Quick guide

Mammalian pregnancy

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What is mammalian pregnancy? Mammalian pregnancy encompasses everything that occurs between fertilization and birth and involves among others internal fertilization, the retention of the developing egg within the female reproductive tract and direct maternal nourishment (matrotrophy).

How did pregnancy evolve in mammals? The first mammals were egg-laying, and, evolutionarily speaking, pregnancy is a relative newcomer. Pregnancy has been described as the superimposition of live birth (viviparity) on mammalian biology. The repurposing of the fetal membranes of egg-laying vertebrates into the placenta of viviparous mammals or the degeneration and loss of yolk genes are just two of the many hallmarks of this remarkable evolutionary transition (Figure 1).

What are the advantages of pregnancy? Why not just lay eggs? It may come as a surprise that it is far from clear what the right answer is. Numerous benefits of pregnancy have been proposed, from protection against thermal extremes, osmotic stress or predation, to the advantages associated with unremitting provisioning of offspring. But there are clear costs associated with pregnancy as well, including increased maternal energy expenditure, reduction in female mobility and fecundity, and risk of injury to both mother and fetus from immunological and inflammatory responses *in utero*, or inadvertent exchange of molecules and cells. It is unlikely that any single factor accounts for the evolution of pregnancy.

So, do all mammals get pregnant? Not quite! For example, the monotreme mammals (think of the platypus) are egg-laying (Figure 1). Monotremes nourish their embryos with yolk, but they also have a transient embryonic structure for maternal and fetal exchange of nutrients and gases, which some consider a rudimentary placenta. In contrast, marsupials (kangaroos and kin) and eutherians (all the rest, including us) give birth to live young (Figure 1). Marsupial and eutherian embryos are also nourished by placentas, but these are much more complex in structure and function; however, the two lineages differ in the particular mix of membranes they use to form their placentas. Of the many important differences between mammals, the length of gestation is a big one: gestation in marsupials and monotremes is extremely short relative to adult lifespan, and much of development is completed after birth with the help of mother's milk. Eutherians lactate as well, but gestation is much longer and their offspring are much further developed when born (Figure 1).

Are you going to tell me that there is also variation within eutherian mammals? Of course! Eutherians express a bewildering range of gestational traits, particularly so in the placenta, arguably the most structurally variable and functionally diverse eutherian organ. For example, humans have a very invasive, disk-shaped

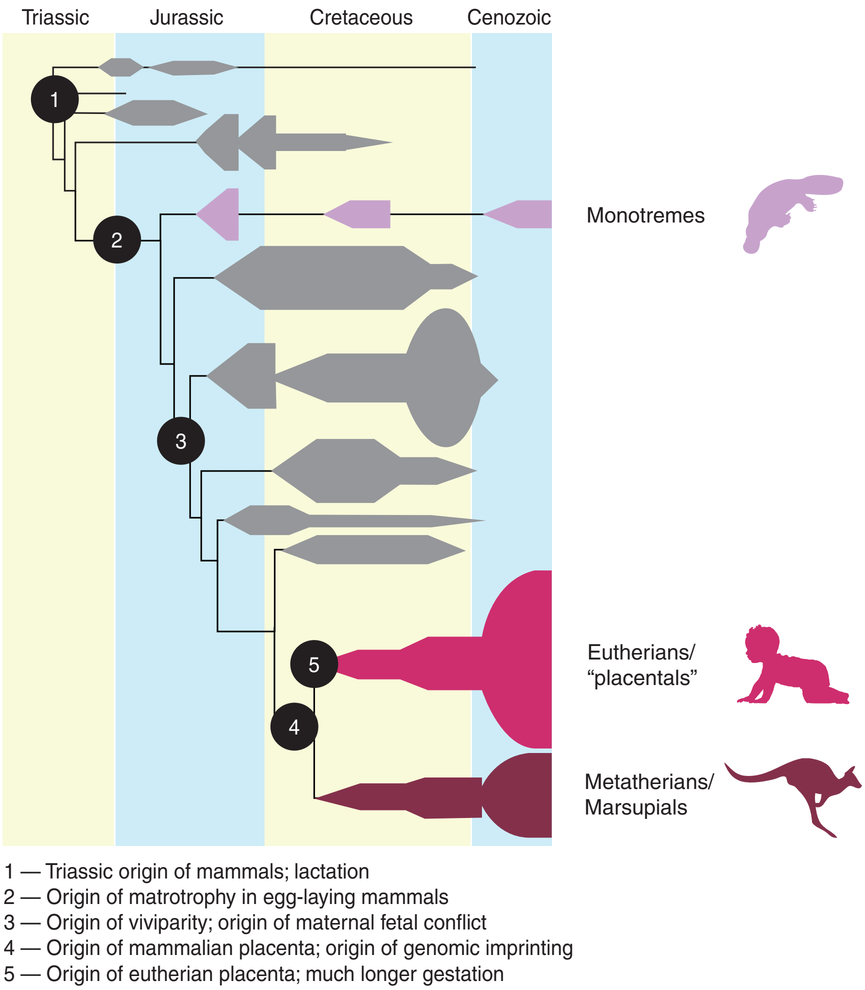

Figure 1. Cartoon depiction of the likely origins of key aspects of mammalian pregnancy.
The diversification of mammalian lineages is based on the diagram by Luo (2007, *Nature*, 450: 1011–1019), redrawn by permission from Macmillan Publishers Ltd: Nature, copyright 2007. The width of branches is illustrative of the taxonomic diversity of each lineage over time. Extinct lineages are shown in gray and their names have been omitted; the three extant lineages (monotremes, eutherians, and marsupials) are shown in different colors. All animal silhouettes were obtained from http://phylopic.org and used under the Creative Commons Attribution 3.0 Unported license. Platypus and kangaroo images were created by Sarah Werning; human baby image was created by Andrew A. Farke.

placenta that is bathed directly in maternal blood. And your canine or feline friend, with whom you may share a house or perhaps a bed? A completely different placenta in almost every respect. It is as if you were interested in planting a garden, and as you shopped for plants, you discovered that nearly every type of plant required water from its own peculiar garden hose.

Why so much variation? Placental diversity is organized along several interrelated dimensions having to do with its structure and the relationship between maternal and fetal circulatory systems. One long-standing idea has been that variation in the maternofetal interface must reflect the differing physiological needs of pregnancy across organisms. Certain placental types might be better at extracting maternal resources, for example, and groups with energetically 'expensive' pregnancies might require such placentas. But it turns out that it is not quite so simple. Recent phylogenetic analyses indicate that, in some eutherian mammals, what might seem to be more efficient placentae for nutrient transfer have been replaced with placentae that are well-separated from the maternal circulation, or have a smaller area of contact with maternal tissues.

That does seem odd. Isn't pregnancy optimized for reproduction? Maybe not quite. It is only during pregnancy that the cells of two genetically distinct individuals come into such prolonged and intimate proximity. Live birth opens the door for 'negotiations' between the developing fetus and the mother over provisioning *in utero*, something not possible in oviparous species. Since viviparity requires a significant investment of maternal resources into fetal growth, conflict can occur because the fetus only shares half of its genes with its mother. In certain situations, the paternally and maternally derived genes in the fetus can 'disagree' with the amount of maternal provisions the fetus receives, favoring greater investment than the mother would otherwise provide.

What evidence is there for conflicts in pregnancy? An unusual fraction of genes expressed in the eutherian placenta is imprinted, and in particular genes involved in nutrient transfer. Imprinted genes show bias in the expression of one allele over the other based on the parent each allele came from. For these imprinted genes, alleles inherited from the dad tend to promote fetal growth, whereas those from the mom tend to control it. Genomic imprinting apparently is not present in monotremes, and seems to have evolved in concert with placentation in marsupials and eutherians (Figure 1). In this light, the evolution of non-invasive placentation in organisms with expensive investment strategies might be seen as a means to manage the perils of fetal demands. Less invasive placentation transfers greater control over investment to the pregnant mother; in effect, a small step back towards the relative conflict-free bliss of egg-laying.

It's all conflict then, and no cooperation? Not at all. Pregnancy clearly works most of the time, and there are ingenious feats of cooperation at the interface between mother and fetus. For example, following implantation, the uterine lining of some mammals forms a temporary tissue barrier on which the fetal placenta will attach and grow. This barrier nourishes the embryo, regulates the interaction between maternal and fetal tissues, while protecting the fetus from the maternal immune system. In some mammals, such as elephant shrews, bats, and the great apes (including us), this process occurs spontaneously, in anticipation of implantation; when fertilization does not take place, the consequence is menstruation. On the fetal side, specialized trophoblast cells with secretory properties fuse to form an unbroken multinucleate outer sheath or syncytium that entirely envelops the placenta, helping to protect it and the developing fetus from the maternal immune system. Without these cells, both mother and fetus would be at risk of a damaging immune reaction. Amazingly, formation of this sheath comes courtesy of domesticated viral genes that express cell fusion-promoting proteins in fetal trophoblast cells, helping to convert these into a syncytium. Have you thanked your retroviruses today?

I have now! But what is special about pregnancy in humans? Human babies have big brains when they are born. However, relative to adult brain size, their brains are actually smaller than other primates, and consequently, at the time of birth they are behaviorally at an earlier developmental stage than what might seem optimal. Shouldn't human pregnancy be longer than nine months? Evolutionary anthropologists have long hypothesized that this 'obstetric dilemma' has something to do with our bipedalism and how it constrains the pelvic birth canal. The relative immaturity of human babies, they hypothesize, is a solution to the trade-off between having a big brain and walking upright. A competing theory is that birth timing is set by the point at which it becomes metabolically inefficient or even impossible for the mother to nurture the fetus within her uterus, relative to the provisioning she could accomplish after birth. Whatever the explanation, the factors that determine birth timing are clearly important in humans; pregnancy complications such as pre-eclampsia, pre-term birth, and spontaneous abortion have all been associated with defective placentation and dysregulation of birth timing. A key to understanding and solving some of the most pressing health issues in human pregnancy lies in a better understanding of how pregnancy evolved, and the adaptations, constraints, and conflicts that have shaped mammalian gestation.

Where can I find out more?

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