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Surrogacy in India: A DOHaD Perspective

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Abstract
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Commercial surrogacy in India saw a dramatic rise and fall between 2002 and 2015, during which it is estimated that over 325,000 children were born to surrogate mothers. At least 50% of these children are estimated to have been commissioned by Western parents. Until now surrogacy in India, and the effects it may have on the future health of surrogate children, has not often been discussed. Using the theory of Developmental Origins of Health and Disease, which says the way one develops and grows in the womb affects one's health later in life, potential, unforeseen consequences of surrogacy in India are examined through the cues of maternal diet and maternal body composition. A total of 46 primary literature papers – 38 papers concerning humans and 8 papers concerning animals – were drawn from to form the foundation of the stance concerning surrogacy taken here. Maternal intake of protein, carbohydrates, lipids, and the ratios concerning those macronutrients have an effect on fetal development measured by birthweight, length, and adiposity. As it is affected by the mother's immediate surroundings, maternal diet acts as a short term cue for the growing fetus. Maternal body composition, composed of lean mass and fat mass, also has an effect on fetal development measured by similar markers of growth. Unlike maternal diet, maternal body composition is representative of the woman's entire history and everything she has been exposed to in life that may have an effect on her lean and fat mass. The fetus receives cues from both maternal diet and maternal body composition. In India, the thin-fat phenotype – one does not appear obese or overweight but has high levels of adipose tissue – is very prevalent and raises concerns regarding surrogacy due to the effects maternal body composition has on development. An obesogenic environment has negative implications and effects on fetal development and for the child's future health. While it is impossible to change past decisions, being aware of the potential impacts surrogacy may have on the health of these children is important as is being proactive about one's health.

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Introduction

There are many ways to have children in the modern world. People may have their own biological children or they may foster. They may choose to adopt domestically or internationally. For some, this process of starting a family may involve trying for many years, undergoing fertilization treatments, using in-vitro fertilization, and even hiring someone to carry and give birth to the child, a process known as gestational surrogacy. Gestational surrogacy, commonly referred to as just “surrogacy” is the process where a woman has a fertilized egg implanted into her uterus after in-vitro fertilization and carries the child to term. This child is often not genetically related to her and is given to its intended parents at birth. The woman, called the gestational mother, agrees to relinquish her parental rights at the beginning of the process and often has no contact with the child ever again (Gugucheva, 2010). Since the turn of the century this process has become more widespread and has overtaken traditional surrogacy.

Traditional surrogacy, a process in which the surrogate mother both contributes the egg and carries the child to term, can be traced across the centuries (Gugucheva, 2010). Often cited as the first recorded case of traditional surrogacy is the Biblical account of Abraham and Sarah. Unable to conceive a child, Sarah gave her maidservant, Hagar, to her husband with the intent that Hagar bear the child that Sarah would claim as hers. Since the birth of this child, named Ishmael, the rate of surrogacy has risen dramatically both in the United States and around the world. This rise in surrogacy has also led to an increase in legal cases surrounding the practice, cases which have helped to bring surrogacy to the public’s attention. Perhaps one of the most famous cases concerned Baby M. Baby M was an American surrogate child born in 1986 via

traditional surrogacy and was the subject of the first custody battle over a surrogate child in a case that concerned the legality and validity of surrogacy (New Jersey. Superior Court, 1988). While the custody of Baby M ultimately went to her biological father, the New Jersey Supreme Court did rule that surrogacy was an affront to public policy and commercial surrogacy – being paid to carry someone else’s child – was “illegal, perhaps criminal, and potentially degrading to women” (Haberman, 2014). This case helped to create the different policies seen around the United States surrounding surrogacy – for example surrogacy is illegal in Arizona, whereas gestational surrogacy is legal in Nevada – and has affected the quality of the data from this practice ("Contract requirements; treatment of intended parents as natural parents; unlawful acts," 2013; Haberman, 2014; "Surrogate parentage contracts; prohibition; custody; definition," 2015).

While there are no official public data, in the United States, between 2004 and 2008, surrogacy rates grew by 89% (Gugucheva, 2010). Furthermore, it is estimated that between 2009 and 2011, over 3,000 children were born to surrogate mothers. (D. L. Cohen, 2013) However, the US is not the only country where surrogacy takes place, but rather it takes place all over the world. For example, in the UK, 167 babies were registered as having been born to a surrogate mother in 2013 (Dugan, 2014). Compared to the UK, the rates of surrogacy in the United States are quite high, but compared to India, one of the most well-known locations for surrogacy and medical tourism, the rate is actually quite low (Shetty, 2012). Statistics from India are sparse, but between 2002 and 2015, a conservative estimate puts the number at 325,000 children or approximately 25,000 children per year were born to surrogate mothers with at

least 50% of these children being commissioned by Western parents (Desai, 2012; Shetty, 2012).

The practice of surrogacy and its ethicality have been debated for years, yet these debates rarely consider the effects surrogacy may have on the later health of the child. These children are conceived through in-vitro fertilization, a practice that has been standardized since it first began and is often thought to be “safe” for the resulting child (Sifferlin, 2013). This conception of in-vitro fertilization helps to reduce the potential concerns parents may have about pursuing surrogacy in India and its effects on their child’s health. However, further consideration is needed regarding surrogacy. The theory of Developmental Origins of Health and Disease proposes that the way a fetus grows and develops in the womb in response to the various cues and potential insults they are exposed to, shapes their later health, particularly during critical periods of development (Barker, 2007; Wadhwa, Buss, Entringer, & Swanson, 2009). These cues that result in the various changes to the fetus’ body come from the maternal environment; an environment that is not only the child’s biological mother’s body, but also, and perhaps more importantly, also that of its gestational mother. These changes during development can have lifelong effects on the health of children born to surrogate mothers, as the trajectory for one’s life is mainly set during development (Barker, 2007; Gluckman, Hanson, Spencer, & Bateson, 2005). During development, the cues received from the maternal body drive every process that is required to create a new life: cell differentiation, organogenesis, the laying down of muscle and adipose tissue, the development of the brain, the nervous system, and the body overall (Chandler-Laney, Bush, Rouse, Mancuso, & Gower, 2011; Painter, Roseboom, & Bleker, 2005). All of these processes influence how that child will be able to react

to and recover from various insults they may experience later in life (Thornburg et al., 2011). Two of the main cues from the maternal environment originate from maternal diet and maternal body composition. Maternal diet has the potential to change throughout the pregnancy depending on environmental factors and thus has been the source of investigations into how a fetus responds to “short term” cues. Maternal body composition, on the other hand, acts as if it is a history book of everything the mother has gone through in her life and the effects that has had on her health and body. When looked at in tandem, these two cues provide the fetus with a clearer picture of the environment it will live in after birth. Thus, the present investigation looks at both maternal diet and maternal body composition during pregnancy for the effects those cues may have on the fetus in order to gain a clearer picture of the potential impacts surrogacy may have on later life.

Background

The case for surrogacy

While there are other factors driving the rise in gestational surrogacy, for example an increase in number of same sex couples, one of the major factors driving the rise in gestational surrogacy is infertility. According to the CDC, in 2013, 12.3% of women between the ages of 15-44 had impaired fecundity, which is the inability to get pregnant and sustain the pregnancy to term, with the numbers only increasing since then (Centers for Disease Control and Prevention, 2016). While this number may look small, this translates to approximately 7.5 million women or 1.23 women out of every 10 who struggle to get pregnant or carry the child to term in the United States alone (Centers for Disease Control and Prevention, 2016). Globally, these

numbers may be even higher. The World Health Organization reports that more than 186 million women struggle with fertility issues worldwide (World Health Organization, 2017).

While there are various routes that couples can pursue in order to have a child, for those that wish to have their own biological child, but cannot carry the child to term, gestational surrogacy is often turned to. Unfortunately, for many people, with the cost of surrogacy on average between \$50,000 and \$250,000, surrogacy is not a financially reasonable or feasible option for many (Shetty, 2012). This price may prevent couples from pursuing gestational surrogacy in the United States and may force them to look outside of the country. In India, hiring a surrogate mother costs about \$25,000, one-half of the lowest price of surrogacy in the US (Shetty, 2012). Due to this lower cost, many couples have turned to Indian surrogate mothers to have their wishes of biologically-related children fulfilled (Shetty, 2012). Medical tourism – not just surrogacy – has become a booming industry in India with the Confederation of Indian Industry – an association of businesses in India whose goal is to increase industrial growth - predicting that medical tourism produces more than \$2.3 billion USD annually (Shetty, 2012). While estimates for the number of children born via surrogacy are not widely publicized, it is estimated that since surrogacy was legalized in 2002, over 325,000 babies, approximately 25,000 children each year, have been born to surrogate mothers with at least 50% of these children being commissioned by Western parents (Desai, 2012; Shetty, 2012). However, while the technology may exist to allow couples to pursue gestational surrogacy, the laws or regulations in that particular state or country may prevent them from using option.

Legal Issues concerning surrogacy

There are no national laws surrounding surrogacy in the United States, rather, it is regulated on the state level and thus differs from state to state. Surrogacy in California, for example, is not only legal, but the state also allows the intended parents to be considered the child's legal parents without having to go through the adoption process that is often required in other states before birth (Lawrence, 1991). Michigan, in contrast, forbids all commercial surrogacy agreements and if one is entered into, anyone involved in arranging, procuring, assisting, or entering the agreement can be fined and/or imprisoned (Legislature, 1988). Just as laws concerning surrogacy differ state by state, they also differ country by country. Similar to Michigan, altruistic surrogacy is legal while commercial surrogacy is not legal in the United Kingdom (Frankford, Bennington, & Ryan, 2015). In France, on the other hand, both altruistic and commercial surrogacy are illegal (Frankford et al., 2015).

There are some countries, however, where fertility and surrogacy tourism is legal and even relatively easy to pursue. The country of Georgia passed a law in 1992 that said the surrogate mother does not have parental rights (to the child she carried and gave birth to) and in 2002, Ukraine passed a similar law. Likewise, Israel both allows and funds surrogacy – in accordance with the Embryo Carrying agreement of 1996 – although every surrogacy contract must be approved, overseen at the state level, and regulated according to religious law. Furthermore, not only does a religious official have to serve on the committee that regulates surrogacy agreements, but both the surrogate mother and the gestational mother must be of the same religion (Levush, 2012). In the case that both mothers do not share the same faith, the

religious official committee member must give his approval regarding the arrangement (Levush, 2012).

In India, however, the case is a little different. From 2002 to 2015, commercial surrogacy was legal and available to everyone, both those holding Indian passports and those not (Deonandan, 2015; Sugden, 2015). This changed in October, 2015, when the Indian Council of Medical Research, a part of the government, announced that only married Indian couples could pursue surrogacy services in India (Deonandan, 2015; Sugden, 2015). Legislation was then introduced on November 21, 2016, by J.P. Nadda, the minister of Health and Family Welfare. Titled “Surrogacy (Regulation) Bill 2016,” this bill proposed to ban commercial surrogacy but continues to allow altruistic, domestic surrogacy. Unlike commercial surrogacy, in altruistic surrogacy the gestational mother – and the clinic she is working for – does not get paid; she provides this service free of charge. While the bill has yet to be passed, it did receive approval from the Union Cabinet in August, 2016 (Press Information Bureau, 2016; PRS India, 2016). In banning commercial surrogacy, the government hopes to protect women from being exploited by various “rent a womb” fertility centers, ensure the rights of the child and prevent cases like that of Baby Gammy in Thailand where misrepresentation on both sides of the matter caused an international issue and brought surrogacy into the spotlight (Deyl, 2016).

Since the first description of surrogacy in the Bible, the underlying tensions of motherhood have given surrogacy the potential to be very volatile. With the added aspect of the media, this only intensifies the potential situations that may ensue. For example, in the case of Baby Gammy, an Australian couple hired a surrogate mother in Thailand to have their child. The surrogate mother ended up carrying twins and when the children were born, only the

female twin went back to Australia with her biological parents. The male twin – known as Gammy - who also had Down's syndrome, was left behind with the gestational surrogate mother. This case became an international incident when the gestational mother started to raise funds for Gammy's medical care and claimed that the child had been left behind. In response to the outrage Gammy's story raised, Thailand placed stricter restrictions on gestational surrogacy and drafted a law making it a criminal offense (Pearlman, 2016). This controversy concerning surrogacy not only helped to bring surrogacy and its practices into the light, but it also raised questions about its practices, ethics, and "the rent a womb" business. This sort of controversy and mass media frenzy is something the Surrogacy (Regulation) Bill 2016 is trying to avoid (Deyl, 2016). If approved by the Indian Parliament, there are many restrictions that will be enforced in regard to surrogacy. While all surrogacy will not be considered illegal, as it is in the state of Michigan, only altruistic surrogacy would be allowed. Furthermore, according to the bill, only Indian citizens would be allowed to pursue surrogacy. This would limit surrogacy to nationals and bring legal surrogacy tourism in India to a halt. Furthermore, only Indian couples who have been legally married for at least 5 years are allowed to pursue surrogacy, and those that do would be required to have a certificate from a doctor saying that they are medically unable to have a child. Finally, the surrogate mother has to be a close relative (e.g. sister or sister-in-law) between the ages of 23 to 50, have at least one healthy biological child, and could only serve as a surrogate once (Deyl, 2016). That said, as the bill has yet to be passed by Parliament, at this time, commercial surrogacy is still legal. According to news reports concerning the battle over gestational surrogacy and its legality, some surrogate mothers are still participating in the practice in order to take advantage of the

money they are paid and the possibilities said money allows their families to have (Srivastava, 2017).

Benefits for surrogate mothers

On average, surrogate mothers in India earn between \$5,000 and \$7,000 USD. Compared to the annual median per capital income - \$616 USD – is a huge financial boon for the entire family (Shetty, 2012). According to the official poverty line set by the Indian government in 2014, people who lived in rural areas and spent over 32 Indian Rupee (RS) per person per day lived above the poverty line (Singhl, 2014). For urban areas, the poverty line was set to RS 47 (Singhl, 2014). When converted to dollars (USD) using an average exchange rate from 2014, the year that paper was published, RS 61.0130552 traded for 1 USD (Singhl, 2014; X-Rates, 2017). The poverty lines, in USD, are then \$0.524 USD per person per day for the rural areas and \$0.770 USD for urban areas. This translates to about \$16 USD and \$23 USD per month, respectively, and about \$192 USD and \$276 USD per year per person. In regards to the poverty line, the money earned from being a surrogate mother has the potential be financially beneficial for a family. With the average family size in India being 4.8, in the rural areas this would mean a family would have to have an income of over 921.6 USD to live above the poverty line and in an urban area, have an income of over 1,324.8 USD (Srivastava (Sashakt), 2015). By working as a gestational mother, these women would be bringing into the home an income that is 4 to 5 times that which is needed to live above the poverty line and additional money that could be used to benefit their family. For example, some women partake in surrogacy to send their children to good schools while others use it to help pay off debts (Bengali, 2016; McCarthy, 2016). According to ethnographic data that was collected in India at a

surrogacy clinic between 2006 and 2008, out of the 42 Indian surrogate mothers who participated in the study, 34 of them reported living below the poverty line (Pande, 2011). Additionally, the majority of women acting as a surrogate mother had husbands who were either unemployed or whose employment/work was unstable (Pande, 2011). Finally, the study found that the income earned via surrogacy was equal to almost 5 years of the family's total income (Pande, 2011).

A second thought about surrogacy

At first glance, this arrangement seems to be beneficial for both parties involved. Parents who were not able to have children are finally able to have a biological child of their own and the surrogate mother is able to improve the lives of her own children and her family (Pande, 2011). There is more to surrogacy, however, than what appears as a mutually beneficial transaction. Surrogacy is the process of hiring another woman – often someone in a different country – to carry one's child to term. Not only is the developing child affected by its biological mother's health and body as well as that of its father, but its development is influenced by its surrogate mother's health and body composition. Both one's genes and the environment the child is exposed to during pregnancy have an effect on the growth and health of that child. While one's genes cannot be changed, the fetal environment can act to influence which genes are expressed via DNA methylation, or through epigenetic effects. The genes provide the framework, or the blueprint for how the fetus should develop, but the environment affects how those genes are expressed. In the context of surrogacy, the child has its parents' DNA, but the blueprint that it's biological parents have provided is being followed and created using

materials from the surrogate mother's body and is influenced by the messages that her body is sending to the fetus.

No two people are exactly the same, not even twins, as the environment that one is raised in and the health of one's mother/family can – and does – affect the health of the individual (Maiti, Kumar, Castellani, O'Reilly, & Singh, 2011). Looking particularly at the case of monozygotic twins, or twins who came from the same egg and sperm cells and thus have identical DNA, DNA methylation and the way the environment acts on which genes are expressed can be different and can lead to different health outcomes later in life (Zheng, Xiao, Zhang, & Yu, 2014). Even though they are exposed to the same environment and have the same DNA, it has been found that monozygotic twins can still experience a wide range of epigenetic discordance via DNA methylation (Loke et al., 2013). If all uteri, and all women, and all circumstances that occur during pregnancy that can affect the development of a fetus were exactly the same, growing a child in another person's womb would be acceptable as there would be no potential detriments or unexpected outcomes that could arise from the arrangement, but that is not the case.

DOHaD, The Barker Hypothesis and Surrogacy in India

The Barker Hypothesis, also known as the theory of Developmental Origins of Health and Disease, DOHaD, proposes that the health for one's lifetime is determined before birth (Barker, 2007; Wadhwa et al., 2009). This means that one's health is not only influenced by their mother's lifetime health but also their grandmother's lifetime health. Furthermore, as the egg that creates oneself is developed while her mother is developing in their grandmother's womb, their grandmother's health while she was pregnant with their mother, and the

environment their mother experienced during her development also affects the child's health. For example, exposure to maternal diabetes mellitus during development is associated with increased BMI for the child later in life (Monteiro, Norman, Rice, & Illanes, 2016). Exposure to gestational diabetes mellitus or type 1 diabetes through exposure to a hyperglycemic intrauterine environment increases the risk of type 2 diabetes later in life (Clausen et al., 2008; Lawlor, Lichtenstein, & Langstrom, 2011). The fetus is not simply a group of cells which grow undisturbed in the uterus and unaware of what may be happening in the world around it. The fetus is influenced by the cues – or signals – it receives from the maternal body, be it that of the biological mother or surrogate mother, in the form of diet, body composition, stress, inflammation and many other factors. These cues are 'heard' by the fetus, processed and responded to.

Maternal diet and body composition

In general, this paper will address two main maternal pathways which may influence fetal development during pregnancy, the first being maternal diet and the second, maternal body composition. Both of these areas will be addressed, but it is important to keep in mind that diet can be changed and improved whereas maternal body composition is not as easily changeable and thus may have more of an effect on the long term health of a child.

Maternal diet serves as a snapshot in time and tells the fetus about what is going on at that moment. Maternal body composition, on the other hand, sketches a long term image of what the environment has been like previously. These two cues have different effects on fetal development.

For example, if dietary intake is poor during the third trimester of pregnancy, the fetus will not weigh as much at birth as it might have, because it did not have access to as much energy (Lumey, 1992). If the same dietary restriction were to take place during the first trimester, there are far more potentially devastating changes that could occur in the fetus (T. Roseboom, de Rooij, & Painter, 2006). One such example of the importance of timing is the occurrence of kidney disease later in life, an example that during development the fetus prioritizes other “more vital” organs (e.g. the brain) over its kidneys, as there is little need for kidney function due to the actions of the placenta (Tain & Hsu, 2017). The problem arises, however, after birth and in later life when the pressure exerted on the organs is greater than what they can handle after poor early development. For example, poor early kidney development poses a risk for an adult who constantly consumes more alcohol than the kidneys can support, and lead to decreased kidney functioning and ultimately kidney failure. Other examples of poor early development and later mismatch, such as high adiposity driven by high maternal fat mass, can result in increased risk of other chronic non-communicable diseases (e.g. coronary artery disease and metabolic diseases). Some of these conditions can be expressed as the maternal body is stressed during pregnancy, influencing the prenatal development of the affected individuals own child, perpetuating the cycle of chronic disease across generations and creating a vicious cycle. In light of this – that one’s health is influenced by cues received from the gestational mother’s body – surrogacy in India deserves further consideration.

Thus, in order to gain a better sense of the potential consequences of surrogacy in India, both maternal diet and maternal body composition were studied with the hypothesis being that

obesogenic and inflamed environment would have negative consequences in regards to the body composition of the infants (Joshi, 2012; Yajnik & Ganpule-Rao, 2010). This paper will first present the methods used to conduct this study, discuss the results and why they are important, and then examine the potential implications of these results.

Methods

The present investigation is a review of evidence regarding effects during development related to maternal diet and body composition to position a more comprehensive view of the implications of surrogacy, with a focus on surrogacy in India. *Fetal programming* is the idea that permanent changes in the fetus may occur in response to stimuli or insults it is exposed to during development (Godfrey & Barker, 2001). These responses, occurring while the fetus is in the womb, are mainly driven by cues received from the mother. In the case of surrogacy, not only is the fetus influenced by the cues it receives from its genetic mother, but also by its gestational mother. For this investigation, both maternal diet and body composition are the focus. Maternal diet is examined by a consideration of the potential influences of the three major macronutrient categories (carbohydrates, protein, and lipids). Maternal body composition was considered in terms of the fat vs lean mass compartments. These two categories were considered from the perspective of the three trimesters of pregnancy in order to gain a more comprehensive picture of the implications of surrogacy. During development, maternal diet acts as a short term marker of nutritional status while maternal body composition acts as a long term one, both of which influence the fetus.

India, in particular, was looked in part due to the high number of parents who pursued surrogacy in India, averaging about 25,000 couples each year, and also due to the thin-fat phenotype which many people of Indian descent share (Desai, 2012; Joshi, 2012). We hypothesized that this particular phenotype would have effects on the body composition of the infants as well as their future health. Commercial surrogacy was legal in India for 13 years, during which it is estimated that over 325,000 children were born, of which over 50% of those children went home with Western parents (Desai, 2012). For many parents, once their child was born, they had no second thoughts about the potential effects pursuing surrogacy in India might have on the future health of their child, which we hoped to bring to light. Furthermore, while not every country where surrogacy is legal has the same distinct phenotype that India does, both Russia and the Ukraine – where commercial surrogacy is still legal – have suffered from famines in the past century, an event which can, and does, affect health history and body composition (Cheung, 2014; Lumey, Khalangot, & Vaiserman, 2015; T. Roseboom et al., 2006; Wang, Wang, Lei, Xiao, & Luo, 2012). So, India can be used as a case study to hypothesize what sort of affect may occur as a result of being born to a surrogate mother.

A review of the literature was conducted employing PubMed, Google Scholar and JSTOR as search engines and searches were conducted using the key terms “human” and “protein,” “carbohydrates,” “lipids,” “macronutrients,” “macronutrient ratio,” “maternal diet,” “maternal nutrition,” “maternal body composition” and “fetal body composition.” and investigations with a focus on maternal dietary influences on fetal body composition or health outcomes were interrogated and the key data results were organized by trimester of pregnancy.

Likewise, for maternal body composition, PubMed, Google Scholar and JSTOR were employed as search engines and searches were conducted using the key terms “human” and “maternal body composition” and “fetal development.” Papers were selected if researchers looked at fetal development and maternal body composition during pregnancy. In addition, animal models were investigated for evidence of the effects of maternal body composition on fetal development under conditions of either “low protein” or “high fat.” Altogether this generated 38 applicable articles regarding humans and 8 papers concerning animals. These papers specifically looked at measurable associations seen between the maternal diet or maternal body composition and the fetal birthweight, adiposity, length, or other size outcome.

The Indian Context

In general, people from the Indian subcontinent have a very distinct phenotype, one that is composed of high fat and low lean body mass (Joshi, 2012) This phenotype confers higher risks for diabetes, due to increased insulin resistance and various chronic diseases associated with higher percentages of adipose tissue (Choe, Huh, Hwang, Kim, & Kim, 2016), which can have specific effects on fetal development. This paper considers surrogacy in the specific context of the Indian phenotype. As maternal pre-pregnancy BMI has been found to be positively associated with increased birthweight and inversely related to risk of preterm birth, factors that help the infant to thrive after birth and influence its long term health (Ehrenberg, Dierker, Milluzzi, & Mercer, 2003; Frederick, Williams, Sales, Martin, & Killien, 2008; Salihu, Mbah, Alio, Clayton, & Lynch, 2009), the importance of surrogate maternal health status is important for the lasting impacts on the health of the infant which must be considered in the case of surrogacy.

Finally, in order to find the data on surrogacy in India and policy PubMed, Google Scholar, and JSTOR were employed as search engines and supplemented with results from Google with attention paid to news articles from newspapers based in India. This was done to gain both a scholarly understanding of the policy surrounding surrogacy as well as one which was the most in touch with the circumstances in India.

Findings

Comparison of Cohorts Cited

A summary of the nature of the evidence that bears on these questions is as follows:

Adelaide, South Australia

This prospective, observational cohort was based in Adelaide, South Australia. The cohort was composed of 557 Caucasian women who were over 18 years old and non-diabetic. These women gave birth between October 1998 and April 2000 (Moore, Davies, Willson, Worsley, & Robinson, 2004). Their mean age was 29 ± 5 years, and had a mean BMI of 24.9 ± 5.7 (Moore et al., 2004). In the cohort, only 187 of the women were primiparous, and 109 women smoked during pregnancy (Moore et al., 2004). Data were at two time points: the first before 16 complete weeks of gestation and the second between 30 and 34 weeks of gestation (Moore et al., 2004). At each interview, a dietary assessment, in the form of a food frequency questionnaire (FFQ), was given (Moore et al., 2004). This semi-quantitative FFQ included 200 food items with photos used to ascertain serving size (Moore et al., 2004). To estimate the daily intake of total energy, Australian food composition tables were used (Moore et al., 2004). For the mother, height was measured at the first interview and weight was measured at both

times. The midwifery staff measured each child at birth and weighed the placenta, and further data concerning the child was collected from hospital records (Moore et al., 2004).

Project Viva

This prospective, observational cohort study included 2128 women in Eastern Massachusetts, USA where women were recruited between April 1999 and November 2002, (Oken et al., 2015). While this was a multiethnic cohort, it was predominately Caucasian middle and upper class who had completed a college education (Oken et al., 2015). A little more than half of the women who participated were multiparous, with a wide range of BMI among whom more than half were of normal BMI (between 18.5-24.9 kg/m²) (Switkowski et al., 2016). Data, collected in the form of a self-administered, semi quantitative, 166 question FFQ, was collected twice (Switkowski et al., 2016). Data were collected first at enrollment, which happened between 4.8 and 23.7 weeks of gestation, and once again between 26 to 28 weeks of gestation (Switkowski et al., 2016). The data collected from the first visit were meant to measure maternal dietary intake during early pregnancy and the data collected at the second visit measured dietary intake from the previous 3 months (Switkowski et al., 2016). Protein intake was calculated using the Harvard nutrient composition database (Switkowski et al., 2016).

Aarhus Birth Cohort

Women were recruited for this prospective cohort study between April 1988 and January 1989 in Aarhus, Denmark with 965 women enrolling in the study (Maslova et al., 2014). Data concerning diet for the previous 3 months were collected via a self-administered FFQ and a face-to-face interview at 30 weeks of gestation (Maslova et al., 2014). The FFQ used was validated for marine foods but not foods or nutrients (Maslova et al., 2014). At the interview,

attempts were made to quantify the commonly used ingredients in cooked meals (Maslova et al., 2014). Emphasis was put on accurately assessing macronutrient intake, which was then quantified using the 1996 Danish Food-Composition Table (Maslova et al., 2014). The average age of mothers was 29.1 ± 4.1 , the average pre-pregnancy BMI was $21.4 \pm 2.9 \text{ kg/m}^2$, and 41.1% of the cohort was multiparous (Maslova et al., 2014).

Growing Up in Singapore Towards healthy Outcomes (GUSTO) birth cohort study

The GUSTO birth cohort aimed to examine if programming for obesity and other non-communicable diseases occurred in utero through the use of epigenetic biomarkers (Soh et al., 2014). Women were recruited between June 2009 and September 2010, were Singapore citizens or permanent residents of a homogeneous Chinese, Malay or Indian background and their husband/partner had to be of the same ethnic background (Chen et al., 2016; Soh et al., 2014). In order to participate, the women had to be 18 years or older, and the mean age of mothers in the study was 30.6 years (Soh et al., 2014). To assess gestational age and fetal growth, women underwent ultrasound scans at 19-21, 26-28, and 32-34 of gestation (Soh et al., 2014). At the 26-28 week visit, data concerning maternal anthropometric measurements (e.g. skinfold thickness), glucose tolerance, and maternal diet were collected (Soh et al., 2014). In this study, maternal diet was assessed using a prospective 3-day diary (Soh et al., 2014). A total of 1176 babies were born, the cohort was followed for 3 years (Soh et al., 2014).

Tasmanian Infant Health Survey (TIHS)

The Tasmanian Infant Health Survey was a prospective cohort study created to study sudden infant death (Dwyer, Ponsonby, Newman, & Gibbons, 1991). Mothers and their infants were enrolled in the study from January, 1988 to 1995 and the cohort was predominately

Caucasian (Dwyer et al., 1991; Yin, Quinn, Dwyer, Ponsonby, & Jones, 2012). Criteria for inclusion required the mother-child pairs to have a score of over 532 based on various factors which would provide a different score depending on certain characteristics; the higher the score, the higher risk for sudden infant death (Andreasian et al., 2007). Young maternal age, male sex, low birthweight, autumn birth, maternal intention to bottle feed, and duration of the second stage of labor provided the highest scores (Andreasian et al., 2007). Dietary data were only collected between September 1988 and December 1989 though an FFQ sent out after delivery asked about dietary intake during the third trimester (Andreasian et al., 2007). 179 food categories were included on the FFQ and frequency was measured using standard serving sizes; mothers were forced to estimate how often they had consumed a standard serving size of each food category during the last trimester (Andreasian et al., 2007). The Australian Tables of Food Composition were used to measure the energy and nutrient content of maternal diet (Andreasian et al., 2007). 1361 mothers completed the FFQ, but some exclusions were subsequently made: mothers of multiple births and those who inadequately completed the FFQ (e.g. provided multiple answers regarding food frequency, used a range, omitted more than one page of the FFQ, or reported having eaten fewer than 15 foods) (Andreasian et al., 2007). Once excluded, data from 1040 women remained (Andreasian et al., 2007). While data concerning maternal diet were being collected, 21% of the infants in the study were born to teenage mothers, 24.6% of the infants were low birthweight, 69.6% were boys, and 70.8% were fully or partially bottle fed at 1 month of age (Andreasian et al., 2007). Gestational age, birthweight, crown-to-heel length, head circumference and placental weight were ascertained from hospital obstetric records (Andreasian et al., 2007).

Lifeways Cross-Generation Cohort

The Lifeways Cross-Generational Cohort was a longitudinal observational study conducted in Ireland whose participants were Irish born mothers and their children (Murrin, Shrivastava, Kelleher, & Lifeways Cross-generation Cohort Study Steering, 2013). 1124 mothers were recruited between 2001 and 2003; 1094 live birth occurred of which there were 12 sets of twins (Murrin et al., 2013). In 2007 to 2008, the 1082 families were contacted for follow up and height and weight measurements were taken from 585 children (Murrin et al., 2013). Diet was assessed using a 149 item semi-qualitative food frequency questionnaire based on the European Prospective Investigation into Cancer and Nutrition instrument which had been validated for several populations (Murrin et al., 2013). Mothers were asked to indicate average use of each food item listed since becoming pregnant, or during the first 12 to 16 weeks of pregnancy; this period was considered “early pregnancy” (Murrin et al., 2013). Energy and nutrient intake was calculated using McCance and Widdowson Food Tables (Murrin et al., 2013). The same questionnaire was given at follow up and mothers were asked about dietary intake for the past year (Murrin et al., 2013). Maternal pre-pregnancy height and weight were self-reported and hospital records were used for obstetrical and birth outcomes (e.g. birthweight and occurrence of gestational diabetes) (Murrin et al., 2013). At follow up, height and weight measurements for the child and mother were taken in the home by trained researchers (Murrin et al., 2013).

Randomized Control Trial of Low Glycemic Index Diet in Pregnancy (ROLO)

ROLO was a randomized controlled trial conducted in Ireland on secundigravid women who had previously given birth to a macrosomic (>4000 g) infant (Walsh, Mahony, Foley, & Mc

Auliffe, 2010). The intent of the study was to look at the effects a low glycemic index carbohydrate diet on the prevention of the reoccurrence of fetal macrosomia when compared to no dietary intervention (Walsh et al., 2010). Women were excluded if they had diabetes or other medical disorders (Walsh et al., 2010). Women in the intervention group received low glycemic index (GI) dietary advice, were educated on what the glycemic index was and why it was useful during pregnancy, and were encouraged to consume low GI foods (Horan, Donnelly, McGowan, Gibney, & McAuliffe, 2016). The dietary education the women received was designed to meet the Irish nutritional recommendations for pregnant mothers (Horan, Donnelly, et al., 2016). Maternal height and weight were recorded during early pregnancy with maternal weight being measured throughout the study and infant anthropometrics (e.g. birthweight, length, circumference, and skinfold thickness) were measured at birth (Horan, Donnelly, et al., 2016). A fasting blood glucose test was taken at 12 weeks and a glucose challenge test was taken at 28 weeks (Walsh et al., 2010). Three 3-day food diaries – one for each trimester – provided the data concerning maternal dietary intake (Walsh et al., 2010). Thirty-five percent of the women in the study, however, were recruited after the first trimester, so their first trimester food diary was reflective of their early second trimester diet (McGowan, Walsh, Byrne, Curran, & McAuliffe, 2013).

Southampton Women's Study (SWS)

SWS is an ongoing prospective cohort study that was started in April 1998 in Southampton, United Kingdom (Okubo et al., 2014). 12,583 non-pregnant women were recruited to the study, and 1981 women became pregnant and gave birth to a live singleton before the end of 2003 (Okubo et al., 2014). During pregnancy, women were followed up at 11,

19, and 34 weeks of gestation and their offspring were followed through infancy and childhood (Okubo et al., 2014). Dietary information was collected through the use of an interviewer-administered FFQ at 11 and 34 weeks of gestation with the data being representative of maternal diet during the previous 3 months (Okubo et al., 2014). Validity of the FFQ was established through the use of a 4-day food diary in a subset of 569 pregnant women (Robinson, Godfrey, Osmond, Cox, & Barker, 1996). At birth the children were weighed and the crown-heel length was measured, with height measured at ages 4 and 6 years (Okubo et al., 2014). Subsets of the cohort underwent DXA scans at ≤ 2 weeks of birth, 4, and 6 years of age (Okubo et al., 2014).

Healthy Start Study

The Healthy Start Study was a prospective cohort study based in Colorado, USA (Crume et al., 2015). Mothers who enrolled in the study had to be older than 16 years, live in Colorado, and be ≤ 24 weeks of gestation (Crume et al., 2015). Mothers were excluded if they had serious chronic disease (e.g. pre-existent diabetes) (Crume et al., 2015). Data were collected 3 times: in early gestation (11 to 20 weeks of gestation, median gestational age, 17 weeks), mid to late gestation (20 to 34 weeks, median gestational age, 27 weeks), and after delivery but before discharge (median, 1 day) (Crume et al., 2015). Maternal height, weight, and blood samples were taken at each visit, however hemoglobin A1c was only measured at the second visit (Crume et al., 2015). After birth, neonatal anthropometric measurements and air displacement plethysmography were taken (Crume et al., 2015). All measurements on the mother and infant were taken by trained clinical nurses (Crume et al., 2015). Data concerning maternal diet were collected using computer-based 24-hour dietary recalls, with up to 6 being collected over the

course of the study (Crume et al., 2015). These recalls used graphics and pictures to help mothers estimate portion size (Crume et al., 2015). Using an abbreviated FFQ in the form of two food propensity questionnaires, data were collected during the second visit to ascertain the usual maternal intake of particular foods or food groups during the 3 months (Crume et al., 2015).

GI Baby 3

This was a two-arm randomized control trial created to look at the effects a low GI diet during pregnancy could have on perinatal outcomes, compared to a conventional high fiber diet set in Sydney, Australia (Kizirian et al., 2016). Only women who were at risk for gestational diabetes were recruited, of which they had to have at least one of the following risk factors: pre-pregnancy BMI $\geq 30 \text{ kg/m}^2$, ≥ 35 years of age, polycystic ovary syndrome, previous history of GDM, previous history of a macrosomatic baby ($>4000 \text{ g}$), immediate family history of type 2 diabetes, or belonging to an ethnic group that traditionally was at high risk for gestational diabetes (Kizirian et al., 2016). Maternal dietary intake was assessed using 2 three-day food diaries given once during mid-pregnancy (14 to 20 weeks of gestation) and once during late pregnancy (34 to 36 weeks of gestation) (Kizirian et al., 2016). These food diaries were kept over 2 week-days and one weekend day (Kizirian et al., 2016). In keeping these food diaries, participants were asked to weigh or measure everything they ate using kitchen scales or measuring cups (Kizirian et al., 2016). They were also asked to take note of brand names, cooking methods, and recipes used to cook the meal, if relevant (Kizirian et al., 2016). Neonatal anthropometric measurements were gain from hospital records, body composition was obtained using an air-displacement plethysmograph device (PEA POD), and infant weight-for-

age-z score was calculated using gender-specific data from the World Health Organization (Kizirian et al., 2016).

Women and Their Children's Health Study (WATCH)

WATCH was a prospective, longitudinal cohort study in Newcastle, Australia (Blumfield et al., 2012). Women were recruited from July 2006 to December 2007, and 179 women participated (Blumfield et al., 2012). Participants were predominately born in Australia and were relatively well-educated (at or above a high school education) (Blumfield et al., 2012). Over the course of the study, 4 visits were conducted at ~19, 25, 30, and 36 (± 1) weeks of gestation, during which an ultrasound scan was performed and fetal biometric and body composition measurements were taken (Blumfield et al., 2012). These included biparietal diameter, head circumference, abdominal circumference, femur length, and measurements of fat and lean muscle/visceral area (Blumfield et al., 2012). Maternal anthropometric data were collected by an accredited practicing dietician with pre-pregnancy weight being self-reported (Blumfield et al., 2012). Maternal biochemical data were collected at 20 (± 2) weeks of gestation and at 36 (± 2) weeks of gestation (Blumfield et al., 2012). Maternal dietary information was collected twice over the course of the study, once between 18 and 24 weeks of gestation and once at 36 and 40 weeks of gestation through the use of the Dietary Questionnaire for Epidemiologic Studies, a validated 74 item FFQ (Blumfield et al., 2012). The data collected by the FFQ were reflective of maternal diet during the previous 3 months (Blumfield et al., 2012).

Wollongong, Australia

This cohort was composed of 62 women from Wollongong, Australia, who either consumed a low glycemic index diet or a high glycemic index diet with dietary intake data being

obtained through the use of two 3-day food diary taken once at enrollment and the other at 36 weeks of gestation and two 24-hour recalls at 22 and 30 weeks of gestation (Moses et al., 2006). Women were separated into 2 different groups: one of the groups received dietary counseling and encouragement to eat a low glycemic index diet, while the other group was being encouraged to eat high-fiber, moderate to high glycemic index foods (Moses et al., 2006).

Amsterdam Born Children and their Development (ABCD)

ABCD was a prospective community based cohort study whose intent was to study the relationship between maternal lifestyle and psychosocial conditions while pregnant and her child's health (van Eijsden, Hornstra, van der Wal, Vrijkotte, & Bonsel, 2008). All women who were pregnant between January 2003 and March 2004 were invited to enroll and if they agreed, data were collected concerning socio-demographics, obstetric history, lifestyle, and psychosocial factors (van Eijsden et al., 2008). The women did not have to be Dutch to enroll, as immigrant mothers were also invited to enroll in the study. 8266 women filled out the questionnaire and 4389 women participated in the subsequent biomarker study where blood was taken and fatty acid analysis was done using the blood (van Eijsden et al., 2008). Data concerning birthweight and gestational age were obtained in regards to the child (van Eijsden et al., 2008).

Pune Maternal Nutrition Study (PMNS)

PMNS was a community-based observational study in Pune, India (Yajnik et al., 2003). The intent was to enroll women who had yet to conceive and follow them and their children through childhood. Enrollment began in September 1993, and the last delivery occurred in April 1996 (S. R. Kulkarni et al., 2013; Yajnik et al., 2003). Of the 2466 women who consented to take

part, 797 women enrolled in the study, and 762 delivered offspring (S. R. Kulkarni et al., 2013). Anthropometric measurements, physical activity, and dietary intakes using a semi-weighted 24-hour recall and FFQ were collected at 18 ± 2 weeks of gestation and at 28 ± 2 weeks of gestation (S. R. Kulkarni et al., 2013). Blood samples were collected at each visit and plasma glucose, total cholesterol, HDL-cholesterol, and triglycerides were measured at each time point (S. R. Kulkarni et al., 2013). Neonatal measurements were taken within 72 hours of delivery by one of 5 trained field workers and included: birthweight, crown-to-heel length, triceps and subscapular skinfold thickness, head circumference, mid-upper arm circumference (MUAC) and abdominal circumference (S. R. Kulkarni et al., 2013). Placenta weight was measured as well (S. R. Kulkarni et al., 2013).

The importance of maternal diet on development

What a mother eats during pregnancy plays an important role in the development of her child because it provides the nourishment for the growing fetus, with effects that include the potential to alter the anatomy and/or physiology of the child if insults occur during a critical period of fetal development (Godfrey & Barker, 2001). This occurs through a process of fetal programming, the process where a prenatal stimulus or insult can change the responses that a child makes in response to the cues it receives, in ways that will shape its future health (Godfrey & Barker, 2001).

Maternal diet is comprised of everything a mother eats during pregnancy, and as such can change rapidly over the course of 9 months due to outside influences. In light of this, maternal diet at any one time point is only a snapshot of what is available to the fetus

cumulatively. While maternal diet is composed of more than just proteins, carbohydrates, and lipids, these macronutrients will serve as dietary proxies in the present investigation.

The importance of maternal protein for fetal growth

During development, a completely new body is created from just one cell over the period of about 9 months. Protein, more specifically amino acids, are needed to aid in this process. They are essential to synthesis all of the cells necessary for life itself, as well as the development, structure, functioning and regulation of the fetus' organs and tissues (Genetics Home Reference, 2017), and protein is also essential for the creation of enzymes, messenger proteins and the transportation and storage of molecules throughout the body (Genetics Home Reference, 2017). Therefore, it is not a surprise that protein plays an important role in development across pregnancy.

First Trimester

A review of nine studies identified a positive association between maternal protein intake and neonatal birthweight. During the first trimester, data analyzed from the Adelaide, South Australia cohort showed that the percentage of energy obtained through maternal consumption of protein was not only positively associated with infant birthweight, but also with the ponderal index and the newborn's placental weight (Moore et al., 2004). Specifically, a 1% isoenergetic increase in protein was found to be associated with a 16g increase in birthweight and a 1% isoenergetic increase in dairy protein, in particular, was associated with both a 25g increase in birthweight and an increase in the ponderal index of 0.12 kg/m^3 (Moore et al., 2004). While this study relied on a food frequency questionnaire, which may be subject to recall bias, the relatively homogeneous cohort's data help to show that access to protein during this

period is vital for fetal development, even in a well-nourished population like Australia (Moore et al., 2004). As it is during the first trimester that the majority of organogenesis takes place (Hill, 2017), this is a critical period and any insult that may affect the amount of protein that the fetus is receiving from its mother, can influence its development.

Second trimester

While increased protein was associated with increased birthweight during the first trimester, during the second trimester more specific relationships have been reported. Maternal protein affects growth as measured by length. Using data from 1961 mother-child pairs from Project Viva, increased maternal dietary protein (as g/kg prepregnancy weight per day) was found to be associated with *decreased* length at birth and *slower* linear growth into mid childhood (7 years of age) (Switkowski et al., 2016). In these data, for every increase in standard deviation, there was a 0.1 decrease in the z-score for birth length when compared to their peers whose mothers consumed less protein (Switkowski et al., 2016). As indicated by the difference in the slope of a linear model of length gain from 6 months to seven years of age these children also did not grow as fast as their peers whose mothers consumed less protein (Switkowski et al., 2016). Project Viva's cohort was composed of relatively well-off, healthy women (Oken et al., 2015). This finding is similar to that of the Adelaide, South Australia cohort, where maternal protein intake also played a positive role in the growth of the infants independent of maternal background (Moore et al., 2004). Data from the Aarhus Birth Cohort suggest that these results may reflect that looking at protein alone may not be sufficient as an inquiry, but rather, protein in balance with maternal carbohydrates. After 433 mother-child pairs were followed-up for 20 (± 1) years after enrollment, increased protein that was

substituted for carbohydrates during pregnancy was found to be associated with increased BMI at 20 years of age and an increased risk of being overweight in females (Maslova et al., 2014). It is unclear if these studies are strictly comparable as they took place on three different continents (Australia, North America, and Europe) and 2 during different time periods (1998 to 2002, and 1988 to 1989), differences that can affect the background and health history of the women, and thus of the children, involved in the cohorts. All three studies used food frequency questionnaires (FFQ) to obtain maternal diet information, but none of them used the same. Nonetheless, the data illustrate that maternal protein consumption has an impact on fetal and subsequent child growth.

Maternal protein intake has also been negatively associated with offspring adiposity. Using data collected from 320 mother-child pairs from GUSTO, a negative relationship between maternal protein and fetal abdominal internal adipose tissue was found (Chen et al., 2016). As maternal protein increased, fetal abdominal internal adipose tissue, or visceral fat, measured using an MRI, decreased in a sample of Chinese and Indian neonates, but not in a sample of Malay neonates (Chen et al., 2016). The researchers hypothesize that these differences may be partially due to differences in body composition and the dietary intakes among the different ethnic groups. Furthermore, in the same cohort, increased protein was also associated with lower deep subcutaneous adipose tissue in a sample drawn from the Indian subpopulation. Moreover, relationships evidenced sex differences with stronger negative associations among males than females (Chen et al., 2016). This may reflect a differential sensitivity during development, with males more vulnerable to the cues of maternal diet, as has been previously suggested by data from Finland (Eriksson, Kajantie, Osmond, Thornburg, & Barker, 2010). Using

data from men and women born between 1924 and 1933, it was found that no matter the placental weight, the males tended to be longer than the females (Eriksson et al., 1999; Forsen, Eriksson, Tuomilehto, Osmond, & Barker, 1999). This was interpreted by the authors to suggest that while the placentas of the males were more efficient than that of the females, they may have stored less as reserves in case of a potential insult making them more vulnerable to undernutrition (Eriksson et al., 2010). Furthermore, males grow faster during development than females do, which, if maternal diet is compromised, means that they are more vulnerable to those effects (Pedersen, 1980). The relationship between maternal protein intake and adiposity was also seen in the WATCH cohort. When maternal protein intake made up less than 16% of the diet, adiposity increased as protein decreased, a result that was not found to be ethnic-specific (Blumfield et al., 2012). This relationship was seen both in an Asian population and a predominately Caucasian one, suggesting that ethnicity may play a role in determining adiposity, in addition to dietary intake of protein (Blumfield et al., 2012; Chen et al., 2016).

Third Trimester

Not only does the fetus continue to grow during the third trimester, but during this time begins to store energy in the form of fat (Borazjani, Angali, & Kulkarni, 2013; National Research Council, 1992). Data from the Tasmanian Infant Health Survey found that increased protein was associated with an increase in head circumference and a decreased ponderal index (Andreasyan et al., 2007). In these data, a 10-gram increase in protein was associated with a decrease of 17.8g in birthweight and a 1% increase in energy intake due to protein was associated with a decrease of 12.7 grams in birthweight (Andreasyan et al., 2007). These findings are supported by Campbell et al. (1996) in a population of 253 men and women born in Aberdeen, Scotland,

between 1948 and 1954, among whom an association between increased maternal protein intake and decreased birthweight (Campbell et al., 1996) was reported. However, while a high protein intake was associated with decreased birthweight in these two samples, in a population of Ecuadorian primiparous mothers, low protein intake was associated with increased risk of low birthweight (Weigel, Narvaez, Lopez, Felix, & Lopez, 1991). These conflicting results suggest both study cohort differences and methodology differences between studies. Data from 264 participants of the Tasmanian Infant Health Survey, when followed up 16 years later (2004 to 2005), showed that increased maternal gestational protein was also found to be associated with an increase in fat mass among adolescents with each portion of maternal dietary protein associated with a 0.9% increase in fat mass (Yin et al., 2012).

One interpretation of these results may be related to how the body handles increased protein (Jeremy M. Berg, 2002). Excess protein may be subject to decarboxylation and the carbon moiety simply enters the Krebs's cycle, fueling energy storage.

The importance of carbohydrates on fetal development

Just as protein is needed during development, carbohydrates are fundamental. Carbohydrates are the main source of energy – in the form of glucose – for the growing fetus and are required for a properly functioning body, a working brain and the correct operation of organs (Tzanetakou, Mikhailidis, & Perrea, 2011).

First Trimester

During the first trimester, increased carbohydrates, as measured by increased maternal sugar intake was associated with increased weight of children at 5 years of age and risk of being overweight according to data from the Lifeways Cross-Generation Cohort (Murrin et al., 2013).

Using data collected from a semi-quantitative food frequency questionnaire in the first trimester and height and weight measurements of their children at age 5, a clear association was seen between maternal sugar intake, and the percentage of energy from the sugar, and offspring obesity/overweight at five years of age. Mothers in the highest quartile for sugar intake were 4.5 times more likely to have a child who was overweight or obese (Murrin et al., 2013).

Other markers that can be used to study the effects of carbohydrates on fetal development and postnatal growth include maternal glycemic index and glycemic load. Glycemic index is the effect of food 2 hours after consumption on a person's blood sugar level (Jenkins et al., 1981). Foods are assigned a number depending on how quickly they cause the blood sugar level to rise after consumption in comparison to other foods. A low glycemic index food will cause blood sugar to raise more slowly than a high glycemic index food. Glycemic load, on the other hand, is related to both glycemic index and carbohydrate intake and is calculated by multiplying glycemic index and grams of carbohydrates per serving size of the food. One glycemic load unit estimates the effect of 1 gram of glucose on blood sugar (Silvera et al., 2005). Overall, both glycemic index and glycemic load measure the effects of food on blood glucose levels.

Data from 906 women-child pairs from the Southampton Women's Study (SWS), identify an increased maternal dietary glycemic index and glycemic load to be associated with increased fat mass in offspring at ages 4 and 6 years (Okubo et al., 2014). Increased carbohydrates, increased energy, in this study was found to be associated with increased adiposity, as measured by fat mass in offspring (Okubo et al., 2014). In contrast, data from the

ROLO cohort found that increased glycemic index was associated with decreased BMI-for-age z-score, decreased hip circumference and a decreased sum of all skinfold thickness in offspring, and increased glycemic load was associated with decreased adiposity at 2 years of age (Horan, Donnelly, et al., 2016) While both of these studies took place in Europe – the United Kingdom and Ireland, respectively – their study populations were very different (Horan, McGowan, et al., 2016; Okubo et al., 2014). The ROLO cohort was composed of women who previously had given birth to a macrosomic infant and were, thus, at-risk for giving birth to another macrosomic infant, while the women from the SWS study were not (Horan, McGowan, et al., 2016; Okubo et al., 2014). None of the mothers in the ROLO study were primiparous, whereas 48.7% of the mothers in the SWS were (Horan, McGowan, et al., 2016; Okubo et al., 2014). Furthermore, the data for the ROLO study concerned 281 mother-infant pairs, whereas 906 women and their children were included in the study from Southampton (Horan, McGowan, et al., 2016; Okubo et al., 2014). These differences in the study populations may underlie the results. While the ROLO cohort saw that increased glycemic index during the first trimester was associated with decreased adiposity among 2 year olds, 4- and 6-year olds born to mothers in the SWS experienced increased adiposity (Horan, McGowan, et al., 2016; Okubo et al., 2014).

Insulin resistance is another marker that can be examined to investigate the effect carbohydrates may have on fetal development. Insulin resistance occurs when cells (muscle, fat, and liver cells) are unable to properly respond to insulin, increasing the amount of glucose in the bloodstream as they are unable to easily absorb it (National Institute of Diabetes and Digestive and Kidney Diseases, 2009). Therefore, the more insulin resistant a person is, the higher their blood glucose levels are. Results from the Healthy Start Study reported that

increased maternal insulin resistance – measured in the homeostasis model of assessment for insulin resistance or HOMA-IR, and the equation $\text{glucose (mg/dL)} \times \text{insulin } (\mu\text{U/mL}) / 405$, was associated with increased fat mass and increased fat percentage in neonates taken within 48 hours of birth (Crume et al., 2015). While 52.1% of the cohort had a healthy BMI, 44.7% of the cohort was classified as being overweight or obese. These results identify that controlling for maternal BMI is important when looking at insulin resistance. Analyzing data from 771 mother-infant pairs, while controlling for maternal BMI, revealed that there was a statistically significant positive relationship between HOMA-IR and both fat mass and fat mass percent during the first trimester (Crume et al., 2015). Looking at data from SWS, ROLO and the Healthy Start Cohort shows that, in general, increased carbohydrates are associated with increased adiposity in offspring. These findings are important with respect to India, as the typical Indian diet is rather heavy in carbohydrates and many suffer from type 2 diabetes (Kaveeshwar & Cornwall, 2014). This will increase the glucose concentrations in the blood of the mother, sending a signal to the fetus indicating a high-energy environment leading to increased adiposity.

Second Trimester

The second trimester is a period of increased growth for the fetus and high levels of carbohydrates during this time period are associated with increased adiposity (Aris et al., 2014; Crume et al., 2015; Johns Hopkins Medicine, n.d.). Aris et al. (2014) noted that data from the GUSTO study showed that increased maternal glucose was associated with increased neonatal adiposity and Crume et al. (2015) reported that not only was maternal insulin resistance associated with increased neonatal fat mass and fat percentage, but increased glucose levels as

well. These similar findings are important as these two cohorts were set in two different continents, North America and Asia, and had distinctly different ethnic populations – GUSTO was composed of “ethnic minorities” (Chinese, Indian, and Malay mothers), and the Healthy Start Study was composed of mainly Caucasian mothers from Colorado, United States (Aris et al., 2014; Crume et al., 2015). Furthermore, in young, relatively thin but short women of high adiposity from Pune, India, increased fasting plasma glucose concentrations were associated with increased body mass and mid-upper arm circumference as seen in data from the Pune Maternal Nutrition Study (S. R. Kulkarni et al., 2013). Based on these data, the researchers noted that in their model, a one unit increase in standard deviation of plasma glucose was associated with a 37-gram higher birthweight (S. R. Kulkarni et al., 2013). This relationship is also seen in the data from GI Baby 3 when looking just at carbohydrates and energy derived from carbohydrates (Kizirian et al., 2016). In that cohort, energy from carbohydrates was negatively correlated with offspring fat-free mass index, a measurement of infant body composition, during the second trimester. Hence, increased energy from carbohydrates was associated with increased adiposity (Kizirian et al., 2016). In summary, not only is the relationship between increased carbohydrates and fetal adiposity seen in cohorts located in Singapore and in the USA, but the relationship is also seen in India and Australia (Aris et al., 2014; Crume et al., 2015; Kizirian et al., 2016; S. R. Kulkarni et al., 2013). The positive relationship between carbohydrates and adiposity is seen in people of different background, health histories, and nutritional status; it is seen all over the world (Aris et al., 2014; Crume et al., 2015; Kizirian et al., 2016; S. R. Kulkarni et al., 2013).

Similar to the first trimester, high levels of carbohydrates seem to signal to the developing fetus that there is excess energy and encourage the laying down of fat. This positive relationship between carbohydrates and adiposity was also seen in studies looking at glycemic indices, where an increase in ponderal index and increased risk of being large-for-gestational age was described, in data from the Wollongong, Australia cohort (Moses et al., 2006). When a low glycemic index diet – one that is not high in carbohydrate rich food – was examined, it was associated with decreased thigh circumference at birth as well as a lower birthweight, as seen in data from the ROLO study and from the Camden Study (Donnelly, Walsh, Byrne, Molloy, & McAuliffe, 2015; Scholl, Chen, Khoo, & Lenders, 2004). The Camden Study, based in Camden, New Jersey, looked at a 1082 mothers-child pairs who were enrolled in the study between August 1996 and October 2002 (Scholl et al., 2004). Dietary data were ascertained using three 24-hour recalls, once upon entry, and again at 20 and 28 weeks of gestation, with food models and household and fast-food cups and bowls being used to help measure serving size (Scholl et al., 2004). The Camden study cohort was a multiethnic one, primarily composed of Hispanic and African American mothers, with less than 20% of the population being Caucasian (Scholl et al., 2004). In their model, children born to mothers in the lowest quintile for glycemic index diet had a birthweight that was reduced by 116 grams (Scholl et al., 2004). Cues suggesting higher levels of energy led to increased adiposity and increased growth, whereas the opposite cue – one of lower energy – led to decreased adiposity and less growth as indicated by birthweight (Donnelly et al., 2015; Moses et al., 2006; Scholl et al., 2004). The ROLO and Camden findings should, however, be considered carefully as ROLO was composed of mothers who had previously given birth to a macrosomic infant, whereas the Camden Study was set in one of the

poorest cities in the US, factors which may have affected the outcome due to maternal background and health history (Donnelly et al., 2015; Scholl et al., 2004).

Third Trimester

The third trimester is often characterized by increased fat being laid down between the 35th and 40th weeks of pregnancy, something that is exacerbated by increased carbohydrates as seen in a number of studies (Ebrahim, 2005; Pereira-da-Silva et al., 2014; Renault et al., 2015). Increased carbohydrates are associated with increased fat mass in neonates, according to data from a cohort of 222 Danish mother-child pairs whose mothers were obese when they were enrolled in the study, called the Treatment of Obese Pregnant Women (TOP) (Renault et al., 2015). Women in this study were randomly assigned to the physical activity + dietary intervention group, the physical activity intervention group, or the control group (Renault et al., 2015). If they were assigned to the dietary intervention group, mothers were encouraged to follow a hypocaloric Mediterranean style-diet (1200-1700 kcal) (Renault et al., 2015). Dietary intake data were collected through the use of a 360-item FFQ which was intended to reflect dietary intake during the previous 4 weeks (Renault et al., 2015). This was given at the beginning of the study (11-14 weeks of gestation) and at the end (36-37 weeks of gestation) (Renault et al., 2015). Compared to children born to mothers in the lowest quintile for digestible carbohydrates (188 grams per day), children born to mothers in the highest quintile (238 grams per day) had a higher total fat mass (a 103 gram increase) and higher abdominal fat mass (11 gram increase) (Renault et al., 2015). Similar results were seen for maternal glycemic index and glycemic load; they were positively associated with fat mass (Renault et al., 2015). Similarly, percentage of total energy value from carbohydrates during the third trimester was

positively associated with offspring mid-arm circumference and weight/length in a population of Portuguese women and their children (Pereira-da-Silva et al., 2014). This cross-sectional study collected data from 100 full-term, primiparous, healthy women (the mothers did not have high blood pressure, type 2 diabetes, reported consumption of alcohol, tobacco, or drugs) with dietary intake assessed by FFQ and neonates assessed within 75 hours of birth (Pereira-da-Silva et al., 2014). Data from the Healthy Start Study and Wollongong, Australia study found that increased carbohydrates are associated with increased fat mass percent, increased ponderal index, and increased risk of being large-for-gestational age (Crume et al., 2015; Moses et al., 2006). Specifically, in the Healthy Start Study cohort, when adjusted for maternal BMI, a significant positive relationship remained between maternal glucose and fat mass percent (Crume et al., 2015). While the Healthy Start Study took place at in Colorado, USA, Moses et al. looked at women in Wollongong, NSW, Australia (Moses et al., 2006). From the data they collected on the 62 women who completed the study, they found that children born to mothers who consumed the moderate-to-high glycemic index diet were at higher risk for being born large-for-gestational age and had a higher ponderal index than their peers whose mothers ate a low glycemic index diet (Moses et al., 2006). Looking specifically at a low glycemic index diet, data from the ROLO study showed that there was an association between a maternal low glycemic index diet and decreased thigh circumference at birth (Donnelly et al., 2015). 265 neonates were compared with each other after their mothers were split into two groups – one receiving a low glycemic index diet and the other receiving no intervention – and it was seen that while there was no difference in head, chest, abdominal, or mid-upper arm circumference, there was a significant decrease in thigh circumference suggesting that a low glycemic index is

associated with lower adiposity in the infant (Donnelly et al., 2015). Overall, even with the ethnic differences and health history differences that can exist due to the different populations and different sample sizes of the cohort studies, the compiled data shows that there was an overall positive relationship between carbohydrates and fetal adiposity.

Studies have also found, however, that increased carbohydrates can sometimes be associated with a decrease in fat mass index and ponderal index (Kizirian et al., 2016; Moore et al., 2004). A comparison of two studies is specifically useful. Among mothers and their infants in Australia, Kizirian et al. (2016) worked with the GI Baby 3 cohort, composed of mothers who were at-risk for gestational diabetes (Kizirian et al., 2016) defined as women who had at least one of the known risk factors for gestational diabetes: a pre-pregnancy BMI of over 30 kg/m², 35 years of age or older, had polycystic ovary syndrome, a previous history of GDM, previously delivered an infant weighing more than 4000g, a family history of type 2 diabetes (to be included the relative had to be a first degree relative), and/or belonged to an ethnic group that is at high-risk for gestational diabetes (Kizirian et al., 2016). Moore et al. (2004) studied the Adelaide, South Australia cohort, in which women did not carry the same collection of risk factors for gestational diabetes, but did include women with a BMI of 30 kg/m² or greater as 25% of the cohort (Moore et al., 2004). The data from the GI Baby 3 cohort found that higher carbohydrate intakes - increased energy from carbohydrates – was associated with a lower fat mass index in neonates (Kizirian et al., 2016). Moore et al's cohort (2004) showed that a 1% isoenergetic increase in carbohydrates was found to be associated with a 0.04 kg/m³ decrease in ponderal index in neonates (Moore et al., 2004). Fat mass index is a way to measure body composition and, it has been argued, that compared to BMI, fat mass index may be a better

judge of body adiposity as it takes into account not only body height and weight, but also fat mass content (Peltz, Aguirre, Sanderson, & Fadden, 2010). The formula for fat mass index is fat mass divided by height squared ($\text{fat mass}/\text{height}^2$), so if the fetus has a low fat mass index, the fetus has less adipose tissue than one who has a high fat mass index (Schutz, Kyle, & Pichard, 2002). In other words, according to the results from the GI Baby 3 study, increased maternal energy from carbohydrates was associated with less fat compared to length, with length being measured from crown to heel, and neonatal body composition measured through use of an air-displacement plethysmograph device (Kizirian et al., 2016). While adiposity was measured in different ways, fat mass index vs. ponderal index, both the GI Baby 3 and the Adelaide, South Australia cohort found that increased maternal carbohydrates during the third trimester was associated with decreased fetal adiposity (Kizirian et al., 2016; Moore et al., 2004). These findings are similar even though there were significant differences between the two cohorts as mothers who participated in GI Baby 3 were required to be at-risk for developing gestational diabetes while those in the Adelaide, South Australia cohort were not (Kizirian et al., 2016; Moore et al., 2004). Furthermore, high proportions of carbohydrates, or greater than 50% of energy in relation to other macronutrients, as gained especially from high glycemic index foods, were found to be associated with a lower fat free mass index in the infant (Kizirian et al., 2016). So, having a high proportion of energy derived from carbohydrates was associated with increased adiposity and decreased fat free mass among their infants. These findings help to suggest that the effects of maternal carbohydrate consumption on fetal development do not simply occur in a vacuum. Rather, maternal carbohydrate balance interacts with the other maternal macronutrients and optimal fetal growth may be best served by a balance.

The overall findings concerning carbohydrate consumption during pregnancy suggest that carbohydrates play an important role during development in regards to energy and in the cues given to the fetus about the situations in which its mother finds herself. High levels of carbohydrates signal an energy-rich environment and encourage the laying down of adipose tissue as evidenced by the many studies that found that increased carbohydrates were associated with increased fetal adiposity (Kizirian et al., 2016; Moses et al., 2006; Renault et al., 2015). However, it is not just the increased intake of carbohydrates that can lead to such a signal being given, as insulin resistance and maternal glucose levels, two measurements that are affected by diabetes, can also give such a signal (Crume et al., 2015). So not only can the fetus receive such signals from maternal diet, but it can also receive signals from its mother's health.

Implications for Surrogacy

In the context of surrogacy in India, people from the Indian subcontinent have very high risks of diabetes and many women suffer from high blood glucose levels and insulin resistance, factors which have been shown to be associated with increased body mass and neonatal adiposity (Yajnik & Ganpule-Rao, 2010). Increased maternal BMI is positively associated with increased adiposity and inflammation among neonates (McCloskey et al., 2016). While Indian surrogate mothers may not necessarily have a high BMI, much like the men of the Indian subcontinent, they do have high levels of adiposity (Yajnik, 2004). Furthermore, in a birth cohort located in New Delhi, India, data have shown that being thin at birth or during infancy and then experiencing accelerated BMI gain during childhood is associated with a pro-inflammatory state in adulthood (Lakshmi et al., 2012). High levels of adiposity and chronic

inflammation are risk factors for many chronic diseases, such as kidney disease and cardiovascular disease, suggesting that further consideration is needed when thinking about surrogacy in India in regards to the effects that it may have on the future health of surrogate children (Gupta et al., 2013; Siti, Kamisah, & Kamsiah, 2015).

The importance of lipids on fetal development

The last macronutrient considered were lipids, a fundamental source of energy as well as a way for the body to store energy for future use. Lipids help build the membranes of the cells in the body and are vital in the creation of certain classes of hormones (e.g. steroids). During development, lipids play a large role in the creation of the central nervous system where they help in its development, migration, and nerve differentiation (Gonzalez & Visentin, 2016). There exist many different types of lipids and each type plays a different role during development/can affect development differently.

First Trimester

During the first trimester, data from the ROLO cohort described an association between an increased maternal intake of saturated fatty acids and increased weight of children at five years of age (Murrin et al., 2013). The data further showed that mothers who were in the highest quartile for saturated fatty acids during pregnancy and postpartum were 3.7 times more likely to have a child who was overweight or obese at age 5 (Murrin et al., 2013). In regards to trans fatty acids, no association was found during the first trimester with fetal outcomes, but during the second trimester increased trans fatty acids were associated with increased fetal growth according to data from Project Viva (J. F. Cohen, Rifas-Shiman, Rimm, Oken, & Gillman, 2011). In their model, for every 1% of energy from carbohydrates that was

replaced by 16.1 TFA, the fetal growth z score, as measured by birth-weight-for-gestational-age, increased by 0.12 units, and for every 1% of energy from carbohydrates that was replaced by 18:2tc, the fetal growth z-score increased by 0.533 units; the more energy derived from maternal consumption of carbohydrates, the more the infant weighed at birth (J. F. Cohen et al., 2011). The ROLO study was composed of mothers who were at-risk of delivering a macrosomic infant, while Project Viva's mothers were not, yet both saw effects due to maternal consumption of fatty acids (J. F. Cohen et al., 2011; Murrin et al., 2013). These results suggest that maternal fatty acid consumption can affect a child's growth in regards to weight, both immediately after birth and at 5 years old and in particular, that saturated fatty acids were associated with increased adiposity in children and increased trans fatty acids were associated with weight overall (J. F. Cohen et al., 2011; Murrin et al., 2013).

Second Trimester

In women who participated in the GI Baby 3 cohort – women who were at-risk for developing gestational diabetes mellitus (GDM) – during the second trimester, total fat and saturated fat, which were calculated as percentages of energy, were positively associated with the neonatal fat-free mass index (Kizirian et al., 2016). Data from the same cohort showed that during late pregnancy, this relationship changed, and high intakes of total fat and saturated fat were associated with higher fat mass index (Kizirian et al., 2016; Markovic et al., 2016).

Maternal intake of polyunsaturated fat, on the other hand, is negatively associated with the waist:length ratio, a measure of adiposity, of children at 2 years of age according to data from the ROLO study (Horan, Donnelly, et al., 2016). Both of these populations looked at the effects of a low glycemic index diet, and while the study population was not the same, and there were

differences in the ways in which the intervention occurred, these two results concerning saturated and unsaturated fat help to tease out the different effects that can occur due to the different types of fat mothers consume during pregnancy (Horan, Donnelly, et al., 2016; Kizirian et al., 2016).

Third Trimester

Prospective data collected from a cohort of 179 Australian women who participated in the Women and Their Children's Health Study (WATCH), reported an association between the intake of saturated fatty acids and the mid-thigh area during development, with data for nutrient intake collected from FFQ and body composition measurements collected using cross-sectional MRI images of the thigh (Blumfield et al., 2012). They found that for each isoenergetic 1% increase in saturated fatty acids, the mid-thigh lean area decreased by 0.27% and for every isoenergetic 1% decrease in saturated fatty acids the mid-thigh subcutaneous area decreased by 0.27% (Blumfield et al., 2012). The data from this study help show that maternal lipids influence the body composition – both fat-free mass as well as fat mass – of the fetus. This relationship was also seen in results from the ROLO study, where increased maternal intake of saturated fatty acids was associated with increased weight-for-age z-score at age 2 years (Horan, Donnelly, et al., 2016). ROLO and WATCH are distinctly different cohorts. While ROLO's intent was to see if a low glycemic index diet could reduce the risk of macrosomia among offspring, WATCH simply wanted to observe if maternal diet had any effect on fetal body composition (Blumfield et al., 2012; Horan, Donnelly, et al., 2016). Yet, even with these differences in study populations (e.g. different health histories and different backgrounds), both cohorts saw similar effects in terms of associations between maternal saturated fatty acid

intake: WATCH describing effects among fetuses and ROLO describing the effects two years after birth. Taken together, these studies suggest that maternal saturated fatty acid intake does have an effect on fetal body composition and health after birth (Blumfield et al., 2012; Horan, Donnelly, et al., 2016).

During pregnancy, dietary fat and maternal lipid consumption can not only affect the outcome of pregnancy, but it also may effects the infant's growth and development as well as their short-term and long-term health (Koletzko et al., 2007). The results of the data from the various studies presented here, help show that maternal lipid consumption does no merely influence fetal adiposity or waist:length ratio, but a variety of different anthropometric measurements which are used to measure the growth of the infant (Blumfield et al., 2012; Horan, Donnelly, et al., 2016; Kizirian et al., 2016).

The importance of balance in maternal macronutrient intake

Many of these studies look at the individual effects that each macronutrient has on development (e.g. maternal protein intake and birthweight) and while that is beneficial, nothing in the body occurs in a vacuum and functions by itself. Likewise, during development everything works in tandem to build the best body according to the signals the fetus is received from the maternal body, signals such as those contained/relayed by macronutrients.

First Trimester

High maternal intake of carbohydrates during early pregnancy and low intakes of dairy protein during late pregnancy were found to be associated with increased risk of thinness at birth among the 538 mothers from Southampton, UK, (Godfrey, Barker, Robinson, & Osmond, 1997). In these data, a relationship was seen between the effects of early nutrition during

pregnancy coupled with nutrition during late pregnancy on the development of fetal adipose tissue (Godfrey et al., 1997). The British women in the sample had both a low intake of protein during early and late pregnancy and a high intake of carbohydrates (Godfrey et al., 1997). By contrast, studies conducted among Danish and Portuguese cohorts have shown that high maternal intake of carbohydrates during late pregnancy were associated with increased fetal adiposity. This outcome was not seen among the of British women and their children, suggesting the importance of the overall balance in dietary nutrients and emphasizing the importance of protein intake for proper fetal development (Genetics Home Reference, 2017; Godfrey et al., 1997; Pereira-da-Silva et al., 2014; Renault et al., 2015). The Southampton study helps to show that having a high intake of carbohydrates and a low intake of protein during early and late pregnancy can have detrimental effects on fetal adiposity.

Second Trimester

Looking at the second trimester, a relationship can also be seen in regards to protein and carbohydrates, where high protein intake coupled with a low intake of carbohydrates was associated with a decrease in adipose tissue (Chen et al., 2016). Using data from 320 mother-child pairs who participated in the GUSTO study conducted in Singapore, a diet composed of high protein and lower carbohydrates was specifically associated with a decrease in abdominal internal adipose tissue (IAT) (Chen et al., 2016). IAT is the internal fat contained in the abdominal region, and synonymous with visceral fat in adults (Chen et al., 2016). Specifically, a 1% energy substitution of protein for carbohydrates in the maternal diet was associated with a 0.18 mL lower IAT in neonates, after adjusting for potential confounders such as gestational diabetes (Chen et al., 2016). In regards to protein and fat, according to data from the same

cohort, a negative association was seen where a 1% energy substitution of protein for fat was associated with a 0.25 mL lower IAT in newborns (Chen et al., 2016). These two relationships stayed the same when fiber, type of carbohydrate, and type of fat were considered (Chen et al., 2016). Furthermore, when infants born to mothers in the highest tertile for protein intake at the expense of fat were compared to infants born to mothers who were in the lowest tertile, the former infants had a IAT that was lower by 2.10 mL (Chen et al., 2016). This finding is in line with the data from the WATCH study (Blumfield et al., 2012). In analyzing the results from 179 mother-child pairs, a 0.36% increase in fetal abdominal subcutaneous fat area was associated with a 0.1-unit decrease in the maternal protein to carbohydrate ratio (increased carbohydrates and decreased protein); this is similar to the Chen et al. (2016) investigation (Blumfield et al., 2012). This relationship was reversed when the protein to carbohydrate ratio increased, and saw that a 0.1 increase in the maternal protein to carbohydrate ratio was associated with a 0.36% increase in fetal abdominal visceral area (Blumfield et al., 2012). Blumfield et al. (2012) further found that fetal abdominal visceral area was greatest when protein was equal to 20% of maternal energy and Chen et al. (2016) found that males were more affected by maternal nutrient intake than females, with increasing protein intake replacing carbohydrates or fat associated with decreased birth length (Chen et al., 2016). These studies help to show the importance of the macronutrient ratio and balance. Importantly, these two studies looked at two completely different ethnic populations. Chen et al. (2016) looked at an Asian cohort based in Singapore that was composed of Chinese, Malay, and Indian women who were married to someone of the same ethnicity (Chen et al., 2016). Blumfield et al. (2012), was based in Australia and investigated a sample composed of a more homogenous population (Blumfield et

al., 2012). However, even with these differences in location, ethnicity, weight gain during pregnancy, and height, the effects that the macronutrient ratios had on fetal development were similar, suggesting that while the differences in the cohorts may have an effect on development, the macronutrient ratios play a larger role in development (Blumfield et al., 2012; Chen et al., 2016).

Third Trimester

Finally, in the third trimester, in women at-risk for GDM in the GI Baby 3 study, an association was found between the fat mass index of the infant and a maternal diet of low carbohydrates and high fat. Here, the fat mass index of the infant was greatest when carbohydrates composed less than 45% of maternal energy and fat made up more than 40% of maternal energy (Kizirian et al., 2016).

These studies help to show that, during development, a balance between protein, carbohydrates, and lipids is important in the development of fetal adiposity, which can have huge impacts on future health (Blumfield et al., 2012; Chen et al., 2016; Godfrey et al., 1997; Kizirian et al., 2016). Increased adiposity is associated with increased inflammation, which can not only increase a person's risk for certain chronic diseases such as cardiovascular disease, but maternal inflammation during pregnancy can have effects on fetal development through epigenetics (Gemma et al., 2009; Ridker, Hennekens, Buring, & Rifai, 2000). While none of these studies took place in the same location, all of their outcomes dealt with fetal adiposity (Blumfield et al., 2012; Chen et al., 2016; Godfrey et al., 1997; Kizirian et al., 2016). The women in the 4 different cohorts did not have the same background, health history, or ethnicity, and yet when there was a "misbalance" of maternal macronutrient intake, fetal adiposity was

affected (Blumfield et al., 2012; Chen et al., 2016; Godfrey et al., 1997; Kizirian et al., 2016). In regards to India, these findings are significant as the balance between the macronutrients in the Indian diet is not always “optimal” for development and thus affects the cues the fetus receives, with developmental implications for future health (Green, Milner, Joy, Agrawal, & Dangour, 2016; Satija et al., 2015).

India and the thin-fat phenotype

Individuals from the Indian subcontinent have been reported to have a very unique phenotype. While they outwardly appear thin and have a low BMI, they actually have a high percentage of body fat and a low percentage of lean body mass or muscle (Joshi, 2012). Along with these characteristics come increased risks for diabetes (insulin resistance) and other chronic diseases, such as cardiovascular disease, that are associated with inflammation that is caused by the high levels of adiposity (Joshi, 2012; Prabhakaran & Yusuf, 2010).

This phenomena – having a low BMI and outwardly appearing to be thin yet in reality carrying high levels of fat on the body – has been documented in many cases. According to the World Health Organization (WHO), just based on BMI, a BMI of over 30.0 kg/m² is considered obese and a BMI of over 25 kg/m² is considered overweight (World Health Organization, 2006). In a study that examined adiposity in Indian men, it was found that 149 men from rural villages had a mean BMI of 21 and that 34% of those same men had a body fat percentage greater than 25% (Yajnik, 2004). This is important, as a body fat percentage of over 25% is commonly considered to be obese; so, while the mean BMI was 21, which puts the men in the “normal” category according to the CDC, 34% of those men were actually obese based on body fat percentage (Centers for Disease Control and Prevention, 2015). A further example derives from

a sample of 142 men from the slums, who had a mean BMI of 22, with 45% of them also characterized by a body fat percentage over 25% (Yajnik, 2004). Finally, among a sample of 150 middle class residents from Pune, India, a mean BMI of 24 was found accompanied by a body fat percentage over 25% among 84% of them (Yajnik, 2004). In other words, while none of these groups had a mean BMI that would place them in the overweight or obese category, their body fat percentage firmly placed them in the obese category. BMI is one way to measure obesity, but not the only or the best parameter. Among those who are thin-fat, they may be obese in the absence of a BMI that is diagnostic and is not reflected in their outward appearance. One limitation of this study was that it looked only at men. However, the overall findings, that while the men appeared to be thin and had a BMI that would commonly be considered thin, they were actually obese and had high levels of adiposity, can be applied to Indian women as well. To complicate matters further, in general, women have higher levels of body fat than men do (Blaak, 2001). Taking this into account, the relatively short height among women in India exacerbates the risk to the developing fetus (Yajnik et al., 2003). Therefore, not only do women from the Indian subcontinent weigh less in general, they also carry high levels of fat on a relatively small and thin frame.

This phenotype is present at birth as seen in data from both Pune, India and Mysore, India. Children born to Indian mothers in Pune, India, when compared to children born to mothers in Southampton, UK, were found to have a lower birthweight and placental weight, as well as a smaller head circumference, mid-arm circumference, and abdominal circumference (Yajnik et al., 2003). Just as their mothers were smaller, so were they. However, by comparison, the length of the Indian infants was relatively spared and the subscapular skinfold thickness

showed the least amount of difference between the two populations (Yajnik et al., 2003). As subscapular skinfold thickness is used to measure adiposity, this suggests that while there was a relatively large difference in birthweight between the 2 populations, the difference in adiposity – or fat – was not as great. Herein lies a potential issue. The Indian infants may have weighed less, but they had a greater percentage of fat than the English children. This relationship remained true across the birthweights, not only for low birthweight infants, but also for infants of higher birthweights. When low birthweight babies were specifically looked at, in comparison to babies born in Southampton, the Indian babies tend to preserve fat relative to birthweight; they had a higher percentage of adipose tissue. When infants at higher birthweights were compared, not only were the Indian infants longer, but they were also characterized by greater adiposity by comparison to the British infants (Yajnik et al., 2003). Children born to mothers in Mysore, India (which has officially been renamed Mysuru) who were compared to children born in Southampton, UK, were found to have the lower birthweight, 2983 grams vs. 3472 grams, smaller upper arm, head and abdominal circumferences (Krishnaveni et al., 2005). Just as the data from Pune showed, the least amount of change occurred in length and subscapular skinfold thickness in terms of absolute measures (Krishnaveni et al., 2005). While Pune is located in the western central part of India, Mysuru is located in the central southern part of India. These similar findings from 2 different geographic populations show that this phenotype is not unique to subset population of India, but rather likely to be an inborn trait among populations across regions.

The relatively high levels of adiposity and relatively long length of infants at birth persist and data collected at 1 year of age among Mysuru Indian children found that they were still

both smaller and weighed less compared to peers from Southampton, just like their mothers (Krishnaveni et al., 2005). BMI, head circumference and subscapular skinfold thickness were also decreased in the Indian cohort, although just like at birth, the smallest difference between the two cohorts was seen in length and subscapular skinfold thickness (Krishnaveni et al., 2005). At 4 years of age, the Indian children were still smaller than those born in the UK for all measurements except for subscapular skinfold thickness, where their measurements actually surpassed those of the British children (Krishnaveni et al., 2005). The Indian children not only had increased levels of adiposity compared to weight and height, but these levels actually surpassed those of the children from the UK overall. Similar results were seen in children from Pune at 1, 2, 3, and 6 years of age (D'Angelo et al., 2015). While the differences between the children born in Pune and those born in Southampton increased during infancy and early childhood, by 6 years of age, these had decreased and the two populations had become more similar than they were during infancy (D'Angelo et al., 2015). Subscapular skinfold thickness showed the least amount of difference across all time points, just as it did among the Mysuru sample (D'Angelo et al., 2015). Their subscapular skinfold thickness, when compared to a UK skinfold reference, suggested that the children in Pune were relatively truncally adipose (Joglekar et al., 2007). Furthermore, when compared to international references on child development and growth, the Pune cohort was found to be light, short, and thin (Joglekar et al., 2007). The findings from Pune and Mysuru further strengthen the idea of a thin-fat Indian phenotype is something that is already present at birth and does not abate as the children age. This raises the question of whether this is something that is genetically passed down from

parent to offspring, or if it has to do with the environment in which the child develops. It must be asked if this phenotype is affected by maternal body composition.

The importance of maternal body composition on development

Body composition measures the percentage of fat, muscle (lean body mass), water, and bone mass that makes up the human body. Theoretically it can be suggested that during pregnancy, maternal body composition serves as a way to communicate to the fetus what the outside world – the environment they will soon find themselves living in – has historically looked like. It does this as body composition reflects what the environment has looked like over a longer period than current diet does. Current diet gives a snapshot in time, whereas body composition can give information about for a whole lifetime. Additionally, body composition can – and does – affect metabolism and nutrient availability in the mother's body, further affecting the environment in which the fetus develops. In this way, maternal body composition is directly contributing to fetal development.

The effects of fat free mass on fetal outcomes

Current data show that there exists a positive relationship between maternal fat-free mass and birthweight; increased fat-free mass is associated with increased birthweight (Farah, Stuart, Donnelly, Kennelly, & Turner, 2011; Kent et al., 2013; Mardones-Santander, Salazar, Rosso, & Villarroel, 1998; Mongelli, 1996; Sanin Aguirre, Reza-Lopez, & Levario-Carrillo, 2004).

This relationship has been seen in India, specifically. In a study conducted in Hyderabad, India, on a population of Indian women from the slums, maternal lean body mass was found to account for the major variations seen in birthweight (B. Kulkarni, Shatrugna, & Balakrishna, 2006). This means that if the mother had a higher percentage of lean body mass, her child had a

higher birthweight compared to children whose mothers had a lower percentage of lean body mass. This relationship can be extrapolated to suggest that as maternal fat mass increased, birth weight of her neonate decreased. Indeed, low birthweight is quite commonly seen in children born to mothers from the Indian subcontinent (Krishnaveni et al., 2005; Yajnik et al., 2003).

The effect of maternal fat-free mass has on the fetus is not just restricted to birthweight but has also been shown to be associated with fetal length and skinfold thickness (Duggleby & Jackson, 2001; Muthayya et al., 2006) Maternal protein synthesis during the second trimester – found to be driven by maternal fat-free mass – was positively associated with length in a cohort of 27 British women (Duggleby & Jackson, 2002). This means that higher levels of fat-free mass drives protein synthesis, which in turn, is associated with increased fetal growth measured by length. Although Duggleby and Jackson conducted their study in the UK, this relationship was also seen in Indian children born to mothers in Bangalore City (B. Kulkarni et al., 2006). Skinfold thickness is used as a marker of adiposity, meaning that maternal fat free mass was associated with increased adiposity as well as with increased length in the infants from Bangalore City. Maternal fat-free mass not only acts as a source of resources which the fetus uses during development (e.g. protein), but is also the source of energy which sustains life for both the fetus and its mother. By having less fat-free mass – less muscle – there are fewer oxidative metabolic substrates throughout the body. Thus, having less muscle decreases the amount of energy the fetus has access to which, in turn, can influence its growth. Therefore, increased fat-free mass is associated with increased growth measured by birthweight, length, and adiposity, and may be influenced from maternal body composition.

The effects of fat mass on fetal outcomes

In regards to fat mass, there are two major components that play important roles in development: maternal fat mass in general and serum lipid concentrations. In the body, fat acts mainly as a way to store and preserve energy. During pregnancy – particularly early and mid-pregnancy – fat stores are stimulated for use during late pregnancy where it is used to promote increased fetal growth (Butte, Ellis, Wong, Hopkinson, & Smith, 2003).

In general, maternal fat mass is associated with increased weight at birth and, specifically within female offspring, increased maternal fat mass is associated with increased fat mass and fat mass index (Friis et al., 2004; Henriksson, Lof, & Forsum, 2015; Toro-Ramos, Sichieri, & Hoffman, 2016). In these studies from populations in Zimbabwe, Sweden, and Brazil, maternal adiposity predicts female adiposity and is associated with increased weight for both sexes (Friis et al., 2004; Henriksson et al., 2015; Toro-Ramos et al., 2016). These populations are very diverse and have very different backgrounds and histories, yet, they show that maternal adiposity has an effect on birthweight and female fetal adiposity (Friis et al., 2004; Henriksson et al., 2015; Toro-Ramos et al., 2016).

More specifically, when particular serum lipids were looked at with regard to the fetal body, different effects were seen based on the molecule and the trimester. Starting with the first trimester, according to data from the ABCD sample, increased maternal triglyceride serum levels were positively associated with the birthweight standard deviation score (Vrijkotte, Algera, Brouwer, van Eijnsden, & Twickler, 2011). This means that mothers who had higher levels of triglycerides were more likely to have children who weighed more at birth (Vrijkotte et al., 2011). During the first 6 months of life, 24.5% of infants born to mothers in the lowest quartile

for triglyceride levels experienced accelerated growth in weight and length after birth whereas, on average, only 19.6% of children born to mothers in the other quartiles experienced this accelerated growth (Vrijkotte et al., 2011). This relationship – increased triglyceride levels and birthweight – was seen in data from the Healthy Start Study, although it was flipped, as they found that every 1 mg/dL increase in triglycerides was associated with a 0.5-gram increase in birthweight (Crume et al., 2015). The Healthy Start Study was created to look at the effects maternal diet on fetal outcomes, whereas ABCD was created to see how maternal lifestyle and psychosocial conditions during development effected fetal outcomes and had no dietary intervention or assessment (Crume et al., 2015; van Eijsden et al., 2008). This opposite relationship may exist due to women in the Healthy Start Study trying to change their diet, knowing that diet was going to be assessed (Crume et al., 2015; van Eijsden et al., 2008). Furthermore, if sample size were considered, the ABCD cohort of 4389 mothers is far larger than that of the Healthy Start Study of 804 mother-child pairs (Crume et al., 2015; van Eijsden et al., 2008). Data from the ABCD cohort also showed a relationship between fatty acids and birthweight, where decreased fatty acids were associated with increased risk of low birthweight (van Eijsden et al., 2008). Children whose mothers had intermediate concentrations of linoleic acid, AA, adrenic acid, osbond acid or elaidic acid, when compared to children whose mothers were in the highest quintile, were found to be 52 – 90 grams lighter than their peers (van Eijsden et al., 2008). Furthermore, children who were born to mothers with lower concentrations of most n-3 fatty acids (excluding α -linolenic acid and DHA) and DGLA (an n-6 fatty acid) were at higher risk of being born small for gestational age (SGA) (van Eijsden et al., 2008). So, according to data from the ABCD cohort, increased fatty acid concentrations were

associated with increased birthweight and lower risk of being born SGA (van Eijsden et al., 2008). Cholesterol, more specifically HDL-c, is negatively associated with fetal body composition according to data from the Healthy Start Study (Crume et al., 2015). Here each 1 mg/dL increase in HDL-c was associated with a decrease of 2.67 grams in birthweight, a 1.41-gram reduction in fat mass, and a reduction in fat mass percentage by 0.03% (Crume et al., 2015). Overall, while the results concerning the effects of maternal lipid concentrations on fetal development are varied, this may reflect differences in sample size and the characteristics of the study populations. It appears that maternal lipids, particularly triglycerides, cholesterol, and fatty acids do affect fetal body composition as evidenced by data from the Healthy Start Study and the ABCD cohort (Crume et al., 2015; van Eijsden et al., 2008; Vrijkotte et al., 2011). By receiving the signals carried by these molecules, the fetus responds to its environment.

During the second trimester, maternal fatty acids and cholesterol still play a role in development and convey cues to the fetus. During this time, increased levels of free fatty acids are associated with increased neonatal fat percentage where a jump from the 2.5th percentile (0.11 mmol/L) to the 97.5th (0.77 mmol/L) of free fatty acids was associated with an increase in fat percentage by 1.33% and an increase in BMI by 0.30 kg/m² according to data from the ABCD cohort (Gademan et al., 2014). Increased free fatty acid levels were also associated with risk for being overweight as children born to mothers in the 2.5th percentile for free fatty acids were 5.2% more likely to be overweight whereas children born to mothers in the 97.5th percentile were 10.2% likely (Gademan et al., 2014). So, based on the data from the ABCD cohort, increased maternal free fatty acid concentrations during the second trimester are associated

with increased fat percentage and increased risk for being overweight, a similar relationship to the one that has been noticed during the first trimester.

In regards to total cholesterol, increased maternal total cholesterol levels are associated with increased fetal growth according to data from the Pune Maternal Nutrition Study (S. R. Kulkarni et al., 2013). Specifically, increased maternal total cholesterol levels were associated with increased birthweight, increased mid-upper arm circumference (MUAC), and increased abdominal circumference, where a 1 standard deviation increase in maternal total cholesterol was associated with a 39-gram increase in birthweight (S. R. Kulkarni et al., 2013). Abdominal circumference is a way to measure abdominal fat; it is a measure of adiposity, while mid-upper arm circumference is used as a nutritional biomarker (Mwangome, Fegan, Fulford, Prentice, & Berkley, 2012). Increased maternal total cholesterol was associated with increased growth during development as measured through weight, adiposity, and MUAC in an Indian cohort (S. R. Kulkarni et al., 2013). Plasma cholesterol concentration is also specifically associated with increased growth as measured by birthweight and adiposity according to data from the same cohort (S. R. Kulkarni et al., 2013). During fetal development, increased concentrations of plasma cholesterol are associated with increased newborn size for all measurements except head circumference (increased MUAC and abdominal circumference) (S. R. Kulkarni et al., 2013). Specifically, it is also associated with increased weight; a 1 standard deviation increase in maternal concentrations of plasma cholesterol is associated with an increase in birthweight by 54 grams (S. R. Kulkarni et al., 2013). Thus, both total cholesterol and, specifically, plasma cholesterol concentrations are positively associated with fetal growth and development.

Likewise, during the second trimester, increased maternal triglyceride levels were associated with increased abdominal circumference measured at 18 weeks, according to data from the Pune Maternal Nutrition Study (S. R. Kulkarni et al., 2013). At 28 weeks, maternal triglycerides were positively associated with a variety of anthropometric markers such as birthweight, birth length, skinfold thickness and abdominal circumference (S. R. Kulkarni et al., 2013). In particular, a 1 standard deviation increase in maternal triglycerides was associated with a 36 gram increase in birthweight (S. R. Kulkarni et al., 2013). So, not only are maternal cholesterol levels associated with increased triglycerides during the second trimester, but they are associated with increases in adiposity, length and weight of the fetus.

During the third trimester, maternal fatty acids continue to play an important role in fetal development, just as they did during the previous trimesters, however different results have been seen in the different cohorts (Crume et al., 2015; Moon et al., 2013). According to data from the Healthy Start Study, increased maternal free fatty acids were associated with decreased birthweight (Crume et al., 2015). By contrast, data from 293 mother-child pairs from the Southampton Women's Study showed that maternal plasma total n-6 PUFA concentrations and maternal plasma total n-3 PUFA concentrations, specific types of free fatty acids, were positively associated with growth at ages 4 and 6 (Moon et al., 2013). Here, they found that an increased maternal plasma total n-6 PUFA concentration was associated with increased weight and fat mass in children at 4 and 6 years of age and that maternal plasma total n-3 PUFA concentrations were positively associated with height at the same ages (Moon et al., 2013). The differences that can be seen in these results may be due to differences in sample size, as Moon et al. looked at a subsample of 293 women and their children in the SWS whereas Crume et al.

looked at a cohort of 803 mother-child pairs. The sample locations, maternal history and background and socioeconomic status also differed (Crume et al., 2015; Moon et al., 2013). Most importantly, perhaps, is that the studies did not measure the same variables. These results suggest that not only does maternal body composition affect development, but that different lipids, which are affected by maternal body composition, have different and perhaps specific effects on development as well.

Overall, a high percentage of maternal lean body mass is associated with increased growth and development in the fetus, as measured by length and weight, as well as decreased adiposity (Duggleby & Jackson, 2001; Farah et al., 2011; B. Kulkarni et al., 2006). A high percentage of fat, on the other hand, has more contradictory findings, which may be based in the innate differences of the different cohorts, the overall dietary constituents and the specific nature of the fat. Overall, maternal fats are associated with increased birthweight and increased fetal and neonatal adiposity (Crume et al., 2015; S. R. Kulkarni et al., 2013; Moon et al., 2013).

In the context of India and Indian surrogacy, the findings raise particular concerns for fetal outcomes in terms of future health, particularly the high adiposity findings associated with the typical Indian female phenotype. For specific mechanistic implications animal models are useful as these results are not unique to humans, however, and have been seen in animal models as well.

Evidence from animal models

Animal models provide a broader perspective than human models do because experimentation may be done in animal models which allows for more concrete relationships

to be discovered and mechanisms to be teased out. Experimentation in humans is not only ethically inappropriate, but very difficult due to the long lifespan of the human species. Many researchers have turned to animals to help them better understand the underlying mechanisms.

Protein plays an important role during development and the deprivation of protein during pregnancy can have detrimental effects to development and health. A signature study looked specifically at rats, deprived of protein for 12 generations through a low protein diet. The animals in this study experienced decreased birthweight, impaired growth after birth, decreased organ size, and aged faster than rats who were fed a “normal” protein rat diet (Stewart, Preece, & Sheppard, 1975). This experiment showed that the effects of a low protein diet lasted across generations and illustrated that when rats were forced forego access to all of the nutrients which would have been beneficial for development, they changed anatomically and physiologically. This animal model suggests caution with the surrogacy enterprise that has not been entirely recognized. It might be a particularly relevant model for India because India has a history of malnutrition, where its people have gone through cycles of malnutrition. Between 1765 and 1947, 15 famines took place on the Indian subcontinent (Kiple, 2000). While there were not any known studies that were conducted during that time on the effects of famine, there have since been studies conducted on the effects of other famines, but are just as applicable to India. Looking at the effects of the Dutch Hunger Winter, the Ukraine Famine of 1932-33, and the Chinese Great Famine of 1959-1961, researchers have found that exposure to famine during development leads to higher risks of chronic disease such as diabetes, cardiovascular disease, and high blood pressure (Lumey et al., 2015; T. Roseboom et al., 2006;

Wang et al., 2012). Furthermore, it has been seen that the effects of famine are multi-generational and do not simply stop once the famine has passed, but persist and affect later generations as well. Painter et al. (2008) found that while birthweight and cardiovascular and metabolic disease rates in children born to parents who were affected by the Dutch Hunger Winter were not affected as a result of the transgenerational effects of prenatal exposure to famine, they did find that these children did have increased fetal adiposity and poor health later in life (Painter et al., 2008). A subsequent study further found that children of fathers who had been undernourished during development had increased BMI and weight compared to children who were born to parents who were not affected by the Dutch Hunger Winter (Veenendaal et al., 2013). By analogy it is possible that repeated exposure to famine over many generations in India may have severe consequences for the population. The thin-fat phenotype and its persistence in the population may be such an example. While there has not been a famine in India since 1944, the effects of having such a history can be seen in the high rates of adiposity and increased rates of chronic disease that is now seen on the Indian subcontinent (Yajnik, 2014). The women in India have a history of famine written into their health.

These effects have also been seen in mice. Mice born to mothers who were fed a low protein diet during pregnancy experienced intrauterine growth retardation – they were born small and had a low birthweight – and subsequently underwent catch-up growth after birth (Peixoto-Silva, Frantz, Mandarim-de-Lacerda, & Pinheiro-Mulder, 2011). These mice were kept on a low protein diet throughout the rest of their life, and when they were bred, it was found that they, and their offspring, experienced glucose intolerance, insulin resistance and had markers indicating future leptin resistance that was exacerbated in the second generation

(Peixoto-Silva et al., 2011). Similarly, increased adiposity and increased systolic blood pressure have also been seen in mice born to mothers fed a low protein diet during development (Watkins, Lucas, Wilkins, Cagampang, & Fleming, 2011). These results are in line with observations from India, where there are high levels of adiposity and increased rates chronic disease (Yajnik, 2004, 2014). These experiments show that effects due to an insult during development can be seen after just one generation and that sometimes, the effects are even worse in the second generation (Peixoto-Silva et al., 2011; Watkins et al., 2011). These animal models are appropriate in the case of surrogacy as they help to show that even if one generation is exposed to a high fat-low protein environment, which is the environment the child is exposed to in surrogacy in India, the effects can persist for a lifetime.

Potential mechanisms

While the exact mechanisms of the effects seen in offspring born to women of a thin-fat phenotype are unknown, several mechanisms have been proposed and range from down regulated mitochondrial activity, to DNA methylation, to inflammation itself (Gemma et al., 2009; Pileggi et al., 2016; Soubry et al., 2015). In order to understand the mechanisms underlying the observed effects, a similar body composition must be created. In animals this has been achieved by feeding them a high fat diet throughout their life and/or during pregnancy. In rats, this high fat diet results in higher fat mass and a lower lean mass:fat mass ratio, creating a similar body composition to that of surrogate mothers in India (Howie, Sloboda, Kamal, & Vickers, 2009). In that particular population of rats, a high fat diet decreased offspring birthweight, increased offspring adiposity (measured by total body fat mass and fat:lean mass ratio), and offspring exposed to this maternal body composition were found to be

predisposed to obesity in later life, irrespective of postnatal diet (Howie et al., 2009). It has also been observed that a maternal high fat diet in rats negatively affects metabolic activity, which can increase the risk of insulin resistance or other metabolic disorders in offspring (Pileggi et al., 2016). In these rats, it was found that a maternal high fat diet decreased skeletal muscle mitochondrial activity by down regulating necessary factors and decreasing needed protein expression for appropriate mitochondrial activity (Pileggi et al., 2016). By being exposed to a high fat environment before birth, the metabolic activity of these rats was changed due to decreased skeletal mitochondrial activity that was negatively affected by the high fat environment (Pileggi et al., 2016). This in turn decreased the way their bodies could process glucose and create energy, and put them at higher risk for metabolic diseases such as type 2 diabetes (Hesselink, Schrauwen-Hinderling, & Schrauwen, 2016; Pileggi et al., 2016).

DNA methylation is another potential mechanism and is the process by which gene expression is “turned on” and “turned off” (Jin, Li, & Robertson, 2011). According to data from 79 infants born to obese mothers, the cord blood – the infant’s own blood – was found to have altered methylation of imprinted genes maternally expressed gene 3 (MEG3) and pleiomorphic adenoma gene-like 1 (PLAG1) (Soubry et al., 2015). These data were collected from the prospective cohort NEST located in Durham County, NC, between July 2005 and November 2006, and maternal obesity was measured using BMI calculated with maternal pre-pregnancy weight (Soubry et al., 2015). These genes are associated with early growth regulation and down regulation of MEG3 has been associated with increased adipocytes, increased risk of obesity and several types of tumors (Soubry et al., 2015). Likewise, increased maternal BMI – increased maternal adiposity – was positively associated with the DNA methylation of peroxisome

proliferator activated receptor γ co-activator 1 α (PPARGC1A) promoter, as indicated in the DNA of the umbilical cord according to cross-sectional data collected from 88 mother-child pairs in Argentina (Gemma et al., 2009). This gene codes for PGC-1 α , the master regulator of mitochondrial biogenesis (Gemma et al., 2009). So, based on the data from the Nest cohort and Argentina, the increased methylation of this gene in humans, by a maternal high fat environment, is associated with decreased mitochondrial activity in the fetus which leads to overall less energy for the fetus and worse health outcomes later on in life (Gemma et al., 2009; Soubry et al., 2015). The increased methylation of this gene is associated with metabolic outcomes, just like those of Pileggi et al., 2016, which was looking at the effects of a maternal high fat diet/environment in rats. These similar outcomes help strengthen the link between a maternal body composition that has a high percentage of fat and negative metabolic outcomes (Gemma et al., 2009; Pileggi et al., 2016; Soubry et al., 2015). Exposure to a high fat environment leads to the methylation of genes that are vital for development and long-term health as it affects growth regulation and control of adiposity as well as energy production.

Obesity, or high levels of adipose tissue, is associated with chronic inflammation that has been proposed to negatively influence development (Tilg & Moschen, 2006). For example, according to data from Project Viva concerning 1116 mother-child pairs, increased c-reactive protein – an inflammatory marker – during the second trimester was associated with increased adiposity in mid-childhood (Gaillard, Rifas-Shiman, Perng, Oken, & Gillman, 2016). This relationship was also seen in rats where maternal obesity was positively associated with increased inflammation, which in turn was associated with ectopic lipid accumulation and lipid metabolic gene expression in the fetus (Shankar et al., 2011). Ectopic lipid accumulation is a

known mechanism, which can impair insulin signaling in the muscles and liver leading to increased risk of type 2 diabetes and organ damage (Guebre-Egziabher et al., 2013).

Furthermore, mitochondrial gene expression (TFAM and NRF1) decreased in the embryos of rats that were exposed to maternal obesogenic environment, a finding that is in line with both Pileggi et al., 2016 and Gemma et al., 2009 (Shankar et al., 2011).

Summary

There are many potential mechanisms that may be the reason why children born to mothers who are thin-fat have high levels of adiposity and yet appear thin, and DNA methylation and inflammation, which in turn affect mitochondrial activity, are just two of these potential mechanisms. As these mechanisms have shown, permanent changes occur in the body due to the environment in which the fetus is exposed during development. This is important as not only do these changes persist for a lifetime, but they can also be transmitted to future generations, even when individual has been removed from the environment that originally induced these effects (Jimenez-Chillaron et al., 2009; Painter et al., 2008). In the human fetus, DNA methylation occurs, downregulating certain genes that are associated with controlling adiposity as well as genes that code for mitochondrial activity, meaning that the fetus may have increased adipose tissue as well as a decreased number of mitochondria (Gemma et al., 2009; Soubry et al., 2015). Evidence from rats has also shown other genes, which code for mitochondrial activity, that are affected by an obesogenic environment, strengthening the link between maternal obesity and potential negative metabolic outcomes (Shankar et al., 2011). Data from children exposed to famine in utero has shown that these children pass onto their children various negative effects – such as increased adiposity – which

may have adverse outcomes for their children (Painter et al., 2008; Veenendaal et al., 2013). Even though a child born via surrogacy is removed from the environment to which it was exposed during development, the effect that the body composition of its gestational mother, her health and her diet had on its health, through epigenetic mechanisms, has been shown via both human studies and that of animals, to not only last for a lifetime, but can also negatively impact the health of that child's children and potentially that child's grandchildren as well (Gemma et al., 2009; Howie et al., 2009; Pileggi et al., 2016; Shankar et al., 2011; Soubry et al., 2015).

Discussion

Commercial surrogacy in India saw a dramatic rise and fall between 2002 and 2015. During this time, it is estimated that over 325,000 children (25,000 children per year) were born to Indian surrogate mothers (Desai, 2012). Although parents from all over the world have visited India to hire a woman to have their child, the vast majority of them were from the Western World (e.g. the United States and the United Kingdom) where more often than not commercial surrogacy was illegal (Shetty, 2012). Furthermore, in the places where surrogacy is legal, it is often extremely expensive (Shetty, 2012). So, in order to have their own biological child, in a manner that was both legal and financially feasible, they turned to India, a country that was, at the time, open and friendly to medical tourists. While these practices have since been declared illegal for clients who do not hold an Indian passport – and further restrictions may soon be passed concerning surrogacy – unintended consequences related to surrogacy may still exist. The practice of surrogacy has been the topic of many debates over the years as

people have questioned if it is ethical to hire women to use their own bodies to carry someone else's child to term. Often called exploitation or a "rent a womb" business, these debates frequently center on the rights of the surrogate mother. They question if these women are being treated fairly, if their decision to partake in surrogacy is of their own free will, and if this process should continue. They hypothesize what is considered right if the surrogate mother refuses to respect the terms of her contract and hand over the child to its biological parents. They wonder what should be done based on the horror stories have risen concerning the places where surrogate mothers are required to stay during their pregnancy and how they are treated and seen by those running the clinic, their own families, and society itself (Carney, 2010). They discuss if these women are even thought of as people due to stories that have come to light about women who have died in childbirth, or due to complications, and nothing was done because the child that was ordered was delivered and given to its new family and the woman's family was paid, thus completing the transaction (Carney, 2010). These debates are good and needed in order to bring to light issues concerning surrogacy and women's rights, yet one party tends to be overlooked and seemingly forgotten in the chaos of the arguments – the child itself. More often than not, debates concerning surrogacy and its practices focus on the gestational mother's rights and the rights of the biological parents with little thought being given about the child. However, the child is truly at the center of all of this and it is the child that is being ultimately affected by such practices.

Perhaps it is incorrect to say that the child has been forgotten in the debates that surround surrogacy, as children have been at the center of some debates. Yet these debates ask what should and can be done if the gestational mother does not want to give up the child, what

happens to the child if there are legal issues bringing it into its parent's home country, and what happens to said child if its biological parents no longer want it due to reasons such as divorce, medical issues, or if they simply do not want the child they commissioned (Saul, 2014; Sodoma, 2016). These sort of questions are often the only ones that come to mind when potential issues surrounding surrogacy, concerning the child, are discussed. While they are important, and need to be discussed, there is another aspect of surrogacy that should be considered – not just what happens to the child in the case of an unfortunate situation, but also their health.

Without a doubt, every parent wants what is best for their child. They push them to do the best they can at school. They work, not only, to provide for them and for their needs, but also for their wants. They protect and love them, and want them to live the fullest life that they can. However, according to DOHaD and the framework it presents in the case of surrogacy, they may not be able to live the fullest life that they otherwise might have been able to have. As seen in the findings presented in this paper, maternal diet and body composition provide important cues during development that influence fetal growth. The cues sent by maternal diet and body composition influence the way the fetus reacts and develops. While these changes may sometimes be beneficial, problems can arise when the cues the fetus receives from its mother and the way it reacts are not beneficial in the long run and there is mismatch between the fetal environment and cues received and the actual environment. In a normal pregnancy, the fetus receives all of its cues from its mother. In contrast, in gestational surrogacy the developing fetus is exposed to multiple environments: its biological mother, the culture medium it is initially grown in during preimplantation, and its gestational mother. Multiple exposures can lead to different – and at time, contradictory – cues being given and can lead to

changes that are more harmful than beneficial. In other words, when mismatch occurs between the way the child was developed in the womb and said exposures and the environment after birth, the child is at increased risk for various diseases (T. Roseboom et al., 2006; T. J. Roseboom et al., 2000). Many of these diseases are chronic ones for which there are no cures and can affect the quality of life of the child (T. Roseboom et al., 2006; T. J. Roseboom et al., 2000).

Both maternal diet and maternal body composition have an effect on fetal development and the image the fetus receives regarding their future environment. Maternal diet provides a short term or immediate picture of the environment whereas maternal body composition acts as a long term one. In regards to maternal diet, the macronutrients: protein, carbohydrates, and lipids, have been found to act as cues during development (Andreasyan et al., 2007; Chandler-Laney et al., 2011; J. F. Cohen et al., 2011). As seen in the results, not having enough dietary protein can lead to the need for catch up growth after birth (Switkowski et al., 2016). This rapid growth can lead to increased amount of pressure being put on the child's organs as they were created during development with a certain body size in mind. In turn, this increased pressure can lead to higher risk of organ disease and organ failure in late life, something which also negatively impacts quality of life and increases the risk of early mortality (Kelishadi, Haghdoost, Jamshidi, Aliramezany, & Moosazadeh, 2015). Maternal dietary protein is also associated with birthweight, in that a decrease in protein is linked with low birthweight (Moore et al., 2004). This, in itself, is important as low birthweight has been found to negatively impact future health and confer increased risk of certain chronic diseases (e.g. ischaemic heart disease) (Barker, Winter, Osmond, Margetts, & Simmonds, 1989). Furthermore, an increase in protein is

linked with a decrease in fetal visceral adiposity, something that, in regards to fetal adiposity, is important (Chen et al., 2016). There are two types of white fat: visceral fat and subcutaneous fat. Subcutaneous fat is the fat that is located directly under the skin and is much easier to lose and see. Visceral fat, on the other hand, is located around the organs and is much more difficult to see and lose. For these reasons, a decrease in the amount of visceral fat a child is born with has benefits for that child's future health.

During pregnancy, maternal carbohydrates – in particular glucose – serve as a major source of energy and allow the fetus to grow. So, increased maternal carbohydrates are associated with increased growth as measured by birthweight, but can also be linked with increased adiposity and higher risk of obesity in later life (Aris et al., 2014; Kizirian et al., 2016; Murrin et al., 2013). Carbohydrates give the fetus the energy to grow, but too much energy can lead to it being converted to fat or adipose tissue.

In terms of maternal lipids, these also serve to aid in the development of the fetus and can be used in the production of hormones and growth. That said, too high levels of maternal lipids can be detrimental and have been linked with increased weight, increased obesity and adiposity, and a decrease in muscle mass or lean mass (Kizirian et al., 2016; Murrin et al., 2013).

While these macronutrients can influence fetal development independently, they also work together and the ratio, or balance, of macronutrients can be thought of as another cue for development. Without specifically studying maternal macronutrient balance and its effect on fetal development, this relationship can be inferred from the results of other studies as mothers who have high levels of one of the individual macronutrient most often have lower levels of other macronutrients. However, the specific relationships between protein,

carbohydrates, and lipids have also been examined. For example, looking at carbohydrates and protein, having too high levels of carbohydrates and not enough protein can lead to increased development of fetal visceral fat and high levels of carbohydrates or lipids and low levels of protein can lead to decreased length (Blumfield et al., 2012; Chen et al., 2016).

Not only does maternal diet provide cues to the fetus, but so does maternal body composition. Composed of lean body mass and fat mass, this can influence the way the fetus develops through epigenetic mechanisms (Gemma et al., 2009; Howie et al., 2009; Pileggi et al., 2016; Shankar et al., 2011; Soubry et al., 2015). Body composition is important in regards to surrogacy as the people on the Indian subcontinent have high levels of adiposity and low levels of lean mass (Yajnik, 2004). This phenotype is not one that develops throughout the life, but rather, is something they are born with and worsens throughout life (Krishnaveni et al., 2005; Yajnik et al., 2003). As shown by the results, maternal fat free mass or lean body mass was associated with increased growth as measured by birthweight and length (Duggleby & Jackson, 2001; B. Kulkarni et al., 2006). Energy is created by the mother's lean mass, specifically her muscle tissue, so having a high percentage of lean mass increases the amount of energy the fetus has access to and allows for greater fetal growth during development. Increased maternal fat mass, on the other hand, was associated with increased adiposity measured through fat mass and fat mass index and increased birthweight (Friis et al., 2004; Henriksson et al., 2015; Toro-Ramos et al., 2016). However, maternal fat mass measured by lipid concentrations play an important role in development, as not having high enough levels of triglycerides has been associated with increased risk of being born small for gestational age and at a low birthweight

(Vrijkotte et al., 2011). So, while having adequate maternal lean body mass is important to development, having fat stores and certain levels of lipid concentrations are also vital.

The potential mechanisms, or underlying reasons of these results are suggested to be DNA methylation and inflammation. DNA methylation, or the turning “on” and “off” of specific genes, in obese mothers leads to decreased production of mitochondria and increased production of adipocytes (Gemma et al., 2009; Jin et al., 2011; Soubry et al., 2015). Looking at these mechanisms specifically in obese women is important as an obesogenic environment can be different from a non-obesogenic one. Furthermore, due to the thin-fat phenotype, Indian surrogate mothers are likely to have high levels of adiposity (Yajnik, 2004). Maternal inflammation has not only been associated with increased c-reactive protein in offspring, which itself has been associated with increased adiposity, but can also influence mitochondrial gene expression and lead to its downregulation (Gaillard et al., 2016; Shankar et al., 2011). It – inflammation – has also been associated with accumulation of ectopic lipids which is associated with increased risk of metabolic disorders, organ damage, and the expression of lipid metabolic genes (Shankar et al., 2011). Here, it is notable that both inflammation and DNA methylation have been found to impact mitochondrial production, as this is something that has been shown to be an underlying cause of metabolic diseases such as type 2 diabetes (Lowell & Shulman, 2005). This is important to keep in mind as type 2 diabetes is highly prevalent in the Indian population and has been associated with high levels of adiposity (Yajnik & Ganpule-Rao, 2010). In terms of increased adiposity, this was also linked with both potential mechanisms and, as seen by the data presented from India, is quite prevalent in the Indian population.

With all this in mind, surrogacy in India has consequences in regards to the health of the surrogate child. Many of these consequences stem from the mismatch between maternal environment and the environment the child will grow up, and are long lasting. In surrogacy, a “famine to feast” mismatch scenario is created where the child, based on the cues received from maternal diet and maternal body composition, reads them as a sign that the environment in which it will grow up is one where resources may not always be readily available, and reacts accordingly. This leads to the increased deposition of adiposity – or energy stores – which influences the balance between fetal lean mass and fat mass and tips the balance towards fat mass. Increased adiposity, in turn, is not only associated with an increased risk of obesity, but carries with it other risks for chronic diseases such as type 2 diabetes, hypertension, heart diseases and certain cancers, as well as lower quality of life and increased risk of mortality (Centers for Disease Control, 2016; Clark & Brancati, 2000). In other words, while it was not at all intended, these parents who hired a surrogate mother to carry their child, have given it a legacy of malnutrition and all the consequences that come with that. This is further evidenced by the fact that most of the women who act as surrogate mothers are from lower castes and have had a poorer upbringing, a legacy that is passed on to their surrogate child (Bindel, 2016). While their – the biological parents’ – legacy might not have been the same legacy as that of the surrogate mother, the fetus does not just take cues from the environment in which the egg and the sperm that create it come from. Rather, it takes cues from every environment it is exposed to, be it the same environment across development (as is the case in a traditional pregnancy) or 3 different ones as is the typical case in surrogacy.

However, not only have they given their child such a legacy, but these physiological changes – lower lean mass and increased adiposity – have consequences for future generations as well. As seen from the results in regards to body composition and the data from India, children born with this legacy carry it with them for the rest of their life (Krishnaveni et al., 2005; Yajnik et al., 2003). This is something that may be assumed to be the same in the case of surrogate children. Yet this legacy does not just stop with the child, but rather continues into future generations as well. During development the egg cells are created and thus are affected by the maternal environment. In other words, in the case of surrogacy, the maternal environment is that of the surrogate mother, and thus the eggs cells are developed in a body that has a legacy of malnutrition and are given that legacy as well. This transgenerational effect has also been seen in data from children who were exposed to famine in-utero and their children (Painter et al., 2008; Veenendaal et al., 2013). Body composition has been shown to have an effect on fetal development, and as such, creates a vicious cycle of high adiposity and low lean mass and confers on the child (and their future children) all the health consequences that come with that phenotype.

In light of this, surrogacy should be thought about more carefully as it can have detrimental effects not only for the surrogate child, but future generations as well. What has been done is done and cannot be changed, but by being aware of, thinking about, and preparing for the potential consequences of having been born to an Indian surrogate mother, some of the detrimental consequences may be avoided or mitigated. While these children cannot change the legacy to which they were born, they can take active measures to minimize the harm that it may cause. This can be done by being more active and being aware of what

they are eating in order to decrease adiposity. They can take better care of their health and look for potential signs or markers of the diseases for which they are at high risk for and, if female, they can be aware of their diet during pregnancy. Yes, body composition plays a large role and impacts the development of the fetus, and yes, their egg cells were developed in a body that had a legacy of malnutrition, but just as maternal body composition is a cue during development, so is maternal diet. So, while body composition may be hard to change and the environment that the egg cells develop in cannot be changed, diet can be, and in the case of surrogacy, should be changed in order to afford the future generation the best health that they can have.

This was a review of the existing data regarding the effects of maternal diet and maternal body composition on the anthropometric outcomes of their children. While this data is from primary research, for this study, there were no firsthand interactions that took place between those writing the paper and the participants of the studies included. Furthermore, none of this data comes from children who were born to surrogate mothers in India, but rather from mother-child pairs where the child's biological mother was also its gestational mother. The data was used as a proxy and as a means of hypothesizing what exposure to a high fat-low lean mass environment would have on children born to surrogate mothers. In addition, some studies and cohorts may have been excluded from this study due to the way the searches were conducted. While this study was meant to be as inclusive as possible, it is still very true that some studies were excluded because they did not appear as results in any of the database searches. Due to the state of maternal nutrition and body composition work that currently exists, much of the research has been conducted in western countries, something that is reflected in this

study due to where each of the cohorts took place. Furthermore, the work in this study was an effort to tease apart the different effects of the macronutrients that compose a diet. However, not every study measures macronutrient consumption in the same manner which, while it was attempted to be taken into account, may not have fully been accounted for. Finally, it is acknowledged that macronutrients and micronutrients play a role in fetal development. Unfortunately, much of the literature does not look at both macronutrients and micronutrients at the same time,

However, while this study did pull data from many different cohorts and studies as a way to give the best overview and insight into what has been seen and documented concerning maternal diet and maternal body composition and fetal development. Not only did the women in these studies come from diverse backgrounds, but also from different countries and continents. This was done in order to best ascertain how similar or diverse the fetus's reactions were to the cues it was exposed to. Finally, many of the studies included in this paper and the data that was drawn from them, such as Project Viva and the Southampton Women's Survey, are from well-established and well-known studies which are highly respected in the field.

Overall, while this study has its weaknesses, it does serve as a good baseline to hypothesize the potential effects of surrogacy in India on surrogate children.

Conclusion

The intent of this investigation was never to cast a negative light on parents who pursue surrogacy as a way to create their family. Rather, the goal was to gain better insight on the potential and previously unthought-of consequences of surrogacy in India. Based on findings

from studies looking at the effects maternal diet and maternal body composition have on fetal development, and seen through the theory of DOHaD, surrogacy in India does indeed warrant further consideration. While the active practice of commercial surrogacy for “Westerners,” or people not carrying an Indian passport, currently is not taking place, or at least it is not legally taking place, it is estimated that at least 325,000 children may have been born using this process. What has happened has happened and cannot be changed; the only thing that can be done is to prepare for the future.

According to the data presented here, children born to surrogate mothers in India may have a body composition with a lower percent of lean mass and a higher percent of adiposity than if they had been born to their biological mother. This occurs due to cues that the child receives from maternal diet and maternal body composition during development. However not only is the fetus influenced by the environment created by its surrogate mother once it has attached itself to the side of her uterus, but it also receives cues from her body during the perinatal period, and is thus influenced by her pre-pregnancy state as well (Fleming, Velazquez, & Eckert, 2015). This phenotype – one that is very similar to their surrogate mother’s phenotype – can be exacerbated due to the mismatch between their environment in-utero and that which they live after birth. This may put them at higher risk than their peers who were born to their biological parents for diabetes, cardiovascular disease, high blood pressure and other chronic diseases as well as metabolic disorders. Yes, conversations about the ethical implications of surrogacy and women’s rights are needed, but so is a conversation about the implications surrogacy may have for the surrogate child. Conversations must be had about not just about their immediate circumstances and the legal issues that may surround them, but also

about their future health and all the implications that being developed in body that has a legacy of malnutrition may have for those children.

In 2015, India closed their doors to foreigners – those not of Indian descent – attempting to pursue surrogacy. With both Thailand and India, countries that had been popular choices for surrogacy, having banned surrogacy for foreigners, potential parents may turn to countries like Russia and the Ukraine, where commercial surrogacy is still legal, to fulfill their wishes of having a biological child. While there is no distinct phenotype associated with those of Russian or Ukrainian descent, these countries also have suffered from various droughts which have affected food supply as well as several famines in the last century. This sort of history, as evidenced by data from the Dutch Hunger Winter and the Chinese Great famine, can have long lasting, transgenerational effects on the health of children exposed to this in-utero as well as their children; a legacy children born to these surrogate mothers would be part of due to cues received during development (Lumey et al., 2015; T. Roseboom et al., 2006; Wang et al., 2012). Furthermore, it has been found that the prevalence of type 2 diabetes in Russia have been rising, and while not at the levels of that of India, they are still higher than the overall prevalence of type 2 diabetes in Europe, something which could be linked with their history of famines (Golubev & Dronin, 2004; International Diabetes Federation, n.d.).

Ultimately, a cohort study is needed which would follow surrogate children throughout their life in order to better understand the effects surrogacy may have on health. While the legality of this sort of study may be an issue, until then, further research could also be done in animal models in order understand the potential effects of surrogacy as well as preventative measures which could be taken to help reduce the resulting effects. These findings could then

be used to help provide better information and support for parents who choose to pursue surrogacy. Furthermore, simply educating parents about the potential effects of surrogacy on the health of their children could also be beneficial. Every parent wants what is best for their children and are willing to take the steps necessary to provide them with the best future possible. In the case of surrogacy, that sort of knowledge simply has not been shared with the public, and is an area, not only in which further studies are needed, but also one where people are simply aware of the potential consequences.

The past cannot be changed, but one may change one's habits and lifestyle, what one eats, and if one is physically active. Yes, according to the data compiled and what has been hypothesized in line with the theory of DOHaD, these children may be at higher risk for certain chronic diseases and certain metabolic disorders than other children. However, these risks can be mitigated or lowered by being proactive about one's health and knowing and understanding that one is at higher risk and acting on that knowledge. The past may have already been set by maternal diet, body composition and a legacy of malnutrition, but the future is in their hands, not the body of their surrogate mother.

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Figures

Table 1: **Cohort Characteristics** – A summary of the characteristics of the cohorts which were included in this paper.

Cohort	Characteristics	
Adelaide, South Australia (Moore et al., 2004)	Location	Adelaide, South Australia
	Type of study	Prospective, observational cohort
	Method	200 item FFQ given twice
	Population	Caucasian women
	Size	557 women
Project Viva (Oken et al., 2015; Switkowski et al., 2016)	Location	Eastern Massachusetts, USA
	Type of study	Prospective, observational cohort
	Method	166 question FFQ given twice
	Population	Multiethnic, but predominately Caucasian middle and upper-class women
	Size	2128 women
Aarhus Birth Cohort (Maslova et al., 2014)	Location	Aarhus, Denmark
	Type of study	Prospective cohort
	Method	FFQ given at 30 weeks and a face-to-face interview
	Population	Danish women
	Size	965 women
Growing Up in Singapore Towards healthy Outcomes (GUSTO) (Chen et al., 2016; Soh et al., 2014)	Location	Singapore
	Type of study	Prospective, observational birth cohort
	Method	Prospective 3-day food diary between 26-28 weeks of gestation
	Population	Women of homogeneous Chinese, Malay, or Indian backgrounds
	Size	1176 Mother-child pairs
Tasmanian Infant Health Survey (TIHS) (Dwyer et al., 1991; Andreasyan et al., 2007)	Location	Tasmania
	Type of study	Prospective cohort study looking at causes of sudden infant death
	Method	179 item FFQ during third trimester
	Population	Predominately Caucasian women
	Size	1040 mother-infant pairs
Lifeways Cross-Generation Cohort (Murrin et al., 2013)	Location	Dublin, Ireland and Galway, Ireland
	Type of study	Longitudinal, observational cohort
	Method	149 item semi-qualitative FFQ during early pregnancy and during follow-up
	Population	Irish mothers
	Size	585 mother-child pairs

Table 1: **Cohort Characteristics** – A summary of the characteristics of the cohorts which were included in this paper. (Continued)

Randomized Control Trial of Low Glycemic Index Diet in Pregnancy (ROLO) (Walsh et al., 2010; Horan et al., 2016)	Location	Dublin, Ireland
	Type of study	Randomized Controlled Trial
	Method	Women were randomized into the control group which received no dietary intervention or one that urged a low glycemic index diet from early pregnancy. Three 3-day food diaries were kept; one for each trimester.
	Population	Irish mothers who had previously given birth to a macrosomic infant
	Size	800 women
Southampton Women's Study (SWS) (Okubo et al., 2014; Robinson et al., 1996)	Location	Southampton, United Kingdom
	Type of study	Prospective cohort
	Method	2 interviewer-administered FFQs at 11 and 34 weeks of gestation
	Population	British mothers
	Size	1981 mother-child pairs
Healthy Start Study (Crume et al., 2015)	Location	Colorado, USA
	Type of study	Prospective cohort
	Method	Biomarkers taken during early, mid to late gestation, and after birth; up to six 24-hour dietary recalls were collected and two food propensity questionnaires collected during the second visit.
	Population	Women in Colorado
	Size	804 mother-child pairs
GI Baby 3 (Kizirian et al., 2016)	Location	Sydney, Australia
	Type of study	Randomized control trial
	Method	Women were randomized into a low GI diet or a conventional high fiber one. Two 3-day food diaries, one collected during mid-pregnancy and one during late-pregnancy
	Population	Australian women who were at risk for gestational diabetes
	Size	139 women

Table 1: **Cohort Characteristics** – A summary of the characteristics of the cohorts which were included in this paper. (Continued)

Women and Their Children's Health Study (WATCH) (Blumfield et al., 2012)	Location	Newcastle, Australia
	Type of study	Prospective, longitudinal cohort
	Method	Fetal ultrasound scans taken at ~19, 25, 30, and 36 (\pm 1) weeks of gestation. Maternal diet assessed using 2 validated 74 item FFQs collected during mid and late pregnancy.
	Population	Relatively well-educated women predominately born in Australia
	Size	179 women
Wollongong, Australia (Moses et al., 2006)	Location	Wollongong, Australia
	Type of study	Parallel controlled study
	Method	Women received dietary counseling that either encouraged a low glycemic index diet or a high-fiber, moderate-to-high glycemic index diet. Dietary data was collected through the use of two 3-day food diaries and two 24-hour recalls.
	Population	Australian women who were at risk for gestational diabetes
	Size	62 women
Amsterdam Born Children and their Development (ABCD) (van Eijsden et al., 2008)	Location	Amsterdam, Netherlands
	Type of study	Prospective community based cohort study
	Method	A questionnaire socio-demographic characteristics, obstetric history, lifestyles and psychosocial conditions and a blood biomarker test
	Population	All pregnant women in Amsterdam were invited to enroll; the women did not have to be Dutch.
	Size	4389 women
Pune Maternal Nutrition Study (PMNS) (Kulkarni et al., 2013; Yajnik et al., 2003)	Location	Pune, India
	Type of study	Community-based observational study
	Method	Anthropometric measurements, physical activity, and dietary intakes using a semi-weighted 24-hour recall and FFQ were collected at 18 ± 2 weeks of gestation and at 28 ± 2 weeks of gestation. Blood samples were taken at each visit and neonatal measurements were taken within 72 hours of birth.
	Population	Indian women and children from Pune, India
	Size	762 mother-child pairs

Table 2: Effects of Maternal Protein Intake – An overview of the findings of the effects that maternal intake of protein has on fetal outcomes.

PROTEIN		
Trimester	Study	Overall relationship
First	Moore, Davis, Willson, Worsley, & Robinson, 2004	↑ Protein --> ↑ Birthweight and ↑ Ponderal index
Second	Chen et al., 2016	↑ Protein --> ↓ Adiposity
	Blumfield et al., 2012	↓ Protein --> ↑ Adiposity
	Switkowski et al., 2016	↑ Protein --> ↓ Length
		↑ Protein --> ↓ Catch-up growth
	Maslova et al., 2014	↑ Protein --> ↑ BMI and Risk of being overweight
Third	Andreasyan et al., 2007	↑ Protein --> ↑ Head Circumference
		↑ Protein --> ↓ Growth
	Campbell et al., 1996	
	Yin, Quinn, Dwyer, Ponsonby, & Jones, 2012	↑ Protein --> ↑ Fat Mass
	Weigel, Narvaez, Lopez, Felix, & Lopez, 1991	↓ Protein --> ↑ Risk of Low Birthweight

Table 3: Effects of Maternal Carbohydrate Intake – An overview of the findings of the effects that maternal intake of carbohydrates has on fetal outcomes.

CARBOHYDRATES		
Trimester	Study	Overall Relationship
First	Murrin, Shrivastava, Kelleher, & Lifeways Cross-generation Cohort Study Steering, 2013	↑ Carbohydrates --> ↑ Risk of being overweight
	Okubo et al., 2014	↑ Carbohydrates --> ↑ Adiposity
	Horan, Donnelly, McGowan, Gibney, & McAuliffe, 2016	↑ Carbohydrates --> ↓ BMI z-score and Adiposity
	Crume et al., 2015	↑ Carbohydrates --> ↑ Adiposity and Birthweight
Second	Aris et al., 2014	↑ Carbohydrates --> ↑ Adiposity
	Crume et al., 2015	↑ Carbohydrates --> ↑ Birthweight and Adiposity
	S. R. Kulkarni et al., 2013	↑ Carbohydrates --> ↑ Birthweight, Adiposity, and Ponderal Index
	Moses et al., 2006	
	Donnelly, Walsh, Byrne, Molloy, & McAuliffe, 2015	↓ Carbohydrates --> ↓ Adiposity
	Scholl, Chen, Khoo, & Lenders, 2004	↓ Carbohydrates --> ↓ Birthweight
Third	Renault et al., 2015	↑ Carbohydrates --> ↑ Birthweight and Adiposity
	Pereira-da-Silva et al., 2014	↑ Carbohydrates --> ↑ Adiposity
	Kizirian et al., 2016°	
	Crume et al., 2015	
	Moses et al., 2006	↑ Carbohydrates --> ↑ Ponderal Index
	Donnelly, Walsh, Byrne, Molloy, & McAuliffe, 2015	↓ Carbohydrates --> No effect on adiposity
	Moore, Davis, Willson, Worsley, & Robinson, 2004	↑ Carbohydrates --> ↓ Ponderal Index

Table 4: **Effects of Maternal Lipid Intake** – An overview of the findings of the effects that maternal intake of lipids has on fetal outcomes.

LIPIDS		
Trimester	Study	Overall Relationship
First	Murrin, Shrivastava, Kelleher, & Lifeways Cross-generation Cohort Study Steering, 2013	↑ Saturated fatty acids --> ↑ Weight at 5 years
Second	Cohen, Rifas-Shiman, Rimm, Oken, & Gillman, 2011	↑ Trans fatty acids --> ↑ Fetal growth score
	Horan, Donnelly, McGowan, Gibney, & McAuliffe, 2016	↑ polyunsaturated fat --> ↓ waist:length ratio at 2 years old
	Kizirian et al., 2016°	↑ fat & saturated fat --> ↑ adiposity
Third	Blumfield et al., 2012	↑ saturated fatty acids --> ↓ midhigh lean area
		↓ saturated fatty acids --> ↓ midhigh subcutaneous area
	Horan, Donnelly, McGowan, Gibney, & McAuliffe, 2016	↑ saturated fatty acids --> ↑ weight at 2 years

Table 5: Effects of Maternal Macronutrient Ratio Intake – An overview of the findings of the effects that the ratios of maternal macronutrients have on fetal outcomes.

RATIOS			
Trimester	Study	macronutrients	Overall Relationship
First	Godfrey, Barker, Robinson, & Osmond, 1997	Carbohydrates and protein	↑ Carbohydrates & ↓ Protein --> ↑ Risk of thinness at birth
Second	Chen et al., 2016	Protein and carbohydrates	↑ Protein & ↓ Carbohydrates --> ↓ Adiposity
		Protein and fat	↑ Protein & ↓ Fat --> ↓ Adiposity
	Blumfield et al., 2012	Protein and carbohydrates	↑ Protein & ↓ Carbohydrates --> ↑ Visceral area ↓ Protein & ↑ Carbohydrates --> ↑ Subcutaneous area
Third	Kizirian et al., 2016°	Fat and carbohydrates	↑ Fat & ↓ Carbohydrates --> ↑ Adiposity

Table 6: Effects of Maternal Lean Body Mass on Fetal Outcomes – An overview of the findings of the effects that maternal lean body mass has on fetal outcomes.

MATERNAL BODY COMPOSITION - Lean body mass		
Trimester	Study	Overall Relationship
N/A	Mardones-Santander, Salazar, Rosso, & Villarroel, 1998	↑ Fat-free mass --> ↑ Birthweight
	Sanin Aguirre, Reza-Lopez, & Levario-Carrillo, 2004	
	Mongelli, 1996	
	Muthayya et al., 2006	↑ Fat-free mass --> ↑ Adiposity
	B. Kulkarni, Shatrugna, & Balakrishna, 2006	
First	Kent et al., 2013	↑ Fat-free mass --> ↑ Birthweight
Second	Duggleby & Jackson, 2002	↑ Fat-free mass --> ↑ Length
Third	Farah, Stuart, Donnelly, Kennelly, & Turner, 2011	↑ Fat-free mass --> ↑ Birthweight

Table 7: Effects of Maternal Fat Mass on Fetal Outcomes – An overview of the findings of the effects that maternal fat mass has on fetal outcomes.

MATERNAL BODY COMPOSITION - Fat mass		
Trimester	Study	Overall relationship
N/A	Friis et al., 2004	↑ Fat mass --> ↑ Adiposity
	Henriksson, Lof, & Forsum, 2015	
	Toro-Ramos, Sichieri, & Hoffman, 2016	
First	Vrijkotte, Algera, Brouwer, van Eijsden, & Twickler, 2011	↑ Fat mass --> ↑ Birthweight & ↓ Catch-up growth
	Crume et al. 2015	↑ Triglycerides --> ↑ Birthweight
		↑ HDL-c --> ↓ Birthweight and adiposity
van Eijsden, Hornstra, van der Wal, Vrijkotte, & Bonsel, 2008	↓ Fatty acids --> ↑ Risk of low birthweight & small for gestational age	
Second	Gademan et al., 2014	↑ Fatty free acids --> ↑ Adiposity
	S. R. Kulkarni et al., 2013	↑ Cholesterol --> ↑ Adiposity & birthweight
		↑ Triglycerides --> ↑ Adiposity, birthweight, and length
Third	Crume et al. 2015	↑ Fatty free acids --> ↓ Birthweight
	Moon et al., 2013	↑ Fatty free acids --> ↑ weight, adiposity, and length at 4 and 6 years old