Chapter 14
Maternal Obesity and Implications for Fetal Programming

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Key Points

- Obesity develops as a result of the imbalance between energy intake and energy expenditure.
- Obesity among women of reproductive age ranges from 20% to 30% rendering maternal obesity a major public health concern worldwide.
- Human clinical findings demonstrate that both maternal obesity prior to conception, and excessive weight gain during pregnancy have the greatest impact on increasing childhood obesity and metabolic dysregulation in their offspring.
- Obesity is an important contributor to the global incidence of cardiovascular disease, type 2 diabetes mellitus, osteoarthritis, workforce disability and sleep apnea.
- Studies in animal models indicate that these metabolic sequelae are initiated by a proinflammatory milieu in the placenta creating an inflammatory environment for the fetus.
- This leads to alterations in fetal growth, metabolism and organ development resulting in metabolic dysregulation in the postnatal offspring.
- Our research further indicates that maternal obesity has multigenerational effects, thus intervention strategies aimed at mitigating nutritional stress in the mother not only benefit the mother and her own health, but also the health of her progenies and their progenies.

Keywords Maternal obesity • Animal models • High fat diet • Rodents • Sheep • Non-human primates

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Current State of Clinical Understanding of the Impacts of Maternal Obesity on Offspring

We have been asked to summarize our current understanding of the impacts of maternal obesity, which has doubled since 1980, on programming the health of future generations. Our group has spent the past decade developing and characterizing an ovine model of diet-induced maternal obesity (MO) that has critically important developmental and physiological similarities to humans. In the analyses for the Global Burden of Disease Study, it was reported that between 1980 and 2013 the worldwide proportion of adults with a body mass index (BMI) of 25 or greater, signifying overweight/obesity, increased from 29% to 37% in men and from about 30% to 38% in women [1]. Further, it was reported that the prevalence of overweight and obesity among children and adolescents in developed countries was also very high, averaging about 24% for boys and 23% for girls [1]. This study also reported that a trend for increasing overweight/obesity was also seen in developing countries increasing from 8% in 1980 to 13% in 2013 for boys and girls. Further, the WHO (www.who.int/nut/obs.htm) has declared obesity one of the top ten adverse health risks in the world and one of the top five in developed nations where obesity among women of reproductive age ranges from 20% to 34% [2]. Thus, maternal obesity has become a major public health issue with maternal complications as well as programming of offspring metabolic disease risk. In particular, obesity is an important contributor to the global incidence of cardiovascular disease, type 2 diabetes mellitus, cancer, osteoarthritis, work disability and sleep apnea [3, 4].

A longitudinal study of 179 individuals, found that children exposed to MO, with or without gestational diabetes, exhibit an increased incidence of obesity and metabolic disease [5, 6]. This may relate to the fact that obese pregnant women exhibit an increased incidence of glucose intolerance, hypertensive disorders, hyperlipidemia and increased circulating inflammatory markers [7]. Maternal obesity is often but not always associated with the birth of large for gestational age infants [8, 9]. This increase in birth weight of infants born to obese women is a result of increased fat mass and not lean body mass [10]. Further, this increased body fat is centrally distributed [11] and there is a strong correlation between this increased fetal adiposity and insulin resistance [12].

Both maternal obesity prior to conception, and excessive weight gain during pregnancy are highly associated with increased childhood obesity [13] and metabolic dysregulation [5]. Further, newborn offspring of obese women were more obese and insulin resistant than offspring born to normal weight women [14]. These data suggest that MO has already impacted offspring prior to birth and underpins the need to study the specific mechanisms mediating the effects of MO on both the fetus and newborn [15]. Mother-child cohorts show associations between maternal BMI and/or gestational weight gain and childhood metabolism and cardiovascular function [16, 17] but although these associations are vitally important they remain only associations, due to the presence of uncontrolled confounders. This conclusion is highlighted by the results of the UPBEAT study, a large multicenter, randomized controlled trial conducted in the UK targeting diet and physical activity in obese patients to reduce the incidence of gestational diabetes and large-for-gestational-age infants [18]. These authors reported no intervention associated reductions in gestational diabetes or large-for-gestational-age fetuses, and concluded that the current focus on behavioral interventions to prevent gestational diabetes would seem to be unwarranted.

The phenotype of each unique mammalian organism is the result of the interaction of that organism's genotype with environmental influences exerted upon it. The principle of developmental programming is based on strong evidence that there are critical periods of vulnerability to suboptimal conditions during development both pre- and post-natally. Overwhelming evidence from animal studies shows that these critical vulnerable periods occur at different times for different tissues and that timing and susceptibility differ between species and sex [19]. Human epidemiological and controlled animal studies show that unwanted effects of altered in utero development may persist into later life

and predispose to chronic diseases such as type 2 diabetes mellitus, obesity, and hypertension [20, 21]. Unwanted effects of changed development may remain dormant for years to reemerge and cause health problems when the internal and/or external environment (e.g. pregnancy, challenges to the immune system by infectious diseases, nutritional challenges of deficiency or excess, stress, etc.) of the individual changes. While puberty is one particularly important time of endocrine change, human epidemiological studies suggest that the chronic diseases programmed by MO now occur well before puberty. The incidence of type 2 diabetes (T2D, a condition clearly related to MO) in metropolitan Tokyo in prepubertal children between 6 and 15 years quadrupled between 1975 and 1995 [22].

Multigenerational Versus Transgenerational Impacts of Maternal Obesity

This topic is complicated by the fact that besides in utero exposure of first filial [F1] offspring during the time of maternal obesity, their developing gonads and the associated germ cells were also exposed to the same in utero insult. Thus both the F1 and F2 generations are not independent of the initial obesity exposure and the potential impact on these offspring and are referred to as multigenerational effects [23]. The mechanisms underlying the effects of multigenerational programming of obesity are largely unknown, but are likely a result of interplay between environmental, metabolic and epigenetic factors [24]. The programming impacts on offspring beginning in the F3 generation and beyond are considered independent of the initial in utero obesity exposure of the fetus or its germ cells to MO. These impacts are thought to result from meiotically-stable epigenetic inheritance, resulting from altered DNA methylation patterns, histone modifications or siRNA expression differences, and are referred to as transgenerational effects [24–26].

As one might surmise, it is much easier experimentally to discern transgenerational inheritance through the paternal lineage as the male only contributes gametes as opposed to the female who has a prolonged physiological interaction with the progeny. There is also the possibility of nongenomic transmission of F1 phenotype through altered maternal responses to the significant physiological stresses of pregnancy which may be equated to a “second hit” and unmask sub-clinical tendencies in these women such as type 2 diabetes and vascular dysfunction [27, 28]. Thus F1 females expressing a relatively normal phenotype outside of pregnancy may fail to adapt to this significant metabolic stress and thus pass on adverse effects to the F2 generation. The most obvious example would be gestational diabetes where the resulting hyperglycemia exerts significant and well characterized impacts on the fetus, as it readily crosses the placenta [29]. As evidence of this possibility, transmission of gestational diabetes via the maternal line in the rat to an F2 generation was one of the earliest transgenerational developmental programming phenotypes reported [30]. A suggested potential mechanism may be through early reprogramming of oocyte mitochondria [31] which are derived exclusively via the maternal line in mammalian species [32]. While studies have presented evidence demonstrating the impacts of multigenerational familial patterns of adult obesity on the development of childhood overweight/obesity [33, 34], they do not differentiate between behaviors, genetics or environmental impacts. Interestingly, Davis et al. [34] reported that childhood overweight was associated with grandparental obesity whether or not parents were overweight, suggesting multigenerational programming effects.

As previously discussed, human epidemiological studies investigating the transmission of maternal obesity to subsequent generations are largely observational in nature and thus poorly controlled, therefore providing little information on the mechanisms involved. It is well controlled and relevant animal models that will help elucidate whether physiological or epigenetic programming is involved. The remainder of this paper will focus on what is known about the multigenerational impacts of maternal obesity on offspring (F1 and F2 generations), as little evidence has been presented to date for transgenerational epigenetic inheritance.

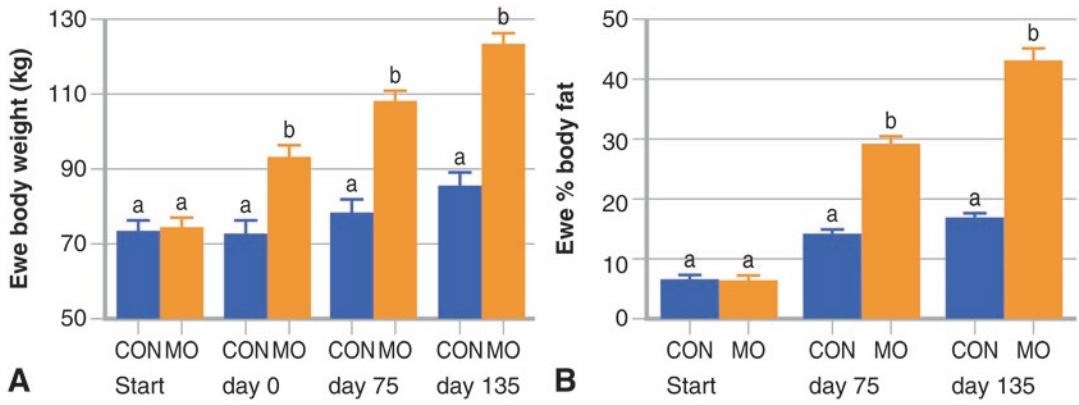

Fig. 14.1 Ewe body weight (**a**) and % body fat (**b**) for control (CON) and obese (MO) groups at different time points of gestation. (**a**, **b**) Means ± SEM between treatment groups within a time point differ ($P < 0.01$) (Adapted with permission from Ref. [46])

Animal Models of Maternal Obesity

Effects of maternal obesity in the offspring have been evaluated in several animal species, with rodents, sheep and nonhuman primates (NHP) being the most cited. Further, chronic long term MO studies have almost exclusively been conducted in rodents [35]. In rodent studies, obesogenic diets are imposed on dams either through feeding of high fat/energy diets (HFD) or allowing dams to choose among obesogenic food items often referred to as 'cafeteria' diets. High fat/energy diets have fixed ratios of nutrients hence animals can only regulate how much is consumed, whereas cafeteria diets permit active adjustment of energy intake thereby allowing animals to potentially stay closer to their nutritional optimum by balancing nutrient ratios depending on the compositional range of food components [36]. Similarly in NHP, obesity is induced nutritionally through high fat diets or by overfeeding highly palatable diets as in rodents [37–39]. In ovine studies carried out by our group at the University of Wyoming, highly palatable pelleted feed has been fed at 150% of National Research Council (NRC) requirements for adult pregnant sheep. Our feeding regimen begins 60 days prior to breeding and continues to term, resulting in the MO animals becoming overweight/obese by conception and to progressively develop to severe obesity by the end of gestation [40, 41], (Fig. 14.1).

Offspring Obesity Studies in Animal Models

Obesity develops as a result of the imbalance between energy intake and energy expenditure. In rodents, maternal cafeteria or high fat diets (HFD) during gestation induced obesity in adult offspring despite offspring being raised on standard chow during postnatal development [42, 43] and this offspring obesity was independent of maternal preconception diet [44].

Studies in sheep models provide data that parallels those in the rodent model. Further, we have reported that these metabolic sequelae are initiated by a proinflammatory milieu in the placenta creating an inflammatory environment for the fetus [45]. Our own previously published work has shown that maternal obesity at conception and throughout gestation increased adiposity of late gestation fetuses [46] and neonatal lambs [40], (Fig. 14.2). Of interest, offspring born to these obese ewes exhibited no phenotypic differences from offspring born to ewes fed only to requirements from weaning

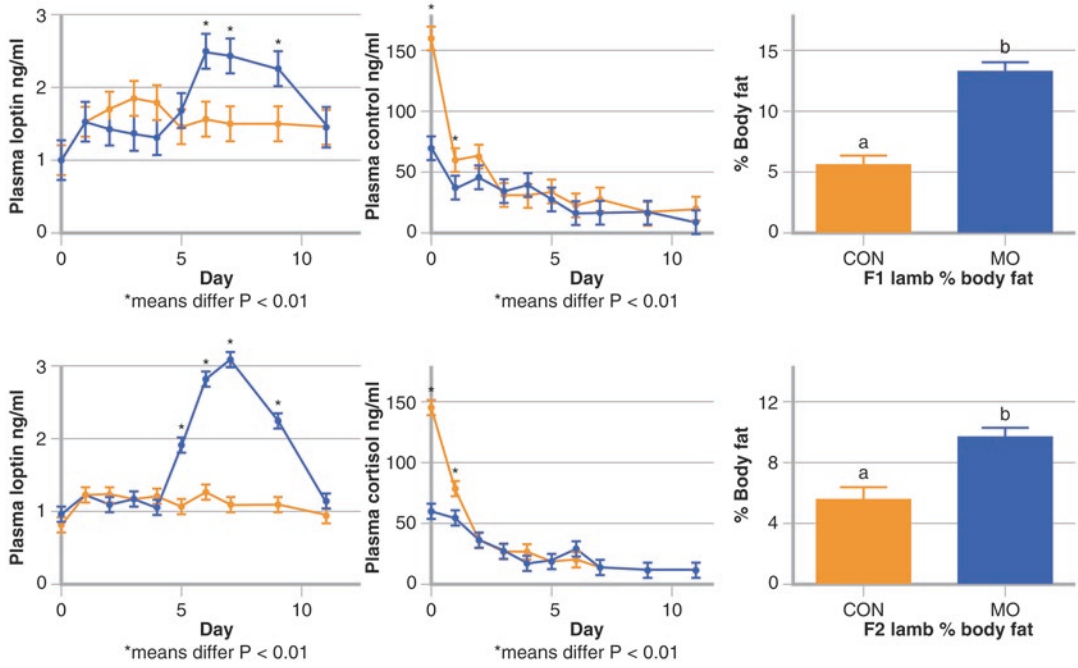

Fig. 14.2 Plasma leptin, cortisol, and % body fat in the early postnatal period in F1 (*top row*) and F2 (*bottom row*) lambs from control (CON, *open symbols*) and obese (MO, *closed symbols*) mothers and grandmothers respectively. (**a**, **b**) Means ± SEM differ ($P < 0.01$) (Adapted with permission from Refs. [55, 58])

to adulthood. When subjected to ad libitum feeding as adults, however, offspring from obese mothers exhibited macrophagia, as well as increased body weight gain and adiposity compared to offspring of control fed mothers [41, 47].

In NHP, McCurdy et al. [37] observed a twofold increase in body fat accumulation in HFD fetuses compared to fetuses gestated by control fed mothers by day 130G of gestation (gestation length = 180 days). Further, offspring of HFD mothers maintained this increased adiposity into the postnatal period and also developed early-onset obesity independent of postnatal diet [48]. This increased risk of obesity in the offspring of HFD mothers was linked to a reduction in central dopamine signaling [49]. Indeed, decreased abundance of dopamine fiber projections to the prefrontal cortex as well as decreased dopamine receptor expression have been observed in the offspring of HFD dams indicative of impairments to the development of the dopamine system [49].

Offspring Insulin Resistance

Several animal studies have demonstrated that maternal overnutrition/obesity perturbs the development of the fetal pancreas resulting in hyperinsulinemia, impaired glucose sensing and β-cell dysfunction. In rodents insulin resistance expressed as the ratio of insulin: glucose was markedly increased by a maternal HFD during gestation in neonates, weanlings and adult offspring [50, 51]. Even mild maternal overnutrition has been shown to induce glucose intolerance [52] and hyperinsulinemia independent of the level of obesity before pregnancy [44]. Further, offspring of HFD mothers exhibited reduced glucose tolerance at weaning following either an oral glucose bolus [35] or an intra-peritoneal glucose bolus [53].

In sheep studies, maternal overnutrition/obesity resulted in glucose/insulin dysregulation in mid- and late gestation fetuses and neonatal lambs [46, 54]. Further, the dysregulation of glucose control has been observed to persist into adulthood in F1 offspring of obese dams and F2 neonates of obese grand dams [55]. This dysregulation is attributed to accelerated pancreatic growth and β-cell development as observed in first half of gestation, followed by a reduction in pancreatic growth and insulin secretory capacity demonstrating the failure of the pancreas to return to normal cellular composition and function postnatally [40, 54].

Very limited data exists on diet-induced insulin resistance in NHP offspring. A recent study demonstrated that offspring born to dams fed high-fat/calorie diets during pregnancy displayed increased plasma insulin levels and glucose-stimulated insulin secretion compared to those of control-fed dams at 13 months of age [56]. An earlier study utilizing the same model observed an early activation of gluconeogenic genes in fetal liver of HFD dams and hypothesized that this might predispose the offspring to increased hepatic gluconeogenesis and insulin resistance [37].

Impact of Maternal Obesity on Offspring Blood Metabolites and Hormones

It is well recognized that maternal obesity during gestation markedly influences the metabolite and hormonal milieu in the developing fetus thereby potentially increasing the risk of metabolic disease later in life. Notable metabolites impacted by maternal obesity include glucose and lipids whereas cortisol, insulin, and leptin are some of the widely investigated hormones in most animal models of maternal obesity. In the rat model, when the maternal cafeteria diet was fed throughout lactation and gestation, there was a sexually dimorphic pattern of glucose and insulin secretion, with male offspring displaying normal glycaemia and hyperinsulinemia and female offspring exhibiting hyperglycemia, but normal insulin levels [57]. Sex differences were, however, not apparent for serum lipid levels with triglycerides and cholesterol being elevated in both males and females from the cafeteria fed dams. In the same study, leptin gene expression in perirenal fat pads of female offspring was greater compared to male offspring. In another study, Howie et al. [44] reported that offspring of high fat fed dams exhibited lower plasma insulin and leptin concentrations at postnatal day 2 compared to those from control-fed dams, however, these patterns were later reversed in adulthood (postnatal day 160). Plasma glucose was also higher in adult male offspring from HFD dams but not in female offspring [44].

In our sheep model, overfed/obese mothers exhibited hyperglycemia and hyperinsulinemia, as well as a markedly elevated insulin resistance as measured by a midgestation intravenous glucose tolerance test (Fig. 14.3). Fetuses gestated by these obese dams have elevated plasma levels of glucose, insulin, cortisol, triglycerides and cholesterol at mid-gestation and late-gestation [45, 46]. Further, neonatal offspring of obese ewes had increased plasma cortisol and insulin at birth and lacked the early postnatal leptin spike necessary for setting up hypothalamic appetite control centers and leading to hyperphagia and leptin resistance in adulthood [41, 58], (Fig. 14.2). Further, adult F1 offspring from obese ewes had higher baseline plasma glucose and insulin as well as higher concentrations of plasma leptin following a 12-week ad libitum feeding trial than F1offspring from control fed lean ewes [41]. Interestingly, adult F1 ewes from obese dams exhibited hyperglycemia, hyperinsulinemia and marked insulin resistance like their overfed/obese mothers during their subsequent pregnancies despite being fed only to requirements during gestation [55], (Fig. 14.4). As a result, their F2 lambs exhibited elevated plasma glucose, insulin and cortisol at birth and also lacked the postnatal leptin peak exhibited by F2 lambs born to control fed F1 ewes indicating a probable multigenerational programming effect [55], (Fig. 14.2).

Chronic high-fat diets in a primate model resulted in increased serum levels of total triglycerides and glycerol but no change in leptin, insulin or free fatty acids in third-trimester fetuses of high-fat diet dams [37]. Thorn et al. [39] did not find any changes in fasting plasma glucose, glycerol,

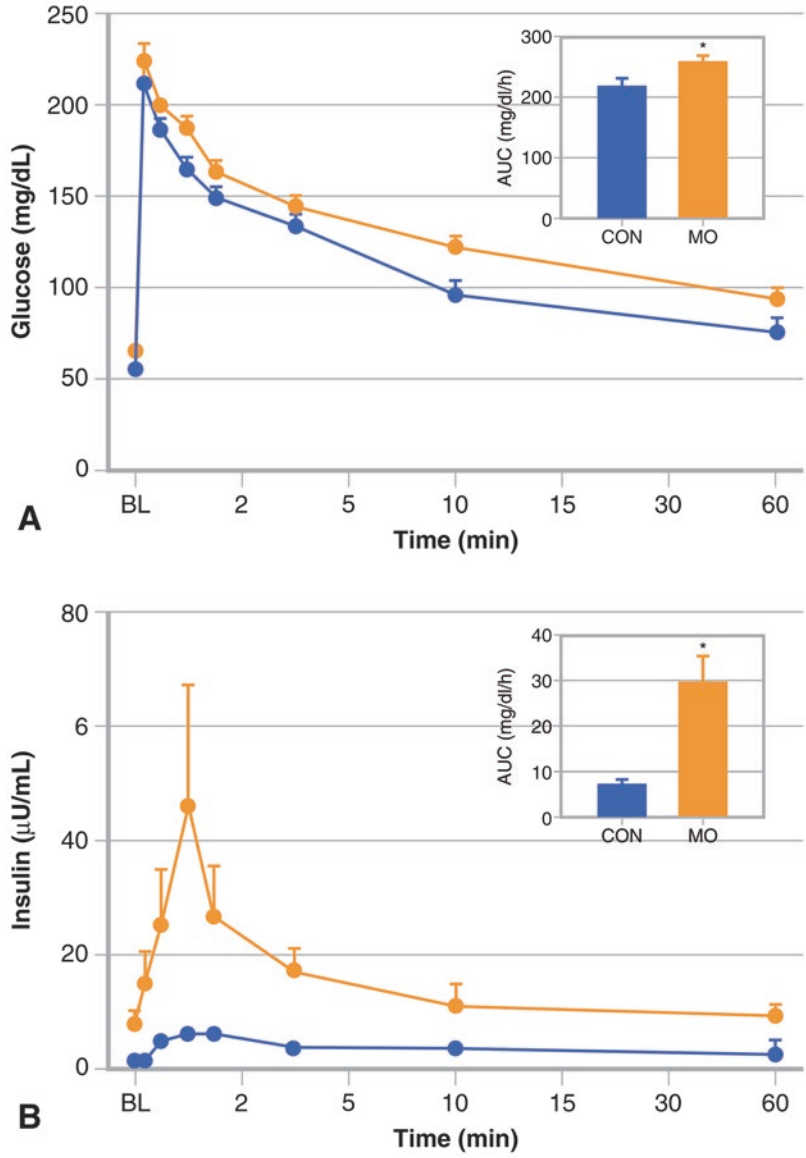

Fig. 14.3 Glucose (**a**) and insulin (**b**) concentrations prior to and after glucose bolus infusion (0.25 g/kg of 50% dextrose solution) during an intravenous glucose tolerance test on 75 days of gestation in F0 ewes fed 100% (control (CON), ○; $n = 6$) or 150% (obese group (MO), ●; $n = 6$) of NRC recommendations from 60 days before conception to day 75 of gestation. (**a**) Glucose concentrations; (**b**): insulin concentrations. Area under curve (AUC) is shown as insets. *Means ± SE differ ($P < 0.05$) (Adapted with permission from Ref. [40])

triglycerides and non-esterified fatty acid concentrations in juvenile offspring of HFD mothers despite of presence of insulin resistance and increased hepatic lipid accumulation in the offspring. In another study, elevated cortisol levels were reported in offspring of HFD mothers without any changes in circulating ACTH levels [48]. Dietary challenge in vervet monkeys (*Chlorocebus aethiops sabaeus*) using high fat diets, however, resulted in increased blood levels of glucose, fructosamine, insulin, triglycerides and cholesterol. Heritability's for these traits in subsequent generations were significant except for blood glucose elevation [59].

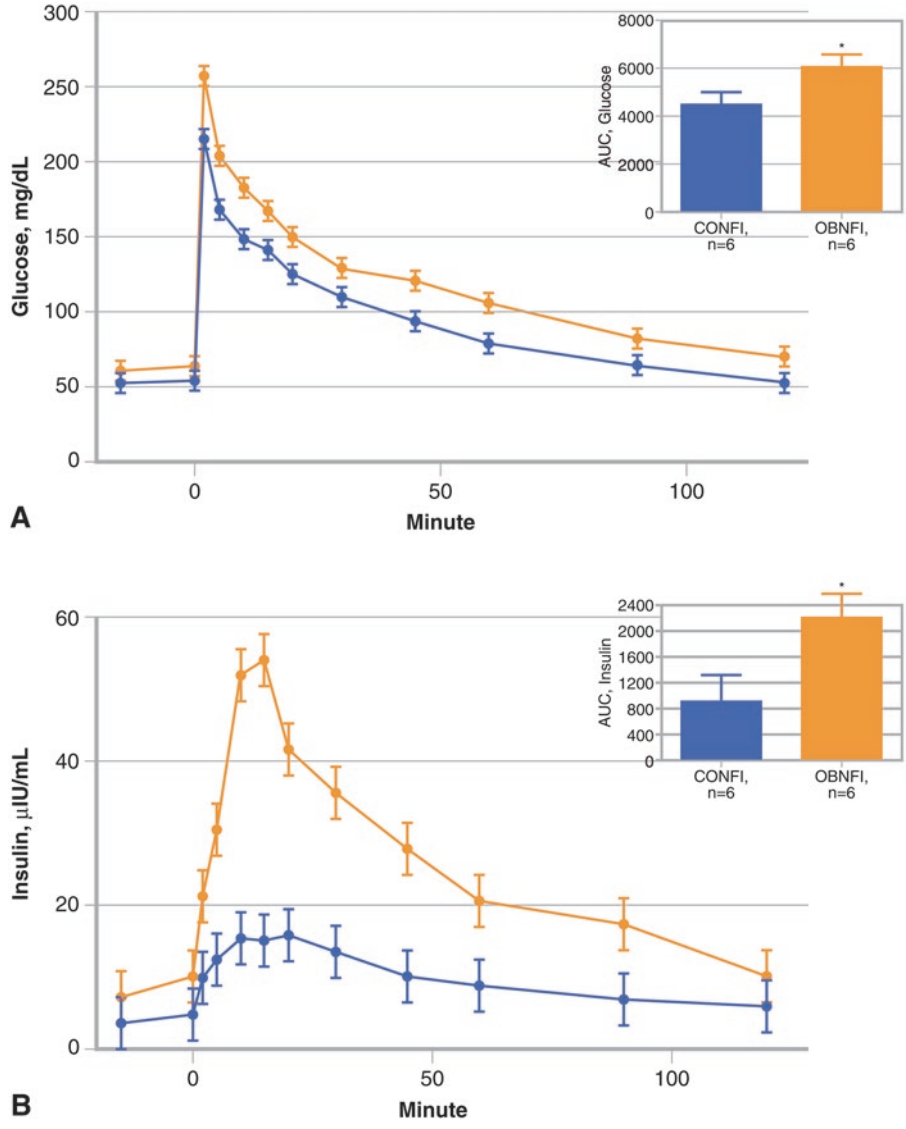

Fig. 14.4 Glucose (**a**) and insulin (**b**) concentrations prior to and after glucose bolus infusion (0.25 g/kg of 50% dextrose solution) during an intravenous glucose tolerance test at day 135 of gestation in female offspring born to obese (OBF1: ●) or control (CONF1: ○) dams, and fed at only 100% NRC recommendations throughout gestation. Area under the curve (AUC) is located in the top right corner of each panel. *Means ± SEM differ ($P < 0.05$) (Adapted with permission from Ref. [55])

Impact of Maternal Obesity on Tissue and Organ Structure and Function

The previous section has highlighted biochemical and hormonal phenotypes associated with maternal overnutrition/obesity in prenatal and postnatal offspring. Most of the changes were apparent during fetal development. Therefore, a crucial unanswered question remaining is whether these changes in the fetal stage will persist into postnatal life and further on into adulthood and consequently impact long-term disease risk.

The long-term consequences on the adult progeny due to consumption of a HFD diet by female rats include impaired glucose homeostasis, cardiovascular dysfunction, and alterations in hypothalamic energy circuitry and liver lipid metabolism. Bayol et al. [57] demonstrated that maternal cafeteria diet during gestation and lactation resulted in increased transcriptional activity in perirenal fat pads leading to greater adipose tissue mass in the female offspring than in males. Further, hepatic steatosis, hepatocyte ballooning and oxidative stress response was observed on offspring of rat dams on the cafeteria diet throughout pregnancy and maintained on the cafeteria diet after weaning. These changes were apparent in offspring of cafeteria diet fed mothers returned to a balanced chow diet after weaning indicating irreversibility of these pathologies once they occur [60]. Offspring of rats exposed to high fat feeding during gestation exhibit pancreatic β-cell hypertrophy early in life leading to an increase in glucose stimulated insulin secretion [51]. However, later in adult life these offspring exhibit declining functional β-cell mass and/or β-cell exhaustion leading to reduction in glucose stimulated insulin secretion. Gender-related cardiovascular dysfunction has also been reported on adult offspring of rats fed diets rich in lard during pregnancy despite being raised on normal chow after weaning, with an elevation of blood pressure (both systolic and diastolic blood pressures) being confined only to female offspring [42, 61]. These female specific effects could be due to glucocorticoid effects of the hypothalamic-pituitary-adrenal (HPA) axis. Indeed, permanent female specific offspring alteration in the HPA axis has been observed in pregnant rats exposed to glucocorticoid excess [61].

In our sheep model of maternal obesity we have also reported similar offspring effects to that observed in the rodent studies. Dysregulation in glucose/insulin dynamics during gestation is linked to pancreatic β-cell hyperplasia at mid-gestation and a decrease in β-cell number due to increased apoptosis in late-gestation (Fig. 14.5) and leading to insulin resistance later in life [40, 54]. In the liver, we have observed upregulation of genes associated with lipogenesis [62], as wells as increased expression of 11β-hydroxysteroid dehydrogenase type 1 (11ß-HSD1) and its cofactor hexose-6-phosphate dehydrogenase (H6PDH), these enzymes are responsible for tissue regulation of cortisol metabolism (Tuersunjiang et al., unpublished observations). Cardiovascular effects reported in our studies included left ventricular hypertrophy [46], fibrosis in myocardium of sheep [63, 64] and decreased insulin signaling pathways leading to insulin resistance and cardiac dysfunction [65]. Insulin signaling was also impaired in skeletal muscles of offspring of obese ewes leading to increased adiposity and fibrosis [63, 66]. Further, maternal obesity induced inflammation was also demonstrated in fetal skeletal muscles in late gestation [66]. During myopathy, inflammation is known to induce expression of cytokines which in turn induces connective tissue expansion necessary for muscle regeneration [63]. Because muscle regeneration involves processes similar to fetal muscle development, it is plausible to suggest that inflammation might alter the normal progression of regenerative events leading to adipogenesis and fibrogenesis in fetal muscle.

In primate studies, fetal offspring of HFD mothers have been shown to exhibit liver related pathologies including nonalcoholic fatty liver disease (NAFLD), hepatic inflammation, oxidative stress and/or damage, triglyceride accumulation and premature gluconeogenic gene expression [37]. Further, the increased risk for fetal NAFLD persisted in the postnatal period predisposing the adult offspring to similar effects even after switching the offspring to a healthy diet after weaning [39]. This fatty liver risk persisted despite the absence of maternal obesity or diabetes [37] or postnatal obesity, insulin resistance, or systemic or local adipose tissue inflammation [39]. Therefore, one can speculate that NAFLD phenotype is due to direct transfer of maternal lipids to the fetus and that this risk might not be reversed by postnatal diet. It is plausible to speculate that the potential adverse effects of excess lipids on the fetal liver during development relates to lack of white adipose tissue (WAT) during critical periods of exposure. Indeed, it is well accepted that WAT is critical for storage of excess lipids and that lack of WAT results in whole body insulin resistance and susceptibility to fatty liver. In most species, WAT develops relatively late in pregnancy [67], therefore, it is plausible that the adverse effects of excess lipids on fetal development may be due to lack of WAT at critical periods of exposure.

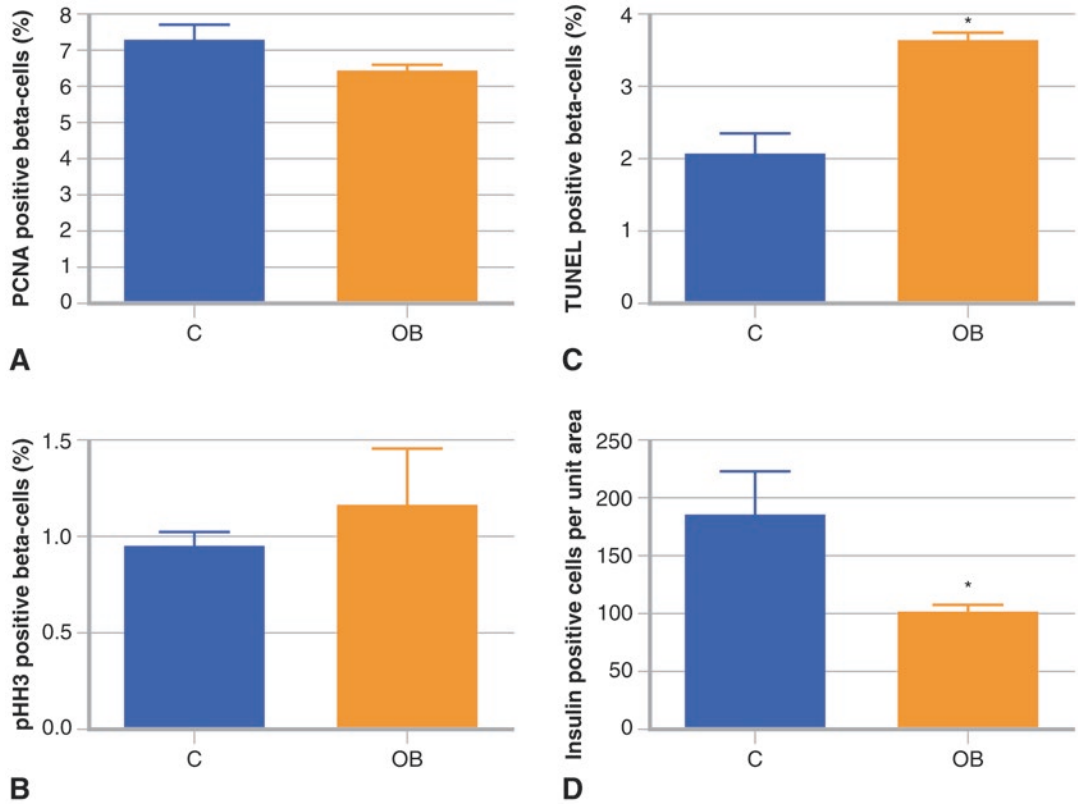

Fig. 14.5 Percentage of fetal pancreatic β-cells proliferating (*panels A* and *B*) and undergoing apoptosis (*panel C*), and insulin positive cells per unit area (mm^2) (*panel D*), in fetal pancreatic islet tissue from Control (CON) and Obese (OB) ewes on day 135 of gestation. *Means ± SEM differ between treatment groups ($P < 0.05$) (Adapted with permission from Ref. [54])

Increased myocardial fibrosis was observed in fetal hearts of baboons fed a HFD diet during pregnancy [38]. The authors attributed this to upregulation of cardiac miRNAs involved in enhancing fibrosis and down regulation of miRNAs responsive for normal cardiac development. Proinflammatory conditions in the developing fetus of HFD mothers can have significant effects in brain development and function. For example, the hypothalamic melanocortin system in third trimester offspring was altered by chronic exposure to HFD in Japanese macaques [48]. The melanocortin system is pivotal to regulation of energy homeostasis; therefore, perturbations to this system during critical periods of development could predispose the offspring to hyperphagia and obesity [48].

Conclusion

To our knowledge, our studies in the sheep are the only studies in a precocial large animal species that have attempted to mimic human clinical findings demonstrating that both maternal obesity prior to conception, and excessive weight gain during pregnancy have the greatest impact on increasing childhood obesity and metabolic dysregulation in their offspring. Table 14.1 depicts the impacts on our model of diet-induced pre-pregnancy maternal obesity followed by excess maternal weight gain on altering metabolic, hormonal, and organ and tissue changes of fetal, neonatal, and adult offspring. We have reported that alterations in fetal metabolism, and organ and tissue development and function,

Table 14.1 Comparison of fetal, neonatal and adult offspring characteristics of overfed-obese (MO) to ewes fed only to requirements

	MO offspring
Mid-gestation fetus	
Fetal weight	+
Crown rump length	+
Liver wt	+
Pancreatic â-cell numbers	+
Cardiac ventricular wt/fetal wt	+
Adiposity	+
Plasma glucose	+
Plasma insulin	+
Plasma cortisol	+
Plasma cholesterol	+
Plasma triglycerides	+
Late-gestation fetus	
Fetal wt	*ND*
Crown rump length	*ND*
Liver wt	*ND*
Pancreatic â-cell numbers	−
Cardiac ventricular wt./fetal wt	+
Adiposity	+
Plasma glucose	+
Plasma insulin	+
Plasma cortisol	+
Plasma cholesterol	+
Plasma triglycerides	+
Newborn lambs unsuckled	
Birth wt	*ND*
Crown rump length	*ND*
Plasma glucose	+
Plasma insulin	+
Plasma cortisol	+
Plasma leptin	−
Adult offspring	
Appetite	+
Plasma glucose to ad. lib. feeding	+
Plasma insulin to ad. lib. feeding	−
Plasma leptin	+
Wt. gain to ad. lib. feeding	+
Adiposity to ad. lib. feeding	+
Left ventricular wall thickness	+

From Refs. [40, 41, 45–47, 54, 55, 58, 62–66]
"+" indicates an increase ($P < 0.05$) and "−" indicates a decrease ($P < 0.05$) relative to controls, while *ND* indicates no difference

are associated with a proinflammatory milieu in the placenta creating an inflammatory environment for the fetus. This proinflammatory condition in the developing fetus leads to systemic effects on the brain, liver, heart, pancreas, adipose tissue, and skeletal muscles resulting in metabolic dysregulation in the postnatal offspring of overfed obese ewes. Outside of our studies, most chronic biomedical studies have been conducted in rodents, an altricial species quite different from the human.

There is a pressing need for additional data from models that extrapolate more directly to clinical human obesity. There are differences in many physiological systems between precocial (sheep, NHP, and humans) and altricial (rodents) species, especially in development, duration of gestation and offspring maturity at birth. For example, rats are polytocous and products of conception have a large biomass. A rat with 16 pups nurtures a biomass of nearly 100 g, equivalent to the weight adjusted nutritional challenge to a pregnant woman nurturing a 30 kg baby. These differences are important when it comes to translating metabolic and growth data obtained in rat pregnancy to precocial species including humans. The stage of organ development at birth is another important difference between sheep and NHP versus rodents used in programming studies – i.e., the developmental stage at which fetuses are exposed to air/nutrients, microbiome changes via the gut and other sources, and the stage of development at which placental support is removed. Each species has strengths, however, and addresses different developmental trajectories. Animals provide readily controllable experimental models, while even the best human case control studies can only provide evidence of associations. Specifically, animal studies (1) permit access to fresh fetal and maternal tissues, (2) allow better control of dependent variables, (3) provide clear answers more rapidly and (4) allow a greater burden of investigation on individual mothers and offspring than tolerated by humans.

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