Title: Prenatal adversity modulates the quality of maternal care via the exposed offspring.

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Abbreviations: HFD, high fat diet; LPD, low protein diet; USV, ultrasonic vocalisation

Abstract

Adversities in pregnancy, including poor diet and stress, are associated with increased risk of developing both metabolic and mental health disorders later in life, a phenomenon described as fetal programming or developmental origins of disease. Predominant hypotheses proposed to explain this relationship suggest that the adversity imposes direct changes to the developing fetus which are maintained after birth resulting in an increased susceptibility to ill health. However, during pregnancy the mother, the developing fetus and the placenta are all exposed to the adversity. The same adversities linked to altered offspring outcome can also result in suboptimal maternal care which is considered an independent adverse exposure for the offspring. Recent key experiments in mice reveal the potential of prenatal adversity to drive alterations in maternal care

through abnormal maternal-pup interactions and via alterations in placental signalling. Together, these data highlight the critical importance of viewing fetal programming holistically paying attention to the intimate, bidirectional and reiterative relationship between mothers and their offspring.

1 Introduction

One of the most common adversities to blight pregnancy is overnutrition, which is estimated to impact one third of all pregnancies in developed countries. Further, there is an increasing burden to developing countries[1]. Obesity in pregnancy is specifically associated with higher risk of pregnancy complications and poorer outcomes for children. These include the increased risk of neurologic disorders including attention deficit/hyperactivity disorder, autism and schizophrenia as well as metabolic syndrome – findings that have, at least in principle, been reproduced in a number of animal models [2]. The reported association between obesity and other prenatal adversities with later life illnesses has led to suggestions that the exposure induces direct changes to the fetus which persist into adulthood increasing susceptibility to disease – a relationship which is often referred to as fetal programming [3] or developmental origins of disease [4]. However, in humans exposures rarely occur in isolation nor are they limited to pregnancy, and there are different patterns and long-term consequences of fetal adversities depending on their timing, nature and magnitude. Considerable progress in our understanding of the mechanisms underpinning the fetal programming phenomenon has been made using animal models but until recently little attention has been paid to the impact of prenatal adversities on the mother's health and behaviour, and how the combination of prenatal adversity and suboptimal maternal care could contribute to offspring outcomes [5]. This is important because variations in maternal care in rodents, independent of prenatal exposures, have been linked to altered offspring behaviour and persistent changes in the offspring brain [6]. High fat diet (HFD) [7-9], low protein diet (LPD) [10], chronic, psychological stress [11],

physical restraint [12], chronic corticosterone administration [13] and vitamin D deficiency [14] in pregnancy are just some of the stressors that have been reported to induce changes in maternal behaviour in animal models. There is very little data on the consequences specifically of high fat diet in a human pregnancy on maternal care but maternal obesity is a well known risk factor for maternal depression and anxiety [15] and there are studies that link maternal obesity to lower quality maternal attachment [16] and maternal parenting stress [17]. Consequently, adversities in the prenatal period may contribute to altered outcomes either directly by impacting the fetus or indirectly by altering maternal care giving, or potentially by both routes. This imposes considerable complexities in the interpretation of studies characterising the causes and consequences of early life adversity. Recent studies have begun to address gaps in our knowledge and, through careful experimental design, demonstrate that both prenatal and postnatal communication between offspring and mother has the potential to influence postpartum maternal care potentially contributing to longer term outcomes.

2 High fat diet influences maternal behaviour through changes to offspring

In a recent study published in *Proceeding of the Royal Society B*, Baptissart and colleagues employed a high fat diet (HFD) intervention with cross fostering to dissect apart the contribution of the stressor of obesity and HFD in pregnancy to alterations in maternal behaviour [18]. HFD has previously been reported to result in alterations in maternal care but in all but one of these studies, dams continued on the dietary alteration while their behaviour was being assessed (**Table 1**). In this study, female C57BL/6 mice were fed either a control diet (10% calories from fat) or a HFD (45% calories from fat) from 3 weeks of age to 9 weeks of age. Prior to mating, dams fed on the HFD gained more weight and were less glucose tolerant than dams fed the control diet. After mating to males maintained on a control diet, pregnant dams remained on their respective diets throughout pregnancy and while mothering their pups. At birth, four experimental groups were generated: 1)

dams fed a control diet caring for control diet-exposed offspring (CT:ct); 2) dams fed a HFD caring for HFD-exposed offspring (HF:hf); 3) dams fed the control diet caring for HFD-exposed offspring (CT:hf); and 4) dams fed a HFD caring for control diet-exposed offspring (HF:ct) (**Figure 1a**). In all cases, pups were either fostered within groups or across groups to control for the disruption of this event, and pup sex was balanced. HF:hf dams spent less time interacting with their pups and nesting, and more time on non-interactive behaviours (exploration, wall-rearing) than CT:cf dams, essentially as previously reported [7, 8]. However, dams nursing mis-matched pups (CT:hf and HF:ct) did not clearly align with either matched pairing. This demonstrated that the HFD is not purely acting as a stressor on the dam altering her behaviour. Instead, both the prenatal and postnatal environment contribute to the altered maternal behaviour. Further analysis in a generalised linear model identified *in utero* exposure of the fetus as the strongest predictor of the postnatal maternal behaviour i.e. pups exposed *in utero* to the HFD appeared to be influencing the behaviour of dams not exposed to the diet. This remarkable study demonstrates that an adversity experienced by the fetus *in utero* has the potential to alter the mother's behaviour postpartum.

3 Offspring communication regulated by imprinting influence maternal behaviour

The newborn is known to elicit maternal care through many different interactions, any one of which could be impacted during fetal development. Newborns influence maternal care-giving behaviour through suckling [19], through calls in the form of ultrasonic vocalisations (USVs) [20] and, potentially, through body temperature changes, as recently reviewed [21]. Although maternal HFD has not been reported to impact suckling behaviour [22], HFD-exposed offspring can exhibit alterations in USVs [23]. Pup USVs normally increase in intensity and frequency during separations from the mothers, hence the term "whistles of loneliness" [24]. These communications from the pups are known to stimulate a number of maternal behaviours including nest building, pup retrieval and nursing [20]. Seven day old pups exposed gestationally to a HFD (60% calories from fat) reportedly vocalise less than non-

exposed controls (13.5% calories from fat) when isolated from their mothers [23]. Therefore, HFD in pregnancy could alter maternal behaviour by impacting the offspring's ability to communicate postnatally. While Baptissart and colleagues did not measure USVs in their study and findings from different HFD studies vary (**Table 1**), nonetheless the observation that prenatally exposed pups can influence a foster mother's behaviour postnatally means that studies in animal models linking prenatal adversity to later life health must be carefully interpreted. Adversities in pregnancy may disrupt maternal care indirectly by changing the way in which the offspring communicate with their mothers after they are born (**Figure 2**).

We recently reported reduced USVs in pups with loss-of-function of *Paternally expressed gene 3* (*Peg3)* [25]. *Peg3* null pups born to wild dams make significantly less USVs when separated from their mothers than wild type pups (**Figure 1b**). Consistent with the importance of USVs in pup retrieval [26], wild type dams who carried and cared for these low vocalising pups were significantly slower to sniff and then to retrieve their pups. We observed no changes in a nest building behaviour nor in the dams' direct interactions with their pup during the nest building task. There was, however, a marked difference in maternal anxiety between the dams carrying and caring for wild type pups and those that carried and cared for *Peg3* null pups with dams exposed to the *Peg3* null pups displaying higher levels of anxiety in the elevated zero maze test. Loss of *Peg3* expression has a significant negative impact on placental development and fetal growth [27, 28]. Importantly, *Peg3* mutant mice display both metabolic [29] and behavioural disorders as adults [27] [30]. The reason this study is relevant to research into fetal programming is because *Peg3* belongs to the remarkable family of imprinted genes that are expressed exclusively or predominantly from one parental allele as a consequence of epigenetic events initiated in the parental germline and consolidated after fertilisation [31]. Changes in epigenetic gene regulation induced by the prenatal adversity have been suggested as a mechanism underpinning the fetal programming phenomenon, recently reviewed

[32]. Epigenetic marks, which are by definition inherited through the cell cycle, play a key role in maintaining a cellular memory of gene transcription patterns. Therefore, environmental exposures that alter epigenetic marks can, in theory, be "remembered" by the organism even after the exposure stops.

4 Prenatal adversities alter the expression of imprinted genes

A number of interventions in pregnancy have been linked to the altered expression of imprinted genes in the offspring (**Table 2**). As an example, we recently showed that a low protein diet restricted to pregnancy results in loss of paternal silencing of the imprinted gene *Cdkn1c* in the offspring maintained into adulthood [33]. This formally demonstrates that adversity in pregnancy can influence the epigenetic processes that maintain allelic gene expression in the developing fetus. High fat diet, in combination with prenatal obesity or just during pregnancy, has not been shown to impact expression of *Peg3*. Further work is therefore required to demonstrate *Peg3* responds epigenetically to prenatal adversity. Moreover, loss of expression is a considerable insult to development and it will need to be shown that more modest changes in gene expression have a phenotypic consequence that could impact another individual's behaviour.

5 Placental imprinting modulates maternal behaviour

Interpreting studies on the interaction between prenatal adversities and later life outcomes is further complicated by the potential of placental endocrine dysfunction to alter outcomes for mother and offspring. The placenta is a fetally-derived organ predominantly recognised for its role as a sophisticated transportation system bringing nutrients to the fetus and removing waste. Less well recognised is the function of the placenta as the signalling coordinator of pregnancy. The placenta manufactures vast quantities of hormones that act on the mother to establish and maintain the adaptations necessary for pregnancy [34] and promote fetal brain development [35].

Hormones produced by the placenta include placental lactogen-like hormones (Prls) some of which are known to bind and activate the prolactin receptor [36]. This receptor is required for the appropriate induction of maternal care in mice [37] with a key site of action being the medial preoptic area of the hypothalamus [38]. Infusion of placental lactogen directly into this area of the brain induces maternal care in the non-pregnant rodent [39]. These indirect infusion experiments highlight the potential function of the placenta in the programming of maternal care. We recently tested this theory in a novel mouse model in which we were able to manipulate the size of the placental endocrine compartment by genetically altering the expression of the imprinted gene *Phlda2. Phlda2* negatively regulates the major endocrine lineage of the mouse placenta [40]. We exposed wild type female mice to fetuses with different doses of *Phlda2*, and thus to different doses of placental hormones. As the dose of placental hormones increased, we observed increased maternal nurturing and pups grooming [41]. This experiment formally demonstrates that imprinted genes expressed in the placenta, and regulated by epigenetic marks, can influence the behaviour of mothers. This opens the possibility that prenatal adversities in pregnancy could influence maternal behaviour via alterations in the placenta mediated by imprinted genes (**Figure 2)**.

6 Potential for prenatal adversity to alter placenta signalling

A number of studies report changes in placental hormones and/or placental endocrine lineages after exposures of pregnant females to a variety of stressors (**Table 3**). One study examining overnutrition in pregnancy specifically assayed the expression of placental hormones and reported a significant decrease in the expression of two hormones [42]. In another study, changes in fat content of the maternal diet altered the expression of a number of hormones in the placenta in a sexually dimorphic manner [43]. Evidence that maternal stressors impact the expression of imprinted genes that regulate development of placental endocrine lineages is less well established. A focused study on the consequences of an obesogenic diet on the placental expression of imprinted genes

reported increased expression of several imprinted genes including *Igf2* and a non-significant increase in expression of *Phlda2* [44]. In rats, LPD resulted in decreased expression of placental *Ascl2* [45]. As well as diet, the infection status of the dams appears to be important for placental imprinted gene expression. Challenging pregnant dams with *Campylobacter rectus*, a periodontal pathogen associated with adverse pregnancy outcomes, resulted in decreased placental expression of several imprinted genes including *Ascl2* and *Igf2* [46]. Together, these data support an interaction between maternal stressors and alterations in the expression of imprinted genes. However, few studies have examined allelic expression changes in the placenta and it is not clear whether these changes in expression occur as a result of changes in imprinting, changes in the expression of the normally active allele or changes in cellular composition, which must be addressed.

7 Conclusions and Outlook

In conclusion, there is considerable experimental evidence that the environment mothers experience in pregnancy can alter her behaviour towards her offspring. There is emerging evidence that adverse exposures may act not directly on the mother but indirectly via her developing fetus and associated placenta. Together, these data highlight the critical importance of viewing fetal programming holistically paying attention to the intimate, bidirectional and reiterative relationship between mothers and offspring (**Figure 2**).

Figure legends

Figure 1. Neonatal and placental influences on maternal behaviour

Dietary influence on maternal behaviour via the exposed neonate. Obese wild type dams exposed to high fat diet (HFD) in pregnancy give birth to pups that can influence a normal weight, non-HFD exposed dam's behaviour. Arrows indicate fostering of pups to generate matched and mis-matched groups.

Programming of maternal care by placental imprinting. Wild type dams exposed to fetuses with different gene doses of the maternally expressed *Phlda2* gene (doses given in top row of table) and consequently different doses of placental hormones (doses given in bottom row of table) show alterations in pup focused behaviours consistent with the role of placental hormones in inducing maternal care. Enhanced behaviour is maintained even when "programmed" dams are given pups from another dam.

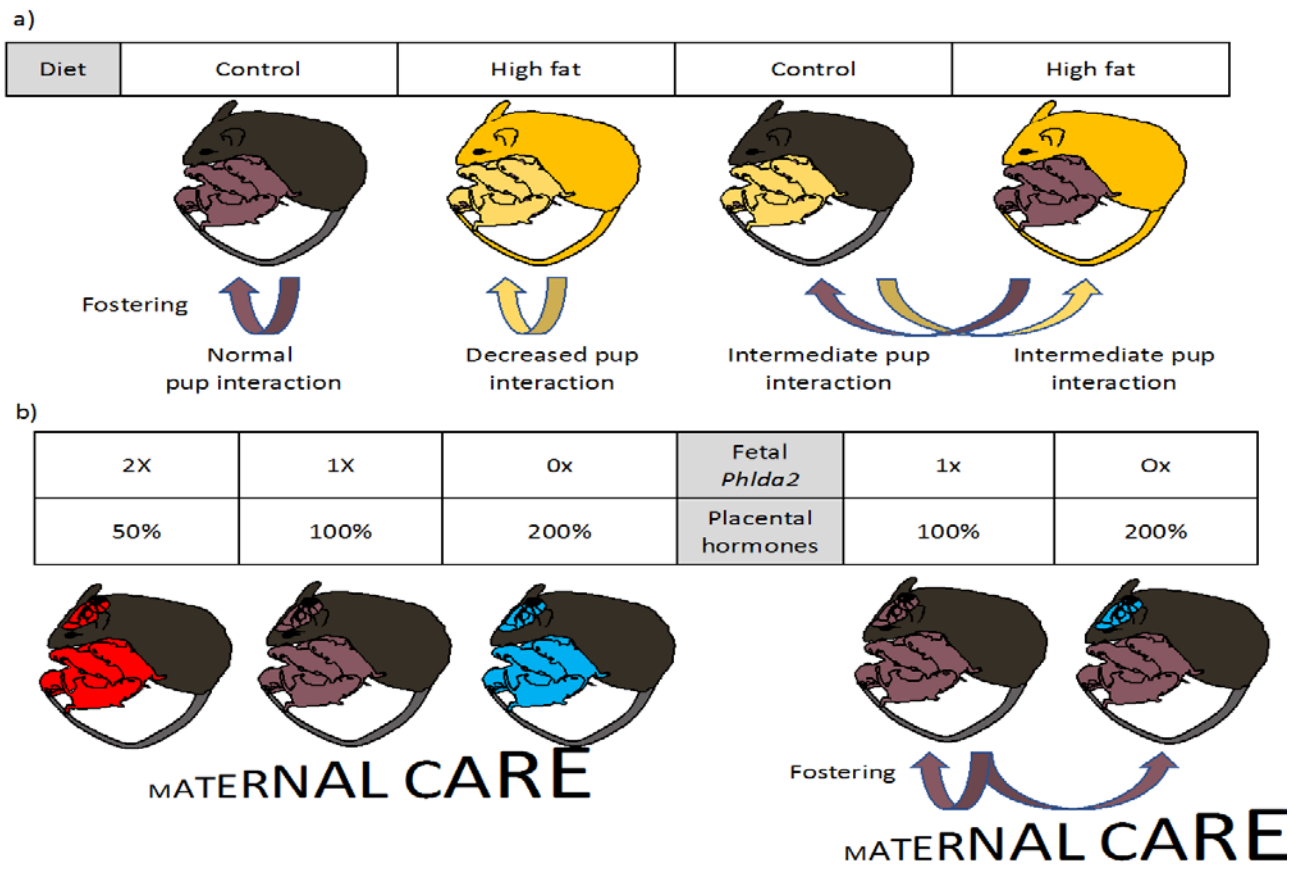
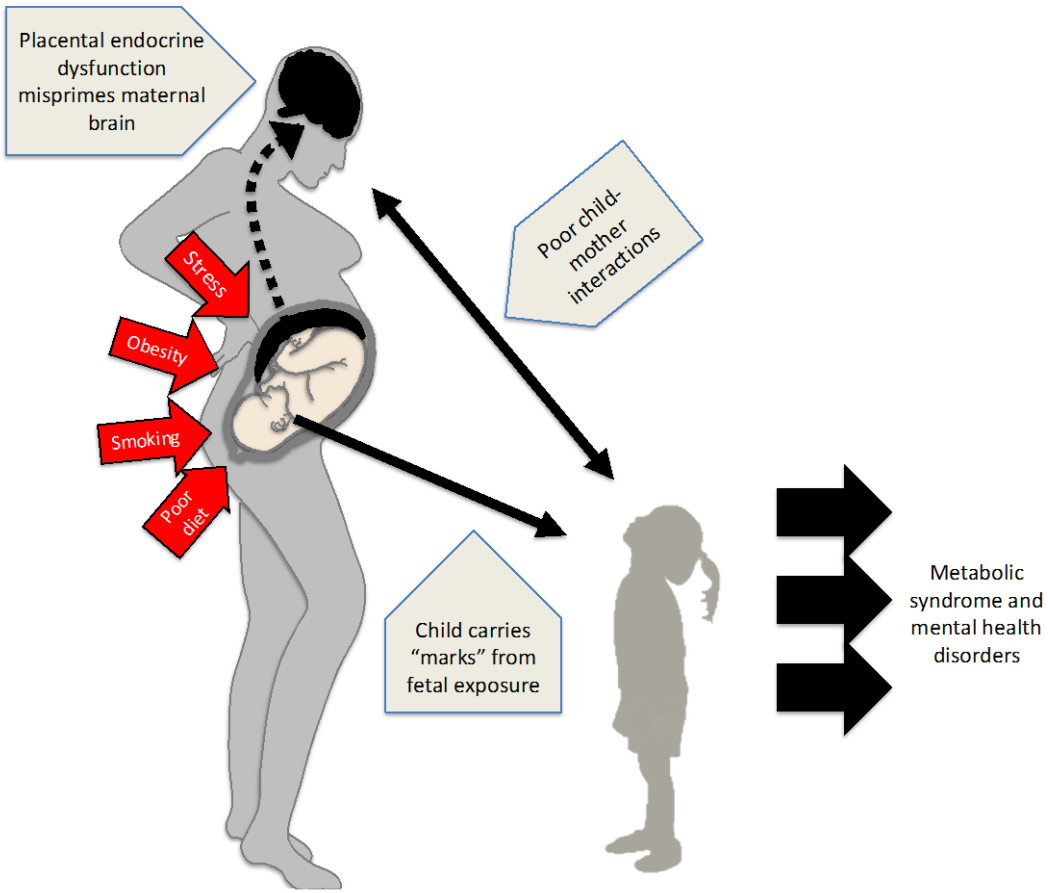


Figure 2. Prenatal adversity and the intimate, bidirectional and reiterative relationship between mother and offspring.

Prenatal adversities expose the mother, the developing fetus and the placenta. Alterations to the fetus have the potential to change the way the child interacts with their mother after birth (solid arrow), resulting in suboptimal maternal care. Alterations to the placenta have the potential to misprogram maternal behaviour (dotted arrow) also resulting in suboptimal maternal care. These misaligned reiterative interactions between mother and child (solid double headed arrow) further contribute to poor outcomes for children later in life.



216 **Tables**

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218 **Table 1. High fat diet protocols associated with alterations in maternal behaviour**

219 Only rodent studies focused on high fat diet protocols and maternal behaviour are reported

Species	Diet	Duration of HFD	Response to HFD	Reference
Sprague-Dawley rats	45% v. 25% v. 5% fat by weight	One week premating for duration	Decreased and delayed non-postural nursing Increased postural nursing Decreased total nursing Increased pup grooming Increased self grooming More time with litter	[47]
Sprague-Dawley rats	60% v. 17% calories from fat	From day 2 of gestation for duration	Dark phase/week one: Increased arch back nursing Increased total nursing Decreased resting	[9]
Wistar rats	45% v. 18% calories from fat	From day 1 of gestation for duration	P3 to P8 Decreased licking and grooming of pups	[7]
C57BL/6 mice	58% v. 10.5% calories from fat	10 weeks premating to E15.5	Increased frequency of cannibalistic episodes	[48]

C57BL/6 mice	45% v. 10% calories from fat	6 weeks premating for duration	Decreased pup interactions/increased exploration	[18]

Table 2. Prenatal adversities resulting the altered expression of imprinted genes.

Only studies explicitly reporting altered expression of imprinted genes are reported. For mouse studies the first day of visible plug is referred to as embryonic day (E) 0.5. For rat studies, first day of observable sperm can be referred to as gestational day (GD) 1. LPD = low protein diet; HFD = high fat diet; QPCR = quantitative real time polymerase chain reaction.

Species	**Stressor**	**Duration**	**Findings**	**Reference**
ICR mice	50% food restriction	E12.5 to E16.5	QPCR: decreased brain *Cdkn1c* and *Snrpn*; increased liver *H19*, *Grb10, Peg3* (male), Igf2r (female) and Zac1 (female) at E16.5	[49]
C57BL/6 mice	LPD (8% calories from protein) v. Control (20%)	E0.5 to term	QPCR at P21: decreased liver *Gnas*	[50]
Wistar rats	Intraperitoneal dexamethasone at GD15	GD15-GD20	QPCR at GD20: increased liver Igf2, Cdkn1c, Grb10 and H19; decreased placental Igf2	[51]

Cdkn1c-FLucLacZ 129S2/SvHsd	LPD (8.1% calories from protein) v control (18.3%)	E0.5 to E18.5	QPCR and Imaging: reactivation of paternal *Cdkn1c* allele	[33]
ICR mice	50% food restriction	E12.5 to E16.5	QPCR at E16.5: Increased placental *Peg3*	[49]
C57BL/6 mice	HFHS (30% calories from fat, 36% sugar) v control diet (11% fat, 7% sugar)	E0.5 to E15.5	QPCR at E15.5: increased placental *Igf2* (non-significant increase in *Phlda2* and *Cdkn1c*)	[44]
C57BL/6 mice	Cafeteria (58% calories from fat) v. control (10.5%)	12 weeks premating to E14.5	QPCR: increased placental *Igf2* (male only).	[52]
Sprague-Dawley rats	HFD (60% calories from fat) v. control (13.5%)	GD2 to GD21	QPCR: increased placental *Igf2* (female only).	[53]
Sprague-Dawley rats	LPD (4.6% calories from protein) v. Control (19%)	GD1 to GD14 or GD18	QPCR: decreased *Ascl2* day 18.	[45]

CD1 mice	LPD (6% calories from protein) v. control (22%)	E4.5 to E17.5 with or without oral gavage of *Heligmosomoides bakeri* worms	Microarray: LPD only - increased placental *Igf2*.	[54]
BALB/c mice	Intra-chamber injection of live *Campylobacter rectus* strain 314 at E7.5	E7.5 to E16.5	Microarray: decreased placental *Ascl2*, *Igf2*, *Cdkn1c*, *Peg3*	[46]

Table 3. Prenatal adversities associated with alterations consistent with placental endocrine dysfunction.

Only changes in members of the placental lactogen-like gene family (*Prls*) or placental endocrine lineages are reported. Where publications state "placental prolactin" in late gestation, they likely refer to placental lactogens. In mice, day of visible plug is embryonic (E) day 0.5 and length of gestation is 19-20 days depending on strain. In rats, day of sperm cell detection in female is day 1 and length of gestation is 21-24 days depending on strain

Species	**Stressor**	**Duration**	**Findings**	**Reference**
Dietary Stressors				
C57BL/6 mice	HFHS (30% calories from fat,	From E0.5 to E15.5	QPCR: decreased placental *Prl2b1* and *Prl7b1*	[42]

	36% sugar) v control diet (11% calories from fat, 7% sugar)			
NIH Swiss mice	LFD (10% calories from fat) versus "control" (26% calories from fat) v. HFD (54% calories from fat)	From 30-35 weeks premating to E12.5	Microarray: changes in male/female ratio of *Prl2c3*, *Prl3b1*, *Prl3d2*, *Prl5a1* and *Prl7c1*.	[43]
Dorset Horn×Mule sheep	Moderate v. high levels of nutrition	After transfer of day 4 embryos (Border Leicester/Scottish Blackface x Dorset Horn) until day 100 of gestation	Radioimmunoassay: low maternal serum placental lactogen	[55]
Swiss Webster (ND4) mice	50% food restriction	From E1.5 to E11.5	Histology: reduced junctional zone Microarray: decreased placental *Prl8a8*.	[56]
Fischer 344 rat	LPD (5% calories from protein) v. 20% alcohol in	From day 6 to day 20	Radio-receptor assay:	[57]

	water v. control (18% calories from protein)		decreased maternal serum and placental levels of "prolactin" (both LPD and alcohol)	
C57BL/6 mice	LPD (6% calories from protein) v. Control (20%)	Two weeks premating to E10.5, E17.5 or E18.5	Histology: reduced junctional zone QPCR: decreased *Prl3a1* at E18.5 (non-signficant decrease in *Prl5a1* and *Prl8a8*)	
Fischer 344 rat	LPD (5% calories from protein) v. control (20% calories from protein)	From day 6 to day 20	Radio-immuno assay: decreased maternal serum levels of rat "prolactin"	[58]
Sprague-Dawley rats	LPD (6% calories from protein) pair matched with control (20% calories from protein)	From day 6 to day 19	Northern: Decreased placental *Prl6a1*; Western: Reduced *Prl6a1* secretion from explant cultures.	[59]
Sprague-Dawley rats	LPD (4.6% calories from protein) v. control (19% calories from protein)	From conception to day 14 or day 18	QPCR: decreased placental *Prl5a1* and *Prl2c1* day 14 and 18	[45]

CD1 mice	LPD (6% calories from protein) v. control (22% calories from protein) with or without oral gavage of Heligmosomoides bakeri worms	From E4.5 to E17.5	Microarray: LPD only - decreased placental "prolactin",	[54]
Other maternal stressors				
Holtzman rats	Continuous infusion of dexamethasone	From day 13 to day 20	Mini-array analyses and Northern: decreased *Prl8a8*, *Prl3b1*, *Prl6a1* and *Prl3d4*; *In situ* hybridisation: mislocalisation of spongiotrophoblast into labrynth	[60]
Suffolk sheep	Heat stress (40^{o}C for 9 hours per day then 30^{o}C for 15 hours/day; 40% humidity) v. thermoneutral	From day 64 to day 136-141	Radioimmunoassay: reduced maternal serum placental lactogen (by >60%).	[61]

	(18-20°C; 30% humidity).			
Fisher rats	Chromium (IV) in tap water	From day 7 to Day 19	Northern blot: decreased placental *Prl3d1* and *Prl3b1*; *Prl4a1*, *Prl8a2*. Radioimmunoassay: decreased maternal serum Prl3d1 and Prl3b1; Histology: reduced "spongiotrophoblast"	[62]
CD1 mice	Perfluorooctanoic acid by gavage	From E10.5 to E15.5	Histology: Decrease in parietal trophoblast giant cells, glycogen cells and sinusoidal trophoblast giant cells; Northern: decreased placental *Prl3b1*, *Prl7a1* and *Prl7a2*.	[63]
Sprague-Dawley rats	Triclosan by gavage	From day 6 to day 20	Radio-immunoassay: decreased maternal serum "prolactin"	[64]
CD1 mice	Reduced utero-placental perfusion pressure	From E12.5 to E16.5-E18.5	*In situ* hybridisation: reduced area of junctional zone.	[65]

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Conflict of Interest

The author declares no conflict of interest.

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