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Early Life Nutritional Programming of Obesity: Mother-Child Cohort Studies

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Pregnancy · Obesity · Insulin resistance

Abstract
Background: The obesity epidemic has resulted in more overweight/obese women before and during pregnancy. Their offspring tend to have higher birth weights and more body fat, and carry an increased risk of obesity later in life. These effects may partly be related to the heightened risk of gestational diabetes, occurring in at least 16% of all pregnancies irrespective of current body weight. ***Methods:*** An ILSI Europe workshop reviewed the key contributors leading to adverse outcomes in pregnancy and childhood, including gestational weight gain and nutrition. New research opportunities from prospective mother-child cohort studies were explored. ***Results:*** Simple measures of gestational weight gain provide insufficient detail of the underlying physiological and metabolic adaptations occurring in pregnancy, and should be complemented by measures of body composition, metabolic and endocrine responses. Recordings of maternal dietary intake and nutrient status are often limited and potential correlations with gestational weight gain have been poorly studied. Many pregnancies in overweight/obese women are uncomplicated and result in offspring of normal weight, leaving the main determinants of later adverse outcomes to be clarified. ***Conclusions:*** The workshop provided insights of primary measurements for the characterization of sustainable nutritional intervention strategies in the mother, infant and child for preventing obesity in later life.

Introduction

The current obesity epidemic has resulted in an increasing number of overweight and obese women entering pregnancy [1]. These mothers are more likely to have infants with increased birth weight, including macrosomia (birth weight >95% percentile) and higher neonatal fat mass at birth, as well as an increased risk of having infants born preterm or small for gestational age [2, 3]. Ultimately, these children carry a greater risk of development of abdominal or general obesity and related metabolic disorders later in life [2]. Despite the growing evidence showing both short and long-term consequences of maternal obesity for child health, there are important gaps in the knowledge about the mechanisms involved.

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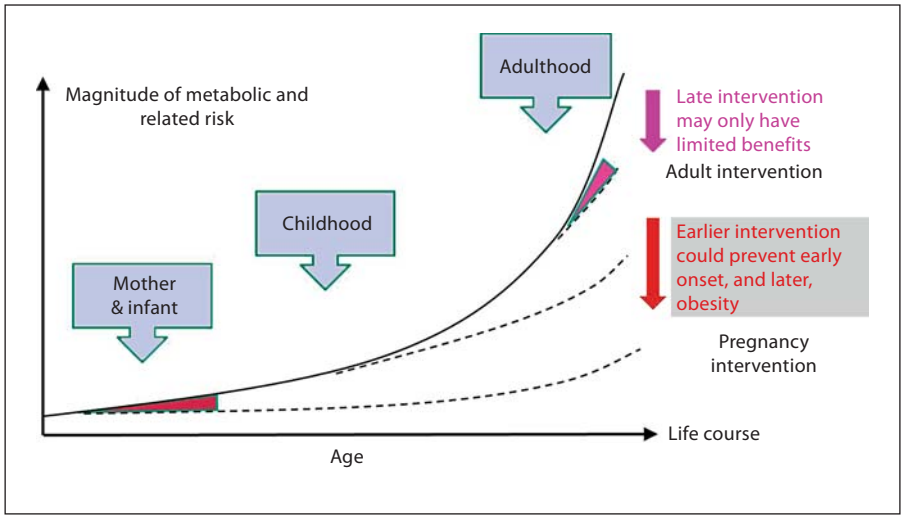

Fig. 1. Summary of the potential lifetime benefits of early intervention in the mother and/or infant for preventing later adverse outcomes of obesity. Derived from Godfrey et al. [73].

These include the potential contribution of factors such as maternal diet, gestational weight gain and metabolic perturbations during pregnancy, and the extent to which the postnatal diet and feeding practices may modify or determine the long-term health risks.

A workshop organized by the International Life Sciences Institute (ILSI) Europe in October 2011 was designed to discuss how current and future cohort studies can increase our knowledge and understanding of the mechanisms, especially those which are nutrition related, that may be associated with an increased risk of adverse pregnancy and childhood outcomes in obese pregnant women. Although maternal obesity during pregnancy has been linked to other adverse child health outcomes, the scope of the workshop was focused upon risk of obesity in childhood and related metabolic disorders. The aim of the workshop was to explore the potential value of combining cohort data in relation to how maternal obesity and diet influence the early nutritional environment of the fetus and interact with the postnatal environment to determine childhood body composition.

This paper summarizes the findings from the workshop and in particular discusses current knowledge in this area to identify research priorities and/or strategies that could help to identify optimal methods for undertaking observational research in humans to address those research priorities, and considers the key challenges in translating this information to potential intervention strategies. Following this approach we address the opportunities and possible limitations of using existing cohorts to increase our understanding of long-term effects of maternal nutrition in pregnancy on child obesity risk. Ultimately we aim to provide guidelines for future research that will enable us to establish the long-term benefits for both the mother and child. Ideally this could establish whether the benefits for long-term metabolic health are enhanced the earlier an intervention is introduced to prevent obesity, as summarized in figure 1.

In many developed countries, and especially in Europe, a significant number of studies on pregnancy, birth and child cohorts are ongoing, enabling collaboration and complementary research in a way not feasible just a decade ago. An overview of these can be found at http://www.birthcohorts.net/. Combining the results from such studies therefore opens the possibility to determine the potential contributions of diet and maternal prepregnancy weight, pregnancy weight gain, birth weight and postnatal growth to adult body composition, as illustrated by the pooled analysis of data from several EU-based cohorts under the CHICOS initiative [4] as well as the recent initiative to combine data from cohorts in low and medium income countries [5, 6].

How Do Maternal Obesity and Diet Influence the Early Nutritional Environment of the Fetus?

The mechanisms through which maternal obesity may 'program' obesity and related metabolic disorders during pregnancy and after birth are uncertain. An increasing number of publications indicate that maternal obesity can result in chronic inflammation and oxidative stress [7]. These conditions may, for example, impair pla-

centation and establishment of adequate blood supply, perhaps altering fetal metabolism [8]. Fetal changes in growth and body composition may also be related to the heightened risk of insulin resistance early in pregnancy and of the development of gestational diabetes [9], though much remains uncertain about the long-term consequences of these metabolic disturbances [10]. Moreover, while obese women are at greater risk, there is increasing evidence that at least 16% of all women can show signs of metabolic disturbances especially in glucose homeostasis irrespective of body weight [11], as raised glucose alone can increase the risk of offspring obesity [12]. Thus, obesity risk in children linked to maternal nutritional status may occur among women at both extremes, both high [13] and low [14] body mass index (BMI), as well as normal weight women.

Differences in dietary intake and diet quality during pregnancy among overweight or obese women may play an important role in the early development of the fetus and increase child obesity risk. There have been a large number of epidemiological studies in both historical and present day mother-child cohorts as well as animal intervention studies that have explored the impact of maternal diet during pregnancy and lactation on the long-term health of the resulting offspring [15]. However, studying these relationships in more detail in animal studies is often hampered by the fact that more extreme over-nutrition than seen in human populations (e.g. a 4-fold increase in total fat intake compared with controls [16]) as well as under-nutrition are the most used approach. Also, data collection on nutrient intake in epidemiological studies are often limited to a single point in time during pregnancy and lack specificity due to an absence of biomarker measurements, e.g. nutrient status. Thus, the evidence-based pool of knowledge enabling us to provide targeted nutritional advice to women, especially those that are obese, to improve nutrition and health status before, during or after pregnancy, remains limited. Although maternal weight gain is clearly associated with birth size, data collected at week 27 of pregnancy in a large cohort study did not show an association between birth weight and the total intake of either energy or specific macronutrients [17]. It was suggested that the immediate effects of maternal obesity on the offspring may be exacerbated only upon further exposure to an obesogenic diet. This has led to an increased focus on the possible contribution of maternal excessive weight gain throughout pregnancy, though again, links with child obesity remain to be established [18, 19].

Clearly, factors other than diet alone can also be important and will include a range of lifestyle components such as exercise and socio-economic status [16]. Indeed, the implications of maternal obesity, gestational weight gain and diet during pregnancy for a child's long-term risk of obesity remain uncertain and this may be partly related to the extent to which such associations are attributable to shared family environments beyond the womb, such as postnatal diet and activity patterns, which have not always been taken into account [20].

An imbalance between food intake and level of physical activity is frequently reported to be a primary mechanism behind the global rise in obesity although again there are likely to be many modifying factors [21]. It is noted that even a small change in energy balance on a daily basis may, over time, lead to obesity [22], which means our ability to prevent excess weight gain, both in women of reproductive age as well as their offspring, remains a challenging target.

A wide range of studies in (non-pregnant) adults are now starting to identify the optimum diets for both promoting and maintaining weight loss [23], as well as for preventing weight gain. Critical components of these diets include their overall energy content together with the quantity and quality of fat and fiber, in addition to glycemic index and protein and micronutrient content. These factors further interact and add more complexity to the topic as a simple focus on energy intake may not solve the problem. Also, a trend for increased intake of nutritional supplements by pregnant women is seen irrespective of their nutritional status and current body weight, and the long-term consequences are currently unknown [24]. In many women, dietary preferences can change, especially in early pregnancy [25], although whether this contributes to the consumption of a nutritionally imbalanced diet or later adverse effects, especially in obese women, remains to be explored. A clear challenge is to establish whether or not these aspects of maternal diet, at defined stages of gestation, may be correlated not only with maternal metabolic status and body composition, but also with gestational weight gain, and importantly with subsequent body composition development in the offspring. Moreover, the extent to which prenatal effects may interact with the long-term impact of postnatal feeding practices, such as duration of breastfeeding and/or timing and type of weaning diets adopted, is of interest [26].

It is now apparent from studies into pregnancy-induced preeclampsia that both the severity of the disease and the birth outcomes are dependent on whether maternal complications commence in early or late pregnancy

[27, 28]. A comparable situation may also occur with regard to potential adverse effects of maternal obesity as well as gestational diabetes (irrespective of maternal body weight before pregnancy). It will therefore be important to identify those women who may show an early adverse response to pregnancy, such as compromised placental function, and consider the relative contribution of total fat as well as body fat distribution and early weight gain together with measurements of both macro- and micronutrient intake [29]. Central as opposed to peripheral adiposity is a primary determinant of the metabolic syndrome [30], so a more detailed assessment of relative fat distribution both before and through pregnancy is necessary. These types of measurements can then be related to body composition outcomes both at birth and through infancy, and are now being examined directly by a European Union Framework project entitled Early Nutrition [31].

An adverse body composition, in terms of relative muscle and fat distribution, and how this may change and/or be nutritionally sensitive in the fetus and offspring remains to be defined. These characteristics also change in women with more extreme BMI, which in terms of dietary guidelines and the validation of biomarkers will mean a range of 'at risk' classifications. For example, prevention of preterm/still birth and/or small for gestational age infants in women with a very high BMI could require separate dietary guidelines and/or interventions. Ultimately we need to provide an evidence-based consensus of the impact of maternal diet and its relationship with metabolism at birth and longer-term outcomes relating to obesity risk. Establishing optimal gestational weight gain in relation to health outcomes in mother and offspring would enable weight control from preconception to postpartum to be integrated into clinical practice. In summary, more research is needed to unravel how maternal obesity, diet during pregnancy and (early) gestational weight gain influence the early nutritional environment of the infant [2].

How Do Maternal Obesity and Diet Interact with the Postnatal Nutritional Environment to Influence Body Composition of the Child?

At present, the specific aspects of maternal diet during pregnancy that may influence later child obesity remain uncertain. Few consistent results have been obtained thus far from trials and observational studies in developed country settings [32]. To date, most animal studies that have induced maternal obesity tend to compare diets that differ greatly in their macronutrient composition and result in a rapid, rather than gradual, increase in maternal body weight [16]. At the same time most interventions do not produce offspring whose birth weight is increased to enable a direct comparison with the human situation. Also, when subjected to meta-analysis they provide a limited evidence base to suggest targeted interventions in obese women [33]. Nonetheless, some studies do provide interesting findings for further investigation. For example, one recent rodent study suggested that shifting from a high-fat diet to standard chow 1 month before mating may help reverse risk of obesity and metabolic programming [34]. Though observational studies have not confirmed this finding, further research is warranted given a potential link between maternal carbohydrate consumption with epigenetic changes and childhood adiposity [35]. For example, an association between 20% increments in methylation of the retinoid X receptor-α chr9:136355885+ in umbilical cord blood and either total or percent fat mass in the offspring at either 6 or 9 years of age was shown in children of normal body weight [35]. Further insights may be gained from well-designed experimental research exploring more moderate changes in micro- as well as macronutrients [36]. These studies may also help us to understand the relative contribution of imbalances in the macronutrient composition, e.g. a relative increase in fat, protein or carbohydrate in an isocaloric setting.

Brown Adipose Tissue Thermogenesis

It should also be noted that the fat mass of newborn infants is much greater than the majority of other animal species used to study adipose tissue development experimentally [37]. Moreover, adipose tissue in the newborn comprises different depots of both brown and white fat. Whereas the latter represents a storage depot, brown fat contains a unique uncoupling protein that is rapidly activated at birth and is essential in enabling the newborn to effectively adapt to cold exposure of the extra-uterine environment [38]. The activity of brown adipose tissue has now been shown to be greater in healthy children than adults [39] and specific depots of brown fat, including those located around the supraclavicular depots, are retained into adulthood and can have an important role in energy balance [40]. Adult obesity is accompanied by a significant reduction in the amount of brown adipose tissue [41], although the extent to which body composition changes with age, BMI and during gestation has yet to be

quantified despite this now being feasible [39]. It is therefore important that the growth, development and function of different fat depots are examined together with how these can be influenced by both the pre- and postnatal nutritional environment. Furthermore, changes in fat growth could be accompanied by changes in the development of appetite control that is centrally regulated and continues into postnatal life [42], both of which are likely to be influenced by the maternal/infant genotype as well as current diet. To date, these aspects have not been included in any mother-child cohorts. Altogether these arguments emphasize the enormous potential of early intervention and the need to identify key diet- and nutrient-related determinants during pregnancy as the most effective way forward to change the developmental path towards future obesity and metabolic-related problems.

Adipose Tissue Growth, Gender and Diet

In terms of examining the long-term outcomes, adipose tissue is one of the fastest growing organs in early life [43] and simply measuring body weight or total fat mass at a fixed time point in infants and/or children provides very limited insights into later body composition or whether that individual is at greater risk of later obesity. Birth weight and body composition, especially fat mass, are gender dependent and these differences persist through infancy, at least in breast-fed infants [44]. A range of factors determine fetal adiposity, including maternal body composition [45], whilst formula feeding can affect adiposity [46], a response that can be transiently enhanced in offspring of obese mothers [47]. The effect of gender on adiposity may be amplified with maternal obesity, as it has recently been shown that post-term girls are slimmer than term girls at birth whereas in boys, those born post-term show accelerated weight gain and subsequently have a much higher incidence of obesity compared to term boys [48]. It remains to be established whether formula feeding per se can have a long-term influence on either weight and/or fat growth in a gender-dependent manner, although accelerated postnatal growth is an established risk of later obesity.

Ultimately the child's own diet and activity patterns, both important influences on obesity risk, will be largely dependent on the type of diet and lifestyle within the family, as will family decisions regarding the duration of breast feeding and both the timing and type of diet introduced at weaning. Currently, the extent to which breast feeding is protective against excess weight gain in early life [49] remains to be fully established although feeding from the breast as opposed to a bottle may influence appetite control [50]. Multi-generational studies also suggest transmission of obesity risk across generations is linked to high birth weight [51], but the transmission of dietary habits is also likely to contribute. Numerous dietary factors are likely to be relevant for child obesity risk, starting with breast versus formula feeding habits and protein intakes, but evaluating the role of multiple factors poses a challenge [52]. Lower breast feeding rates as reported among obese women are likely to contribute to obesity risk and perhaps differences in appetite regulation among their children [53]. With respect to the quality of postweaning diets, it is important to note that the extent to which familial dietary environments are shared is not well established and correlation of intakes within parent child dyads is modest [54].

It is clear that a focus on maternal diet during pregnancy should be combined with a greater understanding of the impact of postnatal factors. For example, the substantial change in plasma concentration of placental hormones following the establishment of the placenta can be accompanied by the onset of maternal nausea and decline and/or change in her food preferences [55]. Ultimately this is a developmental process in which responses that occur initially within the mother on becoming pregnant can impact on embryogenesis and placentation. This can determine placental function and nutrient supply to the fetus, thereby influencing fetal growth and weight and body composition at birth [56]. For those infants that are breast fed, maternal diet may not only influence mammary gland development but also milk composition as seen in a porcine model [57]. However, for those infants who are fed entirely on formula milk, it is easier to record their food intake and make a more direct association between dietary composition and current growth and body composition.

As is the case for maternal diet, animal studies to date on postnatal feeding and obesity have not addressed several key issues. This includes the extent to which formula feeding as opposed to breast feeding influences the intake of bioactive compounds [58] and thus later body composition, and will include modifications in formula with time [59]. Investigations indicate that changes in macronutrient intake together with the amount of food consumed impact on fetal growth and development [60], but the extent to which these adaptations persist, or are modified through lactation or beyond, are unknown.

Table 1. Summary of optimal requirements and outputs when undertaking mother-child cohort studies in order to assess the role of maternal and infant nutrition on later obesity

Dietary intake/ pattern	Nutrient status assessment	Body composition	Other measurements	Stage of development	Potential biases/ confounders
Mother					
Specific dietary components versus patterns of food eaten	Glucose tolerance; prefeeding metabolite concentration	Fat distribution; placental size and function	Physical activity; socio-economic status; parity; ethnicity	Preconception; changes with gestation	Gender of fetus
Infant					
Breast versus formula	Hormones and metabolites in cord blood	Birth and growth weight; adipose tissue mass, distribution and composition; muscle mass	Gender	From birth up to weaning	
Child					
Weaning; childhood	Glucose tolerance; prefeeding metabolite concentration	Adipose tissue mass, distribution and composition; muscle mass	Gender; physical activity	From time of weaning up to puberty	

What Are the Implications and Learning Points for Mother-Child Cohort Studies?

Existing cohorts that have recruited women during pregnancy and begun to follow children to monitor health outcomes provide an opportunity to explore the potential role of specific aspects of the maternal diet, her genotype and social environment on the offspring. In addition to substantial variability in environmental exposures such as pollutants [61], these cohorts span countries with a wide range of food cultures and prevalence of maternal and child obesity [62]. Importantly, within the context of the current obesity epidemic, this enables women of different body mass and nutritional status to be studied in much more detail. It is recognized that dietary assessment is inherently difficult and that the adoption of simplified approaches to characterize diet-based concepts such as 'a prudent dietary pattern' may offer distinct advantages [63]. Furthermore, in cohorts studying a range of disease outcomes, combining data from multiple 24-hour recalls either with data from food frequency questionnaires (FFQs) that better reflect episodic foods [19], or with biomarkers which provide objective estimates of intakes [64], has been shown to increase validity and reduce bias in estimates of associations between dietary intakes and health. These approaches are increasingly feasible with the advent of technological advances that reduce the cost and logistical complexity of collecting valid 24-hour recalls via web-based tools among both adults and older children [65].

As these new cohorts also follow offspring into childhood, they provide the opportunity not only to assess health outcomes including obesity, but to evaluate the role played by a child's postnatal diet and activity. These would have the potential to assess the role of genotype [66] as well as socio-economic and related demographic factors [67].

This introduces the challenge of how to unify the findings made, as each study varies considerably in the breadth and depth of dietary data collected. In addition, most of these data are based on food intake and the extent to which this is translated systemically, perhaps even dependent on maternal health and BMI and/or the pregnancy stage, are not studied.

Examples of the types of data integration that are needed include:

1. Adequate assessment to determine the extent to which data allow an estimate and ranking of intake of specific nutritional factors and related metabolic factors. Dietary assessments will vary in terms of capturing sufficient dietary detail to adequately estimate variability in intakes for the relevant nutrients, foods and food groups, and when precisely data were collected. For example, in FFQs, are different types of fish and seafood assessed in sufficient detail to rank subjects with respect to fatty acid intakes, or types of vegetables disaggregated to allow accurate estimation of folate intake?

2. Measurement error and misreporting may also vary across different protocols, with FFQ tending to

have more error and bias, noting that these issues will be relevant to all methods that rely on self-reported intake. This is particularly problematic in studies on obesity, as misreporting and bias have been found to be strongly linked to weight status [68]. Addressing error and bias may be essential for obtaining valid results. For some dietary factors, biomarkers of intake may be a useful objective tool for calibrating and reducing error and bias in reported intake data. Though dietary recalls and records which also involve self-reporting tend to suffer less from error and bias than FFQs, use of these methods in large-scale studies are currently limited by cost and participant burden. For new studies, including follow-up of children, a range of new technologies and platforms are being developed that would allow more cost-effective assessment of both diet and physical activity via recalls or records, potentially improving data quality and precision [69].

3. Dietary intakes at certain times in pregnancy, including around the time of conception and embryogenesis, may be especially relevant for long-term obesity risk [70]. Although diet is thought to change relatively little during pregnancy, data collected at times closer to the most relevant periods may yield stronger associations with later outcomes [71].

The objectives of undertaking pooled analyses of dietary and related data would aim:

- to provide a more comprehensive review of priority areas that should be addressed in future (and current) studies in order to establish the main mechanisms involved;
- to determine the limitations of individual studies;
- to maximize the research potential of the data through analysis of new pathways;
- to examine the causes of any heterogeneity;
- to assess a wider range of dietary exposure;
- to undertake comparative analyses between different stages of gestation – a key challenge will be to establish the relevant contributions of single compared with multiple dietary factors.

In summary, the majority of mother-child birth cohorts have been studied in isolation with maternal dietary information taken at only one particular stage of gestation. The potential to combine the large number of current studies and include both maternal and infant nutritional data is clearly attractive. It could also lead to the identification of relevant biomarkers from either the mother or her infant to enable early intervention in those women most at risk of producing offspring with disproportionate fat mass. The workshop provided a summary of primary measurements to enable the characterization of sustainable intervention strategies in the mother, infant and child for preventing obesity in later life (table 1).

This type of strategy could match the advances made from a comparable approach adopted within genome-wide association studies [72]. It would therefore require significant computational input together with the utilization of mathematical modeling.

Ultimately, individual dietary factors, or groups of dietary compounds, could be identified as promoting beneficial child health outcomes such as reduced risk of obesity among women defined as being obese or overweight. This could foster the translation to randomized clinical trials in 'at risk' women either before or during pregnancy. In addition, evidence-based public health campaigns could be introduced across the European Union aimed at raising women's awareness of the vital importance of preventing (the development of) excess fat mass to both their own and their infant's future health.

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