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Influences of the perinatal diet on maternal and child health: insights from the GUSTO study

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Maternal and child health are intrinsically linked. With accumulating evidence over the past two decades supporting the developmental origins of health and diseases hypothesis, it is now widely recognised that nutrition in the first 1000 d sets the foundation for long-term health. Maternal diet before, during and after pregnancy can influence the developmental pathways of the fetus and lead to health consequences later in life. While maternal and infant mortality rates have declined significantly in the past two decades, the growing burden of obesity and chronic non-communicable diseases in women of reproductive age and children is on a rapid rise worldwide, in developed and developing countries. A key contributory factor is malnutrition, which is a consequence of consuming poor quality diets. Suboptimal macronutrient balance and micronutrient inadequacies can lead to undesirable maternal body composition and metabolism, in turn influencing the health of the mother and leading to longer-term metabolic and cognitive health consequences in the infant. The GUSTO (Growing Up in Singapore Towards healthy Outcomes) study, a mother–offspring multi-ethnic cohort study in Singapore, has contributed to this body of evidence over the past 10 years. This review will illustrate how nutritional epidemiological research through a birth cohort has illuminated the importance and urgency of maternal and child nutrition and health in a modern, industrialised setting. It underscores the importance of a number of critical nutrients during pregnancy, in combination with healthy dietary patterns and appropriate meal timing, for optimal maternal and child health.

Perinatal diet: Maternal health: Child health

Abbreviations: GDM, gestational diabetes mellitus; GWG, gestational weight gain; GUSTO, Growing Up in Singapore Towards healthy Outcomes.

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Importance of maternal and child health

Historically, the health of populations is depicted by maternal and infant mortality rates, a reflection of the health of women and infants. Often a consequence of poverty, poor sanitation, lack of healthcare and undernutrition, these issues tend to be synonymous with low income, developing countries. However, in a changing global nutrition landscape, influenced by economic and income growth, urbanisation, demographic change and globalisation, maternal and infant mortality rates have declined significantly in the past two decades[1]. Instead, the prevalence of obesity and chronic non-communicable diseases in women of reproductive age and even children are on a rapid rise worldwide, whether in developed or developing countries[2,3].

A key contributory factor is the consumption of poor quality diets, which results in malnutrition irrespective of body weight status. Developing countries, in particular, face the double burden of malnutrition, characterised by the coexistence of undernutrition along with overweight and obesity, or diet-related non-communicable diseases[4]. Consequently, maternal health during pregnancy is now commonly marked by increasing prevalence of pregnancy complications such as excessive gestational weight gain (GWG), gestational hypertension and gestational diabetes mellitus (GDM), these leading to poor birth outcomes such as preterm births and babies born small or large, for gestational age[5].

With cumulative evidence from the past two decades supporting the 'fetal origins of adult disease' hypothesis, it is now recognised that the risk of many non-communicable diseases can begin as early as during fetal development. It is well established that nutrition in the first 1000 d sets the foundation for long-term health[6]. Maternal diet before, during and after pregnancy can influence developmental pathways in the fetus and lead to consequences for disease onset in the future child and adult. Thus, suboptimal macronutrient balance and micronutrient inadequacies during pregnancy or prior can lead to undesirable maternal body composition and metabolism, in turn impacting on the health of the mother and leading to longer-term health consequences in the infant, including metabolic and cognitive health[7].

Using data from the first mother–offspring cohort study in Singapore, the Growing Up in Singapore Towards healthy Outcomes (GUSTO) study, this review describes how nutritional epidemiological research through a birth cohort in the past 10 years has illuminated the importance and urgency of maternal and child nutrition and health in a modern, industrialised setting. It aims to underscore the importance of a number of critical nutrients during pregnancy, in combination with healthy dietary patterns, for optimal maternal and child health.

Methodology

In Singapore, the national nutrition surveys do not routinely capture dietary data of pregnant women, infants and children. One of the aims of the GUSTO study is to fill a void here, collecting data to characterise and understand diets of pregnant women, infant and children in Singapore, a multi-ethnic Asian population, and relating these to health outcomes in the mothers and children. Additionally, in a relatively affluent and developed country such as Singapore, it is unknown if malnutrition, particularly micronutrient insufficiencies, do exist. To what extent is the fetal origins of adult disease hypothesis relevant in such settings? GUSTO set out to uncover some of these questions.

From June 2009, first-trimester pregnant women aged 18–50 years (*n* 1247) were recruited from the two primary public maternity hospitals in Singapore: KK Women's and Children's Hospital and National University Hospital, to participate in the GUSTO study. These participants were citizens of Singapore or permanent residents who intended to deliver in these two hospitals; planned to reside in Singapore for the next 5 years; agreed to donate placenta, cord and cord blood at delivery; and had spouses of the same ethnicity, both of whom had a homogeneous parental background of Chinese, Malayan or Indian descent. Women were not eligible if they received chemotherapy or psychotropic drugs or had serious health conditions such as type-1 diabetes mellitus. Various questionnaires were administered, anthropometric measurements taken and blood and other biological samples collected from the participants at first-trimester, mid-late trimester and at postpartum, while measurements and information on their offspring collected from birth and followed-up at close intervals in the growing up years. Dietary intakes of the participants (mothers) were ascertained by 24 h recalls and food diaries during the 26th–28th week of pregnancy, while plasma nutrient biomarkers from bloods taken during the same period were analysed to measure nutritional status. Details of the GUSTO study and measures collected can be found elsewhere[8].

Maternal macronutrient intakes

Dietary macronutrients were first examined to find out if mothers in GUSTO had suboptimal macronutrient balance during pregnancy. As a cohort, the GUSTO mothers were within the dietary recommendation for energy intakes (7962 (SD 2410) kJ) and macronutrients (15·6 (SD 3·9) % of energy from protein; 32·7 (SD 7·5) % from fats; 51·6 (SD 8·7) % from carbohydrates). When stratified by ethnicity, it was observed that Chinese mothers tended to consume higher amount of energy, particularly from protein and fat, whereas Indian mothers consumed the lowest amount of energy, with a significant proportion from carbohydrates (56·1 %)[9]. When these were examined in relation to GWG, it was observed that mothers with higher energy intakes had greater GWG, which is very much in line with the current literature[10]. Using substitution models, we further demonstrated that on isoenergetic diets, mothers with higher-carbohydrate, lower-fat intakes, particularly from sugary foods, had greater GWG (0·07 SD higher)

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than those with lower-carbohydrate intakes. These mothers also had 14 % higher likelihood of excessive GWG. When food groups were examined, mothers with the highest tertile of fruit and vegetable intake were found to be independently associated with 60 % lower likelihood of inadequate GWG. Additionally, those who had the highest tertile of plant-based protein foods intake were associated with 60 and 34 % lower likelihood of inadequate and excessive GWG, respectively. These provided clear and novel evidence that while total energy does matter in weight gain, the quality of the carbohydrates and the balance of macronutrients consumed are just as important[11].

Mothers' macronutrient intakes during pregnancy were additionally examined with the risk of offspring obesity. Our data revealed that a 25g increment of maternal sugar intake was associated with a 0·02 per month higher infant pre-peak velocity and a 0·07 higher BMI peak. Higher maternal carbohydrate and sugar intakes were also associated with a higher offspring BMI *z* score at ages 2–4 years[12]. A higher infant BMI peak and pre-peak velocity have been shown to predict higher cardiometabolic risk at ages 9–11 years, suggesting that suboptimal maternal nutrition can have long-term influence on offspring health, including heightened obesity risk[13,14].

To examine dietary fat quality, the levels of PUFA of mothers at mid-late trimester were measured in plasma. These were related to symptoms of antenatal and postnatal anxiety in the mothers, measured by the State-Trait Anxiety Inventory questionnaire. Mothers with lower *n*-3 PUFA, and higher *n*-6:*n*-3 ratios had higher likelihood of antenatal anxiety symptoms; no differences in postnatal anxiety symptoms were seen. No relationship between PUFA and symptoms of antenatal and postnatal depression was observed in this cohort[15]. It remains unclear if altered PUFA status is a cause or consequence of antenatal anxiety, but our findings suggest possible links via postulated mechanisms of neuroinflammation. Future studies are required to draw more definitive inferences on the direction of causality.

Interestingly, mothers with higher *n*-3 levels during pregnancy were also found to have smaller weight retention at 18 months postpartum, when compared to those with lower *n*-3 levels during pregnancy[16]. Specifically, after adjustment for confounders, higher plasma EPA, DHA and total *n*-3 PUFA concentrations were associated with lower postpartum weight retention (EPA: $b = 20{\cdot}62$ kg/1 % increase of total fatty acids; DHA: $b = 20{\cdot}24$ kg/1 % increase; total *n*-3 PUFA: $b = 20{\cdot}20$ kg/1 % increase), whereas a higher plasma *n*-6:*n*-3 PUFA ratio was associated with a higher postpartum weight retention ($b = 0{\cdot}21$ kg/unit increase). This suggests that an alternative strategy to assist postpartum weight reduction is by increasing EPA and DHA status together with a decreased *n*-6:*n*-3 PUFA ratio through a diet or fish-oil supplementation during pregnancy.

The benefits of maternal PUFA during pregnancy also extended to their offspring, influencing fetal and child growth and adiposity. Maternal linoleic acid, an essential *n*-6 fatty acid, was found to be positively associated with birth outcomes such as birthweight, BMI, head circumference and neonatal abdominal adipose tissue (measured by abdominal MRI), but not later growth outcomes. DHA levels, while not associated with birth outcomes, were related to postnatal length/height at 1 and 5 years of age[17]. While replication is needed, these findings suggest that maternal PUFA intake and/or metabolism during pregnancy may influence fetal and later child growth.

Maternal micronutrient intakes

Next, the micronutrient statuses of the GUSTO mothers were examined at mid-late trimester using plasma biomarkers. The findings emerged unexpected when compared to internationally recognised cut-offs. Despite routine supplementation during pregnancy (through prenatal supplementations given by gynaecologists), among 998 mothers, 56 % were deficient or insufficient in vitamin B_{12}, 41 % deficient or insufficient in vitamin D, 16·5 % deficient in vitamin B_6, 11 % deficient in folate, and 7 % deficient in iron (unpublished results). These data suggest that despite supplementation, the current diet quality of pregnancy is still far from adequate.

When relating these macronutrient deficiencies and insufficiencies to maternal health outcomes, it was striking to observe that the combination of high folate and vitamin B_{12} deficiency in pregnant mothers was associated with higher risk of GDM. A nearly doubled risk of GDM was observed in pregnant women who were insufficient in B_{12} but had higher concentrations of folate, compared to those with insufficient B_{12} but had the lowest concentration of folate[18]. Our findings replicated those in two other birth cohort studies in India, the Pune Maternal Nutrition study[19] and the Mysore Parthenon Study[20], which may allude to the higher risk of GDM in South Asian mothers and suggest an imbalance in the two B-vitamins being responsible for glucose intolerance. The exact mechanism linking the combined effects of low vitamin B_{12} and high folate on glucose intolerance and insulin resistance is still unclear. One possible explanation is that when vitamin B_{12} is insufficient, the conversion of 5-methyltetrahydrofolate to tetrahydrofolate is inhibited. This in turn disrupts the production of purines and thymidine for DNA/RNA synthesis. Impaired DNA synthesis, particularly of mitochondrial DNA, was observed to be associated with the development of insulin resistance[21]. These findings have much wider implications than for GDM alone, and could potentially contribute to reducing pregnancy complications and adverse birth outcomes associated with having GDM.

In collaboration with other birth cohorts internationally such as Generation R, Pune Maternal Nutrition study and the Norwegian cohorts, a meta-analysis led by Rogne *et al.*[22] found consistent evidence demonstrating that mothers with B_{12} deficiency or insufficiency during pregnancy had higher risk of preterm birth. This further highlights the need to carefully evaluate and

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manage folate and vitamin B_{12} status in pregnant women. Given the widespread vitamin B_{12} insufficiency in our GUSTO sample, this strongly suggests a need to consider shifting our attention to address this nutritional issue within the population particularly in Indian mothers and others at risk of vitamin B_{12} insufficiency.

Another micronutrient of concern is maternal vitamin D. Maternal deficiency and insufficiency levels in 25-hydroxyvitamin D were relatively high, particularly among the Malay and Indian mothers in GUSTO. This is despite Singapore being a tropical country. The influence on maternal pregnancy complications differed across ethnic groups, such that 25-hydroxyvitamin D insufficiency was associated with higher fasting glucose concentrations in Malay mothers and higher risk of emergency caesarean section in Chinese and Indian mothers[23]. Furthermore, neonates of mothers with mid-gestation 25-hydroxyvitamin D insufficiency had a higher abdominal subcutaneous adipose tissue volume, particularly metabolically active deep subcutaneous adipose tissue (metabolically similar to visceral adipose tissue in adults), even after accounting for maternal glucose levels in pregnancy[24]. These findings are consistent with those of previous studies in adolescents and adults, which observed inverse associations between vitamin D levels and visceral adiposity, measured by computed tomography or MRI[25,26]. Observed greater abdominal adiposity in neonates may place them at higher risk of cardio-metabolic diseases later in life. This suggests that beyond its known role in bone mineral metabolism, vitamin D has potential influence on offspring growth and adiposity, potentially extending to a range of chronic diseases including type 2 diabetes mellitus and CVD.

Maternal dietary patterns

Aside from nutrients, examining dietary patterns is of growing interest as it evaluates the overall diet and takes into account the interactive and synergistic effects among nutrients. This is often not achievable by studies that examine singular nutrients or foods[27]. Three distinct maternal dietary patterns were identified amongst the GUSTO mothers during pregnancy: the vegetable, fruit and white rice pattern, characterised by higher intakes of vegetables, fruit, plain white rice, whole-grain bread, fish and nuts and seeds and lower intakes of fried potatoes, burgers, carbonated and sweetened drinks and flavoured rice; the seafood and noodle pattern with its higher intakes of noodle soup, seafood, fish and seafood products, low-fat red meat and lower intakes of legumes, ethnic bread, white rice and curry-based gravies; and the pasta, cheese and processed meat pattern, characterised by high intakes of pasta-, tomato- and cream-based gravies, cheese and processed meat.

It was observed that the maternal vegetable, fruit and white rice diet pattern tended to confer better child health outcomes, such as being associated with lower risk of preterm births[28] and lower child adiposity, indicated by a lower BMI *z*-score and lower sum of skinfold thickness until 4·5 years of age[29]. However, it appeared that high adherence to this pattern was also associated with risk of larger birth size[28]. Conversely, mothers who adhere to the seafood and noodle pattern tended to have lower risk of GDM[30]. We speculate that the quality and quantity of carbohydrates consumed in these diets may explain these findings. For example, the protein-based noodle based diet (seafood and noodle) was likely to be of lower glycaemic index compared to the vegetable, fruit and white rice diet, particularly if large amounts of white rice were consumed in the latter diet[31]. This may explain the adverse effects of high adherence of the vegetable, fruit and white rice diet on large for gestational age babies and the supposed protective effects of seafood and noodle on GDM. However, this plausible explanation will require further confirmation.

In Asian cultures, the period 21–40 d after parturition is believed to be a period of convalescence and also known as the confinement period. During this period, mothers follow specific dietary and behavioural restrictions and prescriptions, which are aimed at promoting restoration of maternal health and to protect mothers from future illnesses[32]. These prescriptions are shaped by cultural beliefs that have common origins[32–34]. However, postnatal dietary patterns followed during confinement period in Asia have not been well characterised. In GUSTO, four distinct dietary patterns were identified during this period: the traditional-Chinese-confinement diet, the traditional-Indian-confinement diet, the 'eat-out' diet and the soup-vegetables and fruits diet. It was observed that adherence to the traditional-Indian-confinement diet, characterised by intake of herbs and legumes, was associated with less symptoms of postpartum depression, while the soup-vegetables-fruits diet high in fruits, vegetables and fish during the postpartum period was associated with less postpartum anxiety symptoms[35]. Our results are in line with previous studies that investigated the association between major food groups of other dietary patterns and mental health outcomes. This study further supports the value of understanding dietary patterns within the relevant cultural context.

Maternal meal timing

Interrogating the data from a different perspective, suggestive evidence of the importance of maternal circadian eating time with maternal and infant health was revealed. Independent of the amount of energy consumed in the evenings/at night, mothers who had shorter night fasting hours (4–9 h; these are often mothers who ate late in the nights) tended to have higher fasting glucose concentrations. Additionally, those who had frequent eating episodes (5–10 times) throughout the day were more likely to have higher 2 h postprandial glucose concentrations[36]. Conversely, mothers with extended night fasting hours were found to have female infants with larger head circumference and greater adiposity, but the associations were not observed in male infants[37]. These findings are in accordance with previous observations that suggest that there are sex-specific responses in brain growth

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and adiposity[38,39], and raise the possibility of the maternal night-fasting interval as an underlying influence. While further findings are required to confirm these associations, they allude to the inclusion of meal timing, frequency and night fasting intervals as important approaches to optimising perinatal nutrition and health.

Conclusion

In summary, through findings from the GUSTO mother–offspring cohort study, we have illustrated the importance of focusing on perinatal nutrition, even in the modern day setting, where often the misperception that people are over-nourished rather than malnourished still persists. While total energy is important, we now better understand that for optimal maternal and infant health, both the quality and quantity of macronutrients also do matter. While emphasis has traditionally been placed on maternal folate and iron, other key micronutrients such as vitamins V_{12} and D should not be overlooked as they too, play synergistic roles in maternal and child health. Insights into dietary patterns have proven to be valuable as they provide an insightful dimension and enable tailoring recommendations appropriate to different populations and cultural contexts. Considering other aspects of the diet, such as meal timing and frequency, is increasingly necessary as people change their dietary habits in this increasingly fast-paced, industrialised and globalised world.

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Conflict of Interest

L. P. C. S., P. G., Y.-S. C. and K. M. G. have received reimbursement for speaking at conferences sponsored by companies selling nutritional products. They are part of an academic consortium that has received research funding from Abbott Nutrition, Nestle and Danone. The other authors have no potential conflicts of interest to disclose.

Authorship

K. M. G., P. G., K. H. T., L. P. C. S., M. M., J. K. Y. C., F. Y. and Y. S. L. designed and led the GUSTO cohort study. M. F. F. C. wrote and finalised the manuscript. All authors contributed to and approved the final manuscript.

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