Chapter 13
Pregnancy Block from a Female Perspective

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Abstract Within a limited time after mating, exposure of female rodents to the scent of an unfamiliar conspecific male results in pregnancy termination. Since its discovery in mice, pregnancy block (or the 'Bruce Effect') has been confirmed in several other murine and microtine rodent species. Adaptive explanations for this behaviour have traditionally focused on advantages to the blocking male, but the suggested benefits to females remain controversial. Consideration of potential female benefits and the implications of female advantage in pregnancy block suggest that this behaviour could evolve with little or no reference to male advantage, and may represent a potential reproductive cost to stud males.

13.1 The Mechanism of Pregnancy Block

Following mating, exposure of female laboratory mice to the urinary scent of an unfamiliar male causes pregnancy disruption and return to oestrus (Parkes and Bruce 1961). The timing of exposure is critical. Around oestrus, female rodents show daily prolactin surges, increasing to twice daily after mating and peaking approximately one hour before the change to light and dark periods (Barkley, Bradford and Geschwind 1978; Ryan and Schwartz 1980). Pregnancy block occurs only if females are exposed to male scent coincident with two prolactin peaks, at least one during the light phase, while exposure outside these peaks fails to cause pregnancy block (Rosser, Remfry and Keverne 1989).

Pregnancy disruption is mediated through activation of a specific vomeronasal neuroendocrine pathway that inhibits prolactin release (Brennan and Binns 2005). As prolactin is essential for maintaining luteal function during early pregnancy in rodents (Stormshak, Zelinski-Wooten and Abdelgadir 1987), this inhibitory pathway causes luteolysis and hence pregnancy failure. The duration of sensitivity to pregnancy blocking signals varies between species, ranging from 4–5 days

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post-mating (pre-implantation) in *Mus* (Parkes and Bruce 1961) up to 17 days post-mating (pre- and post-implantation) in microtine species (Stehn and Jannett 1981).

During the period 4–6 h after mating, females learn the scent signature of the stud male, enabling them to recognise a different male scent as unfamiliar (Brennan, Kaba and Keverne 1990). Studies commonly define familiar and unfamiliar males according to whether they are from the same or different inbred strain of genetically identical individuals, such as C57BL/6, CBA or BALB/c (e.g. Yamazaki, Beauchamp and Wysocki 1983; Rosser et al. 1989; Peele, Salazar, Mimmack, Keverne and Brennan 2003). Other differences such as social status (Labov 1981a; Huck 1982), specific aspects of genotype (Coopersmith and Lenington 1998; Brennan and Peele 2003), or individual differences within an outbred strain (Bruce 1960) have also been investigated. However, exposure to unfamiliar individuals does not necessarily cause pregnancy block in wild mice (Coopersmith and Lenington 1998).

Exposure to the stud male's scent after mating fails to disrupt pregnancy (Bruce 1960) and may reduce the likelihood of pregnancy block if females are concurrently exposed to unfamiliar male scent (Thomas and Dominic 1987). Pregnancy blocking signals are thought to be androgen-dependent, and male scent gradually loses its efficacy to trigger pregnancy block over 6 weeks post-castration (Spironello-Vella and deCatanzaro 2001). However, in early studies castrated males were efficacious in blocking pregnancy throughout the 18 week post-operative period of study (Bruce 1960). Pregnancy disruption was also seen after exposure to the scent of females differing from the stud male's strain only at the major histocompatibility complex (MHC) (Yamazaki et al. 1983). The androgen-dependence of cues triggering pregnancy block is thus not entirely clear.

Memory formation has been shown to be contingent on mating (Kaba, Rosser and Keverne 1989), although some evidence suggests that prior familiarity gained through longer-term exposure to a particular male scent without mating may also reduce the efficacy of that scent to produce pregnancy block (Bloch 1974). Memorising the stud male's scent is thought to be mediated through disruption of the mating male's pregnancy-blocking signal by selectively enhanced inhibition in the accessory olfactory bulb (Binns and Brennan 2005). In the context of pregnancy block, females determine male familiarity via the vomeronasal/accessory olfactory system, through recognition of a combination of male-specific pheromones and MHC peptides (Brennan and Peele 2003; Leinders-Zufall, Brennan, Widmayer, Chandramani, Maul-Pavicic, Jäger, Li, Breer, Zufall and Boehm 2004). Fractionation studies of male urine demonstrate that major urinary proteins (MUPs), known to underlie individual recognition in mice (Hurst, Payne, Nevison, Marie, Humphries, Robertson, Cavaggioni and Beynon 2001), are not involved in the recognition of unfamiliarity in this context (Peele et al. 2003). MHC class I proteins bind a wide variety of peptide ligands (Engelhard 1994; Brennan and Zufall 2006) that stimulate directly both the vomeronasal organ (Leinders-Zufall et al. 2004) and main olfactory epithelium (Spehr, Kelliher, Li, Boehm, Leinders-Zufall and Zufall 2006). As the binding specificities of MHC molecules, and thus the range of bound peptides, vary between alleles (Engelhard 1994), MHC-associated urinary scents reflect the MHC alleles carried by the donor.

13.2 Functional Significance

Despite extensive investigation of pregnancy block since its discovery, a convincing explanation for its functional significance and evolutionary development has remained elusive. The postponement of reproduction inevitably impairs reproductive success, but in order to evolve the Bruce effect must offer an overall benefit. The costs and benefits may be very different for males and females.

13.2.1 Male Advantages

Many early studies into the Bruce effect appear to assume it evolved for male advantage (reviewed by Schwagmeyer 1979). Individual males that cause pregnancy disruption could potentially accrue selective advantages including siring of offspring at the expense of male competitors and avoiding the provision of paternal care to unrelated offspring post-partum (Rogers and Beauchamp 1976; Schwagmeyer 1979). However, male advantage alone cannot explain the evolution of a mechanism that relies on female response. Central to many of the arguments for male reproductive advantage in pregnancy block is the assumption that females will re-mate with the blocking male after terminating their current gestation, but this behaviour has not been demonstrated except in situations of enforced cohabitation (Labov 1981b). Indeed females able to evade such male induced reproductive costs are likely to be at a significant evolutionary advantage, and the adaptive advantages of a passive female response to male scent have been queried repeatedly (e.g. Bronson and Coquelin 1980; Brennan and Peele 2003).

13.2.2 Female Advantages

To address concerns over how apparently passive female responses to pregnancy blocking cues could have evolved, several hypothetical female advantages have been suggested. Pregnancy disruption in response to desertion by the original stud male would enable a female to re-mate and so potentially increase the likelihood of paternal investment in the offspring (Dawkins 1976). However, multiple paternity is common in litters of house mice (Dean, Ardlie and Nachman 2006), and males assist with communal nursing of offspring within their territory without evidence of bias (Manning, Dewsbury, Wakeland and Potts 1995; Lonstein and De Vries 2000).

It has been suggested that in order to avoid male infanticide (and hence wasted investment in gestation), females may terminate pregnancy resulting from an earlier mating and then re-mate with the infanticidal male (Labov 1981b; Storey 1986). However, in free-ranging tests of this hypothesis, artificial replacement of stud males did not alter inter-litter interval, suggesting that females did not block pregnancies when risk of infanticide was apparently increased (Mahady and Wolff 2002).

Others have suggested that females may terminate pregnancy, regardless of infanticide risk, to exert post-copulatory mate choice. Prospective drivers of female choice include competitive ability (Labov 1981a; Huck 1982), advantageous genetic combinations in offspring (Rülicke, Guncz and Wedekind 2006), avoidance of deleterious recessive alleles (Coopersmith and Lenington 1998) or phenotypic (and hence genotypic) rarity (Schwagmeyer 1979). Laboratory-based experiments that have manipulated likely aspects of male attractiveness show contradictory results. Behavioural observations show that inbred laboratory-strain females that mate with a different-strain stud male will block pregnancy if exposed to the scent of a male genetically identical to themselves (Rülicke et al. 2006). However, females are known to prefer less closely related mates (Penn 2002), and inbred offspring suffer poorer competitive success (Meagher, Penn and Potts 2000; Tregenza and Wedell 2000).

In almost all experiments examining potential behavioural and ecological mechanisms (e.g. Bruce 1963; Labov 1981a; Huck 1982), the presence of a male or his scent are assumed to result inevitably in female exposure. Thus most experimental designs have used small cages that prevent females from expressing a choice to avoid or approach male scent, or have applied the stimulus directly to the female nares or vomeronasal organ. Very few studies examine the role of female behaviour in controlling exposure.

The issue of timing has frequently been overlooked, but may be of critical importance in the interaction between behaviour and pregnancy block. As previously described, pregnancy block occurs only if females are exposed to male scent coincident with two prolactin peaks, at least one during the light phase, while exposure outside these peaks fails to block pregnancy (Rosser et al. 1989). By altering their exposure to male scent during these brief periods of sensitivity, females could choose to maintain or terminate pregnancy in the presence of unfamiliar male scent with minimal impact on normal behaviour at other times. Published studies have recorded female behaviour outside the critical period, 3–7 h after the expected dark phase prolactin peak, thus complicating behavioural interpretation. Drickamer (1989) tested female preference by presenting wild-derived females with paired samples of soiled male bedding, and found a general avoidance of unfamiliar male scent during the early stages of gestation. Conversely, an attraction to unfamiliar scent reported by deCatanzaro & Murji (2004) occurred when inbred CF1 females simultaneously chose between two CF1 inbred males, and one outbred laboratory strain male. In this case the increased investigation directed towards the novel strain male may be due to information gathering rather than preference (Hurst, Thom, Nevison, Humphries and Beynon 2005). Neither test corresponded to the sensitive period for the Bruce effect, rendering meaningful interpretation with regard to pregnancy block extremely difficult.

Female ability to control exposure to male scent at critical times may help to explain why similar pregnancy-blocking stimuli have produced conflicting results in different experiments. For example in one study manipulating male social status (Labov 1981a), females were housed directly below males, while a similar study (Huck 1982) housed females adjacent to males, separated by mesh. The pregnancy

blocking ability of dominant males was equal to subordinate males in the former study, but more efficacious in the latter. As the former study enforced female proximity to male scent while the latter did not, female attraction to dominant males may account for their greater efficacy in pregnancy block rather than any intrinsic difference in potency between dominant and subordinate male scents. In another study designed to examine the effect of carrying the deleterious t-complex genotype on male pregnancy blocking efficacy (Coopersmith and Lenington 1998), the apparatus ensured that the female's environment was saturated with male scent, suggesting that t-complex carriers were inherently less able to trigger pregnancy block than unaffected males. Interestingly in this study of genetically heterogeneous wild-derived mice, unfamiliar t-complex carriers induced no more pregnancy block than seen in control females that were not exposed to unfamiliar males, although the unfamiliar males must have differed genetically from the stud male, including MHC type. Thus pregnancy block did not occur in response to individual recognition or MHC differences between the stud versus an unfamiliar male in this study. However, high control blocking rates and behavioural restrictions imposed by the experimental apparatus make functional interpretation of female benefit impossible.

13.2.3 Maximising Female Reproductive Success

Successful reproduction in females demands substantial investment in gestation and lactation (Johnson, Thomson and Speakman 2001). While the reproductive success of males may be determined by the number of mates he can fertilise, females are limited by the number of young they can produce (Andersson 1994). The survival of young is the single most important factor in determining lifetime reproductive success in female mice and other species (Clutton-Brock 1988; König 1994). Optimal timing of reproduction is critical to offspring survival, and may be delayed according to the social environment through pheromonally-mediated mechanisms including puberty delay and oestrus inhibition (Bronson and Coquelin 1980). Female control of the Bruce effect may represent an additional method to avoid suboptimal reproductive timing according to social conditions. As females' home ranges may overlap more than one male's territory (Hurst 1987; Manning 1995), it seems likely that they would have the ability to control their exposure to male scent. Further, limiting sensitivity to a short period of the day considerably reduces opportunities for males to manipulate the Bruce effect to their own advantage (for example, by scent marking resources that females cannot afford to avoid such as food sources, Hurst and Nevison 1994).

The main factor affecting offspring survival in mice is thought to be social disruption of maternal behaviour (Peripato, de Brito, Vaughn, Pletscher, Matioli and Cheverud 2002), although other factors have been implicated including infanticide especially by non-stud males (Huck 1984), infection (e.g. Parker and Richter 1982), and predation (Millar, Havelka and Sharma 2004). The importance of the former effect can be seen in the sharp decrease in pup survival, and hence

female reproductive success, in nest sites that cannot be defended effectively, particularly those used by a large number of animals including non-stud males (Southwick 1955). Indeed, overcrowding has driven the evolution of pheromonally-primed reproductive suppression (Bronson and Coquelin 1980). Together with the timing of sensitivity to the Bruce effect, this suggests a novel functional explanation for pregnancy block in an ecological context—alteration of reproductive investment based on nest stability and the associated likelihood of offspring survival.

The sensitive period, occurring approximately 1 h before dark and up to 4 days post-mating (Parkes and Bruce 1961; Rosser et al. 1989), coincides with the time females are most likely to be in sheltered nest sites (Refinetti 2004). If females remain within the nest during this sensitive period, their exposure will be restricted to other animals that share their nest through the light phase. Pregnant females strongly defend their nest sites (Vom Saal, Franks, Boechler, Palanza and Parmigiani 1995) but their ability to do so depends on the physical protection afforded by the site and social pressure to use limited sites of shelter (Wolff 1985; Hurst 1987). The presence of fresh scents from other males, particularly from outside a familiar stable group, would indicate a nest site not defended effectively. Avoidance of novel male scents would allow pregnant females to avoid settling in such sites and, since pregnancy block occurs only in response to fresh scent (Peele et al. 2003), by the end of the light phase females will have had ample opportunity to exclude males or to leave the nest for an alternative. However, where this is not possible (e.g. because defendable nest sites are limited), females that terminate pregnancy until they can find a more suitable nest will avoid wasted investment, particularly prior to implantation.

Thus, rather than providing a reproductive benefit to males as traditionally assumed, the Bruce effect may have evolved solely to female advantage. Notably, this response also increases selective pressure on stud males to increase their investment in the territorial defence of nest sites that are preferred by females (Ims 1987). Females may improve their own reproductive success through threat of pregnancy block, compelling stud males to invest more heavily in nest defence.

13.3 Future Work: Challenging Assumptions

The hypothesis that nest stability alters the probability of pregnancy block needs to be tested using naturalistic enclosures where animals have the opportunity to exhibit normal choices that are restricted by the laboratory environment. Altering the apparent stability of nest sites artificially by manipulating scent cues and/or their occupation by different males will then allow female nesting decisions to be related to the outcome for the maintenance or blocking of pregnancy. Analysis of re-mating strategies following pregnancy block, including paternity and the subsequent willingness of females to re-mate, is also essential to evaluate advantages from both a female and male perspective.

Male scent is typically used as the pregnancy-blocking stimulus during investigation of the Bruce effect. However experiments addressing the androgen-dependency

of pregnancy block have used only laboratory strains, many of which are thought to be very closely-related intersubspecific hybrids (Yoshiki and Moriwaki 2006). These inbred laboratory mouse strains lack the context of the complex genetic background variation between individuals found in wild populations. Examining androgen-dependent scent characteristics, while ignoring the potential relevance of other scent cues to females in the wild, risks artificially exaggerating the importance of androgens in defining pregnancy blocking scents. The hypothesis that scent unfamiliarity may be additive and multifactorial needs to be tested using genetically disparate mice (e.g. wild-derived) of both sexes as scent donors This would help to evaluate the significance of androgens and individual recognition in pregnancy blocking signals, and the extent to which other aspects of conspecifics' scents are also relevant to the Bruce effect.

Memorising MHC-associated scent enables females to discriminate between stud and unfamiliar males, but may also allow a female to monitor scent changes in the stud male (e.g. during disease). Pregnancy could be disrupted to avoid infection of the offspring, particularly where transplacental infection could result in foetal death (e.g. Fenner 1982). The sensitivity of females to unfamiliar MHC peptide ligands in the context of pregnancy block (Leinders-Zufall et al. 2004) provides a potential mechanism for detecting changes in familiar stud male infection status since MHC molecules bind foreign peptides from pathogens. Future work could include observations of female behaviour towards infected and uninfected males during the critical period for the Bruce effect, and examine the efficacy of such scents in inducing pregnancy block using different pathogens of varying life cycle and virulence.

Lastly, the Bruce effect may be part of a general response to stressful circumstances where reproductive investment may be threatened. Pregnancy block is controlled through selectively enhanced inhibition at the level of the accessory olfactory bulb and medial amygdala (Binns and Brennan 2005). Acute stress has been shown to increase activity in the medial amygdala (Gammie and Stevenson 2006), and wild mice are known to block pregnancy in response to apparently minor stressors such as handling and cage cleaning (Chipman and Fox 1966). The potential for generalising the pregnancy blocking response suggests that detection of unfamiliar scent may be only one aspect of a more complex stress response, and that females may use this behaviour to optimise reproductive investment, taking into account multiple risks present in the natural environment.

The challenges remain to show whether altering the likelihood of offspring survival alters the behaviour of females to maintain or terminate pregnancy, to examine whether males are advantaged or disadvantaged by the Bruce effect, and to understand the importance of this intriguing behavioural and neurophysiological mechanism in house mouse ecology.

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