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1 **Special Edition Review: Lumps and Bumps meeting.**

2

3 **Imprinted genes and the regulation of placental endocrine function: Pregnancy and**
4 **beyond**

5 Rosalind M John

6 Cardiff School of Biosciences, Cardiff University, Cardiff, CF10 3AX, UK

7 JohnRM@cf.ac.uk

8

9 **Genomic imprinting is an epigenetic process responsible for the monoallelic**
10 **expression of a subset of genes in mammals. Imprinted genes have been**
11 **demonstrated to play important functions prenatally regulating fetal growth and**
12 **placental development with some functions persisting beyond pregnancy to**
13 **influence both metabolism and behaviour in adults. This review focuses on the**
14 **function of imprinted genes in regulating placental hormones, and the probability**
15 **that these functions manifest their impact beyond pregnancy.**

16

17 Key words: Genomic imprinting; placental hormones.

18 Central to the reproductive success of mammals is the *in utero* provision of nutrients to
19 their young via specialised extraembryonic lineages [1]. All extant mammals (monotremes,
20 marsupials and eutherians) rely initially on a yolk sac placenta with some marsupials and
21 all eutherians mammals switching to a more substantial chorioallantoic placenta as
22 gestation proceeds. The mammalian mother continues providing nutrients to their young
23 after birth in the form of milk secretions from mammary patches (monotremes) or more
24 complex mammary glands. High quality maternal care is another vitally important factor in
25 newborn survival with mothers providing body warmth, protection against the environment
26 and potentially fending off predators at risk to her personal safety. The provision of
27 nutrients and care is not simply a passive process but requires substantial physiological
28 and behavioural changes in the mother most of which take place during pregnancy and
29 some of which only become apparent after birth. The provision of resources primarily or
30 exclusively by the mother in mammals suggests a conflict between the mother's genes
31 and the father's genes [2, 3]. Simply, it would be advantageous for the paternal genome to
32 extract nourishment from the mother as there is not cost but the maternal genome must
33 ensure a more equitably allocation of maternal resources across numerous pregnancies.
34 Imprinted genes, expressed from a single parental allele as a consequence of germline
35 epigenetic events [4], are thought to be the physical embodiment of this conflict. In support
36 of this hypothesis, the number of genes subject to genomic imprinting correlates well with
37 the progressive trend toward internal development and viviparity in mammals with
38 marsupials possessing fewer imprinted genes than the well studied Eutherian mammals,
39 represented by mice and humans [5, 6]. Moreover, numerous studies in genetically altered
40 mice have identified imprinted genes that influence fetal weight, placental development,
41 maternal behaviour, lactation and thermogenesis [7-9] in a manner generally consistent
42 with the conflict theory.

43

44 A major function of imprinted genes in the placenta is the regulation of nutrient transport
45 primarily inferred from studies on the paternally expressed/maternally silenced *insulin-like*
46 *growth receptor 2* gene, and extensively reviewed [10]. Nutrient transport is determined by
47 the demand requirements of the fetus and placenta, which both place a substantial burden
48 on maternal resources during pregnancy. The mammalian mother also exclusively
49 supplies nutrients, in the form of milk, after birth. The supply of nutrients prenatally and in
50 the immediate postnatal period requires significant adaptations to maternal physiology,
51 which must be carefully balanced for a successful pregnancy. Effectively, the mother must
52 be able to supply all the nutritional requirements of her developing young while
53 maintaining her own health and welfare. To achieve nutrient supply in pregnancy, maternal
54 food intake increases, peripheral insulin resistance increases and there is an up-regulation
55 of maternal pancreatic islet function alongside a lowered threshold for glucose stimulated
56 insulin all of which channel maternal nutrients to the fetus [11]. During pregnancy maternal
57 fat depots are also laid down, and changes take place in the mammary gland in
58 preparation for the supply of milk in the postnatal period. Placental hormones are key to
59 the induction and maintenance of these changes in maternal physiology during pregnancy
60 [12].

61

62 Perhaps the most well studied placental hormones belong to the somatotropin/prolactin
63 family. These belong to a complex family of hormones related to prolactin (expressed in
64 the pituitary) that originated from a common ancestral gene. This same ancestral gene
65 also gave rise to pituitary expressed growth hormone and, in some mammalian species,
66 further duplication to produce placental-specific growth hormone. Together, all these
67 hormones could be viewed as one gene family encompassing both prolactin- and growth
68 hormone-like activities, distinguished by their interaction with their cognate receptors, the
69 growth hormones receptor and the prolactin receptor [13]. In mice, there are 22 prolactin

70 family members expressed almost exclusively in the placenta and no equivalent for
71 placental growth hormone gene [14]. However, only a small subset of these hormones
72 possess the capacity to activate the prolactin receptor [15]. In humans there are two
73 functional prolactin family members expressed in the placenta (*chorionic*
74 *somatomammotropin hormone 1* and 2) encoding placental lactogen, and one placental
75 growth hormone gene [16]. One of the key changes in pregnancy thought to be induced by
76 a growth hormone-like activity is the increase maternal insulin resistance required to
77 channel maternal glucose to the fetus [17]. Glucose is transported via a passive process
78 that requires a higher concentration in the maternal circulation than in the fetus. Insulin
79 resistance contributes to this gradient but must be balanced by the ability to respond
80 rapidly to meals in order to avoid dangerously high levels of blood glucose. This balance is
81 achieved, in part, through the prolactin-like function of this gene family up-regulating
82 maternal islet function and accommodating the increased demand for insulin during
83 pregnancy [18, 19]. Placental lactogens also play an important role in preparing the new
84 mother to provide nutrients after birth by priming the mammary gland for lactation [20].
85 Placental lactogens may additionally be involved in the induction of maternal care. Both
86 pituitary prolactin and placental lactogen have been shown to stimulate maternal care in
87 non-pregnant rodents likely influencing maternal care through their interaction with the
88 maternal prolactin receptor, most clearly demonstrated in rodents [21].

89
90 In mice and humans, placental lactogens are expressed by derivatives of the trophoblast
91 lineage, a specialised cell type that emerges from the first differentiation event in
92 development [22]. Early in pregnancy, trophoblast cells contribute to the choriovitelline
93 (yolk sac) placenta, a structure that is replaced as gestation proceeds by the
94 chorioallantoic (mature) placenta. In mice, there are four main region of the chorioallantoic
95 placenta: the maternally-derived decidua, a single layer of cells with giant nuclei called the

96 secondary parietal trophoblast giant cells (TGCs), the junctional zone and the labyrinth
97 [23]. The junctional zone contains two distinct lineages, the spongiotrophoblast and the
98 glycogen cells, while the bulk of the labyrinth is composed of fetal endothelium surrounded
99 by a trilaminar layer of trophoblast-derived cells consisting of a single mononuclear TGC
100 layer (sinusoidal; previously called trophoblast layer I) and two multinucleated
101 syncytiotrophoblast layers that function in nutrient transport (I and II; previously called
102 layers II and II). Three other distinct TGC placental lineages have been classified. The
103 spiral artery (SpA) TGCs line the maternal blood system on entry to the placenta, the canal
104 (C-) TGCs line the maternal blood canals in the junctional zone and the channel (Ch-)
105 TGCs line the maternal blood spaces located just beneath the decidua where maternal
106 blood leaves the placenta [14, 23-25]. Placental lactogens are expressed by all TGC
107 subtypes, the spongiotrophoblast and the glycogen cells. Moreover, the large nuclei of
108 the TGCs result from endoreduplication with specific parts of their genome further over
109 replicated including regions encoding placental lactogens [26]. Along with their close
110 proximity to the maternal circulation, these gene amplification events suggest TGCs as a
111 major source of placental lactogens in mice. In contrast, the human placenta appears to
112 possess a single major cell type manufacturing hormones termed the syncytiotrophoblast.
113 These multinucleated layer of cells is generated from the fusion of cytotrophoblast cells
114 lying beneath, and both cell types overlie a core of mesenchymal cells that make up the
115 numerous chorionic villi of the human placenta [13].

116

117 The role of placental hormones in manipulating the mother to provide resources to her
118 offspring both *in utero* and in the immediate postnatal period suggested placental
119 hormones as candidates for the expression of parent-offspring conflict [27, 28]. Apart from
120 one rare example in the new world mouse, *Peromyscus* [29], there is no evidence that
121 placental hormones or their maternal receptors are directly subject to genomic imprinting.

122 However, a fetally-derived product of the paternally-expressed imprinted *delta-like*
123 *homolog 1* gene (*Dlk1*) has recently been shown to reach the maternal circulation and
124 influence maternal metabolism [30], and it is possible that the *Igf2* gene product has a
125 similar function [31]. We hypothesised an alternative mechanism whereby imprinting could
126 influence placental hormone production - by regulating the placental lineages that express
127 these hormones [32]. This hypothesis was based initially on our studies on one imprinted
128 gene, *Pleckstrin homology-like domain family a member 2* (*Phlda2*). *Phlda2* is a maternally
129 expressed imprinted gene that encodes a PH domain-only protein expressed most highly
130 in the ectoplacental cone and the visceral endoderm of the yolk sac [33-35]. Our studies
131 on *Phlda2* revealed a precise function for this gene in negatively regulating the size of
132 spongiotrophoblast compartment, without altering the gross contribution of other placental
133 lineages [7, 36-39]. Loss-of-function of *Phlda2* resulted in a much larger
134 spongiotrophoblast, approximately twice the volume normally present. Conversely, a two-
135 fold gain in expression of *Phlda2* (modeling loss-of-imprinting) reduced the size of this
136 compartment by 50%. The spongiotrophoblast is a key site for the production of placental
137 lactogens, pregnancy-specific glycoproteins and a number of other hormones important in
138 pregnancy [14, 37]. Using the same dosage interrogating approach applied to *Phlda2*, we
139 have recently shown that overexpression of a second maternally expressed imprinted
140 gene, *Achaete-scute complex homolog 2* (*Ascl2*), repressed both the spongiotrophoblast
141 and the parietal TGCs [40]. Although mouse models with increased dosage have not been
142 reported, loss-of-function of studies suggest that *Paternally expressed gene 3* (*Peg3*),
143 *Paternally expressed gene 10* (*Peg10*), *Cyclin-dependent kinase inhibitor 1c* (*Cdkn1c*) and
144 several non-classically imprinted genes located on the X chromosome also regulate the
145 placental endocrine lineages positively or negatively in a manner generally consistent with
146 parental conflict [32]. As a consequence, imprinted genes indirectly modulate the
147 expression of placental hormones by regulating the size of the placental endocrine

148 compartment. This is illustrated most elegantly with the *Phlda2* gene where loss of
149 expression resulted in a 2-fold increase in expression of the placental lactogens expressed
150 in the spongiotrophoblast while a double dose of *Phlda2* resulted in a 50% decrease in
151 their expression [41].

152

153 Functional data demonstrating that imprinted genes regulate placental hormone lineages
154 in species other than the mouse is sparse. Reduced expression of *PHLDA2* is a common
155 feature of bovine cloning associated with overgrowth of both the fetus and placenta but not
156 the altered expression of placental hormones [42, 43]. Elevated placental *PHLDA2* has
157 been reported in a number of studies on human fetal growth restriction, fetal death and low
158 birth weight [44]. In our recent study on women with a perception of reduced fetal
159 movements (RFM), we found placental *PHLDA2* expression was 2.3 fold higher in RFM
160 pregnancies resulting in delivery of a growth restricted infant compared with a normal birth
161 weight infant [45]. Importantly, we found a significant inverse association between
162 placental *PHLDA2* levels and maternal serum placental lactogen (hPL) levels suggesting
163 that *PHLDA2* may regulate the production of placental hormones in human pregnancies.
164 In another study focusing on prenatal depression, we examined placental expression
165 levels of four genes, *PHLDA2*, *CDKN1C*, *PEG3* and *PEG10*, based on the conserved
166 imprinting status between mouse and human and their predicted role in regulating
167 production of placental hormones [32]. In women with clinically diagnosed depression
168 during pregnancy, we observed significantly lower expression of placental *PEG3*. We also
169 found low placental *PEG3* in pregnancies where women reported a depressed mood
170 assessed using two self-rating psychometric questionnaires: Edinburgh Postnatal
171 Depression Scale (EPDS), used as a measure of maternal prenatal depressive symptoms
172 [46] and the Spielberger State-Trait Anxiety Inventory (STAI), used as a measure of
173 anxiety symptoms [47]. Both diagnosed and self-reported symptoms of depression were

174 also significantly associated with low expression of *hPL*. Critically, we found a positive
175 correlation between placental *PEG3* and *hPL* expression. In mice, loss-of-function of *Peg3*
176 has been reported to result in changes in the expression of a number of placental
177 lactogens [48, 49] although a specific endocrine lineage analysis has not been performed.
178 Together, these data are consistent with a role for *PEG3* in regulating *hPL* expression in
179 humans. *Peg3* and another paternally expressed imprinted gene, *Peg1*, have previously
180 been linked to maternal care in rodents [50, 51]. In both these reports the dam carried the
181 inactivating mutation for the respective gene, with considerable impact on a number of
182 physiological as well as neurological processes. Moreover, a recent study did not find a
183 maternal care deficit when a second *Peg3* targeted allele was generated, and examined
184 on a different strain background [52]. A role for loss of *Peg3* in the placenta influencing
185 any aspect of maternal behaviour in rodents has yet to be reported.

186

187 In human pregnancies, a number of complications can commonly co-occur. Women with
188 prenatal depression are three times more likely to have a low birth weight baby [53].
189 Maternal depression in the first and second trimester is associated with an increased risk
190 of gestational diabetes while women with gestation diabetes have a >4-fold risk of
191 postnatal depression with elevated depressive symptoms particularly high among non-
192 obese women [54]. A recent systematic review reported that women with symptoms of
193 postnatal depression were less likely to breastfeed exclusively and more likely to terminate
194 breastfeeding earlier [55]. This could be interpreted to mean that postpartum depression
195 negatively impacts maternal breast feeding behaviour or that pressures around breast
196 feeding increase the risk of depression. However, given the potential for placental
197 hormones to influence both lactation and maternal behaviour, it is possible that difficulties
198 with breast feeding and postnatal depression are manifestations of the same underlying
199 problem, placental endocrine dysfunction (Figure 1). Similarly, prenatal depression

200 accompanied by low birth weight could be indicative of placental endocrine dysfunction
201 (Figure 1). As well as these manifestations of maladapted pregnancy, a transient increase
202 in the risk of breast cancer diagnosis has been reported for first time mothers likely linked
203 to the pregnancy induced changes in mammary development [56]. It is therefore possible
204 that placental hormone dysfunction could influence both short term and long term risk of
205 breast cancer. Measuring placental hormones in maternal blood is already an important
206 diagnostic tool early in pregnancy and the use of DLK1 assays in characterising types of
207 fetal growth restriction holds great promise [30]. New techniques such as multiplexed
208 quantification of fetal RNAs circulating in maternal blood may provide even more accurate
209 tools, and for a variety of conditions [57].

210

211 In summary, current data supports a conserved function in mammals for imprinted genes
212 in regulating placental hormones via regulating the size of the placental endocrine
213 compartment. These data essentially support the prediction by David Haig more than 20
214 years ago that imprinted genes would regulate signaling between the mother and her
215 fetus. Importantly for human pregnancies, placental hormones play key roles in driving the
216 physiological and, potentially, behavioural adaptations required to support optimal fetal
217 growth and postpartum care. It is therefore plausible that aberrant imprinting in the
218 placenta contributes to the common co-occurrence of a number of complications of
219 pregnancy including low birth weight, maternal mood disorders, gestational diabetes and
220 poor breast feeding. Finally, given the link between all these complications and poor long
221 term outcomes for children, the detrimental consequences of placental endocrine function
222 may influence offspring wellbeing considerably beyond the period of pregnancy (Figure 1).

223

224

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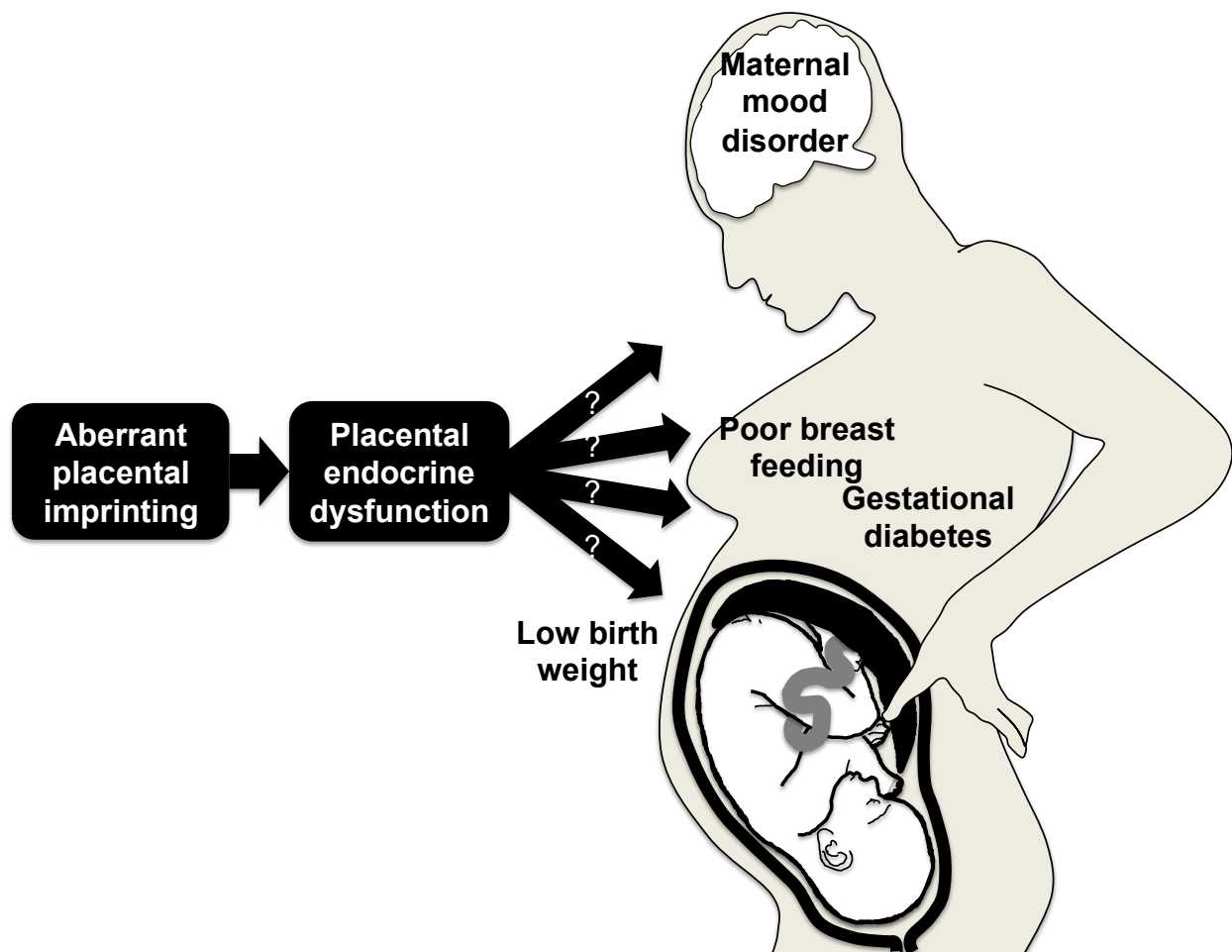
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382 **Figure 1. Aberrant imprinting and placental endocrine dysfunction.**



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