

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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8

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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38 **Introduction**

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

59

60 **Maternal behaviour**

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

75

76 **Placental hormones implicated in the induction of maternal behaviour**

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

107

108 **Sites of placental hormone production in the placenta**

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

112 endocrine signals to the mother, and potentially also the fetus although this has not been
113 demonstrated experimentally. Many prolactin-related hormones are not formally considered
114 to have lactogenic activity (placental lactogens) as they do not appear to have the ability to
115 bind Prlr. Only prolactin family 3, subfamily d, members 1-3 (Prl3d1-3 aka PL-I) and prolactin
116 family 3, subfamily b, member 1 (Prl3b1 aka PL-II) are known to signal via Prlr [21]. The major
117 source of placental lactogenic activity in the first half of pregnancy are the primary and
118 secondary parietal trophoblast giant cells (P-TGCs) [45] (**FIG 2A**). Primary P-TGCs arise
119 directly from trophoblast cells located opposite to the inner cell mass at the time of
120 implantation whereas secondary P-TGCs arise from a region called the ectoplacental cone
121 which is derived from the layer of trophoblast located over the inner cell mass [46, 47].
122 Both primary and secondary TGCs express *Prl3d1-3*, with highest expression from embryonic
123 day (E) 6.5 to E9.5 [45]. The mature mouse placenta, which forms at around E9.5, is
124 organised into three histological distinct regions: the maternally-derived decidual component,
125 and the fetally-derived junctional and the labyrinth zones (**FIG 2B**). Placental hormones are
126 expressed from seven distinct and identifiable lineages which include the glycogen cell lineage
127 and spongiotrophoblast lineage which form the bulk of the junctional zone, and five TGC
128 subtype (parietal-, canal-, channel-, spiral artery- and sinusoidal-) located in close contact with
129 maternal cells [48-51]. *Prl3b1* is expressed from all of these lineages except the glycogen cell
130 lineage and the spiral artery-TGCs [45]. The spongiotrophoblast lineage is the most
131 substantial endocrine lineage to express *Prl3b1* in terms of cell number with an estimated 6.23
132 $\times 10^6$ cells present by E16.5 [52]. In addition to prolactin-related hormones, the
133 spongiotrophoblast lineage expresses *pregnancy specific glycoproteins (Psgs)*, a multigene
134 gene family that contribute to the protection of the semiallotypic fetus from the maternal
135 immune system and are involved in remodelling placental and maternal vasculature [53]. The
136 spongiotrophoblast is therefore the major endocrine lineage of the mouse placenta.

137

138 **Regulation of placental hormone production by imprinted genes**

139 Individual placental hormones have been genetically targeted to study their function in the
140 placenta. Targeted deletion of the prolactin-related genes *Prl4a1* [54] and *Prl7b1* [55] have
141 minor effects on the placenta under normal conditions but major effects in response to
142 stressors such as hypoxia. Targeted deletion of *Prl7d1* results in a reduction of the labyrinth
143 and gain in the junctional zone with a sex specific increase in the number of glycogen cells in
144 the male placenta [56]. Placental hormone levels can be manipulated *en mass* through the
145 genetic modification of imprinted genes which regulate the number of placental cells
146 expressing hormones [57]. Genomic imprinting describes genes expressed only from one
147 parental allele as a consequence of epigenetic marks acquired in the germline [58]. Imprinting
148 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

223 maternal behaviour [13, 72]. From birth pups begin communicating to their mothers using
224 clicks and whistles. These ultrasonic vocalisations (USVs) increase in intensity and frequency
225 when pups are separated from their mothers - hence the alternative and more forlorn term -
226 “whistles of loneliness” [73]. USVs are known to induce maternal behaviours such as nest
227 building, pup retrieval and nursing [74-77]. However, no difference in USVs was noted for the
228 *Phlda2* mutant pups. Moreover, exposed dams continued to exhibit heightened maternal
229 caregiving when presented with wild type pups taken from a different litter indicating the
230 prenatal programming of behavioural changes. Together, these data indicate that hormones
231 expressed from the spongiotrophoblast lineage play an important role in determining the
232 priorities of the new mother. These experiments did not identify the specific hormone
233 modulating maternal caregiving. Previous studies suggest that candidate is likely to be Prl3b1
234 [22, 23], but it is possible that other hormones are involved. Irrespective of the exact hormone,
235 this was the first physiologically relevant experiment to demonstrate that the integrity of the
236 placental endocrine compartment is importance for maternal caregiving. In this experiment,
237 placental endocrine insufficiency was found to result in suboptimal maternal care, at least
238 during stressful situations. Two-fold expression of *Phlda2* has previously been demonstrated
239 to restrict fetal growth resulting in asymmetric low birth weight [78]. This model therefore
240 combines placental endocrine insufficiency with low birth weight and suboptimal maternal care
241 **(FIG 3)**.

242

243 **Regulation of *Phlda2***

244 *Phlda2* is a maternally expressed imprinted gene which is not directly DNA methylated either
245 in the germline or somatic tissues [79, 80]. Allelic expression is established through a germline
246 acquired DNA methylation imprint which occurs more that 200 kilobases away from *Phlda2*
247 [81] and is maintained by repressive histone modifications [82]. Expression of *PHLDA2* in
248 primary term human trophoblasts is reduced under conditions of hypoxia [83] and potentially
249 increased in human placenta in relation to smoking [84] and strenuous exercise [85]. In animal
250 models, increased placental *Phlda2* has been reported in response to maternal alcohol [86]
251 and maternal undernutrition in the form of low protein diet before and during pregnancy [87].
252 Consequently, there is potential for expression of *Phlda2* to be modulated by environmental
253 factors that act on the normally active maternal allele or potentially relax silencing of the
254 paternal allele, to then influence the production of placental hormones.

255

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

257 *Peg3* functions antagonistically to *Phlda2* as loss-of-expression (paternal inheritance of
258 *Phlda2* targeted allele) results in a substantial 50% decrease in the spongiotrophoblast lineage
259 [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

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

308

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

319

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

327

328 Like the mouse placenta, the human placenta has the capacity to synthesis neuromodulators
329 [92]. However, in contrast to the mouse, the human placenta directly synthesise progesterone
330 and oestrogens through expression of steroidogenic enzymes.

331

332 **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].

353

354 **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.

362

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368

369 **References**

370 [1] J. Heron, T.G. O'Connor, J. Evans, J. Golding, V. Glover, A.S. Team, The course of anxiety
371 and depression through pregnancy and the postpartum in a community sample, *Journal of*
372 *affective disorders* 80(1) (2004) 65-73.

373 [2] A.B. Janssen, K.A. Savory, S.M. Garay, L. Sumption, W. Watkins, I. Garcia-Martin, N.A.
374 Savory, A. Ridgway, A.R. Isles, R. Penketh, I.R. Jones, R.M. John, Persistence of anxiety
375 symptoms after elective caesarean delivery, *BJPsych Open* 4(5) (2018) 354-360.

376 [3] G. Lockwood Estrin, E.G. Ryan, K. Trevillion, J. Demilew, D. Bick, A. Pickles, L.M. Howard,
377 Young pregnant women and risk for mental disorders: findings from an early pregnancy
378 cohort, *BJPsych Open* 5(2) (2019) e21.

379 [4] V. Glover, Maternal depression, anxiety and stress during pregnancy and child outcome;
380 what needs to be done, *Best practice & research. Clinical obstetrics & gynaecology* 28(1)
381 (2014) 25-35.

382 [5] A.B. Janssen, D.A. Kertes, G.I. McNamara, E.C. Braithwaite, H.D. Creeth, V.I. Glover, R.M.
383 John, A role for the placenta in programming maternal mood and childhood behavioural
384 disorders, *J Neuroendocrinol* (2016).

385 [6] D.E. Kornbrot, R.M. Msetfi, M.J. Grimwood, Time perception and depressive realism:
386 judgment type, psychophysical functions and bias, *PloS one* 8(8) (2013) e71585.

387 [7] K. Savory, S.M. Garay, L.A. Sumption, J.S. Kelleher, K. Daughters, A.B. Janssen, S. Van
388 Goozen, R.M. John, Prenatal symptoms of anxiety and depression associated with sex
389 differences in both maternal perceptions of one year old infant temperament and researcher
390 observed infant characteristics, *Journal of affective disorders* 264 (2020) 383-392.

391 [8] K.M. Godfrey, D.J. Barker, Fetal programming and adult health, *Public health nutrition*
392 4(2B) (2001) 611-24.

393 [9] G.I. McNamara, H.D.J. Creeth, D.J. Harrison, K.E. Tansey, R.M. Andrews, A.R. Isles, R.M.
394 John, Loss of offspring *Peg3* reduces neonatal ultrasonic vocalizations and increases
395 maternal anxiety in wild-type mothers, *Hum Mol Genet* 27(3) (2018) 440-450.

396 [10] H.D.J. Creeth, G.I. McNamara, S.J. Tunster, R. Boque-Sastre, B. Allen, L. Sumption, J.B.
397 Eddy, A.R. Isles, R.M. John, Maternal care boosted by paternal imprinting in mammals, *PLoS*
398 *Biol* 16(7) (2018) e2006599.

399 [11] V. Perez-Garcia, E. Fineberg, R. Wilson, A. Murray, C.I. Mazzeo, C. Tudor, A. Sienerth,
400 J.K. White, E. Tuck, E.J. Ryder, D. Gleeson, E. Siragher, H. Wardle-Jones, N. Staudt, N. Wali,
401 J. Collins, S. Geyer, E.M. Busch-Nentwich, A. Galli, J.C. Smith, E. Robertson, D.J. Adams,
402 W.J. Weninger, T. Mohun, M. Hemberger, Placentation defects are highly prevalent in
403 embryonic lethal mouse mutants, *Nature* 555(7697) (2018) 463-468.

404 [12] R. John, M. Hemberger, A placenta for life, *Reprod Biomed Online* 25(1) (2012) 5-11.

405 [13] H.D.J. Creeth, G.I. McNamara, A.R. Isles, R.M. John, Imprinted genes influencing the
406 quality of maternal care, *Frontiers in neuroendocrinology* 53 (2019) 100732.

407 [14] R.S. Bridges, M.C. Robertson, R.P. Shiu, H.G. Friesen, A.M. Stuer, P.E. Mann, Endocrine
408 communication between conceptus and mother: placental lactogen stimulation of maternal
409 behavior, *Neuroendocrinology* 64(1) (1996) 57-64.

410 [15] R.S. Bridges, R. DiBiase, D.D. Loundes, P.C. Doherty, Prolactin stimulation of maternal
411 behavior in female rats, *Science* 227(4688) (1985) 782-4.

412 [16] H. Moltz, M. Lubin, M. Leon, M. Numan, Hormonal induction of maternal behavior in the
413 ovariectomized nulliparous rat, *Physiol Behav* 5(12) (1970) 1373-7.

414 [17] R.S. Bridges, P.M. Ronsheim, Prolactin (PRL) regulation of maternal behavior in rats:
415 bromocriptine treatment delays and PRL promotes the rapid onset of behavior, *Endocrinology*
416 126(2) (1990) 837-48.

417 [18] R.S. Bridges, M.S. Freemark, Human placental lactogen infusions into the medial preoptic
418 area stimulate maternal behavior in steroid-primed, nulliparous female rats, *Horm Behav* 29(2)
419 (1995) 216-26.

420 [19] R.S. Bridges, M.C. Robertson, R.P. Shiu, J.D. Sturgis, B.M. Henriquez, P.E. Mann,
421 Central lactogenic regulation of maternal behavior in rats: steroid dependence, hormone
422 specificity, and behavioral potencies of rat prolactin and rat placental lactogen I, *Endocrinology*
423 138(2) (1997) 756-63.

424 [20] C.M. Larsen, D.R. Grattan, Prolactin, neurogenesis, and maternal behaviors, *Brain Behav*
425 *Immun* 26(2) (2012) 201-9.

426 [21] M.J. Soares, T. Konno, S.M. Alam, The prolactin family: effectors of pregnancy-dependent
427 adaptations, *Trends Endocrinol Metab* 18(3) (2007) 114-21.

428 [22] B.K. Lucas, C.J. Ormandy, N. Binart, R.S. Bridges, P.A. Kelly, Null mutation of the
429 prolactin receptor gene produces a defect in maternal behavior, *Endocrinology* 139(10) (1998)
430 4102-7.

431 [23] T. Shingo, C. Gregg, E. Enwere, H. Fujikawa, R. Hassam, C. Geary, J.C. Cross, S. Weiss,
432 Pregnancy-stimulated neurogenesis in the adult female forebrain mediated by prolactin,
433 *Science* 299(5603) (2003) 117-20.

434 [24] R.S.E. Brown, M. Aoki, S.R. Ladyman, H.R. Phillipps, A. Wyatt, U. Boehm, D.R. Grattan,
435 Prolactin action in the medial preoptic area is necessary for postpartum maternal nursing
436 behavior, *Proc Natl Acad Sci U S A* 114(40) (2017) 10779-10784.

437 [25] C.M. Larsen, D.R. Grattan, Prolactin-induced mitogenesis in the subventricular zone of
438 the maternal brain during early pregnancy is essential for normal postpartum behavioral
439 responses in the mother, *Endocrinology* 151(8) (2010) 3805-14.

440 [26] A. Rolls, H. Schori, A. London, M. Schwartz, Decrease in hippocampal neurogenesis
441 during pregnancy: a link to immunity, *Mol Psychiatry* 13(5) (2008) 468-9.

442 [27] T.L. Walker, J. Vukovic, M.M. Koudijs, D.G. Blackmore, E.W. Mackay, A.M. Sykes, R.W.
443 Overall, A.S. Hamlin, P.F. Bartlett, Prolactin stimulates precursor cells in the adult mouse
444 hippocampus, *PloS one* 7(9) (2012) e44371.

445 [28] K. Rizzoti, R. Lovell-Badge, Pivotal role of median eminence tanycytes for hypothalamic
446 function and neurogenesis, *Molecular and cellular endocrinology* 445 (2017) 7-13.

447 [29] G. Kempermann, H. Song, F.H. Gage, Neurogenesis in the Adult Hippocampus, *Cold*
448 *Spring Harb Perspect Biol* 7(9) (2015) a018812.

449 [30] M.J. Soares, F. Talamantes, Gestational effects on placental and serum androgen,
450 progesterone and prolactin-like activity in the mouse, *J Endocrinol* 95(1) (1982) 29-36.

451 [31] S.S. Galosy, F. Talamantes, Luteotropic actions of placental lactogens at midpregnancy
452 in the mouse, *Endocrinology* 136(9) (1995) 3993-4003.

453 [32] R.S. Bridges, Neuroendocrine regulation of maternal behavior, *Frontiers in*
454 *neuroendocrinology* 36 (2015) 178-96.

455 [33] N. Scott, M. Prigge, O. Yizhar, T. Kimchi, A sexually dimorphic hypothalamic circuit
456 controls maternal care and oxytocin secretion, *Nature* 525(7570) (2015) 519-22.

457 [34] C.W. Henschen, R.D. Palmiter, M. Darvas, Restoration of dopamine signaling to the
458 dorsal striatum is sufficient for aspects of active maternal behavior in female mice,
459 *Endocrinology* 154(11) (2013) 4316-27.

460 [35] I. Koukoulas, J. Risvanis, R. Douglas-Denton, L.M. Burrell, K.M. Moritz, E.M. Wintour,
461 Vasopressin receptor expression in the placenta, *Biol Reprod* 69(2) (2003) 679-86.

462 [36] S.E. Fahrbach, J.I. Morrell, D.W. Pfaff, Oxytocin induction of short-latency maternal
463 behavior in nulliparous, estrogen-primed female rats, *Horm Behav* 18(3) (1984) 267-86.

464 [37] B.J. Marlin, M. Mitre, A. D'Amour J, M.V. Chao, R.C. Froemke, Oxytocin enables maternal
465 behaviour by balancing cortical inhibition, *Nature* 520(7548) (2015) 499-504.

466 [38] E.S.L.T. Parreiras, P. Vargas-Pinilla, D.A. Duarte, D. Longo, G.V. Espinoza Pardo, A.
467 Dolor Finkler, V.R. Paixao-Cortes, P. Pare, D.L. Rovaris, E.B. Oliveira, R.A. Caceres, G.L.
468 Goncalves, M. Bouvier, F.M. Salzano, A.B. Lucion, C.M. Costa-Neto, M.C. Bortolini,
469 Functional New World monkey oxytocin forms elicit an altered signaling profile and promotes
470 parental care in rats, *Proc Natl Acad Sci U S A* 114(34) (2017) 9044-9049.

471 [39] O.J. Bosch, I.D. Neumann, Brain vasopressin is an important regulator of maternal
472 behavior independent of dams' trait anxiety, *Proc Natl Acad Sci U S A* 105(44) (2008) 17139-
473 44.

474 [40] M. Angoa-Perez, M.J. Kane, C.E. Sykes, S.A. Perrine, M.W. Church, D.M. Kuhn, Brain
475 serotonin determines maternal behavior and offspring survival, *Genes, brain, and behavior*
476 13(7) (2014) 579-91.

477 [41] A. Bonnin, N. Goeden, K. Chen, M.L. Wilson, J. King, J.C. Shih, R.D. Blakely, E.S.
478 Deneris, P. Levitt, A transient placental source of serotonin for the fetal forebrain, *Nature*
479 472(7343) (2011) 347-50.

480 [42] K. Kanasaki, K. Palmsten, H. Sugimoto, S. Ahmad, Y. Hamano, L. Xie, S. Parry, H.G.
481 Augustin, V.H. Gattone, J. Folkman, J.F. Strauss, R. Kalluri, Deficiency in catechol-O-
482 methyltransferase and 2-methoxyoestradiol is associated with pre-eclampsia, *Nature*
483 453(7198) (2008) 1117-21.

484 [43] D.L. Lefebvre, Giaid, A., and Zingg, H.H., Expression of the oxytocin gene in the rat
485 placenta, *Endocrinology* 130 (1992) 1186-1192.

486 [44] S.C. Kim, J.E. Lee, S.S. Kang, H.S. Yang, S.S. Kim, B.S. An, The regulation of oxytocin
487 and oxytocin receptor in human placenta according to gestational age, *J Mol Endocrinol* 59(3)
488 (2017) 235-243.

489 [45] D.G. Simmons, S. Rawn, A. Davies, M. Hughes, J.C. Cross, Spatial and temporal
490 expression of the 23 murine Prolactin/Placental Lactogen-related genes is not associated with
491 their position in the locus, *BMC genomics* 9 (2008) 352.

492 [46] A.H. El-Hashash, D. Warburton, S.J. Kimber, Genes and signals regulating murine
493 trophoblast cell development, *Mech Dev* 127(1-2) (2010) 1-20.

494 [47] L. Woods, V. Perez-Garcia, M. Hemberger, Regulation of Placental Development and Its
495 Impact on Fetal Growth-New Insights From Mouse Models, *Front Endocrinol (Lausanne)* 9
496 (2018) 570.

497 [48] D.G. Simmons, A.L. Fortier, J.C. Cross, Diverse subtypes and developmental origins of
498 trophoblast giant cells in the mouse placenta, *Dev Biol* 304(2) (2007) 567-78.

499 [49] D.G. Simmons, D.R. Natale, V. Begay, M. Hughes, A. Leutz, J.C. Cross, Early patterning
500 of the chorion leads to the trilaminar trophoblast cell structure in the placental labyrinth,
501 *Development* 135(12) (2008) 2083-91.

502 [50] M. Gasperowicz, C. Surmann-Schmitt, Y. Hamada, F. Otto, J.C. Cross, The
503 transcriptional co-repressor TLE3 regulates development of trophoblast giant cells lining
504 maternal blood spaces in the mouse placenta, *Dev Biol* 382(1) (2013) 1-14.

505 [51] A. Rai, J.C. Cross, Development of the hemochorial maternal vascular spaces in the
506 placenta through endothelial and vasculogenic mimicry, *Dev Biol* 387(2) (2014) 131-41.

507 [52] P.M. Coan, N. Conroy, G.J. Burton, A.C. Ferguson-Smith, Origin and characteristics of
508 glycogen cells in the developing murine placenta, *Dev Dyn* 235(12) (2006) 3280-94.

509 [53] T. Moore, G.S. Dveksler, Pregnancy-specific glycoproteins: complex gene families
510 regulating maternal-fetal interactions, *Int J Dev Biol* 58(2-4) (2014) 273-80.

511 [54] R. Ain, G. Dai, J.H. Dunmore, A.R. Godwin, M.J. Soares, A prolactin family paralog
512 regulates reproductive adaptations to a physiological stressor, *Proc Natl Acad Sci U S A*
513 101(47) (2004) 16543-8.

514 [55] P. Bu, S.M. Alam, P. Dhakal, J.L. Vivian, M. Soares, A Prolactin Family Paralog Regulates
515 Placental Adaptations to a Physiological Stressor in the Mouse, *Biol Reprod* (2016).

516 [56] Q. Zhang, J. Hao, G. Li, Deletion of *Prl7d1* causes placental defects at mid-pregnancy in
517 mice, *Mol Reprod Dev* 86(6) (2019) 696-713.

518 [57] R.M. John, Imprinted genes and the regulation of placental endocrine function: Pregnancy
519 and beyond, *Placenta* 56 (2017) 86-90.

520 [58] M.A. Surani, Imprinting and the initiation of gene silencing in the germ line, *Cell* 93(3)
521 (1998) 309-12.

522 [59] D. Haig, Genetic conflicts in human pregnancy, *Q Rev Biol* 68(4) (1993) 495-532.

523 [60] P.B. Vrana, P.G. Matteson, J.V. Schmidt, R.S. Ingram, A. Joyce, K.L. Prince, M.J. Dewey,
524 S.M. Tilghman, Genomic imprinting of a placental lactogen gene in *Peromyscus*, *Dev Genes*
525 *Evol* 211(11) (2001) 523-32.

526 [61] S.J. Tunster, B. Tycko, R.M. John, The imprinted *Phlda2* gene regulates extraembryonic
527 energy stores, *Mol Cell Biol* 30(1) (2010) 295-306.

528 [62] S.J. Tunster, H.D. Creeth, R.M. John, The imprinted *Phlda2* gene modulates a major
529 endocrine compartment of the placenta to regulate placental demands for maternal resources,
530 *Dev Biol* 409(1) (2016) 251-60.

531 [63] F. Guillemot, T. Caspary, S.M. Tilghman, N.G. Copeland, D.J. Gilbert, N.A. Jenkins, D.J.
532 Anderson, A.L. Joyner, J. Rossant, A. Nagy, Genomic imprinting of *Mash2*, a mouse gene
533 required for trophoblast development., *Nature Genetics* 9 (1995) 235-242.

534 [64] A.B. Bogutz, R. Oh-McGinnis, K.J. Jacob, R. Ho-Lau, T. Gu, M. Gertsenstein, A. Nagy,
535 L. Lefebvre, Transcription factor ASCL2 is required for development of the glycogen
536 trophoblast cell lineage, *PLoS genetics* 14(8) (2018) e1007587.

537 [65] S.J. Tunster, G.I. McNamara, H.D. Creeth, R.M. John, Increased dosage of the imprinted
538 *Ascl2* gene restrains two key endocrine lineages of the mouse Placenta, *Dev Biol* 418(1)
539 (2016) 55-65.

540 [66] K. Takahashi, T. Kobayashi, N. Kanayama, p57(Kip2) regulates the proper development
541 of labyrinthine and spongiotrophoblasts, *Mol Hum Reprod* 6(11) (2000) 1019-25.

542 [67] S.J. Tunster, M. Van de Pette, R.M. John, Fetal overgrowth in the *Cdkn1c* mouse model
543 of Beckwith-Wiedemann syndrome, *Dis Model Mech* 4(6) (2011) 814-21.

544 [68] D.R. Esquiliano, W. Guo, L. Liang, P. Dikkes, M.F. Lopez, Placental glycogen stores are
545 increased in mice with H19 null mutations but not in those with insulin or IGF type 1 receptor
546 mutations, *Placenta* 30(8) (2009) 693-9.

547 [69] S.J. Tunster, R. Boque-Sastre, G.I. McNamara, S.M. Hunter, H.D.J. Creeth, R.M. John,
548 *Peg3* Deficiency Results in Sexually Dimorphic Losses and Gains in the Normal Repertoire of
549 Placental Hormones, *Front Cell Dev Biol* 6 (2018) 123.

550 [70] J. Kim, W.D. Frey, H. He, H. Kim, M.B. Ekram, A. Bakshi, M. Faisal, B.P. Perera, A. Ye,
551 R. Teruyama, *Peg3* mutational effects on reproduction and placenta-specific gene families,
552 *PloS one* 8(12) (2013) e83359.

553 [71] K.M. Hillerer, V.R. Jacobs, T. Fischer, L. Aigner, The maternal brain: an organ with
554 peripartal plasticity, *Neural Plast* 2014 (2014) 574159.

555 [72] H.G. Potter, D.G. Ashbrook, R. Hager, Offspring genetic effects on maternal care,
556 *Frontiers in neuroendocrinology* 52 (2019) 195-205.

557 [73] H.M.a.S. Zippelius, W.M., Ultraschall-Laute bei jungen Mäusen, *Die Naturwissenschaften*
558 43 (1956) 502-502.

559 [74] M. Wöhr, R.K. Schwarting, Affective communication in rodents: ultrasonic vocalizations
560 as a tool for research on emotion and motivation, *Cell Tissue Res* 354(1) (2013) 81-97.

561 [75] M.L. Scattoni, J. Crawley, L. Ricceri, Ultrasonic vocalizations: a tool for behavioural
562 phenotyping of mouse models of neurodevelopmental disorders, *Neuroscience and*
563 *biobehavioral reviews* 33(4) (2009) 508-15.

564 [76] F.R. D'Amato, E. Scalera, C. Sarli, A. Moles, Pups call, mothers rush: does maternal
565 responsiveness affect the amount of ultrasonic vocalizations in mouse pups?, *Behav Genet*
566 35(1) (2005) 103-12.

567 [77] S. Okabe, M. Nagasawa, T. Kihara, M. Kato, T. Harada, N. Koshida, K. Mogi, T. Kikusui,
568 Pup odor and ultrasonic vocalizations synergistically stimulate maternal attention in mice,
569 *Behav Neurosci* 127(3) (2013) 432-8.

570 [78] S.J. Tunster, M. Van De Pette, R.M. John, Isolating the role of elevated *Phlda2* in
571 asymmetric late fetal growth restriction in mice, *Dis Model Mech* 7(10) (2014) 1185-91.

572 [79] D. Frank, C.L. Mendelsohn, E. Ciccone, K. Svensson, R. Ohlsson, B. Tycko, A novel
573 pleckstrin homology-related gene family defined by *Ipl/Tssc3*, *TDAG51*, and *Tih1*: tissue-
574 specific expression, chromosomal location, and parental imprinting, *Mamm Genome* 10(12)
575 (1999) 1150-9.

576 [80] N. Qian, D. Frank, D. O'Keefe, D. Dao, L. Zhao, L. Yuan, Q. Wang, M. Keating, C. Walsh,
577 B. Tycko, The IPL gene on chromosome 11p15.5 is imprinted in humans and mice and is
578 similar to *TDAG51*, implicated in *Fas* expression and apoptosis, *Hum Mol Genet* 6(12) (1997)
579 2021-9.

580 [81] G.V. Fitzpatrick, P.D. Soloway, M.J. Higgins, Regional loss of imprinting and growth
581 deficiency in mice with a targeted deletion of *KvDMR1*, *Nat Genet* 32(3) (2002) 426-31.

582 [82] A. Lewis, K. Mitsuya, D. Umlauf, P. Smith, W. Dean, J. Walter, M. Higgins, R. Feil, W.
583 Reik, Imprinting on distal chromosome 7 in the placenta involves repressive histone
584 methylation independent of DNA methylation, *Nat Genet* 36(12) (2004) 1291-5.

585 [83] H.S. Kim, C.R. Roh, B. Chen, B. Tycko, D.M. Nelson, Y. Sadovsky, Hypoxia regulates the
586 expression of PHLDA2 in primary term human trophoblasts, *Placenta* 28(2-3) (2007) 77-84.

587 [84] H. Bruchova, A. Vasikova, M. Merkerova, A. Milcova, J. Topinka, I. Balascak, A.
588 Pastorkova, R.J. Sram, R. Brdicka, Effect of maternal tobacco smoke exposure on the
589 placental transcriptome, *Placenta* 31(3) (2010) 186-91.

590 [85] R.M. Lewis, Cleal, J.K., Ntani, G., Crozier, S.R., Mahon, P.A., Robinson, S.M., Harvey,
591 N.C., Cooper, C., Inskip, H.M., Godfrey, K.M., Hanson, M.A., the Southampton Women's
592 Survey Study Group and John R.M., Relationship between placental expression of the
593 imprinted PHLDA2 gene, intrauterine skeletal growth and childhood bone mass, *Bone* 50
594 (2012) 337-342.

595 [86] P.K. Shukla, L.J. Sittig, T.M. Ullmann, E.E. Redei, Candidate Placental Biomarkers for
596 Intrauterine Alcohol Exposure, *Alcohol Clin Exp Res* 35(3) (2011) 559–565.

597 [87] M. Eaton, A.H. Davies, J. Devine, X. Zhao, D.G. Simmons, E. Mariusdottir, D.R.C. Natale,
598 J.R. Matyas, E.A. Bering, M.L. Workentine, B. Hallgrimsson, J.C. Cross, Complex patterns of
599 cell growth in the placenta in normal pregnancy and as adaptations to maternal diet restriction,
600 *PLoS one* 15(1) (2020) e0226735.

601 [88] L. Li, E.B. Keverne, S.A. Aparicio, F. Ishino, S.C. Barton, M.A. Surani, Regulation of
602 maternal behavior and offspring growth by paternally expressed Peg3, *Science* 284(5412)
603 (1999) 330-3.

604 [89] A.M. Carter, Evolution of placental function in mammals: the molecular basis of gas and
605 nutrient transfer, hormone secretion, and immune responses, *Physiol Rev* 92(4) (2012) 1543-
606 76.

607 [90] G.J. Burton, E. Jauniaux, What is the placenta?, *Am J Obstet Gynecol* 213(4 Suppl)
608 (2015) S6 e1, S6-8.

609 [91] G.J. Burton, A.L. Fowden, The placenta: a multifaceted, transient organ, *Philos Trans R*
610 *Soc Lond B Biol Sci* 370(1663) (2015) 20140066.

611 [92] Y. Liu, X. Fan, R. Wang, X. Lu, Y.L. Dang, H. Wang, H.Y. Lin, C. Zhu, H. Ge, J.C. Cross,
612 H. Wang, Single-cell RNA-seq reveals the diversity of trophoblast subtypes and patterns of
613 differentiation in the human placenta, *Cell Res* 28(8) (2018) 819-832.

614 [93] D. Newbern, M. Freemerk, Placental hormones and the control of maternal metabolism
615 and fetal growth, *Current opinion in endocrinology, diabetes, and obesity* 18(6) (2011) 409-
616 16.

617 [94] Y. Su, S.A. Liebhaber, N.E. Cooke, The human growth hormone gene cluster locus control
618 region supports position-independent pituitary- and placenta-specific expression in the
619 transgenic mouse, *J Biol Chem* 275(11) (2000) 7902-9.

620 [95] R.L. Butcher, N.W. Fugo, W.E. Collins, Semicircadian rhythm in plasma levels of prolactin
621 during early gestation in the rat, *Endocrinology* 90(4) (1972) 1125-7.

622 [96] M.E. Freeman, M.S. Smith, S.J. Nazian, J.D. Neill, Ovarian and hypothalamic control of
623 the daily surges of prolactin secretion during pseudopregnancy in the rat, *Endocrinology* 94(3)
624 (1974) 875-82.

625 [97] M.J. Soares, The prolactin and growth hormone families: pregnancy-specific
626 hormones/cytokines at the maternal-fetal interface, *Reprod Biol Endocrinol* 2 (2004) 51.

627 [98] R. Romero, O. Erez, E. Maymon, P. Chaemsathong, Z. Xu, P. Pacora, T.
628 Chaiworapongsa, B. Done, S.S. Hassan, A.L. Tarca, The maternal plasma proteome changes
629 as a function of gestational age in normal pregnancy: a longitudinal study, *Am J Obstet*
630 *Gynecol* 217(1) (2017) 67 e1-67 e21.

631 [99] N. Aghaeepour, B. Lehallier, Q. Baca, E.A. Ganio, R.J. Wong, M.S. Ghaemi, A. Culos,
632 Y.Y. El-Sayed, Y.J. Blumenfeld, M.L. Druzin, V.D. Winn, R.S. Gibbs, R. Tibshirani, G.M. Shaw,
633 D.K. Stevenson, B. Gaudilliere, M.S. Angst, A proteomic clock of human pregnancy, *Am J*
634 *Obstet Gynecol* 218(3) (2018) 347 e1-347 e14.

635 [100] C.R. Roh, V. Budhraj, H.S. Kim, D.M. Nelson, Y. Sadovsky, Microarray-based
636 identification of differentially expressed genes in hypoxic term human trophoblasts and in
637 placental villi of pregnancies with growth restricted fetuses, *Placenta* 26(4) (2005) 319-28.

638 [101] P.J. Dutton, L.K. Warrander, S.A. Roberts, G. Bernatavicius, L.M. Byrd, D. Gaze, J. Kroll,
639 R.L. Jones, C.P. Sibley, J.F. Froen, A.E. Heazell, Predictors of poor perinatal outcome

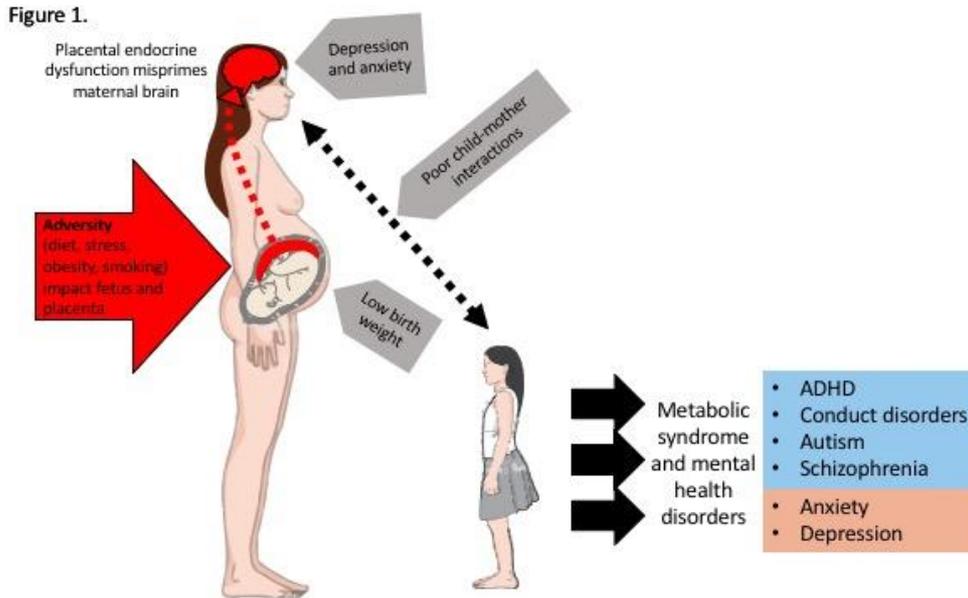
640 following maternal perception of reduced fetal movements--a prospective cohort study, PloS
641 one 7(7) (2012) e39784.
642 [102] H. Vakili, Y. Jin, S. Menticoglou, P.A. Cattini, CCAAT-enhancer-binding protein beta
643 (C/EBPbeta) and downstream human placental growth hormone genes are targets for
644 dysregulation in pregnancies complicated by maternal obesity, J Biol Chem 288(31) (2013)
645 22849-61.
646 [103] Y. Jin, H. Vakili, S.Y. Liu, S. Menticoglou, M.E. Bock, P.A. Cattini, Chromosomal
647 architecture and placental expression of the human growth hormone gene family are targeted
648 by pre-pregnancy maternal obesity, Am J Physiol Endocrinol Metab 315(4) (2018) E435-E445.
649 [104] E. Molyneaux, L. Poston, S. Ashurst-Williams, L.M. Howard, Obesity and mental
650 disorders during pregnancy and postpartum: a systematic review and meta-analysis, Obstet
651 Gynecol 123(4) (2014) 857-67.
652 [105] A.B. Janssen, S.J. Tunster, A.E. Heazell, R.M. John, Placental PHLDA2 expression is
653 increased in cases of fetal growth restriction following reduced fetal movements, BMC medical
654 genetics 17 (2016) 17.
655 [106] M.T. Abou-Saleh, R. Ghubash, L. Karim, M. Krymski, I. Bhai, Hormonal aspects of
656 postpartum depression, Psychoneuroendocrinology 23(5) (1998) 465-75.
657 [107] M.W. Groer, K. Morgan, Immune, health and endocrine characteristics of depressed
658 postpartum mothers, Psychoneuroendocrinology 32(2) (2007) 133-9.
659 [108] I. Asher, B. Kaplan, I. Modai, A. Neri, A. Valevski, A. Weizman, Mood and hormonal
660 changes during late pregnancy and puerperium, Clinical and experimental obstetrics &
661 gynecology 22(4) (1995) 321-5.
662 [109] A.B. Janssen, L.E. Capron, K. O'Donnell, S.J. Tunster, P.G. Ramchandani, A.E. Heazell,
663 V. Glover, R.M. John, Maternal prenatal depression is associated with decreased placental
664 expression of the imprinted gene PEG3, Psychological medicine 46(14) (2016) 2999-3011.
665 [110] L.A. Sumption, S.M. Garay, J. R.M., Low serum placental lactogen at term is associated
666 with postnatal symptoms of depression and anxiety in women delivering female infants,
667 Psychoneuroendocrinology in press (2020).
668 [111] L.M. Glynn, C.A. Sandman, Evaluation of the association between placental
669 corticotrophin-releasing hormone and postpartum depressive symptoms, Psychosomatic
670 medicine 76(5) (2014) 355-62.
671 [112] L.M. Osborne, F. Gispen, A. Sanyal, G. Yenokyan, S. Meilman, J.L. Payne, Lower
672 allopregnanolone during pregnancy predicts postpartum depression: An exploratory study,
673 Psychoneuroendocrinology 79 (2017) 116-121.

674

675 **FIGURE LEGENDS**

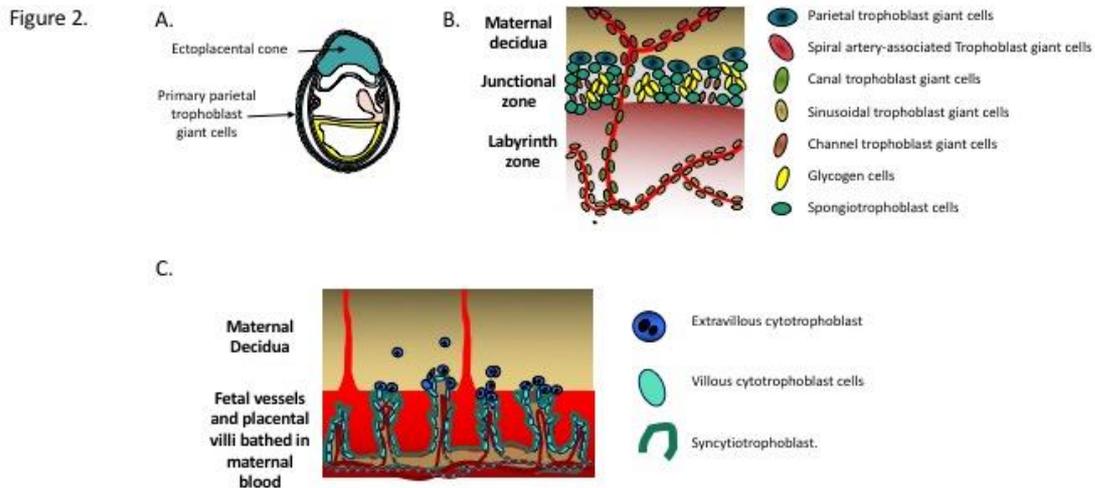
676

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.



684

685 **Figure 2. Placental endocrine lineages.** A. In mice, the major source of placental lactogenic activity between embryonic day (E6.5) and E9.5 is encoded by the prolactin-related *Pr13d1-3*
 686 activity between embryonic day (E6.5) and E9.5 is encoded by the prolactin-related *Pr13d1-3*
 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 *Pr13b1* expressed in seven
 689 placental lineages including the spongiotrophoblast. C. In human placenta, the major source
 690 of lactogenic hormones are the syncytiotrophoblast and the extravillous cytotrophoblast which
 691 express genes encoding human placental lactogen (*CSH1/hPL-A* and *CSH2/hPL-B*)

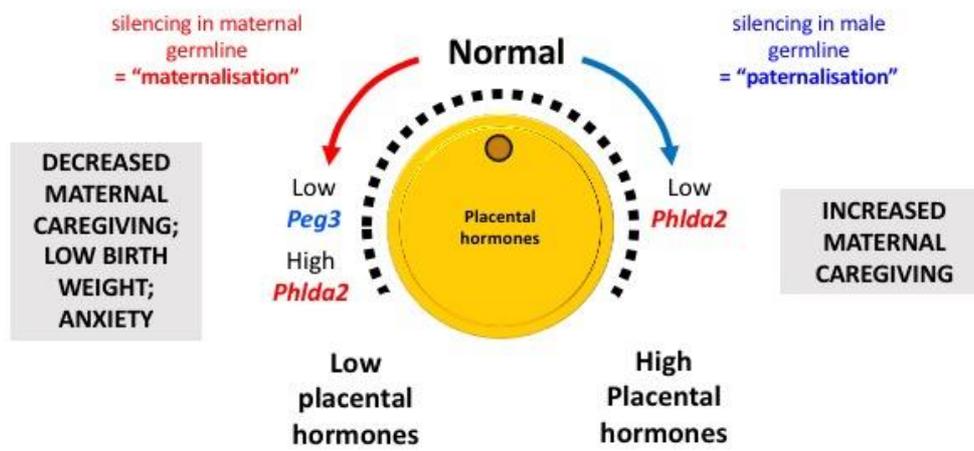


692

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