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

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Abstract

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

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

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].

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 × 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

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

whereas in the female placenta fewer cells are lost and some hormones are expressed overall at higher than normal levels. As previously reviewed, there are a number of other genes paternally silenced by virtue of their location on the paternally inactivated X chromosome that regulate placental endocrine lineages [12]. The finding that several imprinted genes control the production of placental hormones by modulating the number of endocrine cells in the placenta has provided a tool to experimentally assess the function of placental hormones in inducing maternal behaviour, predicted by many indirect experiments.

Impact of different doses of *Phlda2* in the placenta on the behaviour of wild type dams

Phlda2 is considered a negative rheostat for placental hormones because two-fold expression of *Phlda2* results in a 50% loss of the spongiotrophoblast lineage whereas loss-of-expression of *Phlda2* (maternal inheritance of *Phlda2* targeted allele) results in a substantial 200% increase in the spongiotrophoblast lineage [62]. This rheostat function provided a system to test the behavioural consequences on dams after exposure to different levels of spongiotrophoblast-expressed placental hormones [10]. In this study, embryos expressing different doses of *Phlda2,* obtained by mating genetically modified parents, were surgically transferred into pseudopregnant wild type female mice (recipient transfer) to generate genetically wild type dams carrying offspring with either two active alleles (loss-of-imprinting; low hormone levels), one active allele (normal imprint; normal hormone levels) or no active allele (loss of maternal allele; high hormone levels) of *Phlda2*. Dams exposed to either abnormally low or abnormally high levels of placental hormones showed gene changes in the hypothalamus, important for the onset, maintenance and regulation of maternal behaviour, and the hippocampus, important for memory, learning and responses to fear and stress [71]. Alterations in G protein-coupled receptors (GPCR) pathways, olfactory transduction pathways and the gonadotropin-releasing hormone signalling pathway were consistent with the maternal brain responding to the different levels of placental hormones. Importantly, these changes were present before the dams gave birth. After birth, dams were able to care for their newborns, effectively make nests and gather their pups within the nest, and all pups gained weight indicative of adequate maternal caregiving. However, when the dams were challenged with either a pup retrieval task or a nest building task, those exposed to the highest levels of placental hormones in pregnancy performed less well than either the control group or the dams exposed to the lowest levels of hormones. In the disturbed situation (nest building task) dams exposed to the lowest levels of placental hormones prioritised nest building, neglecting their pups and themselves. In contrast, dams exposed to the highest levels of placental hormones prioritised caring for their pups and self-directed nurturing over the nest building. The presence of pups is important for the manifestation of maternal behaviour and any mutation impacting pup characteristics has the potential to result in a secondary effect on

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

[88]. However, loss of function of *Peg3* in the placenta also appears to have consequences for maternal behaviour [9]. In this study natural matings were used to generate all wild type pregnancies and pregnancies where the dam was wild type but all the pups were heterozygous for paternal loss-of-expression of *Peg3*. No detectable differences in transcriptional signature of the maternal hypothalamus or the hippocampus were present four days before birth, in contrast to the *Phlda2* model where wild type dams showed changes in both these regions of the maternal brain at the same point in pregnancy [10]. During the pregnancy, there were no differences in nest building, anxiety-related behaviour or locomotor activity but pregnant dams carrying *Peg3* mutant fetuses travelled significantly less distance when first transferred to a novel environment. After the pups were born, dams caring for mutant pups were slower to sniff and to retrieve pups. Dams were equally good at making nests and there were no changes in pup-directed behaviour or self-directed behaviours during the distracting nest building task. Also, in contrast to the *Phlda2* model, dams mothering mutant *Peg3* pups displayed heightened anxiety-related behaviour. *Peg3* mutant pups were found to call less to their mothers, with a significant decrease in USVs. This deficit in communication may underlie the delay in pup retrieval and potentially also the heightened anxiety. However, the subtle changes in maternal behaviour that were detectable before the pups were born indicate some element of prenatal programming by the placenta. More extreme changes may not have been observed in this model due to the sexually dimorphic impact of loss of expression of *Peg3* in the placenta [69] with the presence of the less impacted female placentas compensating for the defect in the male placenta. Currently, it is not possible to test this hypothesis as mouse litters are composed of both males and females. It will also be important to determine to what extent the placental defect versus the communication deficit contribute to the altered maternal behaviour after birth. Nonetheless, this is a second example where placental endocrine insufficiency [69] is found in combination with low birth weight [88] and alterations in maternal behaviour (**FIG 3**). Appropriate expression of *Peg3* in the brain and the placenta is therefore important for maternal behaviour.

Humans

These studies in mice highlight the functional importance of placental hormones in the induction of maternal caregiving, and the potential for placental endocrine insufficiency to contribute to suboptimal maternal care and anxiety, at least in mice. This raises the possibility that placental endocrine insufficiency could contribute to mood symptoms in a human pregnancy as a consequence of the mis-priming of the mother's brain. There are clear and significant differences between mice and humans in their placentae [89] (**FIG2 C**). The human and mouse placenta are both haemochorial with the fetally-derived trophoblast cells in direct 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**

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

Conclusion

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

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References

[1] J. Heron, T.G. O'Connor, J. Evans, J. Golding, V. Glover, A.S. Team, The course of anxiety and depression through pregnancy and the postpartum in a community sample, Journal of affective disorders 80(1) (2004) 65-73.
[2] A.B. Janssen, K.A. Savory, S.M. Garay, L. Sumption, W. Watkins, I. Garcia-Martin, N.A. Savory, A. Ridgway, A.R. Isles, R. Penketh, I.R. Jones, R.M. John, Persistence of anxiety symptoms after elective caesarean delivery, BJPsych Open 4(5) (2018) 354-360.
[3] G. Lockwood Estrin, E.G. Ryan, K. Trevillion, J. Demilew, D. Bick, A. Pickles, L.M. Howard, Young pregnant women and risk for mental disorders: findings from an early pregnancy cohort, BJPsych Open 5(2) (2019) e21.
[4] V. Glover, Maternal depression, anxiety and stress during pregnancy and child outcome; what needs to be done, Best practice & research. Clinical obstetrics & gynaecology 28(1) (2014) 25-35.
[5] A.B. Janssen, D.A. Kertes, G.I. McNamara, E.C. Braithwaite, H.D. Creeth, V.I. Glover, R.M. John, A role for the placenta in programming maternal mood and childhood behavioural disorders, J Neuroendocrinol (2016).
[6] D.E. Kornbrot, R.M. Msetfi, M.J. Grimwood, Time perception and depressive realism: judgment type, psychophysical functions and bias, PloS one 8(8) (2013) e71585.
[7] K. Savory, S.M. Garay, L.A. Sumption, J.S. Kelleher, K. Daughters, A.B. Janssen, S. Van Goozen, R.M. John, Prenatal symptoms of anxiety and depression associated with sex differences in both maternal perceptions of one year old infant temperament and researcher observed infant characteristics, Journal of affective disorders 264 (2020) 383-392.
[8] K.M. Godfrey, D.J. Barker, Fetal programming and adult health, Public health nutrition 4(2B) (2001) 611-24.
[9] G.I. McNamara, H.D.J. Creeth, D.J. Harrison, K.E. Tansey, R.M. Andrews, A.R. Isles, R.M. John, Loss of offspring Peg3 reduces neonatal ultrasonic vocalizations and increases maternal anxiety in wild-type mothers, Hum Mol Genet 27(3) (2018) 440-450.
[10] H.D.J. Creeth, G.I. McNamara, S.J. Tunster, R. Boque-Sastre, B. Allen, L. Sumption, J.B. Eddy, A.R. Isles, R.M. John, Maternal care boosted by paternal imprinting in mammals, PLoS Biol 16(7) (2018) e2006599.
[11] V. Perez-Garcia, E. Fineberg, R. Wilson, A. Murray, C.I. Mazzeo, C. Tudor, A. Sienerth, J.K. White, E. Tuck, E.J. Ryder, D. Gleeson, E. Siragher, H. Wardle-Jones, N. Staudt, N. Wali, J. Collins, S. Geyer, E.M. Busch-Nentwich, A. Galli, J.C. Smith, E. Robertson, D.J. Adams, W.J. Weninger, T. Mohun, M. Hemberger, Placentation defects are highly prevalent in embryonic lethal mouse mutants, Nature 555(7697) (2018) 463-468.
[12] R. John, M. Hemberger, A placenta for life, Reprod Biomed Online 25(1) (2012) 5-11.
[13] H.D.J. Creeth, G.I. McNamara, A.R. Isles, R.M. John, Imprinted genes influencing the quality of maternal care, Frontiers in neuroendocrinology 53 (2019) 100732.
[14] R.S. Bridges, M.C. Robertson, R.P. Shiu, H.G. Friesen, A.M. Stuer, P.E. Mann, Endocrine communication between conceptus and mother: placental lactogen stimulation of maternal behavior, Neuroendocrinology 64(1) (1996) 57-64.
[15] R.S. Bridges, R. DiBiase, D.D. Loundes, P.C. Doherty, Prolactin stimulation of maternal behavior in female rats, Science 227(4688) (1985) 782-4.
[16] H. Moltz, M. Lubin, M. Leon, M. Numan, Hormonal induction of maternal behavior in the ovariectomized nulliparous rat, Physiol Behav 5(12) (1970) 1373-7.
[17] R.S. Bridges, P.M. Ronsheim, Prolactin (PRL) regulation of maternal behavior in rats: bromocriptine treatment delays and PRL promotes the rapid onset of behavior, Endocrinology 126(2) (1990) 837-48.
[18] R.S. Bridges, M.S. Freemark, Human placental lactogen infusions into the medial preoptic area stimulate maternal behavior in steroid-primed, nulliparous female rats, Horm Behav 29(2) (1995) 216-26.
[19] R.S. Bridges, M.C. Robertson, R.P. Shiu, J.D. Sturgis, B.M. Henriquez, P.E. Mann, Central lactogenic regulation of maternal behavior in rats: steroid dependence, hormone specificity, and behavioral potencies of rat prolactin and rat placental lactogen I, Endocrinology 138(2) (1997) 756-63.

[20] C.M. Larsen, D.R. Grattan, Prolactin, neurogenesis, and maternal behaviors, Brain Behav Immun 26(2) (2012) 201-9.
[21] M.J. Soares, T. Konno, S.M. Alam, The prolactin family: effectors of pregnancy-dependent adaptations, Trends Endocrinol Metab 18(3) (2007) 114-21.
[22] B.K. Lucas, C.J. Ormandy, N. Binart, R.S. Bridges, P.A. Kelly, Null mutation of the prolactin receptor gene produces a defect in maternal behavior, Endocrinology 139(10) (1998) 4102-7.
[23] T. Shingo, C. Gregg, E. Enwere, H. Fujikawa, R. Hassam, C. Geary, J.C. Cross, S. Weiss, Pregnancy-stimulated neurogenesis in the adult female forebrain mediated by prolactin, Science 299(5603) (2003) 117-20.
[24] R.S.E. Brown, M. Aoki, S.R. Ladyman, H.R. Phillipps, A. Wyatt, U. Boehm, D.R. Grattan, Prolactin action in the medial preoptic area is necessary for postpartum maternal nursing behavior, Proc Natl Acad Sci U S A 114(40) (2017) 10779-10784.
[25] C.M. Larsen, D.R. Grattan, Prolactin-induced mitogenesis in the subventricular zone of the maternal brain during early pregnancy is essential for normal postpartum behavioral responses in the mother, Endocrinology 151(8) (2010) 3805-14.
[26] A. Rolls, H. Schori, A. London, M. Schwartz, Decrease in hippocampal neurogenesis during pregnancy: a link to immunity, Mol Psychiatry 13(5) (2008) 468-9.
[27] T.L. Walker, J. Vukovic, M.M. Koudijs, D.G. Blackmore, E.W. Mackay, A.M. Sykes, R.W. Overall, A.S. Hamlin, P.F. Bartlett, Prolactin stimulates precursor cells in the adult mouse hippocampus, PloS one 7(9) (2012) e44371.
[28] K. Rizzoti, R. Lovell-Badge, Pivotal role of median eminence tanycytes for hypothalamic function and neurogenesis, Molecular and cellular endocrinology 445 (2017) 7-13.
[29] G. Kempermann, H. Song, F.H. Gage, Neurogenesis in the Adult Hippocampus, Cold Spring Harb Perspect Biol 7(9) (2015) a018812.
[30] M.J. Soares, F. Talamantes, Gestational effects on placental and serum androgen, progesterone and prolactin-like activity in the mouse, J Endocrinol 95(1) (1982) 29-36.
[31] S.S. Galosy, F. Talamantes, Luteotropic actions of placental lactogens at midpregnancy in the mouse, Endocrinology 136(9) (1995) 3993-4003.
[32] R.S. Bridges, Neuroendocrine regulation of maternal behavior, Frontiers in neuroendocrinology 36 (2015) 178-96.
[33] N. Scott, M. Prigge, O. Yizhar, T. Kimchi, A sexually dimorphic hypothalamic circuit controls maternal care and oxytocin secretion, Nature 525(7570) (2015) 519-22.
[34] C.W. Henschen, R.D. Palmiter, M. Darvas, Restoration of dopamine signaling to the dorsal striatum is sufficient for aspects of active maternal behavior in female mice, Endocrinology 154(11) (2013) 4316-27.
[35] I. Koukoulas, J. Risvanis, R. Douglas-Denton, L.M. Burrell, K.M. Moritz, E.M. Wintour, Vasopressin receptor expression in the placenta, Biol Reprod 69(2) (2003) 679-86.
[36] S.E. Fahrbach, J.I. Morrell, D.W. Pfaff, Oxytocin induction of short-latency maternal behavior in nulliparous, estrogen-primed female rats, Horm Behav 18(3) (1984) 267-86.
[37] B.J. Marlin, M. Mitre, A. D'Amour J, M.V. Chao, R.C. Froemke, Oxytocin enables maternal behaviour by balancing cortical inhibition, Nature 520(7548) (2015) 499-504.
[38] E.S.L.T. Parreiras, P. Vargas-Pinilla, D.A. Duarte, D. Longo, G.V. Espinoza Pardo, A. Dulor Finkler, V.R. Paixao-Cortes, P. Pare, D.L. Rovaris, E.B. Oliveira, R.A. Caceres, G.L. Goncalves, M. Bouvier, F.M. Salzano, A.B. Lucion, C.M. Costa-Neto, M.C. Bortolini, Functional New World monkey oxytocin forms elicit an altered signaling profile and promotes parental care in rats, Proc Natl Acad Sci U S A 114(34) (2017) 9044-9049.
[39] O.J. Bosch, I.D. Neumann, Brain vasopressin is an important regulator of maternal behavior independent of dams' trait anxiety, Proc Natl Acad Sci U S A 105(44) (2008) 17139-44.
[40] M. Angoa-Perez, M.J. Kane, C.E. Sykes, S.A. Perrine, M.W. Church, D.M. Kuhn, Brain serotonin determines maternal behavior and offspring survival, Genes, brain, and behavior 13(7) (2014) 579-91.

[41] A. Bonnin, N. Goeden, K. Chen, M.L. Wilson, J. King, J.C. Shih, R.D. Blakely, E.S. Deneris, P. Levitt, A transient placental source of serotonin for the fetal forebrain, Nature 472(7343) (2011) 347-50.
[42] K. Kanasaki, K. Palmsten, H. Sugimoto, S. Ahmad, Y. Hamano, L. Xie, S. Parry, H.G. Augustin, V.H. Gattone, J. Folkman, J.F. Strauss, R. Kalluri, Deficiency in catechol-O-methyltransferase and 2-methoxyoestradiol is associated with pre-eclampsia, Nature 453(7198) (2008) 1117-21.
[43] D.L. Lefebvre, Giaid, A., and Zingg, H.H., Expression of the oxytocin gene in the rat placenta, Endocrinology 130 (1992) 1186-1192.
[44] S.C. Kim, J.E. Lee, S.S. Kang, H.S. Yang, S.S. Kim, B.S. An, The regulation of oxytocin and oxytocin receptor in human placenta according to gestational age, J Mol Endocrinol 59(3) (2017) 235-243.
[45] D.G. Simmons, S. Rawn, A. Davies, M. Hughes, J.C. Cross, Spatial and temporal expression of the 23 murine Prolactin/Placental Lactogen-related genes is not associated with their position in the locus, BMC genomics 9 (2008) 352.
[46] A.H. El-Hashash, D. Warburton, S.J. Kimber, Genes and signals regulating murine trophoblast cell development, Mech Dev 127(1-2) (2010) 1-20.
[47] L. Woods, V. Perez-Garcia, M. Hemberger, Regulation of Placental Development and Its Impact on Fetal Growth-New Insights From Mouse Models, Front Endocrinol (Lausanne) 9 (2018) 570.
[48] D.G. Simmons, A.L. Fortier, J.C. Cross, Diverse subtypes and developmental origins of trophoblast giant cells in the mouse placenta, Dev Biol 304(2) (2007) 567-78.
[49] D.G. Simmons, D.R. Natale, V. Begay, M. Hughes, A. Leutz, J.C. Cross, Early patterning of the chorion leads to the trilaminar trophoblast cell structure in the placental labyrinth, Development 135(12) (2008) 2083-91.
[50] M. Gasperowicz, C. Surmann-Schmitt, Y. Hamada, F. Otto, J.C. Cross, The transcriptional co-repressor TLE3 regulates development of trophoblast giant cells lining maternal blood spaces in the mouse placenta, Dev Biol 382(1) (2013) 1-14.
[51] A. Rai, J.C. Cross, Development of the hemochorial maternal vascular spaces in the placenta through endothelial and vasculogenic mimicry, Dev Biol 387(2) (2014) 131-41.
[52] P.M. Coan, N. Conroy, G.J. Burton, A.C. Ferguson-Smith, Origin and characteristics of glycogen cells in the developing murine placenta, Dev Dyn 235(12) (2006) 3280-94.
[53] T. Moore, G.S. Dveksler, Pregnancy-specific glycoproteins: complex gene families regulating maternal-fetal interactions, Int J Dev Biol 58(2-4) (2014) 273-80.
[54] R. Ain, G. Dai, J.H. Dunmore, A.R. Godwin, M.J. Soares, A prolactin family paralog regulates reproductive adaptations to a physiological stressor, Proc Natl Acad Sci U S A 101(47) (2004) 16543-8.
[55] P. Bu, S.M. Alam, P. Dhakal, J.L. Vivian, M. Soares, A Prolactin Family Paralog Regulates Placental Adaptations to a Physiological Stressor in the Mouse, Biol Reprod (2016).
[56] Q. Zhang, J. Hao, G. Li, Deletion of Prl7d1 causes placental defects at mid-pregnancy in mice, Mol Reprod Dev 86(6) (2019) 696-713.
[57] R.M. John, Imprinted genes and the regulation of placental endocrine function: Pregnancy and beyond, Placenta 56 (2017) 86-90.
[58] M.A. Surani, Imprinting and the initiation of gene silencing in the germ line, Cell 93(3) (1998) 309-12.
[59] D. Haig, Genetic conflicts in human pregnancy, Q Rev Biol 68(4) (1993) 495-532.
[60] P.B. Vrana, P.G. Matteson, J.V. Schmidt, R.S. Ingram, A. Joyce, K.L. Prince, M.J. Dewey, S.M. Tilghman, Genomic imprinting of a placental lactogen gene in Peromyscus, Dev Genes Evol 211(11) (2001) 523-32.
[61] S.J. Tunster, B. Tycko, R.M. John, The imprinted Phlda2 gene regulates extraembryonic energy stores, Mol Cell Biol 30(1) (2010) 295-306.
[62] S.J. Tunster, H.D. Creeth, R.M. John, The imprinted Phlda2 gene modulates a major endocrine compartment of the placenta to regulate placental demands for maternal resources, Dev Biol 409(1) (2016) 251-60.

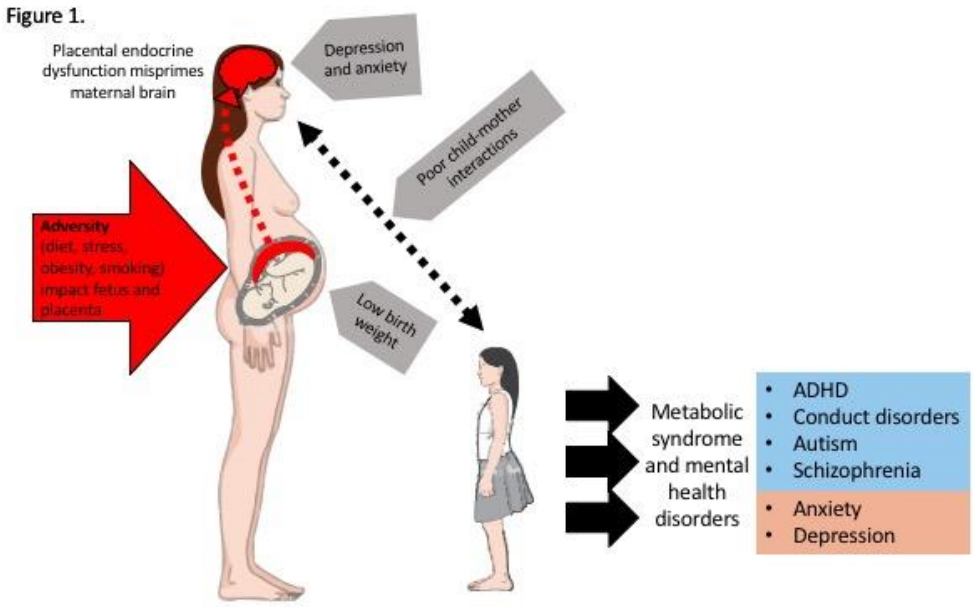
[63] F. Guillemot, T. Caspary, S.M. Tilghman, N.G. Copeland, D.J. Gilbert, N.A. Jenkins, D.J. Anderson, A.L. Joyner, J. Rossant, A. Nagy, Genomic imprinting of *Mash2*, a mouse gene required for trophoblast development., Nature Genetics 9 (1995) 235-242.
[64] A.B. Bogutz, R. Oh-McGinnis, K.J. Jacob, R. Ho-Lau, T. Gu, M. Gertsenstein, A. Nagy, L. Lefebvre, Transcription factor ASCL2 is required for development of the glycogen trophoblast cell lineage, PLoS genetics 14(8) (2018) e1007587.
[65] S.J. Tunster, G.I. McNamara, H.D. Creeth, R.M. John, Increased dosage of the imprinted Ascl2 gene restrains two key endocrine lineages of the mouse Placenta, Dev Biol 418(1) (2016) 55-65.
[66] K. Takahashi, T. Kobayashi, N. Kanayama, p57(Kip2) regulates the proper development of labyrinthine and spongiotrophoblasts, Mol Hum Reprod 6(11) (2000) 1019-25.
[67] S.J. Tunster, M. Van de Pette, R.M. John, Fetal overgrowth in the Cdkn1c mouse model of Beckwith-Wiedemann syndrome, Dis Model Mech 4(6) (2011) 814-21.
[68] D.R. Esquiliano, W. Guo, L. Liang, P. Dikkes, M.F. Lopez, Placental glycogen stores are increased in mice with H19 null mutations but not in those with insulin or IGF type 1 receptor mutations, Placenta 30(8) (2009) 693-9.
[69] S.J. Tunster, R. Boque-Sastre, G.I. McNamara, S.M. Hunter, H.D.J. Creeth, R.M. John, Peg3 Deficiency Results in Sexually Dimorphic Losses and Gains in the Normal Repertoire of Placental Hormones, Front Cell Dev Biol 6 (2018) 123.
[70] J. Kim, W.D. Frey, H. He, H. Kim, M.B. Ekram, A. Bakshi, M. Faisal, B.P. Perera, A. Ye, R. Teruyama, Peg3 mutational effects on reproduction and placenta-specific gene families, PloS one 8(12) (2013) e83359.
[71] K.M. Hillerer, V.R. Jacobs, T. Fischer, L. Aigner, The maternal brain: an organ with peripartal plasticity, Neural Plast 2014 (2014) 574159.
[72] H.G. Potter, D.G. Ashbrook, R. Hager, Offspring genetic effects on maternal care, Frontiers in neuroendocrinology 52 (2019) 195-205.
[73] H.M.a.S. Zippelius, W.M., Ultraschall-Laute bei jungen Mäusen, Die Naturwissenschaften 43 (1956) 502-502.
[74] M. Wohr, R.K. Schwarting, Affective communication in rodents: ultrasonic vocalizations as a tool for research on emotion and motivation, Cell Tissue Res 354(1) (2013) 81-97.
[75] M.L. Scattoni, J. Crawley, L. Ricceri, Ultrasonic vocalizations: a tool for behavioural phenotyping of mouse models of neurodevelopmental disorders, Neuroscience and biobehavioral reviews 33(4) (2009) 508-15.
[76] F.R. D'Amato, E. Scalera, C. Sarli, A. Moles, Pups call, mothers rush: does maternal responsiveness affect the amount of ultrasonic vocalizations in mouse pups?, Behav Genet 35(1) (2005) 103-12.
[77] S. Okabe, M. Nagasawa, T. Kihara, M. Kato, T. Harada, N. Koshida, K. Mogi, T. Kikusui, Pup odor and ultrasonic vocalizations synergistically stimulate maternal attention in mice, Behav Neurosci 127(3) (2013) 432-8.
[78] S.J. Tunster, M. Van De Pette, R.M. John, Isolating the role of elevated Phlda2 in asymmetric late fetal growth restriction in mice, Dis Model Mech 7(10) (2014) 1185-91.
[79] D. Frank, C.L. Mendelsohn, E. Ciccone, K. Svensson, R. Ohlsson, B. Tycko, A novel pleckstrin homology-related gene family defined by Ipl/Tssc3, TDAG51, and Tih1: tissue-specific expression, chromosomal location, and parental imprinting, Mamm Genome 10(12) (1999) 1150-9.
[80] N. Qian, D. Frank, D. O'Keefe, D. Dao, L. Zhao, L. Yuan, Q. Wang, M. Keating, C. Walsh, B. Tycko, The IPL gene on chromosome 11p15.5 is imprinted in humans and mice and is similar to TDAG51, implicated in Fas expression and apoptosis, Hum Mol Genet 6(12) (1997) 2021-9.
[81] G.V. Fitzpatrick, P.D. Soloway, M.J. Higgins, Regional loss of imprinting and growth deficiency in mice with a targeted deletion of KvDMR1, Nat Genet 32(3) (2002) 426-31.
[82] A. Lewis, K. Mitsuya, D. Umlauf, P. Smith, W. Dean, J. Walter, M. Higgins, R. Feil, W. Reik, Imprinting on distal chromosome 7 in the placenta involves repressive histone methylation independent of DNA methylation, Nat Genet 36(12) (2004) 1291-5.

[83] H.S. Kim, C.R. Roh, B. Chen, B. Tycko, D.M. Nelson, Y. Sadovsky, Hypoxia regulates the expression of PHLDA2 in primary term human trophoblasts, Placenta 28(2-3) (2007) 77-84.
[84] H. Bruchova, A. Vasikova, M. Merkerova, A. Milcova, J. Topinka, I. Balascak, A. Pastorkova, R.J. Sram, R. Brdicka, Effect of maternal tobacco smoke exposure on the placental transcriptome, Placenta 31(3) (2010) 186-91.
[85] R.M. Lewis, Cleal, J.K., Ntani, G., Crozier, S.R., Mahon, P.A., Robinson, S.M., Harvey, N.C., Cooper, C., Inskip, H.M., Godfrey, K.M., Hanson, M.A., the Southampton Women's Survey Study Group and John R.M., Relationship between placental expression of the imprinted PHLDA2 gene, intrauterine skeletal growth and childhood bone mass, Bone 50 (2012) 337-342.
[86] P.K. Shukla, L.J. Sittig, T.M. Ullmann, E.E. Redei, Candidate Placental Biomarkers for Intrauterine Alcohol Exposure, Alcohol Clin Exp Res 35(3) (2011) 559–565.
[87] M. Eaton, A.H. Davies, J. Devine, X. Zhao, D.G. Simmons, E. Mariusdottir, D.R.C. Natale, J.R. Matyas, E.A. Bering, M.L. Workentine, B. Hallgrimsson, J.C. Cross, Complex patterns of cell growth in the placenta in normal pregnancy and as adaptations to maternal diet restriction, PloS one 15(1) (2020) e0226735.
[88] L. Li, E.B. Keverne, S.A. Aparicio, F. Ishino, S.C. Barton, M.A. Surani, Regulation of maternal behavior and offspring growth by paternally expressed Peg3, Science 284(5412) (1999) 330-3.
[89] A.M. Carter, Evolution of placental function in mammals: the molecular basis of gas and nutrient transfer, hormone secretion, and immune responses, Physiol Rev 92(4) (2012) 1543-76.
[90] G.J. Burton, E. Jauniaux, What is the placenta?, Am J Obstet Gynecol 213(4 Suppl) (2015) S6 e1, S6-8.
[91] G.J. Burton, A.L. Fowden, The placenta: a multifaceted, transient organ, Philos Trans R Soc Lond B Biol Sci 370(1663) (2015) 20140066.
[92] Y. Liu, X. Fan, R. Wang, X. Lu, Y.L. Dang, H. Wang, H.Y. Lin, C. Zhu, H. Ge, J.C. Cross, H. Wang, Single-cell RNA-seq reveals the diversity of trophoblast subtypes and patterns of differentiation in the human placenta, Cell Res 28(8) (2018) 819-832.
[93] D. Newbern, M. Freemark, Placental hormones and the control of maternal metabolism and fetal growth, Current opinion in endocrinology, diabetes, and obesity 18(6) (2011) 409-16.
[94] Y. Su, S.A. Liebhaber, N.E. Cooke, The human growth hormone gene cluster locus control region supports position-independent pituitary- and placenta-specific expression in the transgenic mouse, J Biol Chem 275(11) (2000) 7902-9.
[95] R.L. Butcher, N.W. Fugo, W.E. Collins, Semicircadian rhythm in plasma levels of prolactin during early gestation in the rat, Endocrinology 90(4) (1972) 1125-7.
[96] M.E. Freeman, M.S. Smith, S.J. Nazian, J.D. Neill, Ovarian and hypothalamic control of the daily surges of prolactin secretion during pseudopregnancy in the rat, Endocrinology 94(3) (1974) 875-82.
[97] M.J. Soares, The prolactin and growth hormone families: pregnancy-specific hormones/cytokines at the maternal-fetal interface, Reprod Biol Endocrinol 2 (2004) 51.
[98] R. Romero, O. Erez, E. Maymon, P. Chaemsaithong, Z. Xu, P. Pacora, T. Chaiworapongsa, B. Done, S.S. Hassan, A.L. Tarca, The maternal plasma proteome changes as a function of gestational age in normal pregnancy: a longitudinal study, Am J Obstet Gynecol 217(1) (2017) 67 e1-67 e21.
[99] N. Aghaeepour, B. Lehallier, Q. Baca, E.A. Ganio, R.J. Wong, M.S. Ghaemi, A. Culos, Y.Y. El-Sayed, Y.J. Blumenfeld, M.L. Druzin, V.D. Winn, R.S. Gibbs, R. Tibshirani, G.M. Shaw, D.K. Stevenson, B. Gaudilliere, M.S. Angst, A proteomic clock of human pregnancy, Am J Obstet Gynecol 218(3) (2018) 347 e1-347 e14.
[100] C.R. Roh, V. Budhraja, H.S. Kim, D.M. Nelson, Y. Sadovsky, Microarray-based identification of differentially expressed genes in hypoxic term human trophoblasts and in placental villi of pregnancies with growth restricted fetuses, Placenta 26(4) (2005) 319-28.
[101] P.J. Dutton, L.K. Warrander, S.A. Roberts, G. Bernatavicius, L.M. Byrd, D. Gaze, J. Kroll, R.L. Jones, C.P. Sibley, J.F. Froen, A.E. Heazell, Predictors of poor perinatal outcome

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

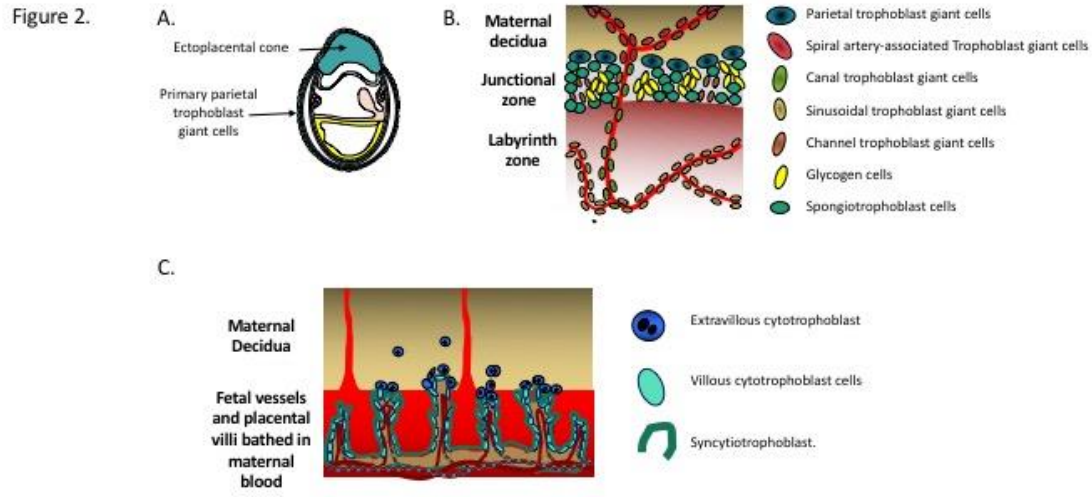
FIGURE LEGENDS

Figure 1. Placental programming hypothesis. Both the fetus and the placenta are exposed to adversities in pregnancy. Adversities driving changes in the endocrine function of the placenta may impact fetal growth through reduced nutrient supply resulting in low birth weight. Placental endocrine insufficiency may also prevent the appropriate adaptations of the maternal brain required for motherhood manifesting as symptoms of depression and anxiety. Continued exposure of the offspring to maternal mood symptoms may further contribute to poor outcomes for children.



684

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

of cells expressing placental hormones, and increased care provision by the mother to the offspring. Conversely, silencing of imprinted genes in the female germline may have limited the number of cells expressing placental hormones, potentially to preserve maternal resources for subsequent pregnancies. Placental endocrine insufficiency in mice results in low birth weight, suboptimal maternal care and maternal anxiety

Figure 3.