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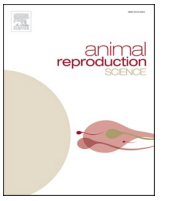

Role of the placenta in developmental programming: Observations from models using large animals

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ABSTRACT

Developmental programming, which proposes that "insults" or "stressors" during intrauterine or postnatal development can have not only immediate but also long-term consequences for healthy and productivity, has emerged as a major biological principle, and based on studies in many animal species also seems to be a universal phenomenon. In eutherians, the placenta appears to be programmed during its development, which has consequences for fetal growth and development throughout pregnancy, and likewise has long-term consequences for postnatal development, leading to programming of organ function of the offspring even into adulthood. This review summarizes our current understanding of the placenta's role in developmental programming, the mechanisms involved, and the challenges remaining.

1. Introduction

The concept of developmental programming posits that insults, or "stressors," that affect growth and development of the fetal organs, including the placenta, have not only short-term (i.e., during the neonatal period and infancy) but also long-term (post-infancy through adulthood) consequences. Stressors that are associated with developmental programming include poor maternal nutrition, multiple fetuses, maternal obesity and diabetes, maternal and fetal genotype, maternal exercise, parity and a host of environmental factors such as high altitude, high temperature, exposure to endocrine disruptors, etc. (Armitage et al., 2004; Wu et al., 2006; Caton and Hess, 2010; Funston et al., 2010; Harris et al., 2013; Nathanielsz et al., 2013; Reynolds and Vonnahme, 2016; Reynolds et al., 2010b, 2019, 2022a; 2022b; Caton et al., 2019; Cushman and Perry, 2019; Dahlen et al., 2021; Hammer et al., 2023).

Altered development of the fetus and placenta, in turn, is associated with preterm delivery, low birth weight, and poor survival of newborns as well as many chronic pathologies in the offspring as newborns, infants, adults, and even across generations (Reynolds

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et al., 2010b, 2019, 2022a; b; Pankey et al., 2017). Such chronic pathologies, also known as non-communicable diseases or NCDs, include abnormal growth and body composition, behavioral or cognitive abnormalities, metabolic syndrome, and cardiovascular, gastro-intestinal, immune, musculoskeletal and reproductive dysfunction (Barker, 2004; Wu et al., 2006; Caton and Hess, 2010; Reynolds and Vonnahme, 2016; Reynolds et al., 2010b, 2019, 2022a; b; Caton et al., 2019; Cushman and Perry, 2019; Dahlen et al., 2021; Hammer et al., 2023). Additionally, chronically altered function of organ systems may contribute to aging and, importantly for livestock production, reduced productivity and longevity (Zambrano et al., 2014, 2015, 2020, 2021; Du et al., 2015; Franke et al., 2017; Kuo et al., 2017a; 2017b; Pankey et al., 2017; Yang et al., 2017; Broadhead et al., 2019; Cushman and Perry, 2019; Wang et al., 2019; Hulsman Hanna et al., 2023).

Of note, however, the responses to these stressors can have both negative and positive outcomes. That is, despite its well-known negative consequences, developmental programming must have entered and remained in the genome because of its adaptive advantages (Bateson et al., 2014; Nettle et al., 2013; Mueller et al., 2015). It has even been suggested that we could capitalize on these adaptations to improve fitness and therefore productivity of the offspring (Dahlen et al., 2022, 2023; Reynolds et al., 2022a; b; Hammer et al., 2023). For example, our studies of maternal nutritional status during the first 50 days of pregnancy in cattle showed that the vast majority of genes in fetal liver, muscle, and brain were upregulated in fetuses from nutrient-restricted dams, leading us to suggest that the upregulation of genes may represent an adaptive response to maternal nutrient restriction (Crouse et al., 2019; Reynolds et al., 2022a; 2022b). This suggestion seems likely because cattle in an extensive pasture-based systems, which is common in much of the western US and many places in the world, are often under nutritional stress during early pregnancy due to the declining yield and quality of pastures as the grazing season progresses (Krysl et al., 1987; Wu et al., 2006; NASEM, 2016; Caton et al., 2019, 2020). Thus, the adaptive response to limited maternal nutrient intake seems to involve upregulation of fetal and placental genes and has even been shown to result in "rewiring" of gene networks at the systems level (Caton et al., 2020; Diniz et al., 2021a).

We now know that in addition to maternal stress, paternal stress, including dietary and environmental, also contributes to developmental programming (Dahlen et al., 2023; Hammer et al., 2023). Similar to maternal programming of fetal and placental development, paternal programming likely involves a combination of epigenetic mechanisms such as alterations in DNA methylation, histones, or non-coding RNAs (Kretschmer and Gapp, 2022), oxidative stress leading to damage of sperm DNA (Billah et al., 2022), and/or the seminal microbiome (Luecke et al., 2022). In addition to sperm, alterations in seminal plasma also contribute to developmental programming of the offspring (Watkins et al., 2020; Dahlen et al., 2023; Hammer et al., 2023).

2. Placental programming

Important to this review, fetal intrauterine growth restriction (**IUGR**) due to poor parental nutrition or other stressors is closely linked to placental development and function. For example, Coan et al. (2010) used a mouse model of moderate maternal dietary restriction beginning early in pregnancy (day 3, or 0.14 of gestation) to examine the mechanisms of fetal growth restriction. Their studies suggested that placentas from the maternal undernutrition group, although smaller by late (0.8–0.95) gestation, adapted to accommodate fetal nutrient demand by increasing the expression of transporters for glucose (*SLC2A1*, or *GLUT1*) and neutral amino acids (*SLC38A2*, or *SNAT2*).

The idea that the placenta is 'programmed' in response to a maternal stressor such as maternal nutrient restriction is supported by a body of literature in various animals including rodents and sheep (Fowden et al., 2006a; 2006b, 2008; Reynolds et al., 2006, 2010a; 2010b, 2013; 2019, 2022a, 2022b; Burton et al., 2016). Placental programming in turn can lead to altered nutrient transport to the fetus and hence to altered fetal growth and development (Reynolds et al., 2010b, 2019, 2022a; b; Vonnahme et al., 2007, 2008, 2015; Reynolds and Caton, 2012; Reynolds and Vonnahme, 2017). Physiologically, there are several ways in which placental nutrient transport can be altered (Fowden et al., 2006a; 2006b, 2008; Borowicz et al., 2007; Reynolds et al., 2010a; b, 2013; 2019, 2022a, 2022b; Burton et al., 2016; Crouse et al., 2021), including changes in:

(1) placental size and(or) morphology,
(2) placental nutrient transporter abundance or function,
(3) placental vascular development, or
(4) placental blood flow.

Another important concept is that placental programming may lead to a compensatory increase in placental function, but this may not be enough to overcome the negative consequences. For example, as mentioned already, in the studies of Coan et al. (2010) placental weight was reduced in late gestation in their model of maternal dietary restriction in mice, but there was a compensatory increase in placental glucose and amino acid transport and transporter expression. Nevertheless, fetal weight was reduced in spite of the increase in nutrient transporters, at least in part because placental surface area and capillary volume were also reduced in the nutrient-restricted dams (Coan et al., 2010). In addition, these observations confirm the important concept that placental morphology and vascular growth and development are critical components of placental function (Reynolds and Redmer, 1995; Mayhew et al., 2004a; b; Reynolds et al., 2006, 2010a; b, 2013, 2014, 2019; Funston et al., 2010; Bairagi et al., 2016; Burton et al., 2016).

These observations also confirm another concept, which is that the placental response to maternal stress is likely to be quite complex, and may depend on the type of stressor (e.g. nutrient restriction or excess, maternal age, maternal steroid exposure, maternal environmental stress such as high altitude or high ambient temperature and humidity, numbers of fetuses, etc.). This concept is supported by observations in several species including not only livestock but also exotic animals, rodents, and humans (Fowden et al., 2006b; Coan et al., 2010; Reynolds et al., 2010b, 2019, 2022a; b; Vonnahme et al., 2007, 2008a, 2015; Reynolds and Caton, 2012;

Reynolds and Vonnahme, 2017; Dahlen et al., 2021). Moreover, Coan et al. (2010) found that the reduction in placental weight preceded fetal growth restriction, confirming that placental programming can lead to a reduction in fetal growth. Again, this concept is supported by numerous studies in other species (Fowden et al., 2006b; Redmer et al., 2005; Reynolds and Caton, 2012; Reynolds et al., 2010b, 2013, 2014, 2019; Reynolds and Vonnahme, 2017).

That there may be a compensatory increase in placental functional capacity in response to placental growth restriction is supported by previous studies in rodents (Fowden et al., 2006b), sheep (Redmer et al., 2005; Wallace et al., 2006), and other mammals (Fowden et al., 2006b; Reynolds et al., 2010). As we have already mentioned, altered placental angiogenesis, as demonstrated not only by Coan et al. (2010), including in some cases a compensatory increase in vascularity, is a critical component of placental programming, as shown by numerous studies in humans, rodents, pigs and sheep (Fowden et al., 2006b; Reynolds et al., 2006, 2010; Reynolds and Vonnahme, 2017). We will discuss this component of placental function in much more detail in the following sections of this review.

All of these observations related to placental adaptation and programming support the contention that a more complete understanding of the factors regulating placental growth, morphology, nutrient transport and transporters, angiogenesis and vascular function will require investigating these processes from the earliest stages of gestation using a variety of animal models. We have argued that using this comparative approach may eventually lead to therapeutic and management strategies designed to optimize placental growth and function, and thereby minimize the negative consequences of placental programming on growth of the fetus and subsequent health and productivity of the resulting offspring (Reynolds et al., 2005a; b, 2006, 2010a,b, 2013, 2019, 2022a,b; Reynolds and Vonnahme, 2017; Caton et al., 2019, 2020; Crouse et al., 2021; Dahlen et al., 2021, 2023; Amat et al., 2022; Hammer et al., 2023).

3. Determinants of placental function

Once it is established and functional, by the end of the first 20–30% of pregnancy, the placenta is the primary means of exchange of nutrients, respiratory gas, and metabolic waste between the fetal and maternal systems and also serves as the fetal lungs, liver, gut, kidneys and endocrine glands (Burton and Fowden, 2015; Burton et al., 2016). In addition, uterine secretions termed histotroph serve as the primary source of nutrients (e.g., glucose, amino acids, electrolytes) as well as other factors (e.g., proteins, cytokines, hormones, extracellular vesicles, RNAs) critical to fetal development early in pregnancy and continue to provide for fetal nutrition through most of pregnancy (Bazer et al., 1979; Moffatt et al., 1987; Koch et al., 2010; Zhang et al., 2017).

As an organ of transport/exchange, the placenta also is highly vascular (Reynolds and Redmer, 1995; Reynolds et al., 2010, 2013, 2014). Importantly, because the microcirculation is a parallel system, blood flow to any organ, including the placenta, is primarily a function of the *total* cross-sectional area of the capillary bed, which determines, to a large extent, the resistance to flow (Reynolds et al., 2005a). Thus, vascular development of the placenta is not only critical to placental function, but placental angiogenesis also has been shown to continue throughout gestation (Reynolds and Redmer, 1995; Borowicz et al., 2007; Reynolds et al., 2010, 2013).

Blood flow, on the other hand, seems to be the primary determinant of placental transport capacity, which on a practical basis can be determined by using the Fick Principle. (Fig. 1). The Fick Principle states that uptake (or, conversely, secretion, which is represented as negative uptake) of any substance across a vascular bed is equal to the arterio-venous concentration difference (i.e., exchange per unit of blood) multiplied by the rate of blood flow. Thus, gravid uterine (utero-placental + fetal) uptake equals the uterine A-V difference times uterine blood flow (Fig. 1). Similarly, fetal uptake equals the umbilical v-a difference (note that the fetus is supplied by the umbilical vein) times umbilical blood flow (Fig. 1). Utero-placental uptake is calculated as the difference between gravid uterine uptake and fetal uptake (Fig. 1).

Using the Fick Principle, one can determine transplacental fluxes (Fig. 2). For example, if gravid uterine uptake exceeds fetal uptake, as in the case of α-amino nitrogen (total amino acids), oxygen and glucose, the utero-placenta must be consuming a portion of

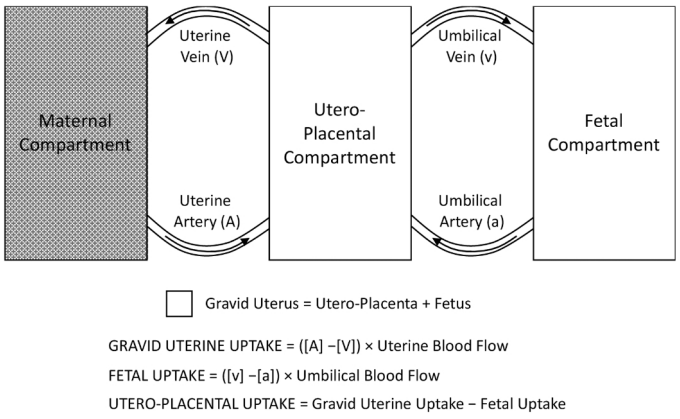


Fig. 1. Schematic showing application of the Fick Principle to determine gravid uterine, fetal and utero-placental uptakes. The maternal compartment is shown in grey stippling, and the gravid uterus (utero-placenta + fetus) is shown in solid white. The arrows within the blood vessels (e.g., uterine vein) show the direction of blood flow. Taken from Reynolds and Redmer (1995). See Fig. 2 for how uptake (or secretion, which equals negative uptake) can be used to determine transplacental fluxes.

that substrate. If gravid uterine and fetal uptake are both negative, then they are both secreting the substrate, as in the case of urea nitrogen (urea N); in this particular case gravid uterine secretion exceeds fetal secretion, indicating that the utero-placenta is producing urea N (Fig. 2). If gravid uterine uptake is negative but fetal uptake is positive, as in the case of lactate, then the utero-placenta is producing the substrate and secreting it in both directions (Fig. 2).

Of critical importance to placental function, the Fick Principle also can inform us about the relative contributions of blood flow vs. exchange (i.e., the arterio-venous concentration difference) to transplacental flux. For example, from mid to late gestation in cattle, gravid.

uterine and umbilical blood flows increase by 3.5- and 20-fold, respectively (Fig. 3). Conversely, gravid uterine A-V and umbilical v-a differences in both oxygen and glucose change vary little (Fig. 3).

This paradigm of large increases in gravid uterine and umbilical blood flows seems to be consistent across species (Fig. 4). Thus, changes in blood flow rather than changes in arterio- venous concentration differences explain the majority of the large changes in transplacental flux of nutrients, respiratory gases and metabolic wastes that occur during the last half of pregnancy, which are critical for sustained fetal and placental growth and development. An additional consideration, of course, is the continued growth and development of the placenta; e.g., approximately 2.5-fold increase in weight for the fetal portion (the cotyledon) and 4-fold increase in weight for the maternal portion (the caruncle) of the placenta as well as continued increases in cotyledonary and caruncular vascular development (Reynolds et al., 1990, 2010a; Borowicz et al., 2007).

4. Patterns of placental vascular development

As already mentioned, placental vascular growth is critical to the large increases in placental blood flows that occur during pregnancy. Not only does placental vascular growth continue throughout gestation, but the pattern of vascular growth differs between the maternal and fetal compartments. For example, during the last two-thirds of gestation in sheep, the fetal placental compartment, or cotyledon (COT), exhibits large increases in capillary area, number and surface densities, but a decrease in capillary size compared with the maternal placental compartment (the caruncle, or CAR) (Fig. 5**, upper panel**). Using this quantitative evaluation, we developed a model of the microvascular architecture of the capillary beds of the maternal (CAR) and fetal (COT) placental compartments of the sheep (Fig. 5**, lower panel**), and we later confirmed this model using placental corrosion casts (Hafez et al., 2010; Fig. 6). Based on their architectural differences, we have proposed that the vascular sinusoids and very large capillaries on the maternal side would dictate low-velocity blood flow, which has been described as 'irrigation flow,' and is optimal for delivery and exchange. Conversely, because of the very small capillaries on the fetal side, flow would be either high or normal velocity (this has not been confirmed quantitively in fetal capillaries), but regardless because of the large surface area, flow would be optimal for transport.

Interestingly, the same differences in architecture of the maternal and fetal capillary beds have been observed in mice (Adamson et al., 2002), which despite having a different placental morphology from that of livestock (discoid, labyrinthine, deciduate, hemochorial vs. cotyledonary, villous, adeciduate, epitheliochorial; Ramsey, 1982). Moreover, we have proposed that the human placenta, which has a morphology much more similar to that of rodents and in which the fetal placental villi (or cotyledons) are bathed in a maternal blood pool (Ramsey, 1982), represents the ultimate irrigation flow system (Reynolds et al., 2010a).

5. Mechanisms and models of placental programming

We have already discussed the normal pattern of placental vascular development and its importance to increased placental blood flows and thus placental function throughout pregnancy. Not surprisingly, in humans the normal increases in placental blood flow and vascularity are affected in pregnancies compromised by altered feto-placental growth and development. For example, although uterine blood flow increases exponentially in IUGR pregnancies, it is always 30–40% less than in pregnancies exhibiting normal fetal growth

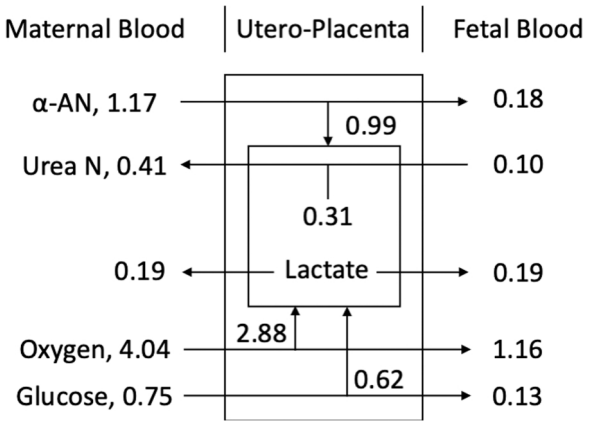


Fig. 2. An example of how the Fick Principle can be used to determine transplacental fluxes. See text for detailed explanation. Data are from day 165 (0.59) of gestation in cows (Ferrell et al., 1983). α-AN = α-amino nitrogen (i.e., total amino acids). Values are in meq/min.

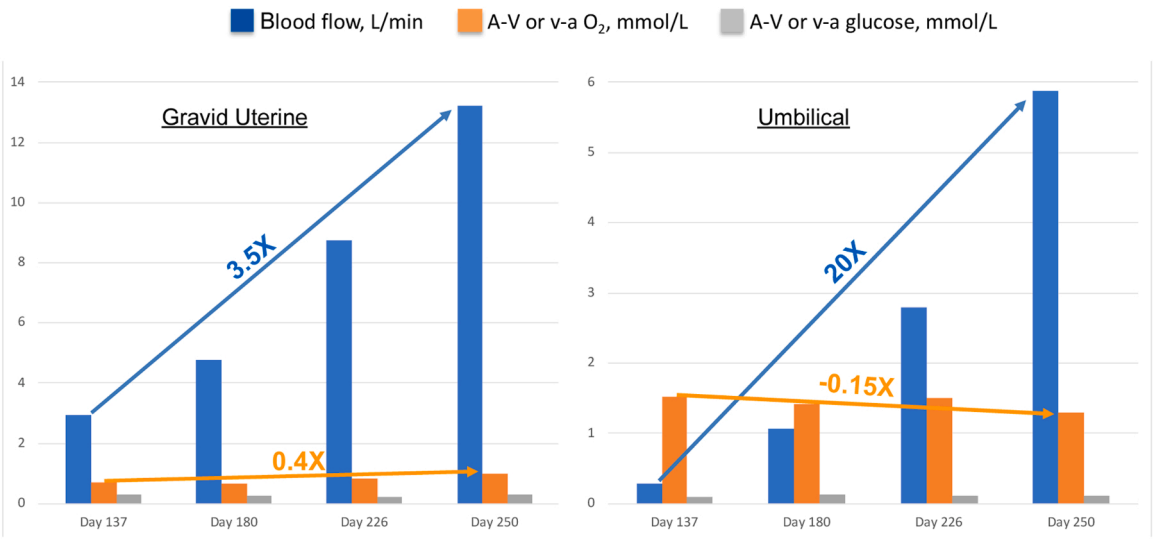


Fig. 3. Changes in gravid uterine (left-hand panel) and umbilical (right-hand panel) blood flows and A-V (gravid uterine) or v-a (umbilical) concentration differences for oxygen and glucose from day 137 (0.49 of gestation) to 250 (0.89 of gestation) of gestation in cows. The blue arrows show the relative changes in blood flows and the orange arrows show the relative changes in A-V or v-a concentration differences. Data from Ferrell and Reynolds (1985).

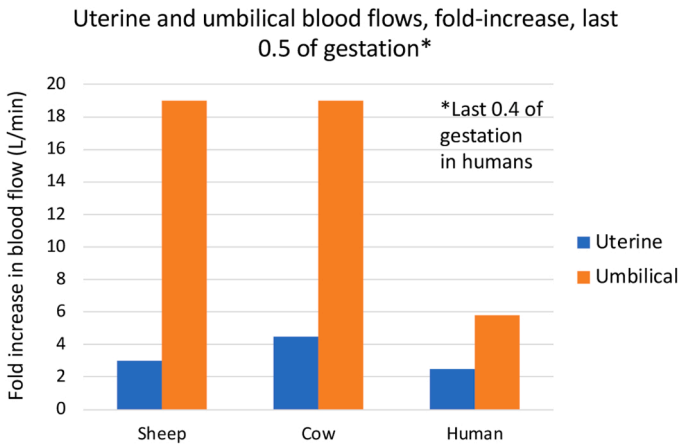


Fig. 4. Fold-increases in uterine and umbilical blood flows during the last half of pregnancy (as noted, the last 0.4 of pregnancy in humans) in three species. Data taken from Meschia (2011); from Rosenfeld et al. (1974), Reynolds et al. (1986) and Konje et al. (2003).

(Fig. 7). In addition, such IUGR pregnancies in humans exhibit reduced growth (villous volume, surface area and length) and vascular development of the fetal placental villi (Fig. 8). Similarly, in livestock models maternal stressors usually lead to not only fetal growth restriction but also altered placental size, vascular development and blood flows (Table 1).

The question then becomes, " What are the mechanisms by which maternal stressors affect fetal and placental growth and vascular development?" Although reduced placental weight may indeed underlie, at least in part, reduced gravid uterine and umbilical blood flows, it does not explain reduced placental vascularity, nor does it explain the increased placental vascularity seen in some of the models (Underfed Adult cow, Vitamin-Mineral Supplemented cow, One-Carbon Metabolite Supplemented cow; Table 1). Similarly, although maternal nutritional status may provide a partial answer for alterations in feto-placental growth and vascular development, it does not explain why there is no effect of underfeeding on placental size in the adolescent sheep (Table 1), nor does it explain reduced fetal and placental size, placental vascular development and placental blood flows in overfed adolescent sheep (Table 1). These types of conundrums can be applied to essentially all of the models.

What is clear is that when fetal and placental growth and development are altered, gene expression is similarly altered, and in fact changes in gene expression can be detected in fetal organs and placenta very early in pregnancy. For example, gene expression is altered in fetal organs and placenta by day 50 (0.18) of pregnancy in the underfed cow model (Crouse et al., 2017, 2019, 2020, 2021; Diniz et al., 2021a, 2021b; 2023). In addition, placental expression of energy metabolism and transport-related genes is altered by day

	Fold change, day 50 to 140 (0.34 to 0.96 of gestation)			
Placental Tissue	Capillary area density	Capillary number density	Capillary surface density	Capillary size (cross sectional area)
Maternal Caruncle (CAR)	3.3	1.7	1.8	2.2
Fetal Cotyledon (COT)	6.1	12.2	6.1	−2.0

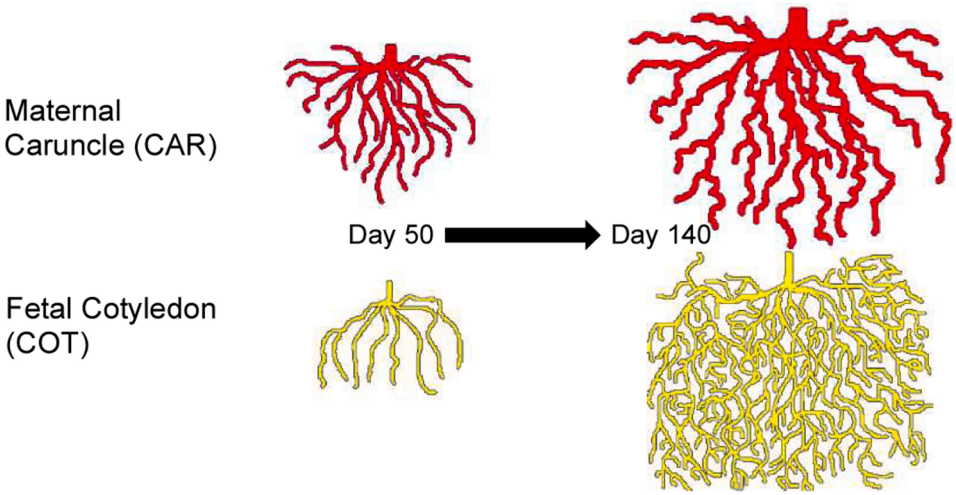


Fig. 5. Top panel – relative changes in measures of capillary development in maternal (caruncle; CAR) and fetal (cotyledon; COT) placenta from day 50 (0.34) to day 140 (0.96) of pregnancy (i.e., the last two-thirds of gestation) in sheep. Bottom panel – model of capillary bed development in the maternal (CAR) and fetal (COT) placental compartments from day 50–140 of gestation. Note, in the top panel, the large increases in capillary area, number and surface densities, but a decrease in capillary size in the COT (fetal) compared with the CAR (maternal) placental compartment. These differences are reflected in the models in the bottom panel. Taken from Borowicz et al. (2007).

83 (0.30) of pregnancy in the vitamin and mineral supplementation model in cows (Diniz et al., 2021b). In the same model, fetal liver expression of genes related to energy and lipid metabolism as well as the profiles of lipids, amino acids, carbohydrates and energy substrates are altered in fetal liver (Crouse et al., 2022; Diniz et al., 2023; Menezes et al., 2023). These changes in gene expression and metabolic profiles involve organ-specific regulators of fetal growth and development as well as placental nutrient transporters.

Similarly, in the sheep assisted reproduction model, placental expression of angiogenic factors is reduced in conjunction with reduced placental vascularity, again very early in pregnancy (day 22, or 0.15 of gestation; Grazul-Bilska et al., 2014). In calves produced by assisted reproduction, and especially somatic cell nuclear transfer, numerous defects have been reported, including abnormal placental development and vascularization, somatic overgrowth, abnormal development of fetal organs including musculo-skeletal defects, and increased rates of embryonic and fetal loss (Heyman et al., 2002; Farin et al., 2006; Li et al., 2019; Rivera, 2020). Interestingly, a similar syndrome of fetal overgrowth, termed Beckwith-Wiedemann Syndrome, occurs in humans (Li et al., 2019).

6. Conclusions/Implications/future directions

It seems clear that maternal stressors can have both negative and positive effects on placental growth and development. Based on this observation, we are suggesting that the placenta may be key to understanding the mechanisms by which maternal stressors affect

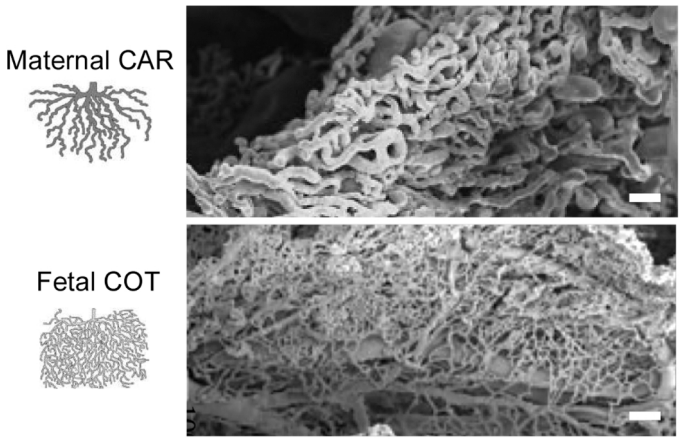


Fig. 6. Electron micrographs of corrosion casts of maternal (caruncle, CAR) and fetal (cotyledon, COT) placental capillary beds from day 90 (0.6) of pregnancy in sheep. To the left of the micrographs is a depiction of the model we developed for the structure of these capillary beds (see Fig. 5 and the text for a complete explanation). Note how the micrographs, which were taken at the same magnification (scale bars represents 50 μm), confirm the model of large diameter capillaries in maternal placenta and much smaller diameter capillaries in fetal placenta. Model and micrographs taken from Borowicz et al. (2007) and Hafez et al. (2010).

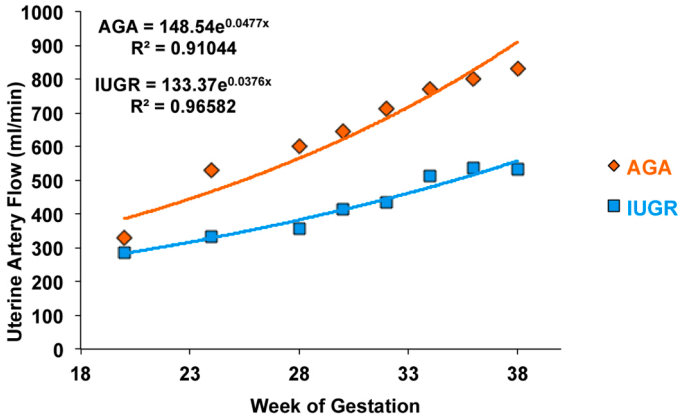


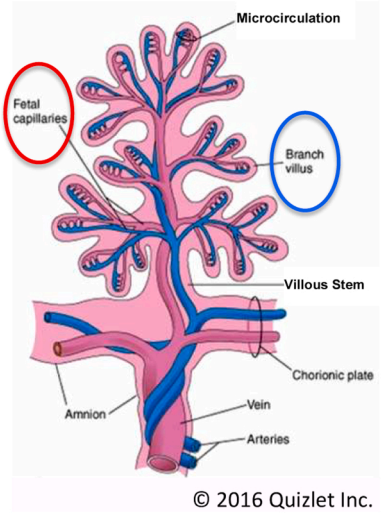
Fig. 7. Uterine blood flows in human pregnancies exhibiting fetuses that were intrauterine growth restricted (IUGR; blue line and squares) of average for gestational age (AGA; orange line and diamonds). Taken from Konje et al. (2003). Exponential regressions are of the form, $y = ae^{kt}$, where y = blood flow in ml/min, a = the y-intercept, e = the natural logarithm (Euler's constant), k = a constant and x = week of gestation.

fetal growth and development, and thereby developmental programming.

It seems equally clear that we need a much better understanding of the mechanisms involved. For example, maternal and paternal nutrition and other stressors affect the fetal organs and placenta very early in pregnancy, but we do not have a clear understanding of the specific mechanism by which such stressors affect feto-placental development or gene expression. Similarly, although we have found that assisted reproductive techniques affect feto-placental development and gene expression very early in pregnancy, we do not have a clear understanding of the mechanisms by which this occurs (Arnold et al., 2008; Reynolds et al., 2013, 2014, 2022a).

Especially ripe for future studies, because of the paucity of data in species other than rodents, is paternal programming of feto-placental development. Several studies have evaluated the impact of paternal experiences leading up to mating on developmental outcomes of offspring. Implicit in these outcomes are some effects that are manifested in the placenta. Not only does the paternal contribution control paternally imprinted genes important for placental nutrient delivery (Kaur, 2023), but other placental alterations have been detected in response to paternal diabetes, high fat diets, and exercise (Claycombe-Larson et al., 2020; Bhadsavle and Golding, 2022; Fornes et al., 2022).

Lastly, it is clear that although some of the observations discussed in this review have been corroborated in humans, defining the molecular mechanisms will depend heavily on the use of a variety of animal models (Amat et al., 2022; Armitage et al., 2004; Reynolds and Vonnahme, 2017; Reynolds et al., 2005b, 2010b; Hammer et al., 2023).



Placental Variable	Normal Fetal Weight	IUGR
Villous volume**	219 ± 19	130 ± 25 (0.59)§
Villous surface area	11.1 ± 0.7	6.6 ± 1.5 (0.59)
Villous length	60.6 ± 6.8	30.9 ± 7.0 (0.51)
Capillary volume**	65.5 ± 8.7	35.3 ± 8.6 (0.54)
Capillary surface area	10.8 ± 1.4	5.4 ± 1.4 (0.54)
Capillary length	233 ± 33	110 ± 28 (0.47)

Fig. 8. Growth and microvascular development of fetal placental villi in human pregnancies exhibiting normal or intrauterine growth restricted (IUGR) fetuses. * *Note that measures of villous morphology (blue font in table, blue oval in schematic) and capillary morphology (red font in table, red oval in schematic) are reduced ($P < 0.05$) by 40–50% in IUGR vs. normally grown fetuses. §Numbers in parentheses represent IUGR as a proportion of normal fetuses. Taken from Mayhew et al. (2004a); b).

Table 1
Fetal and placental weights, placental vascularity and placental (gravid uterine§ or umbilical†) blood flows in various models of maternal stress in livestock.*.

Model	Day of Gestation	Species	Fetal Wt	Placental Wt	Placental Vascularity	Gravid Uterine§ or Umbilical† Blood Flow
Overed Adolescent	130–135	Sheep	− 20–40%	− 20–45%	− 31%	− 36%§-37%†
Underfed Adolescent	130–135	Sheep	− 17%	NSE	− 18%	—
Underfed Adult	130–135	Sheep	− 9–12%	—	− 14%	− 25%§ or NSE†
	250	Cow	NSE	− 34%	+ 40%	—
Protein Suppl.	Parturition	Cow	+ 12%	—	—	—
Vitamin-Mineral Suppl.	Parturition	Cow	NSE	—	+ 47%	—
One-Carbon Metabolite Suppl.	63	Cow	—	—	+ 28%	—
Heat-Stress	130–135	Sheep	− 42%	− 51%	—	− 26%§ to − 60%†
	170	Cow	− 14%	—	—	− 30%§ to − 28%†
Exercise/Activity	94–104	Pig	NSE	NSE	—	+ 18%†
Multiple Pregnancy	130–135	Sheep	− 30%	− 37%	− 30%	− 23%§
Maternal Genotype	130–135	Sheep	− 44–54%	− 28%	− 33%	—
Adolescent vs. Adult	130–135	Sheep	− 16%	− 26%	− 24%	—
Assisted Reproduction	22	Sheep	—	—	− 63–85%	—

* Table modified from Reynolds et al. (2006), which see for references to original data; for Assisted Reproduction (natural, in vitro fertilized and parthenogenic embryos, all transferred on day 6 post-fertilization/activiation) in sheep see Grazul-Bilska et al. (2014); for cows, see Ford et al. (2007) and Vonnahme et al. (2007) for Underfed Adult; Sletmoen-Olson et al. (2000) for Protein Supplementation; Dávila Ruiz et al. (2021) and Hurlbert et al. (2022) for Vitamin-Mineral Supplementation; and Kanjanaruch et al. (2022) for One-Carbon Metabolite Supplementation; for Pig, see Harris et al. (2013). All differences were significant ($P < 0.10$–0.01). NSE = no significant effect.

CRediT authorship contribution statement

Reynolds LP: Writing, revision (editing) of manuscript, figures and table; Dahlen CR, Ward AK, Crouse MS, Borowicz PP, Dávila-Ruiz BJ, Kanjanaruch C, Bochantin KA, McLean KJ, McCarthy KL, Menezes ACB, Diniz WJS, Cushman RA, and Caton JS: Conceptualization, review, editing.

Declaration of Competing Interest

All authors confirm they have no conflicts of interest.

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