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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 primates 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.

1. 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 primates 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 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

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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."

2. 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 (*Callithrix jacchus*), 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 (~400 g in adulthood, about the size of an adult Sprague-Dawley rat), achieve sexual maturity relatively quickly (16–20 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].

3. 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, multizygotic 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 twinners, 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-Mullerian 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.

Tardif and colleagues have 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 preconceptual 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