In the last three decades, the proportion of children and adults who are obese or overweight has increased rapidly in the United States and other developed countries. Moreover, the frequency of obesity is now increasing in developing countries such as China. This increase is of great concern because obesity is associated with a wide range of metabolic abnormalities and an increased risk of many different types of diseases.

It is well known that thin or malnourished mothers have an increased risk of adverse pregnancy outcomes. However, it is not as widely recognized that maternal obesity is also associated with adverse pregnancy outcomes. The purpose of this chapter is to review the literature on these associations.

We begin with a discussion of the methodological issues pertinent to the measurement of obesity in epidemiologic studies. Then the effect of obesity on reproductive function and pregnancy complications is discussed. Finally the effect of obesity on four adverse outcomes of pregnancy, late fetal death, small-for-gestational age infants, preterm birth (birth weight ≥4,000 g) and birth defects is discussed.

Methodological Issues in Measuring Obesity

Obesity has been defined as excessive accumulation of fat or adipose tissue in the body. Methods that directly measure the percentage of body fat are considered the gold standard for classifying individuals as obese or not obese. These methods include bioelectrical impedance, densitometry (hydrostatic weighing) and dual energy X-ray absorptiometry. However, for studies of large populations, the most practical method of measuring obesity is measurements (or self-reports) of height and weight or skinfold measurements. The most
widely used weight-for-height index is the body mass index (BMI), or Quetelet index, defined as (weight in kilograms)/(height in meters)$^2$. The World Health Organization and the National Heart Lung and Blood Institute recognize the following system of classifying men and women according to their BMI: underweight $<$18.5; healthy weight 18.5–24.9; overweight 25.0–29.9, and obese $\geq$30.0.

It is important to remember that although BMI is highly correlated with excess adipose tissue, it is not a direct measurement of percent body fat and therefore use of BMI to classify study participants as obese results in some degree of misclassification.

Most epidemiologic studies use self-reports of height and weight to estimate BMI and then classify individuals as obese or non-obese. There are several studies that have examined the validity of self-reported weight and height among women.

Studies are consistent in reporting that on average women underestimate their weight by small amounts, i.e. 0.80–0.85 kg [1, 2], and slightly overestimate their height, 0.40 cm [1]. When these errors are expressed as percentages of the total weight or height, women of child-bearing age were found to underestimate their weight by 0.64–0.83% and to overestimate their height by 0.40–0.42% [3]. Studies of women are also consistent in reporting high correlations between self-reported weight and measured weight (correlation coefficient $= 0.98$, $p \leq 0.001$) [1] and high correlations between self-reported height and measured height (correlation coefficient $= 0.98$, $p \leq 0.001$) [1]. Thus although, on average, women underestimate their weight by small amounts, their rank order by weight and height is similar regardless of whether self-reported values or actual measurements are used.

A number of studies have found that obese women are more likely to underestimate their weight compared with women who are not obese. For example, Nieto-Garcia et al. [3] observed that, among obese women, the average size of the underestimate of weight is increased by twofold compared with the size of this underestimate among underweight women, so that on average obese women underestimate their weight by 1.5%. Nieto-Garcia et al. [3] further observed that using self-reports of weight and height, the sensitivity of a BMI cutoff of 30 kg/m$^2$ to detect obesity among women of child-bearing ages was 82–85% compared with a gold standard of BMI based on measurements.

Maternal Obesity and Reproductive Function

Among women of child-bearing age (15–44 years) obesity is known to affect the female reproductive system. Because adipose tissue synthesizes estrogen, obese women have higher levels of endogenous estrogen compared
with women who are not obese. They are also much more likely to have irregular menstrual cycles and to have difficulty becoming pregnant.

All or part of these reproductive abnormalities may be explained by the very large increase in the risk of developing polycystic ovarian syndrome among obese women. Women with this syndrome usually present with amenorrhea, irregular menstrual periods or difficulty becoming pregnant. Clinical findings include anovulation, multiple cysts on both ovaries, insulin resistance, symptoms of hyperandrogenism (acne and hirsutism or male pattern of hair distribution), increased fat around the abdomen and elevated levels of serum testosterone [4]. However, the occurrence of polycystic ovaries on ultrasound can be a normal finding, occurring in 21% of Australian women aged 15–44 years [5]. Thus, polycystic ovarian syndrome has been defined as occurring in women who have two of the following three conditions: polycystic ovaries; hyperandrogenism, and anovulation. In developed countries, this condition affects 5–10% of women of child-bearing age [6, 7]. Since this condition is strongly linked to obesity, it probably occurs less frequently in countries were the frequency of obesity is low.

**Maternal Obesity and Complications of Pregnancy**

In some women, the metabolic effects of pregnancy induce the onset of glucose intolerance, resulting in the development of gestational diabetes. Obese women are considered to be at a high risk of developing this condition which can only be diagnosed by screening. Screening is usually performed between 24 and 28 weeks of gestation using a 50-gram oral glucose load followed by serum glucose measurement 1 h later.

In the United States gestational diabetes is a relatively common complication of pregnancy occurring in between 2.4 and 4.0% of all women who are screened. A study of 9,471 pregnant women screened for gestational diabetes in Tianjin City, China, found that the prevalence of gestational diabetes was 2.3% [8].

Gestational diabetes ranges in severity from a mild condition of questionable significance to a severe disturbance in glucose tolerance necessitating administration of insulin. In many cases it remains undetected and in some populations less severe cases may be more likely to be detected than more severe ones. This occurs because criteria for conducting screening are variable and women of higher socioeconomic status – and leaner body mass – often receive more prenatal testing, although they are at lower risk of developing the disease. In the United States, there are large numbers of women who have little or no prenatal care and therefore have no opportunity to be screened for gestational diabetes.

Since so many cases remain undetected and because these undetected cases of gestational diabetes differ from cases that are detected, it is difficult
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to determine the magnitude of the association between maternal obesity and
the increased risk of gestational diabetes. In unpublished data from interviews
of control mothers participating in the National Birth Defects Prevention
Study, the great majority of whom entered prenatal care prior to 24 weeks of
gestation, 12% of women who were obese prior to their pregnancy reported
having gestational diabetes, compared with 5.7% of women who were not
obese prior to their pregnancy [9].

Both obese women and women who develop gestational diabetes during
one or more pregnancies have an increased risk of having an infant with
macrosomia or a birth weight in excess of 4,000 g. Macrosomia is thought to
be due to high levels of glucose in the fetal serum, which stimulate the fetal
pancreas causing fetal hyperinsulinemia. Fetal insulin acts as a growth hormone
causing excessive fetal growth. Macrosomia is of concern because there is a
higher risk of shoulder dystocia, dysfunctional labor and cesarean birth
among these infants. Obese women and women who develop gestational
diabetes also share an increased risk of developing non-insulin-dependent
diabetes later in life.

Obese women also have an increased risk of having hypertension or
preeclampsia during their pregnancies and they have increased rates of blood
loss and postoperative infection following cesarean deliveries [10].

Maternal Obesity and the Risk of Late Fetal Death,
Small-for-Gestational Age Infants and Preterm Birth

Studies are consistent in reporting that obese women have an increased risk
of late fetal death [11, 12]. Cnattingius et al. [11] examined the medical records
for a population-based cohort of 167,750 women who delivered in Sweden in
1992 and 1993. They used self-reported measurements of weight and height
assessed at or before 15 weeks of gestation. Compared to women with lean
body mass, they observed that women who were obese and those who were
overweight early in their pregnancy had increased risks of late fetal death:
odds ratio 1.7, 95% CI 1.1–2.4, and odds ratio 2.7, 95% CI 1.8–4.1, respectively.
These findings are adjusted for maternal age, parity, education, cigarette
smoking, height, and whether the mother was living with the father.

The association between maternal obesity and an increased risk of late
fetal death may be due to the increased rate of diabetes, hypertension and
preeclampsia among obese women. It is also noteworthy that an estimated
25% of late fetal deaths have major births defects [13]. Thus, a portion of the
association between maternal obesity and late fetal death may be due to the
excess risk of lethal birth defects among infants born to obese mothers
(discussed below). Also, Cnattingius et al. [11] suggested that thinner women
may have healthier habits or may be more likely to detect a decrease in fetal
movements, thereby explaining this association.
Studies are also consistent in reporting that obese women have a decreased risk of having a small for gestational age infant, compared to thin women. Cnattingius et al. [11] observed that obese, overweight, and normal weight women were less likely to have small for gestational age infants compared with women with lean body mass, odds ratio 0.5, 95% CI 0.4 to 0.6, odds ratio 0.5, 95% CI 0.4 to 0.7, odds ratio 0.7, 95% CI, respectively. These results were adjusted for maternal age, parity, education, cigarette smoking, height, whether the mother lived with the father and weight gain during pregnancy.

The reasons for this association are not completely understood. However, the fact that it is independent of maternal weight gain during pregnancy suggests that the amount of calories consumed at the time of conception and during the first trimester may have an important effect on the final size of the newborn infant. The fact that the protective effect was similar for women of average body mass, overweight women and obese women suggests the possibility of a threshold effect. Therefore, the goal in reducing the risk of small-for-gestational age infants should be to encourage women to be well-nourished, of normal weight and to have adequate caloric intake prior to and after conception.

Studies of the association between maternal obesity and preterm delivery have shown inconsistent results. Naeye [14] analyzed data from the Collaborative Perinatal Study for 56,857 deliveries occurring in different regions of the United States between 1959 and 1966. In this prospective cohort study maternal heights were obtained by measurement and maternal weights were self-reported at the first prenatal visit. He reported that obese women had a 1.5-fold increase in the risk of preterm birth compared to women who were thin or had a normal body mass. This finding was not adjusted for confounders and because the measurement of weight was taken during pregnancy the results of this study may have mixed the effect of weight gain and weight prior to pregnancy. In contrast, Cnattingius et al. [11] observed that obese women had no increase in the risk of preterm delivery at ≤32 or 33–36 weeks. However, Cnattingius et al. [11] did observe an increased risk of preterm delivery at ≤32 weeks among women who were having their first delivery (odds ratio 1.6, 95% CI 1.1–2.3).

**Maternal Obesity and the Risk of Birth Defects**

In Naeye’s [14] study of 56,857 deliveries in the US between 1959 and 1966, women who were obese or overweight had a 1.4-fold increase in the frequency of infants with major congenital malformations compared to thin women. In 1994, we published the first article showing that obese women had an increased risk of having an infant with a neural tube defect compared with women of normal weight (odds ratio 1.8, 95% CI 1.1–3.0) [15]. Women known to be diabetic prior to becoming pregnant were excluded and the results
Maternal Obesity and Adverse Pregnancy Outcomes

Table 1. Summary of studies of the association between maternal obesity and the risk of having offspring with neural tube defects

<table>
<thead>
<tr>
<th>Lead author</th>
<th>Year</th>
<th>Design</th>
<th>Height and weight</th>
<th>Relative risk</th>
<th>Confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naeya</td>
<td>1990</td>
<td>cohort</td>
<td>mixedb</td>
<td>1.4</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>Waller</td>
<td>1994</td>
<td>case-control</td>
<td>self-report</td>
<td>1.8</td>
<td>1.1–3.0</td>
</tr>
<tr>
<td>Werler</td>
<td>1996</td>
<td>case-control</td>
<td>self-report</td>
<td>1.9</td>
<td>1.2–2.9</td>
</tr>
<tr>
<td>Shaw</td>
<td>1996</td>
<td>case-control</td>
<td>self-report</td>
<td>1.9</td>
<td>1.3–2.9</td>
</tr>
<tr>
<td>Watkins</td>
<td>1996</td>
<td>case-control</td>
<td>self-report</td>
<td>1.9</td>
<td>1.1–3.4</td>
</tr>
<tr>
<td>Kallen</td>
<td>1998</td>
<td>cohort</td>
<td>mixedb</td>
<td>1.3</td>
<td>0.8–2.1</td>
</tr>
<tr>
<td>Shawc</td>
<td>2000</td>
<td>case-control</td>
<td>self-report</td>
<td>NG</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>Hendricks</td>
<td>2001</td>
<td>case-control</td>
<td>self-report</td>
<td>1.7</td>
<td>1.0–2.8</td>
</tr>
<tr>
<td>Watkinsd</td>
<td>2003</td>
<td>case-control</td>
<td>self-report</td>
<td>3.5</td>
<td>1.2–10.3</td>
</tr>
</tbody>
</table>

All but one of the studies in this table observed a statistically significant increase in risk of neural tube defects (or all major birth defects) among obese women. Kallen (1998) observed a similar increase in risk that was not statistically significant.

aThis relative risk refers to the risk of all major birth defects in aggregate.
bThese studies used measurements of maternal height and self-reports of maternal weight.
cShaw et al (2000) used an additive logistic regression model and reported regression coefficients rather than relative risks or odds ratios, NG (not given).
dThis relative risk refers to spina bifida only.

were adjusted for maternal age, race, education and family income. Mother’s height and weight prior to pregnancy were self-reported and were collected by maternal interview no later than 5 months after delivery.

Including our study, 7 case-control studies addressing this topic have been published. All of them reported that obese women have an approximately twofold increase in the risk of having an infant with a neural tube defect compared with normal weight women [15–21]. All of the case control studies used methodologies similar to ours including self-reports for maternal weight and height. All of these studies were based on maternal interview after delivery and therefore may have suffered from differential (case versus control) maternal recall of weight before pregnancy or from a greater likelihood that obese women who had case infants would choose to participate in the interview. In addition, there are 2 cohort studies that have reported similar findings [22, 23]. These two cohort studies are important to the argument that maternal obesity may be part of the causal pathway for neural tube defects, because they are not susceptible to the same biases as the case-control studies.

The studies on neural tube defects are summarized in table 1. All of them observed that the association between maternal obesity and spina bifida was stronger than the association between maternal obesity and anencephaly (table 1). This supports the suggestion of other researchers that anencephaly and spina bifida have different etiologies.
Watkins et al. [21] have written a thorough summary of studies on the association between maternal obesity and all types of birth defects. A number of studies have addressed the possibility that obese women have an increased risk of birth defects other than neural tube defects.

Two studies have observed an increased risk of oral clefts among obese women [23, 24]. However, two other studies of oral clefts found no association [20, 21]. There are four studies that examined the association between maternal obesity and all types of heart anomalies. All of these studies observed significantly elevated odds ratios [21, 25–27].

There are also two studies that have observed that obese women have an increase in the risk of having an infant with hydrocephaly with an odds ratio of 2.0 or more, compared with women with normal weight [23, 28]. A third study of hydrocephaly observed that obese women had a more modest increase in the risk of hydrocephaly, although the results may have been due to chance (odds ratio 1.5, 95% CI 0.3–7.2) [21]. Two studies have reported that obese mothers have an elevated risk of infants with abdominal wall defects [15, 23]. As abdominal wall defects are comprised of two birth defects with separate etiologies – gastroschisis and omphalocele – a third study separately examined the risk for these two birth defects and found that obese women had an elevated risk of having an infant with omphalocele, but not with gastroschisis [21]. There are also two studies that found an association between maternal obesity and multiple congenital anomalies [15, 29].

Evidence is accumulating to support the idea that the mechanism that causes the excess of birth defects among infants of obese women is similar to the mechanism that causes the well-established excess of major birth defects among infants of diabetic mothers [28]. The increased risk that occurs among diabetic women can be ameliorated by controlling blood glucose during the periconceptional period. Obese women, although not overtly diabetic, are more likely to have high levels of serum insulin and altered response to glucose tolerance testing. Thus, alterations in glycemic control may contribute to the increased risk of birth defects among both obese women and diabetic women [30]. Also, the observation that maternal obesity is associated with an increase in a number of different birth defects is consistent with the literature on diabetic women, which also indicates an increased risk of a number of different birth defects.

A number of other explanations have been posited to explain the association between maternal obesity and an increased risk of birth defects. Increased levels of maternal intake of folic acid are known to be protective against the development of neural tube defects. It has been proposed that obese women may have lower levels of folic acid, due to lower dietary intake, poorer absorption or higher metabolic requirements for this vitamin. It has also been proposed that behaviors associated with obesity and dieting, such as fasting, self-induced vomiting and the use of appetite suppressants, might be associated with an increased risk of birth defects among obese women. Nonetheless,
current evidence suggests that the most likely explanation for this association is altered glycemic control.

**Conclusions**

Obese women have more difficulty becoming pregnant and once they are pregnant they have an increased risk of having infants with adverse outcomes, including macrosomia, late fetal death, and congenital malformations. The association between maternal obesity and these conditions is summarized in table 2.

The majority of the epidemiologic studies based their measurements of obesity on self-reports of pre-pregnancy weight and height. There are two sources of error in this approach. First, indexes of weight relative to height, such as the BMI, are imperfect measures of the percentage of body fat, i.e. increased weight relative to height may also be due to increased bone and muscle mass. Second, compared with measurements, self-reported weight and height have been shown to underestimate the true BMI in women and hence to underestimate the prevalence of women with a BMI of \( \geq 30.0 \). Case-control studies may suffer from the possibility that obese women who have affected infants would have been motivated to recall their weight differently compared with other women. However, many of the findings reported above were based on cohort studies and therefore cannot suffer from this flaw. As noted above, for birth defects the case-control studies and cohort studies reported very similar findings. We believe that the errors we have described in the assessment of obesity are likely to occur with similar frequency among mothers who have affected infants and those that do not. Thus, the effect of these errors will most likely prove to be to underestimate the adverse effects associated with obesity.

Women with android obesity (more adipose tissue on the trunk relative to the hips) are much more likely to have high serum insulin levels and altered response to glucose tolerance testing, compared with women who have gynoid obesity (more adipose tissue on the hips). Thus, it may be useful that future studies attempt to examine these two types of obesity separately.

Almost all of the studies discussed in this review were conducted in well-nourished populations in developing countries. These populations contain relatively few women who are extremely thin. Thin or malnourished women have a well-known increase in the risk of small-for-gestational age infants and may possibly be at risk for other types of adverse pregnancy outcomes. Existing studies observed that thin women had an average or reduced risk of most birth defects. However, given studies that include larger numbers of extremely thin women, an association between extreme thinness and an increased risk of birth defects may yet be discovered. Across different countries, obesity and thinness may be associated with different types of diets.
and differences in other exposures and hence may prove to have differences in the risks associated with them.

Future studies should anticipate the possibility of nonlinear or U-shaped relationships between maternal BMI and some adverse pregnancy outcomes. Causal inferences may be strengthened by looking at risk among women with extreme values of BMI. For example, in a recent study we observed that the increased risk of neural tube defects was much greater among women who were extremely obese, BMI $\geq 35.0$, compared with those who were moderately obese, BMI $30.0–24.99$.

This review has documented that obesity is associated with a number of adverse pregnancy outcomes in Western countries. As obesity has wide ranging metabolic effects, it seems likely – although not proven – that obesity will also prove to be associated with adverse pregnancy outcomes among

\[\text{Table 2. Reproductive and perinatal outcomes associated with maternal obesity}\]

<table>
<thead>
<tr>
<th>Increased risk of reproductive problems</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irregular menstrual cycles</td>
</tr>
<tr>
<td>Anovulatory cycles</td>
</tr>
<tr>
<td>Difficulty in becoming pregnant</td>
</tr>
<tr>
<td>Polycystic ovarian syndrome</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Increased risk of complications during pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational diabetes</td>
</tr>
<tr>
<td>Pregnancy-induced hypertension</td>
</tr>
<tr>
<td>Chronic hypertension</td>
</tr>
<tr>
<td>Cesarean delivery</td>
</tr>
<tr>
<td>Blood loss during cesarean delivery</td>
</tr>
<tr>
<td>Wound infection after cesarean delivery</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Increased risk of adverse birth outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Late fetal death</td>
</tr>
<tr>
<td>Macrosomic infant ($\text{birth weight} \geq 4,000 \text{ g}$)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Birth defects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anencephaly</td>
</tr>
<tr>
<td>Spina bifida</td>
</tr>
<tr>
<td>Hydrocephaly$^1$</td>
</tr>
<tr>
<td>Omphalocele$^1$</td>
</tr>
<tr>
<td>All heart defects$^1$</td>
</tr>
<tr>
<td>Multiple congenital anomalies$^1$</td>
</tr>
<tr>
<td>Other congenital anomalies$^1$</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Decreased risk of adverse birth outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small for gestational age</td>
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</table>

<table>
<thead>
<tr>
<th>Increased risk of the development of disease during the infants life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Heart disease$^1$</td>
</tr>
</tbody>
</table>

$^1$Further evidence is needed to definitely establish these associations.
Maternal Obesity and Adverse Pregnancy Outcomes

Asian populations. Currently, China has much lower rates of obesity than the United States and other Western countries. Thus, China should encourage programs to prevent children and adolescents from becoming obese. Such programs may be particularly effective in China and other Asian countries, because the problem of obesity is not yet fully entrenched in these countries.

References

Discussion

Dr. Pencharz: I really enjoyed your talk. I just wanted to point out to you and to others that insulin has effects on protein and lipids as well as on glucose. The way you and many other people have talked about it the focus has really been on glycemic control. In work that we have done in conjunction with people at McGill University in type-2 diabetics who are on low energy diets, we were actually able to correct their glycemic control with just low energy but we weren’t able to correct their protein metabolism. So if you go back to Banting and Best when they discovered insulin, they said that lean tissue was wasted through the urine, so in fact you need more insulin action to affect lean mass, affect your protein mass and so on. We are finding that in cystic fibrosis-related diabetes as well. So just remember that insulin action involves protein and all that is involved in laying down protein and growth, and lipids as well, but in fact the most effect is in protein. We tend to forget that because we focus on glucose control.

Dr. Waller: Thank you, I think that is an excellent suggestion. I have to look into it.

Dr. Endres: I would like to add another immediate consequence of maternal overweight or obesity, and that is that these women either do not breast feed or terminate breast feeding earlier than other mothers, and that by itself could also lead to obesity later in life of their offspring. There are several studies, one very big by Sebire et al. [1] with about 287,213 mother–child pairs, demonstrating that these mothers are breast feeding less that others.

Dr. Waller: I was not aware of that. So we can add that to the adverse pregnancy outcomes.

Dr. Rosenquist: I just have a question about gestational diabetes. I am not sure why it manifests itself, but it seems to me that it must have something to do with the metabolic load that the baby places upon the mother. In order for gestational diabetes to be effective in producing spina bifida and anencephaly, it would have to be fully manifested very early in pregnancy, it would have to be fully manifested before 8 weeks when the embryo actually and all of the associated membranes weigh less than 1 g. I would like to hear your comments.

Dr. Waller: I am glad you asked that because that is the question that most people ask, and I forgot to cover it. Basically my look at interaction came about because I was looking at all these studies showing that obese women have an increased risk of certain birth defects, and I asked why. Could it be something similar to what goes on with
diabetic women? So I then had the idea of looking at women who have gestational diabetes and obesity. I knew of course that gestational diabetes does not occur; in other words they don’t become diabetic until much later in pregnancy than the period of organogenesis. But still obese women who do develop gestational diabetes are different from obese women who do not develop gestational diabetes, and so I think of it more as a continuum of glycemic control and other factors. The obese women who develop gestational diabetes are also more likely to develop maturity onset diabetes in their 40s, 50s and 60s. So these are women who are more susceptible to alterations in their glycemic control. But I am aware that gestational diabetes does not start that early.

Dr. Cai: In your conclusion you mentioned that in China we should encourage education programs for obese children and adolescents, and I totally agree with your suggestion. My question is what about American children, because the incidence of obesity in American children is very high and the level of education in the United States is much higher than it is in China. So what is your opinion about a childhood obesity program?

Dr. Waller: So you want to know why I think we have so much obesity in children and what should we do about it?

Dr. Cai: Yes, and even in the United States, education is high.

Dr. Waller: I am going to try. I am not a behavior scientist but you would not believe how many obese children we have in Houston and there are a lot of behavior scientists in my school working on this. They are working on how they can change behaviors and are trying to get children to walk to school instead of their parents driving them; trying to increase physical activity by getting the children to watch less television because children who watch television don’t get as much physical activity; they are working on trying to change the food that is served in the school cafeteria, but unfortunately they put Coke and candy bar machines in the schools and even the school cafeteria, which is supposed to serve healthy food, is serving hamburgers and French fries I believe, I haven’t been in a school lately. They are working on that and they are going into the schools and trying to educate the children. Myself I feel that it is better to have interventions that do not require much participation. In other words I favor going into the schools and taking all the candy bar machines and these sorts of machines out of schools. That may seem draconian to some but I just think it is a lot more effective. Does anybody else want to comment on this interesting issue?

Dr. Cai: But the results are not very good. This program was implemented about 10 years ago but even now in the United States you still have a very high incidence of obesity in children. In China it is also a problem.

Dr. Waller: I guess my point is yes, we are trying to prevent our children from becoming obese, but it is a very bad problem and we are not having success. So my point is you have an opportunity to perhaps prevent this, prevent the machines, the candy bar machines and the Coke machines from being placed in the schools in the first place because once they are there it is hard to get them out. This is one disease that you have less of than we; you have a good opportunity for prevention. We are in a harder situation with prevention now.

Dr. Butte: Do you have any data on the effect of gestational weight gain in obese women on birth defects? Overweight women tend to gain weight like normal weight women, but very obese women on average gain less, but there is a subset of obese women that gain an extraordinary amount. So do you have any information on those who gain too much and those who gain too little?

Dr. Waller: Yes, Shaw et al. [2] did look at it and theirs is the only paper on it that I know of. Of course weight gain largely occurs after the period of organogenesis, so we were not really thinking of it initially. But Shaw et al. did look at it and it is only paper on it that I know of.
**Dr. Butte:** There can even be weight loss of course in the first trimester due to nausea.

**Dr. Waller:** Actually I do have a paper published on this [3]. I looked at whether or not women were dieting at the time they became pregnant and that was not associated with birth defects in my study. But Carmichael et al. [4] did a similar study, which they just published in the *American Journal of Epidemiology*, showing that women who were dieting at the time of conception have a small increase in the risk of babies with birth defects. I also asked women if they had fasted any time early in the first trimester for a period of a day or more, and it was not associated with birth defects in my study. I didn't have the weights but we looked at a variety of dieting behaviors.

**Dr. Moore:** I was interested in the table showing the ratios between obesity and neural tube defects. What other factors were adjusted for? I was wondering whether obesity is an indicator of some other factor that may actually be responsible.

**Dr. Waller:** You are talking about the slides in which I showed ratios from different studies and they were all about the same magnitude.

**Dr. Moore:** I just wonder whether it wasn't necessarily obesity per se, but it was what caused the obesity in the sense of whether it is a socioeconomic thing or whatever.

**Dr. Waller:** Generally, all of the studies would have adjusted for maternal education, maternal race, maternal age, maternal parity, and some would have also adjusted for family income. As I said they all excluded diabetics, and virtually all of them adjusted for folic acid intake at the time of conception.

**Dr. Moore:** So in respect to that it seems that it is a consequence of being obese. I wonder whether you have considered any products of adipose tissue, such as leptin which can cross the placenta, or other cytokines or hormones that may play a role?

**Dr. Waller:** I haven’t done any such studies but Shaw et al. [5] did look at the gene for leptin and found no association with neural tube defects. I don’t know how many different parts of the gene they have looked at because they looked at the gene and they published a negative study. Then they started looking at the gene some more because there were different parameters at different parts. But they first looked at the gene for leptin and it was negative. I don’t know of anybody that has looked at serum leptin. You would have to figure out when you are going to measure that too, and it is always a problem trying to get serum levels of folic acid or whatever you want to look at the time of organogenesis.

**Dr. Uauy:** How about the Pima Indians where both obesity and gestational diabetes are more frequent. Do they have more neural tube defects? Or are other groups especially sensitive to obesity and gestational diabetes?

**Dr. Waller:** I don’t know that the Pima living in the United States are covered by a good birth defects monitoring registry. I think they are starting birth defects monitoring in New Mexico, and there are some hot spots in Mexico. Anecdotally, the Indians living in Mexico have high rates of neural tube defects and there are some studies going on down there. I know there is a high rate of neural tube defects in northern China because of the CDC paper [6], but some of the clinicians here tell me they are not seeing babies with spina bifida. It may just be that when the babies are born at home those with anencephaly and spina bifida never come to attention; they may just die at home and they don’t really get to a hospital. So there are a lot of complications with measuring birth defects in Mexico and China, and there are a couple of places in Mexico where very high rates have been documented; some people say the highest rates of neural tube defects in the world are among Indian populations. I don’t know whether they are Pima or not.

**Dr. Yang:** I just want to mention some studies on birth defects with gestational diabetes. I remember one publication in *Obstetrics and Gynecology* last year that included more than 2,000 diabetic patients and showed that for the gestational
diabetes mellitus (GDM) A1 type, the birth defect rate is only 1.2% which is similar to that of normal pregnant women, but for the GDM A2, which means that diabetics need insulin, the birth defect is very high, around 4.8%, and in patients who are diabetic before pregnancy the birth defect rate is about 6.8. So in conclusion in early pregnancy, blood glucose is related to birth defects. So if we talk about gestational diabetes with birth defects perhaps we should measure blood glucose in early pregnancy. I think it would be very accurate.

**Dr. Waller:** You brought up a number of very good points. The first point I think is that gestational diabetes can range from mild to very severe and so there are a lot of studies in women with gestational diabetes which don’t show much of an increase in birth defects, and that is probably because the studies mainly include mild cases. A lot of the most severe cases of gestational diabetes in the United States may be going undiagnosed because the women do not come for early prenatal care, at least they don’t get diagnosed early. So in my next study I am hoping that I can at least divide gestational diabetics into those who were treated with insulin or treated with an oral agent versus those who were just being treated with diet and watchful management, so I can divide them into two categories of severity and I think that will help to look at things. Your final point was that you thought I should get blood glucose measurements at the time of organogenesis. I would love to have blood glucose measurements at the time of organogenesis, that would be very good. There are some studies that have had that.

**Dr. Waller:** You make a good point there and I think most of the studies that have been published did point out that we could not exclude diabetic women who were undiagnosed at the start of their pregnancy. So they could be in there although about 10% of the women in these studies are obese, and I don’t think they (diabetic women)
are a large enough group to drive this kind of odds ratios. But I appreciate your comment because you remind me that I could look at this more thoroughly in some data that we have. I think there are some ways I could try to get at this bias and look more carefully just to make sure it is not causal.

*Dr. Yajnik:* Recently we analyzed 250 women with gestational diabetes in my department. 40% of them continued to be diabetic and 30% women became diabetic within next 4 years. They had a strong family history and were the more adipose.

*Dr. Waller:* In fact when you brought that up I was thinking about some other data by Hendricks et al. [8]. They didn’t have glucose tolerance tests but they have post-partum measurements of serum glucose and serum insulin on mothers of cases and mothers of controls. So we could look at that.

*Dr. Yajnik:* In fact we are concentrating on this group now for analysis of various genetic types of diabetes. Women who continue to be diabetic after pregnancy are the ones who are going to have a higher yield of genetic markers depending on the phenotype. Thus gestational diabetes is full of difficulties because it is a very heterogeneous condition, it may be type-1 diabetes which is diagnosed in pregnancy, it may be MODY, or it may be the real gestational diabetes which comes and goes. No one has large serial data on testing women before, during and after pregnancy.

*Dr. Waller:* I agree with you.

*Dr. Hornstra:* Just to follow up on the remark of Dr. Endres about breast feeding in obese mothers. It may be that also the quality of human milk in obesity is not optimal because we know that the docosahexaenoic acid status of obese women is lower than of the normal-weight women [9], and so this may be an additional factor that should be taken into account.

*Dr. Waller:* Interesting point.

**References**
