1   The placenta; a multifaceted, transient organ

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20   **Abstract**

21   The placenta is arguably the most important organ of the body, but paradoxically

22   the most poorly understood. During its transient existence it performs actions

23   that are later taken on by diverse separate organs, including the lungs, liver, gut,

24   kidneys and endocrine glands. Its principal function is to supply the fetus, and in

25   particular the fetal brain, with oxygen and nutrients. The placenta is structurally

26   adapted to achieve this, possessing a large surface area for exchange and a thin

27   interhaemal membrane separating the maternal and fetal circulations. In

28   addition, it adopts other strategies that are key to facilitating transfer, including

29   remodelling of the maternal uterine arteries that supply the placenta to ensure

30   optimal perfusion. Furthermore, placental hormones have profound effects on

31   maternal metabolism, initially building up her energy reserves and then

32   releasing these to support fetal growth in later pregnancy and lactation post-

33   natally. Bipedalism has posed unique haemodynamic challenges to the placental

34   circulation, as pressure applied to the vena cava by the pregnant uterus may

35   compromise venous return to the heart. These challenges, along with the

36   immune interactions involved in maternal arterial remodelling, may explain

37   complications of pregnancy that are almost unique to the human, including pre-

38   eclampsia. Such complications may represent a trade-off against the provision

39   for a large fetal brain.

40

41 **Introduction**

42 For the nine months of its intrauterine existence the human fetus is totally

43 reliant on the placenta, a transient extracorporeal organ that interfaces with the

44 mother, to sustain and protect it. This dependency is reflected in the way that

45 various societal groups consider the placenta as a twin or guardian angel, and

46 venerate it as a sacred object [1, 2]. Hence, the placenta is often accorded ritual

47 burial, for in some beliefs the soul must be re-united with its placenta before

48 being able to pass through to the afterlife.

49 What then is the placenta? The wide variety of morphological forms seen

50 amongst mammals makes the organ hard to define, but the comparative

51 placentologist Harland Mossman captured the essence by stating 'The normal

52 mammalian placenta is an apposition or fusion of the fetal membranes to the

53 uterine mucosa for physiological exchange' [3]. This definition rightly recognises

54 physiological exchange as the prime function of the placenta, but it fails to

55 emphasise the other tasks the organ has to perform in order to achieve that

56 function; for example, its remodelling the uterine spiral arteries in early

57 pregnancy to establish the maternal circulation, its endocrine activity that has a

58 profound effect on maternal metabolism, and its metabolic role in providing

59 protected substrates for the fetus. This article provides a brief overview of the

60 development and function of the human placenta so that its pivotal role in

61 supporting fetal development, including the large brain, can be appreciated more

62 fully in the context of the theory of pelvic constraint.

63

64 **Structure and development of the human placenta**

65 The placenta and associated extraembryonic membranes are formed from the

66 zygote at the start of each pregnancy, and thus have the same genetic

67 composition as the fetus. The two principal tissue sources are the

68 trophectoderm that forms the wall of the blastocyst, and the underlying

69 extraembryonic mesoderm. The trophectoderm differentiates into trophoblast,

70 which in turn forms the epithelial covering of the placenta but also gives rise to

71 the sub-population of invasive extravillous trophoblast cells. The

72 extraembryonic mesoderm forms the stromal core of the placenta, from which

73 originate the fibroblasts, vascular network and resident macrophage population.

74 The mature placenta has been described in detail elsewhere [4, 5], but is a

75 roughly discoid organ, on average 22 cm in diameter, 2.5 cm thick at the centre

76 and weighing approximately 500 g. Its surfaces are the chorionic plate that faces

77 the fetus and to which the umbilical cord is attached, and the basal plate that

78 abuts the maternal endometrium. Between these plates is a cavity, the

79 intervillous space, into which 30-40 elaborately branched fetal villous trees

80 project. Each villous tree arises from a stem villus attached to the deep surface of

81 the chorionic plate, and branches repeatedly to create a globular lobule 1-3 cm in

82 diameter. The centre of a lobule is located over the opening of a maternal spiral

83 artery through the basal plate. Maternal blood released at these openings

84 percolates between the villous branches before draining into openings of the

85 uterine veins and exiting the placenta. Each lobule thus represents an

86 independent maternal-fetal exchange unit.

87 The final branches of the villous trees are the terminal villi. These present a

88 surface area of 12-14 m^2 at term, and are richly vascularised by a fetal capillary

89   network. The capillaries display local dilations, referred to as sinusoids, which

90   bring the endothelium into close approximation to the covering of trophoblast.

91   This is locally thinned and the diffusion distance between the maternal and fetal

92   circulations may be reduced to as little at 2-3 μm. The morphological

93   resemblance of these structures, termed vasculosyncytial membranes, to the

94   alveoli of the lung has led to the assumption that they are the principal sites of

95   maternal-fetal exchange. Terminal villi are formed primarily from 20 weeks of

96   gestation onwards, and elaboration of the villous trees continues until term [6].

97   The epithelial covering of the villous tree is the syncytiotrophoblast, a true

98   multinucleated syncytium that presents no intercellular clefts to the intervillous

99   space. This arrangement may assist in preventing the vertical transmission of

100   pathogens from the maternal blood [7], but may also facilitate regional

101   specialisations of the syncytiotrophoblast. Because of its location, the

102   syncytiotrophoblast is involved in many of the functions of the placenta, such as

103   the synthesis and secretion of large quantities of steroid and peptide hormones,

104   protection against xenobiotics and active transport. Hence it has a high

105   metabolic rate, and accounts for ~40% of the total oxygen consumption of the

106   feto-placental unit [8]. Interposing such an active tissue between the maternal

107   and fetal circulations potentially reduces the oxygen available for the fetus, and

108   so the syncytiotrophoblast shows regional variations in thickness around the

109   villous surface, being very thin and devoid of organelles at the site of

110   vasculosyncytial membranes and thicker over non-vascular parts of the villous

111   surface. Having no lateral cell boundaries may facilitate flow of the

112   syncytioplasm, and so help to optimise oxygen supply to the fetus [9].

113   The syncytiotrophoblast is a highly polarised epithelium, bearing a dense

114   covering of microvilli on its apical border. The projections provide a surface

115   amplification factor of 5-7x for insertion of receptor and transporter proteins. At

116   the base of each microvillus is a clathrin-coated pit, which is capable of forming a

117   coated   vesicle   for   the   transport   of   macromolecules   across   the

118   syncytiotrophoblast [10].

119   The syncytiotrophoblast is a terminally differentiated tissue, and its expansion

120   during pregnancy is achieved by the fusion and incorporation of underlying

121   mononuclear progenitor cytotrophoblast cells that rest on the underlying

122   basement membrane. Fusion is a complex event that is still not fully understood,

123   but involves exit of the progenitor from the cell cycle, the formation of gap

124   junctions with the syncytiotrophoblast, externalisation of phosphatidylserine

125   and the expression of two endogenous retroviral proteins that entered the

126   primate genome 25 and >40 million years ago [11, 12].

127

128   **Placental transport**

129   The absence of intercellular junctions in the syncytiotrophoblast layer suggests

130   that exchange must take place through the apical and basal plasma membranes,

131   although there are two possible exceptions. Firstly, the presence of water-filled

132   transtrophoblastic channels has been postulated. The main evidence for such

133   channels is that the human placenta is freely permeable to solutes of 1,350-5,200

134   daltons, whereas in the epitheliochorial placenta of the sheep diffusion is

135   restricted to molecules of <400 daltons [13, 14]. By measuring the transplacental

136   flux of four permeants of different molecular sizes infused into patients prior to

137   elective caesarean section, it was concluded that pores of different sizes must

138   exist in the human syncytiotrophoblast [15]. However, the putative channels

139   have never been visualised in the human [16], although this lack may reflect the

140   complexity of the syncytioplasm and the limitations of current imaging

141   techniques. Secondly, it is well recognised that there are small, scattered defects

142   in the syncytiotrophoblastic surface of all human placentas, leading to deposition

143   of fibrin plaques [17, 18]. In this context the plaques represent a possible route

144   for the diffusion of hydrophilic molecules, whereas in broader terms they may

145   also be potential portals for the ingress of maternal immune cells and the vertical

146   transmission of pathogens. Immunohistochemical studies have localised transfer

147   of alphafetoprotein to these sites [19], suggesting they may play a significant role

148   physiologically.

149   Exchange across the intact placental membrane can occur through three main

150   processes; diffusion, transporter-mediated mechanisms and

151   endocytosis/exocytosis.

152   The rate of diffusion of an uncharged molecule is determined by Fick's Law of

153   diffusion, and so is proportional to the surface area for exchange, the diffusivity

154   of the molecule in question and its concentration gradient, and inversely

155   proportional to the diffusion distance between the circulations. Given the

156   importance of these structural parameters, it is not unreasonable to assume that

157   the requirements for diffusional exchange, and in particular oxygen exchange,

158   are the principal drivers of placental architecture. Hence, the elaboration of

159   terminal villi and vasculo-syncytial membranes as gestation advances will

160   increase the diffusing capacity of the organ. This view is supported by the fact

161 that the specific theoretical diffusing capacity (ml/min/kPa/kg fetus) of the

162 placenta for oxygen estimated stereologically remains constant across

163 gestational age [20]. Furthermore, a reduction in the mean thickness of the

164 villous membrane is observed in placentas from pregnancies at high altitude,

165 enhancing the theoretical diffusing capacity [21].

166 In addition to these structural parameters, the exchange of charged molecules

167 will be influenced by any electrical gradient existing between the maternal and

168 fetal circulations. In the human, a small but significant potential difference of -2.7

169 ±0.4mV fetus negative has been measured in mid-gestation [22], reducing to zero

170 or close to it at term [23]. A potential difference also operates across the

171 microvillous membrane of the syncytiotrophoblast, decreasing between the early

172 (median **-**32 mV) and late first trimester (median -24 mV), with a small

173 subsequent fall to term (-21 mV). These data suggest that the driving force for

174 cation flux into the syncytiotrophoblast decreases, and that for anions increases,

175 as pregnancy advances.

176 Diffusion of small, relatively hydrophobic molecules, such as the respiratory

177 gases, across the plasma membrane occurs rapidly. Hence, their flux depends

178 more on the concentration gradient across the villous membrane rather than its

179 surface area or thickness. The concentration gradient in turn is determined in

180 part by maternal and environmental factors, but is predominantly influenced by

181 the rate of blood flow across the membrane. Hence, the exchange of such

182 molecules is referred to as being 'flow limited'. Impairment of the uterine or

183 umbilical circulations can therefore have a profound impact on the rate of fetal

184 growth. By contrast, the concentration gradient for lipid insoluble (hydrophilic)

molecules, such as glucose, that do not diffuse across plasma membranes so easily is often more stable. In this case, the structural parameters of the villous membrane are more significant, and exchange is said to be 'membrane- or diffusion-limited'.

To aid the exchange of hydrophilic or charged molecules, transporter proteins may be inserted into the plasma membrane. Transporter proteins form a large and diverse family, but share common features such as substrate specificity, saturation kinetics, and the ability to be competitively inhibited [24]. Transporter proteins may simply allow exchange down a concentration gradient at a faster rate than simple diffusion alone, often referred to as facilitated diffusion. The classic example in the placenta is the GLUT family of transporters handling glucose. Alternatively, they can enable exchange of molecules, such as amino acids, against a concentration gradient, referred to as active transport, which is an energy dependent process. Expression of the genes encoding transporter proteins is in part under endocrine control, and leptin upregulates glucose and amino acid transporters, facilitating nutrient transfer [25]. In addition, one of the major benefits of transporter-mediated exchange is that under adverse conditions the rate can be modulated by altering the number of proteins inserted into the plasma membrane [26]. Thus, if the surface area for exchange is reduced experimentally in mice, or the mother is subjected to undernutrition, placental expression of certain amino acid transporters is increased, enhancing the flux [27, 28]. Full details of the signalling pathways involved are not available at present, although experimental data implicate placental Igf2 [29].

209   Endocytosis is the process by which invaginations form at the apical cell surface

210   pinch off, and then move deeper into the cytoplasm. There, they may fuse with

211   vesicles of the lysosomal pathway, or traverse the cell and fuse with the basal

212   surface in the process of exocytosis. The former delivers nutrients for

213   breakdown by proteolytic enzymes molecules and use by the cell, whilst the

214   latter represents a transport pathway. Both are active in the syncytiotrophoblast

215   of the human placenta [30, 31]. During the first trimester a number of proteins of

216   maternal origin accumulate in the coelomic and amniotic fluids [32], whereas

217   later in pregnancy evidence suggests that immunoglobulin G (IgG) crosses the

218   placenta by this mechanism [24]. Specificity and the ability to avoid lysosomal

219   degradation during the endocytosis phase may be provided by the presence of

220   receptors for IgG in the microvillous membrane invaginations and vesicles.

221

222   **Establishing the maternal placental circulation**

223   For effective transplacental exchange there must be matched perfusion in the

224   maternal and fetal placental circulations, especially for those hydrophobic

225   molecules whose transfer is 'flow-limited'. Establishing the maternal circulation

226   to a haemochorial placenta, such as the human, where the maternal-fetal

227   interface is represented by maternal blood bathing the trophoblast surface is a

228   major haemodynamic challenge. It requires the trophoblast to tap into branches

229   of the maternal uterine arteries that carry blood at a higher pressure than the

230   fetus can ever generate. Hence, there is a danger that the fetal capillaries within

231   the terminal villi will be compressed, impeding the umbilical circulation and

232   preventing the formation of vasculosyncytial membranes [33]. Equally, the high

233 velocity of maternal arterial blood flow can potentially cause mechanical damage

234 to the delicate villous trees [34], with high shear rates also causing oxidative

235 stress [35]. In many mammals these dangers are avoided as there is either no or

236 only limited invasion of the maternal tissues by the trophoblast, so-called

237 epitheliochorial and endotheliochorial placentation respectively [36]. The

238 trophoblast is simply apposed to the uterine epithelium or the underlying

239 stromal matrix, and the maternal blood is retained within the uterine vascular

240 network.

241 In all mammals, the uterine arteries undergo dilation during pregnancy in order

242 to meet the metabolic demands of the feto-placental unit, and this is mediated by

243 a combination of endocrine and local flow-dependent responses. In addition, in

244 those species with a haemochorial placenta the final branches that deliver the

245 blood to the placenta undergo considerable remodelling, resulting in their

246 dilation as they approach the organ. In the human, data collected from pregnant

247 hysterectomies near term indicate the diameter of the spiral arteries increases

248 from ~0.5 mm at the endometrium/myometrium boundary to ~2.4 mm at their

249 opening through the basal plate [37]. Mathematical modelling based on these

250 dimensions predicts that as a consequence the velocity of maternal blood flow

251 will reduce by an order of magnitude, from 2-3 $m \cdot s^{-1}$ to ~10 $cm \cdot s^{-1}$ [35].

252 The remodelling process involves the loss of smooth muscle cells from the walls

253 of the spiral arteries, either through dedifferentiation or apoptosis, and their

254 replacement by an inert, amorphous fibrinoid material [38, 39]. The molecular

255 mechanisms involved are still unclear, but it is now recognised that there is an

256 initial phase of endocrine priming followed by a second phase that is dependent

257   on the presence of extravillous trophoblast cells [40, 41]. Extravillous

258   trophoblast cells are most common during the first trimester of pregnancy, and

259   arise from the tips of anchoring villi that attach the villous trees to the

260   endometrium. The cells proliferate and then migrate away from the placenta,

261   either down the lumens of the spiral arteries or through the endometrial stroma.

262   Along the latter pathway they interact with maternal immune cells, particularly

263   the uterine Natural Killer (uNK) cells of the innate immune system. The uNK

264   cells accumulate in the endometrium in the late secretory phase of the non-

265   pregnant cycle, and are particularly numerous around the early implantation

266   site. Despite their name, uNK cells do not engage in killing the migrating

267   trophoblast cells. Rather, it is thought that upon appropriate stimulation they

268   release proteases and cytokines that regulate trophoblast migration and mediate

269   the arterial remodelling [42-44]. There is a carefully orchestrated dialogue

270   between the two cell types involving polymorphic HLA-C ligands on the

271   trophoblast and killer-cell immunoglobulin-like receptors (KIR) on the uNK cells.

272   Certain combinations of ligand and receptor are associated with an increase risk

273   of complications of pregnancy, including miscarriage, pre-eclampsia and growth

274   restriction [45].

275   Deficient remodelling of the spiral arteries has been associated with the 'Great

276   Obstetrical Syndromes' [46]. The mechanistic link is strongest in the case of pre-

277   eclampsia, when the resultant malperfusion of the placenta is thought to cause

278   oxidative stress [47]. Oxidative stress is able to stimulate the release of

279   proinflammatory cytokines and angiogenic regulators from the

280   syncytiotrophoblast, which in turn leads to activation of the maternal

281   endothelium and hence the pre-eclamptic syndrome [48, 49]. Recently, closely

282   related endoplasmic reticulum stress has been identified in placentas from cases

283   of early-onset pre-eclampsia [50], and also normotensive fetal growth restriction

284   [51]. One of the consequences of endoplasmic reticulum stress is the suppression

285   of protein translation, which *in vitro* leads to a reduction in cell proliferation rate.

286   Hence, we speculate that placental endoplasmic reticulum stress is principally

287   causally associated with growth restriction [52], although at high levels the same

288   pathways can also contribute to activation of pro-inflammatory responses [53].

289   These stresses may be exacerbated in the human by the adoption of bipedalism,

290   for in the upright position the pregnant uterus compresses the inferior vena cava

291   against the lordosis of the lumbar vertebral column [54]. Such compression will

292   reduce venous return to the heart and so compromise cardiac output. In

293   addition, it will cause venous engorgement of the intervillous space, restricting

294   arterial inflow into the intervillous space and so potentially causing fluctuations

295   in oxygenation. The effect is particularly marked when the mother is in the

296   supine position [55], and fluctuations in oxygenation are a powerful stimulus for

297   generation of placental oxidative stress [56].

298

299   **Development of the fetal placental vascular tree**

300   The placenta is one of the principal sites of vasculogenesis and angiogenesis, and

301   in the space of 9 months develops a vascular network over 500 km in length.

302   Vasculogenesis starts with the differentiation *in situ* of haemangioblastic clusters

303   within the mesenchymal core of early villi during the third week post-

304   fertilisation [57]. The clusters form cords of cells, usually located immediately

305   beneath the trophoblastic basement membrane. Indeed, it is thought that their

306 differentiation is induced by angiogenic growth factors secreted by the

307 cytotrophoblast cells [58]. The cords gradually expand to form a network

308 comprised of endothelial cells linked by tight junctions, the molecular

309 organisation of which undergoes maturation with increasing gestational age

310 [59]. Once a lumen is formed, haematopoietic stem cells delaminate from the

311 inner surface of the clusters, and following further differentiation form a

312 characteristic clump of tightly packed nucleated erythrocytes. These are not

313 displaced until onset of the fetal placental circulation towards the end of the first

314 trimester. The villous capillary networks undergo continued sprouting and

315 remodelling throughout gestation [60], regulated most likely by angiogenic

316 factors in response to changes in oxygen tension and mechanical stimuli such as

317 shear stress and cyclic strain [57].

318 In the absence of an autonomic nerve supply to the placenta, vasomotor control

319 of the fetal placental circulation is regulated by the local release of factors. The

320 muscular arteries contained within the stem villi are thought to represent the

321 principal resistance vessels within the placenta, and the gasotransmitters nitric

322 oxide and carbon monoxide have been implicated in modulating their vasomotor

323 tone [61, 62]. Hydrogen sulphide has recently been demonstrated to be a potent

324 vasodilator [63]. In this way, fetal blood flow within a lobule may be matched to

325 maternal perfusion, ensuring maximal placental efficiency, although as yet there

326 are no experimental data to support this suggestion.

327

328

329 **Endocrine modulation of maternal metabolism**

330   Glucose is the principal substrate for placental and fetal metabolism, and as

331   discussed previously it crosses the placenta by facilitated diffusion. The flux to

332   the fetus is thus critically dependent on the concentration gradient acting across

333   the placenta, as well as the density of transporter proteins in the trophoblastic

334   membranes. Placental hormones modulate maternal metabolism in order to

335   increase maternal blood glucose concentrations, and maximise transfer.

336   The placenta is a major endocrine organ, and placental hormones have diverse

337   profound effects on maternal physiology and behaviour [64, 65]. During early

338   pregnancy they drive an increase in food intake and energy storage, whereas

339   towards term they mobilise these reserves to support fetal growth and

340   preparation for lactation [66, 67]. The most important hormones in this respect

341   are the family of closely related placental lactogens (hPL) and placental growth

342   hormone (hGH) (96% amino acid sequence homology). Their importance for

343   maternal-fetal allocation of resources is exemplified by the fact that evolution of

344   the primates was associated with considerable duplication of the genes encoding

345   these hormones [68]. This is in marked contrast to most genes that are involved

346   in placental evolution, which are represented by single copies that have been

347   recruited from other developmental systems [69]. In the human, there is a gene

348   cluster on chromosome 17 that encodes 5 growth hormone-like proteins; *hGH-N*

349   encoding pituitary growth hormone, *hGH-V* encoding placental growth hormone,

350   and *hPL-A*, *hPL-B* and *hPL-L* encoding placental lactogens.   All except hGH-N are

351   expressed in the syncytiotrophoblast, but most circulating hPL originates from

352   *hPL-A*, *hPL-B*.

353 Both progesterone and hPL are appetite stimulants, and maternal food intake

354 increases by the end of the first trimester when the metabolic demands of the

355 conceptus are still relatively low. The result is increased deposition of fat

356 reserves, which represents a loss of the normal homeostatic mechanisms that

357 regulate energy balance. Leptin secreted by adipose tissue normally feeds back

358 on the hypothalamus to suppress intake, but pregnancy is a state of central

359 leptin-resistance. During pregnancy, leptin is secreted in large quantities by the

360 syncytiotrophoblast, regulated in part through human chorionic gonadotropin

361 and 17ß-estradiol [25]. Expression levels correlate closely with maternal serum

362 concentrations, peaking at the end of the second and during the early third

363 trimesters. The hormone has local effects on placental transporter expression ,

364 as well as central effects on appetite. Experimental data from rodent models

365 indicate that placental lactogen and prolactin, secreted by the trophoblast and

366 decidua respectively, appear to mediate the central insensitivity [70]. These

367 hormones also stimulate beta cell proliferation in the maternal pancreas during

368 early pregnancy, increasing insulin concentrations and so again aiding fat

369 deposition [67].

370 Later in pregnancy the mother develops insulin resistance, with an

371 accompanying increase in lipolysis and in circulating triglycerides and free fatty

372 acids. In the past these changes have been attributed to placental lactogen

373 and/or prolactin, but more recent evidence casts doubt on this assumption [66].

374 Instead, it appears that placental growth hormone may play a more important

375 role. Placental growth hormone is secreted tonically by the syncytiotrophoblast,

376 unlike the pituitary form that is secreted in a pulsatile fashion. The two variants

377 differ in only 13 amino acids out of a total of 191, and the similarity is sufficient

378 for the placenta to suppress maternal pituitary growth hormone production by

379 mid-pregnancy. As its name suggests, it has strong growth promoting effects

380 acting through GH receptors. Overexpression of the hormone in mice leads to a

381 reduction in signalling through the insulin receptor secondary to altered

382 expression of the p85 regulatory subunit of phosphatidyl-inositol 3-kinase [71].

383 Furthermore, there is a reduction in insulin-stimulated translocation of the

384 transporter protein GLUT-4 to the plasma membrane of skeletal muscle, and a

385 modest reduction in insulin receptors at the protein level. Collectively, these

386 effects could explain the development of maternal insulin resistance.

387 Placental growth hormone is also an important regulator of insulin-like growth

388 factor 1 (IGF-1) [67, 72]. Although this protein does not cross into the fetal

389 circulation, it does have powerful effects on fetal growth. Maternal

390 concentrations correlate with birth weight, and its actions are thought to be

391 mediated through changes in maternal metabolism and nutrient partioning,

392 stimulation of placental morphogenesis, and an increase in maternal blood flow

393 to the placenta [26, 73].

394

395 **Placental metabolism**

396 Placentally-induced changes in maternal blood flow, appetite and metabolism

397 thus ensure a plentiful supply of nutrients to the placenta. However, the placenta

398 has its own metabolic demands, and there is a danger that as it is interposed in

399 the maternal-fetal nutrient pathway it may preferentially deplete the supply

400 before it reaches the fetus. Indeed, it has been estimated that the placenta

401 consumes 40% of the oxygen supplied to the feto-placental unit, with about one

402   third supporting protein synthesis and another third supporting active transport

403   and ionic pumping [8]. There are structural and metabolic aspects of the placenta

404   that are likely to limit this potentially adverse effect. Firstly, the formation of

405   vasculosyncytial membranes ensures that there is only a minimal amount of

406   syncytioplasm interposed between the maternal and fetal circulations.

407   Mitochondria and other oxygen consuming organelles, such as the endoplasmic

408   reticulum, are generally absent from these sites, and are concentrated in thicker

409   areas of the syncytioplasm away from the fetal capillaries. By analogy with

410   electrical circuitry, the formation of vasculosyncytial membranes places the

411   metabolic demands of the placenta and fetus in parallel rather than in series as

412   would be the case if the syncytiotrophoblast layer was uniformly thick over the

413   villous surface.

414   Secondly, placental metabolism is heavily glycolytic even once the maternal

415   circulation is established at the end of the first trimester [74]. Analysis of the

416   coelomic fluid that is in communication with the placental tissues at 7-11 weeks

417   of pregnancy showed evidence of anaerobic glycolysis, with a pH of 7.18

418   compared to 7.38 in the maternal serum, a lactate concentration of 0.6 mmol/L

419   compared to 0.3 mmol/L, and a base excess of -7.8 mmol/L compared to -2.6

420   mmol/L [75]. Estimates based on placental tissues delivered at term and

421   perfused *in vitro* suggest that 22% of the glucose consumed is converted to

422   lactate even under conditions of high oxygenation [76]. Converting some of the

423   glucose consumed to lactate rather than to carbon dioxide via the citric acid cycle

424   may be beneficial for the fetus, for it is able to use lactate as a substrate whereas

425   the placenta is unable to do so. In this way, the placental metabolism may be

426   setting aside resources for the fetus.

427 However, there are alternative means for regenerating the NAD^+ necessary for

428 maintaining glycolysis in early placental tissues besides fermentation to lactate.

429 The phylogenetically ancient polyol pathways are highly active in the human

430 early placenta, and sorbitol, inositol, erythritol, mannitol and ribitol are present

431 in the coelomic fluid in high concentrations [77]. Many of the polyol pathways

432 are closely integrated with the pentose phosphate pathway, which is important

433 for the synthesis of nucleotides to support rapid cell proliferation. The pentose

434 phosphate pathway also generates NADPH, which is essential for the

435 regeneration of reduced glutathione and proper functioning of antioxidant

436 defences. Hence, having a ready supply of glycolytic intermediates that can be

437 diverted down these pathways will facilitate rapid growth of the placenta whilst

438 conferring protection against free-radical mediated damage.

439 Although glycolysis generates only a small fraction of the ATP per glucose

440 molecule that can be achieved through oxidative phosphorylation, it may be

441 beneficial in situations where resources are not limiting since it relies on simpler

442 intracellular machinery [78]. Mitochondria are energetically costly to generate

443 and maintain, and in view of the transient nature of the placenta it may be more

444 efficient to rely on glycolysis for much of energy production. Certainly, there is

445 no shortage of glucose for the placental tissues during the first trimester as the

446 endometrial secretions are carbohydrate rich and glycogen accumulates in the

447 syncytioplasm [79, 80].

448 This heavy reliance on aerobic glycolysis, also referred to as Warburg

449 metabolism, will reduce the oxygen consumption of the trophoblast compared to

450 what it would be if oxidative phosphorylation was more prevalent. Consequently,

451   more oxygen is available for the fetus, along with protected resources, such as

452   lactate.

453

454   **The placenta as a selective barrier**

455   The fetus requires its own unique microenvironment independent of maternal

456   sex or stress hormones and environmental pollutants so that development of its

457   neuroendocrine and gonadal systems is not compromised. Hence, the

458   syncytiotrophoblast is equipped with a variety of enzymes and transporters that

459   ensure the detoxification and efflux of xenobiotics, playing an equivalent role to

460   hepatic cells in the adult. One of the best characterised examples is the enzyme

461   11-ß-hydroxysteroid dehydrogenase 2 (11-ßHSD2), which oxidises maternal

462   cortisol to the inactive metabolite cortisone. In this way, the placenta limits

463   exposure to the potential harmful effects of maternal stress hormones, which

464   when administered direct to the fetus cause reduced cell proliferation and

465   growth restriction. The activity of placental 11-ßHSD2 can be perturbed through

466   reduced mRNA expression in pathological pregnancies associated with growth

467   restriction [81, 82], leading to hypercortisolaemia in the fetal circulation. This

468   may impact adversely on the development of fetal organ systems, including the

469   brain. It is notable that elevated levels of steroid hormones were recently found

470   in the amniotic fluid of male babies who later developed autism, although

471   whether the steroids were of maternal or fetal origin is unclear at present [83].

472   Sex-specific differences in placental 11-ßHSD2 activity have been reported [84],

473   and may potentially explain the increased risk of disorders, including autism,

474   arising from developmental programming in males following adverse

475   intrauterine experiences.

476   P-glycoprotein and members of the multidrug resistance protein (MRP) family

477   have been localised to the apical surface of the syncytiotrophoblast and to the

478   endothelium of the villous capillaries at term [85]. These transporters mediate

479   the ATP-dependent efflux of a wide range of anionic organic compounds,

480   providing protection to the fetus against exposure to potentially noxious

481   xenobiotics.

482

483   **Conclusion**

484   Fetal growth can only take place at a rate commensurate with that of the delivery

485   of nutrients and oxygen by the placenta. There is now clear evidence that the

486   placenta is not just a passive conduit from mother to fetus, but that it is able to

487   respond to supply signals arising from the mother and demand signals

488   emanating from the fetus [26, 86]. The efficiency of placental exchange is

489   governed by a complex interplay between placental growth, transporter protein

490   expression, rates of placental blood flow, transmembrane concentration

491   gradients, and the metabolic demands of the placental tissues. This interplay is

492   orchestrated by maternal, placental and fetal hormones, and under favourable

493   conditions ensures an adequate supply to the fetus without overdepletion of

494   maternal reserves. The relationship is best viewed as a dialogue to ensure

495   mutual needs are met, rather than a conflict between two individuals. The

496   haemochorial form of placentation displayed by the human provides the most

497   intimate apposition of the maternal and fetal circulations of all the placental

498 types, yet the evolutionary advantages are not immediately obvious. One benefit

499 is that it is more freely permeable to hydrophilic solutes, which are thought to

500 pass through water-filled transtrophoblastic channels. Although the great apes

501 also share haemochorial placentation, trophoblast invasion is deepest in the

502 human [87]. This is consistent with the theory that greater access to the

503 maternal blood supply facilitates growth of our large fetal brain [88]. However,

504 the deep invasion comes at a price, for it is associated with an increased risk of

505 complications of pregnancy, such as pre-eclampsia [89]. Recent evidence shows

506 these complications have in part an immunological basis [45], as explored in

507 other contributions to this issue. Adoption of the upright posture may be another

508 contributor, for it poses unique haemodynamic challenges to the placental

509 circulations [90]. Hence, the interactions between bipedalism and human

510 reproduction extend beyond the issue of pelvic constraint.

511

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