**The evolutionary significance of placental interdigitation in mammalian reproduction: contributions from comparative studies**

Isabella Capellini

Address:

Department of Biological Sciences, University of Hull

Cottingham Road, Hull

HU6 7RX (U. K.)

Phone: +44-(0)1482-46-5508

Email to: I.Capellini@hull.ac.uk

## Abstract

The placenta is fundamental to mammalian reproduction and is surprisingly diverse in gross morphology among species. Whether and how this diversity affects maternal investment and fetal growth is still poorly understood. Contrary to suggestions that highly invasive hemochorial placentation is beneficial to fetal development, recent comparative studies have revealed that interdigitation – the degree of contact between maternal and fetal tissues at the area of exchange – strongly influences fetal growth rates. Species with labyrinthine placentae give birth to neonates of similar size to those of species with villous or trabecular placentae but in less than half the time. These findings suggest that there might be tradeoffs between fetal growth rates (higher with greater interdigitation) and gestation time (shorter with greater interdigitation), in association with type of interdigitation. Such tradeoffs might be the results of maternal-offspring conflict over the allocation of maternal resources, with paternal genes favouring greater interdigitation and so higher fetal growth, and maternal genes responding by reducing gestation time. These results emphasize the role of interdigitation as a means to increase the surface area for exchange, and are consistent with within species studies demonstrating that a higher surface area for exchange is associated with heavier neonates. Further studies could investigate the role of other traits in the evolution of placental diversity and their impact on fetal development.

**Keywords**: comparative placentation; phylogenetic comparative methods; parent-offspring conflict; evolution; phylogeny; fetal development.

## Introduction

The mammalian placenta is central to reproduction, being responsible for supporting fetal growth via transfer of nutrients and oxygen from the mother to the fetus, and for disposing of fetal waste products. It is formed by the contact of extra-embryonic tissues – the chorion and the yolk sac in marsupials, and the chorion and allantois in placental (eutherian) mammals - with maternal uterine tissues (1-6). Within this general framework, however, the placenta exhibits great interspecific diversity in gross morphology (1-5). In eutherian mammals the placenta can be classified, for example, by its shape (the number and distribution of the areas for nutrient exchange on the placental surface), invasiveness (the number of maternal tissue layers separating maternal blood from fetal tissues), interdigitation (the degree of contact between fetal and maternal tissues at the areas for nutrient exchange), placental weight relative to the neonatal weight, and the relative direction of maternal and fetal blood flows (1-5). An open question is whether placental morphology affects the rate of transplacental nutrient transfer and, as a result, fetal development, ultimately leading to the diversity in life history traits that mammals exhibit. Here I focus on the contribution of recent phylogenetic comparative studies to answering this question and investigating the evolutionary history of placental diversity, and argue that the role of placental interdigitation has been mostly overlooked but may provide an important avenue for future studies. I will first briefly present two major hypotheses proposed for the evolution of placental diversity, next discuss studies on the role of interdigitation in fetal growth, and the evolutionary history and plasticity of interdigitation, and lastly propose that future studies could focus on the evolution and implications of other placental traits for maternal investment and fetal development.

## Maternal-offspring interactions: mutual advantage and conflict

What are the selective pressures responsible for the evolution of the morphological diversity in placentation? What are the implications of such diversity for fetal growth and maternal reproductive investment? Two non-mutually exclusive hypotheses have been proposed to answer these questions. The mutual advantage hypothesis holds that some placental characteristics enhance the rate of nutrient transfer, ultimately benefitting both the reproductive success of the mother and the development of the fetus (7,8). Under this hypothesis, the placenta is viewed as part of a cooperative enterprise between mother and fetus in which fetal requirements are optimized in consideration of maternal 'ability' to support fetal growth. Among placental traits that vary across species, invasiveness has attracted the most attention in comparative studies of placentation. Under this hypothesis, for example, the direct contact of fetal tissues with maternal blood in hemochorial placentae is considered crucial to improve fetal uptake of nutrients when compared to the non-invasive epitheliochorial placentation with intact uterine tissues separating maternal blood and fetal membranes. This hypothesis thus predicts that fetal growth rates will be higher in association with hemochorial placentation (9). As a corollary of this, early researchers considered the epitheliochorial placentation ancestral and hemochorial placentation derived in eutherian mammals (7,10); however, this suggestion is not supported by recent comparative analyses (see below) (11-15).

Alternatively, the parent-offspring conflict hypothesis suggests that the great diversity in placentation evolves as a consequence of an arms race between maternal and paternal genes over the allocation of maternal resources to the fetus (16,17). To maximize her lifetime reproductive success (i.e. her fitness), a female mammal needs to allocate her resources to one or more offspring in her present litter while keeping some resources for her future offspring. Conversely, for each offspring and its father, it is more beneficial that the mother devotes all her resources to that

single offspring. Thus, while it is of interest to all parties that the offspring receives sufficient resources to grow, survive, and subsequently reproduce successfully, there is a conflict between mother and offspring over the allocation of *additional* maternal resources beyond this point (18-20). In other words, a conflict between mother and offspring arises because the lifetime reproductive benefits of the mother are greater if she invested in new offspring than if she continued to invest in the current offspring once the resources allocated to the current offspring are sufficient for their survival. Postnatally, maternal-offspring conflict affects behaviours such as begging, used by the offspring to induce the mother to provide further resources, and is well documented in mammals at weaning time when mothers may also display aggressive behaviours towards their own offspring that attempt to suckle (18). Moreover, suckling bout duration and weaning age are shorter in females that are already pregnant while still lactating, and depend on maternal state not on offspring development and requirements (e.g. 21-23). The maternal-offspring conflict is dependent on the relatedness among siblings (present and future) and is exacerbated by sibling competition, particularly when the offspring are sired by different fathers as this reduces the relatedness among them (16,18,20,24). In a seminal paper, Haig (17) developed the argument that a maternal-offspring conflict is already present during pregnancy and manifests itself via hormonal communication between mother and fetus. Specifically, in species with hemochorial placentation the fetus can release hormones directly into the maternal blood stream to manipulate maternal allocation of resources and induce her to release more nutrients (for details see 17,25). Maternal-offspring conflict may explain a large number of puzzling facts of placentation and pregnancy that do not fit with the predictions of the mutual advantage hypothesis, from genomic imprinting and aspects of hormonal communication between mother and fetus, to the evolution of placental diversity, with a variety of traits that arise under antagonistic selection pressures favouring one party being followed by counter-adaptations to serve the interest of the other party

(for additional details see 16,17,20). Under this hypothesis, for example, the hemochorial placentation is interpreted as a condition of fetal advantage given that the fetus can release hormones directly into the maternal blood stream; conversely the epitheliochorial placentation is viewed as a condition of maternal advantage in which the fetus can 'manipulate' the release and allocation of maternal resources less easily because three maternal tissue layers separate the extra-embryonic membranes from maternal blood (16,17).

Both the mutual advantage and the maternal-offspring conflict hypotheses rest on the key assumption that the gross morphology of the placenta influences the rate of nutrient transfer, which in turn determines fetal growth rates. However, the interpretation of associations between morphology, nutrient transfer rates and fetal growth rates, varies between the two hypotheses, such that in the mutual advantage hypothesis higher fetal growth rates are the result of both maternal and fetal advantage and 'cooperation', while in the conflict hypothesis they are also the evolutionary consequence of an arms race between maternal and paternal genes (7,16,17). The assumption that placental structure ultimately determines fetal growth has been tested mostly with regard to placental invasiveness, predicting higher fetal growth rates with hemochorial placentation when compared to less invasive placentae (8,9,26,27). Contrary to these predictions, however, several comparative studies have concluded that invasiveness has no impact on fetal growth rates (8,26,28). Suggestions that an invasive placentation is particularly beneficial for fetal brain growth, because the brain is a highly expensive organ to grow and maintain (9), are also not supported (8,28).

## Interdigitation is associated with fetal growth rates

Surprisingly, little attention has been paid to diversity in other placental traits, such as interdigitation, that may have a great impact on nutrient transfer rates and fetal

growth. Interdigitation refers to the degree of contact between maternal and fetal tissues at the areas of exchange (1-4). In the least interdigitated villous placentae, such as those of primates, the areas for nutrient exchange are made of branched villi, while in more interdigitated placentae the villi are highly branched and fused to form a complex, web-like 'labyrinthine' structure, as in the placenta of most rodents. The trabecular interdigitation of some primates (e.g. macaques, *Macaca* sp.) appears to be intermediate between villous and labyrinthine, with less branched villi only partially connected with one another (1-4). The folded placentae (e.g. of pigs, *Sus scrofa*) and lamellar placentae (e.g. of most carnivores), are characterized by the presence of folds (or ridges) and branched folds (lamellae) instead of villi (1-4), and are considered low and highly interdigitated, respectively (15,28). Crucially, as interdigitation increases, the contact between maternal and fetal tissues at the areas of nutrient exchange also increases (3). Thus, for any given placental size, a villous placentation should have the lowest surface area for exchange, a labyrinthine placentation the highest, and a trabecular placentation should be intermediate. As a result, an increase in the degree of interdigitation should ultimately lead to an increase in fetal growth rates (28).

Recent evidence within species – hence across individuals sharing the same type of interdigitation – supports the suggestion that the surface area for exchange is key in fetal development and that a larger surface boosts fetal growth rates. Studies comparing individuals of the same species reveal fine-grained differences given a species-specific placental structure. The horse (*Equus caballus*), for example, has villous interdigitation and mares whose placentae have a greater villous surface give birth to heavier foals after controlling for confounding factors such as mare age, weight, and duration of gestation (3,29). These results should not be surprising. After all, nature has repeatedly shown that when there are needs for enhanced transfer efficiency, as in the lungs or the intestine, folded, lamellar and labyrinthine structures

evolve because they pack a larger surface area for exchange into a relatively small volume. In agreement with intra-specific studies, an early study showed that labyrinthine placentae and villous cotyledonary placentae (with numerous exchange areas with villi) or villous discoid placentae (with one larger exchange area with villi) have a greater surface area for exchange when compared to diffuse villous placentae (in which the exchange occurs over the whole placental surface) (30). Contrary to predictions, though, the smaller surface area for exchange in the diffuse placentae seems to be associated with a heavier total weight of neonate and placenta (30). However, the results of this early study are confounded by the fact that it considered placentae with different types of interdigitation and shape together, it was based on a relatively small sample of species and it lacked control for similarity between species due to their shared ancestry (phylogeny).

The idea that diversity in placental invasiveness and interdigitation in eutherian mammals impacts fetal growth rates has recently been tested using phylogenetic comparative methods (28) that account for similarity between species due to their shared ancestry (31-33). These methods can test for associations between traits, continuous and/or discrete, while accounting for the species' shared evolutionary path, and allow building complex statistical models (31-33). The analysis revealed that labyrinthine or lamellar interdigitation is associated with significantly shorter gestation than villous, trabecular or folded interdigitation in a sample of 109 species representing most mammalian orders (Figure 1) (28). However, neonatal body mass is similar across species with different mode of interdigitation, even after controlling for maternal body size, maturity at birth (altricial or precocial), litter size and gestation time. There is also no evidence that neonatal brain mass in mammals varies with type of interdigitation (28). These results indicate that an increase in the surface area for exchange with greater interdigitation promotes fetal growth rates such that species with labyrinthine and lamellar placentation give birth to neonates of

similar size to that of species with villous and trabecular interdigitation, but in a much shorter time. The impact of interdigitation on gestation time is large; for example, for a hypothetical female mammal of 10 kg, gestation time is 202 days with a villous, folded or trabecular interdigitation, but only 89 days with a labyrinthine or lamellar interdigitation (a 56% reduction).

Placental invasiveness apparently exhibits similar patterns of association to those found with interdigitation, namely a shorter gestation time in species with hemochorial placentation when compared to less invasive placentae, but no impact of invasiveness on either brain or body mass (28). Crucially, though, the effects of invasiveness disappear when interdigitation and invasiveness are tested together, indicating that interdigitation and not invasiveness is the key factor in fetal growth rate. Within a subsample of species with hemochorial placentation but different in interdigitation, labyrinthine placentae are again associated with shorter gestation time (28). Although other factors are likely to be important, a villous interdigitation helps explain why humans have a relatively long gestation time (11).

Capellini et al. (28) tested the central assumption of the hypothesis that placental gross morphology impacts maternal investment and fetal growth rates and revealed the key role of placental interdigitation while undermining the role of placental invasiveness. However, this study cannot discriminate between the mutual advantage and the maternal-offspring conflict hypotheses. Under a mutual advantage hypothesis, the fact that neonatal size is achieved in less than half the time in labyrinthine placentae than with less interdigitated placentae can be interpreted as the result of cooperation between maternal and fetal needs. Alternatively, these findings imply that higher fetal growth rates in labyrinthine placentae are traded-off against shorter gestation (28). This might be the signature of maternal-offspring conflict over the allocation of maternal resources, such that maternal genes have responded to an increase in fetal growth, promoted by paternal genes, by shortening

gestation time. Indeed, gestation time is shorter in species with high levels of sibling competition, which exacerbates maternal-offspring conflict (24), suggesting that the shorter gestation time in labyrinthine placentae might be the evolutionary result of antagonistic selection pressures (28). Many imprinted genes have a high impact on fetal development, with paternal genes boosting growth and maternal genes restricting it (25,34-38). Thus, the degree of placental interdigitation and gestation time might be under the control of paternal and maternal genes respectively (28) and maternal-offspring conflict models should explicitly incorporate both these factors. While benefits to both parties and conflict are likely to have influenced the evolution of placental diversity, future studies should quantify the relative contribution of each of these processes to the diversity in placental morphology among species and its consequences for fetal development and maternal investment (20).

## Evolutionary history of interdigitation and its plasticity during development

Several studies investigated the evolutionary history of interdigitation. There is no explicit hypothesis regarding the evolutionary history of this trait as most attention has focussed on invasiveness. However, under a mutual advantage hypothesis, one could predict that if the evolution of placental diversity reflects improved nutrient transfer efficiency, a low interdigitated placenta should be ancestral and a labyrinthine interdigitation derived. Contrary to this suggestion, a highly interdigitated labyrinthine interdigitation is likely to be the ancestral condition in eutherian mammals (11,13,15). Moreover, losses of a labyrinthine structure in favour of a villous or trabecular interdigitation are the most frequent and are rarely followed by reversals to a more interdigitated condition (11,13) (Figure 2). Why this is so has yet to be established but it is possible that it reflects, once again, the fact that the placenta is under an intense evolutionary arms-race between maternal and paternal genes over maternal resource allocation (16,17).

Wildman et al. (11) speculate that nutritional demands and maternal-offspring conflict can explain why other types of interdigitation evolved from an ancestral labyrinthine condition. Specifically, these authors suggest that a labyrinthine interdigitation is more costly for the mother as estimated by her daily energetic investment into the fetus and placenta, and, conversely, that a villous interdigitation enables her to sustain a pregnancy for longer but with reduced daily energetic demands. This intriguing hypothesis has yet to be tested. However, this idea is consistent with the suggestion that maternal energetic investment and nutrient allocation to the fetus and placenta is very high and is second only to the investment in maternal central nervous system (39). If so, an increase in surface area for exchange in labyrinthine placentae should then lead to higher metabolic costs of pregnancy when compared to less interdigitated placentae. In this regard, Capellini et al. (28) suggested that environmental conditions might also play a role in the evolution of placental diversity by determining the timing, duration and amount of resources available to the mother during gestation and lactation.

The developmental path of interdigitation during pregnancy generally progresses from villous to trabecular or labyrinthine in species with more interdigitated placentae; however in humans, a labyrinthine-like structure appears during the very early stages of gestation, but becomes villous secondarily (3, p.16). The placenta can respond to the conditions that the mother faces throughout gestation (e.g. diet, lifestyle). For example, reduced food intake in pregnant women leads to an increase in placental weight – a proxy for the actual surface area for exchange - relative to neonatal weight, particularly during the first trimester of gestation, while changes in placental weight in response to reduced nutrient availability are more constrained and less 'efficient' during the second and third trimester (e.g. 40,41). This is partly due to the different developmental trajectories of the placenta and fetus, with the placenta growing quicker early in gestation, reaching

its term size sooner and then plateauing, while the fetus exhibits an exponential growth curve with most of the birth mass being obtained during the second part of gestation (reviewed in 42); therefore plastic responses in placental structure early in gestation can better compensate for changes in maternal conditions than later during gestation. Plastic responses in the structure of the placenta, however, may not compensate fully for reduced resources and neonates are born lighter. The surface area for exchange (rather than the whole surface or weight of the placenta) seems to be central in this regard, being reduced or unable to compensate sufficiently for limited maternal resources (e.g. 43-45). Understanding the evolution of plasticity, whether plastic responses are consistent across species and to what extent, represents a new challenge to which comparative studies can greatly contribute once detailed data for numerous species become available. Similarly, developmental pathways that vary among species can be studied at a comparative level. The developmental trajectory of invasiveness at term, for example, varies across species (46). In some bats with term hemochorial placenta the early placenta is endotehliochorial, while in many species the type of invasiveness is consistent across the whole gestation (46). Why this happens in some species but not others, what implications this has for fetal growth throughout gestation, what genes are involved and how they evolved, are important questions whose answers will greatly enhance our knowledge of how development and evolution interact and determine the diversity in fetal development among species.

## Beyond invasiveness and interdigitation

Altogether, comparative studies have revealed that changes in the surface area for exchange, that directly impact fetal growth rates, are achieved evolutionarily by structural modifications leading to interspecific differences in interdigitation, while within species the placenta responds plastically to enhance the surface area for exchange in response to maternal conditions. Maternal body mass and interdigitation

together explain approximately 40% of variance in gestation time in mammals (28), thus it is likely that other characteristics of the placenta influence mammalian life history traits. Other traits showing great diversity in the mammalian placenta (1-5) are potentially important for enhancing nutrient or gas exchange, but their evolutionary associations with other placental traits and, crucially, with fetal development and maternal investment, have been little investigated. For example, the direction of maternal blood flow relative to the direction of fetal blood flow might be a key factor since it might affect oxygen and nutrient uptake by the fetus (3,47). Both theoretical models and physiological studies have shown that a countercurrent exchange system, with maternal and fetal capillaries parallel to one another and blood flowing in opposite directions, is the most efficient because it provides the strongest gradient leading to the highest exchange rate in the shortest time interval (2,48). This system is common in other organs, such as the gills of fishes, and is found in the placenta of rodents and lagomorphs. However, other less efficient systems are present in the placenta of some eutherian mammals, such as a crosscurrent system (in carnivores and some primates) and multivillous system (in some primates and ruminants) in which fetal and maternal capillaries are perpendicular to one another (2). The limited data currently available on maternofetal blood flow seem to indicate that a countercurrent system is associated with higher fetal growth, as showed by a marked increase in the neonatal on placental weight ratio; neonates appear to be four times as large per unit placental weight in species with countercurrent system than in species with the least efficient multivillous system (2). This relationship is based on a limited number of species, without controlling for confounding factors such as maternal body mass, gestation time, interdigitation and phylogeny, and it should be re-evaluated when more data become available for a larger sample of species. A recent review on oxygen transport across the placenta concluded that the direction of blood flow has relatively little impact on oxygen uptake, at least when oxygen affinity and capacity of the maternal and fetal bloods are high (47). Systematic examinations

of patterns of associations between placental gross morphology, physiological characteristics (such as oxygen affinity of fetal blood or measures of blood flow), and fetal growth rates across numerous species are necessary to answer questions regarding the diversity of exchanger systems, their role in fetal development and how they evolved together with other placental traits (14).

Trophoblast giant cells represent another example of a trait that deserves further investigation. These cells are mostly found at the tips of fetal villi, they can be binucleate or multinucleate, and appear to produce steroids and other molecules that are released into the maternal side (3,49,50). They increase in number throughout pregnancy in camelids and ruminants, and are also present in the placenta of equids, rodents and lagomorphs (3). Klisch and Mess (51) have recently investigated the evolutionary history of the epitheliochorial placentation in cetartiodactyls (cetaceans and ruminants). They emphasize that diversity in the number and branching pattern of the placentomes (from diffuse placentae to cotyledonary placentae with extensively branched villi) and the presence of trophoblast giant cells in camelids and ruminants might ultimately be the consequence of maternal-offspring conflict. Their comparative analysis revealed that a cotyledonary placenta with highly branched villi is a derived condition and that giant cells evolved independently in camelids and ruminants, but did not evolve in suids, hippos (*Hippopotamus* sp.) and cetaceans. These authors point out that the reduced glucose availability resulting from the evolution of the forestomach in ruminants might exacerbate maternal-offspring conflict over maternal nutrient allocation to the fetus. Specifically, a stricter control of glucose levels by the mother would further escalate the arms race that affects the evolution of placental gross morphology. While the mother would benefit from the evolution of a less ‘efficient’ (as estimated by placental on neonatal weight ratio) cotyledonary placenta from a diffuse placenta (30), the fetus would benefit from the evolution of branched villi and higher number of placentomes to increase the surface

area for exchange, and of giant cells that influence maternal metabolism via release of hormones (51).

Beyond the traits discussed here – interdigitation, maternofetal blood flow interrelations, giant cells – the placenta is variable with respect to numerous traits such as the presence of the areolae and uterine glands including their number, size and structure, the shape and number of the exchange areas (placental shape), the presence of yolk sac placentae and subplacentae at different times during gestation (1-5). All these traits are likely to greatly influence the nutrient uptake by the fetus and the maternal release of nutrients through hormonal communication between mother and offspring, and are therefore potentially under intense antagonistic selection. Traits linked to nutrient transfer should be under strong maternal-offspring conflict and thus exhibit fast evolutionary rates and great interspecific variation (16). Finally, placentation in marsupials has received less attention when compared to eutherian mammals, but is likely to reveal key similarities and differences with findings in other mammals (52-54).

## Conclusions

Comparative studies of placental gross morphology can reveal key patterns of associations between placental traits and fetal development, ultimately leading to better understanding of placental evolution and function. Recent analyses have revealed that a higher degree of interdigitation – but not invasiveness – increases fetal growth rates (28), possibly because greater interdigitation enhances the surface area for exchange of nutrients. While these results highlight the importance of interdigitation in fetal development, it remains unclear why placental invasiveness is so diverse among mammals. Numerous traits vary in the mammalian placenta and are likely to reveal important patterns of association with diversity in life history traits, fetal development and maternal investment strategies. More powerful statistical

phylogenetic methods and the increasing number of new phylogenies can help answer old and new questions in comparative placentation, and can play a major role in understanding the function and physiology of the diverse placental traits and their role in fetal development.

## Acknowledgements

I am grateful to Joanna Setchell and Graham Burton for helpful comments on an earlier version of this paper, Derek Wildman, Robert Barton and Anthony Carter for stimulating discussion, and the organizers of the CTR Annual Trophoblast meeting 2011 in Cambridge for the opportunity to present this work.

## References

1. Mossman H. Vertebrate fetal membranes: comparative ontogeny and morphology, evolution, phylogenetic significance, basic functions, research opportunities. New Brunswick, NJ: Rutgers University Press; 1987.
2. Leiser R, Kaufmann P. Placental structure: in a comparative aspect. Experimental and Clinical Endocrinology 1994;102:122–34.
3. Wooding P, Burton G. Comparative placentation: structures, functions and evolution. Berlin: Springer; 2008.
4. Benirschke K, Burton GJ, Baergen RN. Pathology of the human placenta. 6th ed. Springer; 2012.
5. Carter AM, Enders AC. Comparative aspects of trophoblast development and placentation. Reprod. Biol. Endocrinol. 2004;2:46.
6. Carter AM. Evolution of the placenta and fetal membranes seen in the light of molecular phylogenetics. Placenta 2001;22(10):800–7.
7. Haeckel E. Keimesgeschichte des Menschen. Leipzig: Engelmann; 1903.
8. Sacher A, Staffeldt EF. Relation of gestation time to brain weight for placental mammals: implications for the theory of vertebrate growth. Am. Nat.

1974;108:593–612.

9. Elliot MG, Crespi B. Placental invasiveness and brain-body allometry in eutherian mammals. J. Evol. Biol. 2008;21(6):1763–78.
10. Luckett W. Cladistic relationships among higher primate categories: evidence of the fetal membranes and placenta. Folia Primatol. 1976;25:245–76.
11. Wildman D, Chen C, Erez O, Grossman L, Goodman M, Romero R. Evolution of the mammalian placenta revealed by phylogenetic analysis. Proceedings of the National Academy of Sciences. 2006;103(9):3203–8.
12. Vogel P. The current molecular phylogeny of Eutherian mammals challenges previous interpretations of placental evolution. Placenta 2005;26(8-9):591–6.
13. Elliot MG, Crespi B. Phylogenetic evidence for early hemochorial placentation in eutheria. Placenta 2009;30(11):949–67.
14. Mess A, Carter AM. Evolution of the placenta during the early radiation of placental mammals. Comparative Biochemistry and Physiology - Part A: Molecular & Integrative Physiology 2007;148(4):769–79.
15. Mess A, Carter AM. Evolutionary transformations of fetal membrane characters in Eutheria with special reference to Afrotheria. J. Exp. Zool. 2006; 5;306B(2):140–63.
16. Crespi B, Semeniuk C. Parent-offspring conflict in the evolution of vertebrate reproductive mode. Am. Nat. 2004;163(5):635–53.
17. Haig D. Genetic conflicts in human pregnancy. Q Rev Biol. 1993;68(4):495–532.
18. Trivers RL. Parent-offspring conflict. Am Zool. 1974;14(1):249–64.
19. Godfray HC. Evolutionary theory of parent-offspring conflict. Nature 1995;376(6536):133–8.
20. Moore T. Parent-offspring conflict and the control of placental function. Placenta 2012;33(S):S33–6.
21. Pluháček J, Bartoš L, Bartošová J. Mother–offspring conflict in captive plains

zebra (*Equus burchellii*): Suckling bout duration. Applied Animal Behaviour Science 2010;122(2-4):127–32.

22. Rehling A, Trillmich F. Weaning in the guinea pig (*Cavia aperea porcellus*): Who decides and by what measure? Behav Ecol Sociobiol. 2007;62(2):149–57.
23. Maestripieri D. Parent–offspring conflict in primates. International Journal of Primatology 2002;23(4):923–51.
24. Stockley P, Parker GA. Life history consequences of mammal sibling rivalry. Proceedings of the National Academy of Sciences 2002;99(20):12932–7.
25. Petry CJ, Ong KK, Dunger DB. Does the fetal genotype affect maternal physiology during pregnancy? Trends Mol Med. 2007;13(10):414–21.
26. Martin RD. Evolution of placentation in Primates: implications of mammalian phylogeny. Evol Biol. 2008;35(2):125–45.
27. Kihlström J. Period of gestation and body weight in some placental mammals. Comparative Biochemistry and Physiology Part A: Physiology 1972;43(3):673–9.
28. Capellini I, Venditti C, Barton RA. Placentation and maternal investment in mammals. Am. Nat. 2011;177(1):86–98.
29. Allen W, Wilsher S, Turnbull C, Stewart F, Ousey J, Rossdale P, et al. Influence of maternal size on placental, fetal and postnatal growth in the horse. I. Development in utero. Reproduction 2002;123(3):445–53.
30. Baur R. Morphometric data and questions concerning placental transfer. Placenta 1981;Suppl. 2:35–44.
31. Pagel M. Inferring the historical patterns of biological evolution. Nature 1999;401(6756):877–84.
32. Pagel M. Inferring evolutionary processes from phylogenies. Zool Scr. 1997;26(4):331–48.
33. Freckleton R, Harvey P, Pagel M. Phylogenetic analysis and comparative

data: a test and review of evidence. Am. Nat. 2002;160(6):712–26.

34. Vrana PB. Genomic imprinting as a mechanism of reproductive isolation in mammals. J Mammal. 2007;88(1):5–23.
35. Bressan FF, De Bem THC, Perecin F, Lopes FL, Ambrosio CE, Meirelles FV, et al. Unearthing the roles of imprinted genes in the placenta. Placenta 2009;30(10):823–34.
36. Ng HK, Novakovic B, Hiendleder S, Craig JM, Roberts CT, Saffery R. Distinct patterns of gene-specific methylation in mammalian placentas: implications for placental evolution and function. Placenta 2010;31(4):259–68.
37. Reik W, Constancia M, Fowden A, Anderson N, Dean W, Ferguson-Smith A, et al. Regulation of supply and demand for maternal nutrients in mammals by imprinted genes. J. Physiol. 2003;547(1):35–44.
38. Angiolini E, Fowden A, Coan P, Sandovici I, Smith P, Dean W, et al. Regulation of placental efficiency for nutrient transport by imprinted genes. Placenta 2006;27:98–102.
39. Hammond J. Physiological factors affecting birth weight. Proc. Nutr. Soc. 1944;2:8–12.
40. Roseboom TJ, Painter RC, de Rooij SR, van Abeelen AFM, Veenendaal MVE, Osmond C, et al. Effects of famine on placental size and efficiency. Placenta 2011;32(5):395–9.
41. Alwasel SH, Abotalib Z, Aljarallah JS, Osmond C, Alkharaz SM, Alhazza IM, et al. Changes in placental size during Ramadan. Placenta 2010;31(7):607–10.
42. Redmer DA, Wallace JM, Reynolds LP. Effect of nutrient intake during pregnancy on fetal and placental growth and vascular development. Domestic Animal Endocrinology 2004;27(3):199–217.
43. Roberts CT, Sohlstrom A, Kind KL, Earl RA, Khong TY, Robinson JS, et al. Maternal food restriction reduces the exchange surface area and increases the barrier thickness of the placenta in the guinea-pig. Placenta 2001;22(2-

3):177–85.

44. Schlabritz-Loutsevitch N, Ballesteros B, Dudley C, Jenkins S, Hubbard G, Burton GJ, et al. Moderate maternal nutrient restriction, but not glucocorticoid administration, leads to placental morphological changes in the baboon (*Papio* sp.). Placenta 2007;28(8-9):783–93.
45. Rutherford JN, Tardif SD. Developmental plasticity of the microscopic placental architecture in relation to litter size variation in the common marmoset monkey (*Callithrix jacchus*). Placenta 2009;30(1):105–10.
46. Enders AC, Carter AM. The evolving placenta: convergent evolution of variations in the endotheliochorial relationship. Placenta 2012;33(5):319–26.
47. Carter AM. Evolution of factors affecting placental oxygen transfer. Placenta 2009;30:19–25.
48. Faber J, Thornburg K, Binder N. Physiology of placental-transfer in mammals. Am Zool. 1992; 32:343–54.
49. Wooding F, Ozturk M, Skidmore J, Allen W. Developmental changes in localization of steroid synthesis enzymes in camelid placenta. Reproduction 2003;126(2):239–47.
50. Olivera L, Zago D, Leiser R, Jones C, Bevilacqua E. Placentation in the alpaca *Lama pacos*. Anatomy and Embryology 2003;207(1):45–62.
51. Klisch K, Mess A. Evolutionary differentiation of cetartiodactyl placentae in the light of the viviparity-driven conflict hypothesis. Placenta 2007;28(4):353–60.
52. Freyer C, Zeller U, Renfree MB. The marsupial placenta: a phylogenetic analysis. J. Exp. Zoolog. Part A Comp. Exp. Biol. 2003;299(1):59–77.
53. Renfree MB. Marsupials: placental mammals with a difference. Placenta 2010;31(S):S21–6.
54. Freyer C, Renfree MB. The mammalian yolk sac placenta. J. Exp. Zool. 2009;312(6):545–54.

## List of figures

**Figure 1**. Gestation time and interdigitation in mammals. Labyrinthine placentation (red) is associated with a shorter gestation time relative to villous (black) and trabecular (orange) placentae, after controlling for maternal size. Trabecular and villous placentae do not significantly differ in gestation time. Modified after (28).

**Figure 2**. Parsimony reconstruction of the evolutionary history of placental interdigitation in mammals. The ancestral character state is labyrinthine placentation in eutherian mammals; losses of highly interdigitated condition in favour of less interdigitated conditions are more common than reversals. From (11).