Obesity, diabetes, and links to congenital defects: A review of the evidence and recommendations for intervention

E. ALBERT REECE

University of Maryland School of Medicine, Baltimore, Maryland, USA

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Abstract
Objective. To review evidence on the link between obesity and diabetes in pregnant women and the incidence of birth defects. In addition, the article offers recommendations for facilitating the broader scale implementation of evidence-based approaches to preventing obesity, particularly among pregnant women.

Methods. A review of the evidence, primarily from epidemiologic studies, linking obesity and obesity-related metabolic disturbances in pregnant women to a range of birth defects. It also reviews potential mechanisms by which obesity and diabetes during pregnancy lead to damage in the developing embryo and highlights some evidence-based approaches to prevention. Finally it reviews policy options for positively impacting obesity and diabetes in this population.

Results. Obesity and diabetes are a growing problem in the US population. This problem is particularly acute among women of childbearing age because the combination of obesity and diabetes is toxic to the developing fetus, which each contributing independently to embryopathy.

Conclusions. There is an urgent need for a national strategy for combating the growing and related problems of obesity and diabetes in the population. This strategy needs to encompass a spectrum of tax breaks, economic incentives, legislation, and educational approaches in order to be effective.

Keywords: Obesity, diabetes, pregnancy, birth defects

Introduction
Infant mortality has declined in the United States in recent years. However, infant mortality attributable to birth defects has not declined as rapidly as overall infant mortality. Birth defects are the leading cause of infant mortality in this country [1], and there is growing evidence their rate is being inflated by the rising epidemic of obesity among women of childbearing age.

During the past 20 years there has been a dramatic increase in obesity rates in the United States. In 2006, only four states had a prevalence of obesity less than 20% (see Figure 1). The prevalence of obesity among women bearing children in the United States has skyrocketed as well. Between 18.5% to 38.3% of pregnant American women today are obese [2,3], that is, they have a body mass index (BMI) of 30 or higher.

This group of women has a significantly higher risk of developing diabetes than other women in the population [4], and the combination of obesity and diabetes represents a ‘double jeopardy’ for their offspring in terms of quality of life.

This article reviews the evidence, primarily from epidemiologic studies, linking obesity and obesity-related metabolic disturbances in pregnant women to a range of birth defects. It also reviews potential mechanisms by which obesity and diabetes affect metabolic changes that damage the developing embryo. Finally, it highlights some evidence-based policy options for positively impacting two national crises: obesity and infant mortality.

Obesity and birth defects
We have known for some time that obesity in women can cause serious pregnancy-related complications, such as hypertension, diabetes, and large birthweight babies. However, only recently has it emerged that maternal obesity is a significant contributor to birth defects as well.
Studies show that obese women and overweight women are at a much higher risk of having a child with a range of life-threatening birth defects compared to women of normal weight. Watkins et al. [5], for example, compared the risks of obese and overweight women (BMI 25.0–29.9) with average-weight women (BMI 18.5–24.9) for several selected major birth defects. They found that obese women were significantly more likely than average-weight women to have an infant with spina bifida (OR: 3.5, confidence interval [CI]: 1.2–10.3), heart defects (OR: 2.0, CI: 1.2–3.4), omphalocele (a birth defect in which the infant’s intestines protrude outside the abdomen at the umbilicus) (OR: 3.3, CI: 1.0–10.3), or multiple anomalies (OR: 2.0; CI: 1.0–3.8).

Overweight but non-obese women also were significantly more likely than average-weight women to give birth to infants with heart defects (OR: 2.0, CI: 1.2–3.1) and multiple anomalies (OR: 1.9; CI: 1.1–3.4).

This study confirmed previous epidemiological findings of associations between obesity and spina bifida [6]; anencephaly and neural tube defects [7–10]; and a variety of heart anomalies [5,6,11,12]. It also alerted healthcare and public health professionals that they needed to pay attention to not only providing pregnant women with adequate nutrition but also to monitoring their weight.

**Obesity and diabetes: Partners in crime**

More ominous for healthcare experts working to reduce birth defects and infant mortality rates is evidence that diabetes – a common complication of obesity – combines forces with obesity to cause birth defects through a shared pathway.

Anderson et al. [13] recently demonstrated that obesity and diabetes have an ’additive effect’ on the risk of congenital central nervous system defects. This study evaluated births of 477 mothers’ offspring with anencephaly (n = 120), spina bifida (n = 184), holoprosencephaly (n = 49), or isolated hydrocephaly (n = 124). Controls (n = 497) were mothers of live infants without abnormalities randomly selected from the same hospitals as cases. It also evaluated maternal obesity and risks for CNS birth defects as well as whether gestational diabetes influenced the risks.

After adjusting for maternal ethnicity, age, education, smoking, alcohol use, and periconceptional vitamin use, obese women still had a substantially increased risk of giving birth to a child with anencephaly (odds ratio = 2.3; 95%CI = 1.2–4.3), spina bifida (2.8; 1.7–4.5), or isolated hydrocephaly (2.7; 1.5–5.0), but not holoprosencephaly (1.4; 0.5–3.8). Their odds were even higher if they had gestational diabetes.

The finding of gestational diabetes being implicated in birth defects is controversial, however, because it does not typically appear until after the first trimester of pregnancy and would be too late to cause significant embryopathy. An alternate explanation for this result is that cases of gestational diabetes, particularly recurrent cases, linked to birth defects are actually cases of undiagnosed diabetes that was present prior to conception [14].

![Figure 1. Percent of obese (BMI ≥ 30) US adults in 2006. Centers for Disease Control and Prevention.](image-url)
More evidence for obesity and diabetes using a shared pathway to impact birth defects comes from an earlier study by Moore and coworkers [15], who conducted a prospective study of almost 23,000 pregnant women to evaluate the effects of maternal obesity and diabetes mellitus on the risk of nonchromosomal congenital defects. In the absence of diabetes, obese women (body mass index $\geq 28$) had no higher risk, overall, of having an offspring with a major defect (PR = 0.95; 95% CI = 0.62–1.5).

In contrast, pregnant women who were both obese and diabetic were 3.1 times as likely (95% CI = 1.2–7.6) to have a child with a birth defect than non-obese, non-diabetic women. Thus, there is evidence that these two factors act in concert to cause birth defect. Although obese women may or may not give birth to a child with an anomaly, their odds of doing so greatly increase when they also are diabetic.

Even elevated glucose and insulin can be damaging

Obese women need not have fully developed the clinical symptoms of diabetes to be at significantly increased risk of having a child with a birth defect. Chronically high levels of blood glucose, or hyperglycemia, may be sufficient to help trigger the development of birth defects.

Shaw et al. [16] investigated whether maternal periconceptional dietary intakes of sucrose, glucose, fructose, and foods with higher glycemic index values influenced the risk of having a child with a neural tube defect (NTD). They found the risk of having a child with a NTD was not substantially elevated in relation to periconceptional intakes of glucose or fructose. However, there was an elevated NTD risk for high sucrose intake irrespective of whether adjustment was made for other covariates such as maternal folic acid intake. For higher glycemic index values, the investigators observed adjusted elevated risks of birth defects greater than or equal to 4-fold in women whose body mass index was more than 29.

Thus, although obesity is an independent risk factor for birth defects, metabolic abnormalities associated with obesity, particularly hyperglycemia, significantly increase such risks. In fact, birth defects correlate very strongly with blood glucose levels (see Figure 2).

Too much insulin, or hyperinsulinemia, appears to be related to birth defects as well. Hendricks et al. [17], for example, found that both hyperinsulinemia and obesity were related to increased NTD risk [odds ratio (OR) = 1.91, 95% CI = 1.21–3.01 and OR = 1.73, 95% CI = 1.03–2.92, respectively] in a large group of Mexican-American women delivering or terminating pregnancies in hospitals or birthing centers in 14 Texas-Mexico border counties. Adjusting for obesity only slightly reduced the effect of hyperinsulinemia on NTD risk (OR = 1.75, 95% CI = 1.09–2.82).

Obesity, nutrition, and birth defects

Women who are obese also may have nutritional deficits resulting from poor-quality diets that may further increase their risk for giving birth to children with anomalies. Werler and coworkers [9] examined the relationship between prepregnant weight and the risk of NTDs among 604 fetuses or infants with an NTD identified within 6 months of delivery and 1658 fetuses or infants with other major malformations (controls).

Relative to women who weighed 50 to 59 kg, the risk of NTDs increased from 1.9 (95% CI, 1.2–2.9) for women weighing 80 to 89 kg to 4.0 (95% CI, 1.6–9.9) for women weighing 110 kg or more. When women were classified according to daily intake above or below the recommended level of 400 micrograms of folate, there was an estimated threefold increase in risk for the heaviest weights in both groups.

Taking 400 micrograms of folate per day reduced the risk of NTDs by 40% among women weighing less than 70 kg. However, among heavier women, no risk reduction was observed for that level of folic acid intake. Thus, the risk of NTDs increased with increasing prepregnant weight, independent of the effects of folate intake.

Maternal obesity and diabetes appear to increase the risk of central nervous system and other birth defects through shared causal mechanisms. When both are present, they may interact synergistically with the same mechanism. Although that mechanism is still speculative, the next section discusses a likely candidate.
A potential embryopathic pathway

As stated, the mechanism, or pathway, through which obesity and diabetes induce birth defects is still unknown. Research in this area is evolving. There is some experimental evidence, however, that oxidative stress plays a significant role in this process.

The oxidative stress model of diabetic embryopathy

Oxidative stress is a condition of increased oxidant production in cells characterized by the release of excess free radicals that result in cellular degeneration. Hyperglycemia appears to increase the levels of free radicals known as ‘highly reactive’ oxygen and nitrogen species. The overproduction of these molecules, in turn, sets off a cascade of events leading to cell suicide, or apoptosis.

Pampfer and coworkers [18], for example, incubated embryonic cells isolated from diabetic and normal rats with high concentrations of glucose and/or tumor necrosis factor-alpha (TNF-alpha) and demonstrated that high levels of both caused a corresponding increase in the activity of apoptotic pathways. Further, there was an increase in the expression level of clusterin, a gene closely associated with apoptosis.

In addition, Reece and colleagues [19] microscopically examined embryos from three groups of rats: (i) control rats on a normal diet, (ii) experimentally-induced diabetic rats with malformed offspring, and (iii) experimentally-induced diabetic rats with normal offspring. They also determined the activities of a number of cell signaling molecules in yolk sac cells from each group.

They found increased levels of several reactive oxygen molecules previously implicated in activating suicide pathways during hyperglycemia-induced embryopathy. They also found decreased activities of molecules instrumental in cell survival.

A follow-up study [20] found that the expression of the pro-apoptotic protein Bax is upregulated, and the activity of the cell-survival factor, Akt kinase, is decreased in yolk sac cells during hyperglycemia-induced embryopathy.

These observations suggest that hyperglycemia in obese diabetic women triggers the production of reactive species that cause oxidative stress. Oxidative stress somehow increases the levels of apoptosis-inducing signaling molecules while simultaneously decreasing the level of molecules that are protective of the cell (see Figure 3).

A look at prevention options

The growing evidence linking obesity and diabetes to birth defects suggests that a substantial percentage of birth defects (and infant mortality) is preventable. Fetal congenital malformations are most common when maternal glucose control has been poor during the first trimester of pregnancy. Given that many pregnancies are unplanned, the need for preconceptional glycemic control in diabetic women cannot be overstated.

However, once an obese diabetic woman becomes pregnant, prevention options become more limited. For example, putting already pregnant obese women on a weight loss program to prevent birth defects is not an option because low weight gain during pregnancy is associated with increased risks of complications [21].
Dieting during pregnancy appears to impact birth defects effects as well. For example, when Carmichael and coworkers [22] examined whether maternal dieting behaviors were associated with NTD risk among offspring, they found three dieting behaviors involving restricted food intake—diets to lose, fasting diets, and eating disorders—were associated with increased NTD risk during the first trimester of pregnancy.

Therefore, a more prudent approach to preventing birth defects in obese women who become pregnant may be to carefully monitor additional weight gain during pregnancy. This is the approach recommended by the Institute of Medicine (IOM), which in 1990 issued guidelines that gestational weight gain goals be modified according to pre-pregnancy body mass index to produce better maternal and infant outcomes [23] (see Table I).

Some have argued that the IOM's recommendations might actually increase the risk of negative consequences to both infants and mothers. However, Abrams et al. [24] systematically reviewed studies that examined fetal and maternal outcomes according to the IOM's weight-gain recommendations in women with a normal prepregnancy weight. Their analysis found that pregnancy weight gain within the IOM's recommended ranges was associated with the best outcome for both mothers and infants.

Jain and coworkers [25] reached a similar conclusion after assessing whether the risk of the pregnancy outcomes such as rate of cesarean section to primiparous and multiparous women, macrosomia, and breastfeeding at 10 weeks postpartum can be modified by following the IOM guidelines for gestational weight gain irrespective of prepregnancy BMI. The subjects were 7661 women who delivered live births in New Jersey during 2002 through 2005.

After controlling for maternal characteristics, the analysis found that the effect of prepregnancy obesity and weight gain of more than 34 lb independently and significantly increased the risk of all four adverse outcomes. For no outcome was the 25- to 34-pound weight gain category significantly distinguishable from the 16- to 24-pound reference category.

These studies strongly support the IOM weight gain recommendation (education during preconception regarding the importance of optimal BMI at the start of pregnancy) to achieve better pregnancy outcomes in obese and overweight women. The following presents evidence for two evidence-based options for controlling weight gain during pregnancy.

### Weight control options

Potential options for prepregnancy and pregnancy weight control include: (i) increasing activity levels prior to and during pregnancy to include at least 30 minutes of activity per day 4 to 5 times a week, and (ii) improving the quality of diets so that women consume less fats and calories and more fruits and vegetables.

#### Increasing physical activity prior to and during pregnancy

Oken et al. [26] assessed the duration and intensity of physical activity and time spent viewing television both before and during pregnancy among 1,805 women enrolled in a cohort study in eastern Massachusetts. After adjusting for age, race or ethnicity, history of gestational diabetes, family history of diabetes, and prepregnancy body mass index, their analysis found that women who engaged in any vigorous physical activity in the year before pregnancy experienced a significantly reduced risk of gestational diabetes (odds ratio [OR] 0.56, 95% CI 0.33–0.95) and abnormal glucose tolerance (OR 0.76, 95% CI 0.57–1.00).

Furthermore, women who reported vigorous activity before pregnancy and light-to-moderate or vigorous activity during pregnancy had a lower risk of both gestational diabetes (OR 0.49, 95% CI 0.24–1.01) and abnormal glucose tolerance (OR 0.70, 95% CI 0.49–1.01) compared with women reporting these activities in neither time period.

In a review of the literature on the use of exercise in the prevention and treatment of fetal abnormalities, Weissgerber and coworkers [27] found that women who are the most physically active during pregnancy have the lowest prevalence of gestational diabetes. They proposed four mechanisms that may explain this protective effect: (i) enhanced placental growth and vascularity, (ii) reduced oxidative stress, (iii) reduced inflammation, and (iv) correction of disease-related endothelial dysfunction.

#### Increasing the quality of diets

Few studies to date have looked specifically at the effects of dietary interventions on pregnancy outcomes. Rather, most studies have looked at whether dietary interventions can induce significant changes

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<th>Prepregnancy BMI</th>
<th>Recommended total weight gain (in pounds) for singleton pregnancies</th>
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<td>&lt;19.8</td>
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<tr>
<td>19.8–26.0</td>
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Table I. Institute of Medicine guidelines for total weight gain during pregnancy, based on pre-pregnancy body mass index (BMI).
in surrogate markers for better overall health during pregnancy. Thomas et al. [28], for example, compared fatty acid profiles of women with gestational diabetes mellitus (GDM) who had received individualized nutritional counseling with those of non-diabetic women who did not.

After dietary counseling, the GDM group had lower intakes of energy \((p < 0.05)\), refined sugar \((p < 0.0001)\), total and saturated fats \((p < 0.0001)\), and monounsaturated \((p < 0.01)\) and trans fatty acids \((p < 0.0001)\) and higher levels of docosahexaenoic acid and fiber \((p < 0.05)\) compared with the non-diabetic group.

Piirainen and coworkers [29] carried out a similar prospective cohort study of healthy and atopic pregnant women \((n = 209)\), who were randomized into dietary intervention and control groups. The intervention group received dietary counseling and food products to modify the fat composition of their diet to meet current recommendations.

Women in the intervention group consumed more vegetables, fruits, soft margarines and vegetable oils and less butter than those in the control group during the course of pregnancy \((p < 0.05)\). The main distinction between the groups in nutrient intake over the course of the pregnancy was attributable to a higher energy intake \((% \text{ energy})\) of polyunsaturated fatty acids by 0.5% energy \((95\% \text{ CI } 0.1–0.8)\) and to a lower intake of saturated fatty acids by 0.8% energy \((95\% \text{ CI } −1.4–0.4)\) in the intervention group. Dietary intake of vitamin E was 1.4 mg \((95\% \text{ CI } 0.6–2.2)\), folate 20.9 mg \((95\% \text{ CI } 0.8–41.0)\) and ascorbic acid 19.8 mg \((95\% \text{ CI } 3.5–36.0)\) higher in the intervention group compared to the controls, while no differences in other nutrients were detected.

Gillen and Tapsell [30] compared the dietary intakes of women with GDM given general low-fat advice (control group) to women with GDM given the same advice with additional targets for food sources of unsaturated fats (intervention group). After approximately 6 weeks, the intervention group reported more ideal dietary fatty acid intakes than the control group, with polyunsaturated:saturated fat ratios of 1:1 and 0.4:1, respectively \((p < 0.001)\), assessed using repeated measures analysis of variance.

Thus, dietary counseling, particularly when combined with the provision of healthier food products during pregnancy, appears to be successful in modifying food and nutrient intake in women with gestational diabetes. Although more studies are needed to determine the effect of such interventions on birth outcomes, it is likely that such improvements in the dietary intake in obese and overweight women will translate into significant health benefits.

The need for a national commitment against obesity and its complications

The success and prosperity of a country on the world stage is often judged by its infant mortality rate. For most countries, infant mortality rates are inversely proportional to gross domestic product, or GDP. Although the US has the highest GDP in the world, it lags behind 25 countries in the developing world in its infant mortality rate (Figure 4).
Much of the infant mortality rate in this country is being fueled by the growing epidemics of obesity and diabetes among pregnant women. Evidence-based interventions are urgently needed to reverse this trend. However, most people will not change their dietary and exercise habits willingly. Simply counseling women about the birth defect risks of obesity is not likely to be effective.

Rather, a spectrum of actions are needed on the national level to entice not only individuals to make better choices about diet and exercise but also to recruit the food, health insurance, and entertainment industries to become active partners in the effort to eradicate obesity in this county. These actions may include a combination of tax and economic incentives, legislation, and education.

**Tax and economic incentives**

The federal government needs to give tax breaks to the food industry for developing more low-calorie, low-fat and low-cholesterol foods and to promote the use of more fruits, vegetables, and whole grains in their products. Similarly, health insurance companies could be given tax breaks for getting people, especially pregnant women, to exercise more and practice healthier lifestyles and for covering the cost of membership to fitness facilities.

The Federal Government also should use selective taxes and subsidies as incentives to change the foods that are grown, brought to market, and consume. Given recent data indicating that children see from 27 to 48 food advertisements for each 1 promoting fitness or nutrition, incentives could be put in place to shift that balance for sustained social-marketing of the benefits of eating well.

**Legislation**

Recently, a number of states have considered legislation to provide or strengthen private insurance coverage for obesity prevention or treatment, especially for the morbidly obese (those with a body mass index of 40 or higher). Maryland currently requires insurers to cover morbid obesity treatment including surgery, while Georgia, Indiana and Virginia require private insurers to offer general coverage for morbid obesity as an option. As of July 2004, Medicare began to recognize obesity as a medical problem, opening the door to greater coverage for obesity treatments demonstrated as scientifically effective.

There also needs to be a return to an emphasis on physical fitness, particularly in K-12 education. Not only has there been an epidemic of obesity among adults, but equally as important is the obesity in our children. From 1963 until 2000 there was almost a quadrupling of children in the US who are overweight. Unfortunately, most states have no mandatory physical education in schools through high school. The result is that approximately one-third of boys and girls age 12 to 19 in the United States do not meet basic standards for physical fitness.

State and federal governments need to earmark specific funds for restoring K-12 physical education to public schools and promoting it in higher education as well. Connecticut, for example, requires schools to offer students a daily lunch period of at least 20 minutes and to include a daily recess period for physical exercise for all full day students. It also requires schools to offer nutritious, low-fat foods and drink and fresh or dried fruit at all times when students can purchase food or drink during the regular school day.

In response to growing concerns about health, particularly children’s health, the new five-year farm bill going before the Senate now provides a record $2 billion for specialty crops, including money to buy fruits and vegetables for school lunches and to assist organic agriculture. Passing this type legislation, which would help replicate the kinds of programs being instituted in Connecticut, should be a national priority.

**Education options**

Because of the tremendous influence that movies, television, the internet, and other forms of entertainment have on our society, particularly among children and adolescents, ‘pop culture’ stars needed to be educated about obesity and recruited to help in efforts to convince the public that eating right and staying fit has numerous benefits.

Just as tobacco companies have taken advantage of the powerful influence pop culture icon’s have on people’s behavior to popularize and normalize smoking, federal public health agencies should use the same tactics to convince young people that overeating and being overweight are not only undesirable but extremely unhealthy.

Federal agencies also should require more accurate labeling of caloric content and ingredients, especially in fast-food outlets, to make customers more aware of what they are eating. Their buying habits will induce manufacturers to alter food composition.

Many schools have banned the sale of soft drinks and now offer more nutritionally balanced lunches. Opportunities for physical activity at work, in school, and in the community have been expanded in a small but growing number of locations. Federal and state governments can make a tremendous contribution to this effort by helping to educate the public about these efforts and to provide encouragement and support for schools that want to replicate them.
References
