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Interventions designed to prevent adverse programming outcomes resulting from exposure to maternal obesity during development

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Abstract

Maternal obesity is a global epidemic affecting the developed and developing world. Human and animal studies indicate that maternal obesity programs development predisposing offspring to later-life chronic diseases. Several mechanisms act together to produce these adverse health problems. There is a need for effective interventions that prevent these outcomes and guide management in human pregnancy. We report here dietary and exercise intervention studies in both altricial and precocial species, rats and sheep, designed to prevent adverse offspring outcomes. Both interventions present exciting opportunities to at least in part prevent adverse metabolic and other outcomes in mother and offspring.

INTRODUCTION

Worldwide nearly 1.5 billion people are overweight (body mass index – BMI - greater than 25 kg/m²) or obese (BMI greater than 30 kg/m²) ¹. Almost every country is affected: Mexico, 32% of women of reproductive years are obese ^{2, 3}; USA, 35% of women of reproductive years are obese ⁴; Brazil 50% of the population is overweight or obese ^{5, 6}; United Kingdom 33% of pregnant women are overweight or obese ⁷; India 26% of women of reproductive years are overweight and 8% obese ⁸; China 16% of women are overweight or obese ⁹; Ghana 64.7% of women are either overweight or obese¹⁰. The WHO (www.who.int/nut/obs.htm) has declared obesity one of the top ten adverse health risk conditions in the world and one of the top five in developed nations.

As pointed out in our previous review “Animal Studies that Reveal Mechanisms of Programming of Offspring Outcomes of Maternal Obesity”, maternal obesity programs

offspring predisposition to a wide variety of chronic, later-life diseases. A better understanding of developmental programming requires integration of factors involved in challenges, mechanisms and outcomes involved. Reports of experimental interventions in animal models in the setting of obesity are scarce ^{11, 12}. Using nutritional or targeted therapeutic interventions during windows of developmental programming studies in some experimental animal models have shown potential reversibility of unwanted offspring metabolic outcomes ¹². For example, leptin treatment of neonatal female rats born to undernourished mothers prevents development of metabolic compromise in adulthood ¹³; maternal antioxidant supplementation in rats fed with the Western diet partially prevents offspring adiposity and normalizes glucose tolerance ¹⁴. In other studies it has been shown that genistein supplementation in mice during gestation protects offspring susceptibility to obesity ¹⁵. This chapter will focus on animal studies designed to illuminate mechanisms by which interventions involving a change in maternal diet or level of exercise may act to improve maternal and offspring outcomes.

There are many reasons why animal intervention studies are needed. Importantly, animal studies are much more controllable than human clinical interventions which is the parallel human approach to hypothesis driven animal research. In addition a greater depth of mechanistic interrogation is possible resulting from tissue retrieval and multiple testing in animal studies and results are obtained much more quickly to guide management in human pregnancy. Reproducibility and independent confirmation, the indispensable requirements of scientific certainty, are also generally easier to achieve in animal studies. Carefully designed clinical trials to determine effects of interventions and improve maternal health in pregnancy and offspring outcomes are now in progress ¹⁶. However, in addition to the length of time needed to obtain the required data, clinical trials have to contend with multiple confounds related to the mother's socioeconomic status and pre-pregnancy health that not only make their analysis and interpretation difficult but also may limit their usefulness in determining mechanisms. There is a pressing need, as the recent IOM report indicates ¹⁷, for the development of evidence-based interventions that inform and motivate pregnant women to adopt a healthy lifestyle before and during pregnancy. Currently there is much interest in both maternal diet and exercise as potentially modifiable factors to use as interventions ¹⁸⁻²⁰. The optimal timing and extent to which adverse effects of the maternal metabolic phenotype resulting from maternal obesity and associated high calorie diets can be prevented and/or possibly reversed by these interventions remain unanswered questions of considerable physiological interest and importance in clinical obstetric management. Most authorities believe that interventions introduced before conception will have the best results. It should always be born in mind that poor maternal nutrition also programs adverse offspring outcomes ²¹⁻²³ and sudden and excessive restriction of maternal and fetal nutrient availability may well introduce new dangers. Thus firm scientific data are needed to guide interventions.

When considering the goals of specific interventions to beneficially impact developmental programming outcomes, a distinction must always be made between interventions designed to prevent negative offspring outcomes and interventions conducted at later stages of an offspring's life to reverse adverse health outcomes. Clearly prevention is a better strategy

than to try to reverse problems. The present review focuses on maternal intervention to prevent negative offspring outcomes by maternal obesity.

STUDIES ON PRE-PREGNANCY DIETARY INTERVENTION IN THE OBESE RAT

Investigation of programming of offspring by maternal obesity requires that investigators ensure initial phenotypic homogeneity of the different groups of mothers studied - controls, obese mothers and mothers in which interventions are introduced. Care is necessary to achieve this important goal when females who will be the study mothers are purchased from commercial vendors without information on their background. Specific information should be obtained as to the lineage of all females to avoid inclusion of sibling females in the same sub-group. To avoid this and related problems we maintain our own colony of non-pregnant females which are bred to deliver the female pups that will be recruited as the mothers in our studies. All rats are maintained on the same laboratory chow unless exposed to an experimental diet ²⁴. At delivery (postnatal day – PND- 0) litters are culled to 10 pups, each litter containing at least four female pups. This standardization is important since programming effects have been shown in offspring according to different litter sizes reared by mothers during lactation ²⁵.

At weaning (PND 21) female offspring are randomly assigned to either a control (C) group fed normal laboratory chow or to a maternal obesity group (MO) fed a high-energy, obesogenic diet containing 23.5% protein, 20% animal lard, 5% fat, 20.2% polysaccharide, 20.2% simple sugars, 5% fiber, 5% mineral mix, 1% vitamin mix (w/w), energy 4.9 Kcal/g. Only one female from any one litter is assigned to any study group. At PND 90, one month before breeding, half of the obese females are selected at random for the dietary intervention (DINT) group and placed back on the C diet for the rest of the study including pregnancy and lactation. The remaining obese females continue on the high fat diet during pregnancy and lactation. We have chosen to breed females at 120 days as we have shown that at younger breeding ages the mothers are still growing – albeit not as fast as earlier in life - and offspring outcomes of key factors such as growth, triglycerides and leptin are affected by maternal age as well as the nutritional challenge (unpublished data). At PND 120 all three groups C, MO and DINT are bred and fed their pre-pregnancy diet throughout pregnancy and lactation. All mothers deliver by spontaneous vaginal delivery. Day of delivery is considered as post natal day 0 ^{24, 26} (Figure 1).

Changes in maternal and offspring phenotypes resulting from MO and DINT

At breeding MO females were 16% heavier than controls, equivalent to a pregnant women increasing her BMI from 25 (the top of the normal BMI range) to 30.5 (the lower end of the obese range). DINT females were 9 percent heavier than controls (equivalent to BMI in the mid-overweight range) at breeding. Maternal serum leptin at the end of lactation was higher in MO than C. Leptin levels in the DINT group were similar to controls ²⁷.

The effects of MO and DINT have only been reported in male offspring ²⁷. No differences in body weight were seen between pups at birth and at weaning. At weaning MO offspring

had more subcutaneous fat tissue, and higher serum triglycerides and leptin than C offspring – showing dysregulation of lipid metabolism; pre-pregnancy maternal dietary intervention prevented these increases offspring measures. This important finding shows the limitations of weight alone at any age as an assessment of outcomes. Body composition is much more important in predicting future offspring health. Serum glucose did not differ between the three offspring groups, but offspring serum insulin was elevated in MO and returned to C levels in DINT offspring indicating the presence of insulin resistance in MO offspring ²⁷.

At PND 120, male MO offspring had elevated resting serum glucose and insulin and increased insulin resistance compared with C offspring. Insulin remained elevated in DINT compared with C offspring while blood glucose did not differ from either of the two other groups ²⁷. It is important to note that all offspring were on the same post-weaning diet. Thus there was no opportunity for effects of an increase in offspring dietary intake acting as a “second hit” on the background of developmental programming that had already occurred.

STUDIES ON PRE-PREGNANCY EXERCISE INTERVENTION IN THE OBESE RAT

We have recently completed a study of effects of an exercise intervention on mother and offspring of obese and control rats. General management of the pregnancies and lactation were as described above for the dietary intervention. At PND 90, one month before breeding, one half of the group of C non-pregnant females and half of the MO female groups were selected at random to continue on their diet and begin wheel-running exercise (C exercised – CEx; MO exercised - MOEx) (Figure 2). Mothers continued to be placed in the wheel through pregnancy. All females continued on their respective diets. CEx and MOEx rats were trained to wheel run on two separate days the week before they reach PND 90. A training session lasted 15 min which we established was the optimum running schedule that was always completed, followed by a 15 minute rest period and a second 15 minute run. Rats were allowed two days rest every seven days. Before pregnancy, all rats completed the 30 minutes running while during pregnancy rats were placed in the wheel for only one 15 minute session per day and the amount of voluntary exercise completed varied between animals especially in late gestation. During lactation mothers nursed their pups and did not exercise. Therefore, lactating mothers were maintained on their pregnancy diet and not placed in the wheel.

Changes in maternal phenotype and fertility resulting from maternal exercise prior to and during pregnancy

Calorie and food intake per day were similar in all four groups and exercise did not affect calorie or food intake in either group. Exercise had no effect on maternal weight at any stage except for the CEx group in which exercise decreased body weight in comparison with C at parturition. There were no differences between groups in average distance run per session before pregnancy or in the first 15 days of pregnancy but interestingly MO rats that were exercised ran further than control rats in the last few days of pregnancy. We hypothesize that this difference was a result of their lower circulating estrogen levels since a negative correlation has been shown to exist between estrogen levels and physical activity ²⁸.

As in the DINT study mentioned above, at the end of lactation maternal insulin, glucose, HOMA, leptin, triglycerides and cholesterol were all elevated in MO mothers. Exercise did not alter these variables in C mothers but prevented the changes in all these variables except leptin in MO.

Effect of maternal obesity and exercise on male offspring metabolism at postnatal day 36

We evaluated offspring outcomes since the goal of interventions in MO pregnancy is to improve both maternal and offspring outcomes. At offspring PND 36, one male offspring from each litter (n= 8) was chosen at random, fasted for 4 hours and euthanized by decapitation, trunk blood samples obtained and fat depots excised and weighed. Litter size, litter weight individual pup body weight or sex ratio at birth was not affected by either MO or exercise. In male offspring body weight, cholesterol and insulin were not different at PND 36 between the four groups. Maternal obesity increased offspring leptin, triglycerides and fat mass in males. Exercise in MO prevented the male offspring MO leptin increase and partially prevented the increased triglycerides. Maternal exercise in C reduced male offspring glucose and male HOMA. The importance of paying attention to the phenotype of study mothers is shown by the interesting observation that maternal exercise decreased weight and cholesterol in control offspring indicating that even animals recruited as controls may be affected by experimental protocols.

Maternal voluntary exercise intervention has been previously reported in lean pregnant rats in two different models. Male, but not female, offspring of exercised mothers show increased percent lean mass and decreased fat mass percent compared to male offspring from controls, showing that maternal exercise can affect offspring^{29, 30}. These effects on offspring metabolic phenotype show similarities to the effects with our present study in control mothers. In another study normal, lean, pregnant rats performed voluntary exercise^{31, 32} training from 42 days before pregnancy and continued on to day 19 of gestation with the result that maternal plasma antioxidant status was improved. Both of these studies provide important data for design of studies in obese mothers.

Comparison of DINT and Exercise models

One of the important differences between the DINT and the exercise intervention model is the maternal weight. In the DINT model²⁷ the increased maternal body weight of the DINT group at breeding was partially prevented, and there were no differences in maternal body weight during pregnancy and lactation between DINT and C. In contrast, maternal exercise intervention did not modify the maternal body weight at any stage. The weight of MOEx mothers was the same as MO before and during pregnancy as well as during lactation. However, for both models, mothers undertaking the intervention presented a better metabolic and hormonal maternal environment than MO with regards to offspring outcomes.

In a completely independent study we compared all groups with both interventions (maternal dietary and exercise interventions. Corticosterone was increased in serum of MO mothers prior to breeding. Maternal DINT and exercise intervention before pregnancy decreased maternal corticosterone concentration but MOEx values were not returned to those in C (Fig 3 A). A similar picture was seen at the end of lactation (Fig 3 B) and in the

neonate and young adult male offspring (Fig 3 C and D). These changes may be protective mechanisms of future metabolic problems in the offspring by MO.

Both maternal interventions improved the adverse offspring metabolism outcomes produced by MO, but the improvement was different in the two models. Maternal DINT partially prevents glucose, insulin, HOMA, fat and fat cell size, and completely prevents leptin increases offspring by MO. Maternal exercise intervention partially prevents fat and insulin and completely glucose, HOMA and fat cell size increase in offspring by MO.

For both models the data indicate that there were different changes in metabolism in various tissues since no differences in food intake and body weight were found in the young adult offspring. The two intervention models appear to benefit offspring metabolism in diverse ways suggesting dissimilar maternal mechanisms. Excessive gestational weight gain has been associated with adverse maternal pregnancy outcomes. Catalano has clearly indicated that maternal pre-pregnancy BMI is a major factor in determining maternal and offspring outcome³³. One important finding of the exercise intervention study was that the adverse offspring outcomes produced by MO are the result of maternal metabolic changes and/or in increased maternal corticosterone and not due to maternal body weight since MOEx prevented many of the MO offspring outcomes offspring without any change in maternal calorie intake or body weight. This finding again shows that outcomes are more related to body composition rather than body weight. The overwhelming evidence in favor of the importance of body composition clearly indicates that the most successful interventions will at least contain a component of intervention prior to pregnancy. Addition of interventions during pregnancy will further build on the interventions prior to pregnancy.

In our report of effects of maternal dietary intervention on offspring outcomes in the setting of obesity we wrote: *“There is a need to determine optimal timing, nature and extent of interventions. We have taken the view – as others have done - that the optimal time for recuperation would be prior to pregnancy and have sought to develop a model to show the ability and extent of the simplest of interventions, reducing global intake, to produce beneficial results. ... The available evidence indicates that women do not spontaneously alter their dietary patterns when they discover they are pregnant³⁴. Interventions in pregnancy, as in any other major health area, therefore need to be based on firm, reproducible scientific evidence”²⁷.*

Obese women contemplating pregnancy need to be provided with firm information as to the benefits that accrue from decreasing their BMI both before and during pregnancy for at least two reasons. First, they need to be aware of the biological reasons that maternal obesity is harmful to themselves and their baby in many ways. Secondly they need to be confident that appropriately lowering their BMI and food intake will provide significant benefit to themselves and their children.

Influence of interventions on offspring Aging

Maternal low protein diets accelerate aging in rat offspring³⁵. We have shown increased adiposity index, leptin, and triglycerides (TG) in male OFF of MO mothers in young adult life (postnatal day 110)²⁷ with no changes in body weight. However by 650 days MO results

in a more rapid aging of some metabolic indices such as body weight (Figure 4, 5 and 6), fat and adiposity index, increases which were prevented by maternal dietary and exercise intervention (Figure 4).

One good example of positive features of programming is seen in the offspring of CEx mothers which, at this early stage of aging (PND 650), had a better metabolic phenotype than the rest of the groups, including the control group.

STUDIES ON DIETARY INTERVENTION IN OBESE PREGNANT SHEEP

As discussed in our earlier review of developmental programming (“Animal Studies that Reveal Mechanisms of Programming of Offspring Outcomes of Maternal Obesity”), there are differences between pregnancy in altricial, polytocous mammals such as the rat, and precocial, monotocous species such as humans, sheep and nonhuman primates. The pregnant sheep has been extensively investigated to determine the impacts of decreased maternal nutrition but fewer studies have been conducted on effects of maternal overnutrition/obesity on fetuses and offspring in this important, precocial, experimental species³⁶⁻⁴⁴. Although there are differences in some capabilities – locomotion for example - both sheep and pregnant women produce well-developed, precocial offspring, exhibit similar newborn to maternal weight ratios, and temporal pattern of fetal tissue and organ development. Further, investigators worldwide have utilized the fetal sheep as a biomedical model to design studies on human pregnancy such as fetal behavior, heart rate and sleep states⁴⁵⁻⁴⁸.

Our studies on the impact of maternal overnutrition/obesity in the ewe on fetal growth and development and offspring health are conducted with animals from a well-characterized, closed flock at the Center for the Study of Fetal Programming, University of Wyoming. Ewes of similar, size and breeding are maintained in the source flock developed from lambs born within the flock whose mothers were fed National Research Council (NRC) feed requirements throughout pregnancy and lactation. The ewe lambs are then maintained on the same diet and are used as the mothers in all studies and are housed together and fed only to NRC requirements from weaning to maturity. This management policy provides assurance that animals have not been exposed to highly variable environments prior to any investigation and thus limits the chance of markedly different environmental (epigenetic) influences on study results, and other influences such as sibships within groups.

We have developed and characterized a model of maternal overnutrition/obesity (MO) where ewes are fed a highly palatable pelleted diet at 150% of requirements from 60 days before conception through pregnancy. On this diet, ewes become obese by the time they are bred and continue to gain additional weight throughout pregnancy and fetuses show a definitive endophenotype^{36-39, 43, 44, 49, 50}. Overweight and obesity at conception in pregnant women has been shown to have the greatest impact on increasing adiposity of infants at birth, leading to insulin resistance and exhibit obesity in later life. In our model of diet-induced MO, lambs are born with increased adiposity, and by 19 months of age they exhibit hyperphagia, glucose and insulin dysregulation and increased adiposity compared to offspring of ewes fed only to requirements³⁸. Previous studies in our laboratory demonstrated that maternal undernutrition (50% global undernutrition) starting at day 28 of

gestation resulted in delivery of offspring who exhibited metabolic disturbances (i.e. they were hyperphagic, insulin resistant, and were obese) as adults⁵¹. We therefore hypothesized that a dietary intervention in which the obesogenic diet is reduced from 150% to 100% of NRC requirements (MO intervention, MOI) beginning on day 28 of gestation would be early enough to at least in part prevent the negative impacts of maternal overnutrition/obesity on the fetus and resulting offspring. Further, day 28 in the sheep is equivalent to ~day 50 in human pregnancy, which is about the time when women confirm they are pregnant and early enough for their obstetrician to provide overweight/obese women with a corrective dietary regimen if deemed necessary.

MOI eliminated MO-induced fetal macrosomia at mid-gestation, and either reduced (right ventricular weight, liver weight) or prevented MO-induced increases in organ weight (left ventricular weight, total kidney weight, pancreatic weight, and total perirenal fat weight). At day 135, while fetal weight was similar between CON, MO and MOI fetuses, MO fetuses exhibited greater left ventricular weights and thicknesses, right ventricular thicknesses, total kidney weight, and total perirenal fat, and reduced pancreatic weight than CON fetuses. Weights and thicknesses of these organs and tissues were returned to CON levels in the MOI fetuses. The data provide the first indication that alterations in fetal organ and tissue growth as well as endocrine changes (see below) can at least in part, be prevented by early pregnancy MOI in the face of maternal obesity.

To date we have only evaluated the cortisol changes in the MOI model in order to observe any similarities with our findings in the obese rat model described above (Fig 3). MO increased both maternal and fetal cortisol at 0.9G and this increase was prevented by MOI at both ages. Similar results were obtained at 0.9G. Interestingly, while the maternal increases in cortisol were accompanied by increased ACTH, this was not so in the fetus where cortisol but not ACTH, was increased above CON in MO at both ages. We hypothesize two possible mechanisms for this finding. First, MO may change adrenal sensitivity to ACTH. The second hypothesis is that much of the fetal cortisol in the setting of maternal obesity is produced in peripheral fetal tissues by increased activity of 11BHS1, converting inactive cortisone to active cortisol. We have shown that the 11BHS1 system is up-regulated in fetal female perirenal fat and fetal male liver in the setting of maternal under-nutrition supporting a potential role for increased 11BHS1 activity in response to maternal dietary challenges⁵². Importantly, it remains to be seen to what extent inhibition of the increase in fetal cortisol will prevent adverse side effects of MO on offspring. These findings illustrate clearly the value of the combining studies in precocial and altricial species. We are currently evaluating CON, MO and MOI offspring to determine whether reducing maternal nutrition to recommended levels in early pregnancy of overnourished/obese ewes prevents endocrine and metabolic disturbances in offspring in adult life.

How do we get the message of the need for interventions to the general public? Lessons from the anti-smoking campaign

Improved women's health and especially the institution of effective corrective measures is vitally important to obtain the optimal obstetric outcomes in the face of the current epidemic of obesity in women of reproductive years. There may be lessons that can be learned from

the success in the developed world in decreasing the incidence of smoking. The anti-smoking campaign has met with considerable success in the developed world at least. This success suggests that even the strongest of compulsive behaviors can be modified when firm, incontrovertible information on benefit is provided. It has taken over 50 years since Sir Richard Bradford Doll demonstrated the connection between cigarette smoking and lung cancer⁵³. Changing this self-destructive behavior has taken decades but the decrease in smoking has saved thousands of lives. One of the most persuasive pieces of scientific evidence in the antismoking campaign was the demonstration in that while smoking from early adult life tripled mortality rates, giving up smoking at age 50 halved the risk and stopping at age 30 removed virtually all the risk. Human studies indicate that maternal pre-pregnancy BMI in women is a major determinant of adverse offspring metabolic outcomes resulting from maternal obesity⁵⁴. The parallel between smoking and the adverse effects of MO would be the suggestion from the evidence given here that life-style adjustment of life-style aimed at reducing obesity would have the potential to avoid the maternal and offspring hazards.

OVERALL CONCLUSIONS

There are epidemiological studies that shown that once a woman knows is pregnant, she does not modify her life style³⁴. Clearly the earlier the intervention the better the outcome. As the important IOM report and reviews by several clinical and basic science leaders indicate that studies such as those reported here are essential to the determination of mechanistic targets in the mother to develop predictive and clinical tools in human pregnancy⁵⁵. Other potential interventions remain to be investigated to permit evidence-based changes in clinical management. These include supplemented diets with polyunsaturated fatty acids or anti-oxidants. Different interventions to improve outcomes may act through different mechanisms. If so, a combination of approaches may lead to even better results for the mother and the offspring.

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Figure 1.

Time line of the dietary intervention studies in maternal obesity.

Figure 2.

Time line study of the exercise intervention studies in maternal obesity.

Figure 3.

Rat serum corticosterone levels: (A) maternal pre-pregnant, (B) maternal end of lactation (C) 2 days offspring male and female combined neonate and (D) 110 d young adult male. Mean $\pm$ SEM; n = 6. C control diet, MO maternal obesity, DINT maternal dietary intervention, MOEx maternal obesity exercise intervention; $p < 0.05$ for groups not sharing at least one letter.

Figure 4.

Rat male offspring (A) body weight (B) fat and (C) adiposity index at 650 days. Mean $\pm$ SEM; n = 6. C control diet, MO maternal obesity, DINT maternal dietary intervention, MOEx, maternal obesity exercise intervention; $p < 0.05$ for groups not sharing at least one letter.

Figure 5. Representative pictures of male offspring at postnatal day 650. C control diet, MO maternal obesity and DINT maternal dietary intervention.

Figure 6.

Representative pictures of male offspring at postnatal day 650. C control diet, CEx control diet + maternal exercise intervention, MO maternal obesity and MOEx maternal obesity + maternal exercise intervention.

Figure 7.

Sheep fetal A) ACTH and B) cortisol, and maternal C) ACTH and D) cortisol at 75 and 135 days gestation (0.5 and 0.9G; Term 150 days gestation). Control (CON - open), maternal obesity (MO - solid), maternal obesity dietary intervention (MOI - striped); Mean $\pm$ SEM; n = 6; p<0.05 ** vs CON and MO, * vs CON and MOI.