Obesity is increasing at an epidemic rate in women of reproductive age. Not only does obesity during pregnancy lead to increased maternal health concerns, it is also linked to an increase in adiposity and components of the metabolic syndrome in the children and grandchildren of obese women. The potential transgenerational impact of maternal obesity on the health of future generations will undoubtedly result in increasing healthcare costs for society. This review will describe what is known about the specific impacts of maternal obesity on offspring in the human population as well as discuss how controlled animal experiments have shed light on the specific physiological mechanisms involved. Furthermore, preliminary experiments are presented describing potential dietary methods for preventing obesity-induced programming of offspring health concerns in postnatal life.

Keywords: altered fetal growth and development • altered offspring health • fetal programming • maternal overnutrition/obesity • transgenerational

Maternal obesity: how big an impact does it have on offspring prenatally and during postnatal life?

Both the developed and developing world are experiencing an epidemic within their populations that are overweight and obese in both sexes. This obesity is occurring earlier in life and affects women of childbearing age [1–9]. The current global obesity epidemic, together with its associated chronic diseases, represents a major drain on healthcare resources. Estimates suggest that 18–35% of pregnant women in the USA are clinically obese [10]. In the Western world, excess consumption of highly palatable diets combined with maternal obesity (MO) represent a significant problem, because of adverse effects on both maternal health and fetal development, which can result in harmful, persistent effects in offspring [2,3]. It has been previously determined that being overweight is associated with poor maternal health and several chronic conditions, including Type II diabetes mellitus (T2DM), cardiovascular disease, hypertension and stroke [11]. It is estimated that more than 42 million children under 5 years of age are overweight [20] and childhood obesity is strongly associated with obesity in adolescence and adulthood [12,13]. Furthermore, the prevalence of obesity is greatest among children of obese mothers [14] and there is an independent association between maternal BMI and offspring adiposity and insulin resistance [15–18]. Moreover, obesity in pregnancy is strongly associated with the development of gestational diabetes [19,20]. Others report that maternal weight gain in pregnancy is independently associated with offspring adiposity [21,22]. While these associations may be due to shared genetic traits that influence body weight or weight gain [23,24], a more common interpretation is that susceptibility to obesity is partly programmed in the fetus in utero or in the neonate during early postnatal life [25,26]. This is supported by the observation that birthweight, neonatal fat mass and BMI are significantly better correlated with maternal BMI during early pregnancy than with paternal BMI [23,27–31]. Maternal diabetes and offspring insulin resistance and risk of T2DM are similarly linked and some authors also report an independent relationship between maternal diabetes and offspring obesity [32]. Cardiovascular traits in children at the age of 9 years old have also been linked to maternal weight during pregnancy in a recent study [33], where greater maternal weight was positively correlated with more adverse cardiovascular risk factors. Specifically, children who were born to overweight mothers showed higher systolic blood pressure and lower high-density lipoprotein cholesterol levels compared with children who were born to lean mothers [33]. Therefore, there is strong evidence to suggest that the fetal/early postnatal environment associated with MO and diabetes leads to increased risk of obesity, T2DM and coronary heart disease in the offspring. This review will summarize our current knowledge of specific impacts of MO on offspring, using human epidemiological data as well as well-controlled animal studies to discern the mechanisms involved, as well as a discussion of potential strategies to ameliorate these effects.

Evidence that MO leads to offspring obesity

Two notable maternal conditions that predispose offspring to increased size and adiposity at birth are MO and maternal diabetes. Women with elevated pre-pregnancy maternal BMI, an indirect measure of fatness and plasma triglycerides tend to give birth to infants with higher birthweights [34]. These heavier babies are not lean, having an increased bodyfat and fat mass in comparison with infants born to women of normal weight [35]. In this regard, Pederson proposed a ‘hyperglycemia-hyperinsulinism’ pathway to explain the observation that offspring of diabetic mothers tend to exhibit higher birthweights [36]. Furthermore, large-for-gestational-age fetuses have higher proportions of total bodyfat and relatively lower lean body mass than infants who are of an appropriate weight for gestational age [37,38]. Thus, fetal hyperinsulinemia may exert lasting influences on body composition by increasing fat-cell size or number in early life leading to overweight and obesity in adolescence. Evidence for this hypothesis was presented by Silverman et al., who reported that amniotic fluid insulin levels, which reflected fetal pancreatic insulin production, correlated with obesity of offspring of diabetic mothers during adolescence [39]. Among Pima Indians, siblings that were exposed to maternal diabetes in utero had a higher BMI from ages 9 to 24 years than unexposed siblings [40], downplaying the roles...
of both shared genes and postnatal environment. Furthermore, direct associations have been reported between higher birthweight and the attainment of higher BMI in later life [29,41]. In a study of 14,000 US adolescents, it was shown that for every 1 kg increase in birthweight among full term infants, there was a 50% increase in the risk of being overweight at ages 9–14 years [42]. Children who were born to obese mothers (BMI ≥ 30 in first trimester) have been shown to develop obesity at twice the rate of children of non-obese mothers at the ages of 2–3- and 4-years in a retrospective cohort study [15]. These data are consistent with the hypothesis that fetal exposure to maternal nutrient excess and obesity and to elevated insulin concentrations results in long-term impacts on bodyweight regulation.

**Animal models of MO**

Studies in animal models show strong parallels with the human observational studies as reviewed by Poston [32]. They have also provided strong evidence that maternal overnutrition can contribute to this relationship [43,44]. The association between maternal nutritional ‘excess’ and offspring obesity and insulin resistance, sometimes referred to as the ‘Developmental Overnutrition Hypothesis’, has focused on the programming role of ‘fuels’ that can pass directly from the mother to fetus. Maternal hyperglycemia stimulates fetal insulin synthesis and increases fetal adiposity, which may permanently influence fetal adipocyte mass [45,46]. Maternal triglycerides, elevated in obese and insulin resistant women, do not cross the placenta but are hydrolyzed by placental lipases to fatty acids [47] and may thereby affect fetal fuel supply. Indeed, several reports demonstrate independent associations between insulin resistance or plasma triglycerides and offspring adiposity [48,49]. In this regard, Zhu et al. reported that MO in the sheep was associated with increased placental fatty acid transporter activity, mRNA expression and protein content, which was associated with marked elevations in cholesterol and fatty acids in fetal blood [50]. Other studies in pregnant women and also in nonhuman primates have implicated the inflammatory state associated with MO, which may lead to activation of the hypothalamic–pituitary–adrenal pathway and persistent influences on offspring metabolic function [26,51].

Animal models of maternal diabetes have focused on the role of neonatal hyperinsulinemia in the stimulation of pancreatic β-cell hyperplasia and eventual β-cell failure and also persistent effects on the developing hypothalamus leading to increased food intake and offspring obesity later in life [52–59]. Although some human studies reported no differences in food intake of children born to obese mothers or nonobese mothers, the children of obese mothers had an increased percentage of abdominal fat compared with children of nonobese mothers [56]. Gluck et al. concluded that children’s energy intake was closely associated with their mother’s energy intake, and thus was a strong predictor for their children’s energy intake [57]. Furthermore, there are large bodies of data demonstrating that the food preference of children can be inherited from their mother as reviewed by Kral and Rauh [58]. The relatively few animal studies addressing the consequences to offspring of MO combined with high caloric intakes during pregnancy and lactation have mostly been conducted in rodents. The data produced in rodents bolster the view that a diet-induced MO (either maternal cafeteria or high-fat diets) predisposes offspring to obesity and its related pathophysiology’s including obesity, insulin and leptin resistance, hypertension, fatty pancreatic disease, hepatic steatosis and nonalcoholic fatty liver disease, as reviewed by Li et al. [59]. Samper et al. reported that feeding the cafeteria diet resulted in increased inflammation in white fat, brown fat and the liver compared with feeding the high fat diet or a control diet [60].

The authors have used a sheep model to investigate the effects of maternal diet-induced obesity on fetal growth and development at mid-gestation, and metabolic health in their offspring. The authors have chosen to simply feed a highly palatable diet in excess of requirements to induce obesity, as ewes will eat in excess of requirements. The sheep is an appropriate animal model to study the impacts of maternal overnutrition/obesity on fetuses and offspring, as it exhibits many similarities with humans, including its willingness to overeat. The fetal sheep has a metabolism similar to the fetal human as shown by the large number of studies worldwide [61–69]. The importance and relevance of all the metabolic studies is that the fetal sheep, like the fetal human, is dependent on glucose for its major source of energy. Furthermore, both the sheep and human produce well developed precocial offspring, exhibit the same newborn-to-maternal weight ratios, and exhibit the same temporal pattern of fetal tissue and organ development throughout pregnancy [70]. Furthermore, investigators worldwide have utilized the sheep as a biomedical model to conduct controlled studies on human pregnancy. Our studies on the impacts of maternal overnutrition/obesity in the ewe on fetal growth and development and offspring health are conducted with animals from a closed flock at the Center for the Study of Fetal Programming, at the University of Wyoming (WY, USA). Ewes of similar breeding, size, age and weight are fed to National Research Council (NRC) dietary recommendation [71] both before and throughout pregnancy and lactation, and female offspring to be used in ongoing studies are housed together and fed only to requirements from weaning to maturity. This provides assurance that animals have not been exposed to highly variable environments prior to use in ongoing studies and thus, limits the chance of markedly different environmental (epigenetic) influences on study results. Furthermore, all ewes in each experiment are bred to a single intact ram to minimize paternal effects.

Our approach to studying the impacts of MO on fetal growth and development and offspring health, was to feed a highly palatable diet at either 100% (control [CON]) or 150% (MO) of requirements from 60 days before conception through pregnancy [72]. Composition of the experimental diet was: dry matter (DM), 88.54%; neutral detergent fiber, 24.09% of DM; acid detergent fiber, 9.99% of DM; crude protein, 17.39% of DM; in vivo DM digestibility, 93.92%. Using this approach, the bodyweight of MO ewes increases by ~30% from diet initiation to conception, with an additional 20–30% increase in weight from conception to term, while CON ewes exhibit a normal gestational weight gain of only 10–15% [55]. These studies demonstrated that fetuses
gestated by MO ewes are approximately 30% heavier than CON fetuses by mid-gestation and exhibited markedly increased pancreatic weights (236% increase) and β-cell numbers compared with fetuses from CON ewes [73], while by late-gestation, pancreatic weights, β-cell numbers and plasma insulin concentrations were markedly lower in fetuses gestated by MO than CON ewes [74]. The authors previously reported that the mitotic rate of β-cells in the pancreas of MO fetuses dramatically increased by mid-gestation [73]; while increased β-cell apoptosis resulted in a reduced number of β-cells in the pancreas of MO fetuses compared with control fetuses at late-gestation [74]. Furthermore, fetuses from MO ewes exhibited increased blood concentrations of IGF-1, cortisol, glucose, cholesterol and fatty acids as well as markedly increased perirenal fat depots compared with fetuses from CON ewes [50,73]. At birth, lambs born to MO ewes exhibited markedly greater adiposity as determined by dual x-ray absorptiometry than lambs from CON ewes [64]. Furthermore, both male and female offspring born to MO mothers exhibit markedly increased appetites, growth rates, adiposity and insulin resistance when subjected to ad libitum feeding at maturity compared with similarly aged offspring from CON ewes [55]. Interestingly, if MO and CON offspring are maintained together from weaning to maturity and only fed to NRC requirements they exhibit no perceptible differences in growth rate or adiposity. These data suggest that our previously proposed requirement for a ‘two hit’ exposure for developmental programming of offspring obesity [75] may be required to illicit clear differences in postnatal metabolism and body composition, the first being exposure to MO, and the second occurring as a result of ad libitum feeding in postnatal life.

**Currently proposed intervention strategies**

Based on previously presented animal studies, it might be assumed that interventions that improve maternal glucose homeostasis or insulin resistance in obese/or diabetic pregnancies would therefore be expected to reduce the risk of obesity in offspring, but few relevant studies are reported. In a retrospective study, which supports the ‘developmental origins’ hypothesis, treatment (with diet or insulin) of mothers with gestational diabetes eliminated the strong positive association between gestational diabetes and offspring obesity at 5–7 years of age [76]. Several interventional approaches currently under evaluation to improve pregnancy outcome in obese women may theoretically reduce the risk of obesity and diabetes in the offspring. These include lifestyle, for example, diet and physical activity strategies as in the ongoing UPBEAT study in obese women [26], as well as the use of pharmacological agents to improve glucose tolerance [77,78]. The use of pharmacological agents like metformin and insulin in mothers with gestational diabetes has reduced gestational weight gain to a normal range [78]. Furthermore, the children from mothers who were treated with insulin and metformin had a normal bodyfat percentage at 2 years of age [79]. Metformin is also used in treatment of polycystic ovarian syndrome, and a study by Carlsen et al. showed that women who received metformin treatment gained less weight during pregnancy, however, the children born to metformin treated mothers weighed more at 1 year of age compared with children of mothers who only received placebo [80]. Recently, several maternal obese intervention (MOI) studies showed that lifestyle interventions including dietary interventions during pregnancy in obese women resulted in similar gestational weight gain to control women during pregnancy, but did not reduce the risk of large-for-gestational-age newborns [81–84]. A meta-analysis on human MOI studies by Thangaratinam et al. reported that the dietary intervention studies resulted in better pregnancy outcomes among different intervention methods [85]. The authors have recently undertaken studies to determine if an early pregnancy reduction in maternal nutrition to requirements in overnourished/obese ewes will reverse or attenuate the observed negative impacts of MO on fetal growth, adiposity and organ development, and therefore potentially reduce the incidence of obesity, insulin resistance and other components of the metabolic syndrome observed in the resulting offspring. It is felt that the effects of a simple reduction in dietary intake should be evaluated first, before pharmacologic agents are considered for administration to obese pregnant women to increase insulin sensitivity and reduce blood glucose.

Previous studies in our laboratory demonstrated that maternal undernutrition (50% global undernutrition) starting at day 28 of gestation resulted in fetal intrauterine growth restriction (IUGR) by mid-gestation [86] and the resultant offspring exhibited significant metabolic and cardiovascular disturbances as adults (i.e., they exhibited hyperphagia, increased insulin resistance and adiposity and were hypertensive) [87]. It was thus predicted that a dietary intervention where obesogenic diets were reduced from 150 to 100% of NRC requirements (MOI) beginning on day 28 of gestation would be early enough to correct the negative impacts of maternal overnutrition/obesity on the fetus and resulting offspring. Day 28 of pregnancy in the sheep is equivalent to approximately day 50 in human pregnancy, which is approximately the time when women confirm they are pregnant and early enough for a doctor to provide overweight/obese women with a corrective dietary regimen.

Using this MOI model, the authors have investigated the outcomes of early maternal dietary intervention on growth, organ development and hormonal profiles of mid- and late-gestation fetuses and their mothers. The authors found that early maternal dietary intervention reduced the MO-induced increases in baseline cortisol, glucose and insulin in maternal and fetal blood (Table 1), as well as maternal insulin resistance at both mid- and late-gestation. The observed improvements in endocrine profiles of MOI mothers and fetuses are important in that the offspring born to MOI mothers might be less subjected to programming of metabolic syndrome in postnatal life due to reduced level of these hormones to control level. Perhaps more importantly, the authors were successful in eliminating MO-induced fetal macrosomia during mid-gestation. The reduction in fetal weight at mid-gestation was associated with reduced organ weights in MOI fetuses to CON levels, specifically right and left ventricles of the heart, kidney, pancreas and perirenal fat weights were significantly reduced in MOI fetuses when compared with MO fetuses at mid-gestation (Table 2). At day 135, while fetal weight was not
statistically different between CON, MO and MOI fetuses, MO fetuses continued to exhibit greater left ventricular weights and thicknesses, right ventricular thicknesses, total kidney weight, and total perirenal fat, while pancreatic weights were reduced when compared with CON fetuses (Table 2). Interestingly, weights and thicknesses of these organs and tissues were returned to CON levels in the MOI fetuses (Table 2). The data provide the first indication that alterations in fetal organ and tissue growth and development could be prevented by early pregnancy MOI in the face of MO. The authors are currently evaluating the offspring from CON, MO and MOI mothers to determine whether reducing maternal nutrition to recommended levels in early pregnancy of overnourished/obese ewes prevents endocrine and metabolic disturbances in these offspring in adult life.

The hypothalamus, leptin & appetite control
Hypothalamic appetite centers are programmed during prenatal development to maintain a balance between the hypothalamic orexigenic peptides, neuropeptide-Y and agouti-related protein and the anorexigenic peptides, pro-opiomelanocortin and cocaine- and amphetamine-regulated transcript to sustain proper energy homeostasis [88,89]. During this critical period, neuronal extensions are stimulated from the arcuate nucleus (regarded as the principal site to monitor leptin signaling) towards the paraventricular nucleus, the lateral hypothalamus and the dorsomedial nuclei of the hypothalamus to create a circuitry that will mediate food intake and control energy balance in postnatal life [90]. Development of the hypothalamic neural networks occurs prenatally during late-gestation in larger animals, such as humans and sheep [91], and also in rodents; however, in rodents, continued development and maturation of these pathways is not completed until weaning [92]. The network of interconnected pathways within the hypothalamic circuitry is a system that is subjected to alterations by the internal milieu [93,94]. Permanent alterations in one or more of the relevant pathways, including appetite regulation, altered energy expenditure, tissue metabolism and physical activity during early development could program the development of obesity in postnatal life [95]. If the fetus is exposed to either under- or over-nutrition during this time, the differentiation of the hypothalamic centers responsible for the control of food intake may be altered [96], leading to persistent hyperphagia and associated obesity [97]. Samuelsson et al. showed that mouse offspring born to obese mothers not only exhibited increased adiposity and hyperphagia at birth, but at 3 months of age they were insulin resistant and by 6 months of age, male offspring developed glucose intolerance [98]. As previously discussed, similar adverse outcomes were seen in adult lambs born to obese mothers. Birthweights of lambs born to obese and control animals were similar, however, dual energy x-ray absorptiometry scans revealed that lambs born to obese ewes exhibited an increased fat-to-lean mass ratio in comparison to controls [75]. When these offspring were placed on an ad libitum feeding trial at 19.5 months of age, they demonstrated hyperphagia, increased adiposity and weight gain, hyperleptinemia, hyperglycemia and insulin resistance in comparison to offspring gestated by control-fed ewes [55]. In addition to rodents and sheep, human offspring of obese mothers show comparable outcomes and may be predisposed to obesity and metabolic disease later in life attributable to greater adiposity and altered glucose and insulin dynamics in fetal and neonatal life [75].

Transgenerational impacts of maternal overnutrition/obesity on offspring
There is now accumulating evidence that maternal diet-induced epigenetic changes can be transmitted across generations. Epigenetics refers to mechanisms that lead to long-term changes in gene expression through chemical modification to or alterations in the packaging of DNA (independent of changes in the DNA sequence) such that the capacity for transcriptional regulation is altered, impacting the fetal phenotype [99]. Typically, epigenetic modifications include DNA methylation, histone modification and RNA interference, mechanisms that are beyond the scope of this review but are further described in a number of excellent review articles [100-104]. Experimentation with animal models, where controlled manipulation of maternal nutrition can be accomplished, has provided solid evidence of dietary manipulation of gene expression [102]. In a unique validation of epigenetic mechanisms, Vonnahme et al. simultaneously studied two flocks of genetically similar Rambouillet/Columbia ewes, derived from a single flock 30 years earlier, which confirmed that environmentally-induced placental phenotypic changes can be passed from generation to generation [103]. One flock was adapted to a nomadic existence with limited nutrition, located near Baggs, Wyoming (Baggs ewes) and the other flock to a sedentary lifestyle with more than adequate nutrition, at the University of Wyoming (UW ewes).

Table 1. Comparison of glucose and selected hormones in the blood of fetuses from maternal obese and maternal obese intervention mothers at mid- (day 75) and late-gestation (day 135) relative to fetuses from control mothers.

<table>
<thead>
<tr>
<th></th>
<th>MO</th>
<th>MOI</th>
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<tbody>
<tr>
<td><strong>Mid-gestation (day 75) fetus</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose</td>
<td>+</td>
<td>ND</td>
</tr>
<tr>
<td>Insulin</td>
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<td>ND</td>
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<tr>
<td>ACTH</td>
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<td>ND</td>
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<tr>
<td>Cortisol</td>
<td>+</td>
<td>ND</td>
</tr>
<tr>
<td>IGF-1</td>
<td>+</td>
<td>ND</td>
</tr>
<tr>
<td><strong>Late-gestation (day 135) fetus</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Insulin</td>
<td>+</td>
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<tr>
<td>ACTH</td>
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<tr>
<td>Cortisol</td>
<td>++</td>
<td>ND</td>
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<tr>
<td>IGF-1</td>
<td>ND</td>
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</table>

+: Moderate increase; ++: Large increase compared with control fetuses; MO: Maternal obese; MOI: Maternal obese intervention; ND: Similarity to control fetuses.

Data taken from [Long NM et al., Zhang L et al., Ford SP et al., Unpublished Data].
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described again undernourished from early to mid-gestation, as previously sequent evaluation of offspring quality, UW and Baggs ewes were required during the bout of maternal nutrient restriction. In a sub- ing placentomal conversion to more efficient placentomal types, of maternal to fetal nutrient delivery) to more efficient placen- resulted from the early conversion of type A placentomes (sites as reduced blood glucose.

Multiparous ewes of similar age, weight and body condition score were assigned to the control (100% NRC recommendations), or a nutrient restriction (50% of the control-fed diet) diet from early to mid-gestation and necropsied. Surprisingly, fetuses gestated by nutrient restriction (50% of the control-fed diet) from early were assigned to the control (100% NRC recommendations), or a Multiparous ewes of similar age, weight and body condition score.

Late-gestation (day 135) fetus

<table>
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<th>MO</th>
<th>MOI</th>
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<tbody>
<tr>
<td>Fetal bodyweight (g)</td>
<td>ND</td>
</tr>
<tr>
<td>Right ventricle weight (g)</td>
<td>ND</td>
</tr>
<tr>
<td>Right ventricle thickness (cm)</td>
<td>+</td>
</tr>
<tr>
<td>Total kidney weight (g)</td>
<td>ND</td>
</tr>
<tr>
<td>Pancreas weight (g)</td>
<td>ND</td>
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<tr>
<td>Total perirenal fat weight (g)</td>
<td>ND</td>
</tr>
</tbody>
</table>

- Increase; -: Decrease; MO: Maternal obese; MOI: Maternal obese intervention; ND: Similarity to control fetuses.

Data taken from LONG NM et al., ZHANG L et al., FORD SP et al., Unpublished Data.

Multiparous ewes of similar age, weight and body condition score were assigned to the control (100% NRC recommendations), or a nutrient restriction (50% of the control-fed diet) diet from early to mid-gestation and necropsied. Surprisingly, fetuses gestated by UW ewes, but not those from Baggs ewes showed IUGR, as well as reduced blood glucose [103], and amino acid concentrations [104] compared with fetuses of UW control-fed ewes. These differences resulted from the early conversion of type A placentomes (sites of maternal to fetal nutrient delivery) to more efficient placentomal types (B, C, and D) in Baggs versus UW ewes. By increasing placentomal conversion to more efficient placentomal types, Baggs ewes were better able to provide the nutrition their fetuses required during the bout of maternal nutrient restriction. In a sub-sequent evaluation of offspring quality, UW and Baggs ewes were again undernourished from early to mid-gestation, as previously described [103], but this time allowed to lamb [105]. When placed on an ad libitum feeding trial as adults, the lambs born to UW ewes but not Baggs ewes exhibited increased appetites and adiposity, hypertension, insulin resistance, decreased nephron numbers, and reduced skeletal muscle mass when compared with their respective controls fed to requirements [106,107]. In addition, recent human epidemiological evidence and appropriately designed dietary interventions in animal models suggest that abnormal nutrition in early life can influence diabetes risk in subsequent generations [108]. In rats, the adult offspring of diabetic mothers maintain glucose homeostasis under basal conditions, but are unable to handle situations stressing their glucose metabolism such as pregnancy, resulting in hyperinsulinemia and hyperglycemia [109]. Fetuses born to these diabetic dams in both the F0 and F1 generations show the same metabolic alterations including macrosomia, islet hyperplasia, β-cell hyperactivity, and hyperinsulinemia as their mothers suggesting transgenerational effects [110]. Studies have also shown that phenotypic alterations can also occur through the paternal lineage in response to overfeeding. Human epidemiological data suggest that increased food availability during the slow prepuber- tal growth period in grandfathers increases the risk of cardiovas- cular and diabetes-related deaths in their grandchildren [111–114]. In agreement with these findings, Pentinat et al. reported that 4-month old male mice, overnourished during neonatal development, exhibited obesity, insulin resistance and glucose intolerance [115]. Normally fed male offspring and grand-offspring of these overnourished male mice also exhibited features of the metabolic syndrome with aging [115]. Furthermore, results from this model and other animal models suggest that phenotypes progressively weaken across generations, reiterating the role of epigenetic rather than genetic modifications in mediating phenotypic alterations and metabolic dysfunction [115–118]. Further investigations into epigenetic mechanisms, through human epidemiological data and animal models will undoubtedly provide insight into the molecular mechanisms whereby maternal and paternal malnutrition alters postnatal disease susceptibility and genomic imprinting.

Neonatal leptin & appetite regulation

A neonatal leptin peak that occurs between postnatal day 8 and 21 in rodents and between day 4 and 9 in sheep [89,119,120] is thought to program the appropriate balance of orexigenic and anorexigenic appetite neuropeptides and influence future leptin sensitivity [89]. The authors have demonstrated that this neonatal leptin peak was eliminated in lambs born to MO mothers [120] as well lambs whose grandmothers were overnourished/ obese [FORD SP et al., Unpublished Data], suggesting a transgenerational effect. In these studies, the daughters of MO mothers were fed only to requirements from conception to maturity and throughout gestation as were the daughters of control-fed mothers. When subjected to an intravenous glucose tolerance test at mid- and late-gestation, however, the daughters of MO ewes exhibited elevated baseline glucose and insulin concentra- tions and markedly greater insulin resistance than daughters of control-fed mothers [121]. These elevated blood glucose and insulin levels may be the result of metabolic disturbances that were developmentally programmed into the daughters of MO mothers and expressed during pregnancy, a period marked by significant adaptations in maternal pancreatic islet size, secretion capacity and level of insulin at peripheral tissues to meet fetal demands [110]. Bouret et al. has recently reported that leptin is essential for normal development of axonal projections from the arcuate nucleus to surrounding hypothalamic nuclei, thus

### Table 2. Comparison of selected fetal characteristics of fetuses from maternal obese and maternal obese intervention mothers at mid- (day 75) and late-gestation (day 135) relative to fetuses from control mothers.

<table>
<thead>
<tr>
<th>MO</th>
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<tr>
<td>Fetal bodyweight (g)</td>
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<td>Total perirenal fat weight (g)</td>
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- Increase; -: Decrease; MO: Maternal obese; MOI: Maternal obese intervention; ND: Similarity to control fetuses.

Data taken from [LONG NM et al., ZHANG L et al., FORD SP et al., Unpublished Data].
programming the hypothalamic circuitry responsible for regulating appetite during postnatal life [122]. Impairment in leptin receptor signaling may adversely affect axonal projections from the arcuate nucleus to their targets, affecting energy balance. In postnatal lambs, Muhlhausler et al. reported that mRNA expression of the leptin receptor in the arcuate nucleus of the hypothalamus was inversely related to fat mass [123]. Elimination of this leptin peak may predispose rodent offspring of obese overnourished mothers to increased adiposity and decreased sensitivity to leptin in adulthood [89]. Likewise, lambs born to obese ewes exhibited markedly increased appetite, as well as glucose and insulin dysregulation, increased adiposity, and were hyperleptinemic when compared with offspring from control-fed ewes [122]. OBF1 lambs and subsequently their offspring, OBF2 lambs, exhibited elevated plasma cortisol levels on the day of birth and the beginning of postnatal life compared with CONF1 and CONF2 lambs. Cortisol has an important role in prenatal regulation of cell proliferation and differentiation to mature fetal tissues in preparation for extra-uterine life [124]. Cortisol may cause premature differentiation of adipocytes, possibly altering the timing of the neonatal leptin peak and/or the quantity of leptin secreted. This hypothesis is supported by Long et al. who reported that daughters and granddaughters of ewes administered exogenous glucocorticoids at 0.7 gestation exhibited a similar elimination of the neonatal leptin peak as seen in offspring of overnourished/obese ewes [120,121,125]. Additional research will be required to elucidate the specific mechanism(s) whereby elevated cortisol in the fetal circulation suppresses leptin production in early postnatal life, thereby preventing normal development of the hypothalamic appetite centers in postnatal life.

**Placental function & inflammation**

The role of placenta naturally becomes important in the programming events in MO, as any of the perturbing factors must be transmitted across the placenta in order to affect the fetus. Furthermore, placental dysfunction even in the presence of optimal maternal nutrition may result in unfavorable outcomes to fetal growth and development [126]. Dubé et al. recently reported that MO is associated with increased expression of placental fatty acid transporters without altering fetal birthweights in human pregnancies at term [127]. In mice, high fat diets before and during pregnancy caused marked upregulation of glucose transporter 1 and sodium-coupled neutral amino acid transporter 2 protein expression [128]. In sheep, our laboratory and several other laboratories have shown that placental vascularity is reduced in overnourished fetuses than control fetuses in mid- and late-gestation [129–131]. However, fatty acid and glucose transporters are upregulated by MO at mid-gestation and fetuses from obese ewes have significantly increased circulating glucose and triglyceride levels when compared with fetuses of control ewes [50,132].

In human placenta, excessive inflammation can lead to adverse pregnancy outcomes such as spontaneous abortion, preterm labor and IUGR [133]. During an inflammatory response, levels of activated cytotoxic/Th1 lymphocytes and macrophages are elevated at the inflammatory site [134]. Proinflammatory cytokines, including TNF-α, IL-1, IL-2, IL-6, IL-8, IL-12 and IL-18 are Th1 associated cytokines that can promote the differentiation of precursor T cells into Th1 cells [134]. Macrophages express specific membrane markers CD68 or CD11b/CD14 [135], and membrane microbial pattern-recognition receptors such as toll-like receptor (TLR)2 and TLR4 that have been shown to be activated by free fatty acids [136,137]. TNF-α, TLR2 and TLR4 regulate the inflammatory response through NF-kB p65 and c-JNK signaling pathways, both of which promote further production of proinflammatory cytokines [134,138–140]. It has been reported that MO is associated with increased inflammation of the human placenta, in association with elevated macrophage populations (CD68+ and CD11b+/CD14+ cells) and increased expression of TNF-α, IL-1 and IL-6 [139]. Similarly, the authors reported [140] a greater expression of inflammatory markers in the placental tissue of obese overfed ewes at mid-gestation. Interestingly, these obese overfed ewes exhibited a shortened gestation length (~5 days shorter) than controls [73], suggesting inflammation associated preterm delivery.

**Clinical therapeutic implications**

In conclusion, MO is a serious and increasing clinical concern and methods must be developed to reduce the proven transgenerational impacts of this condition on offspring obesity and health. Controlled animal studies have provided and continue to
provide significant information about obesity-induced developmental and hormonal changes in the fetus during \textit{in utero} development. As indicated, these authors feel that developing dietary interventions for overnourished/obese pregnant women are a better approach than the utilization of pharmaceuticals which can have unintended consequences on mother and baby.

**Expert commentary**

While there has been necessary skepticism about \textit{in utero} programming of human offspring, numerous human epidemiological studies as well as controlled animal studies have been conducted and confirmed that developmental programming does occur in response to a variety of maternal stimuli, including overnutrition/obesity (see Figure 1 for details). Currently, approximately 60% of women of reproductive age are overweight or obese. Furthermore, clinical results have reported that women who are overweight/obese at conception are the most at risk of giving birth to babies who have an increased percentage of bodyfat and go on to become insulin resistant and overweight in later life. Extensive animal research shows that the changes in the levels of the adipose tissue hormone leptin in the first weeks of life can program the setting of appetitic drive. If wrongly set, this predisposes to overeating, abnormal fat deposition, metabolic disease and shortening of life span. It is crucial to identify the signals and mechanisms involved in the transmission of this negative phenotype to offspring at the earliest time they emerge, and to develop diagnostic, preventative and therapeutic strategies to prevent it.

**Five-year view**

The obesity epidemic worldwide is significant and is accelerating at an astonishing rate, making this problem one of our most serious public health concerns. Thus, it is imperative that we develop increased understandings of the pathways of transmission of this obese phenotype from mother to offspring. While studies have confirmed and begun to elucidate the impacts of MO on fetal organ and tissue development \textit{in utero} using relevant animal models, we now need to develop more in depth understandings of the molecular and cellular mechanisms involved. Furthermore, we need a greater understanding of the obesity-induced epigenetic mechanisms set in place to alter gene expression in affected offspring. Specifically, a greater focus on fetal hypothalamic, pancreatic and cardiovascular changes are needed to prevent altered appetite control, and the development of insulin resistance/obesity, hypertension and other components of the metabolic syndrome in postnatal life. In addition to pharmacological interventions, which may cause unintended consequences, recent data generated in humans trials and controlled animal studies have suggested that alterations in maternal diet can have a significant impact on fetal and offspring phenotype. Additional maternal nutritional interventions will be accomplished in obese/overweight women in clinical practice, as well as with animal models, providing vital information on optimal timing of dietary interventions, as well as the relative contributions of different dietary components in preventing offspring obesity and associated metabolic disease in postnatal life.

**Key issues**

- Maternal obesity is a significant public health concern and is increasing at an alarming rate worldwide.
- Not only does obesity during pregnancy lead to increased maternal health risks, it is also linked to increased adiposity and components of the metabolic syndrome in the children and grandchildren of obese women.
- Diet-induced maternal obesity from conception results in fetal macrosomia as well as altered growth and development of the hypothalamus, pancreas and heart.
- Fetuses gestated by obese mothers have increased adiposity, are hyperglycemic and hyperinsulinemic, and have elevated blood cortisol levels, a hormone known to alter tissue growth and differentiation.
- Offspring born to obese mothers fail to exhibit a normal leptin surge in the early postnatal period, which functions to set the hypothalamic appetite centers regulating appetite in later life.
- Adult offspring of obese mothers exhibit increased appetites, are insulin resistant and have increased adiposity, when compared with adult offspring born to lean mothers.
- Reduction in food intake to required levels in early pregnancy in overfed/obese mothers eliminates macrosomia and returns fetal tissue and organ development and endocrine patterns to control levels.
- Diet manipulation of obese women during pregnancy may be effective in the production of normal healthy offspring.

**References**

Papers of special note have been highlighted as:
- of interest
- of considerable interest


Impact of maternal obesity on the fetus


Impact of maternal obesity on the fetus

Review


92 Review of action of leptin on brain appetite centers.


**Website**

201 WHO. Global Strategy on Diet, Physical Activity and Health. www.who.int/dietphysicalactivity/chilhood/en
Maternal obesity: how big an impact does it have on offspring prenatally and during postnatal life?

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Activity Evaluation
Where 1 is strongly disagree and 5 is strongly agree

1. The activity supported the learning objectives.
2. The material was organized clearly for learning to occur.
3. The content learned from this activity will impact my practice.
4. The activity was presented objectively and free of commercial bias.

1. You are seeing a 24-year-old primiparous woman for her initial prenatal examination. Her pre-pregnancy body mass index (BMI) was 34 kg/m², and she has already gained 5 kg in the first 6 weeks of her pregnancy. What should you consider regarding the epidemiology of obesity in pregnancy and its potential complications for her offspring?
   - [ ] A The rate of obesity among pregnant women in the United States has fallen under 10%
   - [ ] B There is no established link between obesity during childhood and adulthood
   - [ ] C The effect of maternal obesity on offspring appears to be rendered insignificant by age 5 years
   - [ ] D Higher birthweight is associated with higher BMI later in life

2. What should you consider regarding placental factors and the development of fetal organs in this obese patient?
   - [ ] A Maternal triglycerides cross the placenta directly
   - [ ] B Maternal obesity is associated with increased placental vascularity
   - [ ] C Maternal obesity is associated with increased weight of the fetal heart
   - [ ] D Maternal obesity is associated with increased weight of the fetal pancreas

3. According to the current review, what is the preferred method of treatment for this patient’s obesity?
   - [ ] A Diet only
   - [ ] B Diet plus a thiazolidinedione
   - [ ] C Diet plus metformin
   - [ ] D Diet plus insulin

4. The patient eventually delivers a large-for-gestational-age infant at term. What should you consider regarding the metabolic effects of maternal obesity?
   - [ ] A The normal peak in neonatal leptin levels may be blunted
   - [ ] B The child can be expected to be highly sensitive to leptin for years
   - [ ] C Cortisol levels should be low in the neonatal period
   - [ ] D Maternal obesity generally has no effect on neonatal insulin levels