
**MATERNAL
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Perinatal Influences on the Reproductive Behavior of Adult Rodents

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In litter-bearing rodent species, the location that a male or female fetus occupies relative to siblings of same or opposite sex influences its level of prenatal exposure to gonadal hormones. In particular, varying amounts of prenatal exposure to testosterone produce cascades of neuroendocrine events that, in turn, result in variation in such biologically important characteristics as the timing of puberty, an individual's lifetime fecundity, the sex ratio of its offspring, and the magnitude of its parental investment. Consequently, studies of intrauterine effects on adult patterns of reproduction provide a means of examining the relationship between normally occurring variation in perinatal exposure to hormones and the variation in reproductive tactics often seen in mammalian populations. Dams can only indirectly influence the intrauterine position of their offspring by varying the size and sex ratio of their litters and the distribution of litter members within the uterus. However, because the same hormonal mechanisms that support indirect maternal effects on behavior also support direct maternal influences on the phenotype of offspring, examination of effects of intrauterine position increases understanding of direct maternal effects on phenotypes of adult mammals.

In mammals, as in other vertebrates (Schwabl 1993; Hews et al. 1994), an individual's reproductive performance can be profoundly affected by its level of exposure to gonadal hormones in the days surrounding its birth. Consequently, differences in perinatal exposure to hormones can be used to explain variation in reproductive tactics exhibited by individuals of the same species and sex.

Results of the relatively few studies examining effects of variation in perinatal exposure to hormones on adult reproductive behavior in natural populations of mammals have been less conclusive than have results of studies conducted in the laboratory with domesticated animals. Consequently, when discussing natural populations, we shall have to settle for clues as to effects of perinatal hormonal experiences on reproduction. Definitive evidence of such effects has been provided only in laboratory situations.

House Mouse and Norway Rat

In many litter-bearing rodent species, such as the house mouse (*Mus domesticus*) and Norway rat (*Rattus norvegicus*), the intrauterine position (IUP) that a male or female fetus occupies relative to siblings of same or other sex influences the hormonal milieu in which that fetus matures (Gandelman et al. 1977; Clemens et al. 1978; Meisel and Ward 1981). For example, a male mouse fetus occupying an IUP between two male fetuses (a 2M male) has greater blood concentrations of testosterone than does its brother maturing in an IUP between two female fetuses (2F males). Similarly, female fetuses located between males (2M females) have higher testosterone titers than do their sisters located between females (2F females). (At different times during the exploration of IUP effects, different classification schemes have been used to assign fetuses to IUPs. To simplify matters here, we discuss all the data as though fetuses had been classified in terms of the number of adjacent male and female fetuses, though that is not always the case in the original research.)

There has been some controversy as to how steroid hormones travel between fetuses and, consequently, as to whether the sex of immediate intrauterine neighbors determines the level of exposure to gonadal hormones that a fetus receives (Meisel and Ward 1981; Richmond and Sachs 1984; Houtsmuller and Slob 1990; Houtsmuller et al. 1994). However, recent studies of both dye transport within the uteri of pregnant rats and the movement of radioactively labeled testosterone between fetal rats and fetal mice indicate that, at least in these two species, androgens secreted by the gonads of males late in gestation diffuse through the amniotic fluid and cross fetal membranes to adjacent fetuses (Even et al. 1992; vom Saal and Dahr 1992). Such diffusion causes fetuses located between males to receive greater prenatal exposure to exogenous testosterone than do fetuses located between females.

In house mice, a range of androgen-sensitive, biologically meaningful characteristics are correlated with IUP: 2M females have first estrous at a later age, a longer estrous cycle, a shorter reproductive life, fewer litters during their lifetimes, and a greater percentage of males/litter and are both less attractive to males and more aggressive than are their 2F sisters (vom Saal 1984, 1989; Vandenberg and Huggett 1995). Male mice from 2M IUPs are more aggressive and (perhaps unexpectedly) less sexually active, less infanticidal, and more paternal than are their 2F brothers (vom Saal 1984, 1989).

Some laboratories have failed to observe some of these effects of IUP on the phenotypes of female house mice (Simon and Cologer-Clifford 1991; Juliban and Nyby 1992). However, observations of robust effects of IUP on both the morphology and reproductive behavior of females of another litter-bearing rodent species (the Mongolian gerbil, *Meriones unguiculatus*), quite similar to those observed in mice, suggest that effects of IUP on mice reported in the literature are real.

Below, we first review our studies of effects of IUP on reproduction in Mongolian gerbils, then discuss briefly the effects of stressors applied to rodent dams on the phenotypes of their offspring. A more comprehensive general review of maternal effects on mammalian development can be found in Moore (1995).

Mongolian Gerbils

Females. Our interest in effects of IUP on reproduction in Mongolian gerbils arose from a serendipitous discovery made while studying the development of sexual behavior in female Mongolian gerbils. We discovered that age at vaginal introitus (which, in Mongolian gerbils, is significantly correlated with age at first parturition; Clark and Galef 1988) was bimodally distributed: some gerbils exhibited vaginal perforation before their eyes opened (day 16 postpartum), and others only after they weaned (day 25 postpartum); there also was a period from day 22 to day 27 postpartum when essentially no vaginal opening occurred (Clark et al. 1986).

When we examined the reproductive life histories of samples of such early- and late-maturing female gerbils, we found marked differences in their patterns of reproduction. (1) Early-maturing females were less likely than were late-maturing females to behave aggressively toward, and more likely to be impregnated by, strange males with whom they were randomly paired. (2) Early-maturing females reproduced for the first time at an earlier age, had significantly more litters during their lifetimes, produced slightly more young in each litter, and, consequently, had a lifetime fecundity more than twice as great as that of late-maturing females. (3) Litters delivered by early-maturing females contained a greater proportion of daughters and a greater proportion of early-maturing daughters than did litters delivered by late-maturing females. (4) Finally, early-maturing females directed less maternal behavior toward their young than did late-maturing females; the former animals spent less time nursing their young and were less likely to retrieve offspring displaced from the nest than were the latter (Clark and Galef 1986; Clark et al. 1986).

Some of these differences between early- and late-maturing females reflected differences in their ages at first parturition or responses to litters of varying size and sex ratio. However, when we controlled such factors postnatally, differences in the sex ratios of litters produced by early- and late-maturing females persisted, as did differences in ages at sexual maturation of their daughters (Clark and Galef 1986). Presumably, differences in the prenatal experiences of daughters of early- and late-maturing mothers affected the daughters' patterns of reproduction when adult.

As already noted, early-maturing female gerbils tended to be born as members of relatively large, female-biased litters, while late-maturing females came from relatively small, male-biased litters. The size and sex composition of a litter affect the probability that any fetus in it will occupy an IUP between either two male or two female fetuses: as the proportion of males in a litter increases, the probability that a fetus in that litter will occupy an IUP between males increases; as the size of a litter decreases, the probability of a fetus being located at the end of a line of pups in a uterine horn increases, and the probability of its being between two fetuses of either sex decreases (Clark et al. 1993b). Consequently, it seemed reasonable to ask whether the correlations between age at sexual maturation of a mother, the sex ratios of her litters, and the reproductive behaviors of her daughters might be mediated by different levels of prenatal exposure to gonadal hormones experienced by females that matured either early or late.

We found that, regardless of their respective dam's age at sexual maturation, daughters from 2F IUPs were almost sure to be early maturing, while daughters from 2M IUPs produced slightly more late- than early-maturing daughters (Clark and Galef 1988). Further, within both sexes, fetuses from 2M IUPs had higher circulating levels of testosterone than did fetuses from 2F IUPs (Clark et al. 1991), a result consistent with the hypothesis that dif-

ferences in prenatal exposure to testosterone, resulting from IUP, might mediate some of the observed differences in the reproductive profiles of female gerbils born to early- and late-maturing mothers.

We could not entirely explain the difference in ages at vaginal introitus of daughters born to early- and late-maturing mothers by reference to the IUPs that mothers had occupied as fetuses. Daughters of early-maturing mothers located in 2M IUPs were twice as likely to mature early as were 2M daughters of late-maturing mothers (Clark and Galef 1988). Fetuses located in utero between one male and one female fetus and gestated by late-maturing mothers had higher blood titers of testosterone than did fetuses in similar IUPs gestated by early-maturing mothers (Clark et al. 1991). Thus, while IUP accounted for much variation in both circulating levels of testosterone in gerbil fetuses and age at vaginal opening in female gerbils, there were additional direct maternal effects on the endocrinology of young and their consequent rates of maturation.

Yalcinkaya et al. (1993) have proposed that the malelike aggressive behavior and genitalia of female spotted hyenas (*Crocuta crocuta*) result from exposure of fetal female hyenas to high levels of androstenedione produced in the ovaries of hyena mothers and converted to testosterone in the placenta. Possibly, some effects on female gerbils gestated by 2M mothers also result from exposure of gerbil fetuses to the higher circulating levels of testosterone to be found in 2M than in 2F gerbil dams (Clark et al. 1991).

Whatever the hormonal mechanisms that mediate effects of IUP on the reproductive morphology and behavior of Mongolian gerbils, such effects are profound (Clark and Galef, 1995a, 1995b). As previously noted, because of differences in the sex ratios of litters gestated by 2M and 2F gerbils (and mice; Vandenbergh and Huggett 1995), daughters born to 2M females are more likely to themselves be 2M females than are daughters of 2F females. Conversely, daughters born to 2M mothers are more likely than are daughters born to 2F mothers to be gestated in 2F IUPs. Such influence of the IUP in which a mother matured on the IUP of her daughters results in hormonally mediated transmission between gerbil dams and their daughters of those characteristics affected by levels of prenatal exposure to testosterone. Gerbil daughters resemble their mothers not only because they have in common a large proportion of genes, but also because, as a result of their statistical tendency toward congruence in IUP, mothers and daughters tend to have similar histories of fetal exposure to steroids (Clark et al. 1993b; Clark and Galef 1994).

Males. Given the variable and demanding steppe environment in which Mongolian gerbils evolved, it is not difficult to suggest reasons why natural selection might maintain the reproductive patterns exhibited by both 2M and 2F gerbil females (Clark et al. 1986). Observed effects of IUP on the reproductive profiles of male gerbils are considerably more difficult to understand because male Mongolian gerbils gestated in 2F IUPs appear to be at a distinct reproductive disadvantage.

Adult male gerbils from 2M and 2F IUPs paired for 3 weeks with each of a succession of virgin females differed in the number and size of litters that the females paired with them produced. Litters sired by 2M males were slightly (but not significantly) larger than those sired by 2F males, and 2F males were five times more likely than were 2M males to fail to impregnate a female during a 3-week period of cohabitation (Clark et al. 1992, 1996).

Observation of the copulatory patterns of males from different IUPs revealed consistent inadequacies in the copulatory performance of 2F males: they had longer latencies to intro-

mit, longer latencies to ejaculate, and, of greatest importance, were significantly less likely than were 2M males to achieve ejaculation when paired with an unfamiliar virgin female (Clark et al. 1990, 1996).

As one might expect, given the lower potency of 2F than of 2M males, female gerbils can discriminate between them: females scent mark more frequently in response to scent marks of 2M males than to those of 2F males (Clark and Galef 1994) and, when in estrous (but not at other times during the estrous cycle), prefer to affiliate with the 2M rather than 2F males (Clark et al. 1992).

Differences in both the copulatory behavior of males from different IUPs and the response of females to them may be mediated by differences in circulating levels of testosterone and responsiveness to testosterone found in adult males that were gestated in 2M and 2F IUPs: adult males from 2M IUPs have higher circulating levels of testosterone than do those from 2F IUPs (Clark et al. 1992b), and castrate 2M males are more responsive to fixed levels of exogenous testosterone than are 2F males (Clark et al. 1993a).

The reduced attractiveness to females and lower sexual competence of 2F male gerbils are characteristics one might expect natural selection to have acted vigorously to suppress, and there is some evidence that such selection has been at work. By segregating male and female fetuses in different uterine horns, a gerbil mother could protect her sons from prenatal contact with females and the reduced copulatory success that such contact entails. In fact, female gerbils tend to gestate sons in the right uterine horn and daughters in the left (Clark and Galef 1990), thus producing greater numbers of 2M male and 2F female offspring than would otherwise be expected.

The right ovaries of female gerbils produce a greater proportion of male-destined eggs than do the left ovaries (Clark et al. 1994). When we surgically exchanged right and left ovaries within female gerbils, they produced more male fetuses in their left than in their right uterine horns. On the other hand, female gerbils whose left and right ovaries we removed and reimplanted in their original locations continued to produce more males in right than in left uterine horns (Clark et al. 1994).

There is second way that gerbil mothers might influence the future potency of their sons. It has been known for some time that the amount of anogenital licking that a male rat pup receives can influence its pattern of copulatory behavior when adult: male rats receiving greater amounts of anogenital licking as infants have shorter ejaculatory latencies and shorter interintromission intervals than do brothers receiving less anogenital grooming as infants, though it is not known whether the amount of anogenital stimulation that a pup has received has any affect on its reproductive success (Moore 1983; C. L. Moore, personal communication).

We have found that the greater the number of male intrauterine neighbors a gerbil pup has while a fetus, the more time its mother spends grooming its anogenital area (Clark et al. 1989). And, as already mentioned, there is a correlation between the IUP that a male gerbil fetus occupies and its reproductive success when adult: male gerbils from 2F IUPs that receive relatively little maternal anogenital grooming (like male rats that received relatively little maternal anogenital grooming) have longer ejaculation latencies and longer postejaculatory intervals than do male gerbils from 2M IUPs. Consequently, effects of IUP on copulatory performance may be mediated by differences in maternal anogenital grooming.

Whatever the underlying mechanism, the selective pressures maintaining the copulatory patterns of 2F males are difficult to understand. Fitness costs of reduced potency are obvious;

the benefits of impotence are not. However, in a recent review of effects of testosterone on the reproductive behavior of birds, Ketterson and Nolan (1994) described several cases in which elevated levels of testosterone have two effects, both increasing sexual behavior and decreasing parental behavior. Such negative correlations among testosterone-sensitive behavioral traits might be design constraints that limit adaptation or trade-offs that persist because they provide a simple mechanism by which animals adjust their reproductive tactics in response to variations in environmental conditions.

We have recently begun to explore the possibility that adult 2F male gerbils (with low circulating levels of testosterone), though clearly less potent than their 2M brothers (with high circulating levels of testosterone), may increase their reproductive success by increasing their investment in the relatively few young they sire. The data are very promising. At least in the laboratory, 2F male Mongolian gerbils are consistently more attentive to young than are 2M males. Perhaps in natural circumstances, the increased investment 2M male gerbils make in their offspring compensates for their decreased copulatory success.

15.2 Field Evidence

Because of the difficulty both of identifying rodents from different IUPs in the field and of manipulating early experience in natural circumstances, almost all work on perinatal effects on the behavior of mammals has been carried out in laboratory populations. However, in a few instances, animals have been released into natural environments in experiments studying effects of perinatal experience on fitness. Ims (1987) placed 74, individually marked, laboratory-bred voles (*Clethrionomys rufocanus*) onto a 1.8-hectare island (thus doubling the density of voles there) and live trapped the population at 3-week intervals. Laboratory-bred females that succeeded in establishing themselves on the island came predominantly from litters with a female-biased sex ratio (64% female), while females that failed to establish themselves came from male-biased litters (65% male). Ims, citing vom Saal and Bronson (1980), suggested that voles from female-biased litters were less likely to mature in IUPs adjacent to males and were therefore more likely to be docile and socially tolerant in high-density conditions than were presumably more aggressive female voles from male-biased litters. Of course, it is also possible that intrauterine exposure of female voles to males simply increased their probability of migrating. Indeed, Holekamp et al. (1984) found that experimental perinatal exposure of female Belding's ground squirrels (*Spermophilus beldingi*) to testosterone significantly increased their rate of dispersal.

In an experiment conceptually similar to that of Ims (1987), Zielinski et al. (1992) monitored the movement patterns and reproductive success of laboratory-reared *Mus musculus* from known IUPs after they were released onto highway islands. As predicted from the outcomes of staged encounters between 2F and 2M female mice in the laboratory, 2M females in the wild had significantly larger territories than did 2F females. However, no effect of IUP on either probability of survival or number of uterine scars was found in the released population.

Jacquot and Vessey (1995) examined the relationship between litter composition and dispersal of white-footed mice (*Peromyscus leucopus*) in an oak-hickory woodlot and found that females with many brothers dispersed farther than did females with few brothers.

While such studies provide useful first steps in identifying possible effects of perinatal experience on survival and reproduction in natural circumstances, they have, as yet, failed to

provide compelling evidence of an impact of IUP on reproductive behavior in natural conditions. Technical limitations have made it impossible to monitor the reproductive profiles of animals from different IUPs in natural circumstances, so it is not too surprising that progress has been limited.

Recent evidence both from our laboratory (Forger et al. 1996) and that of Vandenberg (Vandenberg and Huggett 1994, 1995) suggest that it may be possible to determine the perinatal hormonal experience of adults by examining the morphology of their genitals. Vandenberg and Huggett (1994) have described a weight-corrected index of the distance between the anal and genital opening in female house mice that permits discrimination, at weaning, of females exposed to high and low levels of androgens while in utero. Forger et al. (1996) have provided evidence of marked differences in the relative weight of the genital musculature of adult male Mongolian gerbils from 2M and 2F IUPs. In the future it may be possible to correlate differences in the reproductive tactics observed in free-living rodents with morphological characteristics indicative of their early exposure to gonadal hormones and, consequently, to understand some of the variability in individual reproductive tactics exhibited by members of natural populations.

15.3 Effects of Perinatal Stress on Adult Reproduction

The laboratory experiments described above demonstrate that experiences of rodents during the perinatal period, especially experience of prenatal exposure to steroid hormones originating in uterine neighbors, can have important effects on subsequent patterns of reproductive behavior. We focus here on the impact of IUP on adult reproduction because exploration of effects of IUP on adult phenotypes has been the focus of much recent research on effects of perinatal exposure to hormones in mammals. Of course, it has been known for some time that variables other than IUP influence both exposure of fetuses to gonadal hormones and expression of hormone-sensitive aspects of adult phenotypes. Physical stress applied to pregnant rodents affects many of the same anatomical, physiological, and behavioral traits that are affected by IUP: age at vaginal opening, length of estrous cycle, and litter sex ratios are all greater in daughters of stressed than of unstressed females. Daughters of physically stressed mothers are both less fertile and less fecund than are daughters of unstressed mothers (Herrenkohl and Politch 1978; Herrenkohl 1979; Ward and Weisz 1980; Politch and Herrenkohl 1984; Kinsley and Svare 1988). Similarly, daughters born to pregnant house mice housed at high densities (a potential social stressor) have greater anogenital distances and reduced copulatory receptivity relative to controls (Allen and Haggett 1977; Zielinski et al. 1991). Sons of stressed rat mothers are less willing to copulate with females in estrous than are sons of unstressed mothers (Ward 1972), and the impaired sexual behavior of sons of stressed mothers is believed to reflect a shift away from a sensitive period for central nervous system development in the age at which fetal sons of stressed mothers experience a species-typical surge in circulating levels of testosterone (Ward and Weisz 1980).

Given the hormonal basis of both effects of stress and IUP on adult reproductive phenotypes in rodents, it is not surprising to find that effects on reproductive behavior of stressors and IUP interact in important ways. For example, Vom Saal et al. (1990) have reported that physical stress applied to mice during the last week of their pregnancies results in (1) higher circulating levels of testosterone in both male and female mouse fetuses and (2) increases in

anogenital distance and estrous cycle lengths in 2F, but not 2M, female mice. Direct effects of the internal state of a dam and effects of neighboring fetuses interact to produce the adult phenotype.

Conclusion

During prenatal life, the environment in which fetal mammals develop is open to manipulation by their dams. Variation in the hormonal state of dams, as well as in the sex of the uterine neighbors a dam provides for each of her fetuses, can have profound impact on the prenatal microenvironments to which her young are exposed from conception to delivery. As we have seen, the intrauterine environment in which young develop affects biologically important features of their reproductive behavior when adult.

Some maternal effects on adult phenotype are relatively direct. For example, stressors applied to a dam cause changes in the level of prenatal exposure of her young to gonadal hormones, which in turn cause changes in their reproductive tactics when adult: females from 2M IUPs produce daughters with different reproductive profiles than do females from 2F IUPs, and preferential anogenital licking of some sons increases their copulatory efficiency. Other maternal effects are less direct. Females produce litters of varying size and sex ratio and can influence some parameters of the distribution of fetuses in the uterus. In such cases, a mother influences the uterine environment in which her young mature by affecting the probability that they will occupy different IUPs.

Because direct and indirect maternal effects on mammalian development are mediated by similar hormonal mechanisms, study of IUP effects on adult behavior are not merely inherently interesting. Such studies also provide a means of exploring the hormonal mechanisms that underlie direct maternal effects on development of reproductive behaviors.

Perinatal effects on the reproductive behaviors of domesticated rodents are now well established. However, much difficult work remains to determine whether and how variation in conditions of perinatal life affect reproductive behavior of animals living in natural circumstances. Recent discoveries of markers of differential exposure to gonadal hormones in infancy in adult rodents of both sexes offer promise of progress in future studies of the fitness consequences of early exposure to hormones. Should such experiments prove successful, studies of effects on the adult reproductive behavior of naturally occurring variation in perinatal exposure to hormones will provide an opportunity for integrative investigations of mammalian behavior from molecular to population levels of analysis. Analysis of both direct and indirect effects of dams on the reproductive phenotypes of their offspring is prerequisite for development of such innovative research programs.

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