Nutrient availability, the microbiome and intestinal transport during pregnancy

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Abstract

Adequate adaptation of the gastrointestinal (GI) tract is important during pregnancy to ensure that the increased metabolic demands by the developing fetus are met. These include changes in surface area mediated by villus hypertrophy and enhanced functional capacity of individual nutrient receptors including those transporting glucose, fructose, leucine, and calcium. These processes are regulated either by the enhanced nutrient demand or are facilitated by changes in the secretion of pregnancy hormones. Our review also covers recent research into the microbiome, and how pregnancy could lead to microbial adaptations, which are beneficial to the mother, yet are also similar to those seen in the metabolic syndrome. The potential role of diet in modulating the microbiome during pregnancy, as well as the potential for the intestinal microbiota to induce pregnancy complications are examined.

Gaps in the current literature are highlighted including those where only historical evidence is available, and we suggest areas that should be a priority for further research. In summary, although a significant degree of adaptation has been described, there are both well-established processes, and more recent discoveries such as changes within the maternal microbiome that pose new questions as to how the GI tract effectively adapts to pregnancy, especially in conjunction with maternal obesity.

Keywords: gastrointestinal adaptation, nutrition, pregnancy, microbiome, nutrient transport, maternal health.

Introduction

The perinatal period is associated with widespread adaptations in a majority of maternal organ systems in order to ensure that nutrient supply to both the mother and developing fetus can be maintained. These temporary changes, collectively known as homeorhesis (Bauman and Currie 1980), are necessary to optimise health during pregnancy, and to enable the mother to meet the additional energetic and nutrient demands that accompany lactation. Many of these maternal physiological adaptations have been previously reviewed. This includes articles summarising the changes in energy metabolism (Herrera 2000, Prentice and Goldberg 2000), and circulation (Hunter and Robson 1992), in both women of normal (King 2000) and excess body mass index (BMI) (King 2006). There is also a substantial body of literature covering adaptation of the placenta to different nutrient intakes (Jones et al. 2007, Lager and Powell 2012), but there is comparatively little work exploring whether the gut and bacterial inhabitants of the gut are subject to similar changes.

The aim of this review is to discuss the variety of changes that have been demonstrated to occur in the small and large intestine in pregnancy, ranging from the anatomical to the molecular. It will also highlight the need for further research, as much of the evidence discussed is now dated, and therefore has not been considered in light of the significant increases in average pre-pregnancy BMI of women of child-bearing age over the last two decades. Depending on the cut-off used, the incidence of obesity in pregnant women in the USA ranged between 18.5 and 38.3% (Galtier-Dereure et al. 2000, Catalano and Ehrenberg 2006, Guelinckx et al. 2008), and there has been a marked increase in the

prevalence of obesity in women of childbearing age of ~33% between 1988 and 2000 (Kim et al. 2007). Among Canadian women aged 18-79, the proportion with a BMI classified as underweight, normal weight overweight or obese is 2.2%, 44.7%, 29.5% and 23.6% respectively, and the prevalence of obesity among women of child-bearing age (18-44) ranges between 5.5 and 19.4% (Government of Canada 2011).

Changes in gut physiology during pregnancy and lactation

Gross changes of the alimentary tract using wet weight as an indicator of overall size have been assessed in pregnant and lactating rats in studies dating back to the 1930s (Lew et al. 1939), with more detailed documentation focusing on the intestine beginning in the 1960s. Relative to the non-pregnant state, increases in weight of the stomach and the small intestine of rats have been recorded consistently during lactation but not pregnancy (Souders and Morgan 1957, Fell et al. 1963, Campbell and Fell 1964). One study in sheep reported a 45% increase in small intestine weight ($p<0.05$ vs age matched non-pregnant controls) in the third trimester (Fell et al. 1972). Although intestinal weight does not appear to change in pregnant rats, surface area increases throughout pregnancy. Villus height increases in the duodenum by mid-pregnancy (Cripps and Williams 1975) and this is accompanied by intestinal dilatation commencing at the beginning of the final week of gestation; these observations have also been reported in pregnant sheep (Fell et al. 1964). These changes persist through lactation (Fell et al. 1963, Boyne et al. 1966) as evidenced by increased serosal circumference and villus height in the jejunum and ileum at the end of lactation in rats, and lactating mice (Campbell and Fell 1964). More recent research in rats shows villus heights

in the jejunum significantly increasing by gestational day 21, with no change in the ileum or duodenum (Sarvestani et al. 2015). Intestinal length has been reported to be unchanged during pregnancy in rats, but will increase by almost 25% during lactation (Craft 1970, Cripps and Williams 1975).

The mechanisms proposed to mediate these gross anatomical changes include changing caloric intake, so called "work hypertrophy" (Fell et al. 1963). This has been widely debated with two studies in non-pregnant rats showing significant increases in stomach and colon weight with raised nutrient intake but no change in the small intestine (Addis 1932, Dowling et al. 1967). Both an increase in plasma thyroxine and insulin resistance may also play a role, both are known to occur in pregnancy (Branch 1992), and both have been independently associated with intestinal hypertrophy (Middleton 1971, Fujita et al. 1998). However this is currently speculation as both effects have only been shown in non-pregnant animal models.

When relating findings from rodent models to humans, substantial differences in energy expenditure must be taken into account. The higher metabolic rate, shorter gestation and larger litter sizes of rodents compared with human and sheep pregnancies could contribute to more pronounced intestinal adaptations than are observed in humans (Hammond 1997). Detailed information about specific anatomical adaptations in pregnant is limited by the fact that collection of GI tissue from healthy pregnant women throughout pregnancy is not ethically feasible.

Changes in gut motility and transit time

An increased occurrence of heartburn, bloating and constipation during pregnancy has been well documented in humans (Feeney 1982) suggesting that intestinal motility and transit time may both be increased. This was initially thought to be caused by the expanding uterus placing pressure on the GI tract (Byrne 1972) but additional studies suggest hormonally driven changes may add to mechanical influences that slow these processes. Exposure to high concentrations of progesterone reduces GI motility, with in-vitro treatment of rat GI sections with progesterone leading to reduced contractile activity in oesophageal, antral and colonic tissue (Bruce and Behsudi 1979). Studies of the effect of progesterone on motilin, a hormone which stimulates GI motility in the stomach, showed significant inverse correlations between motilin and plasma progesterone both during fasting and after a glucose load in humans (Christofides et al. 1982, Holst et al. 1992). This suggests that progesterone has a direct effect on GI tissue motility as well as an inhibitory effect on the action of other hormones. Studies in humans using the lactulose hydrogen breath test to measure oro-caecal transit report no significant changes in transit time in the first trimester, despite women displaying dyspeptic symptoms such as heartburn and bloating. Gut transit time increases during the third trimester (Chiloiro et al. 2001) when these symptoms can disappear.

Changes in intestinal absorption and permeability

The increased intestinal surface area and transit time observed in pregnancy have the potential to affect fluid and electrolyte balance as well as nutrient absorption. Absorption of sodium and water increases by almost 50%, between

12 to 20 weeks gestation in humans. Such changes could be mediated, in part, by a raised plasma aldosterone concentration (Brown et al. 1992) but may also be affected by hormonal adaptations to pregnancy. Changing concentrations of oestrogen could influence sodium absorption by effects on the adrenal gland and the renin-angiotensin system (RAS). Angiotensin II promotes fluid absorption in the small intestine (Fändriks 2011), and plasma concentrations of several RAS hormones including angiotensin II are elevated during pregnancy (Irani and Xia 2008). Enhanced absorption could reflect the raised transit time in late gestation (Chiloiro et al. 2001), whereas chlorine (Cl) secretion in the colon may be inhibited during pregnancy due to raised oestrogen (Condliffe et al. 2001). In rats this response could be mediated by activating protein kinase-C delta (O'Mahony et al. 2007), whilst blocking its action prevents the decrease in Cl secretion on administration of 17β-oestradiol (Doolan et al. 2000). This is consistent with the water retention observed towards the end of pregnancy, when oestrogen levels are at their highest (Atherton et al. 1982, Schrier et al. 2001) .

Gene expression analyses using microarray and qPCR has shown that several ion transporters associated with sodium, calcium and magnesium are all upregulated in the rat duodenum during pregnancy and lactation (Teerapornpuntakit et al. 2014). This has been suggested to be in part due to the hypertrophy observed in the small intestine, however, as discussed above the absorption of specific nutrients are affected by stage of pregnancy rather than reflecting an increase in absorptive surface.

Absorption of Major Dietary Constituents

Carbohydrates

Carbohydrates are the main substrate of fetal and placental metabolism, and adequate intake, absorption and distribution are required for healthy pregnancy outcome (Battaglia 1989, Hay 1991). Pregnancy is an insulin resistant state, with both hyperinsulinaemia and insulin resistance peaking in the third trimester (Cousins et al. 1980, Buchanan et al. 1990, Catalano et al. 1993). Fructose intake in pregnancy is also becoming increasingly relevant given its increased role in the Western diet since the 1980s, and its potential for inducing lipogenesis much more readily than glucose (Regnault et al. 2013).

The relationship between pregnancy and glucose homeostasis is therefore of clinical relevance, particularly with regard to how carbohydrates are absorbed across the gut. An inhibitory effect of oestrogen on glucose absorption in the small intestine has been demonstrated. Glucose uptake from the small intestine in rats is increased by a third following ovariectomy and is reduced back to the same level as sham-operated controls with 17β-estradiol and progesterone replacement (Singh et al. 1985). This is at odds with more recent research showing an upregulation in both glucose transporter 5 (GLUT5) and sodium-linked glucose transporter 1 (SGLT1) expression in late pregnancy compared to age-matched non-pregnant controls (Teerapornpuntakit et al. 2014). Thus, we speculate that upregulation in transport protein expression may offset reductions in glucose absorption as a result of oestrogen-related changes. In the case of fructose, to our knowledge no research has been conducted focusing on

the transport of fructose during pregnancy. Rat studies have demonstrated that exposure to luminal fructose in the fetus during critical stages of development will program the offspring intestine by increasing expression of the fructose transporter GLUT5 (Jiang and Ferraris 2001, Suzuki et al. 2011), suggesting that fructose intake and intestinal uptake during pregnancy is of interest.

Future pregnancy based studies could utilise Ussing chambers in conjunction with inhibiting SGLT1 or other carbohydrate transporters, techniques that have already been employed when studying transport of other nutrients across the small intestine (Wolffram et al. 2002). Focus on GLUT2 would also be warranted as this has been shown to play an equally important role as SGLT1 in intestinal glucose transport (Kellett and Brot-Laroche 2005, Kellett et al. 2008)

Amino acids

Protein intake, absorption and distribution is also vital during pregnancy, with the fetus, uterus, placenta, and amniotic fluid together accounting for ~925g of protein accreted over pregnancy in humans. This is to be obtained from a recommended dietary intake of 1.1g per kg body weight per day (an average increase of 25g/day compared to the non-pregnant state), and a macronutrient distribution whereby protein contributes between 10 and 35% of total calories (United States National Research Council 2005). The effect of protein restriction during pregnancy on the offspring has been well defined in animal models using <9% of calories from protein (Lakshmy 2013), leading to growth restriction in the offspring and an increase in incidence of the metabolic syndrome in later life. The precise role of a low protein intake in mediating such responses is difficult

to determine as all low protein diets contain additional carbohydrate in order to ensure they are isocaloric compared to the control diet (Symonds et al. 2006). In addition protein requirements are much higher in rodent pregnancies compared to humans (Symonds et al. 2006).

Protein turnover increases linearly throughout pregnancy, shown indirectly from measuring the fate of radio-labelled leucine (Thompson and Halliday 1992) and glycine (de Benoist et al. 1985) in women. A lack of studies covering potential mechanisms for the increase in amino acid absorption has been highlighted in earlier reviews (Karasov and Diamond 1983), and this does not appear to have changed. Therefore research into expression of the variety of different transport proteins present in the small intestine (Bröer 2008) and how expression changes throughout pregnancy is of interest.

Fatty acids

Maternal dietary fat intake is important throughout pregnancy not only as a maternal energy source but also to provide the developing fetus with essential fatty acids for optimal development (Budge and Symonds 2006). It has been suggested that total fat requirements as a proportion of energy intake during pregnancy should not be increased compared to non-pregnant women, as they can be met by small increases in consumption of a balanced diet (United States National Research Council 2005). There is debate as to whether the pre-formed long-chain polyunsaturated fatty acids (LCPUFA) should be considered as conditionally essential in pregnancy, and whether the normal dietary supply of essential fatty acids, specifically linoleic and α-linolenic acid are sufficient for optimal fetal development and long term health (Haggarty 2014). Current

literature has examined the lack of maternal dietary docosahexaenoic acid (DHA), particularly during late pregnancy (Haggarty 2004), and the mobilisation of maternal adipose tissue, but not the intestinal transport of fatty acids. The US Dietary Reference Intakes (United States National Research Council 2005) highlight a lack of evidence available to determine optimal intakes of n-3 and n-6 fatty acids during pregnancy, in part because of difficulties defining a range of intakes in Western populations that would lead to a deficiency. This potentially explains the lack of research interest shown in the uptake of fatty acids during pregnancy.

To summarise, although it is well established that glucose and fructose transport across the intestine is a dynamic process modulated by the expression of transport proteins, very little work has been done to ascertain how pregnancy affects the expression and function of these transporters. Transport of both amino and fatty acids across the intestinal epithelium during pregnancy is even less well studied, despite the fact that in the case of amino acids, increased absorption in pregnancy has been demonstrated.

Absorption of Micronutrients

Micronutrients can have an important role in preventing adverse events such as premature birth and low birth weight (Ramakrishnan et al. 1999, United States National Research Council 2001, 2011). The intestinal absorption of calcium, vitamin D and iron absorption in pregnancy are well described but many other micronutrients remain unstudied. This includes magnesium and zinc, which when deficient are associated with adverse outcomes such as pre-eclampsia and

preterm delivery (Black 2001). There is promising preliminary research into the transport of some of these micronutrients, with microarrays showing upregulation in duodenal transporters of both zinc and calcium during pregnancy in rats; but no associated mechanisms have been identified (Teerapornpuntakit et al. 2014).

Calcium and vitamin D absorption

The human fetus requires the transfer of ~30 g of calcium from maternal stores between conception and birth. Both calcium uptake, excretion (Kent et al. 1991, Ritchie et al. 1998) and regulation of vitamin D metabolism adapt to pregnancy (Phillips et al. 2000, Prentice 2000). In rats, intestinal calcium transport increases throughout pregnancy to peak at day 14 of lactation coincident with changes in plasma 1,25 dihydroxyvitamin D, a hormonally active metabolite of vitamin D. However an increase in absorption was also observed in a cohort of vitamin D deficient rats following the same study design, suggesting the adaptations in calcium uptake may be independent of vitamin D status (Halloran and DeLuca 1980). Further evidence for this is provided from pregnant mice lacking the vitamin D receptor (VDR) which display osteomalacia at baseline (before mating), and an increase in bone mineral content throughout pregnancy, that is comparable to pregnant wild-type controls. (Fudge and Kovacs 2010). Taken together these findings suggest other mechanisms of calcium transport may be active during pregnancy.

Iron absorption

Maternal iron requirements in humans increase during pregnancy in order to meet the needs of the raised erythrocyte mass, formation of the placenta, and ~1g of stored iron accumulated by the fetus at term. These are met through a combination of the maternal mobilisation of stored iron, reduced iron loss, and potentially increased absorption from the maternal diet. Iron deficiency in pregnancy, however, remains a problem, leading to an increased risk of preeclampsia, intrauterine growth restriction and low birth weight (Cetin et al. 2011).

Upregulation of iron absorption has been shown during the second and third trimester of pregnancy irrespective of iron status using labelled ^{54}Fe in a small study of 12 pregnant women (Barrett et al. 1994). Animal studies have proposed potential mechanisms for these changes. For example, duodenal gene expression of Dcytb, an enzyme responsible for converting dietary Fe^{3+} to Fe^{2+} for metabolism, and divalent metal transporter 1 (DMT1), a major intestinal iron transporter, have been shown to increase through pregnancy and decline within 48 hours after birth (Millard et al. 2004). The positive association between the timing of changes in oestrogen concentrations and Dcytb and DMT1 protein expression suggests that oestrogen may regulate iron absorption, but firm evidence for this remains to be established.

Microbial changes

Over the last decade the microbiome has been shown to be an important mediator of human health, and the composition of different bacterial species making up the microbiome and potential mechanisms by which they can be

altered is now a well-established field of research (Cho and Blaser 2012). There is growing appreciation that diet (Tilg and Kaser 2011, David et al. 2014, Walter 2015) and pregnancy (Koren et al. 2012, Jost et al. 2014) modulate the microbiome, as well as speculation that the microbiome can influence offspring development (Ma et al. 2014, Aagaard et al. 2014).

The influence of the microbial environment of the intestine on host physiology is now well established (Hooper and Gordon 2001), and has led to a number of studies examining how diet, and more recently pregnancy, affect it. The maternal GI microbiome undergoes profound changes during pregnancy, some of which are not dissimilar to those characteristics found in obesity (Koren et al. 2012), i.e. a decrease in microbial diversity (Turnbaugh et al. 2009, Qin et al. 2010, Greenblum et al. 2012). An “obese” type microbiome has been defined as one with an increased capacity for energy utilisation, primarily due to the greater abundance of bacterial species capable of fermenting and therefore increasing availability of otherwise indigestible sugars. The most significant example of this is the increased abundance of *Firmicutes* species relative to *Bacteroidetes*, with *Firmicutes* being more efficient sugar fermenters. Analysis of the colonic contents of ob/ob mice also shows an elevated concentration of the fermentation products butyrate and acetate relative to lean controls (Turnbaugh et al. 2006). A shift in *Bacteroidetes* and *Firmicutes* was not observed in the only maternal microbiome sequencing study to date conducted in normal weight participants (Koren et al. 2012), however a greater representation of the lactic acid fermenters *Lactobacillus*, *Streptococcus* and *Enterococcus* was reported in the third trimester. This has been suggested to be an evolutionary adaptation, and

the concomitant transfer of these microbes to the newborn could enable it to take advantage of the lactose in its mother's milk (Cox and Blaser 2013).

Similarities between the pregnant and obese microbiome are of interest since both conditions are associated with increased fat mass, although the relative distribution of this additional fat is different between pregnant and obese individuals (Straughen et al. 2013). There are a number of potential explanations for the development of an "obese type" microbiota during pregnancy. Species of *Bacteroidetes* contain a number of glycoside hydrolases which are able to ferment sugars which would otherwise pass through the large intestine and remain undigested (Bäckhed et al. 2005). Increased availability of polysaccharides is regarded as a hallmark of an obese microbiota (Turnbaugh et al. 2006), but would also result in increased energy availability which may be beneficial in pregnancy. This could help in meeting maternal energy demands and supplying the additional demands of the fetus, and suggest that during pregnancy the microbiome could be modulated to increase energy available for absorption. However, it is currently unclear whether these adaptations are due to the changing microbial environment, or are modulated by the other intestinal adaptations outlined earlier in this review.

It is not only changes in the relative proportion of individual species that occur, as the diversity of the microbiome also adapts, as defined by the relative number and abundance of different types of organism. For example, both obesity and inflammatory bowel disease have been linked with a low diversity of gut microbes (Turnbaugh et al. 2009, Qin et al. 2010). Diversity is measured within

an individual (alpha diversity, for example, the number of different types organisms within an individual's intestinal microbiome) and between individuals (beta diversity). Patterns of alpha and beta diversity differ significantly when making comparisons from the same habitat. For example, a high alpha diversity indicates a diverse microbiome but this can be concomitant with a low beta diversity, with members of a defined population all sharing similar organisms. Currently a functional explanation for changes in diversity has not been identified, with a need for studies taking into account responses to short and long term dietary modifications, diurnal rhythms as well as mode of delivery at birth and host genetics (The Human Microbiome Project Consortium 2012).

The current evidence base for understanding the changing gut microbiome has compared the effect of different diets and physiological states including pregnancy. Although this field is very new, it appears that the gut microbiome does change with pregnancy (Koren et al. 2012), and it has been hypothesised that inappropriate adaptation of the gut microbiome, such as that seen in a number of inflammatory bowel disorders (Kamada et al. 2013) may contribute to the development of pregnancy complications including pre-eclampsia, intrauterine growth restriction and miscarriage (Zhang et al. 2015). Pregnancy is associated with a significant reduction in alpha diversity and an increase in beta diversity by the third trimester (Koren et al. 2012). At the species level, there is a significant increase in abundance of *Proteobacteria* in the third trimester, which has previously been observed in obesity (Turnbaugh et al. 2009) and chronic inflammatory states (Mukhopadhya et al. 2012).

405

406 Changes in intestinal permeability to larger molecules and bacteria are of
407 interest especially given the above changes in the gut microbiota during
408 pregnancy, and the recent description of a unique microbiome in the placenta
409 (Aagaard et al. 2014). The effect of pregnancy on epithelial tight junctions, which
410 mediate intestinal permeability (Turner 2009), has not been studied. There is
411 overlap here with research into the role of the gut microbiota in pregnancy, with
412 lipopolysaccharide (LPS) present on the membranes of Gram-negative bacteria
413 passing into the systemic circulation and leading to the low-level adipose tissue
414 inflammation characteristic of obesity (Lam et al. 2011). Catecholamines
415 released as part of the maternal stress response have been hypothesised to lead
416 to gut barrier failure (Friebe and Arck 2008), and the subsequent release of LPS
417 linked to an increased risk of spontaneous abortion (Friebe et al. 2011).

418

419 Small studies in non-human primates (n=2-4 animals/group) have
420 demonstrated that a high fat diet in pregnancy has potentially adverse effects on
421 the offspring microbiome (Ma et al. 2014). An upregulation in amino acid,
422 carbohydrate and lipid metabolic pathways was observed in 1-year-old offspring
423 exposed to a high-fat diet during gestation and lactation. These changes were
424 partly reversed in offspring switched from a high-fat diet containing 36% fat to a
425 control diet containing 13% fat at weaning suggesting modest flexibility of the
426 offspring microbiome. The authors suggest that these results show the influence
427 of the maternal diet on establishment of the microbiome, rather than an
428 "obesity-causing" microbiome as indicated in the above research. However the
429 small numbers of animals studied together with the lack of an adverse

phenotype in the offspring (McCurdy et al. 2009) suggest that these findings need following-up.

Conclusion

Maternal adaptations occur throughout pregnancy and lactation, ranging from changes in gross gut anatomy to changes in the expression of specific nutrient transporters as summarised in Figure 1. The evidence here demonstrates that adaptation of the intestine to pregnancy is equally important as adaptation of other organs. However much of the material presented here is based on dated research, and there is a clear need for an expanded body of evidence using contemporary techniques in animal models and humans where possible. This would enable the addition of mechanistic data especially in pregnancies at risk from complications. The increasing prevalence of obesity in the Western world makes the study of obesogenic or diabetogenic diets during pregnancy critical to furthering understanding of important adaptations and processes in the gut. The microbiota is now considered a metabolically active organ, and the evidence presented suggests that its adaptation in pregnancy is a part of increasing energy extracted from the diet to provide for the fetus. Understanding these adaptations, and how they may be modulated by diet could therefore be beneficial in treating overweight and obesity during pregnancy.

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Figure caption

Figure 1: Summary of the primary known gastrointestinal adaptations and nutrient transporters affected during pregnancy. All processes shown are upregulated, those with blue arrows have mechanisms suggested in the literature, those without have been demonstrated but currently lack a well-defined mechanism.