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SPECIAL ARTICLE

Obesity in Pregnancy: Implications for the Mother and Lifelong Health of the Child. A Consensus Statement

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ABSTRACT: Obesity among pregnant women is becoming one of the most important women's health issues. Obesity is associated with increased risk of almost all pregnancy complications: gestational hypertension, preeclampsia, gestational diabetes mellitus, delivery of large-for-GA infants, and higher incidence of congenital defects all occur more frequently than in women with a normal BMI. Evidence shows that a child of an obese mother may suffer from exposure to a suboptimal *in utero* environment and that early life adversities may extend into adulthood. In September 2009, ILSI Europe convened a workshop with multidisciplinary expertise to review practices and science base of health and nutrition of obese pregnant women, with focus on the long-term health of the child. The consensus viewpoint of the workshop identified gaps and gave recommendations for future research on gestational weight gain, gestational diabetes, and research methodologies. The evidence available on short- and long-term health impact for mother and child currently favors actions directed at controlling prepregnancy weight and preventing obesity in women of reproductive ages. More randomized controlled trials are needed to evaluate the effects of nutritional and behavioral interventions in pregnancy outcomes. Moreover, suggestions that maternal obesity may transfer obesity risk to child through non-Mendelian (*e.g.* epigenetic) mechanisms require more long-term investigation. **(*Pediatr Res* 69: 175–180, 2011)**

CONSENSUS STATEMENT

Worldwide, obstetricians and midwives are confronted with an escalation of obesity among pregnant women. In England, where the prevalence of obesity in women is among the highest in Europe, ~1 in 5 women of reproductive age are now obese [BMI >30 kg/m^2; 1]. Obese women may present for antenatal care with established hypertension and some may have undiagnosed type 2 diabetes. Other complications emerge later in gestation, at delivery, or postpartum (2,3). Obesity is associated with an increased risk of suboptimal pregnancy outcome, and of maternal and infant death, but most obese pregnant women are quite unaware of the problems they face. Given the incremental costs of these complications, health care budgets will be increasingly stretched (4). In addition, some evidence suggests that a child of an obese mother may suffer from exposure to a suboptimal *in utero* environment and that these early life adversities may extend into adulthood (5,6).

In September 2009, ILSI Europe, a nonprofit scientific foundation, which draws on opinion from academia, government, and industry to identify solutions to topical problems, convened a workshop to review health and nutrition in obese pregnant women, with focus on the health of the child in the longer term. The working party was briefed to discuss and prioritize actions that could lead to improved outcomes in obese pregnancies and protect the health of the mother and the lifelong health of the unborn child. The consensus viewpoint is summarized here.

OBESITY AND PREGNANCY OUTCOME

It is evident that obese pregnant women are at increased risk of maternal death and complications during pregnancy and labor. In the United Kingdom, the latest Confidential Enquiry into Maternal and Child Health (CEMACH) reported that more than half of the deaths from direct or indirect causes during (late) pregnancy or labor were in overweight or obese women (7). Obesity is associated with increased risk of almost all pregnancy complications such as gestational hypertension, preeclampsia, gestational diabetes mellitus (GDM), delivery of a large for gestational age (LGA) infant, and a higher incidence of congenital defects all occur more frequently than in women with a normal BMI (2,3,8). Cesarean section rates

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Abbreviations: GDM, gestational diabetes mellitus; **GWG,** gestational weight gain; **LGA,** large for gestational age; **RCT,** randomized controlled trial; **SGA,** small for gestational age

are also much higher, and anesthesia may be problematic. Notable exceptions are gastroschisis and spontaneous preterm labor, both of which occur less often. Obese women often face difficulties in initiating and sustaining breast feeding (9). Some, but not all studies suggest that preconception weight loss, either through lifestyle or bariatric surgery improves fertility and pregnancy outcomes (10,11) and support a causal link between adiposity and adverse pregnancy outcome. These emphasize the potential benefit of weight loss among obese women of reproductive age.

GESTATIONAL WEIGHT GAIN

The USA Institute of Medicine (IOM) has recently published revised guidelines for gestational weight gain (GWG) in underweight (BMI $<$18.5; recommended weight gain 12.5–18 kg), normal weight (BMI, 18.5–24.9; 11.5–16 kg), overweight (BMI, 25.0–29.9; 7–11.5 kg), and obese (BMI $\geq$30; 5–9 kg) pregnant women (12). The rationale for revision was principally driven by new evidence of the effects of GWG on maternal and infant outcomes, the increase in obesity and average GWG, and the greater ethnic diversity and increasing maternal age of pregnant women in the United States. Evidence from the United States clearly shows that the goals as set in these new guidelines are currently not being achieved by overweight or obese women [*e.g.* Pregnancy Risk Assessment Monitoring System (PRAMS) study, 2002–2003] and attainment will prove a major health care challenge. The USA guidelines are based on a systematic review of the literature on outcomes of maternal weight gain in pregnancy [Agency for Health Care Research and Quality (AHRQ)], a specially commissioned analysis of a study in a large Scandinavian cohort (Dr. Nohr) and the USA National Maternal and Infant Health Survey (1988/1991). As detailed by the IOM report and highlighted by a recent publication, the strength of much of the contributory evidence is moderate or weak (12,13), and the IOM guidelines are understandably cautious. The evidence was drawn predominantly from European-origin women and generalization to other ethnic groups within high-income countries, or to women in low-middle income groups may not be appropriate, especially among populations showing rapid demographic change. Recent studies using different approaches have yielded partly inconsistent results, suggesting that the definition of optimal GWG is highly dependent on the method of assessment and the health outcomes (maternal, fetal/offspring short or long term) to which it is related (14–19). Ideally, recommendations should be developed from stronger evidence drawn from a wide range of short- and long-term outcomes. We emphasize that it should not be assumed that observational studies will translate safely into recommendations for restriction of GWG for perinatal or other long-term outcomes. Indeed, some of the most recent observational studies in obese women report optimal perinatal outcomes at lower GWGs than recommended, including gestational weight loss (15,17,19). Literal translation from these reports to clinical advice for obese pregnant women may have adverse consequences, given the potential risk of weight loss to pregnancy outcome.

Many countries in Europe do not weigh pregnant women, except at their first antenatal appointment, because the value of knowing GWG is uncertain. GWG is a composite of the products of conception, plasma volume expansion, extracellular fluid, and maternal fat deposition and is an imprecise estimate of increasing maternal (or fetal) adiposity. Among obese women, who on average gain less weight than leaner women, higher GWG is associated with postpartum weight retention, for which the evidence is strong (12). However, for obese women, pre-pregnancy BMI is more consistently associated with increased risk of preeclampsia, cesarean section, gestational diabetes, and LGA delivery (16) than is GWG. Therefore, the emphasis on GWG in antenatal care of obese women may be misplaced, and in many countries in Europe, where conformity to these guidelines would require reintroduction of routine weight checks, the efforts are likely to outweigh any potential benefits.

Most importantly, all studies contributing to the development of the new IOM guidelines are observational. None shows that restriction of GWG by behavioral intervention (or any other method) leads to the benefits in outcome anticipated in women in any of the prepregnancy BMI categories defined. Optimal GWG could be further assessed by meta-analysis of the large cohort studies but focusing on those pregnancies characterized by normal maternal and infant health outcomes. Further examination of the global Hyperglycemia and Adverse Pregnancy Outcome (HAPO) data, collected using standardized methods in $>$23,000 women from nine countries, could also provide more evidence (20). However, only randomized controlled trials (RCTs) can provide the definitive evidence needed. These should include not only strategies directed at restricting GWG but also those which target reduction of preconceptional body/fat mass. Some recent small RCTs of behavioral interventions report success in reducing GWG. Most have combined dietary and physical activity advice with individual and stepped targets throughout pregnancy, but protocols are far from standardized (*e.g.* Refs. 21–23) and none was adequately powered to address short- or long-term maternal and child outcomes. As recently reviewed, the effect of providing an antenatal dietary intervention for overweight and obese pregnant women on maternal and infant health outcomes remains unclear (24). Several larger RCTs now underway, with GWG as a primary outcome, and adequately powered for these outcomes will test directly the validity of the IOM recommendations (25). Importantly, the control arms will serve as observational studies. A key priority will be to persuade research funders and the study participants to remain engaged with long-term follow-up.

RECOMMENDATIONS

- Clinical and population health practice should focus on interventions to reduce obesity in all women of reproductive age.
- All pregnant women should be advised to eat a healthy, balanced diet, and obese women should be informed of the potential risks associated with obesity and pregnancy outcome.

- To date, there is insufficient evidence to recommend monitoring GWG in obese (or all) pregnant women to improve perinatal and later health outcomes. We do not recommend the reintroduction of antenatal monitoring of GWG in the United Kingdom and Europe until further evidence informs guidance.
- Should the emphasis remain on GWG, then additional investigations among women of different ethnic subgroups and using standardized measurements with a range of outcomes are required. These could be observational, *e.g.* from contemporary cohorts or by using the control arm of ongoing RCTs.
- Short- and long-term follow-up of participants in large RCTs of interventions that are successful in restricting GWG within IOM guidelines are key to determine the safety and effectiveness of controlling GWG.
- Primary outcomes in RCTs designed to improve pregnancy outcome need consideration; clinical endpoints such as gestational diabetes, preeclampsia, or LGA and small for gestational age (SGA) may be more relevant than GWG.
- There is a need for improved management or treatment of adverse outcomes associated with obesity, such as gestational diabetes and preeclampsia.

MATERNAL OBESITY AND THE HEALTH OF THE CHILD IN LATER LIFE

The "Developmental Origins of Disease" hypothesis, which suggests that elements of heritability can be transmitted in a non-Mendelian way from generation to generation has been proposed for the transmission of obesity risk from mother to child (6,26,27). To date, investigations addressing this in obese pregnancies remain relatively scarce compared with those who have investigated the consequences of fetal growth restriction. However, several cohort studies report an association between maternal early or prepregnancy BMI and offspring BMI assessed at birth, in infancy, childhood, and early adulthood (28–30). Others have shown an association with GWG and offspring BMI (31). Despite the attempts to eliminate confounding, it remains unproven whether these associations represent an intrauterine influence, or more simply, reflect shared familial, genetic, or lifestyle characteristics. Some authors who have compared maternal-offspring with paternal-offspring adiposity associations have reported stronger relationships with maternal BMI (32), but others show the maternal and paternal associations to be similar, even after correction for possible nonpaternity (33). At present, it is concluded that there is no strong evidence of an intrauterine effect (or other maternal specific effects), but with the caveat that the majority of investigations addressing this hypothesis have been carried out in historic cohorts with a low incidence of maternal obesity. One report has assessed obesity in siblings born to women before and after substantial weight loss after bariatric surgery for obesity (BMI >40 kg/m^2). Although a small study that requires replication, the siblings born after maternal weight loss had lower BMI and obesity risk (34).

Thus, given the current level of evidence, we cannot conclude that the current obesity epidemic is driven by intergenerational transmission mediated through the intrauterine environment. However, associations between maternal, paternal, and child obesity urgently need to be addressed in cohorts with an incidence of maternal obesity that reflects contemporary populations. Moreover, better observational studies are needed that exploit within sibling comparisons and perhaps Mendelian randomization approaches (35) with careful follow-up of the offspring. Lifestyle intervention RCTs in obese mothers are likely to be particularly informative.

GDM AND OFFSPRING HEALTH

Maternal prepregnancy obesity is strongly associated with risk of GDM, and so, we also considered the association of GDM with offspring health. Observational evidence from different populations constantly shows an association between GDM and macrosomia. Less-profound disturbance of blood glucose, and perhaps other metabolites, may also influence macrosomia and infant body composition as shown by the HAPO study, in which a strong linear association between fasting and postchallenge glucose and the incidence of macrosomia and neonatal adiposity was found in 23,000 nondiabetic mother-baby pairs (36). Relevant RCTs include the Australian Carbohydrate Intolerance in Pregnant women Study (ACHOIS) in pregnant women with GDM, in which serious perinatal morbidity, including LGA, was reduced by dietary advice and, if needed, insulin (20%). Interestingly, there was 1.4 kg less GWG in the intervention group (37). This and the recent RCT of similar design in women with mild GDM (38) provide some evidence for a causal relationship between maternal glycemic control and delivery of an LGA and fatter infant.

Pima Indians living in the United States (but not in Mexico) have a high incidence of obesity, type 2 diabetes, and GDM, which is associated with greater offspring BMI and obesity risk up to the age of 21 y. Evidence from other, in particular, European and North American populations for this association is less consistent. Among the Pima population, evidence that the association reflects, at least in part, intrauterine mechanisms comes from a sibling study showing increased risk of obesity in offspring born to mothers after their diagnosis of diabetes (*i.e.* offspring exposure to *in utero* maternal GDM) compared with their siblings born before the mothers diagnosis (not exposed to *in utero* maternal GDM) (39). More recent studies from other populations, *e.g.* from Denmark also provide some support for an influence of GDM on offspring overweight/metabolic syndrome (40).

Inevitably, the interdependence or independence of the relationships between maternal diabetes and obesity with offspring adiposity have proven difficult to define, and these will need to be readdressed if the recommendations of the International Association of Diabetes and Pregnancy Study Groups (IADPSG; Ref. 41) are adopted because the lowered threshold for diagnosis of gestational diabetes will increase the number of obese women with a diagnosis of GDM.

INSIGHT INTO MECHANISMS

An in-depth appreciation of the mechanisms responsible for the association between obesity and adverse pregnancy outcome is fundamental if we are to design effective safe interventions. Several metabolic pathways are likely to influence fetal development and neonatal outcomes and contribute to adverse maternal outcomes. Placental nutrient transport could also be influenced by maternal obesity.

Maternal blood glucose is subtly increased among obese women (42). Even modest increments can influence fetal growth and adiposity, as evidenced by the HAPO study (20,36). However, these associations do not provide proof of causality. Other pertinent parameters include raised maternal triglyceride and fatty acids, and fetal insulin concentrations that may contribute to fat accretion in the offspring. The maternal and cord blood leptin concentration is elevated, and there is evidence of a low-grade inflammatory state in the mother with higher levels of C-reactive protein (CRP) and IL-6 (43,44). In adults, this elevation of inflammatory mediators is linked to insulin resistance, suggesting that the same mechanisms may underlie the observed increases in maternal glucose, lipids, and amino acids in obese pregnancy. Importantly, a recent study in obese pregnancies has shown a similar association between fetal adiposity and fetal insulin resistance *in utero* with an increase in the concentration in cord blood of the inflammatory mediator, IL-6, suggesting that metabolism may already be compromised at birth in infants of obese mothers (42).

Although human cohort studies remain equivocal regarding the prolonged consequences of the metabolic sequelae of maternal obesity on the child, animal models have provided strong evidence for persistent and adverse effects of maternal obesity on the offspring (45,46). Most of the earlier studies of "developmental programming" in animals (rodents, sheep, and primates) focused on fetal undernutrition, and these strongly supported the associations reported in human cohorts between fetal growth restriction, LBW, offspring metabolic, and cardiovascular disorders (47,48). Recently, rodent models of diet-induced obesity have reported that the offspring develop increased adiposity, insulin resistance, and hypertension (49–51). The precise mechanisms remain unclear; for effects to be persistent, "programming" must include permanent changes in cellular structure or function in the offspring in response to the metabolic consequences of maternal obesity. For example, the plasma concentration of leptin is increased in neonatal offspring of obese rats, and it is hypothesized that elevated levels of this hormone, recently found to play an important neurotrophic role in hypothalamic development, may disrupt neuronal connections between the nuclei that control energy balance, leading to persistently increased appetite (52,53). Fetal hyperinsulinemia in response to maternal hyperglycemia could also be playing a similar neuroregulatory role (54). Precocious development of neonatal fat depots or persistently altered adipocyte metabolism and proliferation in development in response to the fetal metabolic and hormonal profile may also contribute to obesity in later life, as recently suggested from a human cohort study (55). Although fetal hyperinsulinemia and hypertriglyceridemia most likely fuel fetal growth, some specific hormones and nutrient signals may provide stimuli for precocious adipose tissue development, which could then persist into adulthood. Glucocorticoids may be involved and fatty acids are prime candidates, particularly because a raised n-6:n-3 fatty acid ratio has been implicated from rodent studies in premature adipocyte maturation and proliferation (56). The western diet has changed over the past 50 years because of the increasing use of vegetable oils in the food chain, leading to a higher intake of n-6 fatty acids and a gradual reduction of n-3 intake during the past 2 decades. This shift in n-6:n-3 intake (57) could theoretically have played a mechanistic role in the upsurge in childhood obesity, through changes early in life in adipocyte development or, potentially, through long-term influences of inflammatory cytokines. Because of the potential benefit of lowering the n-6:n-3 ratio, an RCT in pregnant women of low n-6:n-3 enriched fatty acid mix (fish oil capsules, 1.2 g DHA and EPA plus, 300 mg "normalized" arachidonic acid intake; n-6:n-3, 3:1) *versus* a well-balanced healthy diet (n-6:n-3, 6:1) was recently undertaken (58) and the results, which include measures of neonatal adiposity, are awaited with interest.

The mechanism whereby nutrient status in early life can permanently influence the metabolic phenotype of the offspring is likely to involve epigenetic modification of DNA; this may lead to permanent change in organ structure or cell number as outline above or to persistently altered gene expression leading to altered metabolic function. Animal studies have provided some evidence to support this mode of transgenerational non-Mendelian inheritance (59). Studies in animals are now addressing the hypothesis that elements of the obesity-related metabolic dysfunction in the mother may lead to altered DNA methylation or acetylation status or to altered histone structure in the offspring. Such epigenetic processes may contribute, for example, to the recently described altered hepatic expression of IGF-2 and key microRNAs in adult offspring of mice exposed *in utero* and during lactation to a maternal fat rich diet (60).

RECOMMENDATIONS

- Assessment of relationships between maternal obesity and offspring health would be facilitated by studies in contemporary birth cohorts with a higher incidence of maternal obesity, and in children born to women in the intervention and control arms of ongoing studies primarily designed to improve pregnancy outcome (*e.g.* UPBEAT, New Life, LIMIT, and Fit for 2).
- Dietary interventions in future RCTs in obese pregnant women should be better tailored to current theory, *e.g.* to reduce the maternal glycemic load and prevent insulin resistance, reduce maternal dietary n-6:n-3 ratio, and lower neonatal leptin. Relationships between maternal dietary composition and short- and long-term childhood outcomes should be addressed.
- Recent RCTs designed to address efficacy of an intervention in diabetic pregnancies on maternal and short-term neonatal outcomes, and large observational studies such as HAPO

provide an opportunity to interrogate inheritance of obesity through childhood follow-up.

- Long-term follow-up should be included in protocols for studies of obese pregnancies and funding provided to enable follow-up without interruption throughout childhood and into adulthood.
- In interrogation of inheritance of obesity, determination of parental, neonatal, and childhood adiposity and fat distribution using specific methodology may be required, in addition to more conventional measures, *e.g.* BMI. Measurement of growth trajectories in the fetus would be of value.
- Assessment of inheritance of obesity risk would also be facilitated by collection of paternal and maternal and child DNA in addition to maternal and cord blood biomarkers, methylation status of genes to address epigenetic pathways, placental transport pathways, and nutrient transfer mechanisms.

CONCLUSIONS

Obesity among pregnant women is becoming one of the most important women's health issues for this decade. The evidence available on both the short- and long-term health impact for mother and child currently favors actions directed at controlling prepregnancy weight and preventing obesity in women of reproductive ages. This recommendation is driven by the paucity of good research evidence from either RCTs or through basic scientific mechanisms, which would underpin putative benefit from GWG recommendations for health outcomes in mother and child. This applies to all pregnant women and subgroups. RCTs are urgently needed to evaluate the effect of nutritional and behavioral interventions in pregnancy on short- and long-term outcomes in mother and child, with a sound scientific basis. The suggestion that maternal obesity may transfer risk of obesity to the child through nongenomic mechanisms, although supported by studies in animals, requires further detailed investigation in human RCTs with provision for long-term follow-up of the children.

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A list of contributors to the Workshop is available as supplemental digital content on the journal's Web site (http://links.lww.com/PDR/A65).

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