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Toward a nonhuman primate model of fetal programming: phenotypic plasticity of the common marmoset fetoplacental complex

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Abstract

Nonhuman primate models offer unique opportunities as animal models in the study of developmental programming and the role of the placenta in developmental processes. All primates share fundamental similarities in life history and reproductive biology. Thus, insights gleaned from studies of nonhuman primates have a higher degree of biological salience to human biology than do studies of rodents or agricultural animals. The common marmoset monkey is a small-bodied primate from South America that produces litters of dizygotic fetuses that share a single placental mass. This natural variation allows us to model different intrauterine conditions and associated fetoplacental phenotypes. The marmoset placenta is phenotypically plastic according to litter size. Triplet litters are characterized by low individual fetal weights and significantly more efficient placentas and attendant alterations to the microscopic architecture and endocrine function, thus modeling a nutrient restricted intrauterine environment. Consistent with this model, triplet neonates experience a higher risk of perinatal mortality and an increased likelihood of elevated adult weight. Recent evidence has shown that the intrauterine experience of females has an impact on their own pregnancy outcomes in adulthood: triplet females experience significantly greater pregnancy loss than do twin females. The marmoset monkey thus represents a potential powerful nonhuman primate model of multiple pregnancies, restrictive prenatal experiences, and differential reproductive outcomes in adulthood, which may have important implications for studying the impact of in vitro fertilization on adult reproductive health. It is still too early to determine exactly what developmental pathways lead to this disparity or what specific role the placenta plays; future work on this front will be critical to establish the marmoset as an important model of fetal programming of reproductive function in adulthood and across generations.

Introduction

Much of what is known about the role of the placenta in developmental programming comes from clinical and epidemiological studies of humans and experimental animal models other than nonhuman primates. Nonhuman primate models offer unique opportunities as animal models. All primates share fundamental similarities in life history, typically being relatively large-brained, long-lived monotocous species that produce altricial infants requiring a high

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degree of parental and alloparental care. Reproductive endocrinology and physiology is broadly similar across primates [1], and all anthropoid primates (i.e. monkeys, apes, and humans) have hemochorial placentas. Thus, insights gleaned from studies of nonhuman primates have a higher degree of biological salience to human biology than do studies of rodents or agricultural animals. Biomedically, this means fewer steps may need to be taken to develop clinical interventions on the basis of findings in nonhuman primates. Taking an ultimate perspective, evolutionary change relies heavily on reproductive processes (which are inherently intergenerational), thus studies of nonhuman primates allow us to more deeply understand the evolutionary history of the hominin lineage and the primate order overall.

A recent model of the intrauterine environment considers “maternal ecology” as “the nexus of nutritional, metabolic, endocrinological, infectious, genetic, epigenetic, and sociobehavioral inputs that coalesce into a particular pregnancy” [2, p.746]. This ecological view of fetal development as an interaction with maternal behavior, physiology, energetics and other phenomena explicitly contextualizes development as a dynamic system characterized by plasticity and sensitivity. It also reinforces the observation that birth weight is an outcome, not a process [3]. Birth weight, the foundation of much of the developmental programming literature, must be viewed as the outcome, not the process. The placenta – the direct interlocutor between the external world experienced by the mother and the growth, development, and long-term functioning of the resultant fetus/neonate/juvenile/adult – must be factored in to a biologically significant view of fetal programming. In this piece I will discuss the common marmoset monkey as an ideal nonhuman primate species in which to examine placental variation in the context of variable intrauterine ecologies. After reviewing what we know so far about fetoplacental phenotypic plasticity, I will present a case study of reproductive programming, thus linking marmoset generations from “womb to womb.”

Introducing the common marmoset monkey (*Callithrix jacchus*)

The marmosets, tamarins, and callimico monkey form a monophyletic group, the subfamily Callitrichinae (family Cebidae). The Callitrichinae is composed of five genera: the marmosets (*Callithrix* and *Cebuella*, the pygmy marmoset), the tamarins (*Saguinus*), the lion tamarins (*Leontopithecus*), and the callimico, represented by a single species (*Callimico goeldii*) [4]. The callitrichines as a whole are distributed from Panama to southern Brazil and northeastern Paraguay [5]. Common marmosets (*Callithrix jacchus*) are found primarily in the scrub and swamp habitat of coastal northeastern Brazil [6].

Group size in the wild is variable in the common marmoset, with a mean group size of 9 individuals (range 3–15) [7, 8]. Group composition in marmosets appears to be relatively stable over time, particularly in comparison to tamarins [9]. There is generally a single breeding female, even if there are other adult females in the group [9], and reproductive suppression of subordinate females by the breeding female is a hallmark of callitrichine reproductive biology [10]. Callitrichine primates have frequently been described as monogamous. This classification is often predicated on observations of captive groups [11, 12]. However, field studies have contributed to the development of a more nuanced and complex understanding of group dynamics and mating relationships. Monogamy, polygyny, and polyandry have all been observed in wild populations of common marmosets [13, but see 14]. Single female, multi-male groups have been successful in laboratory settings as well [15–17]. Tardif [18] points out that because in polyandrous groups multiple males copulate with the breeding female, paternity in such groups is most likely uncertain. A high degree of communal breeding and alloparenting is standard in callitrichine species.

Common marmosets offer unique opportunities as nonhuman primate models. They are relatively small (~400g in adulthood), achieve sexual maturity relatively quickly (19–20

months of age), can produce offspring twice a year, have a typical lifespan in captivity of 6 years, and pose no known zoonotic risks. This combination of factors lends itself well to studies of reproductive biology, and indeed, much insight into primate pregnancy, development, lactation, and parenting has been gained over nearly thirty years of research [18–23].

The common marmoset monkey as a model for developmental programming in variable intrauterine ecologies

One of the most distinctive features of callitrichine primate reproductive biology is the variability in the number of fetuses produced each pregnancy. Most primates are monotocous, producing a single fetus each pregnancy, but the marmosets and tamarins (but not the callimico) produce litters of at least two, and frequently three or more, dizygotic fetuses. Unlike some other litter-bearing mammals, the marmosets and tamarins possess a simplex uterus, and in a very unusual deviation, all littermates share a single placenta. The common marmoset monkey (*Callithrix jacchus*) is thus a fascinating species in which to consider the impact of the intrauterine environment on developmental sequelae because of the inherently variable landscape of the intrauterine environment.

In the wild, twins are the most common litter size observed. However, in captivity under conditions of nutritional luxury, litter sizes as large as quintuplets have been observed, with triplet litters being the most common [24]. Within a narrow ecological context, it would be accurate to restrict the classification of these primates as being exclusively twinning, but against a broader backdrop, we observe a release of ovarian physiology that allows larger litters to not only be conceived but successfully gestated [25]. Litter sizes greater than two have comprised as much as 33% of recent births in the Southwest National Primate Research Center common marmoset colony in San Antonio, Texas, USA [24]. Recent observations in the wild confirm that triplet litters at birth are indeed part of the natural continuum of reproductive function in these species [26–28].

The determinants of litter size in the marmosets and tamarins are not entirely elucidated. It is known that body mass is a significant predictor of follicle number and litter size [18]: heavier females produce larger litters than lighter ones; individual females produce larger litters when they are heavier. Although the precise mechanisms are as yet undiscovered, it is clear that maternal energetics are very important in determining not only litter size but also overall pregnancy success. This plasticity suggests the possibility of nutritionally-mediated epigenetic regulation of folliculogenesis in this species. Hormones related to ovarian reserve and folliculogenesis (e.g. Anti-Müllerian Hormone, AMH; Bone Morphogenic Protein, BMP [29, 30]) may play an important role. Recently, positive selection of polymorphisms *BMP15* and *4* and growth differentiation factor 9 (*GDF9*) have been demonstrated within callitrichine monkeys [31]; intriguingly, *BMP15* and *GDF9* are associated with twinning in sheep.

Our team has investigated the impact of energy restriction during marmoset gestation [32]. Limiting pregnant marmosets to 75% of *ad libitum* feed during midgestation led to spontaneous abortion of all fetuses without apparent reduction in fetal body weights in all cases (n=8). In contrast, similar restriction during late gestation led to term delivery of normal sized neonates in 4 out of 7 cases, and to preterm birth in the remaining 3 cases. Given that heavier marmoset females are more likely to produce larger litters, it stands to reason that preconceptional energy restriction might lead to reductions in litter size (as has been shown in pigs [33], and guinea pigs [34]) but this has not been tested in the marmoset monkey.

Murphy and colleagues [35] 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 [36]. As a consequence, an additional fetus apparently generates effective restriction of resources available for fetal development, thus actively creating a developmental environment of both low supply and high demand. It must be noted that while maternal mass is greater in the event of a triplet pregnancy, the ratio of maternal mass to fetal mass or number is reduced significantly [23] (Table 1). That combined with the reduced birth weights and increased mortality of individual triplets is consistent with an intrauterine nutrient-restricted phenotype, which frames marmoset litter size variation as a sort of natural experiment in fetal programming. Consistent with this viewpoint is the difference in adult weight between twins and triplets. Triplets tend to be heavier in adulthood than twins. Further, whereas large neonates tend to be heavier adults regardless of their litter size, low birth weight triplets are much likelier to be large adults than are low birth weight twins [37, 38]. This is a highly evocative phenotype in the programming paradigm: low birth weight combined with “centile crossing” into higher weight in adolescence and adulthood [39–41].

Developmental plasticity of the common marmoset fetoplacental unit

Marmosets and tamarins are unique among primates and most other mammals in that individual littermates share a single placental mass [42] and thus a single placental circulation; as a result of this, marmosets and tamarins are hemopoietic chimeras [43] with provocative evidence suggesting germline chimerism as well [44]. In recent years, my team has extensively characterized the placental phenotype associated with triplet marmoset litters [23, 45, 46]. Placental efficiency in the marmoset is thus measured as the total litter mass (i.e. summed mass of all fetuses: two fetuses, three fetuses, etc.) divided by the summed bidiscoid mass of the placenta. Efficiency is significantly higher in triplet litters because although the entire litter mass is much greater than in twin litters, the placenta is not proportionately heavier [23]. Stereological analyses demonstrate that while the volume of neither the placental trabeculae nor the fetal capillaries differs between twin and triplet placentas, the surface area of the maternal-fetal interface is significantly expanded in the triplet placenta, apparent evidence of a compensatory process to maintain adequate surface area for nutrient transport [47]. This expansion of surface area against a backdrop of stable underlying volume yields an isomorphy coefficient indirectly suggestive of a highly complex topography at term. This may be driven by mechanisms consistent with uteroplacental hypoxia but this is so far unstudied in the marmoset placenta.

The picture thus painted suggests that the triplet marmoset placenta compensates via increased growth (and perhaps interhemal attenuation) of the trophoblast. However, when surface area is looked at from the perspective of the individual fetus (i.e. surface area per fetus or gram of fetal mass), the allotment for triplets is significantly reduced (TABLE 2). The placenta is plastic, but only to a point. Just as the mechanisms related to global surface area increases are as yet unknown, the mechanisms that limit the placenta’s ability to continue that increase remain a mystery in the marmoset. To this end, we have looked at placental insulin-like growth factor II (IGFII) concentrations [46]. IGFII is a powerful driver of placental growth (e.g. mitotic activity of the cytotrophoblast) and is usually reduced in fetal growth restriction. At the level of the whole placenta, total number of fetuses, or total fetal mass, IGFII tissue concentrations do not differ between twin and triplet litters. However, we again see individual restriction. IGFII is lower per fetus in triplet litters, and IGFII per unit of surface area is reduced in triplet placentas (TABLE 2).

Together, these findings are indicative of significant divergence in fetoplacental phenotypes across litter size in the marmoset monkey. Triplets are different from twins in many ways: the preconceptional events that determine litter size; the quality of the intrauterine environment and the communication of nutrient availability by the placenta to the fetuses; at birth and as infants; and as adults. Given the complexity of the maternal ecology that gives rise to litter size variation and its downstream effects on birth weight, perinatal outcomes, and adult characteristics, marmosets and the other litter-bearing callitrichine primates represent an important opportunity to unravel not only the life history and evolutionary ramifications of placental function in the intrauterine period but also to develop novel biomedical applications with relevance to human health.

Conclusions and new directions: Marmoset birth condition and reproductive programming

Evidence is accumulating to suggest that the response of the fetus to its local environment during development may program reproductive effort in adulthood. In humans, Ibañez and colleagues have shown that low birth weight predicts reduced ovarian function (reduced Follicle Stimulating Hormone (FSH), reduced ovarian volume) and reduced uterine volume in adolescence, controlling for current BMI [47, 48]. And a recent large-scale epidemiological study in Sweden demonstrated that low birth weight and prematurity in both men and women are associated with reduced probability of reproducing in adulthood [49]. The Dutch Hunger Winter demonstrated that women who themselves experienced intrauterine restriction due to the famine during fetal life, produced lower birth weight infants and experienced more pregnancy loss [50]. This suggests the possibility that the process by which these women produced placentas during their pregnancies was impacted by their own fetal experience, a tantalizing but relatively unexplored area of inquiry.

For marmosets, the consequences of being born a triplet extend beyond lower birth weights and higher perinatal mortality. While adult females born as twins and triplets produce the same lifetime number of offspring, the offspring of triplet females are far more likely to be stillborn, with low birth weight triplet adult females having the highest rate of pregnancy loss, regardless of adult weight [Figure 1; 51, 52]. The difference is tremendous: total fetal loss rate for adult twin females is about 13% compared to 38% for triplet females. The mechanisms underlying these striking differences in the marmoset are as yet unclear, but may relate to initial egg quality, endometrial receptivity, uterine volume, and/or placental biology [52].

Placental data are not yet complete enough from this population of marmosets to definitively determine whether placental phenotypes predict an individual's risk of producing nonviable offspring in adulthood, but tantalizing clues exist. For example, in a small sample of adult females (n=7), there is a positive relationship between the efficiency of the mother's own placenta at birth and the number of offspring she produces [Figure 2]. We've previously demonstrated that triplet litters are associated with the most efficient placentas [23], and yet there is no difference between twin and triplet females in the number of offspring they produce [23], so this small sample may not be representative of broader patterns and may well be mediated by several other variables we currently do not have the power to explore in such a small dataset. However, it does reinforce the supposition that the placenta – and its representative transmission of maternal ecology to the fetus – plays a critical role in determining reproductive function in adulthood, beyond its immediate role as the gatekeeper of a successful gestation [2].

Finally, a robust investigation across primates showing how a female's birth condition programs her ability to conceive, gestate, and raise offspring – and how the placenta

translates maternal ecology into that birth condition in the first place – will help us delve into the reproductive consequences for adults who were conceived by in vitro fertilization and other assisted reproductive technologies. This generation of IVF-conceived adults has only recently become old enough to consider effects on reproduction and pregnancy success, but findings in other domains are troubling: IVF infants are born at lower birth weights, even in cases of singleton births [53]; they have also been found to have increased growth rate, increased risk of precocial sexual maturity, and increased rates of adulthood obesity and diabetes [54, 55]. Many of these risks are amplified for individuals from multiple birth pregnancies. In this regard, the marmoset monkey represents a potential powerful nonhuman primate model of multiple pregnancies, restrictive prenatal experiences, and differential reproductive outcomes in adulthood.

In summary, the common marmoset monkey offers a natural experiment in varying intrauterine ecologies because of plasticity in maternal energetics that drive litter size. The marmoset triplet presents a growth-restricted fetoplacental phenotype: low birth weight fetus with an efficient placenta exhibiting globally expanded but proportionally restricted surface area of the maternal-fetal interface. This is accompanied by accelerated postnatal growth (“centile crossing”), elevated adult weights, and impaired reproductive outcomes in the form of alarmingly high rates of fetal loss. The mechanisms underlying the multiple phenotypic expressions of the restricted intrauterine environment in the marmoset triplet pregnancy are as yet unknown; future work on this front will be critical to establish the marmoset as an important model of fetal programming of reproductive function in adulthood and across generations.

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Figure 1.

Female marmosets who were born as triplets lost significantly more fetuses during pregnancy than did twin females, across tertiles of birth weight: LBW, low birth weight; MBW, medium birth weight; HBW, high birth weight. [51]

Figure 2.

In a small sample of marmosets ($n=7$), the efficiency of a female's own placenta at birth significantly predicts the number of offspring she will produce in adulthood.

Table 1

Maternal mass as a marker of resource availability in a sample of 26 pregnancies *

	Twin litters (n=10)	Triplet litters (n=16)	Triplet difference
Maternal prepregnant weight (g)	376.67	424.31	+12.65%
Total litter weight (g)	63.40	82.10	+29.50%
Maternal mass per fetus (g/individual)	188.34	141.44	-24.90%
Ratio of maternal mass to fetal mass (g/g)	5.94	5.17	-12.96%

*
Table modified from [23]

Table 2

Summary of major fetoplacental findings in the common marmoset monkey

	Twin litters	Triplet litters	Reference
Average fetal weight (g)	+	–	[23]
Average total litter weight (g)	–	+	[23]
Placental weight (g)	Difference not significant		[23]
Placental efficiency	–	+	[23]
Trabecular volume (cc)	Difference not significant		[42]
Trabecular surface area (cc)	–	+	[42]
Trabecular surface area/fetus	+	–	[42]
IGF-II concentration(nm/g)	Difference not significant		[43]
IGF-II concentration/fetus	+	–	[43]

+ Litter category that exhibits larger value.

– Litter category that exhibits smaller value.