malaria, chronic hypertension, and renal disease (Kramer, 1987). Maternal diabetes and obesity lead to increased incidences of both SGA and LGA offspring. Habitation in the chronic hypoxic environment at high altitude lowers birth weight by approximately 100 g for every 1000 m ascent in altitude, especially in nonnative populations (Moore, 2003).

Placental Factors

The placenta is the interface between the mother and fetus, and ultimately regulates the transfer of nutrients and oxygen from the maternal to fetal circulation. Therefore, the size, structural development and functional transport capacity of the placenta are key factors that affect fetal growth. In many animal species, including humans, the size and growth of the fetus correlates with the size of the placenta, although it is important to consider the common genetic make-up of the fetus and the fetal-derived placental tissues.

After implantation, the early development of the placenta is essential for normal growth of the embryo and fetus. In some species, such the sheep, the placenta grows at a rapid rate in early gestation and plateaus in size by mid-gestation, while in human pregnancy, the placenta continues to grow at a steady rate throughout gestation. During late gestation, however, the rise in fetal body weight occurs at a faster rate than the change in placental weight which means that the microstructural and functional properties of the placenta, and the transfer of nutrients, are increased to support fetal growth.

The exchange of nutrients, respiratory gasses, water, and waste products between the mother and fetus is governed by the structural development of the placenta. According to Fick's law of diffusion, the transfer rate of freely-permeable substances such as oxygen is dependent on the placental surface area, thickness of the diffusion pathway and the concentration gradient between the maternal and fetal circulations. The concentration gradient is maintained by adequate maternal oxygenation and nutrient status, and uteroplacental blood flow. For nutrients transferred by facilitated diffusion, such as glucose, the placental expression of transporter proteins contributes to the rate of transfer. Specific transporters are also essential for active transfer processes which use energy to transport nutrients, such as amino acids needed for protein synthesis, from mother to fetus against a concentration gradient.

Several experimental models demonstrate the importance of placental size in determining fetal growth. First, the consequences of decreasing placental size from the outset of the pregnancy have been examined in sheep. A number of the implantation sites in the uterus, the caruncles, were surgically removed before mating; these are the sites where the placental cotyledons form during pregnancy. Removal of some of these caruncles led to a reduction in the number of placental cotyledons and subsequently impaired the growth of the fetus (Robinson et al., 1994; **Fig. 6**). Many of the remaining placental sites were overgrown in an attempt to compensate for the reduction in number, but placental weight overall was still lower which caused poor fetal growth. Placental restriction can also be induced experimentally in rats by ligation of the uteroplacental blood vessels which impairs placental blood flow and leads to significant growth retardation of the offspring.

Data from the Dutch Hunger Winter study also demonstrates the effects of maternal under-nutrition on placental and thereby fetal growth (Lumey, 1998; **Table 1**). These effects depended on the stage of gestation when the famine occurred. For women in the first trimester of pregnancy during the famine, there was an increase in the size of the placenta at birth and the fetuses were born a normal size; the early growth of the placenta was stimulated by maternal under-nutrition and this was able to support normal fetal growth. In the second trimester, placental size was reduced at birth, but offspring birth weight was normal and overall placental efficiency was significantly improved (the ratio of fetal weight to placental weight, as grams of fetus produced for each gram of placenta). This indicates that the placenta increased its functional capacity and effectiveness in nutrient delivery to maintain fetal growth despite being of a smaller size. Finally, when women were exposed to the famine in the third trimester, birth weight was lower and this was related to a profound reduction in placental weight; although the placenta improved its efficiency, the offspring were born smaller than normal.

The placenta may also contribute to the control of growth in utero by the production and metabolism of hormones that have consequences for maternal and fetal physiology. Placental hormones influence maternal physiology and metabolism in a way that promotes nutrient delivery to the fetus. Placental lactogen induces a degree of insulin resistance in the mother such that less glucose

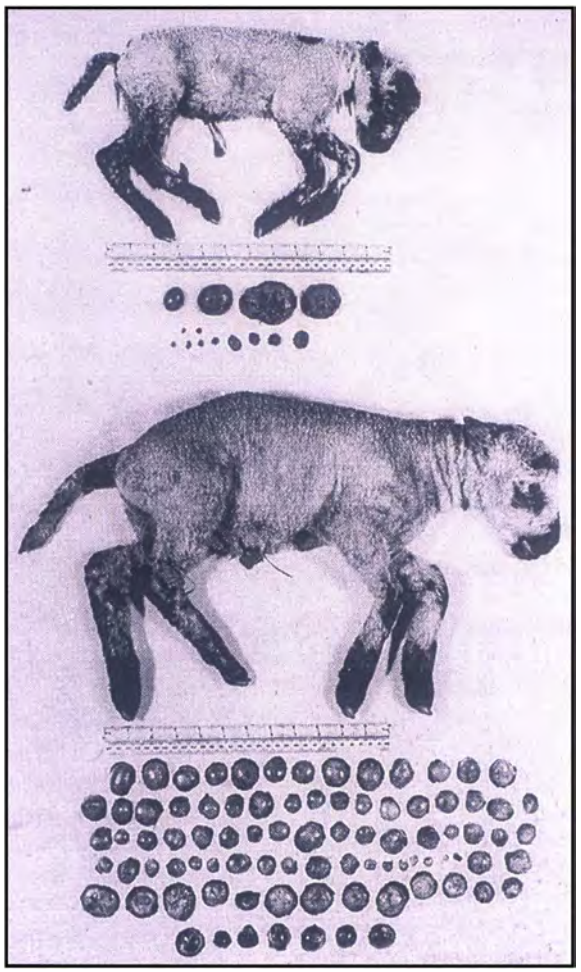

Fig. 6 Effect of reduction in placental size by carunclectomy on fetal growth in sheep. Both fetuses and their placentomes were measured at 127–128 days of gestation (term ~145 days): the upper fetus was taken from a ewe where uterine caruncles were removed before pregnancy, while the lower fetus was taken from a control ewe. Taken from Robinson, J.S., Owens, J.A. and Owens, P.C. (1994). Fetal growth and fetal growth retardation, In Thornburn, G.D. and Harding, R. (eds.) *Textbook of fetal physiology*, pp. 83–94, Oxford: Oxford University Press.

is taken up by maternal tissues and more is readily available for transfer to the fetus. In addition, the pregnancy steroid hormones, progesterone and estrogen, stimulate a range of maternal adaptations in cardiovascular, respiratory and metabolic systems, as well as regulating the contractile activity of the uterine muscles.

The placenta is also the site of metabolism of maternal hormones that can influence fetal growth and development. For instance, the transfer of maternal glucocorticoids to the fetus is limited by the placental enzyme 11β-hydroxysteroid dehydrogenase. This enzyme converts glucocorticoids to biologically-inactive metabolites and thereby protects the fetus from the growth-retarding effects of glucocorticoids from the mother. The placenta also acts as a partial barrier to the transfer of thyroid hormones; placental expression of the type III deiodinase enzyme metabolizes thyroid hormones to inactive forms and regulates circulating thyroid hormone levels in both the placental and fetal circulations.

Fetal Factors

Genetics of the fetus

The genetic makeup or genome of the offspring (which also contributes to the genome of the placenta) influences fetal growth and size at birth. In human populations with diverse backgrounds, there is variation in birth weights between different ethnic groups. For instance, a study in the USA examined the birth weights of infants born 2009–12 from 14 defined races (Morisaki et al., 2017). Compared to non-Hispanic white infants, Japanese babies were on average 289 g lighter and Samoan babies were 126 g heavier. Approximately 60% of the variation in birth weight between ethnic groups, however, was accounted for by differences in the incidence of prematurity, maternal height, body mass index, and gestational weight gain. After adjustment for maternal and socioeconomic factors, black infants were the smallest and American Indians were the largest at delivery.

Several of the genes that are important for placental and fetal growth are imprinted genes (genes that are preferentially expressed from either the maternal or paternal copy). Paternally-expressed genes, such as insulin-like growth factor-II (IGFII), promote feto-placental growth, whereas maternally-expressed genes, such as the IGF type 2 receptor, tend to restrict growth. The conflict theory proposes that the imprinted genes inherited from the father act to maximize growth and survival of the offspring, while those inherited from the mother limit growth of the fetus, in order to conserve resources for the mother and any future offspring. However, the maternal and fetal genomes also have to interact cooperatively during pregnancy to ensure delivery of a viable infant at term.

There are consequences of genetic defects in the fetus for its ability to grow normally. Genetic defects can affect overall body growth or growth of specific tissues to influence birth size. These defects may be due to single gene mutations such as osteogenesis imperfecta, a brittle bone disease where the individual cannot synthesize collagen normally which has consequences for development of the skeletomuscular system. Alternatively, the defect may involve whole chromosomes; for example, Down's syndrome is due to an extra chromosome 21 which reduces birth weight by 240–300 g, as well as leading to facial and other abnormalities in development. Growth defects can also arise from changes in the expression of single genes without any alterations in chromosome number or DNA sequence. For instance, over-expression of the *IGF2* gene on chromosome 11 due to changes in DNA methylation and imprinting status in Beckwith Wiedemann syndrome typically leads to overgrowth of specific organs and larger than normal birth weight.

The sex of the fetus influences the pattern of growth before birth and newborn weight: female fetuses are smaller than male fetuses at the same gestational age and at birth. Multiple offspring in a pregnancy are also smaller than singleton fetuses in human and other species. Growth of individual fetuses may be compromised by the number of fetuses in a pregnancy by competition for resources and uterine space for placental development.

Hormones of the fetus

There are a variety of hormones produced by the fetus that can influence its body growth and organ development, including insulin, IGFs, thyroid hormones, glucocorticoids, and leptin (Fowden and Forhead, 2009, 2013; Sferruzzi-Perri et al., 2013). Experimental and clinical studies have demonstrated that changes in the levels of these hormones in utero have consequences for the growth of the fetus and placenta (**Table 2**). In human infants at term, birth weight correlates positively with umbilical cord blood concentrations of insulin, IGFI, thyroxine, and leptin. Hormones act as signals of the intrauterine environment to both fetal and placental tissues, and serve to match the growth and development of the fetus with the levels of oxygen and nutrients available. They have actions on cell proliferation, growth, differentiation, metabolism, and function in a wide range of fetal tissues, and can influence placental growth and transport capacity.

Insulin promotes growth of the fetus, especially fat mass. In fetal tissues, it stimulates uptake of glucose and amino acids, and therefore glucose utilization and protein synthesis, which encourages further transplacental movement of glucose to the fetus down the maternal-fetal concentration gradient. Insulin is responsible for overgrowth of babies born to mothers with poorly controlled diabetes mellitus. The high circulating levels of glucose in the mother transfer to the fetus and stimulate the fetal pancreas to produce insulin. In turn, the high blood levels of insulin in the fetus stimulate overgrowth and fat deposition. Insulin-like growth factors, IGFI and IGFII, interact with insulin to promote growth of specific tissues such as liver, bones, and adipose tissue, while growth hormone has little effect on fetal body weight and is more important for postnatal growth.

Thyroid hormones are important regulators of fetal growth and the development of the skeletomuscular system, pancreas, brain, and skin. The actions of the thyroid hormones are mediated, in part, by changes in rates of oxygen consumption and oxidative metabolism, and therefore, the energy available for growth. Leptin may also have a role in the control of growth and development of specific fetal tissues, including the pancreas, brain and adipose tissue.

Glucocorticoids, such as cortisol, impair fetal growth in suboptimal intrauterine conditions, such as hypoxia and undernutrition. These hormones are key physiological signals to suppress general body growth and to divert energy resources to important organs during stressful situations. In addition, glucocorticoids induce a switch in cell processes from proliferation to differentiation in several fetal tissues, which contributes to the normal decline in fetal growth rate near term. Over this period, glucocorticoids promote maturation of a variety of fetal organs in preparation for birth.

Importance of Normal Fetal Growth

The control of fetal growth has important consequences for the short term and longer life-time health of the individual. Neonatal mortality and morbidity is closely related to birth weight, with higher rates associated with the extreme range of birth weight (Basso et al., 2006; **Fig. 7**). A study in the USA examined the rates of neonatal death, within 28 days of birth, in relation to birth weight in singleton infants born between 1995 and 2000. When all live births were considered, the overall neonatal mortality rate was 38 per 10,000 births with particularly high rates in the smallest, often preterm, infants. The mortality rate was reduced to 8 per 10,000 live births when data from term infants only were assessed, although the relationship between mortality rate and birth weight was maintained (**Fig. 7**). A number of confounding factors may contribute to the increased risk of death in smaller babies: for example, maternal smoking causes intrauterine growth restriction and increases neonatal mortality by 30% (Basso et al., 2006). Overgrown babies, often born to diabetic mothers, are also at greater risk of neonatal death, in part as a result of obstructed and prolonged labor, and postnatal complications caused by neonatal hypoglycemia and respiratory distress syndrome.

Table 2 Effects of manipulation of hormones on fetal and placental growth

				Weight (% control)		
Hormone	*Manipulation*	*Procedure*	*Species*	*Fetus*	*Placenta*	*Specific tissue effects*
Insulin	Deficiency	Diabetogenic drug treatment	Sheep, monkey	80–85	—	Bone
		Fetal pancreatectomy	Sheep	70	100–110	Liver, spleen, brain
		Insulin gene deletion	Mouse	80	—	Pancreas
		Insulin receptor gene deletion	Mouse	90	100	Liver
		Pancreatic agenesis or insulin receptor defect	Human	50–80	—	
	Overexposure	Fetal insulin treatment	Sheep	100–120	100	Fat
			Monkey	135	—	Fat
		Maternal diabetes	Human	130	—	Fat
IGFI	Deficiency	Igf1 gene deletion	Mouse	60	100	Bone, skeletal muscle
		Igf1 gene defect	Human	50	80	Brain, auditory system
		Igf1r gene deletion	Mouse	45	100	Bone, skin, respiratory muscles
		Igf1r gene defect	Human	50–80	—	Bone, brain
	Overexposure	Fetal IGFI treatment	Sheep	100	100	Liver, lungs, heart, kidney, adrenal gland
IGFII	Deficiency	Igf2 gene deletion	Mouse	60	55	Bone, skeletal muscles
	Overexposure	Igf2 gene expression	Mouse	136	125	Pancreas
		Igf2r gene deletion	Mouse	140	140	Liver, skeletal muscle
		Beckwith–Wiedemann syndrome	Human	150	—	Liver, skeletal muscle
Glucocorticoids	Deficiency	Fetal adrenalectomy	Sheep	115	100	Liver, lungs, gut
	Overexposure	Maternal glucocorticoid treatment	Sheep, monkey, mouse	80–90	65–93	Brain, liver, lungs, heart
			Guinea-pig	84	—	Brain, liver
			Human	85	—	Lungs, gut
		Fetal glucocorticoid treatment	Sheep	80–100	100	Liver, lungs, gut
		Inhibition of placental 11β-HSD2	Rat	88	—	
		11β-HSD2 gene deletion	Mouse	84	90	
Thyroid hormones	Deficiency	Deletion of thyroid hormone receptor genes (TRα1 and β)	Mouse	90	—	
		Fetal thyroidectomy	Sheep	70–80	100	Bone, skeletal muscle, liver, kidneys, heart, fat, pancreas, brain, nervous system
	Overexposure	Fetal thyroxine treatment	Sheep	100	—	Liver, heart
Leptin	Deficiency	Leptin gene deletion	Mouse	100	—	Brain
		Leptin receptor deletion	Mouse	106	100	
	Overexposure	Fetal leptin treatment	Sheep	100	100	Liver, fat, adrenal gland

Adapted from Fowden, A.L. and Forhead, A.J. (2009). Endocrine regulation of feto-placental growth. *Hormone Research* **72**, 257–265, and Sferruzzi-Perri, A.N., Vaughan, O.R., Forhead, A.J. and Fowden, A.L. (2013). Hormonal and nutritional drivers of intrauterine growth. *Current Opinion in Clinical Nutrition and Metabolic Care* **16**, 298–309.

Size at birth is also an important determinant of health in later life. The epidemiologist, Professor David Barker, and his colleagues at the University of Southampton examined the medical records of around 16,000 men and women born in Hertfordshire, UK between 1911 and 1930. Midwives at the time recorded birth weights and body proportions, and the mortality and morbidity statistics of these individuals were traced 50–70 years later. These studies identified an inverse relationship between birth weight and the incidence of death from cardiovascular disease (Barker, 1997; **Fig. 8**). For both sexes, the standardized mortality ratio for cardiovascular disease, which included coronary heart disease and stroke, was greatest in the individuals who were smallest at birth. This association between birth weight and adult mortality was continuous across the normal range of birth weights and was also independent of other known risk factors for cardiovascular disease; multiple, premature or severely growth-retarded babies were not included in the data analysis. Other risk factors such as smoking, alcohol intake, adult obesity, and social class were, however, additive to the effects of birth weight.

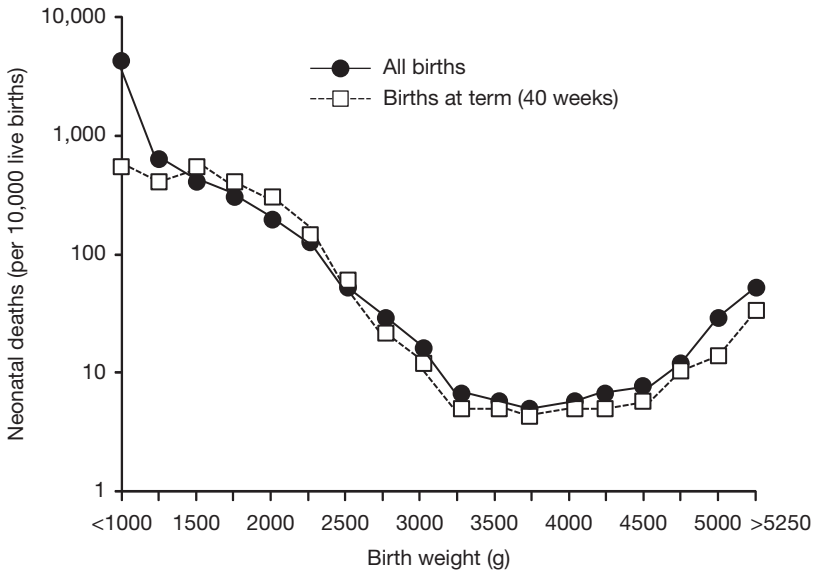

Fig. 7 Relationship between birth weight and neonatal mortality in singleton live births, United States, 1995–2000. All births (*dotted line*) and births at 40 weeks of gestation (*solid line*) by last menstrual period. Redrawn from Basso, O., Wilcox, A.J. and Weinberg, C.R. (2006). Birth weight and mortality: Causality or confounding? *American Journal of Epidemiology* ***164***, 303–311.

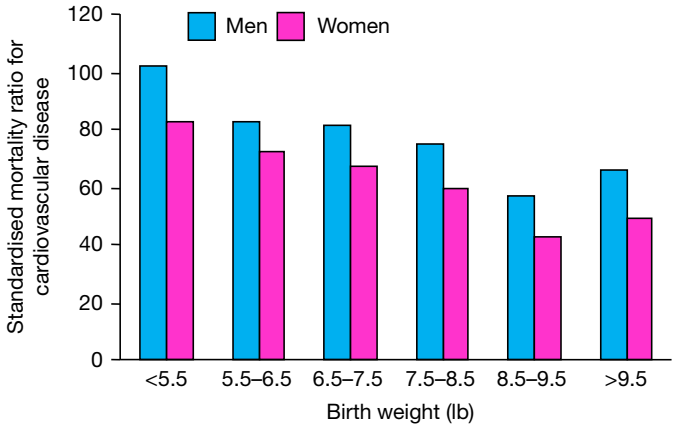

Fig. 8 Relationship between birth weight and risk of death from cardiovascular disease in men and women aged < 65 years. Redrawn from Barker, D.J. (1997). *Mothers, babies and disease in later life*. London: BMJ Publishing Group.

A number of conditions that predispose to cardiovascular disease have also been associated with low birth weight. Individuals that were small at birth have a higher incidence of hypertension, hyperlipidemia, glucose intolerance, and insulin resistance in adulthood. Further epidemiological studies have demonstrated that the relationship is reverse-J-shaped where large babies born to diabetic mothers are also at greater risk of cardiovascular disease and type II diabetes. Therefore, the intrauterine environment has an important role in programming adult pathophysiology, a phenomenon known as the developmental origins of adult disease (Gluckman and Hanson, 2006). Research is on-going to understand the mechanisms by which a suboptimal intrauterine environment, associated with abnormal patterns of fetal growth, leads to long-term consequences for adult health.

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"Systems Biology of Reproduction"

Spring 2024 (Even Years) – Course Syllabus
Biol 475/575 Undergraduate/Graduate (3 Credit)
SLN: (475) – 06763, (575) – 06764
Time - Tuesday and Thursday 10:35 am-11:50 am
Course Lectures in person and recorded on Canvas/Panopto and Discussion Sessions live in person and on WSU Zoom for all campuses (Hybrid Course)
Room – CUE 418
Course Director – Michael Skinner, Abelson Hall 507, 335-1524, skinner@wsu.edu
Co-Instructor – Eric Nilsson, Abelson Hall 507, 225-1835, nilsson@wsu.edu
Learning Objective -
Current literature based course on the Systems Biology of Reproduction. Learning Systems approaches to the biology of reproduction from a molecular to physiological level of understanding.
Schedule/Lecture Outline –

January	9 & 11	Week 1	Systems Biology Introduction
	16 & 18	Week 2	Molecular/ Cellular/ Reproduction Systems
	23 & 25	Week 3	Sex Determination Systems
Jan /Feb	30 & 1	Week 4	Male Reproductive Tract Development & Function
February	6 & 8	Week 5	Female Reproductive Tract Development & Function
	13 & 15	Week 6	Gonadal Developmental Systems Biology
	20 & 22	Week 7	Testis Systems Biology
	27 & 29	Week 8	Ovary Systems Biology
March	5 & 7	Week 9	Epigenetics and Transgenerational Gonadal Disease
	11 – 15	**Week 10**	**Spring Break**
	19 & 21	Week 11	Gametogenesis/ Stem Cells/ Cloning
	26 & 28	Week 12	Hypothalamus-Pituitary Development & Function
April	2 & 4	Week 13	Reproductive Endocrinology Systems
	9 & 11	Week 14	Fertilization & Implantation Systems
	16 & 18	Week 15	Fetal Development & Birth Systems
	23 & 25	Week 16	Assisted Reproduction/Contraception
Apr/May	30 & 2	Week 17	Exam or Grant Review

Spring 2024 – Systems Biology of Reproduction
Lecture Outline – Fetal Development & Birth Systems
Michael K. Skinner – Biol 475/575
CUE 418, 10:35-11:50 am, Tuesday & Thursday
April 16, 2024
Week 15

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

Required Reading

Bazer FW and Fields MJ (2018) Pregnancy and Parturition, Mammals. in: Encyclopedia of Reproduction 2nd Edition, Ed: MK Skinner. Elsevier. Vol. 6, Pages 450-457.

Forhead AJ and Fowden AL (2018) Formation and Growth of the Fetus. in: Encyclopedia of Reproduction 2nd Edition, Ed: MK Skinner. Elsevier. Vol. 3, Pages 370-379.

Spring 2024 – Systems Biology of Reproduction
Discussion Outline – Fetal Development & Birth Systems
Michael K. Skinner – Biol 475/575
CUE 418, 10:35-11:50 am, Tuesday & Thursday
April 18, 2024
Week 15

Fetal Development & Birth Systems

Primary Papers:

1. Glotov, et al. (2015) BMC Systems Biology 9(Suppl 2):S4
2. Pique-Regi, et al. (2019) eLife 8:e52004
3. Winchester, et al. (2022) Scientific Reports 12:3361

Discussion

Student 4: Reference 1 above
- What major diseases are compared with preeclampsia and why?
- What networks were identified and impact?
- What risk factors were identified?

Student 5: Reference 2 above
- What technical approach was used and types of correlations?
- What transcriptome and cellular correlations were made?
- What major insights were provided for preterm birth?

Student 6: Reference 3 above
- What technical approach was used for the study?
- What observations were made for mother, father, child?
- What potential impact to reduce preterm birth?

Maternal-Fetal Interface During Gestation

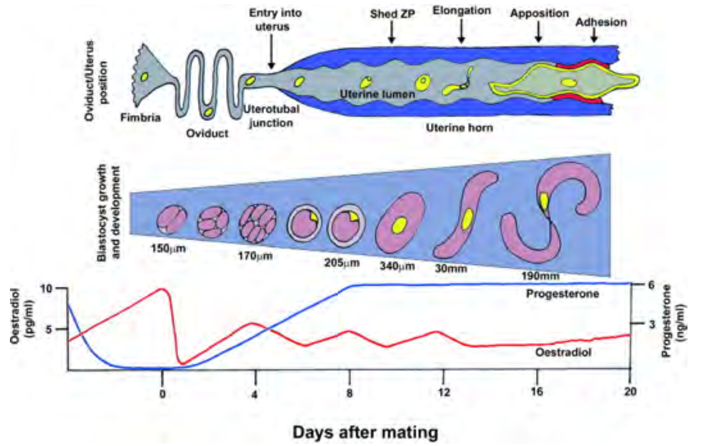


Figure 1 Early pregnancy events in sheep. This schematic summarizes the relative changes in embryo/blastocyst development after fertilization in relation to position in the female reproductive tract and circulating levels of ovarian steroid hormones. Fertilization occurs in the oviduct, and the morula 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 adhesion by day 16.

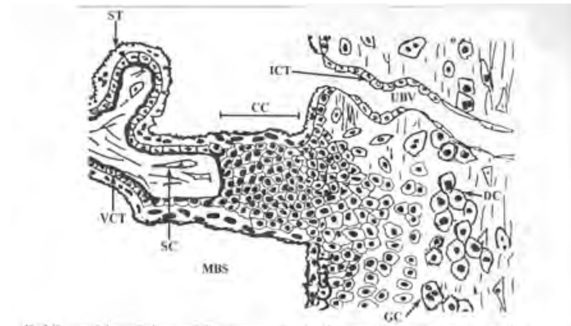


Fig. 2. [illegible]

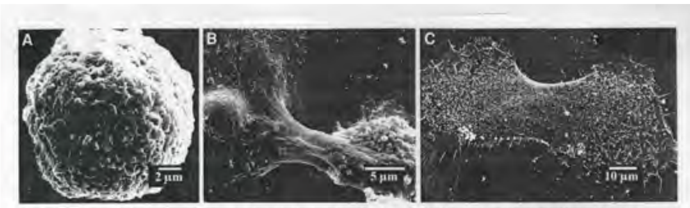


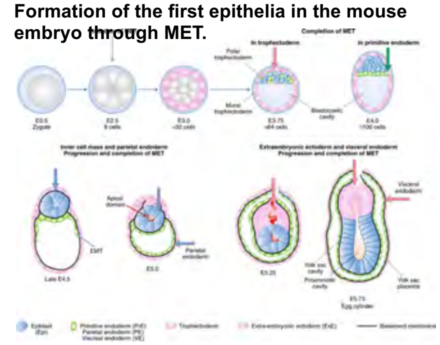
Fig. 3. Villous trophoblast differentiation: morphologic changes in isolated cytotrophoblastic cells cultured on plastic dishes in presence of FCS. Scanning electron micrographs show cytotrophoblastic cells at different times of culture. **(A)** Isolated cytotrophoblastic cells before plating. **(B)** After 1 d, pseudopodia of cytotrophoblastic cells are making contact with a neighboring cytotrophoblastic cells. **(C)** After 3 d, a large syncytiotrophoblast is observed with a central nuclear mount and the extending cytoplasm.

Table 1
Main Factors Modulating
In Vitro the Formation of Syncytiotrophoblast

Stimulating action/reference	Inhibiting action/reference
EGF *(29,31)*	TGF-β1 *(36,37)*
hCG *(19,46)*	LIF *(38)*
cAMP *(9,18)*	Hypoxia *(40,41)*
GM-CSF *(32)*	Endothelin *(7)*
Macrophages and macrophage-conditioned media *(33,34)*	15ΔPGJ2 *(39)*
Dexamethasone *(63)*	
Estradiol *(37)*	

Mesenchymal-epithelial transition in development and reprogramming.
Pei D, Shu X, Gassama-Diagne A, Thiery JP.
Nat Cell Biol. 2019 Jan;21(1):44-53.

Formation of the first epithelia in the mouse embryo through MET.



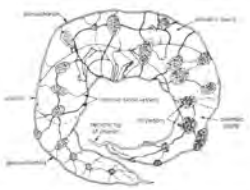


FIG. 11–4. Diagram of the fetal membranes of a 105-day fetal calf to show the allantoic and amniotic cavities. The cotyledons are distributed over the chorioallantoic membrane and the amniochorion.

TABLE 11–3. The Fetal Membranes of Farm Animals

Membrane	Origin	Functions
Yolk sac	Early entodermal layer	Vestigial
Amnion	Cavitation from inner cell mass	Encloses fetus as a fluid-filled cavity
Allantois	Diverticulum of hindgut	Blood vessels connect fetal with placental circulation
		Fuses with chorion to form the chorioallantoic placenta
Chorion	Trophoblastic capsule of blastocyst	Encloses embryo and other fetal membranes
		Intimately associated with lining of uterus to form placenta
Umbilical cord	Amnion wraps about the yolk stalk	Encloses allantoic vessels and acts as the vascular link between mother and fetus

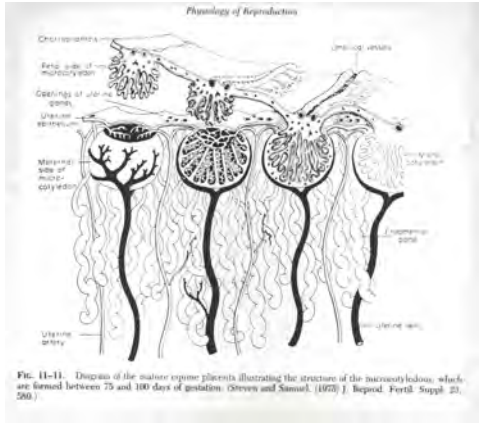


FIG. 11–11. Diagram of the mature eutherian placenta illustrating the structure of the microcotyledons, which are formed between 75 and 100 days of gestation. (Steven and Samuel, (1970) J. Reprod. Fertil. Suppl. 23, 580.)

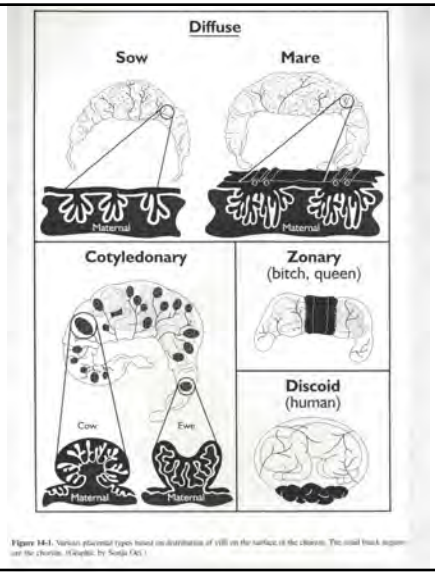


Figure 14-1. Various placental types based on distribution of villi on the surface of the chorion. The solid black region is the chorion. (Graphic by Sonja Orr.)

Developmental Biology 250, 358–373 (2002)
doi:10.1006/dbio.2002.0773

Interactions between Trophoblast Cells and the Maternal and Fetal Circulation in the Mouse Placenta

S. Lee Adamson, Yong Lu, Kathie J. Whiteley, Doug Holmyard, Myriam Hemberger, Christine Pfarrer, and James C. Cross

Mammalian embryos have an intimate relationship with their mothers, particularly with the placental vasculature from which embryos obtain nutrients essential for growth. It is an interesting vascular bed because maternal vessel number and diameter change dramatically during gestation and, in rodents and primates, the terminal blood space becomes lined by placental trophoblast cells rather than endothelial cells. Molecular genetic studies in mice aimed at identifying potential regulators of these processes have been hampered by lack of understanding of the anatomy of the vascular spaces in the placenta and the general nature of maternal–fetal vascular interactions. To address this problem, we examined the anatomy of the mouse placenta by preparing plastic vascular casts and serial histological sections of implantation sites from embryonic day (E) 10.5 to term. We found that each radial artery carrying maternal blood into the uterus branched into 50–100 dilated spiral arteries located within the metrial triangle, populated by uterine natural killer (uNK) cells, and the decidua basalis. The endothelial-lined spiral arteries converged together at the trophoblast giant cell layer and emptied into a few straight, trophoblast-lined canals that carried maternal blood to the base of the placenta. Maternal blood then percolated back through the intervillous space of the labyrinth toward the maternal side of the placenta in a direction that is countercurrent to the direction of the fetal capillary blood flow. Trophoblast cells were found invading the uterus in two patterns. Large cells that expressed the trophoblast giant cell-specific gene Plf (encoding Proliferin) invaded during the early postimplantation period in a pattern tightly associated with spiral arteries. These peri/endovascular trophoblast were detected only 150–300 μm upstream of the main giant cell layer. A second type of widespread interstitial invasion in the decidua basalis by glycogen trophoblast cells was detected after E12.5. These cells did not express Plf, but rather expressed the spongiotrophoblast-specific gene Tpbp. Dilation of the spiral arteries was obvious between E10.5 and E14.5 and was associated with a lack of elastic lamina and smooth muscle cells. These features were apparent even in the metrial triangle, a site far away from the invading trophoblast cells. By contrast, the transition from endothelium-lined artery to trophoblast-lined (hemochorial) blood space was associated with trophoblast giant cells. Moreover, the shaping of the maternal blood spaces within the labyrinth was dependent on chorioallantoic morphogenesis and therefore disrupted in Gcm1 mutants. These studies provide important insights into how the fetoplacental unit interacts with the maternal intrauterine vascular system during pregnancy in mice. © 2002 Elsevier Science (USA)

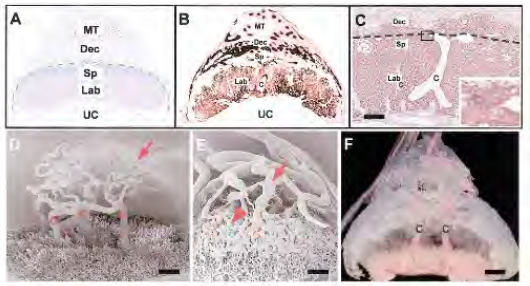


FIG. 1. Overview of maternal blood flow into and out of the placenta. The fetal side of the placenta (base) is presented on the bottom side of the images. (A) Overview of the layers of the mature placenta. Red dots debue position of uNK cells. (B) Histological section of an implantation site at E13.5 following perfusion of the maternal vasculature with Pxative followed by India ink. Uterine vessels were tied before immersion Pxation to maintain vascular volume. The section was stained with PAS to show localization of uNK cells (pink). (C) Histological section of an implantation site at E13.5 immunostained for cytokeratin showing the position of trophoblast cells (brown stain). The inset shows a high magniPcation view of the cells at the interface between the converging spiral arteries and the central arterial canal. Note that the cells are cytokeratin-positive and have extremely large nuclei typical of trophoblast giant cells. (D) Scanning electron micrograph of a maternal vascular cast partially Plled from the arterial side. Arrow indicates spiral arteries. (E) Scanning electron micrograph of a maternal vascular cast partially Plled from the venous side. Arrowhead indicates cup-shaped venous sinuses and arrow indicates large veins. (F) Light micrograph of a cast prepared by simultaneously infusing the maternal inferior vena cava with blue plastic and the maternal aorta with red plastic. The outer portion of the cast has been removed to show the spiral arteries of the metrial triangle and decidual regions coalescing into two large central canals that traverse the labyrinth (red). The labyrinth region (red) Plls from the embryonic side. The labyrinth is incompletely Plled, resulting in an artifactual space between the red sinusoids of the labyrinth and the blue venous channels that surround it. C, central arterial canal; Dec, decidua basalis; Lab, labyrinth; MT, metrial triangle; SA, spiral arteries; ST, spongiotrophoblast; UC, umbilical cord. Arrows, spiral arteries; large arrowheads, venous sinuses; small arrowheads, veins. Bars, 1 mm.

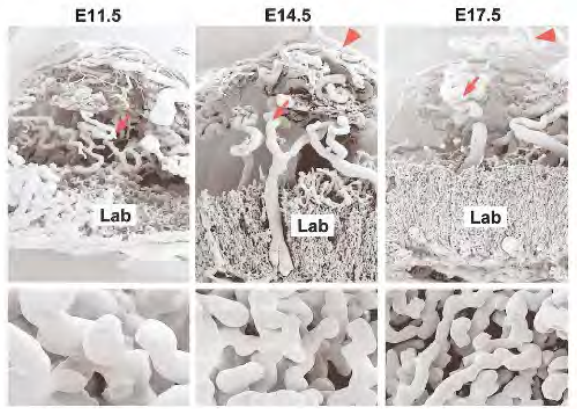
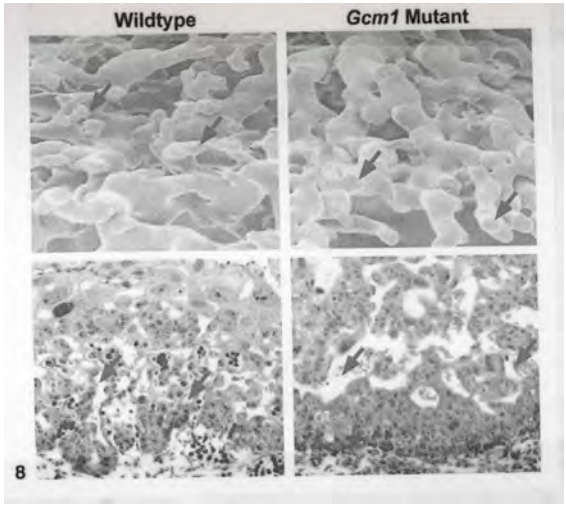


FIG. 2. Changes in the spiral arteries and trophoblast-lined sinusoid spaces of the labyrinth during gestation. Panels show scanning electron micrographs of dissected vascular casts showing spiral arteries supplying the arterial canals and labyrinth at E11.5, E14.5, and E17.5. Bottom panels show high magniPcation views of the sinusoid spaces in the labyrinth. Note the increasing diameter of spiral arteries (arrows) and thickness of labyrinth, and the decreasing size of the sinusoids with increasing gestational age. Also note that spiral artery diameter often exceeds the diameter of the radial arteries that supply them (arrowheads).



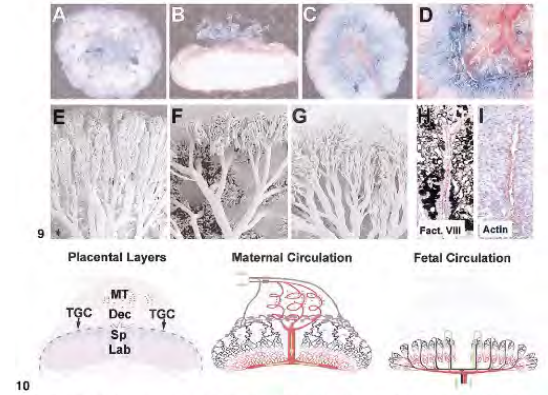


FIG. 9. Anatomy of the fetal blood space within the labyrinth. (AID) Dual-color vascular cast in which blue plastic was injected into the maternal aorta and red plastic was injected into the fetal umbilical vein. (A) View looking down onto the maternal-facing surface of the placenta. (B) Side view. (C, D) Views from the fetal side shown at low (C) and high magniPcation (D). (E) Complete fetal side cast of the labyrinth. Partial casts of the fetal labyrinth after injection into the umbilical artery (F) or vein (G). (H, I) Serial sections of the labyrinth immunostained for Factor VIII (H) or smooth muscle actin (I).

FIG. 10. Diagrams summarizing the structures of the maternal and fetal circulation in the mature mouse placenta and showing their counter-current relationship. Red represents most highly oxygenated blood and blue represents least oxygenated blood. Arrows indicate the direction of blood flow. Dec, decidua basalis; Lab, labyrinth; MT, metrial triangle; Sp, spongiotrophoblast; TGC, trophoblast giant cells.

TABLE 11–1. Differences in Gestation Periods of Farm Mammals

Animal	Average (Range)
Cattle (dairy breeds)	
Ayrshire	278
Brown Swiss	290 (270–306)
Dairy Shorthorn	282
Friesian	276 (240–303)
Guernsey	284
Holstein-Friesian	279 (262–309)
Jersey	279 (270–285)
Swedish-Friesian	282 (260–300)
Zebu (Brahman)	292 (271–310)
Cattle (beef breeds)	
Aberdeen-Angus	279
Hereford	285 (243–316)
Beef Shorthorn	283 (273–294)
Sheep	148 (140–159)
Swine	
Domestic	114 (102–128)
Wild Pig	(124–140)
Horse	
Arabian	337 (301–371)
Belgian	335 (304–354)
Clydesdale	334
Morgan	344 (316–363)
Percheron	(321–345)
Shire	340
Thoroughbred	338 (301–349)

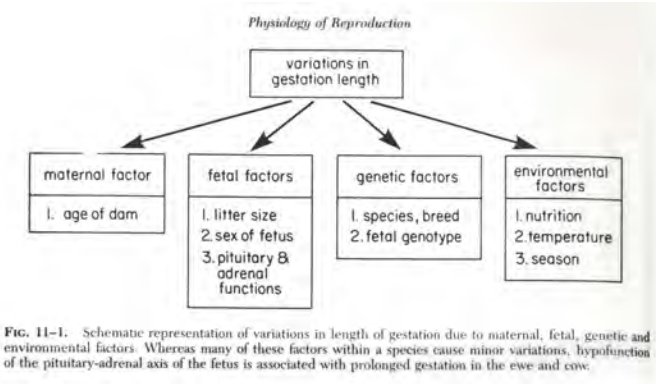
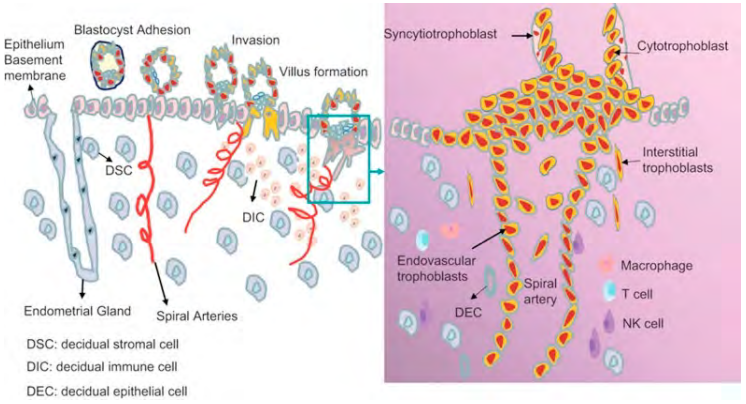
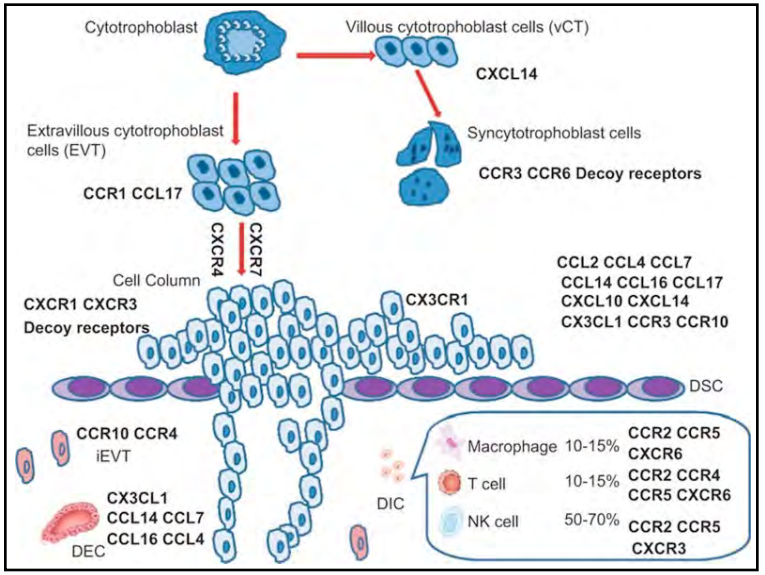


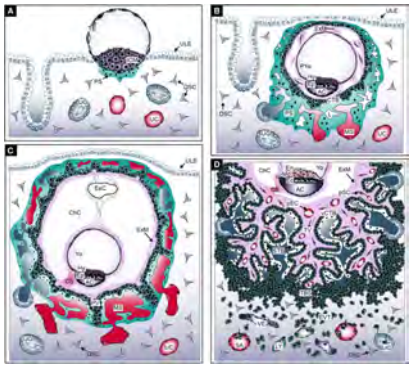
FIG. 11–1. Schematic representation of variations in length of gestation due to maternal, fetal, genetic and environmental factors. Whereas many of these factors within a species cause minor variations, hypofunction of the pituitary-adrenal axis of the fetus is associated with prolonged gestation in the ewe and cow.

The integrative roles of chemokines at the maternal-fetal interface in early pregnancy.
Du MR, Wang SC, Li DJ.
Cell Mol Immunol. 2014 Sep;11(5):438-48.



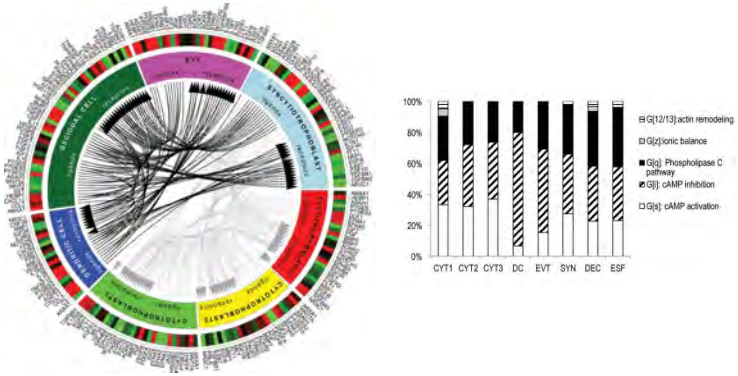


Human placenta and trophoblast development: key molecular mechanisms and model systems.
Knöfler M, Haider S, Saleh L, Pollheimer J, Gamage TKJB, James J.
Cell Mol Life Sci. 2019 Sep;76(18):3479-3496.

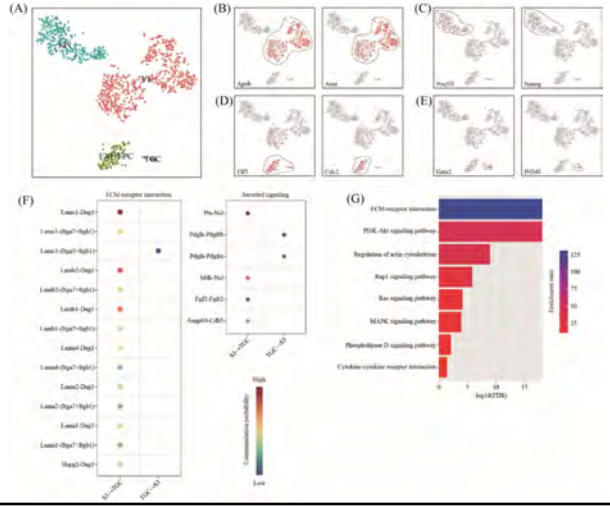


Development of the human placenta during the first 3 weeks of gestation. **a** Human blastocyst implanting into the pregnant uterus. **b** Development of the first placental structures and the embryonic disc. **c** Formation of primary villi and yolk sac. **d** Development of tertiary villi and the embryonic germ layers. *AC* amniotic cavity, *CS* connecting stalk, *ChC* chorionic cavity, *CTB* cytotrophoblast, *DSC* decidual stromal cell, *Ec* ectoderm, *En* endoderm, *Ep* epiblast, *EVT* extravillous trophoblast, *ExC* exocoelomic cyst, *ExM* extraembryonic mesoderm, *Hy* hypoblast, *ICM* inner cell mass, *L* lacunae system, *LY* lymphatic vessel, *Md* mesoderm, *MS* maternal blood sinusoid, *pEC* placental endothelial cell, *PS* primitive syncytium, *pSC* placental stromal cell, *PV* primary villi, *PYo* primitive yolk sac, *SA* spiral artery, *TBS* trophoblastic shell, *TV* tertiary villi, *UC* uterine capillary, *UG* uterine gland, *ULE* uterine luminal epithelium, *VE* venous vessel, *vCTB* villous CTB, *Yo* yolk sac

Single-cell transcriptomics of the human placenta: inferring the cell communication network of the maternal-fetal interface.
Genome Res. 2017 Mar;27(3):349-361.
Pavličev M, Wagner GP, Chavan AR, Owens K, Maziarz J, Dunn-Fletcher C, Kallapur SG, Muglia L, Jones H.

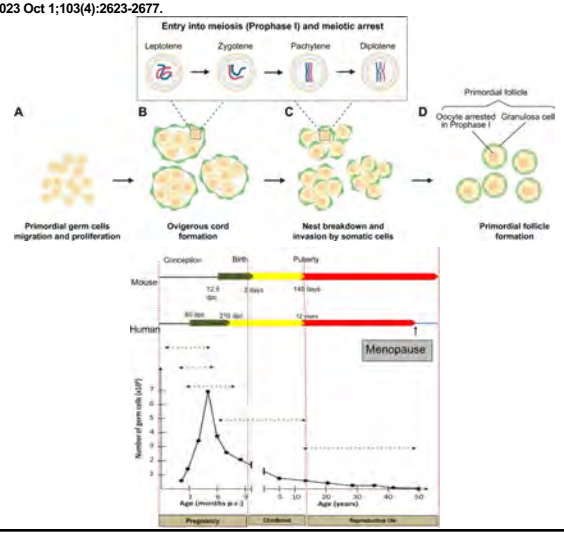


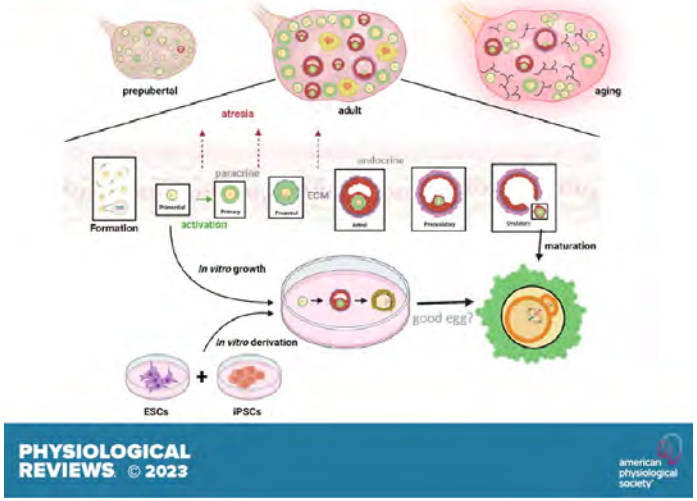
Single-cell analysis of mouse uterus at the invasion phase of embryo implantation.
He J-P, Tian Q, Zhu Q-Y, Liu J-L.
Cell Biosci. 2022 Feb 5;12(1):13.

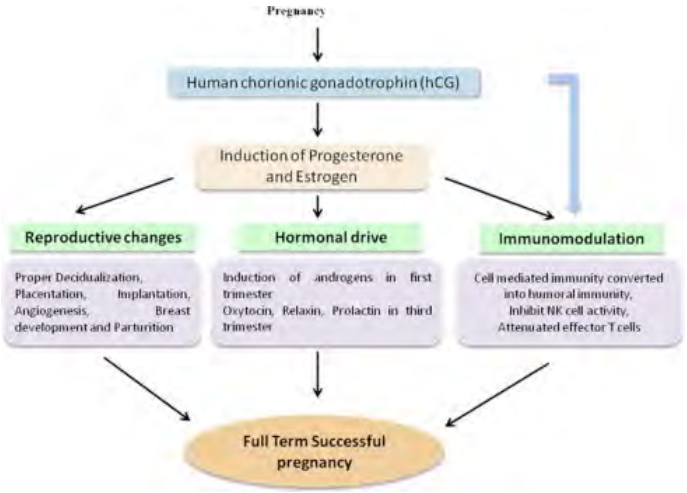


Endocrinology of Pregnancy

Making a good egg: human oocyte health, aging, and in vitro development.
Telfer EE, Grosbois J, Odey YL, Rosario R, Anderson RA.
Physiol Rev. 2023 Oct 1;103(4):2623-2677.







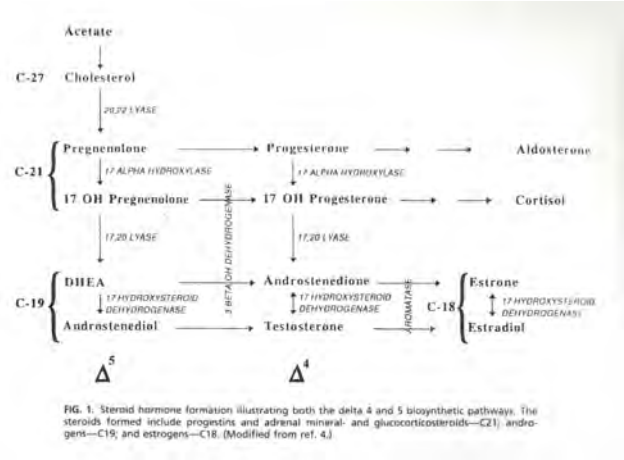
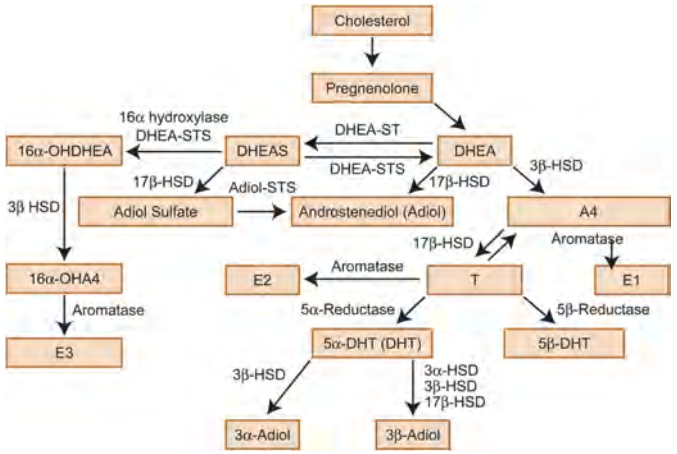
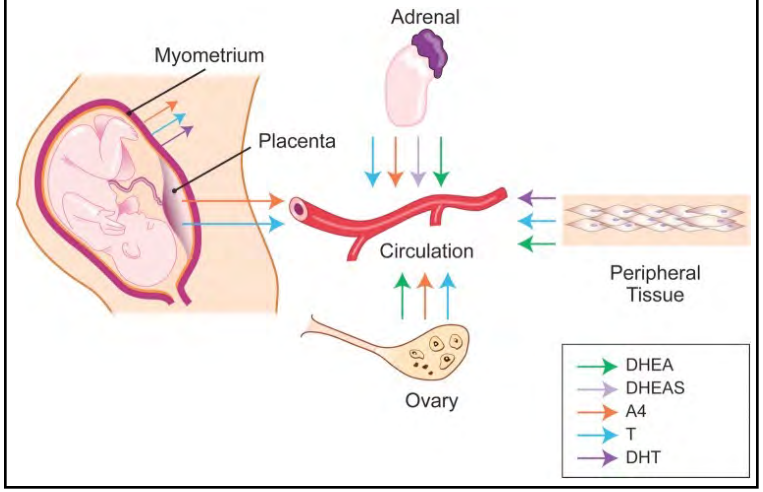


FIG. 1. Steroid hormone formation illustrating both the delta 4 and 5 biosynthetic pathways. The steroids formed include progestins and adrenal mineral- and glucocorticosteroids—C21; androgen—C19; and estrogens—C18. (Modified from ref. 4.)



Androgens in pregnancy: roles in parturition.
Makieva S, Saunders PT, Norman JE.
Hum Reprod Update. 2014 Jul-Aug;20(4):542-59.



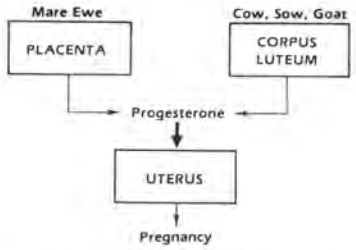


FIG. 11–2. Progesterone secreted by the corpus luteum is essential for the maintenance of early pregnancy in all farm species. The ovaries, however, can be removed (ovariectomy) during the latter half of pregnancy without interrupting pregnancy in the mare and ewe because the placenta produces progesterone in these species.

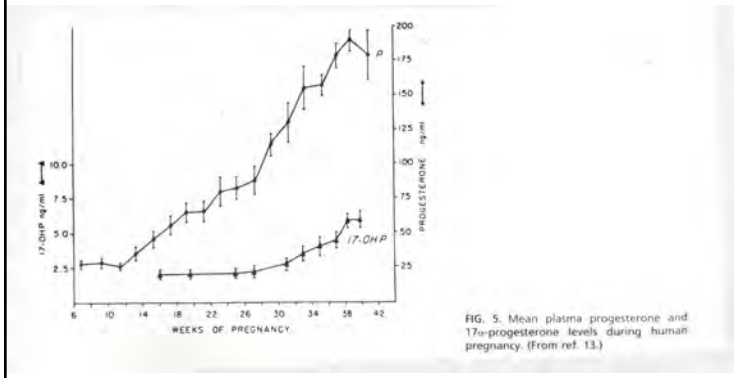


FIG. 5. Mean plasma progesterone and 17α-progesterone levels during human pregnancy. (From ref. 13.)

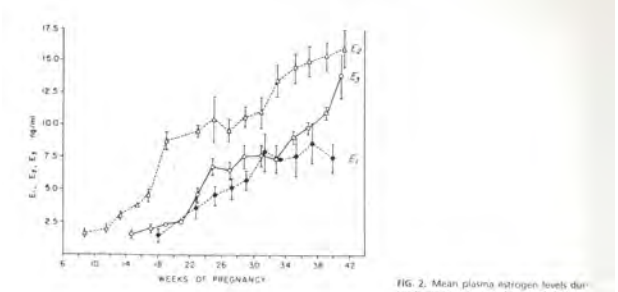


FIG. 2. Mean plasma estrogen levels during human pregnancy. (From ref. 11.)

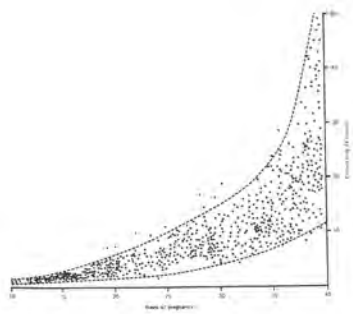


FIG. 4. The 24-hour urinary excretion of estriol-16-glucuronoside throughout pregnancy in humans. (From ref. 127.)

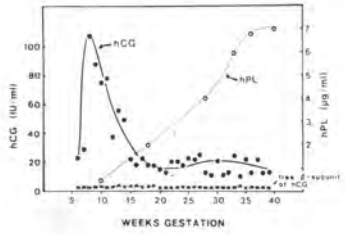


FIG. 6. Mean concentration of hCG and hPL in serum of women throughout normal pregnancy. Free β subunit of hCG is in low concentration or else undetectable throughout pregnancy. The concentration of free α subunit of hCG in serum increases gradually during pregnancy in a manner similar to that of hPL, albeit in much smaller amounts. (From ref. 1.)

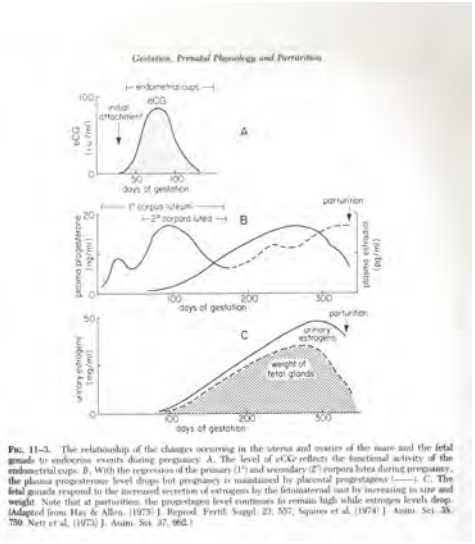


FIG. 11–3. The relationship of the changes occurring in the uterus and ovaries of the mare and the fetal gonads to endocrine events during pregnancy. A, The level of eCG reflects the functional activity of the endometrial cups. B, With the regression of the primary (1°) and secondary (2°) corpora lutea during pregnancy, the plasma progesterone level drops but pregnancy is maintained by placental progestagens (——). C, The fetal gonads respond to the increased secretion of estrogens by the feto-maternal unit by increasing in size and weight. Note that at parturition, the progestagen level continues to remain high while estrogen levels drop. (Adapted from May & Allen, (1973) J. Reprod. Fertil. Suppl. 23, 557; Squires et al. (1974) J. Anim. Sci. 38, 780; Nett et al. (1975) J. Anim. Sci. 37, 962.)

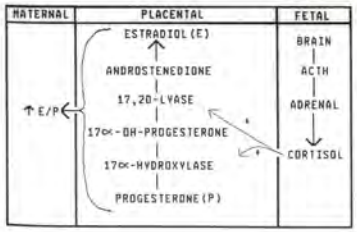


FIG. 11. Diagram of steroidogenesis in the sheep placenta and the effect of fetal adrenal cortisol on the enzymes converting progesterone (P) to estradiol (E).

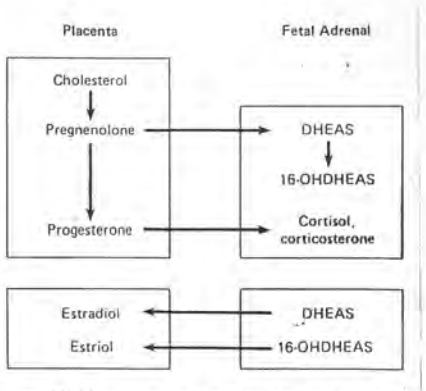


Figure 23–39. Interactions between the placenta and the fetal adrenal cortex in the production of steroids.

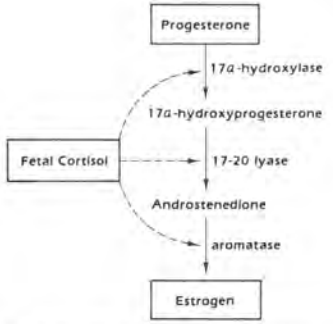


FIG. 11–13. The sequence of enzymatic reactions in the conversion of progesterone to estrogen in the placenta during the latter half of gestation. Fetal cortisol activates the enzymes responsible for the conversion.

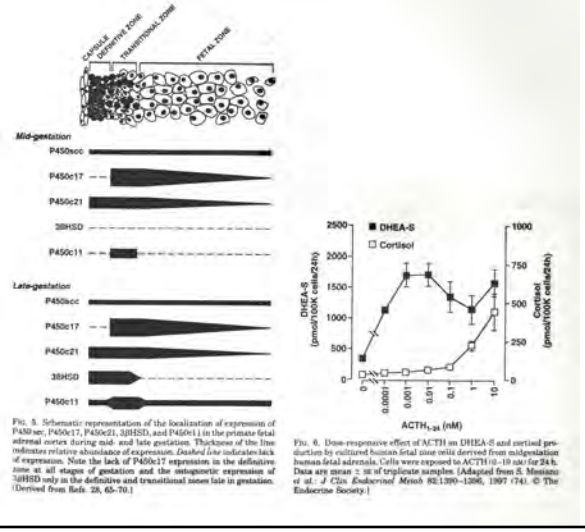


FIG. 5. Schematic representation of the localization of expression of P450scc, P450c17, P450c21, 3βHSD, and P450c11 in the primate fetal adrenal cortex during mid- and late gestation. Thickness of the line indicates relative abundance of expression. *Dashed line* indicates lack of expression. Note the lack of P450c17 expression in the definitive zone at all stages of gestation and the ontogenetic expression of 3βHSD only in the definitive and transitional zones late in gestation. (Derived from Refs. 28, 65–70.)

FIG. 6. Dose-responsive effect of ACTH on DHEA-S and cortisol production by cultured human fetal zone cells derived from midgestation human fetal adrenals. Cells were exposed to ACTH (0–10 nM) for 24 h. Data are mean ± SE of triplicate samples. [Adapted from S. Mesiano *et al.*: *J Clin Endocrinol Metab* 82:1390–1396, 1997 (74). © The Endocrine Society.]

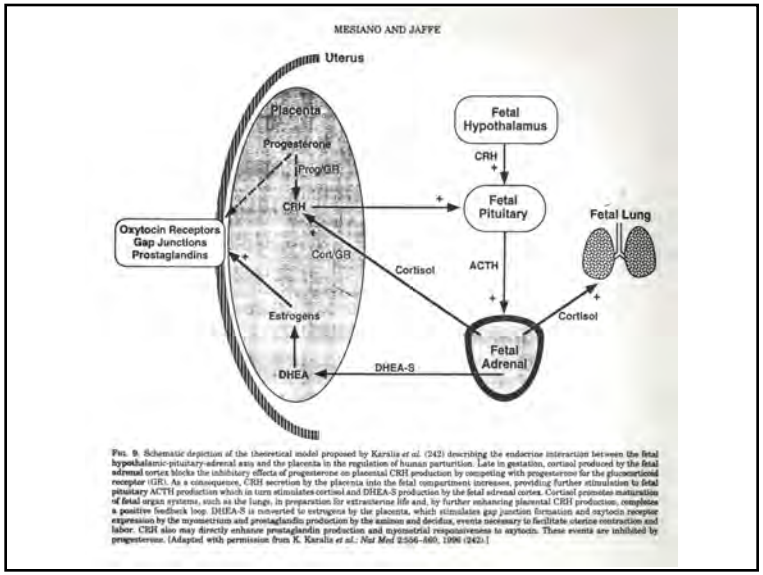


FIG. 9. Schematic depiction of the theoretical model proposed by Karalis *et al.* (242) describing the endocrine interaction between the fetal hypothalamic-pituitary-adrenal axis and the placenta in the regulation of human parturition. Late in gestation, cortisol produced by the fetal adrenal cortex blocks the inhibitory effects of progesterone on placental CRH production by competing with progesterone for the glucocorticoid receptor (GR). As a consequence, CRH secretion by the placenta into the fetal compartment increases, providing further stimulation to fetal pituitary ACTH production which in turn stimulates cortisol and DHEA-S production by the fetal adrenal cortex. Cortisol promotes maturation of fetal organ systems, such as the lungs, in preparation for extrauterine life and, by further enhancing placental CRH production, completes a positive feedback loop. DHEA-S is converted to estrogens by the placenta, which stimulates gap junction formation and oxytocin receptor expression by the myometrium and prostaglandin production by the amnion and decidua, events necessary to facilitate uterine contraction and labor. CRH also may directly enhance prostaglandin production and myometrial responsiveness to oxytocin. These events are inhibited by progesterone. (Adapted with permission from K. Karalis *et al.*: *Nat Med* 2:556–560, 1996 (242).)

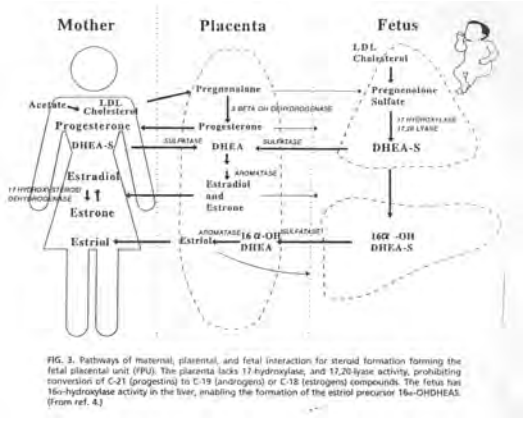
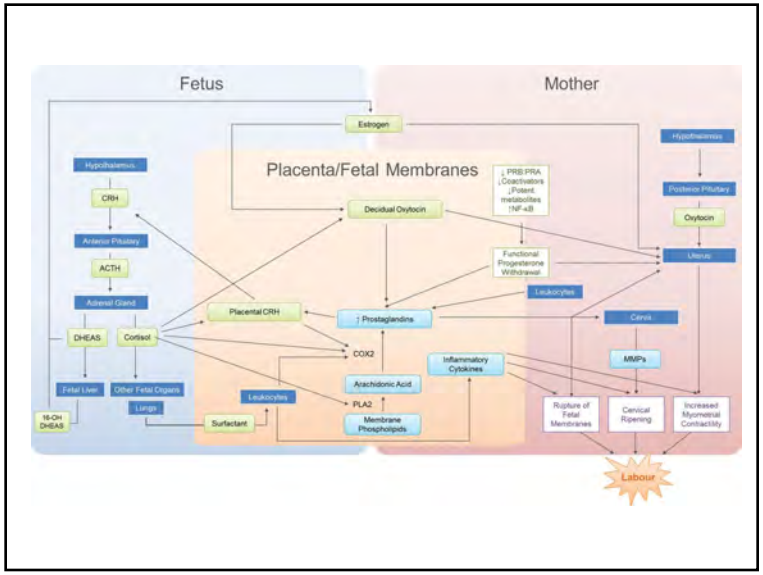


FIG. 3. Pathways of maternal, placental, and fetal interaction for steroid formation forming the fetal placental unit (FPU). The placenta lacks 17-hydroxylase, and 17,20-lyase activity, prohibiting conversion of C-21 (progestins) to C-19 (androgens) or C-18 (estrogens) compounds. The fetus has 16α-hydroxylase activity in the liver, enabling the formation of the estriol precursor 16α-OHDHEAS. (From ref. 4.)



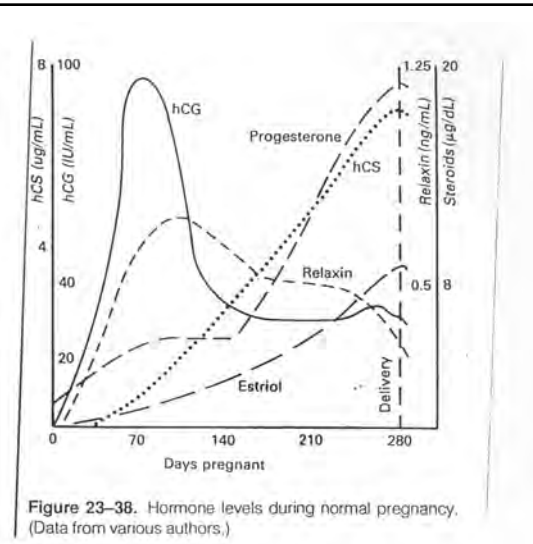


Figure 23–38. Hormone levels during normal pregnancy. (Data from various authors.)

Abnormal Pregnancy Factors

Presenting signs with ectopic pregnancy and percentage occurrence of history

Abdominal pain	97%
Vaginal bleeding	79%
Abdominal tenderness	91%
Adnexal tenderness	54%
History of infertility	15%
Use of an intrauterine contraceptive device	14%
Previous ectopic pregnancy	11%

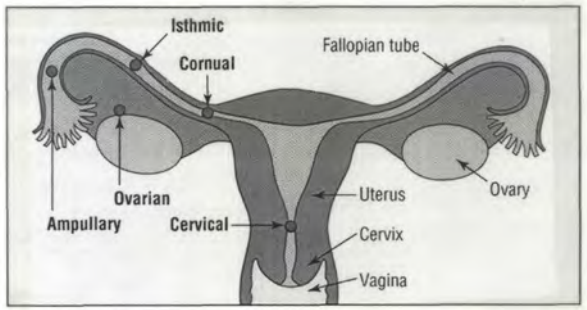


Figure 1 Sites of ectopic pregnancies

Pregnancy Immunology

Box 1. Proposed mechanisms for preventing pregnancy loss (Hill, 1998)

Immune/inflammatory cells
Cytokines/growth factors/hormones
Absence of classical MHC class I and class II molecules
Expression of HLA-C, HLA-G and HLA-E on trophoblast
Expression of complement regulatory proteins on trophoblast
Fas ligand/Fas receptor system
Systemic immunosuppression

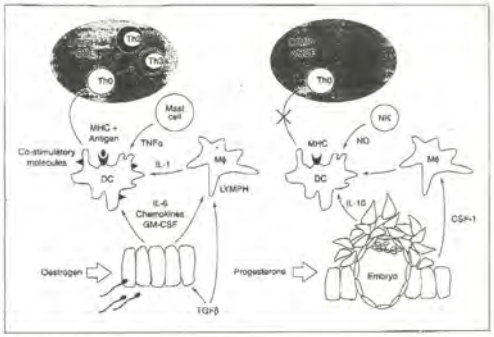


Fig. 2. Effect of ovarian steroid hormones and insemination on the expression of cytokines and the behaviour of antigen-presenting cells in the mouse endometrium. The cytokine environment at the time of insemination is conducive to induction of new immune responses. Transforming growth factor β (TGFβ) contained in seminal plasma induces expression of granulocyte macrophage colony-stimulating factor (GM-CSF), interleukin 6 (IL-6) and chemokines in uterine epithelial cells, which elicit the recruitment and activation of macrophages and dendritic cells in the endometrial stroma. Expression of IL-1 and tumour necrosis factor α (TNFα) in macrophages would augment the effects of GM-CSF in driving the maturation of sentinel dendritic cells (DC) and their emigration to draining lymph nodes. In the absence of 'danger' signals, this cytokine environment would be expected to elicit T lymphocytes with type 2 and T-helper type 3 phenotypes. Conversely, the cytokine environment at the time of implantation is not conducive to the induction of immune responses. Progesterone-induced synthesis of CSF-1, IL-10 and nitric oxide in uterine epithelial cells and leukocytes would be expected to constrain DC activity at the implantation site. In other mucosal tissues, these cytokines act directly and indirectly through the agency of macrophages to inhibit DC transition from the sentinel to the mature state. NK: natural killer cell.

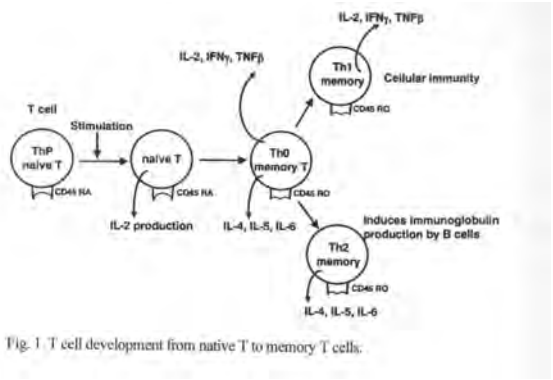


Fig. 1. T cell development from native T to memory T cells.

Table 2. Alternative CD4+ T-lymphocyte phenotypes and their distinguishing characteristics

	Th1	Th2	Th3	Tr1	NK1 + T
Inducing cytokines	IL-12, IFNγ	IL-4, IL-10	IL-4, IL-10	IL-10	
Inducing factors	dsDNA, dsRNA, LPS	TGFβ, PGE	TGFβ		
Eliciting APC	type 1 DC	type 2 DC	DC	DC	DC/epithelial cell
Eliciting MHC	MHC class II	MHC class II	MHC class II	MHC class II	CD1
Major cytokine secreted	IFNγ, IL-2	IL-4, IL-5	TGFβ	IL-10, TGFβ	IL-4
Regulatory phenotype					
Help	Cell-mediated IR	IgG1/IgE	IgA		IgG1/IgE
Suppress	Th2	Th1	Th1/Th2	Th1/Th2	Th1
Antigen specificity					
Activation	Yes	Yes	Yes	Yes	No
Function	Yes	Yes	No	No	No
Bystander suppression	No	No	Yes	Yes	Yes

Tr: T-helper; NK: natural killer; IL: interleukin; IFN: interferon; TGF: transforming growth factor; PGE: prostaglandin E; LPS: lipopolysaccharide; APC: antigen presenting cell; DC: dendritic cell; MHC: major histocompatibility complex; Ig: immunoglobulin; IR: immune response.

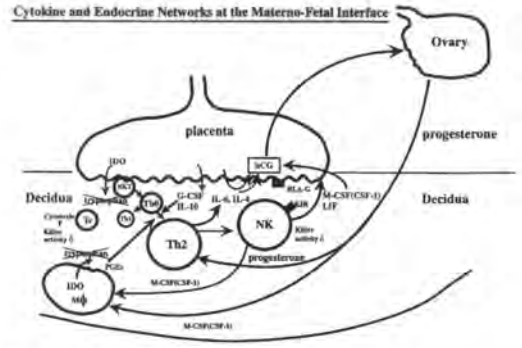


Fig. 2. Cytokine and endocrine networks at the materno-fetal interface.

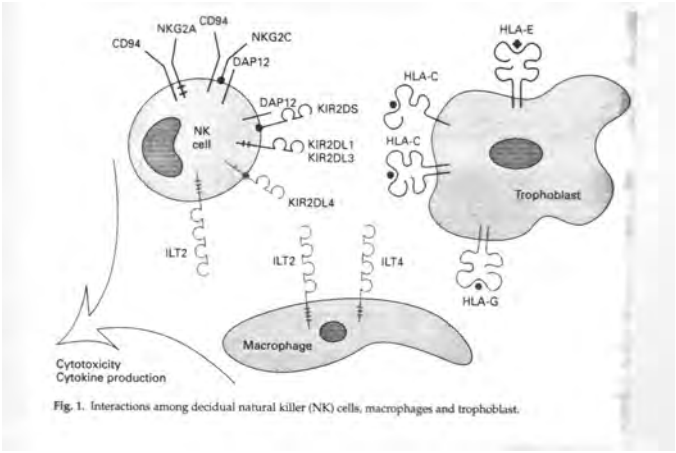


Fig. 1. Interactions among decidual natural killer (NK) cells, macrophages and trophoblast.

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

HLA-C, HLA-G, HLA-E	HLA-A, HLA-B
Low surface expression	High surface expression
Few alleles	Many alleles
Polymorphism not concentrated at antigen-binding site	Polymorphism concentrated at antigen-binding site
T cells reactive to HLA-C are occasionally observed but T cells reactive to HLA-G or HLA-E are not observed	Reactive T cells readily observed

HLA: human leukocyte antigen.

Table 4. Cytokine production in chorionic or placental tissue

Cytokine	Trophoblast	Stromal cell
IL-1α	+ (syncytiotrophoblast	±
IL-1β	±	+
IL-2	–	–
IL-3	–	–
IL-4	+ (syncytiotrophoblast<cytotrophoblast)	+
IL-5	–	–
IL-6	+ (syncytiotrophoblast	+
IL-7	?	+
IL-8	+ (syncytiotrophoblast	+
IL-10	+ (syncytiotrophoblast<cytotrophoblast)	+
G-CSF	+ (syncytiotrophoblast=cytotrophoblast)	+
GM-CSF	–	±
M-CSF	+ (syncytiotrophoblast<cytotrophoblast)	+
LIF	+ (syncytiotrophoblast only)	–
TNFα	+	+
TGFβ	+ (syncytiotrophoblast	+
SCF	+ (cytotrophoblast only)	+
HGF	–	+
VEGF	+ (syncytiotrophoblast<cytotrophoblast) 1st trimester only	+
EGF	+ (syncytiotrophoblast	+
TGFα	+ (syncytiotrophoblast<cytotrophoblast)	+
IFNγ	–	–

Table 1. Pregnancy outcome in gene knockout mice

Disrupted Gene	Pregnancy outcome
Cell surface molecules	
MHC class I (β2μ)	Normal
MHC class II	Normal
CD45 (all white blood cells)	Normal
CD4 (T helper/inducer cells)	Normal
T-cell receptor (TCR) -α, -β	Normal
TCR-γ, -δ	Normal
CD56 (NK cells)	Reduced fetal size and weight
IgM chain	Normal
IgK chain	Normal
Ig heavy chain	Normal
Cytokine/growth factors	
IL-1	Normal
IL-2	Normal
IL-4	Normal
IL-6	Normal
IL-10	Normal
TGF-α	Normal
TGF-β	Normal
IFN-γ	Normal
M-CSF	Failed implantation, but normal with heterozygous males
G-CSF	Normal
LIF	Failed implantation, but strain dependent

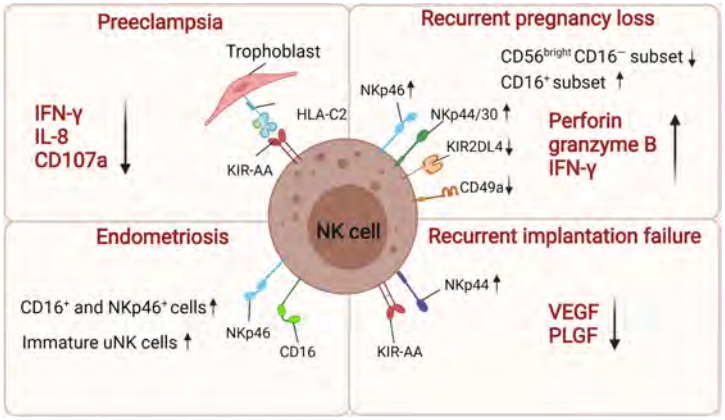
MHC: major histocompatibility complex; NK: natural killer; IL: interleukin; TGF: transforming growth factor; IFN: interferon; M-CSF: macrophage colony-stimulating factor; G-CSF: granulocyte colony-stimulating factor; LIF: leukocyte inhibitory factor.

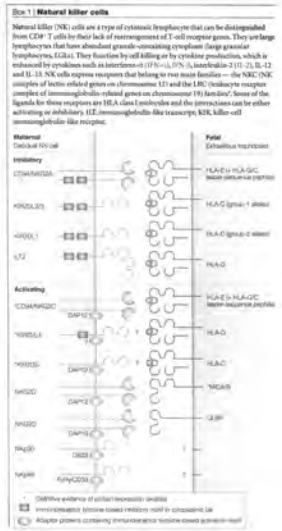
NATURAL KILLER CELLS AND PREGNANCY

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 contact 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.

Role of Decidual Natural Killer Cells in Human Pregnancy and Related Pregnancy Complications
Zhang X, Wei H.
Front Immunol. 2021 Aug 26;12:728291.





Box 1 | **Natural killer cells**

Natural killer (NK) cells are a type of cytotoxic lymphocyte that can be distinguished from CD4+ T cells by their lack of rearrangement of T-cell receptor genes. They are large lymphocytes that have abundant granule-containing cytoplasm (large granular lymphocytes, LGLs). They function by cell killing or by cytokine production, which is enhanced by cytokines such as interferon-α (IFN-α), IFN-β, interleukin-2 (IL-2), IL-12 and IL-15. NK cells express receptors that belong to two main families — the NKC (NK complex of lectin related genes on chromosome 12) and the LRC (leukocyte receptor complex of immunoglobulin-related genes on chromosome 19) families[1]. Some of the ligands for these receptors are HLA class I molecules and the interactions can be either activating or inhibitory. ILT, immunoglobulin-like transcript; KIR, killer-cell immunoglobulin-like receptor.

Table 1 | **Comparison of CD56+ NK cells**

Characteristic	Blood CD56^{dim}	Blood CD56^{bright}	Decidua CD56^{bright}
Phenotypic markers			
CD16	++	+/−	−
CD94	+/−	++	++
KIR	+	−	+
Cytoplasmic CD3	−	−	+
c-KIT	−	+	+/−
CD69	−	−	+
CD45RA	+	+	−
CD45RO	−	−	+
CD62L (L-selectin)	+/−	++	−
αEβ7	−	−	+
CD49a (α1-integrin)	−	−	+
CD49f (α5-integrin)	+	+	−
NK activity	High	Low	Low
Morphology	LGLs	Agranular small lymphocytes	Both agranular small lymphocytes and LGLs
Cytokines			
MIP1α	−	+	++++
GM-CSF	−	+	++++
CSF1	−	+	++++
IFN-γ	+	−	+/−

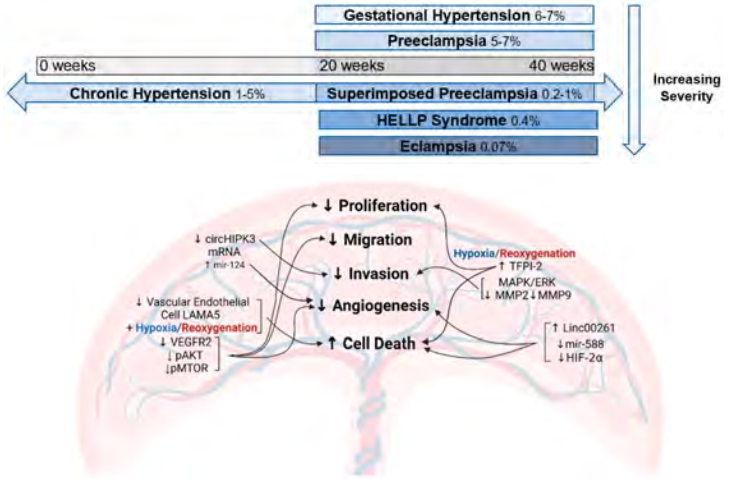
CSF1, colony-stimulating factor 1; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN-γ, interferon-γ; KIR, killer-cell immunoglobulin-like receptor; LGL, large granular lymphocyte; MIP1α, macrophage inflammatory protein 1α; NK, natural killer. For details, see refs [123,124,126,72–74].

Table 2 | **Differences between human and mouse implantation**

Human	Mouse
NK cells present in non-pregnant endometrium	NK cells not present in non-pregnant endometrium
Decidualization commences in each non-pregnant cycle	Decidualization occurs only after implantation
NK cells infiltrate diffusely throughout the decidua	NK cells are confined to central decidua basalis and the mesometrial triangle
Extensive trophoblast invasion into decidual stroma and arteries	Minimal trophoblast invasion of decidual stroma and arteries

NK, natural killer.

Vascular Dysfunction in Preeclampsia
Opichka MA, Rappelt MW, Gutterman DD, et al.
Cells. 2021 Nov 6;10(11):3055.



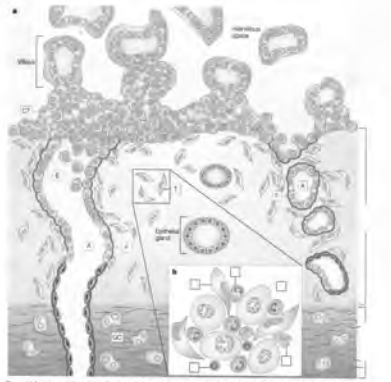


Figure 1 | **Anatomy of the trophoblast populations that are present at the fetal–maternal boundary in the first trimester of pregnancy. a** | The placental villi are covered by villous trophoblast cells — an inner mononuclear cytotrophoblast layer covered by syncytiotrophoblast. The core of each villus contains fetal blood vessels, fibroblasts and fetal macrophages (Hofbauer cells). Maternal blood in the intervillous space reaches the placenta through the uterine spiral arteries (A). The inner layer of villous cytotrophoblast grows out at focal points to form cell columns (CT). These are prominent at the anchoring villi, where attachment to the maternal decidua occurs. At the fetal–maternal boundary, the columns form a partially continuous shell. From this shell, extravillous trophoblast cells enter the decidua as interstitial trophoblast (T) to envelop and destroy the arterial media, which is replaced by fibrinoid material (F). Then, endovascular trophoblast cells (E) move down the arteries in a retrograde manner to replace the endothelial cells. The trophoblast cells move as far as the inner myometrium, where they fuse to become placental-bed giant cells (GC). Extravillous trophoblast cells include cytotrophoblast cell columns and shell, interstitial and endovascular trophoblast and placental-bed giant cells. **b** | A schematic representation of the decidual stroma at the implantation site. Interstitial trophoblast cells (T) are seen between large stromal cells (S). The maternal leukocytes that are present are uterine natural killer cells (K), as well as a few macrophages (M) and occasional T cells (L).

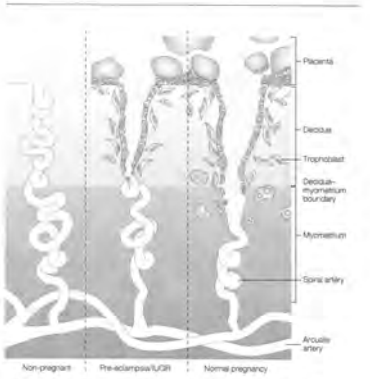


Figure 2 | **The blood flow through the maternal uterine arteries is increased by the infiltration of the arterial media and endothelium by extravillous trophoblast cells.** A comparison between unrivaded arteries (non-pregnant), normal pregnancy and pathological conditions of pregnancy — such as pre-eclampsia and intrauterine growth retardation (IUGR) — is shown. Note that the extent and depth of trophoblast invasion is less in pathological compared with normal pregnancy, which results in inadequate transformation of the spiral arteries in the former. This results in reduced blood flow to the feto-placental unit, which leads to poor fetal growth. The ischaemic placenta can also trigger systemic endothelial dysfunction in the mother and the onset of pre-eclampsia.

Why is placentation abnormal in preeclampsia?

Fisher SJ.

Am J Obstet Gynecol. 2015 Oct;213(4 Suppl):S115-22.

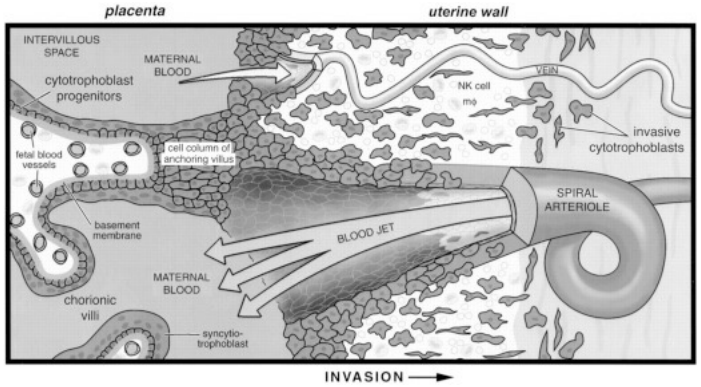


TABLE 1
Summary of Current Concepts of Preeclampsia

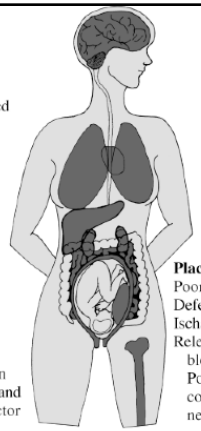
Concept	Basis of theory
Placental ischemia	Hypoxia/reperfusion in the placenta initiates local oxidative processes and leads to release of factors that consequently cause endothelial damage.
Hypertriglyzidemia	High serum lipid (VLDL) levels with insufficient antioxidant activity may lead to oxidative processes and consequently to endothelial damage.
Immune maladaptation	Immune processes at the placenta due to insufficient immune tolerance of the fetus may lead to immune processes, release of cytokines, and consequently endothelial damage.
Genetic imprinting	The development of preeclampsia may be based on a single recessive gene or a dominant gene with incomplete penetrance.
Mitochondrial defects	Invasion of cytotrophoblasts into the maternal endometrium is a highly energy-consuming process. This process may be incomplete in case of a mitochondrial defect.
Disturbance of the invasion of placental extravillous cytotrophoblasts	Histological observations confirmed incomplete invasion of cytotrophoblasts to the maternal endometrium. This failure may be secondary to any predisposing factor.

TABLE 2
Summary of Factors Possibly Predisposing to Preeclampsia

Factors independent from genetics and molecular mechanisms	Poor socioeconomical conditions Primiparity Young age of the mother Maternal stress Low birthweight (prematurity) of the mother
Factors which may have molecular relationship and may be influenced by inheritance	Previously existing hypertension Diabetes mellitus Clotting abnormalities Hyper-dyslipidemias
Susceptibility factors which are possibly influenced by genetics	Preeclampsia genes? Involvement of mitochondrial dysfunction Interactions between maternal and fetal HLA genes Genetic variability of the renin-angiotensin system Genetic variability of endothelial nitric oxide synthase

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 the proxidant and antioxidant species



Endothelial dysfunction
Raised sensistivity to pressors
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:
corticotrophin 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.

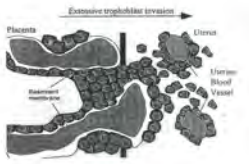


FIGURE 1 Invasion of fetal trophoblasts into maternal decidua and myometrium during normal pregnancy. Numerous trophoblasts invade and subsequently remodel maternal uterine blood vessels. Adapted from Wittschwerdter *et al* 1998 [11].

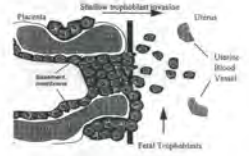


FIGURE 2 Invasion of fetal trophoblasts into maternal decidua and myometrium during preeclampsia (PE). A characteristic feature of PE is the shallow invasion of trophoblasts resulting in inadequate remodelling of maternal uterine blood vessels and, hence, inadequate perfusion of the placental bed.

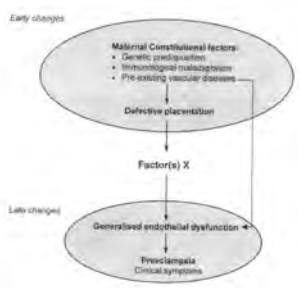


Fig. 1. Schematic representation of the etiology of PE.

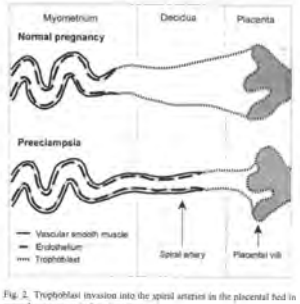
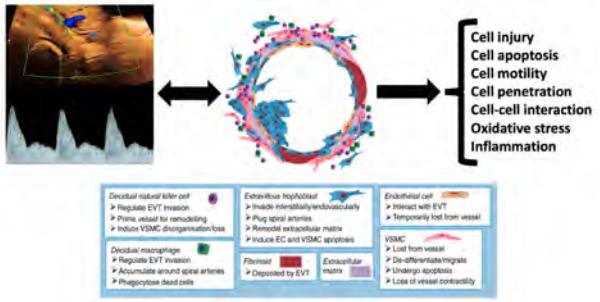


Fig. 2. Trophoblast invasion into the spiral arteries in the placental bed in normal pregnancy and in preeclampsia.

Preeclampsia: The Relationship between Uterine Artery Blood Flow and Trophoblast Function.
Ridder A, Giorgione V, Khalil A, Thilaganathan B.
Int J Mol Sci. 2019 Jul 2;20(13).



Relationship between uterine artery perfusion and cellular function. There are strong associations between maternal uterine artery perfusion and placental cellular function and behaviour. High-resistance Doppler indices (poor placental perfusion) is related to abnormalities of cell motility, penetration, and cell–cell interaction, as well as increased rates of oxidative stress, inflammation, cellular injury, and apoptosis. Adapted with permission from Cartwright et al.

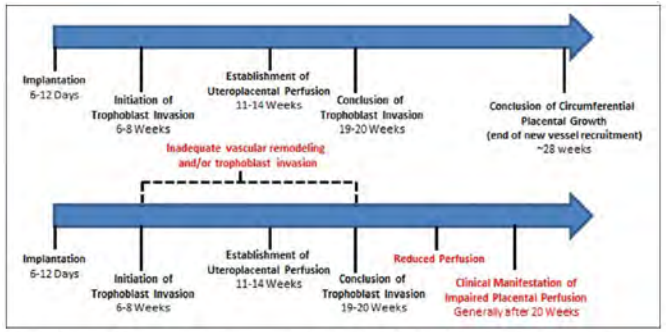


Figure 4. Key events in the establishment of the uteroplacental circulation in normal and complicated pregnancies: In normal pregnancy (top), proper trophoblast invasion and vascular remodeling lay the foundation for a successful pregnancy. In pregnancies where these processes are interrupted or impaired (bottom) complications such as preeclampsia can occur.

Table 1. Vasoactive substances that have been implicated to play a role in PE, along with their vasoactive effect, the reported concentrations (conc.) in preeclamptic patients as compared to normal pregnancy (Conc.: ↑= increased, ↓=decreased, = =no difference, *M*=metabolites measured) in samples from different sampling sites and the relevant references

Substance	Vasoactive Effect	Sample site	Conc.	References
PGI_2	Vasodilatation	Peripheral blood/urine *M*	↓	[85–87]
		Placental production *M*	↓	[89,90]
TxA_2	Vasoconstriction	Urine *M*	↑	[85]
		Placental production *M*	↑	[89,90]
NO	Vasodilatation	Peripheral blood/urine *M*	↑	[96–98]
			↓	[92]
			=	[93–95]
EDHF	Vasodilatation		?	
Endothelin	Vasoconstriction	Peripheral blood/uterine vein	↑	[109–113]
VEGF	Vasoconstriction	Peripheral blood	↑	[122–125]
			↓	[126,127]
ANP	Vasodilatation	Peripheral blood	↑	[117,145]
Renin, Aldosterone, ATII	Vasoconstriction	Peripheral blood	↓	[134]
Catecholamines	Vasoconstriction	Peripheral blood/urine *M*	↓/↑	[141]

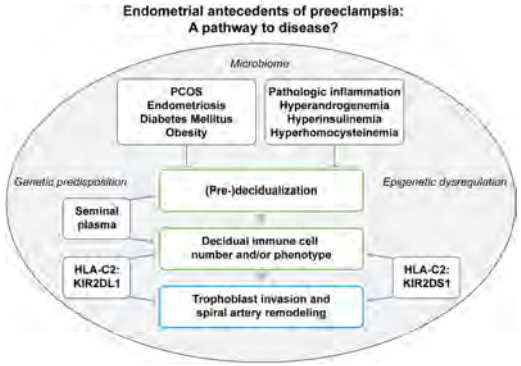
Analysis of the role of HLA-G in preeclampsia

Margaret O'Brien, a, Jean Daussetb, Edgardo D. Carosellaa and Philippe Moreaua

Abstract

Preeclampsia (PE) is a multisystem disorder of human pregnancy, occuring 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 clinicaly 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 focuss on the potential role of HLA-G, a nonclassical class I HLA located on chromosome 6, which appears to be a key component in trophoblast invasion. We examine the hypothesis that HLA-G may have a key role in both genetic susceptibility to, and pathogenesis of, PE.

Emerging role for dysregulated decidualization in the genesis of preeclampsia.
Placenta. 2017 Dec;60:119-129.
Conrad KP, Rabaglino MB, Post Uiterweer ED.

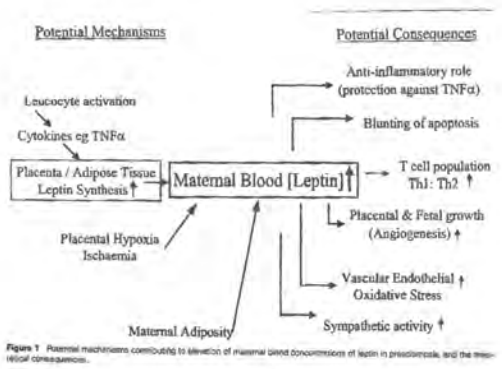


Leptin and Preeclampsia

Lucilla Poston, Ph.D.[1]

ABSTRACT

Preeclampsia, a common complications of pregnancy, is associated with an increase in the concentration of leptin in the maternal blood, which precedes the clinical onset of the disease. This review addresses the potential sources of leptin and considers the possible consequences, although at present these are entirely conjectural. The placenta is likely to contribute to the rise in leptin, and placental hypoxia and inflammatory mediators may be important stimuli. The possible protective and damaging sequelae of an increase in the maternal leptin concentrations may range from beneficial stimulation of fetal growth to an increase in blood pressure through stimulation of sympathetic activity. Further research is needed to determine if the rise in leptin plays a role in preeclampsia or whether it is a secondary and unrelated bystander.



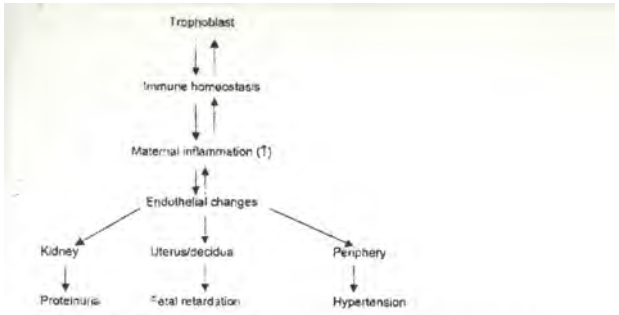
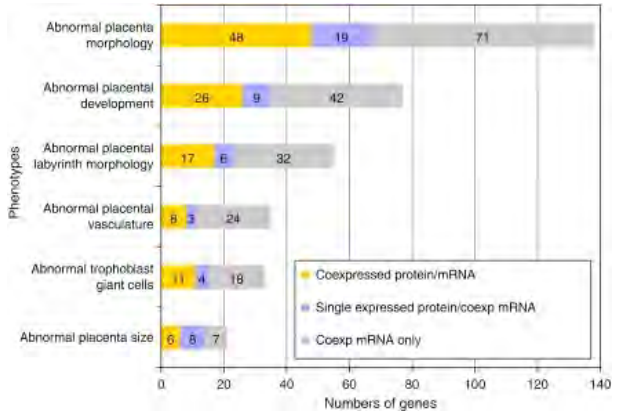
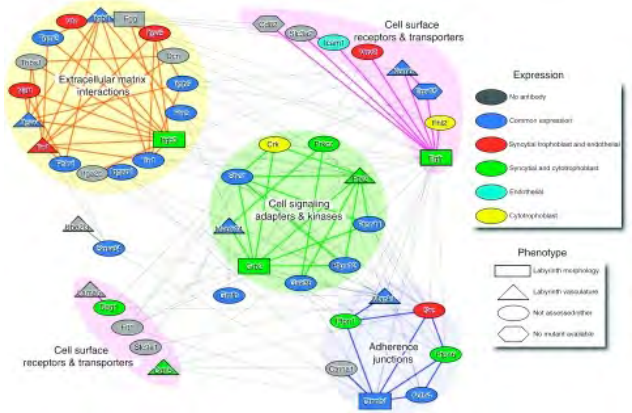


Figure 2. The fetal trophoblast induces an inflammatory response in the mother. In normal pregnancy, the signals produced by the trophoblast and the maternal response (e.g. "cytokine crosstalk") are in equilibrium (immune homeostasis). The maternal inflammation leads to endothelial changes, which, in normal pregnancy, often manifest themselves as edema. The extent of the inflammatory reaction and the endothelial changes are in equilibrium. In pre-eclampsia (↑), a more exaggerated maternal inflammatory response, which shares similarities with the features of sepsis [43], leads, via enzymes, cytokines, etc, to a state of imbalance with endothelial damage. This, in turn, causes damage to various organ systems, the extent of which determines the clinical manifestations of pre-eclampsia.

Comparative systems biology of human and mouse as a tool to guide the modeling of human placental pathology.
Cox B, et al.
Mol Syst Biol. 2009;5:279.





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.

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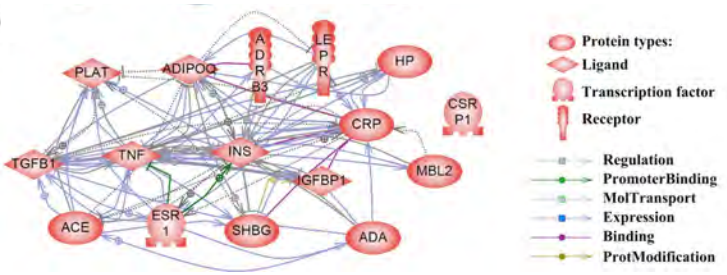
Glotov AS, Tiys ES, Vashukova ES, et al.
BMC Syst Biol. 2015;9 Suppl 2:S4.



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Maeda KJ, Showmaker KC, Johnson AC, Garrett MR, Sasser JM.
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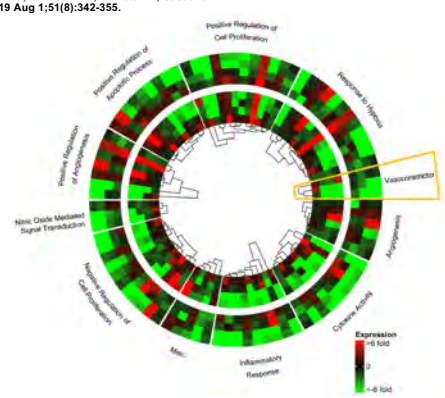
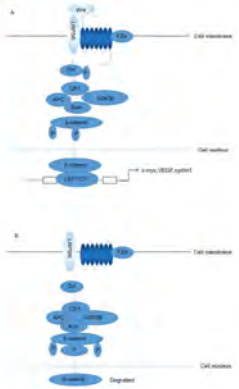
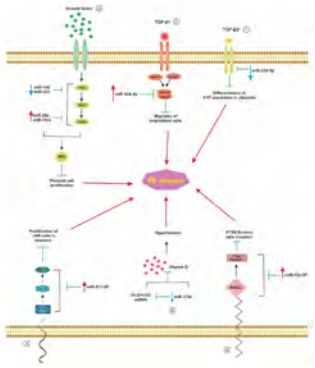


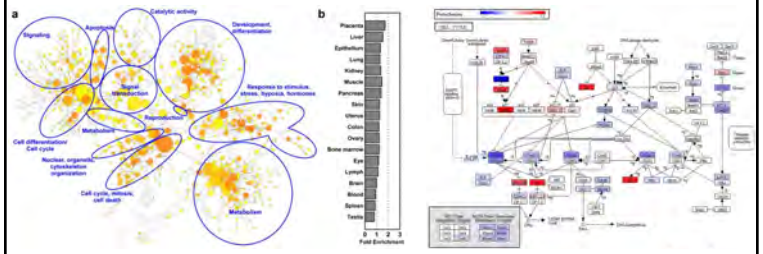
Wnt/β-catenin signaling pathway in trophoblasts and abnormal activation in preeclampsia (Review).
Zhang Z, Wang X, Zhang L, Shi Y, Wang J, Yan H.
Mol Med Rep. 2017 Aug;16(2):1007-1013.



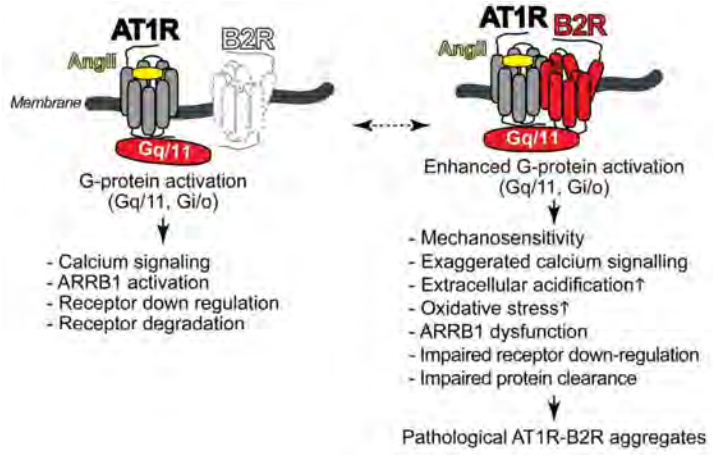
The role of epigenetic changes in preeclampsia.
Kamrani A, Alipourfard I, Ahmadi-Khiavi H, Yousefi M, Rostamzadeh D, Izadi M, Ahmadi M.
Biofactors. 2019 Sep;45(5):712-724.



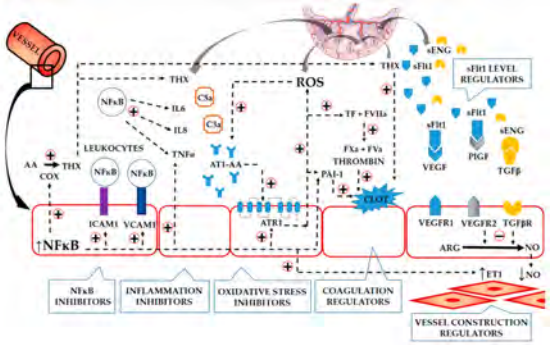
Placenta-Specific Genes, Their Regulation During Villous Trophoblast Differentiation and Dysregulation in Preterm Preeclampsia.
Szilagyi A, Gelencser Z, Romero R, et al.
Int J Mol Sci. 2020 Jan 17;21(2).



Pathological AT1R-B2R Protein Aggregation and Preeclampsia
Quitterer U, AbdAlla S.
Cells. 2021 Oct 1;10(10):2609.

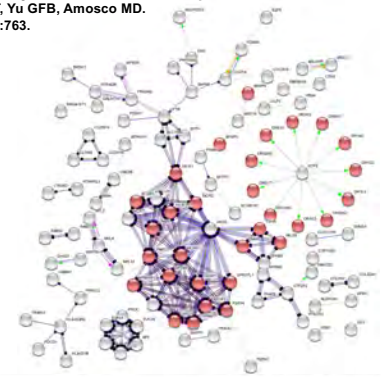


New Ideas for the Prevention and Treatment of Preeclampsia and Their Molecular Inspirations.
Int J Mol Sci. 2023 Jul 28;24(15):12100.
Sakowicz A, Bralewska M, Rybak-Krzyszkowska M, Grzesiak M, Pietrucha T.



The groups of agents adopted for the prevention and treatment of preeclampsia and their molecular inspirations, i.e.,: NFκB inhibitors: aspirin, hydroxychloroquine, metformin, proton pump inhibitors, statins, sulfasalazine; inflammation inhibitors: aspirin, eculizumab, metformin, mesenchymal cells and their exosomes, probiotics, statins, sulfasalazine, vitamin D; oxidative stress inhibitors: aspirin, polyphenols, vitamin C, vitamin D, vitamin E; coagulation regulators: aspirin, antithrombin, hydroxychloroquine, mesenchymal cells and their exosomes; sFlt1 level regulators: apheresis, chimera of elastin like-polypeptide with vascular endothelial growth factor type A or type B, small interfering RNA particles; vessel construction regulators: aspirin, hydroxychloroquine, metformin, L-arginine, L-citrulline, proton pump inhibitors, statins, sulfasalazine. Legend: abbreviations: AA—arachidonic acid; ARG—arginine; AT1-AA—angiotensin II type 1 receptor autoantibody; ATR1—angiotensin II receptor type 1; C3a—complement component 3a; C5a—complement component 5a; COX—cyclooxygenase; ET1—endothelin 1; FVa—active coagulation factor Va; FVIIa—active coagulation factor VII; FXa—active coagulation factor Xa; ICAM 1—intracellular adhesion molecule type 1; IL6—interleukin 6; IL8—interleukin 8; NFκB—nuclear factor kappa B; NO—nitric oxide; PAI-1—plasminogen activator inhibitor 1; PlGF—placenta growth factor; ROS—reactive oxygen species; sENG—soluble endoglin; sFlt1—soluble fms-like tyrosine kinase 1; TF—tissue factor; TGFβ—tumour growth factor beta; THX—thromboxane; TNFα—tumour necrosis factor alpha; VCAM 1—vascular adhesion molecule type 1, VEGFR1—vascular endothelial growth factor receptor type 1; VEGFR2—vascular endothelial growth factor receptor type 2; symbols: ljms 24 12100 i001 process activation; ljms 24 12100 i002 process inhibition; ljms 24 12100 i003 the direction of common relationships between the analysed factors.

G-Protein Coupled Receptor Dysregulation May Play Roles in Severe Preeclampsia-A Weighted Gene Correlation Network Analysis of Placental Gene Expression Profile
Vidal Jr MS, Deguit CDT, Yu GFB, Amosco MD.
Cells. 2022 Feb 22;11(5):763.



#Term ID	Description	Observed Gene Count	Background Gene Count	False Discovery Rate
GO:0004930	G-protein-coupled receptor activity	38	824	0.0007
GO:0008188	neuropeptide receptor activity	8	47	0.003
GO:0004888	transmembrane signaling receptor activity	45	1226	0.0044
GO:0008528	G-protein-coupled peptide receptor activity	12	132	0.0044
GO:0060089	molecular transducer activity	50	1483	0.0105
GO:0038023	signaling receptor activity	48	1429	0.0137

Trophoblast-microbiome interaction: a new paradigm on immune regulation.
Mor G, Kwon JY.
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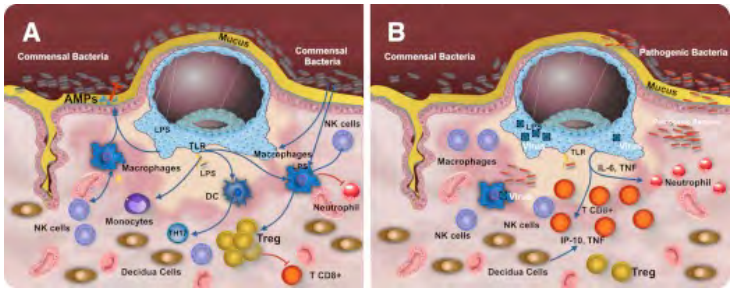

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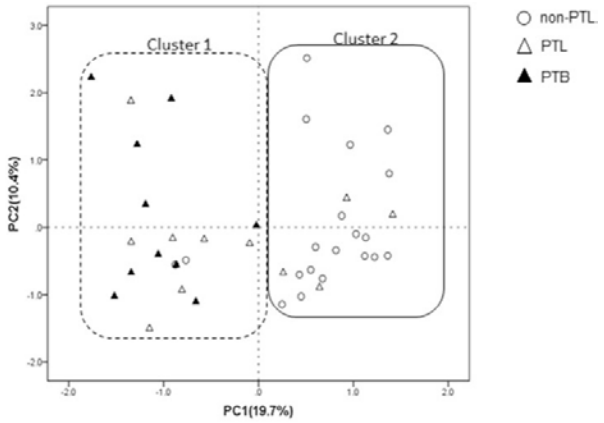

Molecular basis of thyrotropin and thyroid hormone action during implantation and early development.

Colicchia M, Campagnolo L, Baldini E, Ulisse S, Valensise H, Moretti C.
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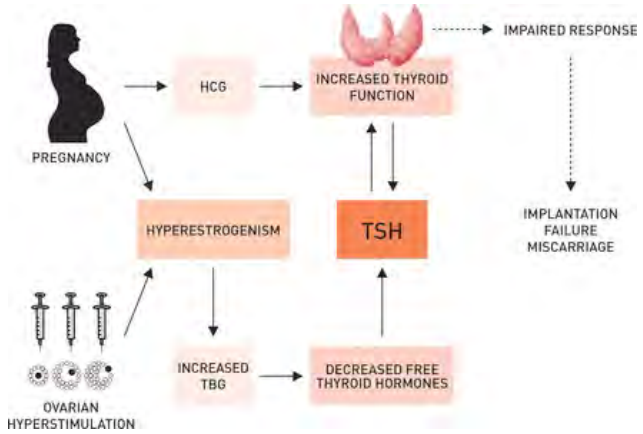
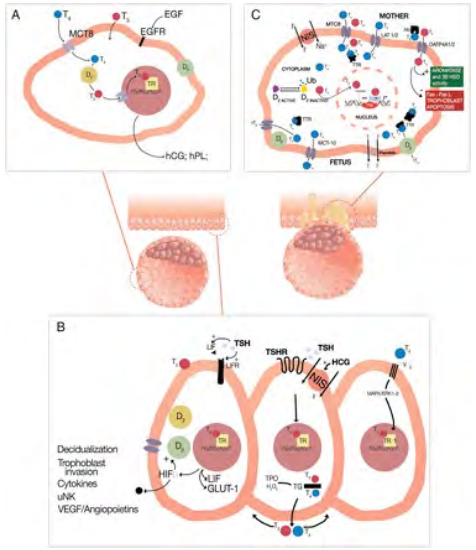




Birth and Parturition

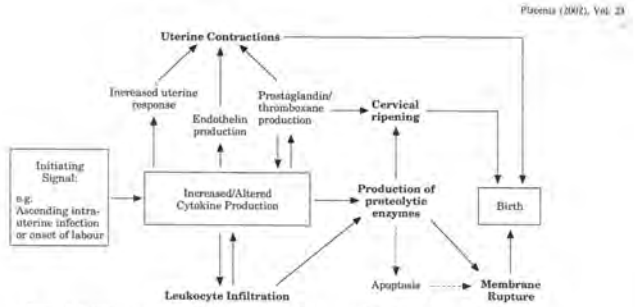


Figure 1. Cytokines play a central role in processes involved in the metabolism of term and preterm parturition.

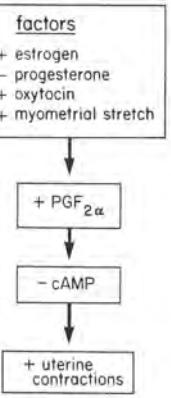


FIG. 11–19. Sequence of events leading to uterine contractions of parturition in sheep. Hormonal changes and myometrial stretch stimulate $PGF_{2\alpha}$ synthesis and release from the uninvaded caruncles and myometrium. The elevated levels of $PGF_{2\alpha}$ lower the threshold to oxytocin and also interact with the smooth muscle adenylate cyclase system to lower cAMP levels, resulting in uterine contractions.

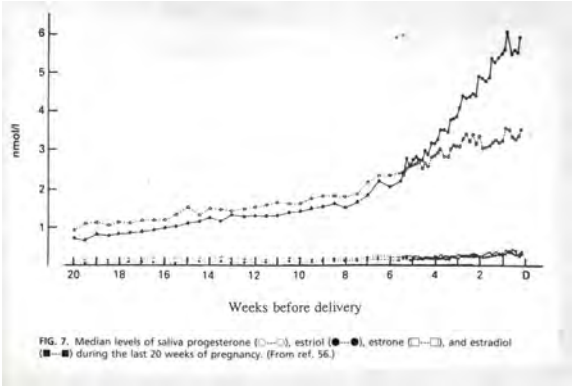


FIG. 7. Median levels of saliva progesterone (○···○), estriol (●—●), estrone (□···□), and estradiol (■—■) during the last 20 weeks of pregnancy. (From ref. 56.)

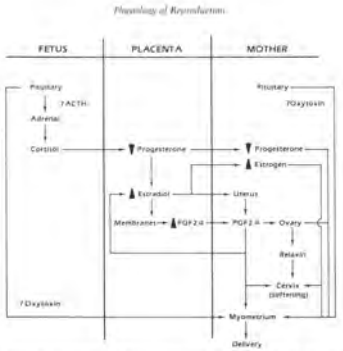


FIG. 11–21. Schematic representation of the endocrine events at parturition in farm animals. Activation of the fetal hypothalamic-hypophyseal-adrenal pathway leads to an increase in cortisol reaching the placenta. Placental progesterone production falls (sheep) and estrogen production increases. Estrogen stimulates $PGF_{2\alpha}$ synthesis from the placental membranes and myometrium. Elevation of $PGF_{2\alpha}$ lowers the threshold to oxytocin, and oxytocin and/or $PGF_{2\alpha}$ leads to myometrial contractility. In CL-dependent species (goat, cattle, pig), $PGF_{2\alpha}$ causes luteal regression and a fall in progesterone. Relaxin may be secreted by the ovary and leads to softening of the cervix. (Adapted from Speroff, L. (1979) Prostaglandins in pregnancy. *In* The influence of maternal hormones on the fetus and newborn. Perloe Adolescence Endocr., 2, 268.)

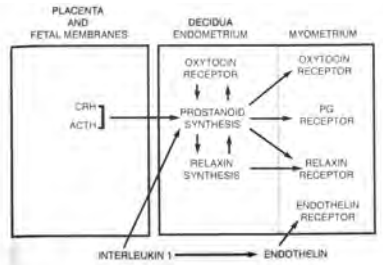


FIG. 9. Complex paracrine relationships between fetal and maternal products involved in parturition.

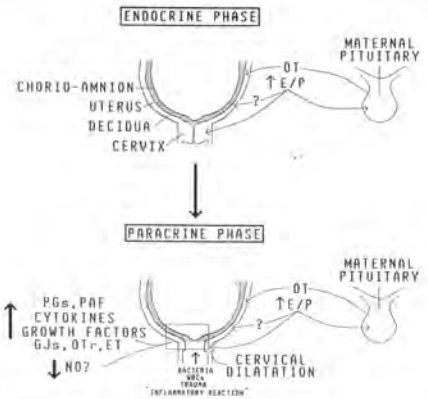


FIG. 12. A hypothesis on parturition in primates. Parturition is a process that begins with an endocrine event and ends as a paracrine event. The endocrine phase is initiated with development of an estrogen environment inducing release of oxytocin and aiding in the ripening of the cervix. As the cervix opens, an inflammatory-like response occurs in the cervical-decidual-chorioamnion region that induces the release of a number of factors and the paracrine effects become dominant over the endocrine effects.

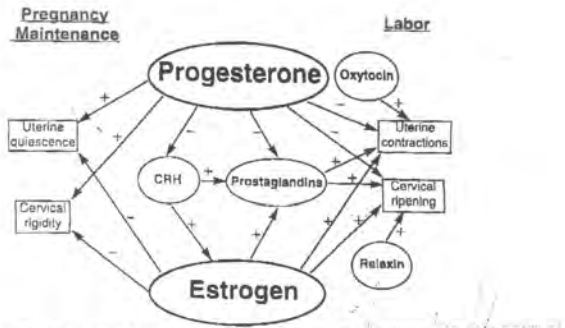


FIG. 1. Simplified scheme of the endocrinological control of pregnancy and parturition in women. The balance between the effects of estrogen and progesterone is critical to maintenance of pregnancy and the onset of labor. Other important hormonal factors modulate this balance as shown in the scheme. Not all factors are represented. Those shown are endocrine factors demonstrated to be significant [illegible]

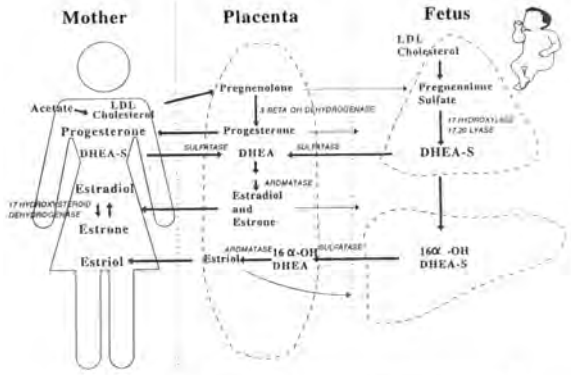


FIG. 3. Pathways of maternal, placental, and fetal interaction for steroid formation forming the fetal placental unit (FPU). The placenta lacks 17-hydroxylase, and 17,20-lyase activity, prohibiting conversion of C-21 (progestins) to C-19 (androgens) or C-18 (estrogens) compounds. The fetus has 16α-hydroxylase activity in the liver, enabling the formation of the estriol precursor 16α-OHDHEAS. (From ref. 6.)

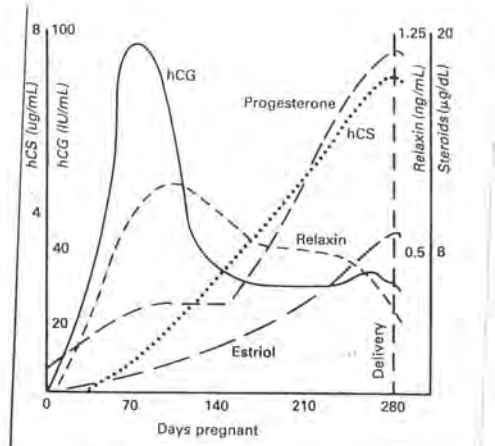


Figure 23–38. Hormone levels during normal pregnancy. (Data from various authors.)

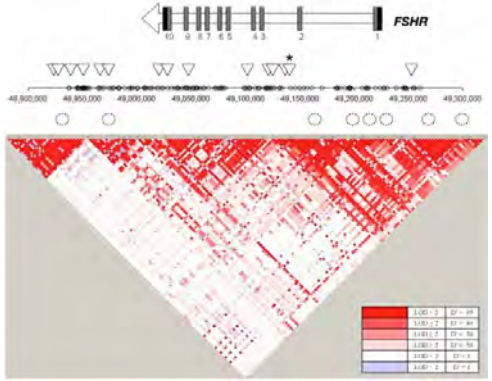
The transcriptome of cervical ripening in human pregnancy before the onset of labor at term: identification of novel molecular functions involved in this process.
Hassan SS, et al.
J Matern Fetal Neonatal Med. 2009 Dec;22(12):1183-93.

Table III. Gene ontology analysis.

	Genes in significant list (91 genes)	Genes on array	*p* value*
Biological process category			
Cell adhesion	12	396	<0.0001
Regulation of anatomical structure	6	71	<0.0001
Regulation of locomotion	5	67	0.005
Multicellular organismal development	25	1891	0.005
Cell motility	6	136	0.008
Phosphate transport	5	82	0.009
Localization	24	1777	0.01
Regulation of cellular component organization and biogenesis	7	207	0.01
Regulation of body fluid levels	5	110	0.02
Skin development	2	7	0.03
Blood coagulation	4	69	0.03
Molecular function category			
Extracellular matrix structural constituent	10	89	2.11×10^{-8}
Protein binding	57	6680	0.0057
Structural molecule activity	13	648	0.0063
Integrin binding	4	43	0.0063
Glycosaminoglycan binding	5	100	0.0127
Polysaccharide binding	5	103	0.0127
Pattern binding	5	114	0.0173
Heparin binding	4	78	0.0304
Actin filament binding	3	37	0.0304
Actin binding	7	284	0.0304
Cytoskeletal protein binding	8	403	0.0495

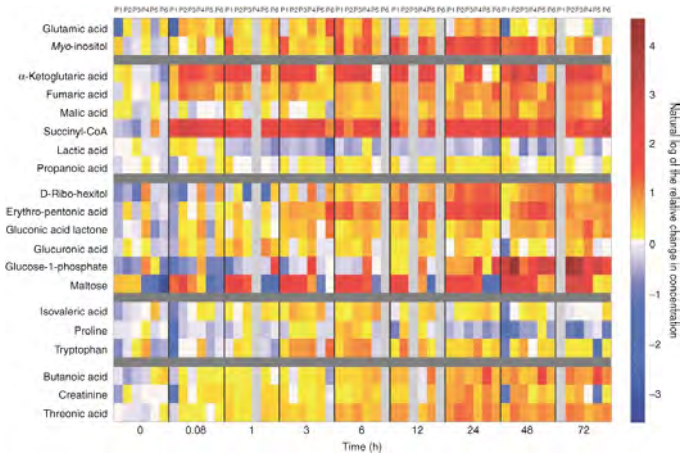
*p values were derived using a hypergeometric distribution and were subsequently FDR corrected.

An evolutionary genomic approach to identify genes involved in human birth timing.
Plunkett J, et al.
PLoS Genet. 2011 Apr;7(4):e1001365.



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 ($p \leq 0.005$). Circles represent conserved elements examined in the region.

The perinatal transition of the circulating metabolome in a nonhuman primate.
Beckstrom AC, et al.
Pediatr Res. 2012 Apr;71(4 Pt 1):338-44.



Preterm delivery

Michael M Slattery and John J Morrison,

Abstract

Preterm delivery and its short-term and long-term sequelae constitute a serious problem in terms of mortality, disability, and cost to society. The incidence of preterm delivery, which has increased in recent years, is associated with various epidemiological and clinical risk factors. Results of randomised controlled trials suggest that attempts to reduce these risk factors by use of drugs are limited by side-effects and poor efficacy. An improved understanding of the physiological pathways that regulate uterine contraction and relaxation in animals and people has, however, helped to define the complex processes that underlie parturition (term and preterm), and has led to new scientific approaches for myometrial modulation. The continuing elucidation of the mechanisms that regulate preterm labour, combined with rigorous clinical assessment, offer hope for future solutions.

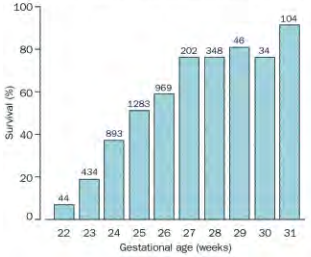
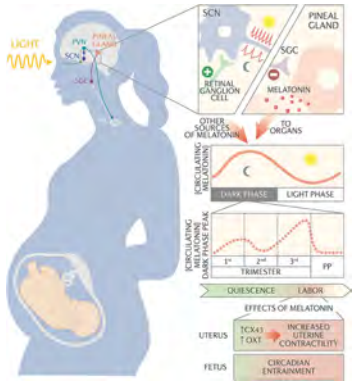


Figure 1. Perinatal survival (%) between weeks 22 and 31 of gestation: Average total number of neonates(9, 11, 12, 13, 14; 15, 16, 17, 18, 19, 20, 21, 22 and 23) for each week of gestationgiven in respective bars. Although denominator data in different studies could vary, the figures presented here are outlined as a proportion of all livebirths as reported.

Panel 1: Causes of preterm delivery

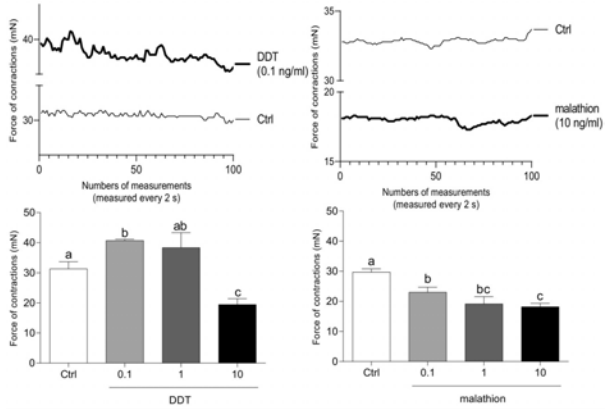
Cause	Frequency
Spontaneous preterm labour	31–50%[2,35]
Multiple pregnancy and associated complications	12–28%[2,24,36]
Preterm prelabour rupture of membranes (pPROM)	6–40%[2,35,37]
Hypertensive disorders of pregnancy	12%[3]
Intrauterine growth restriction	2–4%[3]
Antepartum haemorrhage	6–9%[3]
Miscellaneous — cervical incompetence, uterine malformation	8–9%[3]

Riding the Rhythm of Melatonin Through Pregnancy to Deliver on Time.
McCarthy R, Jungheim ES, Fay JC, Bates K, Herzog ED, England SK.
Front Endocrinol (Lausanne). 2019 Sep 13;10:616.

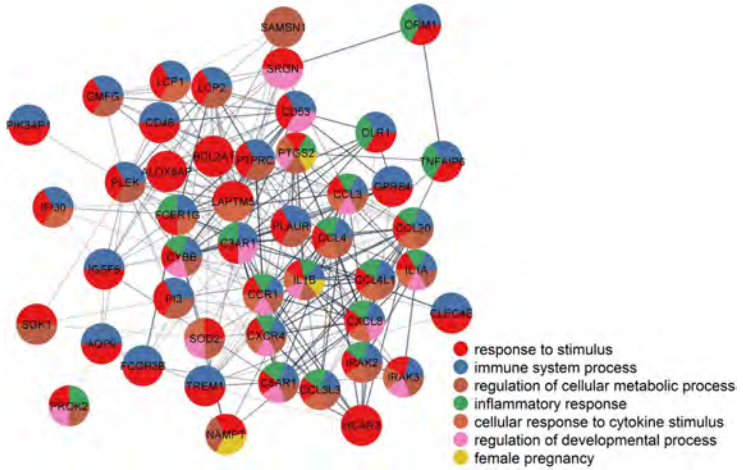


Contractile function of the cervix plays a role in normal and pathological pregnancy and parturition
Tantengco OAG, Menon R.
Med Hypotheses. 2020 Dec;145:110336.

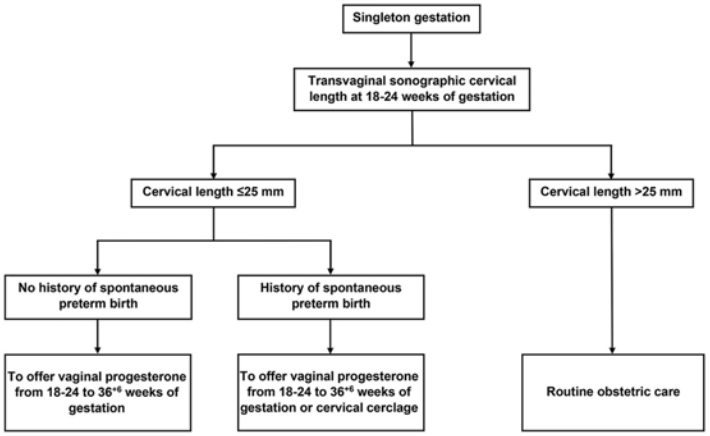
Chloroorganic (DDT) and organophosphate (malathion) insecticides impair the motor function of the bovine cervix.
Wrobel MH, Mlynarczuk J.
Toxicol Appl Pharmacol. 2021 Sep 15;427:115667.



The amniotic fluid cell-free transcriptome in spontaneous preterm labor.
Bhatti G, Romero R, Gomez-Lopez N, et al.
Sci Rep. 2021 Jun 29;11(1):13481.



Vaginal progesterone for the prevention of preterm birth: who can benefit and who cannot? Evidence-based recommendations for clinical use.
Conde-Agudelo A, Romero R.
J Perinat Med. 2022 Dec 7;51(1):125-134.



Evidence-based clinical algorithm for the use of vaginal progesterone in preventing preterm birth among singleton gestations.

Preterm birth buccal cell epigenetic biomarkers to facilitate preventative medicine.
Winchester P, Nilsson E, Beck D, Skinner MK.
Sci Rep. 2022 Mar 1;12(1):3361.

DMR Identification

a Mother DMRs

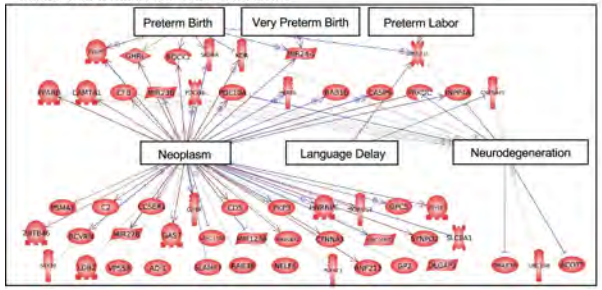
p-value	All Window	Multiple Window
0.001	601	53
1e-04	**165**	**28**
1e-05	56	17
1e-06	32	12
1e-07	20	9

Significant windows (1 kb)	1	2	3	4	≥5
Number of DMR (p<1e-04)	137	16	5	2	3

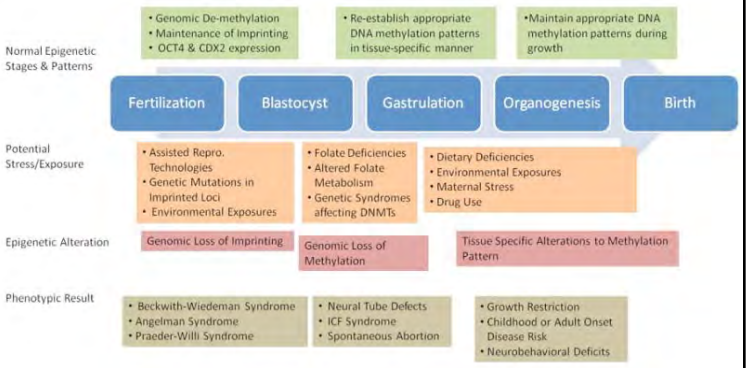
b Extended Overlaps (p<1e-04 vs. p<0.05)

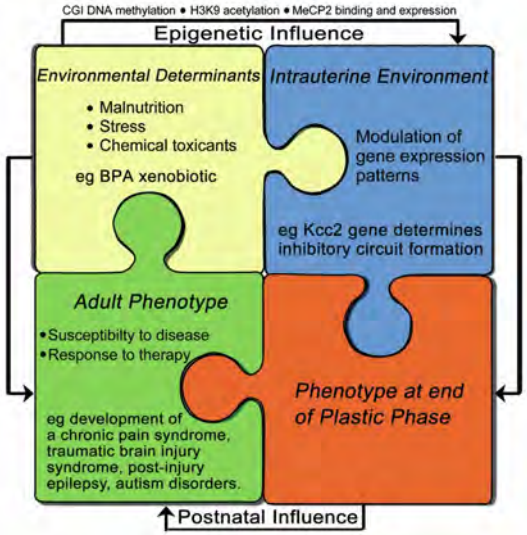
p<1e-04 \ p<0.05	Mother	Father	Female Child	Male Child
Mother	165 (100%)	81 (49%)	96 (58%)	50 (30%)
Father	54 (74%)	73 (100%)	47 (64%)	34 (47%)
Female Child	79 (58%)	62 (46%)	136 (100%)	46 (34%)
Male Child	17 (28%)	15 (25%)	11 (18%)	61 (100%)

Mother DMR Associated Gene Correlations

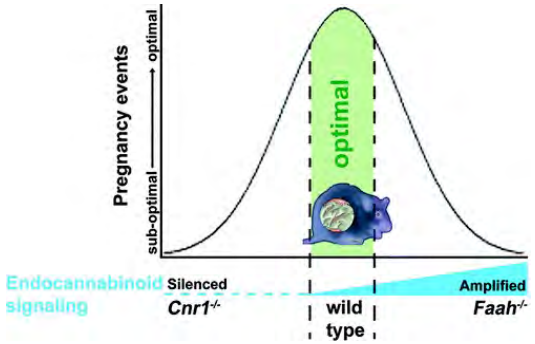


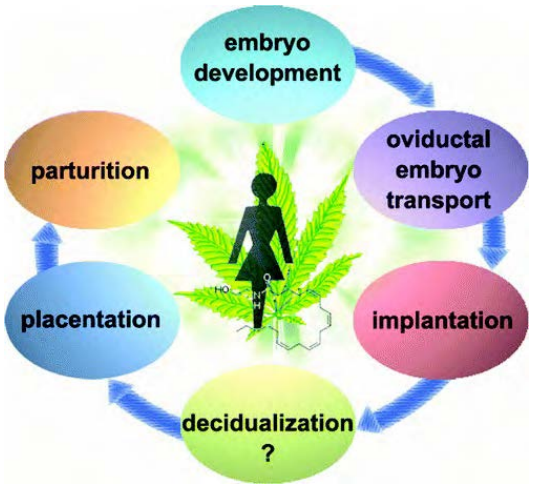
Environmental Insults/Exposures





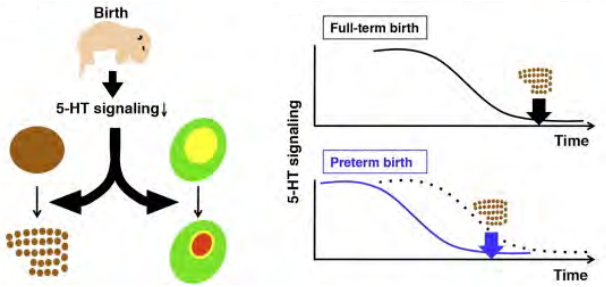
Endocannabinoid signaling in female reproduction.
Sun X, Dey SK.
ACS Chem Neurosci. 2012 May 16;3(5):349-55.

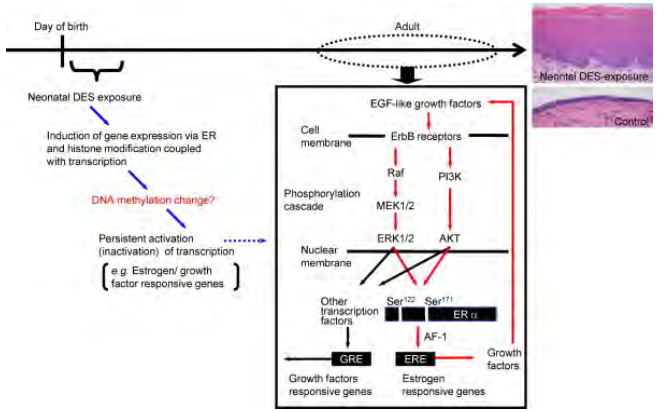




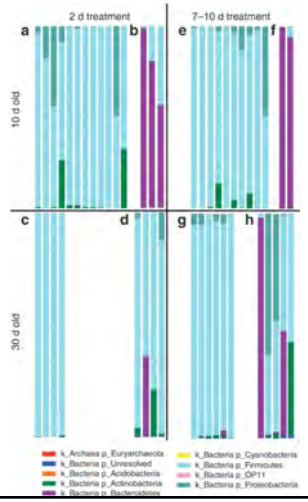
Cannabinoid/endocannabinoid signaling impacts various pregnancy events. Either silenced or augmented cannabinoid/endocannabinoid signaling disturbs pregnancy events including preimplantation embryo development, oviductal embryo transport, implantation, placentation, and parturition. The impact on decidualization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

Birth regulates the initiation of sensory map formation through serotonin signaling.
Toda T, et al.
Dev Cell. 2013 Oct 14;27(1):32-46.

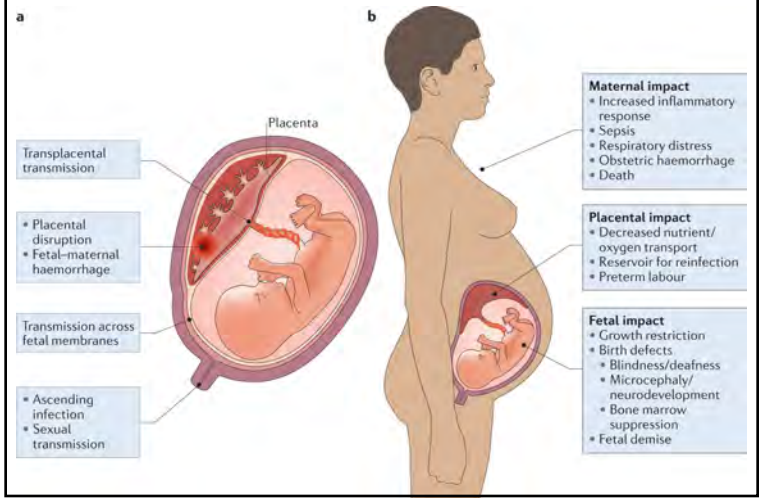




The impact of postnatal antibiotics on the preterm intestinal microbiome.
Dardas M, Gill SR, Grier A, Pryhuber GS, Gill AL, Lee YH, Guillet R.
Pediatr Res. 2014 Aug;76(2):150-8.



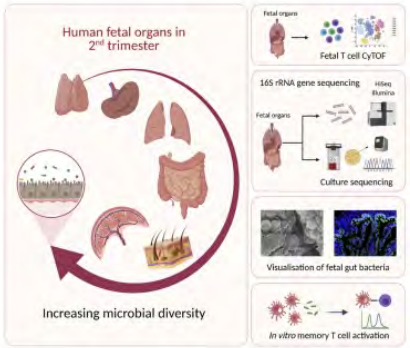
Infections at the maternal-fetal interface: an overview of pathogenesis and defence.
Megli CJ, Coyne CB.
Nat Rev Microbiol. 2022 Feb;20(2):67-82.



Microbial exposure during early human development primes fetal immune cells.
Mishra A, Lai GC, Yao LJ, et al.
Cell. 2021 Jun 24;184(13):3394-3409.e20.

Highlights

- Human fetuses in 2nd trimester show T cell diversity with effector-memory phenotype
- Fetal organs show diverse bacterial genera that can be cultured

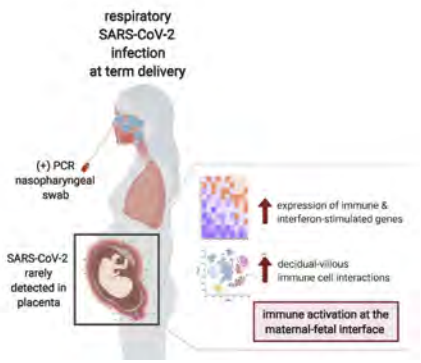


threads are visualized in 14-

emory T cell activation in fetal

In brief
Analysis of human fetal tissues and the placenta in the 2 nd trimester of gestation identifies live bacterial strains that are able to induce the activation of memory T

Maternal respiratory SARS-CoV-2 infection in pregnancy is associated with a robust inflammatory response at the maternal-fetal interface.
Lu-Culligan A, Chavan AR, Vijayakumar P, et al.
Med (N Y). 2021 May 14;2(5):591-610.e10.



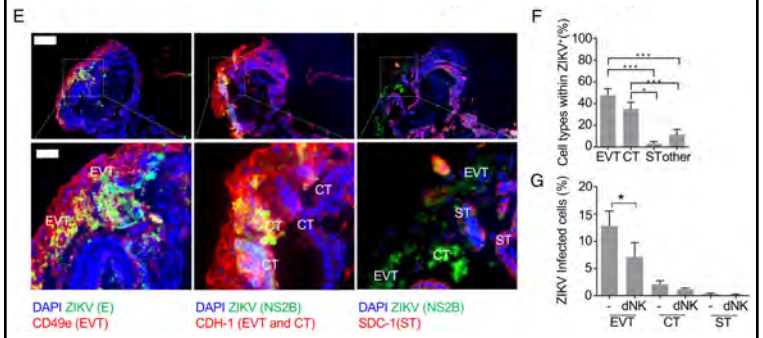
Highlights

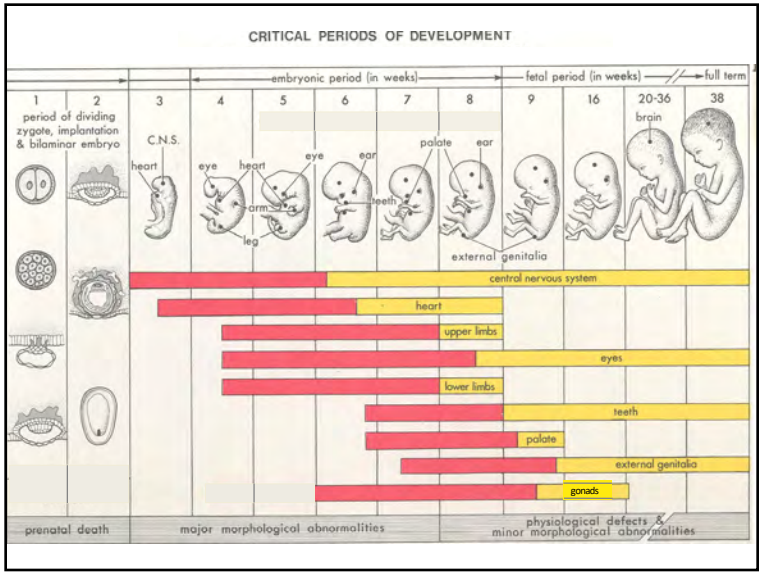
Most women with SARS-CoV-2 at
delivery had no detectable viral
RNA at the placenta

ACE2 is highly expressed in the
placenta during early pregnancy
but rarely at term

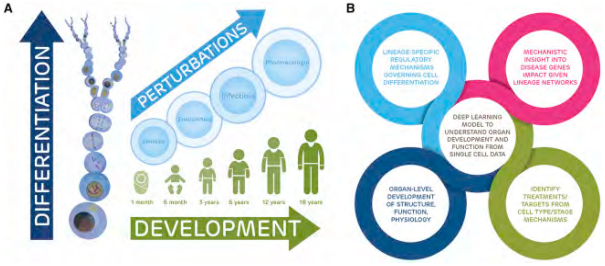
Placental cytotrophoblasts

Decidual NK cells kill Zika virus-infected trophoblasts.
Sen Santara S, Crespo AC, Mulik S, et al.
Proc Natl Acad Sci U S A. 2021 Nov 23;118(47):e2115410118.

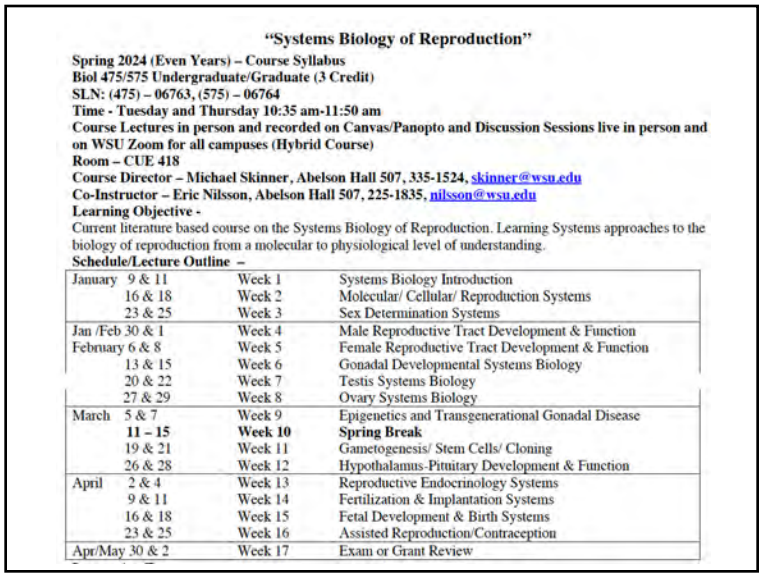




The Pediatric Cell Atlas: Defining the Growth Phase of Human Development at Single-Cell Resolution.
Taylor DM, Aronow BJ, Tan K, Bernt K, et al.
Dev Cell. 2019 Apr 8;49(1):10-29.



Potential Applications for a PCA
The PCA has the potential to map and illuminate the cellular basis of normal and abnormal development, cell- and organ-level differentiation, and compensatory and causal processes of disease.
(A) Healthy children are frequently in a global state of growth activation compared to adults through the effects of growth factors, leading to profound impacts on gene expression and cell and tissue interactions, especially in the context of perturbations due to genetics, acquired somatic mutations, environment, infectious disease, and pharmacologics.
(B) All of the outputs of a pediatric single-cell atlas are interrelated to provide a holistic outlook on how cells and tissues interact, differentiate, and function with each other in times of normal versus disease states.



"Systems Biology of Reproduction"

Spring 2024 (Even Years) – Course Syllabus
Biol 475/575 Undergraduate/Graduate (3 Credit)
SLN: (475) – 06763, (575) – 06764
Time - Tuesday and Thursday 10:35 am-11:50 am
Course Lectures in person and recorded on Canvas/Panopto and Discussion Sessions live in person and on WSU Zoom for all campuses (Hybrid Course)
Room – CUE 418
Course Director – Michael Skinner, Abelson Hall 507, 335-1524, skinner@wsu.edu
Co-Instructor – Eric Nilsson, Abelson Hall 507, 225-1835, nilsson@wsu.edu
Learning Objective -
Current literature based course on the Systems Biology of Reproduction. Learning Systems approaches to the biology of reproduction from a molecular to physiological level of understanding.
Schedule/Lecture Outline –

January	9 & 11	Week 1	Systems Biology Introduction
	16 & 18	Week 2	Molecular/ Cellular/ Reproduction Systems
	23 & 25	Week 3	Sex Determination Systems
Jan /Feb	30 & 1	Week 4	Male Reproductive Tract Development & Function
February	6 & 8	Week 5	Female Reproductive Tract Development & Function
	13 & 15	Week 6	Gonadal Developmental Systems Biology
	20 & 22	Week 7	Testis Systems Biology
	27 & 29	Week 8	Ovary Systems Biology
March	5 & 7	Week 9	Epigenetics and Transgenerational Gonadal Disease
	11 – 15	**Week 10**	**Spring Break**
	19 & 21	Week 11	Gametogenesis/ Stem Cells/ Cloning
	26 & 28	Week 12	Hypothalamus-Pituitary Development & Function
April	2 & 4	Week 13	Reproductive Endocrinology Systems
	9 & 11	Week 14	Fertilization & Implantation Systems
	16 & 18	Week 15	Fetal Development & Birth Systems
	23 & 25	Week 16	Assisted Reproduction/Contraception
Apr/May	30 & 2	Week 17	Exam or Grant Review