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1 **The Placental Programming Hypothesis: Placental endocrine insufficiency and the co-**
2 **occurrence of low birth weight and maternal mood disorders**

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9 **Abstract**

10 Polypeptide hormones and steroid hormones, either expressed by the placenta or dependant
11 on the placenta for their synthesis, are key to driving adaptations in the mother during
12 pregnancy that support growth in utero. These adaptations include changes in maternal
13 behaviour that take place in pregnancy and after the birth to ensure that offspring receive
14 appropriate care and nutrition. Placentally-derived hormones implicated in the programming
15 of maternal caregiving in rodents include prolactin-related hormones and steroid hormones.
16 Neuromodulators produced by the placenta may act directly on the fetus to support brain
17 development. A number of imprinted genes function antagonistically in the placenta to regulate
18 the development of key placental endocrine lineages expressing these hormones. Gain-in-
19 expression of the normally maternally expressed gene *Phlda2* or loss-of-function of the
20 normally paternally expressed gene *Peg3* results in fewer endocrine cells in the placenta, and
21 pups are born low birth weight. Importantly, wild type dams carrying these genetically altered
22 pups display alterations in their behaviour with decreased focus on nurturing (*Phlda2*) or
23 heightened anxiety (*Peg3*). These same genes may regulate placental hormones in human
24 pregnancies, with the potential to influence birth weight and maternal mood. Consequently,
25 the aberrant expression of imprinted genes in the placenta may underlie the reported co-
26 occurrence of low birth weight with maternal prenatal depression.

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30 Key word: Placental endocrine insufficiency, imprinted genes, hormones, maternal behaviour,
31 low birth weight, depression
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Introduction

Women are at high risk of developing mood symptoms in pregnancy with one in seven women reporting clinically concerning symptoms of depression [1-3]. Depression in pregnancy is commonly comorbid with anxiety [4] and these mood disorders have both been linked to a higher risk of low birth weight and difficulties in infant development including emotional and behavioural problems, cognitive impairment and psychopathology [5]. Despite considerable epidemiological data reporting links between these exposures and outcomes, the underpinning biological mechanisms are unknown nor can we currently predict specific outcomes. Progress is hampered because the causes and consequences of maternal mood disorders are complex. There are multiple environmental and genetic components, exposure can be prenatal and/or postnatal, and many studies rely on questionnaires completed by mothers whose perceptions may be impacted by depression [6, 7]. The prevalent explanation for the co-occurrence of mood disorders in pregnancy and adverse outcomes for children is that the mood disorders drive changes in the fetus altering the health trajectory of the child, known as "fetal programming" [8]. However, we suggest an alternative mechanism, supported by recent data from our experimental animal studies [9, 10], which is that placental endocrine insufficiency alone causes both the mood disorder and the adverse outcomes – which we refer to as the "placental programming hypothesis" (**FIG 1**). This hypothesis fits some aspects of the epidemiology of pregnancy, but has not been directly tested in clinical studies. Importantly, this placental mechanism does not exclude the possibility of changes to the fetus driven by other adversities or indeed by placental endocrine insufficiency.

Maternal behaviour

The placenta is a fetally-derived organ fundamental to pregnancy [11, 12]. In addition to transporting nutrients and moderating fetal exposure to maternal factors, the placenta is a super-endocrine organ involved in manufacturing vast quantities of polypeptide and steroid hormones to induce and maintain maternal adaptations in pregnancy, and prepare the mother for her role in caring for her infant [12]. In rodents, maternal adaptations during pregnancy include changes in behaviour such as increased appetite, increased anxiety and altered nest building and grooming. The greatest changes take place after birth with mothers focused on nurturing their offspring, providing food, warmth, shelter and protection [13]. Both virgin females and male rodents can assume parental behaviour but this response requires several days of exposure to the pups in order to be initiated. In contrast, new mothers are already primed by hormonal exposures during pregnancy to respond immediately to the presence of their offspring. Inappropriate maternal behaviour may result from intrinsic deficiencies in the mother, as has been reported in many genetically modified mouse models, or as a consequence of placental endocrine insufficiency [9, 10].

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Placental hormones implicated in the induction of maternal behaviour

Key hormones involved in pregnancy-associated behaviours are the lactogenic hormones pituitary prolactin and prolactin-related hormones manufactured by the placenta, sometimes referred to as placental lactogens (see later). Prolactin is secreted from the pituitary to act locally on the maternal brain whereas the placentally-derived lactogenic hormones are thought to gain access to the maternal brain via the cerebrospinal fluid [14]. Key studies in rodents have experimentally demonstrated the importance of lactogenic signalling for maternal behaviour. These studies involved the infusion of prolactin or placental lactogen directly into the brains of non-pregnant animals which resulted in the stimulation of aspects postpartum maternal behaviour such as pup retrieval [14-19]. Conversely, experimentally-induced low levels of prolactin in pregnancy have been linked to increased postpartum anxiety and decreased pup retrieval [20]. Lactogenic hormones are thought to mediate their activity, at least in part, via the maternal prolactin receptor (Prlr) [21]. Loss of function of Prlr in mice was shown to result in a deficit in maternal behaviour [22, 23] and, more precisely, loss of function of Prlr restricted to the medial preoptic area of the brain [24]. Signalling via Prlr is also required for the pregnancy-related increases in neurogenesis that take place within the subventricular zone, one of three regions of the brain where neurogenesis persists in adults [23, 25]. Lactogenic activity may impact pregnancy-related changes in neurogenesis in the subgranular zone located within the hippocampus [26, 27] but it is not known whether these hormones stimulate neurogenesis in the hypothalamus during pregnancy [28, 29]. Prolactin-related hormones expressed by the placenta are known to stimulate the production of the steroid hormones progesterone and oestrogens, which in mice requires steroidogenic enzymes expressed in the ovary [30, 31]. Steroid hormones are expressed throughout pregnancy and their combined action at term is critical in priming maternal caregiving [32]. The mouse placenta is potentially a direct source of neuromodulators implicated in maternal behaviour including dopamine [33-35], oxytocin [36-38], vasopressin [39] and serotonin [40]. These hormones are either directly expressed in the placenta or components of their synthesis pathways are expressed in the placenta [10]. The levels of expression are uniformly low [10]. However, placentally-derived serotonin has been shown to functionally impact fetal brain development [41-44] which suggests these hormones could target the offspring's brain rather than the mother's.

Sites of placental hormone production in the placenta

In mice there are 22 prolactin-related hormones expressed primarily from the placenta [45]. The considerable variation in expression levels of these placental hormones in the mature mouse placenta suggests some likely only function locally whereas others function as

endocrine signals to the mother, and potentially also the fetus although this has not been demonstrated experimentally. Many prolactin-related hormones are not formally considered to have lactogenic activity (placental lactogens) as they do not appear to have the ability to bind Prlr. Only prolactin family 3, subfamily d, members 1-3 (Prl3d1-3 aka PL-I) and prolactin family 3, subfamily b, member 1 (Prl3b1 aka PL-II) are known to signal via Prlr [21]. The major source of placental lactogenic activity in the first half of pregnancy are the primary and secondary parietal trophoblast giant cells (P-TGCs) [45] (**FIG 2A**). Primary P-TGCs arise directly from trophectoderm cells located opposite to the inner cell mass at the time of implantation whereas secondary P-TGCs arise from a region called the ectoplacental cone which is derived from the layer of trophectoderm located over the inner cell mass [46, 47]. Both primary and secondary TGCs express *Prl3d1-3*, with highest expression from embryonic day (E) 6.5 to E9.5 [45]. The mature mouse placenta, which forms at around E9.5, is organised into three histological distinct regions: the maternally-derived decidual component, and the fetally-derived junctional and the labyrinth zones (**FIG 2B**). Placental hormones are expressed from seven distinct and identifiable lineages which include the glycogen cell lineage and spongiotrophoblast lineage which form the bulk of the junctional zone, and five TGC subtype (parietal-, canal-, channel-, spiral artery- and sinusoidal-) located in close contact with maternal cells [48-51]. *Prl3b1* is expressed from all of these lineages except the glycogen cell lineage and the spiral artery-TGCs [45]. The spongiotrophoblast lineage is the most substantial endocrine lineage to express *Prl3b1* in terms of cell number with an estimated 6.23 $\times$ 10^6 cells present by E16.5 [52]. In addition to prolactin-related hormones, the spongiotrophoblast lineage expresses *pregnancy specific glycoproteins* (*Psgs*), a multigene gene family that contribute to the protection of the semiallotypic fetus from the maternal immune system and are involved in remodelling placental and maternal vasculature [53]. The spongiotrophoblast is therefore the major endocrine lineage of the mouse placenta.

Regulation of placental hormone production by imprinted genes

Individual placental hormones have been genetically targeted to study their function in the placenta. Targeted deletion of the prolactin-related genes *Prl4a1* [54] and *Prl7b1* [55] have minor effects on the placenta under normal conditions but major effects in response to stressors such as hypoxia. Targeted deletion of *Prl7d1* results in a reduction of the labyrinth and gain in the junctional zone with a sex specific increase in the number of glycogen cells in the male placenta [56]. Placental hormone levels can be manipulated *en mass* through the genetic modification of imprinted genes which regulate the number of placental cells expressing hormones [57]. Genomic imprinting describes genes expressed only from one parental allele as a consequence of epigenetic marks acquired in the germline [58]. Imprinting is thought to have evolved in mammals in response to the conflict imposed by pregnancy and

149 lactation, with maternal contributions to offspring significantly exceeding paternal contributions
150 [59]. Given the function of placental hormones in ensuring nutrient allocation to the fetus, it is
151 not surprising that genomic imprinting has influenced the expression of these hormones.
152 Placental hormones can be directly imprinted, as is the case for one prolactin-related gene
153 expressed in the placenta of the new world mouse, *Peromyscus* [60]. Expression of placental
154 hormones is also indirectly regulated by imprinting because several genes controlling the
155 development of the placental endocrine lineages are imprinted [57]. One of these genes is the
156 maternally expressed/paternally silenced *Pleckstrin Homology-Like Domain, Family A,*
157 *Member 2* (*Phlda2*) gene. Loss-of-imprinting of *Phlda2* (two-fold increased expression)
158 reduces the contribution of the spongiotrophoblast lineage to the mature placenta by ~50%
159 [61, 62]. Loss-of-expression of *Phlda2* results in a two-fold expansion of this lineage [62]. As
160 the spongiotrophoblast lineage expresses a number of prolactin-related hormones [45, 48],
161 these manipulations decrease or increase, respectively, all the genes expressed from this
162 lineage, which include *Prl3b1* [62]. The maternally expressed/paternally silenced *Achaete-*
163 *scute complex homolog 2* (*Ascl2* aka *Mash2*) is required for the proper formation of placental
164 endocrine lineages [63, 64] and overexpression of this gene functions to restrict the expansion
165 of both the P-TGCs and the spongiotrophoblast [65]. A third maternally expressed/paternally
166 silenced gene, *Cyclin dependent kinase inhibitor 1c* (*Cdkn1c*), functions to prevent over
167 proliferation of a number of placental lineages [66] and is specifically required for the proper
168 differentiation of the spongiotrophoblast and the S-TGCs [67]. While maternally
169 expressed/paternally silenced genes primarily act to constrain the production of placental
170 hormones, paternally expressed/maternally silenced genes appear to function antagonistically
171 to promote placental signalling. Loss-of-imprinting (two-fold expression) of the paternally
172 expressed/maternally silenced *Insulin-like growth factor 2* (*Igf2*) gene results in a larger
173 labyrinth region with double the number of glycogen cells and more than double the number
174 of P-TGCs, although with no effect on the spongiotrophoblast [68]. Loss-of-expression of
175 *Paternally expressed gene 3* (*Peg3*) results in 50% fewer spongiotrophoblast cells and 40%
176 fewer glycogen cells in male mutant placenta with female mutant placenta having a
177 significantly attenuated placental lineage phenotype, with fewer overall changes in the
178 expression levels of individual placental hormones [69]. *Peg3* is known to function as a
179 transcriptional repressor of a subset of placental hormone genes with loss of function resulting
180 in increased expression in the brain [70]. As *Peg3* encodes a positive regulator of placental
181 lineage development and a negative regulator of a subset of placental hormones, loss-of-
182 expression of *Peg3* in the placenta simultaneously decreases in the number of cells
183 expressing hormones and increases the expression of a subset of hormones from the
184 remaining cells [69]. Because of this sexual dimorphism, the more severe loss of placental
185 cells in the male placenta is not counterbalanced by increased expression of some hormones

186 whereas in the female placenta fewer cells are lost and some hormones are expressed overall
187 at higher than normal levels. As previously reviewed, there are a number of other genes
188 paternally silenced by virtue of their location on the paternally inactivated X chromosome that
189 regulate placental endocrine lineages [12]. The finding that several imprinted genes control
190 the production of placental hormones by modulating the number of endocrine cells in the
191 placenta has provided a tool to experimentally assess the function of placental hormones in
192 inducing maternal behaviour, predicted by many indirect experiments.
193
194 **Impact of different doses of *Phlda2* in the placenta on the behaviour of wild type dams**
195 *Phlda2* is considered a negative rheostat for placental hormones because two-fold expression
196 of *Phlda2* results in a 50% loss of the spongiotrophoblast lineage whereas loss-of-expression
197 of *Phlda2* (maternal inheritance of *Phlda2* targeted allele) results in a substantial 200%
198 increase in the spongiotrophoblast lineage [62]. This rheostat function provided a system to
199 test the behavioural consequences on dams after exposure to different levels of
200 spongiotrophoblast-expressed placental hormones [10]. In this study, embryos expressing
201 different doses of *Phlda2,* obtained by mating genetically modified parents, were surgically
202 transferred into pseudopregnant wild type female mice (recipient transfer) to generate
203 genetically wild type dams carrying offspring with either two active alleles (loss-of-imprinting;
204 low hormone levels), one active allele (normal imprint; normal hormone levels) or no active
205 allele (loss of maternal allele; high hormone levels) of *Phlda2*. Dams exposed to either
206 abnormally low or abnormally high levels of placental hormones showed gene changes in the
207 hypothalamus, important for the onset, maintenance and regulation of maternal behaviour,
208 and the hippocampus, important for memory, learning and responses to fear and stress [71].
209 Alterations in G protein-coupled receptors (GPCR) pathways, olfactory transduction pathways
210 and the gonadotropin-releasing hormone signalling pathway were consistent with the maternal
211 brain responding to the different levels of placental hormones. Importantly, these changes
212 were present before the dams gave birth. After birth, dams were able to care for their
213 newborns, effectively make nests and gather their pups within the nest, and all pups gained
214 weight indicative of adequate maternal caregiving. However, when the dams were challenged
215 with either a pup retrieval task or a nest building task, those exposed to the highest levels of
216 placental hormones in pregnancy performed less well than either the control group or the
217 dams exposed to the lowest levels of hormones. In the disturbed situation (nest building task)
218 dams exposed to the lowest levels of placental hormones prioritised nest building, neglecting
219 their pups and themselves. In contrast, dams exposed to the highest levels of placental
220 hormones prioritised caring for their pups and self-directed nurturing over the nest building.
221 The presence of pups is important for the manifestation of maternal behaviour and any
222 mutation impacting pup characteristics has the potential to result in a secondary effect on

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maternal behaviour [13, 72]. From birth pups begin communicating to their mothers using clicks and whistles. These ultrasonic vocalisations (USVs) increase in intensity and frequency when pups are separated from their mothers - hence the alternative and more forlorn term - "whistles of loneliness" [73]. USVs are known to induce maternal behaviours such as nest building, pup retrieval and nursing [74-77]. However, no difference in USVs was noted for the *Phlda2* mutant pups. Moreover, exposed dams continued to exhibit heightened maternal caregiving when presented with wild type pups taken from a different litter indicating the prenatal programming of behavioural changes. Together, these data indicate that hormones expressed from the spongiotrophoblast lineage play an important role in determining the priorities of the new mother. These experiments did not identify the specific hormone modulating maternal caregiving. Previous studies suggest that candidate is likely to be Prl3b1 [22, 23], but it is possible that other hormones are involved. Irrespective of the exact hormone, this was the first physiologically relevant experiment to demonstrate that the integrity of the placental endocrine compartment is importance for maternal caregiving. In this experiment, placental endocrine insufficiency was found to result in suboptimal maternal care, at least during stressful situations. Two-fold expression of *Phlda2* has previously been demonstrated to restrict fetal growth resulting in asymmetric low birth weight [78]. This model therefore combines placental endocrine insufficiency with low birth weight and suboptimal maternal care (**FIG 3**).

Regulation of *Phlda2*

Phlda2 is a maternally expressed imprinted gene which is not directly DNA methylated either in the germline or somatic tissues [79, 80]. Allelic expression is established through a germline acquired DNA methylation imprint which occurs more that 200 kilobases away from *Phlda2* [81] and is maintained by repressive histone modifications [82]. Expression of *PHLDA2* in primary term human trophoblasts is reduced under conditions of hypoxia [83] and potentially increased in human placenta in relation to smoking [84] and strenuous exercise [85]. In animal models, increased placental *Phlda2* has been reported in response to maternal alcohol [86] and maternal undernutrition in the form of low protein diet before and during pregnancy [87]. Consequently, there is potential for expression of *Phlda2* to be modulated by environmental factors that act on the normally active maternal allele or potentially relax silencing of the paternal allele, to then influence the production of placental hormones.

Impact of loss-of-expression of *Peg3* in the placenta on the behaviour of wild type dams

Peg3 functions antagonistically to *Phlda2* as loss-of-expression (paternal inheritance of *Phlda2* targeted allele) results in a substantial 50% decrease in the spongiotrophoblast lineage [69]. *Peg3* is one of many genes where disruption in the dam results in a maternal care deficit

260 [88]. However, loss of function of *Peg3* in the placenta also appears to have consequences
261 for maternal behaviour [9]. In this study natural matings were used to generate all wild type
262 pregnancies and pregnancies where the dam was wild type but all the pups were
263 heterozygous for paternal loss-of-expression of *Peg3*. No detectable differences in
264 transcriptional signature of the maternal hypothalamus or the hippocampus were present four
265 days before birth, in contrast to the *Phlda2* model where wild type dams showed changes in
266 both these regions of the maternal brain at the same point in pregnancy [10]. During the
267 pregnancy, there were no differences in nest building, anxiety-related behaviour or locomotor
268 activity but pregnant dams carrying *Peg3* mutant fetuses travelled significantly less distance
269 when first transferred to a novel environment. After the pups were born, dams caring for
270 mutant pups were slower to sniff and to retrieve pups. Dams were equally good at making
271 nests and there were no changes in pup-directed behaviour or self-directed behaviours during
272 the distracting nest building task. Also, in contrast to the *Phlda2* model, dams mothering
273 mutant *Peg3* pups displayed heightened anxiety-related behaviour. *Peg3* mutant pups were
274 found to call less to their mothers, with a significant decrease in USVs. This deficit in
275 communication may underlie the delay in pup retrieval and potentially also the heightened
276 anxiety. However, the subtle changes in maternal behaviour that were detectable before the
277 pups were born indicate some element of prenatal programming by the placenta. More
278 extreme changes may not have been observed in this model due to the sexually dimorphic
279 impact of loss of expression of *Peg3* in the placenta [69] with the presence of the less impacted
280 female placentas compensating for the defect in the male placenta. Currently, it is not possible
281 to test this hypothesis as mouse litters are composed of both males and females. It will also
282 be important to determine to what extent the placental defect versus the communication deficit
283 contribute to the altered maternal behaviour after birth. Nonetheless, this is a second example
284 where placental endocrine insufficiency [69] is found in combination with low birth weight [88]
285 and alterations in maternal behaviour (**FIG 3**). Appropriate expression of *Peg3* in the brain and
286 the placenta is therefore important for maternal behaviour.
287
288 **Humans**
289 These studies in mice highlight the functional importance of placental hormones in the
290 induction of maternal caregiving, and the potential for placental endocrine insufficiency to
291 contribute to suboptimal maternal care and anxiety, at least in mice. This raises the possibility
292 that placental endocrine insufficiency could contribute to mood symptoms in a human
293 pregnancy as a consequence of the mis-priming of the mother's brain. There are clear and
294 significant differences between mice and humans in their placentae [89] (**FIG2 C**). The human
295 and mouse placenta are both haemochorial with the fetally-derived trophoblast cells in direct
296 contact with the maternal blood and with cells that invade the maternal uterine wall but they

do not have the same morphologically equivalent structures [47]. Mouse placenta are composed of three major regions whereas human placenta possess villi bathed by maternal blood located in an intervillous space. Villi are composed of a single outermost layer of syncytiotrophoblast cells over a layer of villous cytotrophoblast cells both of which encase a core of mesenchymal cells, fetal blood vessels and Hofbauer cells with some similarity to the mouse labyrinth zone. Cytotrophoblast cell columns protrude from these villi, anchoring them to the maternal decidua. At the end of these columns there are extravillous cytotrophoblast cells which are an invasive cell type with potential similarity to mouse spiral artery trophoblast giant cells. The syncytiotrophoblast layer is the major site of the synthesis and secretion of placental hormones [90, 91] and recent single cell RNAseq analysis identified the extravillous cytotrophoblast as another a major site for the production of hormones [92].

Both the mouse and human placenta express hormones related to prolactin, which shares an ancestral gene with growth hormone. In mice these are the 22 prolactin family members which arose from duplication of the *prolactin* gene whereas in humans four genes expressed in the placenta arose from duplication of the *growth hormone* gene which are *chorionic somatomammotropin 1* (CSH1; aka hPL-A), *chorionic somatomammotropin 2* (aka hPL-B), *chorionic somatomammotropin like hormone* (CSHL; aka hPL-L) and *placental growth hormone* (pGH; aka growth hormone variant; **GH**-**V**) [93, 94]. References to these hormones in the literature can be confusing due to the generic term "placental lactogen" which is refers to hPL-A/B in humans and to Prl3d1-3 or Prl3b1 in rodents, defined by the ability of these hormones to signal via Prlr.

In rodents prolactin secretion from the pituitary is stimulated by the act of mating and provides the major lactogenic activity for the first half of pregnancy [95, 96]. As the placental lineages develop and expand, prolactin is replaced by Prl3d1-3 and then /Prl3b1 from mid-gestation until just prior to delivery [45] when there is a second surge in prolactin [97]. In contrast, in a human pregnancy prolactin and placental lactogen appear to increase linearly throughout pregnancy [98, 99] albeit with hPL present at higher levels than prolactin in maternal serum at term (5–7 vs. 0.15–0.18 µg/ml) [93].

Like the mouse placenta, the human placenta has the capacity to synthesis neuromodulators [92]. However, in contrast to the mouse, the human placenta directly synthesise progesterone and oestrogens through expression of steroidogenic enzymes.

Evidence for placental endocrine insufficiency in maternal mood disorders

333 Maternal serum hPL levels and placental *hPL* expression have previously been shown to be
334 significantly reduced in pregnancies complicated by fetal growth restriction [100, 101] which
335 can co-occur with prenatal depression and anxiety. Similarly, low hPL has been reported in
336 association with maternal obesity [102, 103] which is a risk factor for depression and anxiety
337 in pregnancy [104]. We reported significantly lower levels of maternal serum hPL in
338 pregnancies where mothers gave birth to small for gestational age infants, alongside higher
339 expression of *PHLDA2* in placenta [105] consistent with our observations in the mouse model.
340 Low levels of maternal serum prolactin have been reported in human mothers with postnatal
341 depression symptoms [106, 107] and increased levels in mothers with lower anxiety symptoms
342 during pregnancy [108]. We reported lower placental *hPL* expression in prenatal depression
343 [109]. In this study we reported lower placental expression of *PEG3* in male infants [109]. More
344 recently, we have reported that lower serum hPL at term is associated with higher symptoms
345 of postnatal depression and anxiety exclusively in mothers of girls [110]. In the context of our
346 findings in mouse models, these data suggest that insufficiency in hPL can contribute to
347 maternal mood symptoms in a human pregnancy. Higher levels of *placental corticotrophin*
348 *hormone*, which acts via the pituitary to stimulate release of cortisol (stress hormone) from the
349 maternal adrenal gland, have been associated with postpartum depression [111]. While
350 evidence for the involvement of steroid hormones in depressive or anxiety mood disorder is
351 conflicting lower levels of allopregnanolone, a neuroactive metabolite of progesterone, have
352 been associated with a lower risk of developing postpartum depression [112].

Conclusion

355 In conclusion, studies in mice directly demonstrate that placental endocrine insufficiency can
356 lead to low birth weight, alterations in maternal behaviours and increased anxiety symptoms.
357 Indirect evidence suggests the potential for placental endocrine insufficiency to contribute to
358 low birth weight and mood symptoms in human pregnancies, potentially explaining their
359 observed co-occurrence. However, only a comprehensive assessment of the full repertoire
360 of hormone-related genes from pregnancies impacted by prenatal depression and anxiety
361 will fully address this question.

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674

675 **FIGURE LEGENDS**

676

677 **Figure 1. Placental programming hypothesis**. Both the fetus and the placenta are exposed

678 to adversities in pregnancy. Adversities driving changes in the endocrine function of the

679 placenta may impact fetal growth through reduced nutrient supply resulting in low birth weight.

680 Placental endocrine insufficiency may also prevent the appropriate adaptations of the

681 maternal brain required for motherhood manifesting as symptoms of depression and anxiety.

682 Continued exposure of the offspring to maternal mood symptoms may further contribute to

683 poor outcomes for children.
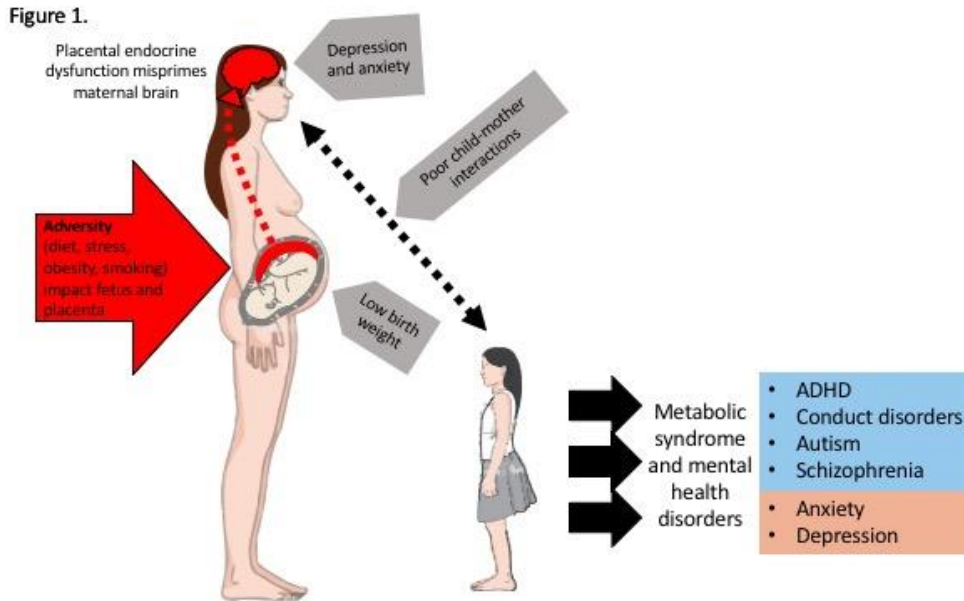
685 **Figure 2. Placental endocrine lineages.** A. In mice, the major source of placental lactogenic

686 activity between embryonic day (E6.5) and E9.5 is encoded by the prolactin-related *Prl3d1-3*

687 genes expressed most highly in the primary and secondary parietal trophoblast giant cells. B.

688 From E9.5 to term in mice, the major source of lactogenic activity is *Prl3b1* expressed in seven

689 placental lineages including the spongiotrophoblast. C. In human placenta, the major source

690 of lactogenic hormones are the syncitiotrophoblast and the extravillus cytotrophoblast which

691 express genes encoding human placental lactogen (*CSH1/hPL-A* and *CSH2/hPL-B*)
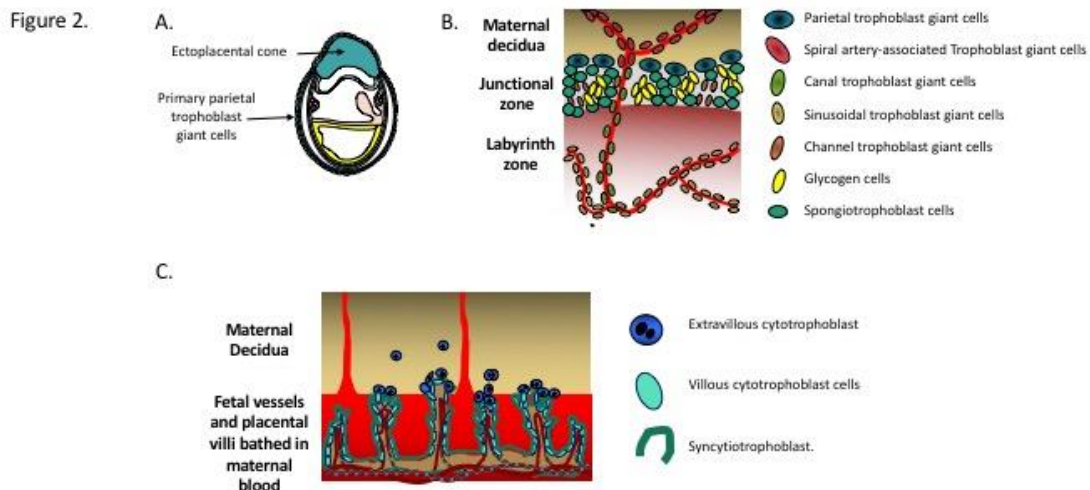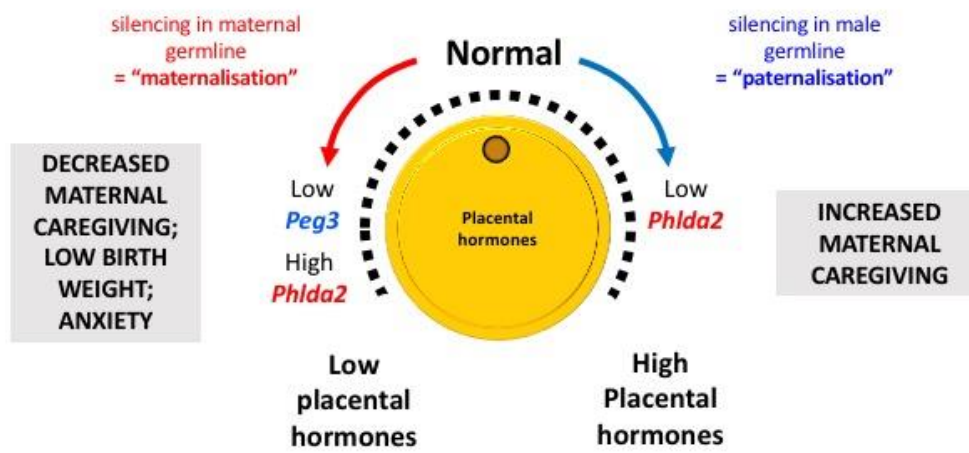
692

693 **Figure 3. Imprinted genes modulate the production of placental hormones.** Studies in

694 mice suggest that the silencing of genes in the male germline may have increased the number

695   of cells expressing placental hormones, and increased care provision by the mother to the

696   offspring. Conversely, silencing of imprinted genes in the female germline may have limited

697   the number of cells expressing placental hormones, potentially to preserve maternal resources

698   for subsequent pregnancies. Placental endocrine insufficiency in mice results in low birth

699   weight, suboptimal maternal care and maternal anxiety

700

701

Figure 3.

702