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Fetal signaling through placental structure and endocrine function: illustrations and implications from a non-human primate model

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Abstract

The placenta is a transmitter of fetal need and fetal quality, interfacing directly with maternal physiology and ecology. Plasticity of placental structure and function across the developmental timeframe of gestation may serve as an important tool by which a fetus calibrates its growth to shifting maternal ecology and resource availability, and thereby signals its quality and adaptability to a changing environment. Signals of this quality may be conveyed by the size of the placental interface, an important marker of fetal access to maternal resources, or by production of placental insulin-like growth factor II, a driver of fetoplacental growth. Litter size variation in the common marmoset monkey offers the opportunity to explore intrauterine resource allocation and placental plasticity in an important non-human primate model. Triplet marmosets are born at lower birth weights and have poorer postnatal outcomes and survivorship than do twins; triplet placentas differ in placental efficiency, microscopic morphology, and endocrine function. Through placental plasticity, triplet fetuses are able to adjust functional access to maternal resources in a way that allows pregnancy to proceed. However, the costs of such mechanisms may relate to reduced fetal growth and altered postnatal outcomes, with the potential to lead to adverse adult health consequences, suggesting an important link between the placenta itself and the developmental origins of health and disease.

Infants and juveniles of species with high degrees of parental investment have a rich vocal and behavioral vocabulary with which to communicate salient cues of need (Maestripieri 2001; Parker and others 2002); in response, parents make investment decisions on the basis of these cues relative to all other offspring, current or future (Trivers 1974). Such communication is a requisite component of intense infant care, and as much as it conveys need, it conveys quality. The failure of an offspring to meet some communicatory threshold may be met with the failure of the parent to continue offering nourishment and protection in the interest of funneling investment either in extant offspring or in opportunities to produce future offspring.

This element of conflict and resolution of agendas between parent and offspring is an extension of a similar communicatory dissonance during mammalian pregnancy, where the fetus is dependent on sustained maternal support but cannot avail itself of behavioral repertoires to convey need and quality. In this case, it is the placenta, which derives from the same fertilized egg as does the fetus, that mediates maternal-fetal communication (Haig 1996). In the anthropoid primate placenta, metabolically and hormonally active tissue of

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embryonic origin, the syncytiotrophoblast, is in direct contact with the maternal circulation (Mossman 1987). Thus, the placenta is an extrasomatic fetal organ. It is a transmitter of fetal need and fetal quality, interfacing directly with maternal physiology and ecology. This anatomical arrangement thus casts the fetus as having direct agency in the framing and maintenance of the intrauterine environment, via plasticity of placental structure and function across the developmental timeframe of gestation.

In this paper, I will focus on the plasticity of placental function as a means of communicating cues of both maternal ecology and fetal quality. To do this, I will first review basic placental development and function, particularly as is relevant to a signaling framework. I will then review previous research I and colleagues have conducted on the fetoplacental unit of the common marmoset monkey (*Callithrix jacchus*), a neotropical primate species with variable litter size, shared placentation, and high degrees of parental care. In particular, I will discuss the relations of litter size in the marmoset to maternal mass, placental size, placental microscopic architecture, and the production of placental insulin-like growth factor-II (IGF-II), a hormone responsible for autocrine and paracrine regulation of placental growth and function, and which may also play an important role in fetus-to-mother signaling. Finally, I will frame these findings in broader perspective, as they may contribute to an understanding of the role of intrauterine endocrine processes underlying developmental origins of health, disease, and life history.

PRIMATE PLACENTATION: IMPLICATIONS FOR FETAL SIGNALING

Embryonic origins of the placenta

The placenta develops from the junction of the outer cell mass of the developing blastocyst early in embryonic development and the uterine wall (Mossman 1987). The outer cell mass forms a hollow sphere surrounding the inner cell mass, the cluster of cells that will give rise to the embryo itself (Figure 1). This outer shell is comprised of placental precursor tissue, the trophectoderm, which will ultimately give rise to the differentiated placenta. All of the anthropoid primates have hemochorial placentation, meaning that, at term, fetal and maternal blood are separated by only three tissue layers: fetal capillary endothelium, fetal mesoderm, and syncytiotrophoblast (Luckett 1974; Mossman 1987). Hemochorial placentation may provide the greatest opportunity for the fetus to manipulate maternal investment upwards because it entails the direct contact between fetal tissue and maternal circulation (Crespi and Semeniuk 2004).The fetus employs indirect processes that release signaling entities into fetal circulation and then diffuse through the three layers of the hemochorial placenta into maternal circulation. Importantly, fetal tissue in the form of the syncytiotrophoblast is also in direct contact with maternal circulation, and thus the developing fetus has direct access to maternal neuroendocrine processes that regulate resource allocation because any endocrine signals produced by the placental interface can enter the maternal bloodstream directly (Figure 2). This is not to suggest that the mother does not have physiological tools by which she can calibrate investment in her fetus; rather, the aim here is to demonstrate that the fetus takes an active role in a dialogue regarding intrauterine resource allocation.

Insofar as fetuses pursue strategies of resource allocation that may conflict with maternal self-interest, variation in placental structure or function is the expected manifestation of such divergent strategies (Haig 1993). Differences in placental structure may reflect feto-maternal conflict over resources. Resource allocation conflicts can arise due to maternal disease or malnutrition, changes in litter size above or below the norm, and genetic abnormalities; placentas from troubled pregnancies may present structural changes that enhance metabolic function in order to maintain fetal growth and pregnancy viability. Structural responses of the placenta that maintain fetal growth in the face of suboptimal gestational conditions are

theoretically within the domain of fetal agency because placental tissue has the same developmental derivation as fetal tissue, and the same genomic identity. Haig (1993) suggests that when faced with maternal restriction of nutrients, a fetus might increase its gross allocation of placental tissue, i.e. increase placental mass relative to fetal mass, as a direct means of altering its access to maternal resources, via hormonal signaling that communicates growth state and need (Haig 1996).

Placental plasticity in the face of changing maternal ecology

The intrauterine environment encountered by the fetus is largely a function of maternal ecology: the nexus of nutritional, metabolic, endocrinological, infectious, genetic, epigenetic, and sociobehavioral inputs that coalesce into a particular pregnancy. Fetal development exhibits an exquisite plasticity in response to changes in this maternal ecology across gestation (e.g. variation in birth weights as a result of maternal dietary composition (Moore and others 2004). A relatively new research program, the developmental origins of adult health and disease, places at its foundation the links between the intrauterine environment, birth weight, and adult outcomes (Barker 2004; Gluckman and others 2007; Godfrey and Barker 2000; Kuzawa 2005). It is critical to this paradigm to note that the placenta mediates fetal reactions to a changing maternal ecology via functional and structural plasticity throughout gestation (Godfrey 2002).

Amino acid metabolism by the placenta is critical for fetal growth, as amino acids are required for protein synthesis and accretion in the fetus (Regnault 2002). Amino acids are actively transported from maternal to fetal circulation by transporters located in the syncytiotrophoblast (Cetin and others 2001; Jansson 2001). Amino acid transport function is reduced in intrauterine growth restriction (Cetin 2003), hypoxia (Nelson 2003), and maternal smoking (Sastry 1991), and increased in macrosomia related to gestational diabetes (Jansson and others 2006), conditions which all have bearing on fetal development and outcome. Maternal condition thus has an impact on fetal growth through disruption of function of amino acid transport at the maternal-fetal interface (Roos and others 2009). In fact, Jansson and Powell (2006) have suggested that placental metabolic dysfunction in response to maternal condition may be the primary determinant, as opposed to being a consequence, of fetal growth disruption. They describe the placenta as a “nutrient sensor” conveying information in the form of amino acid transport rates to the fetus regarding the availability of maternal resources, with the consequence of appropriately calibrating fetal growth (Jansson and Powell 2006).

Maternal ecology can leave a morphological signature in the placenta as well, a signature that sometimes reveals temporality. For example, maternal nutrient restriction early in gestation, during peak placental growth, results in a relative placental overgrowth in rats (Doherty and others 2003; Langley-Evans and others 1996; Woodall and others 1996), sheep (Robinson and others 1994), and pigs (Pond and others 1991). Conversely, the same restriction applied later in gestation, after maximum placental growth velocity has been achieved yields a reduction in relative placental growth (Fowden and others 2006). In humans, extreme nutrient restriction due to wartime famine (i.e. Dutch Hunger Winter) yielded similar patterns of placental size relative to the timing of maternal nutritional restriction (Lumey 1998).

Shifting patterns of the structural correlates of placental function do not provide direct measures of function itself but are an important means by which to understand how constraints of the maternal ecological landscape are transmitted to the fetus and translated into fetal response and outcomes. Alterations in maternal energy balance and health, as well as fetal growth and development, have a direct impact on microscopic placental structure (Mayhew and Jairam 2000; Mayhew and others 2003; Roberts and others 2001; Zamudio

2003). Diabetes expands the placental compartment that houses maternal blood, the intervillous space (Mayhew and Jairam 2000). High altitude hypoxia is associated with a decrease in the diffusion barrier of the placenta, a mechanism to increase oxygen diffusion (Zamudio 2003). Maternal undernutrition before and throughout pregnancy leads to a reduction of the surface area of the labyrinth (the placental compartment in rodents that is analogous to the villous tree of the human placenta and the trabeculae of the marmoset placenta) and increases the thickness of the exchange membrane at the maternal-fetal interface in the guinea pig placenta (Roberts and others 2001). In baboons, maternal nutrient restriction leads to reductions in villous volume and surface area (Schlabritz-Loutsevitch and others 2007). Changes in the size and shape of the placental interface described here have important consequences in terms of surface area available to the fetus for the extraction of maternal resources and the production of hormonal signals.

Placental IGF-II: signal of fetal growth and development

The primate placenta is a critical site of hormone production during pregnancy, producing steroid hormones such as estrogens and progesterone, and peptide hormones such as chorionic gonadotrophin (CG), corticotrophin-releasing hormone (CRH), and the insulin-like growth factors (IGF) (Murphy and others 2006; Pepe and Albrecht 1995). The IGFs are involved in the regulation of fetal and placental growth (Forbes and Westwood 2008). Umbilical levels of IGF-I and –II increase throughout term and are correlated with fetal and placental weight, and low levels of both are associated with intrauterine growth restriction (Bennett and others 1983; Ong and others 2000). Both IGFs are involved in the proliferation, invasion, and differentiation of the trophoblast (Aplin and others 2000; Chakraborty and others 2002; Han and Carter 2000; Lacey and others 2002; McKinnon and others 2001). In addition, IGF-II may play a particular role in regulating placental amino acid metabolism. In a mouse placental-specific IGF-II knockout model, the surface area of the placenta is reduced at the same time that amino acid transport across the placental interface is increased (Constancia and others 2002). This IGF-II mediated connection between morphology and function could be interpreted as a relevant signal to the mother of fetal growth and demand.

Haig (1996) describes the placenta as an allocrine organ, in that it communicates not only with itself or with its “owner”, the fetus, but also with a genetically individuated entity, the mother. Because of the correlations between placental IGF production and fetal and placental growth and development, the IGF system can be considered a signal of fetoplacental growth state, a signal that is produced by the trophoblast and delivered to the mother directly via immediate adjacency to the maternal circulation. Both IGF-I and IGF-II cross the blood-brain barrier (Reinhardt and Bondy 1994), and there are IGF-II receptors in the adult brain (Wilczak and others 2000). While it is as yet unclear whether the maternal brain receptors are capable of distinguishing maternal from fetal IGF-II (Heidenreich and others 1986; Sasaki and others 1991), the ontogeny of circulating placentally-produced IGF-II suggests that increases or changes in the dynamics in circulating IGF-II over time or state could act as a signal of appropriate fetoplacental growth, integration, and communication.

DISSECTING INTRAUTERINE DYNAMICS VIA PLACENTAL PLASTICITY IN THE COMMON MARMOSET MONKEY

The dynamism of the intrauterine environment across gestation is met with plasticity both in fetal development and placental function. Birth weight is the most studied proxy measure of intrauterine processes regulating the interaction between maternal ecology, but birth weight is an end point, not the process itself. While assaying the human placenta is not impossible, it is difficult in research settings without clinical funding or support. Most of the literature

on the human placenta focuses on clinical aspects of placental function, particularly in reference to pathologies of pregnancy and fetal development. Animal models have provided a rich framework for understanding placental ontogeny, function, and pathology, but differences in placental morphology, reproductive biology, and aspects of parental investment between typical animal models such as rodents or sheep, and humans leave unsatisfying gaps in our understanding of primate-specific fetoplacental adaptations to shifting conditions of intrauterine resource availability. Primate models of the intrauterine environment, with an emphasis on placental function, are needed to build bridges between the clinical and lab animal research. Recently, colleagues and I have conducted a series of studies of the common marmoset placenta, to probe plasticity of the structural correlates of placental function in relation to litter size variation (Rutherford under review; Rutherford and Tardif 2008; Rutherford and Tardif 2009). Litter size variation in the marmoset is a phenomenon with consequences for the potential availability of maternal resources and fetal growth, issues relevant to an understanding of the placenta as a translator of signals of maternal ecology and fetal need.

Maternal ecology and litter size variation in marmosets

The marmosets and tamarins regularly produce litters up to twice per year, making them the most potentially fecund of the primates (Hearn 1985). These are dizygotic offspring (Wislocki 1939), resulting from multiple ovulations. Although twins are the normative litter size, triplets are surprisingly common in captivity. Litter sizes greater than two comprise as much as a third of recent births in the Southwest National Primate Research Center common marmoset colony (Tardif et al. 2003). Gestational length is about 143 days, regardless of litter size. Weights for triplets are lower than for twins at birth (Chambers and Hearn 1985; Jaquish and others 1991), and as early as day 120 of a 143 day gestation (Chambers and Hearn 1985) although total fetal mass produced in a triplet litter is significantly greater (Rutherford and Tardif 2008).

Litter size in captivity is related to maternal nutrition, such that larger females have larger litters, suggesting that it is not impossible for triplet litters to occur in wild callitrichine primate populations during seasons with abundant food supplies, particularly if augmented by a relatively stable resource such as plant exudates (Garber 1984). In the wild, Bales et al. (2001) observed a triplet litter in a population of golden lion tamarins. DNA fingerprinting conducted by Dixson et al. (1992) indicated that three same-aged individuals were siblings, evidence of successful rearing. Though few in number, these observations of triplet litters in wild settings suggests that the ability to conceive and gestate large litters is part of an evolved suite of reproductive flexibility in the callitrichine primates.

Marmoset mothers have finite energy and time resources to devote to infant care, even in the relative abundance of captivity. Human intervention is usually necessary to rear triplets successfully to weaning (Hearn and Burden 1979). Mothers devote a finite amount of time to carrying and weaning, whether caring for a twin or a triplet litter, so that triplet infants need to be more vigilant in procuring and maintaining maternal investment than do twins (Tardif and others 2002b). Marmosets do not experience a postpartum anestrus and may conceive within 14 days of delivery, and thus are often pregnant during lactation (Hearn 1983; Power and others 2002). Marmoset mothers decrease caregiving efforts in the event of conception during intense lactation (Fite and others 2005a; Fite and others 2005b).

Even when triplets do occur in captivity, triplet survival is not equivalent to that for twins. In general, marmoset infant mortality in captivity is quite high, regardless of litter size (Jaquish and others 1991). However, survivorship during the first month of life is significantly lower for triplets than that for twins (Jaquish et al. 1991). On average, only one infant per litter survives the first month of life (Jaquish et al. 1991). This means that whereas one out of two

twins (0.50) has a chance of surviving the first month, only one of three triplets (0.33) has a chance. The asymmetry in these postnatal survival probabilities suggests a powerful selective "motive" for pursuing litter size-dependent strategies of resource solicitation. Rutherford and Tardif (2008b) have argued that "a greater number of ova increase the pool of genetic variability from which to select the best candidate for survival.This variation in fetal quality and survivorship may confer a selective advantage to females who employ a flexible, resource based strategy of litter size production" (Rutherford and Tardif 2009, p. 67). This also suggests the utility of flexible *fetal* strategies of resource solicitation and communication of need and quality.

Marmoset mothers: gestational energetics and investment

Maternal energy intake, mass, metabolism, and endocrine function combine to influence total postnatal investment in offspring. However, at no time in development is this interaction of factors more critical than during gestation. Murphy et al. (2006) suggest that maternal investment "may be supply limited, by maternal size or nutrient availability, or may be demand driven, as in the case of multiple pregnancies (p. 142)." In marmosets, mothers do not increase energy intake during gestation compared to nonpregnant intervals, even when carrying triplets (Nievergelt and Martin 1998), suggesting that maternal investment in the marmoset may be both supply limited and demand driven. As a consequence, an additional fetus may cause effective restriction of resources available for fetal development, thus creating an environment of conflict between mother and fetus, and among littermates, over competing thresholds for maternal investment. Even if daily energy intake is not a good indicator of litter size, maternal prepregnant weight (i.e. maternal size) may set the threshold for nutrient availability to the developing fetuses.

In marmosets, heavier females tend to have larger litters (Tardif and Bales 2004; Tardif and Jaquish 1994) and mothers of triplets gain more weight during pregnancy but maternal mass per fetus is lower in triplet litters than in twin litters (Table 1 in Rutherford and Tardif 2008b). Thus, there may still be a net decrease in resources available per fetus in larger litters, even when a) maternal weight is absolutely greater and b) daily energy intake is not reduced.

Litter size effects on placental efficiency and functional morphology: differences in the signaling interface

Marmosets and tamarins are unusual not only because they produce litters, but also because dizygotic littermates share a common placental mass (Benirschke and others 1962). This arrangement is highly unusual among not only other primates, but among mammals (Martin 1993). Typically, dizygotic primate twins have separate placentas; among other litter-bearing primates, this is also typical (Mossman 1987). In the marmoset, the placenta is bidiscoid, regardless of litter size. The two discs are highly integrated by extensive vascular connections known as anastomoses (Wislocki 1932; Wislocki 1939). Across these vascular lines, littermates share a common circulation and access to maternal resources, raising the question whether twin and triplet placentas differ in the physical interface of fetal demand and maternal investment. That is, are there differences in the potential for fetal access to maternal resources via the structural correlates of metabolic and endocrine function of the placenta that presage the disparity in access and investment observed postnatally?

The fetal:placental weight ratio is one way to model fetal access to maternal resources. The ratio measures the amount of fetal mass that is produced by one unit of placental mass. This ratio has also been defined as placental efficiency, and artificial selection based on placental efficiency has been an effective tool in increasing litter size in swine (Wilson and others 1999), indicating that increased efficiency may be a hallmark of litter size scaling. Haig

(1993) has also suggested that fetuses facing a restriction of maternal resources might respond by increasing their allocation to the placenta as a way of maintaining some pre-restriction threshold of investment, or in other words, increasing the relative size of the placenta. If the triplet marmoset pregnancy is characterized, from the perspective of the fetus, as being a restricted nutrient state, then how does the placenta respond: by increasing efficiency or increasing allocation?

In a study of 26 marmoset full-term pregnancies, Rutherford and Tardif (2009) determined that whereas total litter mass was significantly greater in triplet litters (a difference of nearly 30%), placental mass was not significantly different from that of twins. Triplet placentas are thus smaller than twin placentas, relative to fetal mass. The ratio of fetal mass to placental mass was significantly higher in triplet pregnancies, indicating that a single gram of triplet placenta supported 9 grams of fetal mass, compared to only 7 grams of fetal mass supported by a gram of twin placenta (Figure 3). Whereas overall efficiency of the triplet placenta was increased, the allocation of placental tissue to *individual* fetuses is significantly decreased. Thus, whereas there is a global placental response of increased efficiency in the support of total mass, individual triplet fetuses may find themselves at a disadvantage, compared to their twin counterparts, when it comes to accessing maternal resources (Rutherford and Tardif 2008).

It may be this reduction of individual allocation of placental mass that is the limiter of fetal growth, and hence, birth weight in marmoset triplets, as suggested by the nutrient sensor model of Jansson and Powell (2006) which casts the placenta in a causal rather than consequential role in the etiology of fetal growth restriction. However, it is important to note that from a signaling/conflict viewpoint, this shift in placental efficiency, or the ability for a smaller amount of placenta to convert maternal resources into a larger amount of fetal mass, may be critical for triplet intrauterine survival, even if the consequence is lower birth weight. In marmoset neonates, performance on motor skills tests conducted within 24 hours of birth, rather than birth weight, is the best predictor of survival (Tardif and others 2002a), indicating that low birth weight might be a reasonable tradeoff for increased placental efficiency.

How might a relatively smaller placental mass support a larger total fetal mass? In sheep twin litters, not only is total placental mass increased compared to that of singletons (Dwyer and others 2005), but total surface area of the interface is increased as well (Kaulfuss and others 2000). Microscopic analysis of the marmoset placenta in relation to litter size reveals a similar pattern (Rutherford and Tardif 2009). Twin and triplet placentas did not differ significantly in total volume or the volumes of individual placental compartments (e.g. compartments analogous to the human placental villi, maternal blood space, or fetal capillaries, Figure 4). However, despite no significant differences in any global measure of size, the placental surface area is 40% larger in the triplet marmoset placenta. This expansion is due to an increase of the surface area relative to its underlying volume, indicating the potential for a more topographically complex architecture, possibly due to increased branching and/or decreased diameter of the branching structures (Rutherford and Tardif 2008b).

Despite this remarkable global expansion of the interface, per fetus allotment of surface area is significantly reduced for individual triplet fetuses (Rutherford and Tardif, 2008b) (Figure 5a). The biological significance of this reduction is unclear; because individual marmoset fetuses do not have individual placentas, these kinds of relations may be the best indicators of potential resource allocation and growth. What is clear is that the triplet marmoset placenta functions differently than the twin placenta. Per gram it supports a larger total fetal mass (Rutherford and Tardif 2009), a functional feat probably related to an overall

expansion of the microscopic interface with maternal circulation (Rutherford and Tardif 2008b). However, the total expansion is insufficient to yield the same ratio of surface area per fetus as in the twin placenta, at least near or at term, a point at which fetal growth maxima have been achieved. These relationships are suggestive of important differences in the efficacy of the interface to convert maternal resources into fetal mass, perhaps through as yet undetermined differences in amino acid transport efficiency.

The implications for total allocrine signaling capacity of the triplet placenta, with its significantly expanded surface area, are important to consider. Since individual marmoset fetuses do not have individual placentas, placental interface area and function may be at best crude signals of total litter mass, rather than specific messengers of fetal number. However, considering the syncytiotrophoblast is the primary source of placental hormonal production and the location of amino acid transporters, an increase in the surface area of this tissue compartment may have attendant consequences for upregulation of maternal neuroendocrinological and metabolic pathways that impact fetal growth and development.

Determinants of placental IGF-II production in the marmoset

Rutherford (Rutherford under review) measured placental tissue concentrations of IGF-II in 22 full-term marmoset placentas from 10 twin litters and and 12 triplet litters to determine the presence and pattern of variation of IGF-II concentration. IGF-II was extracted from frozen placental tissue, and measured using enzyme-linked immunosorbent assays (Rutherford under review). Tissue concentrations are crude markers of circulating levels, but they may indicate functional patterns relating to differences in growth and signaling pathways (Rutherford under review).

Total IGF-II tissue concentrations from placental samples were unrelated to total litter mass or maternal mass (Rutherford under review) Further, just as previous studies had shown that twin and triplet placentas do not differ significantly in weight (Rutherford and Tardif 2008), neither did they differ in terms of IGF-II (Rutherford under review) Although twin and triplet *placentas* didn't differ significantly in terms of IGF-II concentration, from the perspective of the individual fetus, differences did emerge (Figure 5b). When IGF-II concentration was divided by number of littermates, individual triplet fetuses were associated with significantly lower placental IGF-II concentrations just as they were associated with significantly less placental tissue, both in terms of mass (Rutherford and Tardif 2008) and microscopic surface area (Rutherford and Tardif 2009).

The same study reported very significant inverse relations between interface surface area and IGF-II concentration for a small subset of 9 placentas ($r=-0.867$, $p=0.002$; (Rutherford under review). IGF-II is produced by the syncytiotrophoblast, the tissue comprising the interface so the inverse nature of the relationship is somewhat surprising. It may well be that concentrations at term do not reflect previous developmental processes leading to increases in surface area in the marmoset placenta. Serial sonography is a valuable tool for tracking placental growth processes across term (Rutherford and others 2007), and could be paired with assays of circulating placental hormones to hone in on temporally- and energetically-sensitive signals of fetoplacental development. It is intriguing to note that the three placentas with both the largest interface surface areas and lowest IGF-II concentrations were all triplet placentas (Rutherford under review).

Because the study did not examine circulating placental IGF-II it is unclear whether tissue concentrations can be interpreted as a fetal signal that is released into maternal circulation. However, the inverse relationship between microscopic surface area and IGF-II concentrations indicates that such a signal is possible. Certainly there are placental molecular mechanisms other than IGF-II with roles in signaling fetal growth and quality

(e.g. leptin, insulin, placental growth factor, etc.) that could act in concert with IGF-II to create a signal of fetal number and quality. For example, a reliable signal of overall placental size that is moderated by a variable signal of surface area might be one way maternal resources could be calibrated according to litter size, in the absence of a fetoplacental configuration where an individual placenta serves as a specific interlocutor for an individual fetus.

Plastic signals to navigate variable environments

It is clear that the triplet fetoplacental phenotype is distinct from that of twins. Triplet litters are characterized by higher total litter mass, but lower individual birthweights; the triplet placenta is not significantly heavier, but is more efficient in its production of fetal mass. The surface area of the microscopic interface is significantly larger, but individual triplets are associated with less square footage than their twin counterparts. Placental IGF-II concentration doesn't differ overall, but again, individual triplets have a smaller share than do twins. The global expansion of the interface may increase amino acid transport and the potential for endocrine signaling; this increase is probably necessary to accommodate the increased aggregate metabolic load of a triplet litter (Rutherford and Tardif 2008). However, the per capita reductions in placental allocation, surface area representation, and IGF-II concentration may be important mechanisms constraining fetal growth in triplet litters. Growth constraint does not signify a failed system; rather, it may be that without such plastic signaling pathways (morphological, hormonal) triplets would be incapable of navigating a restricted intrauterine environment. Unfettered fetal growth in a restricted environment is not an adaptive outcome; employing a placental "nutrient sensor" that plastically responds to a changing gestational landscape allows for appropriately calibrated growth (Jansson and Powell 2006).

These findings in the marmoset placenta provide a platform for targeted analysis of amino acid metabolism across different litter sizes. Specifically, the triplet placenta, with its per capita reductions in surface area and IGF-II concentrations may upregulate amino acid transport in order to maintain its overall higher efficiency. This prediction is consistent with intriguing work done in a mouse model demonstrating that complete knockout of placental-specific IGF-II is associated with reduced placental and fetal weights but increased activity of the System A amino acid transport system (Constancia and others 2002) that transports critical amino acids such as leucine across the.

IMPLICATIONS OF PLACENTAL PLASTICITY FOR A COMPARATIVE LIFE COURSE BIOLOGY

I have presented a new primate model here to bolster the argument that reconstruction of the complexity of the intrauterine environment is incompletely done if the emphasis is simply on maternal and fetal characteristics such as weight. Two neonates of similar birth weights can have experienced widely different maternal ecologies with lasting consequences for adequate pre- and postnatal development and later health and disease outcomes. This observation emphasizes that a variety of intrauterine ecologies can yield fetal phenotypes that appear similar but stem from distinct etiologies and thus may have distinct outcome trajectories. In mice, removing one of the uterine horns creates a crowded intrauterine environment that can induce low birth weight without restricting maternal nutrition, a condition that was linked in the same study to the development of obesity in the offspring (Coe and others 2008). Considering that triplet marmosets appear to experience a similarly restricted intrauterine environment, without nutritional or other experimental manipulation, and that low birth weight triplets can exhibit catch-up growth and adult weights that are consistent with a developmental programming phenotype (Tardif and Bales 2004), the

marmoset is an ideal candidate for a primate model of intrauterine programming of chronic conditions such as obesity (Tardif and others in press). Recent work has begun to map out links between adult health outcomes and placental morphology and function in humans (Fowden and others 2008; Godfrey 2002), showing, for example, a relationship between relatively small placental mass and adult type-2 diabetes (Forsen et al. 2000), increased blood pressure (Campbell et al. 1996), and coronary heart disease (Forsen et al. 1997). These links between placental morphology and postnatal outcomes may well be explained by the plasticity of function of hormonally-mediated amino acid transport in response to maternal ecology and the attendant variability in fetal growth patterns, but more remains to be done to fully incorporate the placenta into the developmental origins paradigm.

An evolutionary and ecological emphasis on the entire primate fetoplacental phenotype elucidates a dynamic link between the antecedent of the intrauterine environment, maternal ecology, and the sequelae of that environment; namely, postnatal and adult outcomes. Whereas the emergence of chronic diseases in adulthood may have a more direct link to fetal organogenesis (in that cell size and number determined during gestation may be the limiter of adult function), it is the placenta that directly informs fetal development and forms the foundation of a fetal discourse with the external environment. This placental interrogation, via metabolic and hormonal (allocrine) pathways, of the external environment may provide predictive cues of future environments, thus forging a mechanism for phenotypic inertia across generations (Kuzawa 2005). In addition, through plasticity there is an obvious role for the placenta in the embodiment of disease and disparities through developmental and intergenerational processes (Krieger 2005; Kuzawa and Sweet 2008) (Figure 6). Combining elements of signaling and conflict theory with developmental programming theory may inform the construction of more evolutionarily robust models of developmental processes and their consequences on a range of temporal, biological, and even sociocultural and evolutionary scales. The mechanisms underlying the lasting consequences of the intrauterine environment still remain much of a mystery. The placenta is the key to opening that black box.

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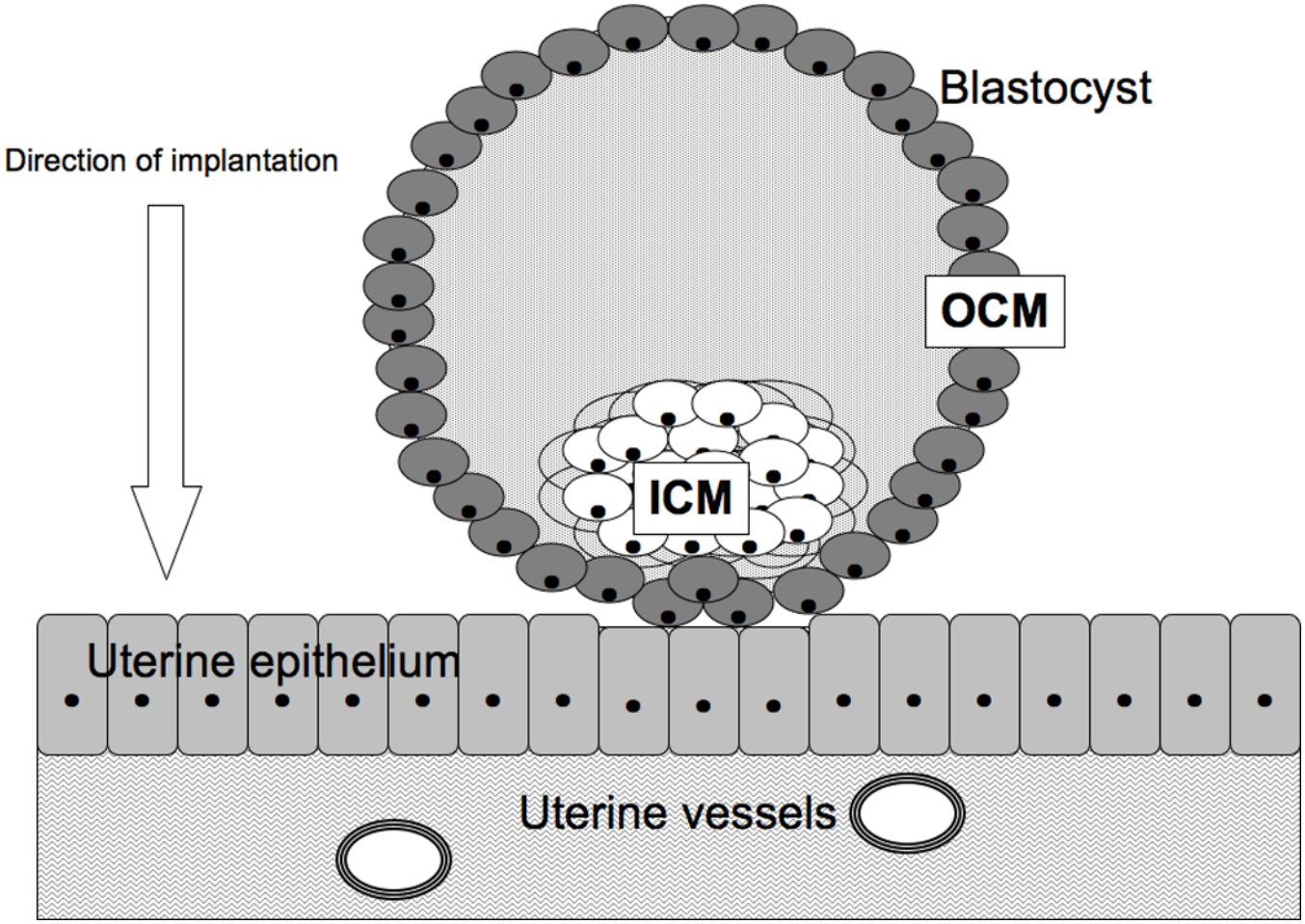

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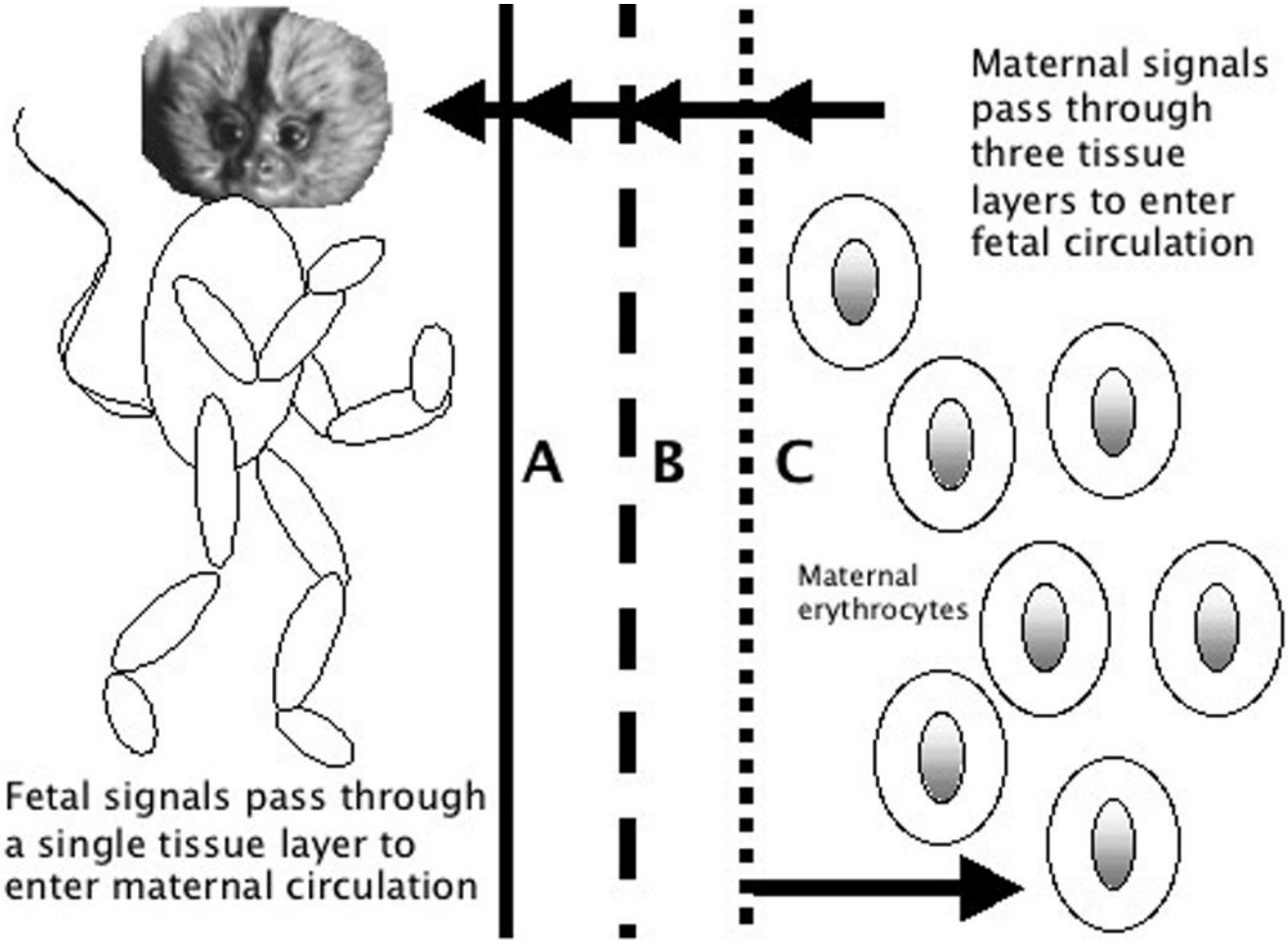

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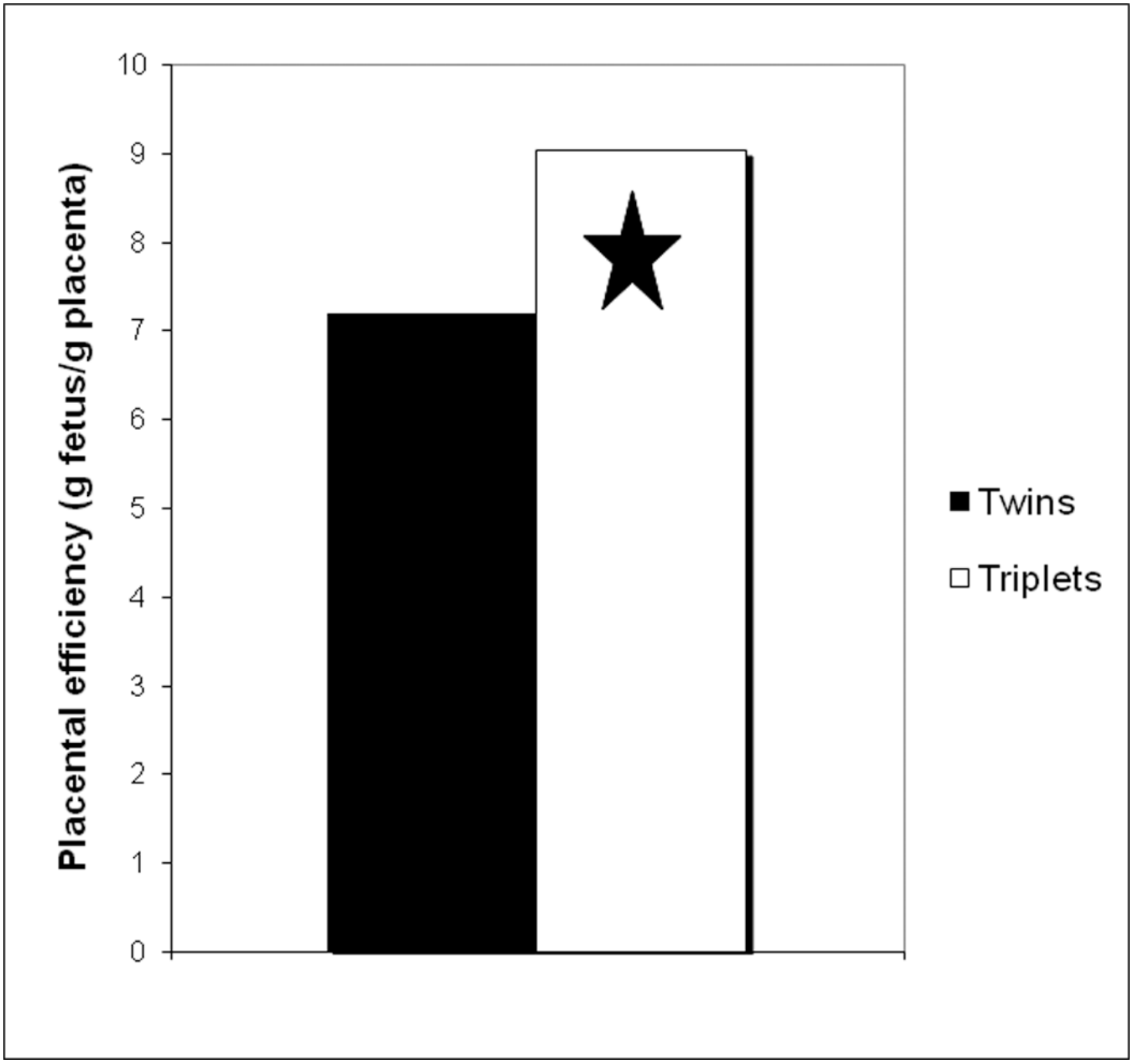

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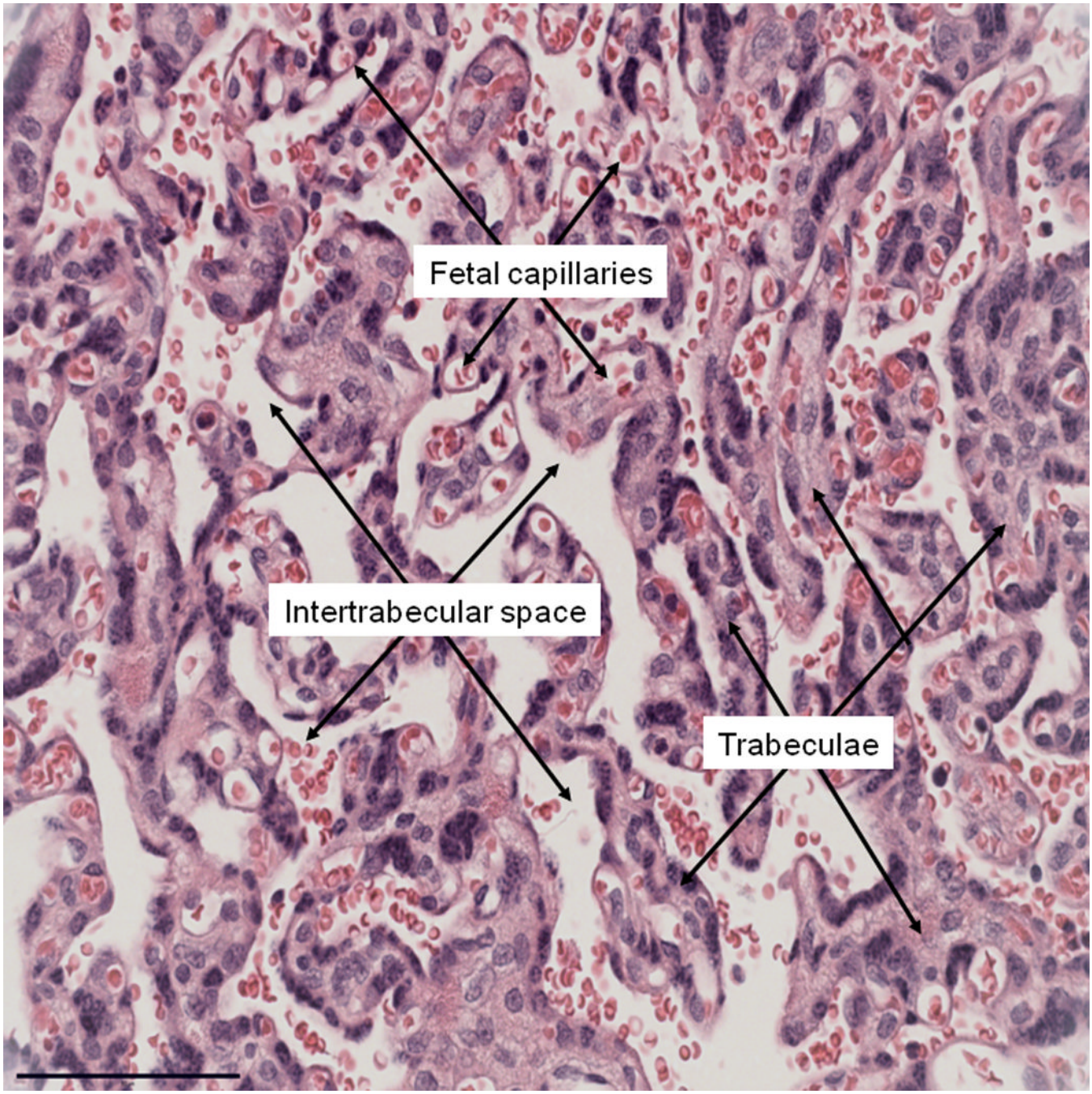

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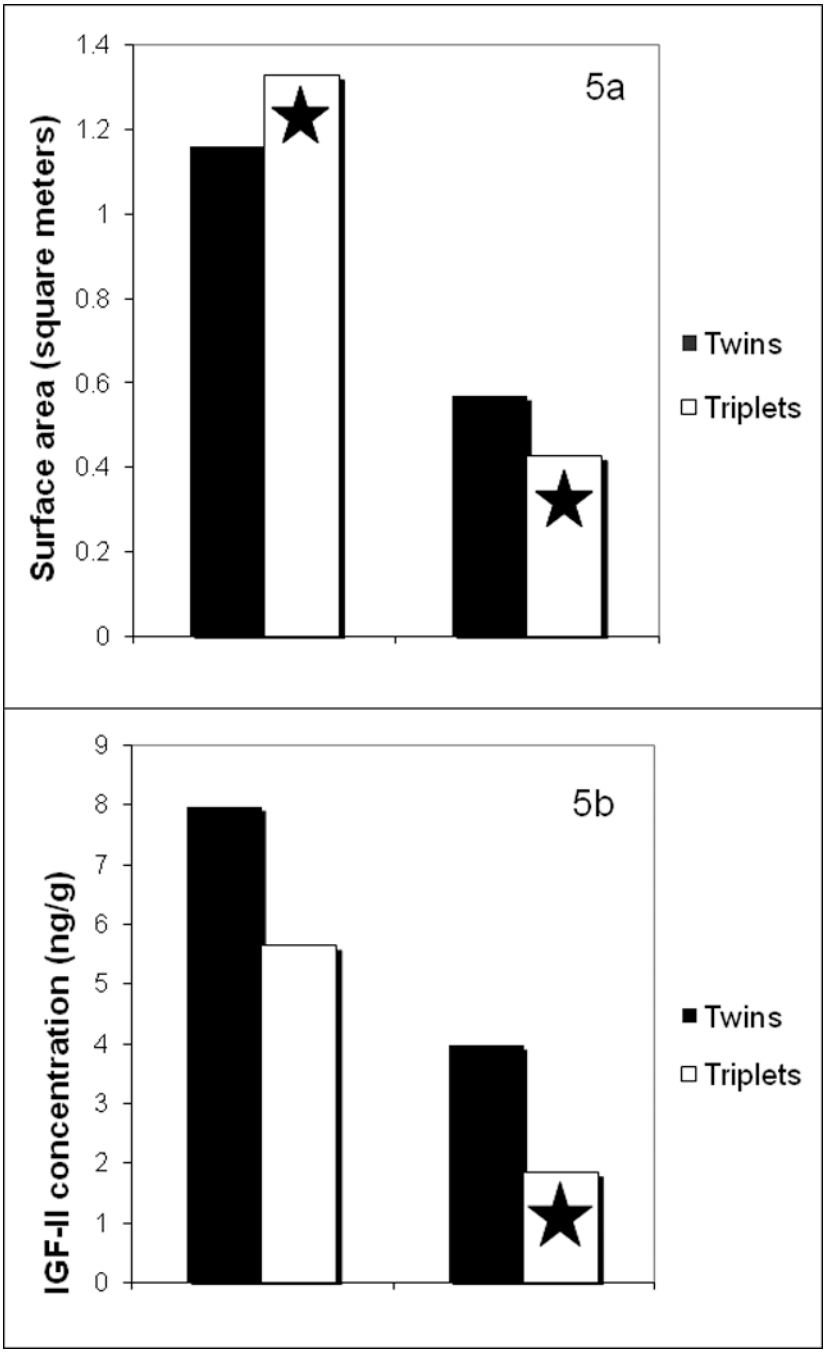

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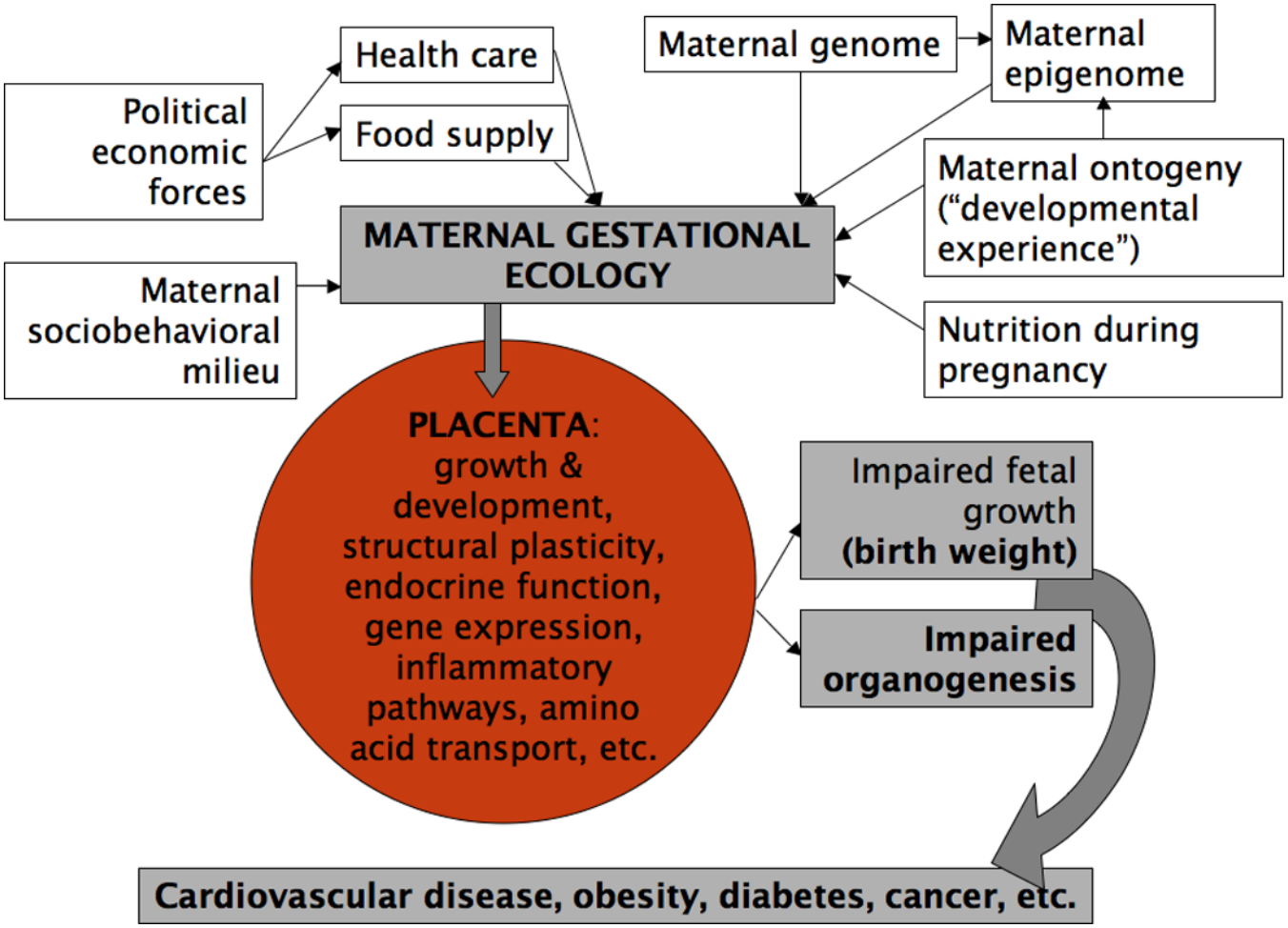

Figure 6.