An examination of maternal contributors and potential modifiers of fetal growth in pregnancy

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ABSTRACT

A greater understanding of critical periods of body weight regulation, including pregnancy, may aid in efforts to optimize weight management strategies for the mother and her baby. The gestational period has been implicated to play, in the child, a vital role in the developmental origins of obesity and other cardiometabolic diseases later in life. Therefore, we initially examined existing literature on the role of maternal obesity and its link to pediatric obesity and documented the known underlying physiological mechanisms responsible for this relationship while suggesting potential intervention targets that may improve maternal-fetal outcomes. In a second paper, we aimed to quantify maternal predictors of large for gestational age (LGA) neonates in the Ottawa and Kingston (OaK) birth cohort with specific hypotheses verifying the independent contribution of maternal prepregnancy body mass index (BMI) and excessive gestational weight gain (GWG) to fetal overgrowth. This paper also highlights the clinical utility of the revised 2009 Institute of Medicine GWG guidelines and discusses the potential role of physiological factors underlying the observed associations between BMI, excessive GWG and LGA neonates. As a follow-up to our population-level analysis (i.e., OAK cohort), papers three and four highlight how the insulin-like growth factor (IGF) axis, a vital regulator of growth and development, may be compromised at the molecular level in cases of maternal obesity (paper 3) and excessive GWG (paper 4). In paper 3 we show that maternal obesity is associated with attenuated expression of IGF binding protein-4 (IGFBP4) in umbilical cord blood and discuss how this may preferentially promote fetal adipogenesis. The effects of excessive GWG on IGF axis protein expression are addressed in paper four where we show
that excessive weight gain during pregnancy is associated with increased expression of IGFBP3 in maternal circulation in normoglycemic term pregnancies. In this paper we discuss the potential inhibitory role of IGFBP3 on adipogenesis and how it relates to glucose intolerance during pregnancy. Recognizing that both obesity and excessive GWG can alter physiological processes in mother and her baby, appropriate evidence-based interventions are warranted to best optimize outcomes. In paper five, we discuss the results of a study which sought to assess patient information channels and knowledge of nutrition and physical activity during pregnancy with the intent that these findings be applied to best design efficacious strategies that cater to the needs of our target group of pregnant women. In our analysis we show that the majority of pregnant women studied would be willing to participate in a lifestyle intervention for their own personal health and that of their child. Of great interest was the observation that most women were not informed of the importance of pregnancy-specific energy intake, or made aware of their own healthy GWG targets. Additionally, many of the respondents reported receiving no information pertaining to appropriate physical activity recommendations; despite the fact that the vast majority of participants consider this lifestyle modality to be safe during their pregnancy. Finally in paper six, we build on the results of our previous work and evaluate the risks and benefits of physical activity during pregnancy on maternal-fetal outcomes through a review of the literature and note that engaging in non-sedentary pursuits during gestation may aid in maternal weight regulation, protect against metabolic disorders and optimize neonatal birth weight and body composition. Overall, the collective nature of the papers presented in this dissertation provides qualitative and quantitative evidence to support not only the
complexity of body weight regulation in the mother and her baby, but also highlights potential avenues for intervention that may improve maternal-fetal outcomes during this critical period.
PRELUDE TO THESIS

Obesity is a complex disease of multifactorial etiology that involves an intricate interaction between genetic and environmental factors that influence energy balance regulation. Given the need to reduce individual risk of obesity-related pathology including type 2 diabetes and cardiovascular diseases, effective weight management strategies are of paramount importance. However, recidivism to common therapeutic paradigms (i.e., diet and exercise intervention) is likely, producing large inter-individual variation in one’s ability to maintain normal body weight, to lose weight and avoid weight regain. As such, a greater understanding of critical periods of body weight regulation, including pregnancy, may aid in efforts to optimize weight management strategies. The gestational period has been implicated, in the child, to play a vital role in the developmental origins of metabolic and cardiovascular diseases later in life. The premise of the following series of papers is to provide an overview of maternal contributors and potential modifiers of fetal growth (Figure 1.1) addressing the question through literature reviews, qualitative sampling using questionnaires, epidemiological analysis of a large birth cohort and quantitative assessment of molecular signalling pathways involved during pregnancy complicated by obesity or excessive GWG.

This thesis guides the reader through a narrative addressing the pertinence of maternal obesity and/or excessive GWG as predictors of infant size at birth and consequently throughout the life-course (Figure 1.2). Through a series of 6 manuscripts that address various aspects of this critical period, this thesis aims to better understand how maternal phenotype, excessive GWG and physical activity affect fetal growth.
Figure 1.1: Critical mediators and potential modifiers of fetal-placental growth during early human development
Figure 1.2: Obesity begets obesity through accelerated growth trajectory throughout the life-course without intervention. OW/OB, overweight and obesity; LGA, large for gestational age neonate
Figure 1.3: The insulin-like growth factor axis during pregnancy. GH, growth hormone; IGF, insulin-like growth factor; IGFBP, IGF binding protein; MGF, mechano growth factor
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Having been an athlete for many years prior, it was in 2004 when I was first given the opportunity to participate in a research project as a study subject for an exercise physiology trial at McMaster University – I loved it. It was so fascinating to be part of the bigger picture of exercise science, to have an array of different tests done, which included catheters and biopsies, and know that this valuable information would contribute a small piece of the puzzle to an exploding domain of research. The following year, Dr. Stuart Phillips, who I am gratefully indebted, gave me a wonderful opportunity to complete a senior thesis under his supervision, and it is safe to say this is where my true passion for the scientific process began. From project planning, coordination and execution I finally found something to keep me out of trouble. However, it was the positive physiological response to the training program I administered to my subjects and their improved health-related outcomes that truly instilled my passion to improve the human condition. This is where my academic interests developed.

In 2007, I completed an MSc with Dr. Alison Duncan at the University of Guelph, and I would like to thank her for the opportunity to work on a clinical nutrition study in men struggling with obesity. This was my first exposure working in the field of obesity; something I thoroughly enjoyed and was the beginning of my transition from a performance driven exercise physiologist to a health oriented scientist.

In 2008 I began my educational journey in Ottawa with Dr. Kristi Adamo and Dr. Denis Prud’homme. I want to express my sincere appreciation to Kristi for her overwhelming support, encouragement and motivation during my adventures at the Children’s Hospital of Eastern Ontario. We’ve had some downs, but many more ups and your perseverance to balance work and life, despite two maternity leaves, while maintaining an excellent research program are lessons I will take with me as I endeavour for such balance. Kristi, you are not just a mentor and someone I look up to, but a friend and I am glad to have had the opportunity to learn and grow with you as I was your first PhD student.

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I must also thank Dr. Andrée Gruslin, who I met in 2008 as a committee member, but has been so much more to me during my tenure as a PhD student. Andrée, you are such an inspirational, motivating and resilient woman who has given me so much encouragement, advice and support words cannot truly express. Your genuine and kind nature as physician and scientist are qualities that I aim to carry with me through my journey. It is so refreshing to see such a successful individual maintain what is truly important – You are a remarkable human being.

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To all the scientists, staff and students in the Healthy Active Living and Obesity (HALO) research group, thank you for contributing to such a dynamic, stimulating work environment. All of you played a supportive role and brought so much to my educational journey.

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To my Mom and Dad, thank you is an understatement. I have been fortunate to have the best teachers from day one and you have given me so many life changing experiences and opportunities - all that I have accomplished is a direct reflection of both of you. You continually believe in me, support me and are always there in the simplest ways that never go unnoticed. Although I still do not think you know what I am doing in school for so long, I know you understand my passion and believe in my work.

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1.0 GENERAL INTRODUCTION

Pediatric obesity is a complex condition of multi-factorial etiology involving, but not limited to, physiological, psychological, social and economic factors [1]. Further, strong relationships have been observed between parental body mass index (BMI) and offspring BMI [2], suggestive of an underlying genetic predisposition to positive energy balance. Also, familial risk factors have been identified [3]. Thus, this thesis will focus on physiological aspects and some modifiable determinants of positive energy balance. However, it is reasonable to postulate that the rising incidence of obesity may be due to gene-environment interactions which predispose humans to epigenetic modifications that alter body weight and composition phenotypes over time [4, 5]. Of great interest is the idea that a predisposition to over-consume energy (i.e., hyperphagia) and high levels of sedentarism may be observed in offspring of women struggling with obesity, a finding documented in experimental animal models [6]. This observation aligns with Barker’s developmental origins of adult health and disease hypothesis [7] which originally linked poor nutrition in utero to chronic disease susceptibility and subsequent risk throughout the life course [4, 8, 9]. For instance, prenatal cues that lead the developing fetus to predict a nutritionally sparse environment (e.g., in undernourished pregnancies) will result in a shift in the structural and functional development toward a phenotype matched to that environment [4]. If the child is born into an environment that does not match the predictive adaptive response in utero they will have a reduced capacity to cope with the environmental stress. In this case, if one is born into a nutritionally rich postnatal environment, after predicting a sparse one, they may be increasing their risk for metabolic disease later in life. Additionally,
postnatal child overnutrition may lead to compensatory changes in growth trajectory that further shift the positioning of the adult phenotype exacerbating the mismatch between pre- and post-natal cues [4]. Yet, in the context of over-nutrition, recent evidence supports the ideology that positive energy balance through maternal obesity, excess gestational weight gain (GWG) and over-feeding can increase offspring predisposition to metabolic disease [10]; an effect thought to be mediated by alterations in epigenetic regulation of metabolic pathways [11, 12]. Given the increased prevalence of obesity, changing societal norms concerning weight regulation and the intergenerational nature of this condition [13], attention has shifted to threats of positive energy balance and excess weight gain during pregnancy as an important contributor to childhood adiposity and predisposition of the offspring to metabolic dysregulation later in life [14-17]. The exact obesogenic factors leading to such disturbances are not fully understood but potential candidates pathways include those involved with maternal hyperleptinemia, hyperglycemia, hyperinsulinemia and chronic low-grade maternal inflammation, as reviewed by Rooney and Ozanne [5]. Despite numerous animal [6, 18-24] and human [2, 3, 25-35] studies that have examined the effects of maternal excess food intake and/or obesity on offspring obesity and type 2 diabetes, our knowledge concerning the precise mechanisms mediating these pathologies are far from complete. Knowing that the growing fetus receives its sustenance from maternal sources through the placenta, much attention has been directed to examining the role of this highly specialized organ on substrate transfer and subsequent fetal growth regulation in pregnancy. It is not unrealistic to presume that behaviours such as healthy eating and physical activity, that alter maternal metabolism and modify the availability of
specific nutrients, could affect fetal weight and body composition and downstream health. Even though the placenta has been implicated as a pivotal substrate and energy regulatory organ [36, 37] few groups have explored the placental mechanisms in pregnancies exposed to maternal exercise or complicated by diabetes [27, 38-45]. However, the precise mechanisms underlying one’s predisposition to accelerated fetal growth and/or altered body composition in pregnancies complicated by obesity and excessive GWG remain to be fully established. Therefore, the following discussion will highlight factors involved with fetal growth with a focus on maternal obesity, gestational weight gain and potential modifiers of these processes.

1.1 Maternal obesity, gestational weight gain, insulin resistance and risk of aberrant fetal growth trajectory

It is well-established that maternal obesity is a risk factor for fetal macrosomia (i.e., birth weight >4000g) and several epidemiological studies have noted a J-shaped relationship between birth weight, adolescent weight and adult fat mass with babies born at birth weight extremes (i.e., small for gestational age (SGA) and LGA) at the greatest risk [46-49]. Additionally, both pre-pregnancy BMI and GWG are positively associated with infant birth weight [50-53]. This is important because higher infant birth weights are associated with higher child BMI [54-56] and overweight during adolescence is a predictor of adult obesity [57]. Obese women are also likely to exceed the Institute of Medicine (IOM) GWG recommendations (see APPENDIX O) more often than mothers at normal pre-
pregnancy weight [58, 59]. Recent findings demonstrate that neonates born from overweight mothers who exceed GWG recommendations have greater body fat percentage and greater fat mass compared to their offspring born to women who gained within the guidelines [60] which strengthens previous findings suggesting a strong link between GWG and downstream childhood obesity [61, 62].

Although pre-pregnancy weight and GWG are surrogate markers of maternal energy reserve and modifiable targets during intervention [63-66], there is limited evidence available to explain the physiological processes underlying the observed associations. However, the pregnancy-induced development of the placenta, a temporary organ facilitating nutrient transport, substrate exchange between mother and fetus, and consequently fetal growth, may provide insight. During gestation, maternal energy surplus exposes both the placenta and fetus to excessive nutrient supply. It is speculated that through various mechanisms mediated by the placenta, enhanced exposure to substrate and hormones may alter the fetal growth trajectory. In fact, maternal insulin resistance, which commences in mid-late gestation [67], and is generally exacerbated in overweight and obese women, [46] has been implicated in cases of fetal overgrowth [33]. Consequently, as a result of excessive nutrient flux (of which glucose predominates) through the placenta, overweight and obese women give birth to a proportionally greater number of LGA (birth weight for gestational age ≥90th percentile) newborns when compared to women at a healthy pre-pregnancy weight. This may be in part due to the teratogenic effects of excessive fetal insulin secretion and the anabolic response to hormones and growth factors.
in utero [68, 69]. Furthermore, alterations in maternal lipid metabolism (i.e., increased circulatory levels of free fatty acids) with the onset of insulin resistance in mid gestation increase fetal exposure to and subsequent storage of free fatty acids [70]. Collectively, these findings support the notion that those born LGA are more likely to struggle with excess weight throughout life; a relationship that appears to be mediated by maternal glucose intolerance, lipid metabolism and other aberrant signaling processes involving growth factors.

1.2 Maternal obesity, insulin resistance and the role of developmental plasticity in regulating offspring weight and body composition

During gestation, and in early postnatal period, the developing fetus/neonate is highly susceptible to an ever-changing external environment, particularly maternal nutrient intake and energy expenditure, and adapts accordingly in attempt to thrive in postnatal life [4, 71]. Commonly referred to as ‘fetal programming’, developmental plasticity establishes pregnancy as a critical period of body weight regulation, for the unborn child, where central homeostatic processes and vital energy control pathways may be permanently altered [15]. For instance, with respect to energy intake, a maternal high-fat diet has been shown to alter the primate epigenome [72]. Further, concerning energy expenditure, regular physical activity exposure and its influence on human skeletal muscle has the ability to alter the expression of histone deacetylases (HDACs), vital proteins known to mediate epigenetic histone modifications and subsequently gene expression [73]. Despite extensive cross-talk
between central and peripheral organs and tissues designed to regulate neurobiological energy balance, in cases of maternal obesity it appears that this balance is perturbed and thus increases the risk for glucose intolerance in the offspring by altering adipocyte and neuroendocrine development of the fetus [9, 15]. Specifically, aberrant synchronization of the orexigenic (e.g., neuropeptide Y and agouti-related protein) and anorexigenic neuropeptide (e.g., pro-opiomelanocortin and cocaine- and amphetamine-regulated transcript) response to metabolic signals including glucose, insulin, ghrelin and leptin within the hypothalamus may alter energy balance regulation in the offspring of the obese mother [9]. For instance, experimental animal studies in the mouse have demonstrated that mothers who consumed an obesogenic diet rich in palatable fat and refined sugar gave birth to offspring who were hyperphagic, had increased adiposity and features of the metabolic syndrome, including hypertension in addition to decreased energy expenditure when compared to controls [6]. Thus, excessive nutrient supply may be categorized as a form of fetal stress that has the potential to initiate metabolic disturbance in the developing offspring which may have lasting effects including predisposition to downstream weight gain if exposed to an obesogenic environment [4, 14].

In fact, Li et al highlighted some of the important factors that contribute to the intergenerational cycle of obesity in humans noting that maternal overweight (OR = 2.2; 95% CI = 1.3-3.7), obesity (OR = 5.1; 95% CI = 2.9-9.1), high birth weight (≥4000 g; OR = 2.0; 95% CI = 1.2-3.4) and maternal weight gain during pregnancy (≥20.4 kg; OR = 1.7; 95% CI = 1.0-2.9) are independently associated with the risk of childhood overweight and obesity, an
observation that holds true after adjustments for multiple confounders [74]. However, an abnormal intrauterine environment, particularly maternal insulin resistance, has demonstrated to be a strong predictor of fetal adiposity and may prove to be more accurate in forecasting down-stream offspring obesity risk than absolute birth weight [75]. The strong, continuous association between neonatal adiposity, cord insulin concentrations and maternal glycemia is evidence supporting the Pederson hypothesis [70] in which a maternal induction of fetal hyperinsulinemia across a range of maternal blood sugar levels (i.e., less severe than diabetes) may alter neonatal adiposity [33]. Although many factors contribute to fetal predisposition to later adiposity, it is difficult to disentangle the single most accurate predictor of childhood obesity given the intimate relationships and interconnectedness of maternal obesity, weight gain, insulin resistance and their effects on fetal growth. This is in part due to a lack of longitudinal follow-up studies in this population as well as methodological limitations inherent to human research studies. However, the gestational period may be an important time point for preventive intervention in an attempt to optimize the intrauterine environment and subsequent downstream child health in pregnancy complicated with obesity and excessive GWG.

1.3 The role of insulin in fetal growth complicated by maternal obesity

Increased fetal growth in pregnancies complicated by obesity is mainly attributed to increased maternal adiposity, maternal insulin resistance, fetal over nutrition and placental hormones, although the underlying mechanisms are not fully understood [5]. Potential
mediators of fetal overgrowth include anabolic hormones, such as insulin, and adipose tissue derived hormones, called adipocytokines. During pregnancy, adipocytokines, including leptin, adiponectin, interleukin-6 (IL-6), tumour necrosis factor α (TNFα) and visfatin are also secreted by the placenta [76-78]. These hormones modulate maternal energy metabolism and insulin sensitivity, and have been implicated in pregnancy conditions that alter fetal growth, including gestational diabetes mellitus (GDM) and intrauterine growth restriction (IUGR). Certain metabolic hormones, such as leptin and insulin, as well as adipokines, such as IL-6 and TNFα, have been shown to stimulate nutrient transporters in the placenta [77, 79]. It has been hypothesized that in maternal obesity and excessive GWG, the elevated calorie intake increases the circulating concentrations of maternal metabolic hormones, which up-regulate placental nutrient transport, thus increasing nutrient delivery to the fetus and accelerating fetal growth [80].

1.4 Insulin and the potential for aberrant fetal growth

Insulin, the major hypoglycemic hormone, is the primary signal regulating metabolic responses to feeding and carbohydrate uptake by peripheral tissues. Produced by the β-cells of the pancreas, insulin is released through hepatic portal circulation and acts in an endocrine fashion where it affects substrate usage in the liver, muscle and fat [81]. Insulin secretion inhibits hepatic glycogenolysis and gluconeogenesis thereby suppressing endogenous glucose production. However, insulin may stimulate glucose uptake and fuel storage of glycogen and triglyceride in the liver, muscle and adipose tissue [82].
Optimal glycemic control is encouraged during pregnancy to attenuate the risk of GDM and fetal macrosomia to mom and baby, respectively. Maternal prepregnancy overweight, obesity and severe obesity, for example, are associated with a 2.14, 3.56 and 8.56 increased likelihood of GDM when compared with normal prepregnancy weight women [83]. Further, mothers with GDM have a 5.5 times greater chance that their child will be born macrosomic, which is also associated with increased susceptibility to childhood overweight [84]. During pregnancy, fasted concentrations of insulin begin to rise from 5mU/L around 20 weeks gestation and remain at roughly 8mU/L from the last half of gestation until term [85]. Insulin release, in response to a carbohydrate challenge, becomes pronounced by the third trimester such that oral or intravenous glucose-stimulated insulin secretion is approximately 1.5-2.5 times greater than in non-pregnant women [86-88]. Contrary to early pregnancy where insulin action is enhanced by estrogen and progesterone leading to lower fasting plasma glucose levels [89], late pregnancy is characterized by accelerated growth of the fetal-placenta unit and increasing insulin resistance [90]. Thus, decreased insulin sensitivity in later gestation may increase fetal anabolic processes in the presence of maternal nutrient excess.

Work from animal models strongly suggests that maternal excess food intake and/or positive energy balance modifies offspring physiology including aspects related to appetite regulation, metabolic homeostasis and habitual physical activity levels [91]. Maternal eating and physical activity behaviour can modify the regulation of fetal energy balance (i.e., nutrient intake and caloric expenditure) and this concept is further exemplified in offspring
of the obese women due to their proportionally greater amount of adipose tissue deposition at birth compared to neonates of normal weight mothers [61, 75]; an effect thought to be partly mediated by insulin. Excessive fat cell accretion during the highly plastic antenatal period may predispose, if exposed to an obesogenic environment, a lifelong excess of body fat in offspring of obese mothers [61]. As such, understanding the metabolic regulation of cell growth and differentiation, especially in vivo triggers of fetal adipogenesis, is pivotal to designing preventive and therapeutic approaches addressing the excessive fetal growth characteristic of maternal obesity and/or excessive pregnancy weight gain.

Although a maternal hyperglycemic state may not reach the levels of clinical diagnosis for GDM, the fetus is more sensitive to slight glucose fluctuations as this substrate freely crosses the placenta via carrier-mediated facilitated diffusion through the glucose transporter proteins (i.e., GLUTs). This ‘fuel mediated teratogenesis’ induces fetal hyperglycemia, subsequent hyperinsulinemia and promotes fetal adiposity [92, 93]. Nonetheless, fetal insulin is required to initiate an anabolic response leading to carbohydrate storage, adipocyte hypertrophy and adipogenesis in response to maternal intake. Fetal fat mass, which contributes to the greatest inter-individual variation in birth weight, is affected by the maternal environment and is more strongly correlated with maternal pregravid weight than GWG [58]. Collectively, fetal anabolic alterations are associated with higher rates of LGA infants and it has been suggested that these in utero
perturbations alter energy balance mechanisms that result in positive energy balance and
greater adiposity in childhood [58, 61].

In addition to carbohydrate substrate, excessive lipids may alter fetal secretion of
anabolic hormones and growth factors and these may act in combination with glucose to
predispose excessive fetal growth, as evidenced in a GDM population [75]. The gestational
diabetic offers a clinical model to examine the effects of excess substrate flux from mom to
baby particularly given the lack of studies examining these phenomena in the obese
population. In an observational study, Hillier et al. [94] showed that in 5-7 year old children,
weight status of offspring of mothers with well-controlled GDM was similar to offspring of
mothers with normal glucose tolerance and that the risk for high weight-for-age was lower
in children whose mothers were treated for GDM compared to those who were not,
supporting the importance of improved glycemic control during pregnancy to improve child
growth outcomes. Moreover, fetal body composition may be altered in GDM and obese
pregnancies by similar mechanisms as the accrual of fat mass during gestation can occur
via: 1) direct transfer of non-esterified fatty acids (NEFA) from mom and, 2) \textit{de novo}
lipogenesis resulting from excessive concentrations of glucose and lactate in fetal
circulation [95]. This effect is compounded in obese and GDM patients due to their
resistance to the anti-lipolytic effects of insulin despite their hyperinsulinemic state [96].
The compounding effects of elevated serum glucose, and increased blood lipid
concentrations provides two potential avenues contributing to metabolic dysfunction in
uterine and its associated increase in fetal adiposity which may result in pro-atherogenic pathology in this population.

Given that both diet and physical activity intervention have demonstrated an ability to normalize glycemic response in the overweight and obese [97], type-2 diabetic [98] and GDM [99] populations, coupled with the finding that physical activity can improve lipid profiles [100] and optimize IGF-I axis dynamics [101, 102], incorporating healthy behaviours into an intervention program for obese pregnant women may be advantageous to fetal development and minimize the intergenerational effects of excess nutrient transfer; as evidenced in numerous animal studies [103]. Overall, these findings suggest that maternal glycemic control may alter fetal birth weight and body composition as well as the downstream metabolic profile of mom and baby and be potentially mediated through the IGF axis.

1.5 Insulin-like growth factors and fetal growth

Optimal fetal development is dependent on a balanced interplay between growth suppressors and promoters originating from fetal, placental and maternal compartments (see Figure 1.1). Of these important regulators, the insulin-like growth factors (IGFs) play a vital role. This includes IGF-I, IGF-II, a family of 6 IGF binding proteins (IGFBP), as well as their receptors (IGF type 1 (IGF1R) and type 2 (IGF2R)) and proteases (e.g., PAPP-A) which
ultimately regulate IGF bioavailability. IGF-I and -II are predominately produced by adult and fetal liver although the placenta also expresses these peptides [104] (see Figure 1.3).

Whereas insulin is generally thought to have metabolic actions initiating a hypoglycemic response (i.e., works as an anabolic hormone peripherally), the IGF family of proteins have mitogenic and meiotic functions regulating cellular proliferation [105]. Of particular interest, however, is the role of IGF-I as this protein complex is both nutrient sensitive and the predominant growth factor involved in fetal growth and development during the later stage of pregnancy. Although IGF-II remains active throughout pregnancy, it plays a lesser role in late gestation as it is maternally imprinted, and predominately involved with early implantation and differentiation [104]. Furthermore, IGF-I is paternally imprinted, and consequently maternally expressed throughout gestation and susceptible to alteration as a result of maternal environment; particularly nutrition. The growth promoting effects of IGF-I include stimulation of fetal substrate uptake, reciprocal catabolic inhibition and improving placental transfer of nutrients from mom to baby [104, 106]. However, the role of the IGF axis in pregnancies complicated by obesity and/or excessive GWG and how this affects fetal growth has yet to be conclusively demonstrated in humans [107].

With respect to the IGFBPs, of particular interest are IGFBP-1 and -3 as these binding proteins are predominant modulators of IGF function; although the other IGFBPs play a vital, yet much less characterized role. By altering the half-life of this complex the binding
proteins aid in transport to specific tissues and promote endocrine, autocrine and paracrine action [105, 108]. For instance, IGFBP-1 forms a binary complex with IGF-I whereas IGFBP-3 forms a ternary complex with IGF-I and an acid labile subunit (ALS) providing a regulatory mechanism that controls the amount of circulating ‘free’ vs. ‘bound’ IGF-I in turn increasing bioavailability for tissue specific growth [104, 105]. IGFBP-3 is the most abundant binding protein and carries ~80-90% of the IGFs found in plasma [104, 105, 108] while IGFBP-1 binds a mere 2% of circulating IGF-I [109]. IGFBP-1 has been cited as a vital down-regulator of IGF bioactivity as levels of IGFBP-1 decrease with increased carbohydrate intake and circulating insulin [110, 111]. Cord blood concentrations of IGFBP-3 have been shown to be elevated in neonates born LGA when compared to controls [112]. Further, IGFBP-1 concentrations in cord blood were significantly reduced in neonates of GDM mothers whereas IGF-I levels were elevated [113]. This suggests that IGFBP-3 and IGF-I are elevated and the inhibitory IGFBP-1 levels may be reduced in LGA infants as there is an increase in the IGF-I free:bound ratio suggesting there to be increased IGF-I bioavailability at the tissue level. Regardless of the complexity of this system, these growth factors must be finely balanced to optimize fetal growth trajectories.

As the predominant mediator of somatic development [108], growth-promoting pathways such as the IGF-I axis, are suspected to be partially responsible for excessive in utero growth characteristic of offspring from pregnancy complicated by obesity and/or excessive GWG. However, a thorough understanding of the processes mediating obesity in the mother to the development of overweight in her child is limited. Catalano et al. [26]
demonstrated that fetuses of obese mothers develop insulin resistance in utero and Clapp et al. [39] suggested that maternal blood sugar levels serve as proxy measures for placental substrate availability throughout pregnancy; which affects feto-placental growth. Consequently, the glucoregulatory capacity of IGF-I, that is its ability to act as a hypoglycemic growth-promoting agent when bioactive, establishes IGF-I as a novel mediator of anomalous fetal growth in mothers with obesity [39, 110]. Conversely, underweight women give birth to proportionately greater number of small for gestational age (SGA), and significantly fewer LGA neonates [114]. In growth restricted fetuses for example, IGF cord serum concentrations remain low compared to appropriately sized neonates [115, 116]. Additional support for the growth-promoting role of IGF-I comes from transgenic mice with a homozygous defect of the igf1 gene (IGF1 knockout) who display significant embryonic and postnatal growth retardation [117, 118].

Furthermore, when considering the growth-promoting role of IGF-I and its regulatory role in fetal body composition it is important to note the strong relationships between third trimester maternal IGF-I, placental mass and neonatal fat mass [39]; suggesting that IGF-I concentrations in maternal serum during late gestation may be valuable markers of deviant fetal growth in cases of severe obesity. The predictive value of IGF-I in cases of severe obesity may result from greater deviation from normative values for circulating levels of IGF-I that are more easily identified at body weight extremes (i.e., severely obese) and represent significant elevations in neonatal fat mass. Conversely, mothers of infants born SGA had lower IGF-I concentrations than did mothers of those born
average for gestational age (AGA) [116]. IGFBP-1 concentrations are negatively correlated with birth weight and growth restricted fetuses have demonstrated elevated concentrations of IGFBP-1 [119]. On the other hand, IGFBP-3 levels gradually increase throughout pregnancy, regardless of birth weight and maternal status, and remain high until delivery [39, 120]. Protease degradation of IGFBP-3 is also observed during pregnancy and it is speculated that this results in decreased affinity for IGF-I and thus increases IGF bioavailability for receptors on maternal tissues as well as the placenta [121, 122]. Chiesa and colleagues [123] observed higher insulin, leptin and IGFBP-3 levels in asymmetric (i.e., disproportionately large head) LGA neonates born to normal weight mothers when compared to symmetric LGA and AGA births further suggesting that excessive in utero fetal growth may be initiated by a teratogenic maternal environment. As such, maternal IGF-I and IGFBP-3 levels in serum are reduced and IGFBP-1 concentrations increased in cases of IUGR pregnancies when compared to control [124, 125]. Further, hepatic production of IGFBP-1 is inversely regulated by the portal supply of insulin [126] which may help explain the higher incidence of macrosomia in GDM [33]. Fetal IGF-I expression is sensitive to fetal insulin levels which are regulated by the presence of glucose transported through the placenta from the maternal circulation via the umbilical vein. Thus, a suboptimal intrauterine milieu caused by deterioration in glucose tolerance may stimulate fetal overgrowth in cases of maternal obesity. Overall, the growth promoting effects of enhanced IGF axis bioactivity likely involve the complex interplay between the maternal-placental-fetal unit. It appears that appropriate coordination is necessary for optimal
growth with potential disturbances in signaling contributing to variation in phenotypes (i.e., LGA or IUGR neonates with varying body composition).

Mechanistic evidence highlights the inhibitory role of IGFBP-1 and growth enhancing role of IGFBP-3 as demonstrated by a reduction in somatic growth and characteristic overgrowth in rodent models in which IGFBP-1 and IGFBP-3 are over-expressed, respectively [127]. What is known from a sheep model of pregnancy is that fetal IGF-I concentrations decline and fetal growth is compromised when the mother is undernourished; however fetal IGF-I levels normalize following glucose or insulin infusion [106]. This suggests that maternal nutrient consumption can either promote or restrict fetal growth dependent on maternal diet, energy intake and expenditure. Numerous studies cite a positive correlation between IGF-I levels in umbilical cord blood and infant birth weight and provide evidence that SGA fetuses display lower IGF-I concentrations [119, 128-130]. However, no correlation was observed between maternal concentrations of IGF-I, cord blood concentrations of IGF-I and absolute birth weight for gestational age suggesting that IGFs in cord blood originates from the feto-placental unit and does not cross the placenta from maternal circulation due to its size [104, 105]. In children with obesity, IGFBP-3, leptin and insulin are elevated and subsequently normalized following a 1-year weight loss intervention [97] supporting the role of lifestyle-induced weight loss in obese patients for improved metabolic health and IGF axis function. Interestingly, regular maternal physical activity throughout pregnancy did not improve maternal insulin sensitivity measured by 3 hour intravenous glucose tolerance tests but demonstrated marked reductions in cord serum levels of IGF-I, -II and infant birth
weight compared to offspring of sedentary controls [30] alluding to the role of the IGF axis in optimizing fetal growth.

In summary, this brief review of the literature provides the reader with fundamental knowledge concerning the relationship between maternal obesity and/or excessive GWG and accelerated fetal growth. Although it is well established that a lack of glycemic control during pregnancy may compromise fetal growth and development, a thorough understanding of various other mediators of this process, including growth factors, are far from conclusive. Given the gap in the literature further research on these topics warrants scientific investigation.

2.0 STRUCTURE OF THE THESIS

An abnormal intrauterine milieu compromised by obesity and/or excessive GWG has demonstrated adverse effects on fetal metabolic function, growth and development. However, the precise ways in which maternal phenotype predicts offspring outcomes are not well characterized. Here we aimed to review the literature attempting to further understand the physiological mechanisms mediating the intergenerational transmission of obesity and adipose-related pathology. An epidemiological analysis of the Ottawa and Kingston birth cohort followed and contributed to our understanding of maternal predictors of infant birth size. By utilizing updated evidence-based guidelines for GWG this work provides support for the clinical utility of this tool for weight management in obstetrical practice. As a follow-up we examined how obesity and/or GWG, strong predictors of
neonatal size, influenced the IGF axis in normoglycemic term pregnancies. This molecular characterization of a vital pathway regulating fetal birth size provides evidence that maternal obesity and/or excessive GWG alter protein expression patterns in the IGF axis when compared to normal weight pregnant controls who gain weight appropriately. Being aware that most women were entering pregnancy at elevated risk and gaining excessively throughout gestation we administered a patient-centred questionnaire inquiring about the use of various information channels and knowledge of physical activity and nutrition best practices during pregnancy. Lastly, we conclude with a narrative review that examines the evidence with respect to the effects of physical activity during pregnancy on improving maternal-fetal outcomes.
3.0 SPECIFIC AIMS AND OBJECTIVES

I: To evaluate the literature concerning the developmental origins of metabolic and cardiovascular disease in pregnancy complicated by obesity and to discuss potential intervention strategies and the need to properly assess knowledge channels and information provided during pregnancy to best design effective interventions to prevent excessive GWG.

II: To determine, through a population level analysis, predictors of infant birth weight in a regional cohort, highlight the maternal characteristics associated with fetal overgrowth and provide evidence that supports the clinical utility of the IOM guidelines to optimize birth weight.

III: To characterize the IGF axis in pregnancy complicated by maternal obesity.

IV: To determine if excessive gestational weight gain alters IGF axis protein expression patterns independent of prepregnancy BMI in normoglycemic term gestation.

V: To determine what information channels pregnant women utilize and understand their knowledge of physical activity and nutrition information during pregnancy to improve intervention efficacy to prevent excessive GWG.

VI: To evaluate the literature on the effects of physical activity during pregnancy on maternal-fetal outcomes, discuss the risks and benefits to mother and baby, highlight the role that a physically active lifestyle plays in preventing aberrant fetal growth and understand how physical activity may optimize maternal-fetal growth trajectory.
Pediatric obesity: it’s time for prevention before conception

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Z. Ferraro searched the literature, retrieved sources, evaluated the evidence and wrote the manuscript. K. Adamo contributed to the evaluation of the extracted sources, critically revised the manuscript, supervised the research and provided guidance and support.
Pediatric Obesity: It’s Time for Prevention Before Conception Can Maternal Obesity Program Pediatric Obesity?

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Abstract: Global increases in obesity have led public health experts to declare this disease a pandemic. Although prevalent in all ages, the dire consequences associated with maternal obesity have a pronounced impact on the long-term health of their children as a result of the intergenerational effects of developmental programming. Previously, fetal under-nutrition has been linked to the predisposition to pediatric obesity explained by the adiposity rebound and ‘catch-up’ growth that occurs when a child born to a nutrient deprived mother is exposed to the obesogenic environment of present day. Given the recent increase in maternal overweight/obesity (GW/OB) our attention has shifted from nutrient restriction to overabundance and excess during pregnancy. Consideration must now be given to interventions that could mitigate pregravid body mass index (BMI), attenuate gestational weight gain (GWG) and reduce postpartum weight retention (PPWR) in an attempt to prevent the downstream signaling of pediatric obesity and halt the intergenerational cycle of weight related disease currently plaguing our world. Thus, this paper will briefly review current research that best highlights the proposed mechanisms responsible for the development of child OW/OB and related sequelae (e.g. type II diabetes (T2D) and cardiovascular disease (CVD)) resulting from maternal obesity.

Keywords: pediatric, maternal, obesity, developmental programming, disease, gestational weight gain, intervention

Introduction

The overwhelming prevalence of obesity in developed, developing and first world nations has lead public health experts to call this increase in adiposity the world’s largest and fastest growing epidemic. Aside from the millions of dollars of health care funding lost on account of obesity, the economic costs fall second to the devastating decline in health and thus quality of life. Obesity is relevant to all age-groups, but has a significant impact on the health, well-being and longevity of two specific populations; women of childbearing age and children. In Canada 23.1% (5.5 million Canadians) are obese and 36.1% (8.6 million) are overweight according to directly measured body mass index scores [BMI] weight (kg)/height (m²). (Tjepkema. 2008). Even more startling is the dramatic and progressive rise in pediatric overweight/obesity accounting for 26% of 2–17 year old Canadian children and youth (Shields, 2008). These are alarming statistics as overweight children have a tendency to remain overweight as adults or progress to an obese state and carry with them an array of obesity-related health problems. Of particular concern, from 1999 to 2002, 54.5% of women of childbearing age (20–39 years) were overweight (BMI > 25), 29.1% were classified as obese (BMI > 30) and 5.6% considered morbidly obese (BMI > 40) (Hedley et al. 2004). The parallel increase in obesity rates in the pediatric and maternal population, supports the relationship that having an obese parent will increase the likelihood that an overweight/obese child will remain obese in adulthood; thus exacerbating the current epidemic (Whitaker et al. 1997) and suggesting that the parental environment can have a significant impact on the long-term health of their child.

As the prevalence of overweight/obese (OW/OB) women and children continues to rise so to does their risk of disease and death. Overweight and obese adults have a 50%–100% increased risk of all-cause mortality, primarily attributed to cardiometabolic disease when compared to normal-weight individuals (National Institutes of Health 1998). Severe obesity may also reduce life expectancy in today’s youth, causing them to live shorter lives than their parents (Olshansky et al. 2005). Irrespective of life-expectancy, obese kids may be forced to cope with increased susceptibility to the many cardiovascular, metabolic,
pulmonary, musculoskeletal, gastrointestinal and psychosocial disorders that accompany increased adiposity such as hypertension, diabetes, sleep apnea, osteoarthritis, fatty liver disease and depression (Princeton University and The Brookings Institution 2008).

The pathophysiological consequences of obesity have a profound impact on the health of OW/ OB pregnant women as they progress to term. Similar to the obese child, OW/ OB women are also at increased risk of diabetes (i.e. gestational diabetes mellitus (GDM)), hypertension, osteoarthritis and certain cancers, including breast, endometrial and colon (Hall and Neubert, 2005; Krishnamoorthy et al. 2006), as well as a decline in psychological well-being and quality of life (Janicke et al. 2007). However, it may be of even greater importance to note that obesity during pregnancy not only directly affects the mother, but has been implicated in many adverse pregnancy outcomes that can influence the child’s short and long-term health. Maternal obesity is strongly associated with increased susceptibility to fetal macrosomia, neural tube defects, preterm birth, increased cesarean section, perinatal infection, pre-eclampsia, gestational hypertension (Smith et al. 2008) and gestational diabetes (GDM) (Arendas et al. 2008), demonstrating that the intrauterine milieu and its regulation throughout gestation must maintain homeostatic balance in order to promote optimal child health.

Whether early life obesity is onset by an imbalance between energy intake and expenditure, possession of a more susceptible genotype or interactive epigenetic mechanisms activated by one’s daily environmental exposure, the adaptive responses that occur in utero and developmentally program the child’s subsequent predisposition to cardiovascular disease and obesity are a potential target for strategic preventive interventions. With the Institute of Medicine making childhood obesity prevention a national priority item in the United States (Office of the Surgeon General 2008), Obesity Canada and the Canadian Medical Association revising clinical practice guidelines calling for innovative preventive measures (Lau et al. 2007), the recently demonstrated poor achievement in the Active Healthy Kids Canada Report Card (Active Healthy Kids Canada 2008) and the Foresight program’s vision to develop a sustainable response to obesity (Foresight, 2007) there is no better time than the present to start to design and implement effective intervention strategies. Targeting women’s health during the pregravid, gestational and postpartum periods, crucial times of growth, development and physiological change in mother and child, may prove to be a worthy pursuit in our attempt to halt the intergenerational cycle of obesity currently plaguing our world.

Thus, the purpose of this paper is to provide an audience of health care providers current information about the intergenerational effects of obesity in support of the fetal origins hypothesis. We highlight how maternal lifestyle, particularly a poor intrauterine milieu (via, excess energy consumption and decreased expenditure), can increase offspring susceptibility to obesity and/or its related precursors presumably through developmental programming. By identifying gaps in the literature and stressing the importance of prevention before conception, we hope to demonstrate the need for multidisciplinary interventions in and around gestation as a means to attenuate the prevalence of pediatric obesity, maternal obesity and their associated complications and comorbidities in the mother, her child and thus future generations.

Methodology

The OVID Medline database was queried using the keywords obesity and pregnancy. From 1950–2008 over 2,000 articles were initially identified from which the authors manually screened the sources to include only those that directly pertained to developmental programming of pediatric obesity, its related co-morbidities and the effects of maternal obesity during pregnancy. After careful examination the remaining 189 sources were assessed for content that was relevant to and could provide the best evidence in support of maternal programming of disease in utero. Finally, articles included in this review were selected based on scientific merit by demonstrating a relationship between maternal obesity and negative offspring health outcomes that may result in clinical manifestation of downstream diseases such as T2D, CVD and/or their precursors. Further articles were included if they supported the purpose of the analysis and were related to an originally queried source, but may not have been initially identified through the OVID Medline search. The following is a brief review that attempts to highlight a chronological continuum from maternal obesity to
disease progression in their offspring, with a focus on metabolic and cardiovascular sequelae.

**Fetal Origins of Obesity—The Role of Undernutrition**

Although this paper will focus on the role of fetal ‘overnutrition’ given the impact of the obesity epidemic on women and children, the concept of developmental programming will be introduced from an ‘undernourished’ perspective as this was the original condition from which the relationship between the maternal intrauterine environment and long-term health of the offspring was first recognized. The intrauterine milieu’s impact on adult health outcome was first described by Barker and colleagues almost two decades ago. By retrospectively studying the effects of intrauterine growth and maternal physique on adult blood pressure, a strong relationship was established between the mother’s internal environment, child’s birth weight and the development of hypertension in adulthood (Barker et al. 1990). Furthermore, it was proposed that improving maternal health, particularly nutrition, may have a role in preventing such outcomes later in life. Arising from this original work, ‘The fetal origins of adult disease hypothesis’ has since attributed early environmental factors, predominantly maternal nutritional status and its effect on the fetus in utero, to the premature programming of risk for cardiovascular and metabolic disease in adulthood (Barker et al. 2002; Barker, 2005; Barker et al. 2005; McMillen and Robinson, 2005). Developed as a causal explanation related to low birth weight leads to disease progression, the ‘thrifty phenotype hypothesis’ was proposed. Briefly, it states that having a suboptimal intrauterine milieu, as a result of fetal nutrient deprivation, will facilitate an adaptive growth and development response of vital tissues and organs at the expense of others. This is proposed to lead to altered metabolic mechanisms that enhance postnatal survival in a time of nutrient restriction. However, this relationship becomes problematic when the postnatal nutritional environment is one of abundance, not deprivation as experienced in utero, and a metabolic mismatch is established developmentally programming the child for ‘catch up’ growth and susceptibility to cardiometabolic disease later in life (Hales and Barker, 1992; Hales and Barker, 2001; Hales and O’zanne, 2003). As a result of maternal undernutrition, metabolic adaptive responses that occur in the fetus initially designed to enhance survival may in fact be undesirable for postnatal growth and development if the child’s environmental exposure pre and post natal are dissimilar.

**Maternal Obesity Programs Pediatric Obesity and Metabolic Function**

Despite the abundance of research that links ‘catch up growth’, ‘adiposity rebound’ and early onset obesity to fetal nutrient deprivation in utero (Ong et al. 2000), the developmental programming of pediatric obesity, its precursors (i.e. impaired glucose tolerance (IGT), insulin resistance, etc) and resulting co-morbidities (e.g. T2D, CVD, cancer) will be discussed from here, with a focus shifted towards maternal overnutrition and the corresponding habits of obesity.

Viewing pregnancy as a critical period of pediatric obesity prevention is a relatively novel area of study given the significant rise in maternal obesity in recent years. As such, the acute effects on fetal growth and development in utero and subsequent predisposition to obesity in response to maternal over nutrition and obesity are just beginning to attract attention in the literature. Maternal obesity is a well-recognized risk factor for fetal macrosomia and several epidemiological studies have highlighted a U or J-shaped curve/relationship between birth weight and adolescent weight as well as adult fat mass with babies large or small for gestational age being at increased risk (Curhan et al. 1996; Pettitt and Jovanovic, 2001; Rogers, 2003; Wei et al. 2003; Ozaanne et al. 2004; Ong, 2006; Dmet and Ong, 2008) as well as increased maternal BMI leading to greater susceptibility of fetal death due to placental dysfunction (Nohr et al. 2005). Thus, as weight increases above and beyond that considered healthy so to does the risk of chronic disease, pregnancy complications and all-cause mortality.

Furthermore, pregravid OW/OB and surpassing gestational weight gain (GWG) requirements are strongly associated with an increased risk of fetal overgrowth, having a child born large for gestational age, infant fatness (Ehrenberg et al. 2004) and post-partum weight retention (PPWR) (Amorim et al. 2007; Huang et al. 2008). These women are also at higher risk of maternal hyperglycemia and GDM (Hillier et al. 2007), conditions that have also been independently linked to having
an overweight/obese child (Pettitt et al. 1983; Pettitt et al. 1985; Pettitt et al. 1987; Pettitt et al. 1993; Nonnemacher et al. 2005; Rosemberg et al. 2005; Schaefer-Grant et al. 2005; Malcolm et al. 2006; Allen et al. 2007; Chen et al. 2007; de Campos et al. 2007). The resulting implications of increased maternal adiposity and the corresponding risk this has on the child’s future health must be addressed.

During pregnancy maternal insulin sensitivity is naturally decreased as a protective mechanism of survival that directs the allocation of nutrients consumed by the mother to the developing fetus to ensure adequate energy partitioning for optimal growth (King 2000). However, when exposed to an obesogenic environment, we presume that maternal overnutrition results in a positive energy balance. The surplus of energy would then need to be stored by the mother with additional fuel redirected to the child and stored, increasing their risk for metabolic disease; a situation that is exacerbated in children of GDM pregnancies (Dabelea et al. 2008).

This association between maternal OW/OB and childhood overweight was first demonstrated in rodent models (Vickers et al. 2000; Vickers et al. 2003; Bayol et al. 2007; Ferezou-Viala et al. 2004; Harvey et al. 2007; Sannellson et al. 2008; Shankar et al. 2008). The resultant sequelae (i.e. obesity) present in offspring of OW/OB mothers has been most strongly attributed to altered neuroendocrine regulation of appetite signaling pathways (Muhlhauser et al. 2006). However, since the appetite regulatory system of the rat develops postnatally and the same system develops before birth in sheep and humans, investigations utilizing lamb models are more relevant to human physiology and reproduction, and thus warrant discussion.

Appetite regulation and energy homeostasis are regulated through a variety of intricate neuroendocrine pathways that act in response to systemic ghreline, insulin and leptin concentrations at the level of the hypothalamus to control the expression of the orexigenic neuropeptides, neuropeptide Y (NPY) and agouti-related peptide (AGRP) and their orexigenic counterparts, pro-opiomelanocortin (POMC) and cocaine-and amphetamine-regulated transcript (CART) (Kalra et al. 1999). The novel work of Muhlhauser and colleagues, demonstrated for the first time, an alteration in offspring appetite regulatory system function in response to increased maternal nutrition during late gestation (Muhlhauser et al. 2006). This group demonstrated that at 30 days of age, lambs born to ewes that consumed 40% more than their daily energy requirements in late gestation displayed increased milk intake, plasma glucose concentrations and subcutaneous adiposity when compared to controls. The relative increase of adipose tissue was directly related to circulating glucose concentrations in early life, which is consistent with children born to mothers with GDM or glucose intolerance (Dabelea et al. 2008). Furthermore, a decrease in leptin sensitivity with increased adiposity was seen in lambs of over-nourished ewes and this was attributed to down-regulation of the leptin receptor in the arcuate nucleus of the brain resulting in leptin resistance. Increased maternal nutrition resulted in increased, appetite inhibiting, POMC expression as plasma glucose concentration increased. Although NPY and AGRP expression was not different when compared to controls, CART expression in response to increased nutrient intake and fat mass was also reduced when lambs were exposed to excess nutrient supply before birth which could have implications for regulation of energy balance. Overall, the authors attributed the inability of over-nourished mothers to up-regulate hypothalamic anorexigenic pathways in response to increased adiposity to a central resistance to the actions of leptin and consequently may lead to increased childhood obesity in OW/OB mothers consuming excess calories in gestation (Muhlhauser et al. 2006). These findings, which accord with the programming of pediatric obesity to leptin resistance, are in agreement with others rodent models (Franke et al. 2005; Ferezou-Viala et al. 2007) including those which demonstrated reversal of glucose intolerance and diet induced obesity through maternal leptin administration (Stocke et al. 2007). It has also been cited that untreated GDM and hyperglycemia in pregnancy can result in inappropriate programming of appetite regulating networks in the brain contributing to development of later OW/OB (Franke et al. 2005). Increased caloric consumption above that needed for optimal growth and development of the fetus can result in excessive GWG and subsequent PPWR. This demonstrates that increased maternal adiposity may enhance the susceptibility to glucose intolerance, T2D and metabolic dysfunction in both mother and child.

Maternal Obesity Programs Pediatric Obesity and Cardiovascular Disease
Overfeeding practices leading to excessive energy intake, coupled with decreased expenditure through
reductions in daily physical activity have contributed to global increases in maternal obesity. In addition to the concept that obesity begets obesity, increased maternal adiposity has also been identified as an important determinant of the metabolic syndrome in children (Boney et al. 2005). A poor intrauterine environment and the resultant presentation of pediatric obesity leads to a plethora of metabolic abnormalities, particularly a proinflammatory response as a result of increased fat mass and release of adipokines in the blood, that predispose the child of an OW/OB mother to cardiovascular disease in adulthood (Weiss and Caprio, 2005). As the rates of pediatric and maternal obesity continue to rise, it is important to understand the underlying mechanisms that increase one’s susceptibility to comorbidities (e.g. hypertension) directly related to pediatric obesity in an attempt to improve the quality of life of this population and prevent disease progression into adulthood.

Initially, epidemiological evidence showed a non-significant relationship between maternal obesity and offspring blood pressure, yet demonstrated that underweight resulted in increased blood pressure, supporting the Barker hypothesis (Godfrey et al. 1994; Clark et al. 1998). However, in light of the current obesity epidemic, more recent research draws parallels between increased maternal adiposity and offspring hypertension (Phillips et al. 2005) while making associations with GDM (Lee et al. 2007). In fact, it is now accepted that maternal obesity is associated with a poor maternal metabolic profile which is partially attributed to increased blood pressure, insulin resistance, hyperglycemia, and elevated blood lipids (Wilson and Grundy, 2003). The resulting metabolic platform, if not transformed prior to conception, may result in a suboptimal ‘obesogenic’ intrauterine environment that has great potential to developmentally program pediatric obesity and cardiovascular disease. Recent work in animal models, mimicking the human obese condition, has provided impressive evidence linking the obesogenic gestational environment to negative health consequences in offspring (i.e. hyperphagia, insulin resistance, obesity, and hypertension) (Samuelsson et al. 2008). Obesity, induced in female mice by feeding an obesogenic diet (16% calories from saturated fat, 30% simple sugar) 6 weeks before mating and maintained during pregnancy and lactation was examined and compared to a control to assess effects on offspring metabolic and cardiovascular health.

Offspring of both groups were weaned onto a standard diet and studied at 3 and 6 months post-partum. The obesogenic diet was designed to resemble that which is consumed by many of us in today’s society and was compared to a control diet which consisted of 3% fat and 7% sugar. The mothers consuming the obesogenic diet, comprised of highly palatable fats and refined sugar, had offspring who displayed hyperphagia, increased adiposity, adult symptoms of the metabolic syndrome, including hypertension, as well as decreased physical activity patterns (Samuelsson et al. 2008). Both maternal caloric intake and weight gain were significantly greater in the mice fed the obesogenic diet resulting in 4-fold increase in abdominal fat mass (4.00 ± 0.42 g) when compared to control fed a standard diet (1.02 ± 0.08 g). Offspring of the obese mothers were hyperphagic from 4 to 6 weeks, with increased adiposity and reduced activity levels at 3 months when compared to controls (Samuelsson et al. 2008). Furthermore, at 6 months offspring of obese mothers were heavier, displayed increased abdominal obesity associated with adipocyte hypertrophy and arterial endothelial dysfunction. Of greatest concern was the presentation of hypertension in the offspring of the obese mothers at 6 months postpartum (134 mmHg in obese offspring vs. 124 mmHg in controls), as measured by systolic radiotelerometry (Samuelsson et al. 2008). The phenotypic characteristics presented in the offspring of obese mothers demonstrate, for the first time, the drastic metabolic and cardiovascular effects induced by excessively feeding on high-fat diets during pregnancy and throughout lactation, which promoted maintenance of their obese state. In an attempt to quantify the results and understand the ramifications of maternal obesity, Samuelsson and colleagues, suggested that in addition to genetic predisposition, a complex interaction between dietary and obesity related metabolic sequelae initiate a cascade of internal processes with the final outcome being increased susceptibility to pediatric obesity in their offspring. However, increased adiposity (Rahmouni et al. 2005) and endothelial dysfunction (Armitage et al. 2004) have both been cited as possible independent mechanisms contributing to the hypertensive condition of obese offspring.

Presently, the literature has demonstrated that not only feeding preferences for a palatable high fat diet can be programmed in utero as a result of maternal behavior (Bayol et al. 2007), but physical
activity habits as demonstrated through a reduction in energy expenditure and excessive food consumption (i.e. hyperphagia) can be programmed as well (Samuelsson et al. 2008). Misinformed maternal lifestyle choices, especially poor feeding preferences during pregnancy, may predispose the developing child to traits that result in perpetual weight gain and early onset of overweight, premature metabolic and cardiovascular disease and significant decline in quality of life.

Although the molecular mechanisms of action are likely related, the interaction between these complex systems have not, as of yet, been completely identified or studied sufficiently to establish concrete therapeutic targets due to the relative novelty of the research addressing maternal obesity and its related sequelae on mother and child. This ‘gap’ in the literature suggests that prevention before conception might be an optimal, albeit potentially unrealistic, clinical strategy for reducing pediatric obesity prevalence. Preliminary research has identified the role of excess glucocorticoids and circulating proinflammatory cytokines as a result of increased fat mass in females of childbearing age and their corresponding effects on the hypothalamic-adrenal-pituitary axis (Mohan Kumar et al. 2007), leptin resistance (Rahmouni et al. 2005) and dysfunction of the appetite regulating neuropeptides POMC, AGRP, NPY and CART (Mühlhauser et al. 2006) as the most promising areas of future research proposed to identify therapeutic targets that would offer clinical benefits by altering the appetite regulatory center.

The literature associated with the fetal programming of pediatric obesity is derived from multiple levels of research (i.e. epidemiological, animal model, and human studies) which presents evidence suggesting that a highly palatable diet, rich in refined sugar and saturated fat and consumed beyond the nutritional requirements of pregnant women, combined with inactivity, can be detrimental to fetal development in utero. As a result, this exposure may have drastic ramifications on the long-term health of the child. In essence, the child will then carry with them these risk factors and/or conditions into adulthood, perpetuating the intergenerational effects of obesity exacerbated by maternal adiposity (Fig. 1). By modifying the behavior of women during pregnancy and preventing abnormal/excessive GWG through nutritional and activity interventions, the burden of increased fat mass can be minimized and a healthy, optimal lifestyle and future for the child could potentially be ‘programmed’. Animal model results from female offspring born to high-fat diet-induced

![Developmental Programming of Pediatric Obesity and Related Sequelae via Excessive Maternal Adiposity](image)

**Figure 1.** The role of maternal obesity in development of childhood OW/ OB, T2D and CVD (GWG, gestational weight gain; PPWR, postpartum weight retention; T2D, type 2 diabetes; CVD, cardiovascular disease; OW/OB, overweight/obesity).
obese mothers are encouraging. In an investigation in which obese mothers who switched from a high-fat diet to one of balance nutrient composition during the periconceptional, gestation and lactation periods birthed female offspring that were 'resistant' to the deleterious effects of consuming a high fat diet at weaning (Gallou-Kabani et al. 2007). The ability of female offspring to 'resist' impaired glycemia, increased body fatness and a hyperphagic state postpartum with ad libitum access to fatty foods suggests that interventions during pregnancy can have important health implications. These findings stress the need to test the effects of lifestyle interventions (i.e. diet and exercise) aimed at preventing excessive GWG in a controlled, clinical setting as a means to prevent abnormal developmental programming or attenuate the mechanisms that promote such drastic alterations. To prevent the onset of pediatric obesity and the associated problems associated with deleterious downstream signaling as a result of poor maternal lifestyle choices, innovative intervention strategies are needed that cater to the lifestyle of the mother and encourage support from the entire family.

Where Should We Go from Here?
Poor maternal lifestyle behavior leading to in utero exposure to an obesogenic fuel supply, rich in saturated fat and sugar, may alter hypothalamic regulatory centers that control appetite, food consumption and activity patterns thereby programming pediatric obesity. Of great concern are those behaviors that lead to excessive GWG. An increase in adiposity beyond the Institute of Medicine recommendations, in addition to having OW/OB parents, has been linked to early childhood overweight (Dubois and Girard, 2006; Wrottiak et al. 2008). Thus, strategies that reduce ‘risky’ lifestyle behaviors such as poor dietary choices leading to overconsumption and energy storage, lack of physical activity resulting in suboptimal energy expenditure or a combination thereof, warrant clinical intervention that educate those involved so they can reap the benefits of prevention before conception or at least during gestation. Recently, one controlled trial has had success in preventing excessive GWG and deterioration of glucose metabolism in obese women using dietary counseling sessions (Wolff et al. 2008). A few have successfully limited PPWR (Leermakers et al. 1998; O'Toole et al. 2003), whereas others displayed an inability to limit GWG in obese women (Gray-Donald et al. 2000; Polley et al. 2002; Olson et al. 2004; Kimmich et al. 2007). To date, a small number of trials have assessed the combined effects of nutrition and exercise on limiting GWG in a controlled fashion. Artal and colleagues were able to attenuate GWG in obese women with GDM (Artal et al. 2007) whereas others not were not as successful (Hui, 2006). The need for interactive, educational and activity-based interventions during pregnancy highlighting individualized ways in which nutrition and physical activity can be incorporated into daily life to improve child health outcomes are desperately needed. Promoting a balanced lifestyle during pregnancy and making changes to one’s habits during this time are not only ideal, but are supported by the recent call in the literature for well-designed, randomized controlled trials evaluating the effectiveness of lifestyle interventions during this period (Dodd et al. 2008; Gavard and Artal, 2008). Achieving this objective through an intensive family-centered approach that is individualized to meet the needs of each person, while adhering to an overall group treatment plan has potential for success as long as it is sustainable. Exercise participation has been deemed safe during pregnancy (Davies et al. 2003; Gavard and Artal, 2008), and resistance training has been shown to limit the need for insulin therapy in overweight women with GDM (Brankston et al. 2004), demonstrating clear clinical advantages. The benefits of this type of exercise delivered in a pregnancy-specific modality may prove beneficial in limiting GWG. Furthermore, greater nutrition knowledge has been linked to lower PPWR one year postpartum in a low income population (Nuss et al. 2007). Thus, the possibility exists that pregnancy-specific, individualized, family-centered lifestyle interventions focusing on nutrition and physical activity may have a beneficial effect on limiting GWG and PPWR, and in turn, limit the future presentation of pediatric obesity and its related sequelae.

By quantifying the needs and wants of pregnant women through prenatal lifestyle questionnaires and discussions in a clinical setting focused on nutrition and exercise, healthcare teams will be able to design and implement intervention strategies that aim to prevent the programming of pediatric obesity adding more weight to the statement.
that 'an ounce of prevention is worth much more than a pound of cure'.

Acknowledgements
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Disclosure
The authors report no conflicts of interest.

References


Preamble: Manuscript II

Following our review of the literature it became apparent that a suboptimal intrauterine milieu may compromise downstream offspring health. Mounting evidence was also available to suggest that excessive GWG may impair physiological function independent of obesity. In 2009, responding to evidence linking maternal obesity and GWG to childhood obesity, the Institute of Medicine (IOM) revised the GWG guidelines for pregnant women. However, it was unknown whether exceeding the updated recommendations that imposed an upper limit of GWG (i.e., 5-9 kg) for obese (i.e., BMI ≥ 30) women could predict large neonates as previous guidelines did not restrict GWG for this group of patients. Therefore, we hypothesized that both prepregnancy obesity and exceeding GWG guidelines would significantly increase the likelihood of having a large neonate and thus we undertook a population level analysis aimed to verify predictors of infant size in the Ottawa and Kingston birth cohort. The following article outlines maternal characteristics associated with fetal overgrowth and describes the clinical utility of the 2009 IOM guidelines to prevent poor fetal outcomes. It was our intent that the target audience for this manuscript be any health provider offering care to a pregnant population with an interest in halting the intergenerational cycle of obesity.
5.0 MANUSCRIPT II

Excessive gestational weight gain predicts large for gestational age neonates independent of maternal body mass index


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Z. Ferraro assisted with study conception, assisted with the data analysis, interpreted the data and drafted the manuscript. N. Barrowman assisted with data analysis, helped interpret the data, and critically reviewed the manuscript. D. Prud’homme helped interpret the data and approved the final version of the manuscript. M. Walker, S.W. Wen and M. Rodger lead the design of and received funding for establishment of the OaK birth cohort and approved the final version of the manuscript. K. Adamo assisted with study conception, helped interpret the data and critically reviewed the manuscript.
Excessive gestational weight gain predicts large for gestational age neonates independent of maternal body mass index


Objective: To determine the effects of maternal pre-pregnancy body mass index (BMI) and gestational weight gain (GWG) on large-for-gestational-age (LGA) birth weight (≥90th % Ile).

Methods: We examined 4321 mother-infant pairs from the Ottawa and Kingston (O&K) birth cohort. Multivariate logistic regression (controlling for gestational and maternal age, pre-pregnancy weight, parity, smoking) were performed and odds ratios (ORs) calculated.

Results: Prior to pregnancy, a total of 23.7% of women were overweight and 16.2% obese. Only 29.3% of women met GWG targets recommended by the Institute of Medicine (IOM), whereas 57.7% exceeded the guidelines. Adjusting for smoking, parity, age, maternal height, and achieving the IOM's recommended GWG, overweight (OR 1.99; 95% CI 1.17–3.37) or obese (OR 2.64; 95% CI 1.59–4.39) pre-pregnancy was associated with a higher rate of LGA compared to women with normal BMI. In the same model, exceeding GWG guidelines was associated with higher rates of LGA (OR 2.86; 95% CI 2.09–3.92), as was parity (OR 1.49; 95% CI 1.22–1.82). Smoking (OR 0.53; 95% CI 0.35–0.79) was associated with decreased rates of LGA. The adjusted association with LGA was also estimated for women who exceeded the GWG guidelines and were overweight (OR 3.59; 95% CI 2.68–4.95) or obese (OR 6.71; 95% CI 4.83–9.31). Conclusion: Pregadiv overweight or obesity and gaining in excess of the IOM 2009 GWG guidelines strongly increase a woman’s chance of having a larger baby. Lifestyle interventions that aim to optimize GWG by incorporating healthy eating and exercise strategies during pregnancy should be investigated to determine their effects on LGA neonates and down-stream child obesity.

Keywords: Gestational weight gain, maternal obesity, macrosomia, pediatric obesity

Introduction

Overweight and obesity affects 50% of women of reproductive age [1] and weight loss and maintenance is difficult for most [2]. This suggests that conceiving at a healthy body weight poses a challenge for the majority of women. Gestational weight gain (GWG) recommendations are often exceeded in those with high pre-pregnancy body mass index (BMI), given the narrow range of acceptable gain for higher BMI categories (Table I) [3,4]. Recent studies have demonstrated that exceeding GWG recommendations may increase the risk of downstream cardiometabolic complications in children [5]. Li et al. articulated some of the factors that contribute to the intergenerational cycle of obesity noting that maternal overweight, obesity, high birthweight (≥4000 g) and maternal weight gain during pregnancy (≥20.4 kg) are independently associated with the risk of childhood overweight and obesity, even after adjustments for multiple confounders [6]. Overall, given the available evidence we felt it was important to determine which modifiable risk factor (i.e. pre-pregnancy BMI or GWG) was most strongly associated with a neonate being large-for-gestational-age (LGA) in a regional cohort of Canadians.

Several studies [7–21] have examined various relationships between maternal pre-pregnancy weight and GWG on maternal and/or neonatal outcomes. While some suggest that GWG has a greater effect [10,12,14] others note that pre-pregnancy BMI plays a dominant role in the predisposition of being born large [9]. It has been suggested that GWG does not significantly impact infant birth weight in overweight and obese women [16,17,19] and that heavier women may deliver average to large-sized infants in the absence of weight gain or even loss [11,13,17,19]. Furthermore, not all studies have used the most recent GWG guidelines [10,12,14,22] and others have relied on self-reported BMI and weight gain data [14]. There have also been discrepancies when classifying infant birth weight, with some studies using an absolute cut-off for macrosomia (i.e. ≥ 4000 g) [10,12] and others [14,20] utilizing birth weight percentiles for gestational-age. Lastly, there is limited evidence [12] specifically addressing the effects of maternal weight gain on infant birth weight from an obesity prevention standpoint.

This study aims to determine whether maternal pre-pregnancy BMI or adherence to the 2009 GWG guidelines better predicts neonates born LGA using a cohort from a region of Canada. We hypothesized that being obese pre-pregnancy and exceeding the GWG guidelines would increase the likelihood of giving birth to larger babies.

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Material and methods

We performed a secondary analysis of the Ottawa and Kingston (OAK) Birth Cohort which recruited women between 12–20 weeks gestation during their prenatal visit at either the Ottawa Hospital or Kingston General Hospital. The current analysis included subjects from phases I and II of the OAK Birth Cohort, which ran from October 2002–April 2009 and is primarily Caucasian. Demographic and clinical data were collected by structured interview and chart review by the OAK study staff. Pre-pregnancy weight was self-reported and height was measured by the study nurse upon enrolment. Maternal weight at delivery was measured by study staff and GWG was calculated by subtracting pre-pregnancy weight from weight at delivery. Newborn weight was obtained by the study nurse immediately following delivery using a calibrated electronic balance scale and recorded to the nearest gram according to standard operating procedures at participating centres. Gestational age at delivery was determined by last menstrual period (LMP) or estimated date of confinement (EDC) from ultrasound and confirmed using crown-rump length (CRL) by ultrasonography. The Canadian Perinatal Surveillance System birth weight for gestational age classification charts were used as gender-specific population-based reference standards to determine small for gestational age (SGA), AGA and LGA as previously described by Kramer et al. [23]. Additional chart review or participant contact was performed if ambiguities or missing data were encountered. Statistical analysis was performed using SPSS version 16.0 for Windows (SPSS Inc., Chicago, IL) and R. [R Development Core Team (2009). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0. URL http://www.R-project.org]. Descriptive statistics and frequencies were used for the pre-pregnancy BMI categories with respect to the outcome variables of interest. To predict the likelihood of giving birth to a LGA neonate, we used multivariate logistic regression to independently assess the contribution of maternal pre-pregnancy BMI and GWG while controlling for maternal age and height, parity, and smoking status. Comparisons were made between those women who fell below, met or exceeded the GWG recommendations in each BMI category. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. Two-sided p values less than 0.05 were taken to be statistically significant. This study was approved by the Ottawa Hospital Research Ethics Board.

Results

The initial OAK cohort consisted of 7228 cases. We first removed cases that were ineligible: GWG >75 kg or <−25 kg (n = 18), gestational age >45 weeks (n = 3), gestational age <22 weeks (n = 72), multiple birth (i.e. twins) (n = 105), and then excluded cases with missing values: maternal weight at delivery (n = 2669), pre-pregnancy weight (n = 72), BMI (n = 12), the number of babies (n = 8), maternal age (n = 2), GTPAL (Gravida, term, pre-term, abortions, living children) status (n = 1), maternal smoking status (n = 2), alcohol use (n = 2), or neonate gender (n = 1). The remaining 4321 cases were included in our analysis. Subject characteristics are presented in Table II and a comparison of the distribution of included and excluded cases, based on eligibility criteria, is noted in Table III. Of the 4321 mother-infant pairs, 56.2% of women had normal pre-pregnancy BMI (18.5–24.9), while 39.9% were overweight or obese (Table IV). With respect to GWG guideline adherence, 78% of overweight and 72% of obese women exceeded the recommendations, compared to 47% and 27% of normal- and overweight women (Figure 1). Obese women gave birth to the greatest percentage of LGA neonates when compared to other pre-pregnancy BMI categories (Table V).

Results from the multivariable logistic regression analyses are summarized in Table VI. Independent of the amount of GWG, being classified as overweight pre-pregnancy and smoking during the index pregnancy were associated with a decreased likelihood of giving birth to a large baby when compared to mothers of normal weight who did not smoke. Conversely, being classified as overweight or obese based on pre-pregnancy BMI significantly increased the rate of LGA neonates. Furthermore, as parity increased so too did the chance of the child being born LGA. When compared to normal weight women who met the IOM guidelines, gaining in excess of the updated GWG recommendations was significantly associated with greater likelihood of birthing a LGA neonate. These effects were compounded when assessing the joint-association of being overweight or obese pre-pregnancy and gaining in excess of the recommendations. When compared to normal weight women who met the IOM guidelines, both overweight and obese women who exceeded the GWG recommendations had over three (OR 3.59; 95% CI 2.60–4.95) and six times (OR 6.71; 95% CI 4.83–9.31) the chance of giving birth to a large baby, respectively.

Table I. Gestational weight gain recommendations, by pre-pregnancy BMI.

<table>
<thead>
<tr>
<th>Classification</th>
<th>Mean (std deviation)</th>
<th>Mean (std deviation)</th>
<th>Mean (std deviation)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BMI (kg/m²)</td>
<td>Range (kg)</td>
<td>Range (lb)</td>
</tr>
<tr>
<td>Underweight</td>
<td>&lt;18.5</td>
<td>12.5–18</td>
<td>28–40</td>
</tr>
<tr>
<td>Normal</td>
<td>18.5–24.9</td>
<td>11.5–16</td>
<td>25–35</td>
</tr>
<tr>
<td>Overweight</td>
<td>25–29.9</td>
<td>7–11.5</td>
<td>15–25</td>
</tr>
<tr>
<td>Obese</td>
<td>&gt;30</td>
<td>5–9</td>
<td>11–20</td>
</tr>
</tbody>
</table>

Adapted with permission from weight gain during pregnancy: recommodating the guidelines (1).

Table II. Descriptive characteristics of mothers and infants, n = 4321.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean ± SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>30 ± 5.1</td>
<td>16–50</td>
</tr>
<tr>
<td>Pre-pregnancy BMI (kg/m²)</td>
<td>25 ± 5.6</td>
<td>15–61</td>
</tr>
<tr>
<td>Pre-pregnancy weight (kg)</td>
<td>68.2 ± 16.0</td>
<td>30–161</td>
</tr>
<tr>
<td>Gestational age (weeks from LMP)</td>
<td>39.2 ± 2.0</td>
<td>22–42</td>
</tr>
<tr>
<td>Maternal weight at delivery (kg)</td>
<td>84.2 ± 16.3</td>
<td>47–180</td>
</tr>
<tr>
<td>Infant birth weight (g)</td>
<td>3449.6 ± 576.8</td>
<td>260–5277</td>
</tr>
</tbody>
</table>

BMI, body mass index; LMP, last menstrual period; SD, standard deviation.

Table III. Comparison of the distribution of included and excluded cases based on study eligibility criteria.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Included</th>
<th>Excluded</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal weight at delivery</td>
<td>84.23 (16.35)</td>
<td>91.61 (22.01)</td>
<td>0.001</td>
</tr>
<tr>
<td>Pre-pregnancy weight</td>
<td>68.10 (15.96)</td>
<td>67.81 (20.65)</td>
<td>0.541</td>
</tr>
<tr>
<td>Gestational weight gain</td>
<td>16.13 (6.76)</td>
<td>16.42 (6.25)</td>
<td>0.808</td>
</tr>
</tbody>
</table>

Table IV. Pre-pregnancy BMI distribution.

<table>
<thead>
<tr>
<th>BMI category</th>
<th>n</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight, &lt;18.5</td>
<td>169</td>
<td>3.9</td>
</tr>
<tr>
<td>Normal, 18.5–24.9</td>
<td>2428</td>
<td>56.2</td>
</tr>
<tr>
<td>Overweight, 25–29.9</td>
<td>1025</td>
<td>23.7</td>
</tr>
<tr>
<td>Obese, &gt;30</td>
<td>699</td>
<td>16.2</td>
</tr>
<tr>
<td>Total</td>
<td>4321</td>
<td>100.0</td>
</tr>
</tbody>
</table>

BMI, body mass index (kg/m²).
Table V. Percentage of offering in each category of neonatal size for gestational age by pre-pregnancy BMI category.

<table>
<thead>
<tr>
<th>Neonatal size for gestational age</th>
<th>Pre-pregnancy BMI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Underweight, &lt;18.5</td>
</tr>
<tr>
<td>SGA</td>
<td>21</td>
</tr>
<tr>
<td>AGA</td>
<td>76</td>
</tr>
<tr>
<td>LGA</td>
<td>3</td>
</tr>
</tbody>
</table>

AGA, appropriate for gestational age; BMI, body mass index (kg/m²); LGA, large for gestational age; SGA, small for gestational age.

Table VI. Logistic regression analyses showing the independent likelihood of having a large baby based on selected maternal factors.

<table>
<thead>
<tr>
<th>Odd ratio</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight, BMI &lt; 18.5</td>
<td>0.55</td>
<td>0.17–1.78</td>
</tr>
<tr>
<td>Normal, BMI 18.5–24.9</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Overweight, BMI 25–29.9</td>
<td>1.99</td>
<td>1.17–3.37</td>
</tr>
<tr>
<td>Obese, BMI ≥30</td>
<td>2.64</td>
<td>1.59–4.39 &lt;0.001</td>
</tr>
<tr>
<td>Parity</td>
<td>1.49</td>
<td>1.22–1.82 &lt;0.001</td>
</tr>
<tr>
<td>Age</td>
<td>1.02</td>
<td>1.00–1.04 0.13</td>
</tr>
<tr>
<td>Maternal Height</td>
<td>1.54 (per 10 cm)</td>
<td>1.34–1.77 &lt;0.001</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.53</td>
<td>0.35–0.79 0.002</td>
</tr>
<tr>
<td>Exceed IOM GWG Guidelines</td>
<td>2.86</td>
<td>2.09–3.92 &lt;0.001</td>
</tr>
</tbody>
</table>

IOM, Institute of Medicine.

Discussion

We determined that maternal pre-pregnancy overweight, obesity and gaining in excess of the 2009 GWG guidelines independently increase a woman’s chance of having a larger baby. This confirms previous work suggesting that excessive GWG plays a strong and independent role in predisposing women to birthing heavier neonates [12]. By using the most recent IOM evidence-based recommendations for GWG, we were able to assess the validity of the guidelines as a predictive tool for LGA and suggest that these recommendations do offer clinical utility in prenatal care with a focus on obesity prevention for mom and baby. This finding has far-reaching public health implications knowing that pregnancy is a critical period of body weight regulation where natural fluctuations in weight are common and frequently large.

To our knowledge, the strength of the joint-association we observed between pre-pregnancy obesity and excessive GWG on LGA births in accordance with the 2009 IOM guidelines has not been reported elsewhere providing a unique contribution in the context of accelerated fetal growth and potentially obesity prevention. We speculate that the strength of our odds ratios differ than those previously published given that it was our a priori intent to classify weight-for-gestational age using a validated, population-based Canadian reference for birth weight for gestational age. Using normative data for our outcome of interest (i.e. LGA neonates) coupled with our use of the 2009 IOM GWG guidelines that impose an upper limit of GWG for obese women (i.e. 9kg) may have contributed to the strength of the joint-association we present in this paper. Thus, our design and analysis plan may have lead to higher odds ratios than previously described.

Using our sample population, we have validated previous findings that found avoidance of higher amounts of GWG, in heavier women, to be advantageous for optimal neonatal birth weights [10,12,14]. Nohr and colleagues assessed the combined association of pre-pregnancy BMI and GWG on both maternal and fetal outcomes and concluded that overweight, obesity and GWG of >16kg resulted in an increased risk of delivering LGA neonates [14]. While our findings support these results we aligned our GWG categories with those of the IOM guidelines to confirm two potential modifiable determinants of infant size at birth (i.e. pre-pregnancy BMI and GWG). We suggest that the guideline recommendations offer tremendous clinical value for primary care as women and providers can track and monitor weight status throughout pregnancy to reduce the likelihood of a large baby. Specifically, if altering weight pre-pregnancy is not a feasible option, being aware of another modifiable factor, GWG, that may promote down-stream infant health could provide motivation for women to gain weight within the limits. This notion is supported by others [14] who found that the overall contribution of GWG was modest except for infant size at birth and postpartum weight retention. This reinforces the need to optimize GWG for all women as this determinant contributes to postpartum weight retention and infant birth weight, known contributors to the intergenerational obesity cycle.

Furthermore, Ludwig and Currie [12] noted a consistent genetic-independent association between GWG and birth weight using a large within-family comparison, observing a 2.26 (95% CI 2.09–2.44) greater risk of giving birth to an infant weighing >4000g when gaining more than 24kg compared to women who gained 8–10kg. Making a direct comparison with these findings poses a challenge as their reference group for GWG (i.e. 8–10kg range) falls in between the IOM recommendations for overweight and obese women with their most pronounced effects demonstrated when gains exceeded 24kg which is above the recommended
GWG for women who are underweight pre-pregnancy. Crane et al. [10] reported similar results for birth weight <2400 g in women who gained weight in excess of the 1990 IOM recommendations had an increased odds of birth to a large baby. However, our findings are slightly different than Choi et al. [9] who suggest that pre-pregnancy overweight and obesity has a stronger association with LGA whereas GWG had no effect. In their study, GWG did not have a positive relationship with LGA in overweight and obese women. This difference may be partially explained by ethnic differences in GWG given their predominately Asian cohort as the amount of body fat for a given BMI in these populations tends to be higher when compared to individuals of European decent [24]. While they attempted to correct for differences in weight accretion and distribution by classifying women according to the suggested Asian BMI cut-offs for overweight (≥23) and obesity (≥25) [24], they used the GWG guidelines which have not been validated in Asian cohorts leading us to consider that this may contribute to the observed differences. Others have also noted that GWG has a greater effect based on BMI weight for overweight and obese women [16,17,19]. In a recent review of obesity and pregnancy, Melzer and Schütz [25], conclude that heavier women may deliver average- to large-sized infants with virtually no GWG or even weight loss [11,13,17,19]. This suggests that mechanisms independent of GWG prevail in some women thereby influencing higher birth weights and leads us to speculate that genetic and epigenetic contributions to growth factor and hormone response may mediate this relationship [26,27]. Recently, it was reported that fetal exposure to high maternal glucose in the absence of pre-existing or gestational diabetes, may influence offspring obesity at age 3, independent of maternal pre-pregnancy BMI [28]. Whether obesity presents as a result of a child's unique susceptibility, maternal influence or combination of both, the effects of pre-pregnancy BMI and excessive GWG on infant size at birth cannot be overlooked as both determinants may affect infant health and development [29]. Fewer women in our study were overweight or obese at pre-pregnancy compared to Canadian national averages [29]. We also observed higher rates of LGA neonates with increasing maternal height, a relationship previously described [21]. Finally, we were able to confirm extensive evidence in support of the growth restrictive effects of smoking during pregnancy, a behaviour strongly linked to higher incidence of SGA neonates [30,31].

Our study is not without limitations. We cannot infer that the observed associations are causal in nature, are also aware our primarily Caucasian patient population may not be representative of all ethnic groups, and that our inability to control for socioeconomic status, education level or marital status may have influenced our outcomes. With respect to study outcomes that differed from ours, we suggest that methodological differences between directly measured and self-reported values (e.g. GWG) may have led to the discrepancy. Although we acknowledge that missing data for maternal weight at delivery may increase the propensity for bias within our subsample, given the well documented notion that pregnancy-related complications are more common to maternal obesity than women of normal BMI [32] it is possible that obesity-related complications in these precluded documentation. Thus, if mother's struggling with obesity required immediate clinical attention, we speculate that any bias that exists may potentially strengthen our observations. It is well understood that individuals under-report body weight when compared to direct measures [33] although maternal recall of pregnancy-related events tends to be more reproducible and valid [34]. To our credit, we have also considered some of the main pregnancy-related factors targeted in a complex system affecting birth weight, including maternal age and parity. While we acknowledge that mom and baby share similar obesity-related genes and that this may affect the underlying predisposition to macrosomia and excessive GWG, our results are in agreement with recent work that accounted for this using a within-family comparison [12]. In consideration, the present findings reinforce the need to encourage individualized GWG targets that balance the demands of adequate fetal growth and development with the risks of excessive pregnancy weight gain, complicated deliveries (e.g. macrosomia) and excess postpartum weight retention.

Having an awareness of the joint-effects that higher maternal pre-pregnancy BMI and excessive GWG have on the predisposition to giving birth to a LGA baby is of utmost importance for prevention and management of obesity in primary care. Identifying those at greatest risk may facilitate appropriate preventive triage and allow for the introduction of strategies tailored to individual needs (i.e. target therapies based on BMI, GWG or both for those struggling with weight in the family planning stages). This may lead to more favourable maternal outcomes postpartum and benefit downstream child health. Encouraging healthy eating and regular physical activity during pregnancy may optimize fetal size at birth and promote adaptive benefits in the child [35,36]. For care provision during the early years of the child’s life, utilizing the information gained from a thorough obstetrical history (i.e. being aware of birth weight and maternal GWG) may promote a more focussed, specialized care and healthful developmental trajectory with virtually no increase in time or resources.

We have shown that the majority of women in our birth cohort population entered pregnancy at an unhealthy weight and gained in excess of recommendations during gestation. At any weight, excessive GWG has a significant effect on the likelihood that their child will be born LGA, and research [6] has demonstrated that size at birth contributes to obesity development downstream. Knowing that modification of pre-pregnancy BMI may be a challenge for many, focusing on GWG may be advantageous for mothers who aim to limit their weight retention postpartum as well as optimize infant growth trajectory in the early years. Although this hypothesis remains to be tested, the use of the GWG guidelines may have tremendous utility in clinical practice and serve as a monitoring tool for providers and pregnant women. As a result, adherence to the recommendations may attenuate the incidence of LGA births and in turn potentially optimize tracking of excess weight from early childhood into adulthood.

Declaration of interest: Funding support was received from the Ministry of Research and Innovation- Early Researcher Award (KA) to help support the doctoral training of ZMF who is also supported by an Ontario Graduate Scholarship. Dr. Mark Walker is a CIHR New Investigator. Dr. Shi Wu Wen is a recipient of Ontario Women’s Health Council-CIHR Mid-Career Salary Award. An abstract of this paper was presented by ZMF at the 2nd National Obesity Summit in Montreal, Quebec on April 28, 2011.

References


Modifiable determinants of fetal birth size

Preamble: Manuscript III

In our epidemiological analysis of the Ottawa and Kingston birth cohort we identified strong independent contributors to fetal overgrowth including obesity and/or excessive GWG in reference to the updated recommendations. This finding has significant clinical relevance as it provides support to suggest that mothers who adhere to GWG recommendations can decrease their own postpartum weight retention and optimize the birth weight of their child which may promote a healthy growth trajectory. However, the mechanistic evidence attempting to explain the observed associations between maternal phenotype and neonatal size is limited. Therefore, we hypothesized that the growth-enhancing components of the IGF system would be expressed to a greater extent and the growth inhibiting peptides down-regulated in pregnancy complicated with obesity. To verify our hypothesis we designed a series of small molecular studies to help expand the knowledge base in maternal-fetal medicine by examining the influence of obesity and excessive GWG on IGF axis protein expression patterns in mom and baby.
Characterization of the insulin-like growth factor axis in term pregnancies complicated by maternal obesity

Z.M. Ferraro, Q. Qiu, A. Gruslin, K.B. Adamo

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Z. Ferraro conceived the study, recruited the patients, collected the samples, ran the experiments, analysed the data and lead manuscript drafting. Q. Qiu supervised the experiments and assisted with data analysis. A. Gruslin assisted with study design, helped interpret the data and critically reviewed the manuscript. K. Adamo assisted with study design, data interpretation and critical review of the manuscript.
Characterization of the insulin-like growth factor axis in term pregnancies complicated by maternal obesity

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Keywords: obesity, insulin-like growth factor, insulin-like growth factor binding protein, pregnancy

Running title: IGF axis in obese pregnancy
ABSTRACT

Study question: To determine if maternal obesity affects insulin-like growth factor (IGF) axis protein expression patterns in maternal and cord blood.


What is known and what this paper adds: The IGF axis plays a critical role in fetal growth and development. Maternal obesity compromises IGF axis protein expression in fetal circulation and aligns with epidemiological studies suggesting that maternal obesity has an independent effect on fetal growth signals during in utero development.

Design: Cross-sectional case control study involving 12 lean (BMI 18.5-24.9 kg/m²) and 12 obese (BMI ≥30 kg/m²) women and their neonates at term. At study completion, IGF axis protein expression and hormone concentrations in both maternal and cord blood were examined.

Participants and Setting: We obtained fasting serum samples from cases and controls matched for age, duration of gestation, mode of delivery, parity and glucose tolerance prior to, and the corresponding umbilical cord blood, immediately following elective caesarean section.

Main results and the role of chance: Between group comparisons were made and revealed elevated maternal insulin (p=0.03) and leptin (p<0.01) concentrations in obese gravidas. After adjustment, maternal HOMA-IR score was positively correlated with both maternal BMI and leptin levels (p<0.01). Umbilical cord blood levels of IGFBP-3 were directly related
to fetal-placental weight ratio (p<0.01) and showed an inverse trend to maternal HOMA-IR (p=0.03). However, in cord serum from obese mothers IGFBP-4 expression was attenuated when compared to controls (p<0.05).

**Bias, confounding and other reasons for caution:** None to report

**Generalizability to other populations:** Our results provide preliminary evidence to support the applicability of our findings to other ethnic groups when pregnancy is complicated by obesity.

**Study funding/competing interests:** This work was supported by the University of Ottawa, Faculty of Health Sciences/Children’s Hospital of Eastern Ontario Research Partnership Grant awarded to KBA and ZMF. The authors have no conflicts of interest to declare.
INTRODUCTION

The insulin-like growth factor (IGF) family of ligands and binding proteins (IGFBP) are anabolic hormones involved in a diverse set of actions controlling metabolic function, cell growth and differentiation (Chiesa et al., 2008; Monaghan et al., 2004). The IGF system is composed of two growth factors, IGF-I and IGF-II, six binding proteins; IGFBP-1-6, and the IGF type 1 and 2 receptors (IGF-1R and IGF-2R). IGF-I and –II form ternary complexes with an acid labile subunit and their binding proteins within the circulation and are expressed in adipose (Wabitsch et al., 2000) placental, fetal and maternal tissues (Han et al., 1996).

Despite its synthesis in nearly every mammalian cell and ability to act in an auto-, para- and endocrine fashion, the dominant source of IGF in human circulation is hepatic (Juul, 2003). The formation of the IGF ternary complex and subsequent proteolytic IGFBP cleavage regulates the amount of free or bioavailable IGF able to bind to its receptor(s). By binding to and activating IGF-1R via autophosphorylation of tyrosine residues in the intracellular β-subunits, the IGFs activate downstream signalling pathways within the targeted system (Jones and Clemmons, 1995). Of the binding proteins, IGFBP-3 is the most ubiquitous in adult human circulation binding 95% of the total IGFs (Holly and Perks, 2006) with the remaining IGFs binding to IGFBP-1 through IGFBP-6 regulating bioactivity (Frystyk et al., 2002; Jones and Clemmons, 1995).

The maternal IGF system plays a vital role in fetal growth regulation via stimulation of extravillous trophoblast migration/invasion and facilitation of nutrient exchange through
the promotion of growth and development of the placenta (Qiu et al., 2005). Elegant experimental animal models and observations from rare human genetic variants have highlighted the growth promoting potential of the IGF system (Dunger et al., 2006). When compared to wild type, igf1 knockout mice exhibit reduced birth weight, remain at a lower weight during the postnatal period and continue to weigh less throughout life (Baker et al., 1993). Additional evidence for the pivotal role of the IGF system in optimal development comes from humans born with defects of the igf1 gene who are born small (Bonapace et al., 2003; Woods et al., 1996) and the resulting fetal overgrowth when igf2 is over-expressed in Beckwith-Wiedemann syndrome (Morison et al., 1996). Observational data from population studies also report positive relationships between infant size at birth and cord blood levels of IGF-I, IGF-II and insulin (Ong et al., 2002) suggesting that up-regulation of IGFs may accompany fetal overgrowth. Maternal obesity is strongly associated with an increased risk of delivering a large-for-gestational age neonate (Ferraro et al., 2011) and impaired maternal glycemic control is associated with increased neonatal adiposity, a relationship mediated by fetal insulin production in response to a hyperglycaemic environment in utero (Metzger et al., 2008).

The IGF system may be a candidate pathway involved in nutrient flux through the placenta during pregnancy complicated by obesity. Positive energy balance and subsequent aberrant fetal hormone response may contribute to heavier neonates or altered body composition. For instance, fetal adipogenesis peaks in late gestation (Mandrup and Lane, 1997), with greater than 90% of fetal body fat accrued in the third trimester (Widdowson, 1974). In obese women, bioactive IGF-I is directly associated with IGFBP-3 concentration in blood.
(Frystyk et al., 2009) and IGF-I stimulates the differentiation of preadipocytes through modulation of the IGFBPs (Boney et al., 1994). At term, the pregnancy-associated rise in maternal IGFBP-3 serum levels correlate positively with birthweight (Giudice et al., 1995; Osorio et al., 1996), while the increase in free IGF-I during pregnancy is thought to be mediated by IGFBP-3 proteolysis (Hasegawa et al., 1995). Traditionally, IGFBP-1 acts to inhibit IGF function and is inversely related to insulin levels. In obesity, low serum concentrations of IGFBP-1 may regulate in vivo IGF-I bioavailability based on fuel supply (Frystyk et al., 2009). Lastly, although, the exact function of IGFBP-4 is not known, it may play a role in stem cell differentiation into muscle and fat and be modified in both pregnancy and obesity (Du et al., 2010).

Therefore, we aimed to examine protein expression of vital regulatory components of the IGF system in control and obese mothers and their term neonates. Specifically we aimed to determine if IGF-I, IGF-II, and IGFBP-1,-3 and -4 differed between lean and obese mother-infant dyads. Given that obese women generally give birth to larger infants we hypothesized that the growth-enhancing components of the IGF system would be expressed to a greater extent and the growth inhibiting proteins down-regulated in pregnancies complicated with obesity.

**METHODS AND PROCEDURES**

**Participants.** Patients were recruited from the Ottawa Hospital General Campus, Maternal Fetal Medicine and Obstetrics clinics after the study was approved by the Ottawa Hospital
Research Ethics Board. Informed consent was obtained from all participants. Women who smoked, those with type 1, type 2 or gestational diabetes or any other medical complication such as hypertension, cardiac, vascular, autoimmune diseases and thrombophilias and a past history of fetal loss, fetal growth restriction or hypertensive diseases of pregnancy were excluded from either group such that we can examine the influence of obesity alone. Women carrying fetuses with congenital or chromosomal anomalies were also excluded. All women were classified as glucose tolerant following their prenatal glucose challenge test.

Sample Collection. Fasting blood samples were obtained via peripheral venipuncture from 12 normal weight pregnant women with pregravid body mass index (BMI) 18.5-24.9 kg/m$^2$ and 12 obese pregnant women with pregravid BMI ≥30 kg/m$^2$ immediately prior to elective caesarean section to avoid any potential influence of labour. Corresponding venous serum was obtained from the umbilical cord following removal of the placenta as clinically indicated. The placenta was then weighed to the nearest gram using a calibrated electronic scale (Olympic Smart Scale, Natus Medical Inc. Seattle, WA, USA). Following blood draws, the samples remained at room temperature for 30 minutes to allow for clotting and were subsequently spun at 1700xG for 15 minutes at 4°C. The supernatant was removed, aliquoted into separate cryovials and frozen at -80°C for batch analysis. Maternal and fetal clinical variables were collected through a chart review upon study completion.

Determination of IGF-II via Western Blot. The presence of IGF-II in human circulation was determined as previously described by Qiu et al. (Qiu et al., 2007). Briefly, aliquots of 0.5 µl of sera were diluted with 1X SDS non-reducing sample buffer (62.5 mM Tris-HCl, pH 6.8, 2%
SDS, 10% glycerol, 0.01% Bromophenol Blue), and subjected to electrophoresis with 10% tricine SDS-PAGE. The separated proteins were blotted onto a nitrocellulose membrane, treated with an antibody extender solution (Pierce, Rockford, IL), blocked with 5% dehydrated nonfat milk in TBS-T (Tris-Buffered Saline, pH 7 with 0.3% Tween 20), and subsequently probed with mouse anti- IGF-II (1-67) monoclonal antibody (clone S1F2; Upstate Biotechnology, Lake Placid, NY) and HRP-conjugated anti-mouse IgG. Bands of IGF-II variants were visualized with ECL, and their relative contents quantified using densitometry with Alpha Ease FCTM software (Alpha Innotech, San Leandro, CA). This assay can detect a quantity of recombinant human IGF-II as low as 6.25 pg (Qiu et al., 2007).

**Determination of IGF-I and IGFBP-4 via Western Blot.** The presence of IGF-I and IGFBP-4 in human and cord serum was determined as described above with the following modifications. Aliquots of serum (0.5µl) were resolved by 15% glycine SDS-PAGE under non-reducing conditions and electrotransferred to nitrocellulose membranes. The membranes were blocked for 1 hour in 5% milk, immunoblotted with highly specific antibodies for IGF-I (#ab9572, Abcam, CA, USA) and IGFBP-4 (#sc6005, Santa Cruz Biotech, CA, USA) and quantified as described above.

**Determination of IGFBP-1 and -3 via Western-Ligand Blot.** IGFBPs were determined using aliquots of 0.5µl of sera subjected to electrophoresis, transfer and antibody extend solution treatment and blocking agents as described above for the determination of IGF-I and –II. The membranes were subsequently probed with biotinylated IGF-II (GroPep Ltd., Adelaide Australia, 50ng/ml prepared with TBS-T) at 4˚C overnight, followed by antibody highly specific to IGFBP-1 (#sc55474, Santa Cruz Biotech, CA, USA) and IGFBP-3 (#sc135947,
Santa Cruz Biotech, CA, USA) and finally by streptavidin-HRP (GE Healthcare, Buckinghamshire, UK, 1h at RT). Bands of IGFBPs were visualized, after being independently probed on separate days with highly specific antibodies targeting solely the protein of interest, with ECL and their relative contents were quantified via densitometry with Alpha Ease FCTM software as described above.

**Biochemical analyses of glucose, insulin, and leptin.** Glucose was measured by oxidase enzymatic methodology using the Cholestech LDX analyzer as described by the manufacturer (Hayward, CA, USA). Circulating insulin and leptin were analyzed in duplicate by ELISA using Luminex xMAP technology for the human metabolic hormone magnetic bead panel assay as described by the manufacturer (Millipore- Billerica, USA). The intra- and inter-assay CVs were 3% and 6% for insulin and 3% and 4% for leptin.

**Computation of outcome variables.** GWG was calculated from anthropometric values obtained from the medical record using the difference of directly measured maternal weight at last prenatal visit minus directly measured prepregnancy weight. Homeostasis Model of Assessment – Insulin Resistance (HOMA-IR) was calculated as fasting glucose (mmol/L) x fasting insulin (pmol/L) /22.5 and subsequently log-transformed (Vogeser et al., 2007). Fetal-placental weight ratio was calculated as birth weight (g)/placenta weight (g).

**Statistical Analysis.** SPSS Statistics software version 19 was used for outcome analysis (IBM, USA). Protein band optical densities were log-transformed and presented as the mean ± standard deviation (SD) percent above internal control (IC). The IC used was a pooled sample consisting of equal volumes of maternal and fetal sera taken from each
subject in the study. All other outcome variables are presented as the mean ± SD unless otherwise specified. A non-parametric two-tailed independent samples Kruskal-Wallis test was used to make conservative comparisons between groups for all patient characteristics as well as maternal-fetal levels of glucose, insulin and leptin. Spearman correlations were used to examine relationships between maternal and fetal characteristics and outcomes of interest. Significance was set to p≤0.05. Adjustments for multiple comparisons were made if necessary and presented within.

RESULTS

Patient characteristics

Twelve obese (BMI ≥ 30 kg/m²) and 12 control (BMI 18.5-24.9 kg/m²) gravidas of comparable age and height were studied. As designed, mean BMI and pre-pregnancy weight differed between groups. Absolute amount of gestational weight gain (GWG) showed a trend towards difference between the groups as the controls tended to gain more overall. Fetal-placental weight ratio was significantly greater in the obese group compared to control (Table I). However, birthweight, gestational age at delivery, prenatal glucose screen and placenta weight did not differ between groups, yet a direct relationship was observed between BMI and HOMA-IR (Table III and Figure IIA).

IGF and IGFBP
Expression of IGFBP-4 was reduced in cord blood from the obese sample (Figure I).

Maternal expression of IGF-I, -II, IGFBP-1,-3, and -4 and cord blood expression of IGF-I, -II, IGFBP-1 and -3 were similar between groups (p>0.05, Figure III). HOMA-IR and cord blood IGFBP-3 expression showed an inverse trend, but did not remain significant following Bonferroni adjustment (Table III and Figure IIB). However, cord blood IGFBP-3 expression and fetal-placental weight ratio were directly related (Table III and Figure IID).

**Glucose, insulin and leptin**

Maternal glucose and cord levels of insulin, glucose and leptin did not differ between groups, although both maternal leptin and insulin were elevated in obesity (Table II). Further, maternal leptin was directly related to HOMA-IR (Table III and Figure IIC) and maternal BMI (Table III).

**DISCUSSION**

Maternal obesity contributes to adverse fetal outcomes including the development of insulin resistance *in utero* (Catalano *et al.*, 2009) and large-for-gestational age (Ferraro *et al.*, 2011). The present study illustrates, for the first time, a comprehensive description of the IGF axis in mothers and newborns in the context of maternal obesity. Our data reveals a difference compared to controls in the IGF axis, particularly in the down-regulation of IGFBP-4 cord blood expression in normoglycemic obese pregnancy. Although we are unable to make causal inferences due to the nature of our study and relatively small sample size, the metabolic dysregulation of growth controlling factors we present aligns with previous
observations of fetal insulin resistance in utero and greater accumulation of adipose in offspring of the obese (Catalano et al., 2003; Catalano, 2003).

It is possible that attenuated expression of IGFBP-4 in cord blood from obese mothers may be in part due to proteolytic activity promoting IGF bioavailability which may alter regulatory processes involved with fetal growth and development. Whether increased binding protein cleavage exists in cord blood and contributes to the bioactivity of IGF-I in maternal obesity is not known. It is well documented, however, that the IGFBPs serve many functions including prolonging the half-life of, and providing a circulating storage reserve for, IGFs. They also have higher affinity for the IGFs than the IGF receptors (Jones and Clemmons, 1995). As such, IGFBPs have traditionally been described for their ability to act as IGF inhibitors preventing interaction with the receptors and reducing potential for excessive growth in response to the maternal milieu. Conversely, while IGFBP-4 and IGF-II are co-expressed in early development, an IGFBP-4 knockout mouse study showed that IGFBP-4 can be both a positive and negative regulator of IGF activity in vivo identifying a dual role for this peptide (Ning et al., 2008). Nonetheless, in the context of positive energy balance and obesity, the inhibitory role of IGFBP-4 in IGF-regulated growth, deserves investigation as a protein not necessarily promoting excessive growth, but potentially failing to control optimal growth. This may be related to the fact that obesity is a chronic low-grade inflammatory state that has been shown to, for example, inhibit fetal stem cell differentiation in myocytes, while promoting adipogenesis (Du et al., 2010). Moreover, experimental mouse models examining myogenesis show that, when present in the
extracellular environment, the proinflammatory cytokines tumor necrosis factor-alpha and Interferon-gamma can alter the bioavailability of IGF-I by inhibiting IGFBP-4 expression and myogenic activity (Wieteska-Skrzeczynska et al., 2011). With respect to the growth inhibitory capacity of IGFBP-4, recent evidence suggests that in lung adenocarcinoma cells, epigenetic silencing of IGFBP-4 may also disrupt IGFBP-4-mediated growth inhibition (Sato et al., 2011). Epigenetic modifications during in utero development have also recently been identified as potential mechanisms promoting intergenerational transmission of obesity (Gluckman and Hanson, 2008). Collectively, these findings propose that aberrant IGFBP-4 expression, potentially mediated through altered pregnancy-associated plasma protein-A (PAPPA) proteolytic activity may be implicated in failure to control optimal growth in the context of maternal obesity. It is important to note, however, that we were unable to directly observe potential cleavage products in the IGFBP-4 blots presented in the current study as the antibody used solely detected intact forms of IGFBP-4 thereby making visualization of potential proteolytic fragments impossible. Future studies should measure PAPPA expression in maternal and fetal blood as well as in placental tissue. Thus, if maternal obesity were to alter proteolytic cleavage of IGFBP-4 through epigenetic or inflammatory processes and result in attenuated expression of a regulatory peptide, this mechanism may be implicated in fetal growth abnormalities. For instance, although fetal birth weights did not differ between groups, we cannot overlook the possibility that perturbations in the IGF axis may alter neonatal body composition favouring increased fat mass; an effect thoroughly documented in offspring of the obese (Catalano et al., 2009).
Although it remains to be established whether post-translational modification of IGFBP-4 (e.g., phosphorylation and proteolysis) increases bioavailability of IGF in cases of maternal obesity, proteolytic cleavage of the other IGFBPs \textit{in vitro} has been documented to increase IGF bioavailability (Forbes \textit{et al.}, 2008; Forbes and Westwood, 2008). For example, PAPPA, produced by human fibroblasts, enhances IGF bioactivity \textit{in vitro} by proteolytic degradation of IGFBP-4 in pregnancy serum (Byun \textit{et al.}, 2001). This observation may offer insight to the difference we observed in IGFBP-4 expression in cord blood from maternal obesity. In fact, overexpression of a protease-resistant form of IGFBP-4 inhibits the ability of IGF-I to stimulate normal smooth muscle cell growth in mice and pigs (Nichols \textit{et al.}, 2007) demonstrating a cleavage-dependent effect necessary for IGF bioactivity. Given that no clinical pathologies (e.g. GDM, pre-eclampsia) are overtly evident in our patient population, the reduction of inhibitory IGFBP-4 observed in cord blood from obese mothers, a finding not matched in maternal circulation, suggests the involvement of the placenta. Such adaptations may act in an obesity-dependent manner and augment fetal nutrient flux in this population; a notion supported by recent evidence identifying placental mTOR as an intracellular mediator linking growth factor and hormone signalling to maternal nutrient availability and fetal growth (Roos \textit{et al.}, 2009). Overall, our findings lead us to suggest that sub-clinical perturbations throughout pregnancy in maternal-fetal glucoregulatory capacity may be one contributing factor altering the developmental program of the child through the IGF axis.
Currently, examinations of IGF protein expression patterns in maternal obesity and insulin resistance are lacking and the regulatory mechanisms affecting IGFBP expression are not completely understood. While there are many unknowns regarding the precise function of the IGF axis (Murphy, 1998), the dual ability of the IGFBPs to inhibit and stimulate the effects of IGF, or act independently of IGF, is a subject of ongoing research. In the present study we confirm that maternal BMI and leptin levels positively relate to HOMA-IR, a marker of maternal insulin resistance previously been linked to enhanced fetal growth (Yajnik et al., 2003). Although failing to reach statistical significance in the present study after adjustment for multiple comparisons, both cord insulin and leptin levels have been identified as mediators in the direct relationship between higher birthweight, neonatal adiposity and insulin resistance in utero (Catalano et al., 2009;Sewell et al., 2006). We also show an inverse trend between cord expression of IGFBP-3 and maternal HOMA-IR. In our study, no women met the clinical diagnostic criteria for impaired glucose tolerance. As such, it is possible that sub-clinical deterioration of glycemic control may be in part regulated by the IGFBPs attempt to normalize growth under these conditions. Although we observed a non-significant trend between attenuated expression of cord IGFBP-3 with maternal insulin resistance, a larger sample size may validate this finding. Interestingly, if such a significant correlation existed one could speculate that it may be related to a placenta-derived adaptive response to increase bioavailable IGF delivery to peripheral tissues in the maternal and fetal compartments with increasing peripheral insulin resistance and deteriorating glucose homeostasis. In fact, Heald and colleagues demonstrated that higher circulating levels of IGFBP-3 are inversely related with insulin sensitivity (Heald et al., 2003). Such an
adaptation may help explain enhanced fetal growth characteristic of maternal glucose intolerance (Yogev and Visser, 2009). With respect to fetal-placental weight ratio, a marker of placenta efficiency (Myatt, 2006), a further role of IGFBP-3 as a growth regulator emerges. Here we show a direct relationship between IGFBP-3 and placental efficiency. Whether this is a protective mechanism, guarding against excessive growth, is unknown. Collectively, aberrant regulation of IGFBPs in the context of obesity may influence fetal development and be related to maternal-fetal glycemic control, placental metabolism and substrate regulation.

In the present investigation we did not find group differences between IGF-I, -II, IGFBP-1, and -3 expression patterns. However, given the complexity of the IGF axis, variation in proteolytic processing and difficulty measuring bioactive peptides, we cannot rule of the possibility that in vivo IGF bioactivity during pregnancy may differ between groups of free living humans. However, the similarities between obese and control in our study suggest that the growth-potentiating effects of maternal obesity on fetal development may be attenuated as an evolutionary conserved mechanism protecting against excessive fetal growth which the postnatal environment may not support. In fact, women in the obese group did not present with any adipose-related co-morbidities such as Type-2 diabetes or hypertension, were considered metabolically healthy and not at increased health risk solely based on BMI (Sharma and Kushner, 2009; Sharma and Padwal, 2010); an effect which in theory may have precluded differences in IGF axis perturbation in our study. However,
whether differences in IGF axis protein expression exist in more severe cases of obesity remains to be established.

The limitations of our study include the cross-sectional design, relatively small sample size and inability to control for maternal dietary intake and physical activity patterns. However, we present a novel finding identified with validated methodology, while controlling for the acute effects of postprandial metabolism as all women were fasted for at least 12 hours. Through this design, we also attempted to control for diurnal variation in IGF metabolism given that all blood was drawn at the same time of day (i.e., the morning upon arrival to hospital admitting). Further, other than obesity as defined by BMI, our study population was homogenous in nature as all women were normoglycemic as defined by clinical standards. Lastly, in an attempt to avoid a confounding effect of mode of delivery on cord blood IGF profile all women in our study underwent elective caesarean section. Future studies are needed to confirm our findings using a larger sample size to eliminate the possibility of bias.

Our findings align with epidemiological data suggesting that maternal obesity has an independent effect on fetal growth signals during in utero development. Although it appears that protective mechanisms attempt to offset adiposity-related impairments in IGF axis function, this study suggests that small deviations in IGFBP-regulated IGF bioavailability, arising from maternal obesity, may influence control of cellular anabolism in
fetal circulation. Overall, maternal obesity may not promote excessive fetal growth, however may negatively affect control of growth inhibiting peptides, thus effecting optimal fetal growth.

**Authors’ roles:** ZMF conceived the study, recruited the patients, collected the samples, ran the experiments, analysed the data and lead manuscript drafting. QQ supervised the experiments and assisted with data analysis. AG assisted with study design, helped interpret the data and critically reviewed the manuscript. KBA assisted with study design, data interpretation and critical review of the manuscript. All authors approved the final manuscript.

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Table I: Patient characteristics

HOMA-IR, homeostasis model of assessment insulin resistance; BMI, body mass index; GWG, gestational weight gain; GCT, glucose challenge test
### Table II: Kruskal-Wallis test for between group differences in maternal and fetal endpoints

<table>
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<tr>
<th></th>
<th>Control</th>
<th>Obese</th>
<th>p</th>
<th>n</th>
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<tr>
<td><strong>Maternal endpoints</strong></td>
<td></td>
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<tr>
<td>Maternal Insulin (log pg/ml)</td>
<td>2.63(.11)</td>
<td>2.85(.35)</td>
<td>0.03</td>
<td>21</td>
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<tr>
<td>Glucose (mmol/l)</td>
<td>3.64(.50)</td>
<td>4.12(.53)</td>
<td>0.15</td>
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<tr>
<td>Leptin (pg/ml)</td>
<td>14537.36(9191.77)</td>
<td>33656.33(15333.87)</td>
<td>&lt;0.01</td>
<td>21</td>
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<tr>
<td><strong>Fetal endpoints</strong></td>
<td></td>
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<tr>
<td>Cord Insulin (log pg/ml)</td>
<td>2.67(.31)</td>
<td>2.76(.24)</td>
<td>0.96</td>
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<td>Glucose (mmol/l)</td>
<td>3.23(.37)</td>
<td>3.08(.23)</td>
<td>0.48</td>
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<tr>
<td>Leptin (pg/ml)</td>
<td>14406.22(10632.73)</td>
<td>24512.11(19018.80)</td>
<td>0.20</td>
<td>18</td>
</tr>
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Data are presented mean (standard deviation)

### Table III: Spearman correlations between outcomes of interest

<table>
<thead>
<tr>
<th>Spearman Correlations</th>
<th>BMI (kg/m^2)</th>
<th>Cord IGFBP3 Expression</th>
<th>Maternal Leptin</th>
<th>HOMA-IR (log.)</th>
<th>Birthweight (g)</th>
<th>Fetal-placental wt ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m^2)</td>
<td></td>
<td>*-0.27</td>
<td></td>
<td>*0.64</td>
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<td>0.17</td>
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<td>Cord IGFBP3 Expression (log. % IC)</td>
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<td>*0.77</td>
<td>**-0.57</td>
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<td>*0.55</td>
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<td>Maternal Leptin (pg/ml)</td>
<td></td>
<td>*0.81</td>
<td></td>
<td>0.33</td>
<td>-0.32</td>
<td></td>
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<tr>
<td>HOMA-IR (log.)</td>
<td></td>
<td></td>
<td></td>
<td>0.14</td>
<td>-0.04</td>
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<tr>
<td>Birthweight (g)</td>
<td></td>
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<tr>
<td>Fetal-placental wt ratio</td>
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Table III: Spearman correlations between outcomes of interest

HOMA-IR (n=14), homeostasis model of assessment insulin resistance; BMI (n=24), body mass index; IGFBP3 (n=21), insulin-like growth factor binding protein-3; Leptin (n=21); Fetal-placental weight ratio (n=23). Bonferroni adjustment for multiple comparisons, *p≤0.01, ** p=0.03
Figure I: Cord serum IGFBP4 expression is reduced in maternal obesity

Results shown display optical densities relative to internal control and are representative of study population. IGFBP4, insulin-like growth factor binding protein-4; IC, internal control.
Figure II: Observed relationships in our patient population

Maternal insulin resistance directly associates with A. BMI and C. Maternal leptin levels; B. Cord serum IGFBP3 expression inversely associates with maternal insulin resistance and directly relates to D. fetal-placental weight ratio. HOMA-IR (n=14), homeostasis model of assessment insulin resistance; BMI (n=24), body mass index; IGFBP3 (n=21), insulin-like growth factor binding protein-3; Leptin (n=21); Fetal-placental weight ratio (n=23). Bonferroni adjustment for multiple comparisons, *p≤0.01, ** p=0.03
Figure III: IGF axis expression patterns in maternal and fetal circulation. A. Maternal IGF-I expression; B. Fetal IGF-I expression; C. Maternal IGF-II expression; D. Fetal IGF-II expression; E. Maternal IGFBP-1 expression; F. Fetal IGFBP-1 expression; G. Maternal IGFBP-3 expression; H. Fetal IGFBP-3 expression; I. Maternal IGFBP-4 expression. Each image is representative of the study population for the protein of interest. IC = Internal Control.
As noted above, in our epidemiological analysis of the Ottawa and Kingston birth cohort we identified strong independent contributors to fetal overgrowth including obesity and/or excessive GWG; a finding that has significant clinical relevance. In fact, LGA neonates have been reported to develop more adipose tissue, as measured by sum of skinfold thickness, than appropriately grown infants and tend to track that excess weight throughout the life-course. However, the evidence describing potential physiological mechanisms that explain the observed associations between excessive GWG and neonatal size is limited. Therefore, we hypothesized that the growth-enhancing components of the IGF system would be expressed to a greater extent and the growth inhibiting peptides down-regulated in pregnancy where GWG was excessive. Thus we followed-up on the previous manuscript characterizing the IGF axis in pregnancy complicated by obesity and designed a small molecular study that examined the influence of excessive GWG on IGF axis protein expression patterns in mom and baby.
7.0 MANUSCRIPT IV

Excessive gestational weight gain augments expression of maternal insulin-like growth factor binding protein-3

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Z. Ferraro conceived the study, recruited the patients, collected the samples, ran the experiments, analysed the data and lead manuscript drafting. Q. Qiu supervised the experiments and assisted with data analysis. A. Gruslin assisted with study design, helped interpret the data and critically reviewed the manuscript. K. Adamo assisted with study design, data interpretation and critical review of the manuscript.
Excessive gestational weight gain augments expression of maternal insulin-like growth factor binding protein-3

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Running title: excessive gestational weight gain and the IGF axis
ABSTRACT

BACKGROUND: Excessive gestational weight gain (GWG) increases risk of large for gestational age neonates and subsequent tracking of excess weight throughout the life-course for both mom and child. Although the physiological mechanisms underlying these associations are incomplete the IGF axis has garnered attention for its role in fetal growth and development. Our purpose was to characterize the independent effects of excessive GWG on IGF axis protein expression patterns in mother-infant dyads.

METHODS: We obtained fasting serum samples and corresponding cord blood from 8 control [(ADHERE group) i.e., those who gain in accordance to Institute of Medicine (IOM) GWG recommendations] and 13 exceeders [(EXCEED group) i.e., those who exceeded IOM GWG recommendations)]. At study completion, we examined protein expression of IGF-I, -II, IGF binding protein (IGFBP) 1, -3, -4 and hormone concentrations in both maternal and cord blood.

RESULTS: Between group comparisons were made and revealed elevated maternal leptin (p≤0.05) concentrations in gravidas who exceeded recommendations. After adjustment, maternal leptin levels were positively correlated with maternal HOMA-IR score and excessive GWG (p≤0.01). However, serum IGFBP-3 expression in the EXCEED mothers was greater than that in the ADHERE group (p≤0.05).

CONCLUSIONS: Our findings suggest that small deviations in IGFBP-regulated IGF bioavailability, arising from excessive GWG/positive energy balance, may affect adipocyte differentiation through subclinical insulin resistance as measured by HOMA-IR.
INTRODUCTION

Excessive gestational weight gain (GWG), defined as that above the 2009 Institute of Medicine (IOM) recommendations [1], is associated with greater likelihood of having a large for gestational age neonate [2] with increased adiposity and insulin resistance [3]. However, GWG in excess of the recommendations is also implicated in adverse maternal outcomes including gestational diabetes [4], hypertension and preeclampsia [5] as well as greater postpartum weight retention (PPWR) [6]. The insulin-like growth factor axis plays a vital role in growth and development, particularly in regulating cellular differentiation and hypertrophy as well as glycemic homeostasis [7]. IGFs elicit their intracellular effects by interacting with the IGF type 1 (IGF-1R), type 2 (IGF-2R) or insulin-IGF receptor hybrids [8]. Initial reports identified IGFBP-3 as an insulin-antagonizing peptide, binding with high affinity to free IGF(s) and controlling bioactivity. In recent years, IGFBP-3 has been shown to act independent of the traditional receptors via nuclear translocation thereby capable of interrupting transcriptional regulation directly [8]. Of interest with respect to excessive GWG is that IGFBP-3 has been shown to inhibit adipocyte differentiation [9] and induce insulin resistance in vivo and in vitro [10]. Data from our group has demonstrated that IGF axis protein expression is compromised in pregnancies complicated by obesity [11], however the effects that excessive gestational weight gain has on IGFs and IGF binding protein (IGFBP) expression during human pregnancy, independent of maternal body mass index (BMI), is unknown. Understanding differences in weight accretion during critical periods of maternal-fetal growth and development may lead to more efficacious obesity
management strategies as PPWR is a known contributor to the intergenerational cycle of obesity [12].

Thus, the IGF system may be a candidate pathway involved in maternal substrate storage and/or nutrient flux through the placenta during pregnancy where excessive weight is gained. Positive energy balance and subsequent aberrant hormone responses may contribute to alterations in maternal and/or fetal body composition. For instance, fetal adipogenesis peaks in late gestation [13], with greater than 90% of fetal body fat accrued in the third trimester [14]. In obese women, bioactive IGF-I is directly correlated with IGFBP-3 concentration in blood [15] and IGF-I stimulates the differentiation of preadipocytes through modulation of the IGFBPs [16]. At term, the pregnancy-associated rise in maternal IGFBP-3 serum level correlates positively with birthweight [17, 18] while the increase in free IGF-I during pregnancy is thought to be mediated by IGFBP-3 proteolysis [19]. Traditionally, IGFBP-1 acts to inhibit IGF function and is inversely related to insulin levels. Instances of chronic weight gain over time (i.e., obesity), display low serum concentrations of IGFBP-1 that may regulate in vivo IGF-I bioavailability based on fuel supply [15]. Lastly, although, the exact function of IGFBP-4 is not known, it may play a role in stem cell differentiation into muscle and fat and be modified in both pregnancy and weight gain [20]. Therefore, we aimed to examine protein expression of vital regulatory components of the IGF system in controls [(ADHERE group) i.e., those who gain in accordance to IOM GWG recommendations] and mothers and their term neonates who exceeded IOM recommendations [(EXCEED group) i.e., those who exceeded IOM GWG recommendations].
Specifically we aimed to determine if IGF-I, IGF-II, and IGFBP-1,-3 and -4 levels differed between groups of mother-infant dyads. Given that mothers who gain excessively during pregnancy generally give birth to larger infants, we hypothesized that; i) the growth-enhancing components of the IGF system would be expressed to a greater extent and, ii) the growth inhibiting proteins down-regulated, in pregnancies with excessive GWG.

METHODS AND PROCEDURES

Participants. Patients were recruited from the Ottawa Hospital General Campus (a tertiary care center), Maternal Fetal Medicine and Obstetrics clinics after the study was approved by the Ottawa Hospital Research Ethics Board. Informed consent was obtained from all participants. Women who smoked, those with type 1, type 2 or gestational diabetes or any other medical complication such as hypertension, cardiac, vascular, autoimmune diseases and thrombophilias and a past history of fetal loss, fetal growth restriction or hypertensive diseases of pregnancy were excluded from either group such that we can examine the independent contribution of excessive GWG. Women carrying fetuses with congenital or chromosomal anomalies were also excluded. All women were classified as glucose tolerant following their prenatal glucose challenge test.

Sample Collection. Fasting blood samples were obtained via peripheral venipuncture from 21 gravidas (8 who met and 13 who exceeded IOM GWG recommendations relative to prepregnancy BMI) immediately prior to term elective caesarean section to avoid any potential influence of labour. Corresponding venous serum was obtained from the umbilical cord following removal of the placenta as clinically indicated. The placenta was then
weighed to the nearest gram using a calibrated electronic scale (Olympic Smart Scale, Natus Medical Inc. Seattle, WA, USA). Following blood draws, the samples remained at room temperature for 30 minutes to allow for clotting and were subsequently spun at 1700xG for 15 minutes at 4°C. The supernatant was removed, aliquoted into separate cryovials and frozen at -80°C for batch analysis. Maternal and fetal clinical variables were collected through a chart review upon study completion.

**Determination of IGF-II via Western Blot.** The expression of IGF-II in human circulation was determined as previously described by Qiu et al. [21]. Briefly, aliquots of 0.5 µl of sera were diluted with 1X SDS non-reducing sample buffer (62.5 mMTris-HCl, pH 6.8, 2% SDS, 10% glycerol, 0.01% Bromophenol Blue), and subjected to electrophoresis with 10% tricine SDS-PAGE. The separated proteins were blotted onto a nitrocellulose membrane, treated with an antibody extender solution (Pierce, Rockford, IL), blocked with 5% dehydrated non-fat milk in TBS-T (Tris-Buffered Saline, pH 7 with 0.3% Tween 20), and subsequently probed with mouse anti-IGF-II(1-67) monoclonal antibody (clone S1F2; Upstate Biotechnology, Lake Placid, NY) and HRP-conjugated anti-mouse IgG. Bands of IGF-II variants were visualized with ECL, and their relative contents quantified using densitometry with Alpha Ease FCTM software (Alpha Innotech, San Leandro, CA). This assay can detect a quantity of recombinant human IGF-II as low as 6.25 pg [21].

**Determination of IGF-I and IGFBP-4 via Western Blot.** The presence of IGF-I and IGFBP-4 in human and cord serum was determined as described above with the following modifications. Aliquots of serum (0.5µl) were resolved by 15% glycine SDS-PAGE under non-reducing conditions and electrotransferred to nitrocellulose membranes. The membranes
were blocked for 1 hour in 5% milk, immunoblotted with highly specific antibodies for IGF-I (#ab9572, Abcam, CA, USA) and IGFBP-4 (#sc6005, Santa Cruz Biotech, CA, USA) and quantified as described above.

**Determination of IGFBP-1 and -3 and via Western-Ligand Blot.** IGFBPs were determined using aliquots of 0.5µl of sera subjected to electrophoresis, transfer and, antibody extend solution treatment and blocking agents as described above for the determination of IGF-I and –II. The membranes were subsequently probed with biotinylated IGF-II (GroPep Ltd., Adelaide Australia, 50ng/ml prepared with TBS-T) at 4˚C overnight, followed by antibody highly specific to IGFBP-1 (#sc55474,Santa Cruz Biotech, CA, USA) and IGFBP-3 (#sc135947, Santa Cruz Biotech, CA, USA) and finally by streptavidin-HRP (GE Healthcare, Buckinghamshire, UK, 1h at RT). Bands of IGFBPs were visualized, after being independently probed on separate days with highly specific antibodies targeting solely the protein of interest, with ECL and their relative contents were quantified via densitometry with Alpha Ease FCTM software as described above.

**Biochemical analyses of glucose, insulin, and leptin.** Glucose was measured by oxidase enzymatic methodology using the Cholestech LDX analyzer as described by the manufacturer (Hayward, CA, USA). Circulating insulin and leptin were analyzed in duplicate by ELISA using Luminex xMAP technology for the human metabolic hormone magnetic bead panel assay as described by the manufacturer (Millipore- Billerica, USA). The intra- and inter-assay CVs were 3% and 6% for insulin and 3% and 4% for leptin.
**Computation of outcome variables.** GWG was calculated from anthropometric values obtained from the medical record using the difference of directly measured maternal weight at last prenatal visit minus directly measured pre-pregnancy weight obtained preconception by their general practitioner. Percent (%) exceed GWG was calculated as the quotient of total GWG divided by the upper limit of recommended gain using the 2009 IOM guidelines relative to pregravid BMI then multiplied by 100 [1]. This allowed us to categorize women into ADHERE (≤100% recommended GWG) or EXCEED (>100% recommended GWG) groups independent of pregravid BMI to assess the effect of excessive GWG. Homeostasis Model of Assessment – Insulin Resistance (HOMA-IR) was calculated as fasting glucose (mmol/L) x fasting insulin (pmol/L) /22.5 and subsequently log-transformed [22]. Fetal-placental weight ratio was calculated as infant birth weight (g)/placenta weight (grams).

**Statistical Analysis.** SPSS Statistics software version 19 was used for outcome analysis (IBM, USA). Protein band optical densities were log-transformed and presented as the mean± standard deviation (SD) percent above internal control (IC). The IC used was a pooled sample consisting of equal volumes of maternal and fetal sera taken from each subject in the study. All other outcome variables are presented as the mean ± SD unless otherwise specified. A non-parametric two-tailed independent samples Kruskal-Wallis test was used to make conservative comparisons between groups for all patient characteristics as well as maternal-fetal levels of glucose, insulin and leptin. Spearman correlations were used to examine relationships between maternal and fetal characteristics and outcomes of interest.
Significance was set to \( p \leq 0.05 \). Adjustments for multiple comparisons were made if necessary and presented within.

**RESULTS**

**Patient characteristics**

Eight women who met and 13 who exceeded 2009 IOM GWG recommendations, of comparable age and height, were studied. As designed to assess the effects of relative excessive GWG, the mean percentage in excess of the GWG guidelines, based on pre-pregnancy BMI differed between the groups. Mean pre-pregnancy BMI and weight were greater in the EXCEED group as expected given the narrower range of acceptable gain as pregravid BMI increases (Table 1). In the ADHERE group, 7 had pregravid BMIs classified as normal weight whereas one was classified as obese. In the EXCEED group, 4 and 9 women were categorized as normal weight and obese, respectively. However, birthweight, gestational age at delivery, prenatal glucose screen, placenta weight and fetal-placental weight ratio did not differ between groups.

**IGF and IGFBP**

Maternal expression of IGF-I, -II, IGFBP-1 and -4 and cord blood expression of IGF-I, -II, IGFBP-1, -3 and -4 were similar between groups \((p > 0.05\), data not shown\). Expression of IGFBP-3 was increased in maternal blood from the EXCEED group compared to ADHERE \((p \leq 0.05\) (Figure 1).

**Glucose, insulin and leptin**
Maternal glucose, insulin and cord levels of insulin, glucose and leptin did not differ between groups (Table 2). However, maternal leptin was elevated in the EXCEED group (Figure 2) and showed a strong direct relationship with excess GWG and HOMA-IR (Figure 3 and Table 3). Following Bonferroni adjustment, non-significant trends (i.e., where \( p < 0.05 \) prior to adjustment and between 0.01-0.05 post adjustment) were observed between excessive GWG and infant birthweight, maternal IGFBP-4 expression and HOMA-IR (Table 3).

DISCUSSION

The present study illustrates, for the first time, an examination of the IGF axis in otherwise healthy mothers and newborns that adhere to and exceed 2009 IOM GWG guidelines. The fact that the participants suffered no medical or obstetrical complications (i.e., no GDM, hypertension, etc.) provided us with a unique opportunity to examine the influence of excessive GWG without the potential effects of the commonly associated complications or co-morbidities. This investigation reveals a small, albeit significant difference, in the IGF axis in the EXCEED vs. ADHERE group, particularly up-regulation of IGFBP-3 expression in maternal blood from normoglycemic pregnancies where GWG is excessive. Given our study design we are unable to assess causality, however, the metabolic dysregulation of maternal growth controlling factors we present in excessive gainers aligns with previous observations demonstrating that IGFBP-3 induces insulin resistance in adipocytes [10] via inhibition of adipocyte differentiation [9] and thus alters metabolic homeostasis.
Although induced during adipocyte differentiation, IGFBP-3 can paradoxically inhibit this process [23] and as adipogenesis proceeds, increasing adipose tissue IGFBP-3 levels may eventually signal a feedback mechanism limiting further differentiation of preadipocytes [9]. In fact, the dual regulatory role of IGFBP-3 in differentiation has been identified in other cell types including myoblasts [24], keratinocytes [25] and chondrocytes [26]. As such, it is possible that augmented expression of maternal IGFBP-3 may be in part due to a feedback response to excessive weight gain where IGFBP-3 sequesters free IGFs, preventing further differentiation of adipocytes and antagonizing IGF-induced glucose uptake and insulin-like activity. Previous investigations have demonstrated that IGFBP-3 [10, 27] inhibits insulin-mediated glucose uptake in adipocytes and have suggested that the increase in free IGF-I during pregnancy is mediated by IGFBP-3 proteolysis [19]. In fact, Chan et al [9] using 3T3-L1 adipocytes demonstrated that IGFBP-3 inhibits peroxisome proliferator activated receptor (PPAR) γ-dependent process of adipocyte differentiation by inhibiting the dimerization of retinoid X receptor (RXR) α and PPARγ. These findings suggest that IGFBP-3 has the potential to disrupt glycemic control and substrate uptake in adipose tissue. This notion aligns with the findings of Kim et al [10] who convincingly demonstrate that IGFBP-3 induces insulin resistance in adipocytes in vitro and in vivo, and those of Nguyen et al [28] who show that in mice overexpressing human IGFBP-3 in vivo, insulin clearance is delayed and glucose-stimulated insulin secretion in pancreatic islets is reduced by both IGF-dependent and IGF-independent mechanisms. Although several physiological factors are suspected to regulate IGFBP-3-induced alteration of glycemic control, we cannot preclude the possibility that augmented IGFBP-3 with excessive weight gain may preferentially elicit
a hypertrophic response in existing adipocytes at the expense of attenuated adipogenesis. If so, this may predispose women to preferentially store substrate in existing adipocytes; a fuel partitioning strategy that is metabolically disadvantageous when adipocyte proliferation rates are low [29, 30]. If excessive GWG compromises functional components of the IGF axis as demonstrated in the present investigation this might suggest that the IGF axis may be involved in maternal fat accretion, leptin production and subsequently the onset of insulin resistance in women who exceed recommendations.

It is known that serum levels of leptin correlate with total body fat content and insulin resistance [31] in pregnant [32] and non-pregnant women [31-33]. In a group of healthy pregnant women in the first trimester [34] as well as those with gestational diabetes [35], serum leptin positively relates with insulin resistance a finding we substantiate at term in pregnancy complicated with excessive GWG. Given that serum leptin concentrations decrease following delivery, it has been argued [36] that factors other than fat mass alone cause increased leptin production throughout pregnancy, including placental contributions. However, Eriksson et al [37] showed that serum leptin was elevated in gestational week 8 when increases in fat mass are minimal and when the placenta is not fully established providing support that increased leptin levels are not only due to increased fat mass but influenced by other unknown factors as well. These findings parallel with our observation in women who gain excessively, as leptin levels have been reported to be commensurate with adipose stores in pregnant women at term [32, 37]. Although, we acknowledge the possibility that the observed differences in maternal leptin at the end of pregnancy may
simply reflect between group differences in pregravid BMI, Shaarawy et al [38], comparing non-pregnant and pregnant women matched for pregravid BMI, determined that elevated serum leptin was directly associated with maternal adiposity of pregnancy. Furthermore, observations from a randomized controlled trial with and without GWG restriction in BMI-matched obese pregnant women, Wolff et al [39] showed that when patients in the intervention group successfully limited food intake and restricted GWG a significant 20% reduction in both insulin and leptin was observed. Collectively, these results suggest that independent of pregravid BMI and maternal leptin levels, appropriate GWG may attenuate adipose accretion and the commensurate leptin response, while excessive GWG may exacerbate maternal fat accretion thus raising leptin levels.

Further, we present a strong direct relationship between maternal leptin levels and HOMA-IR supporting previous work identifying pregnancy as both an insulin- and leptin-resistant state [32] partly mediated by increasing adiposity during pregnancy [37]. Indeed, Eriksson et al [37] showed that total body fat percentage was significantly correlated with HOMA-IR and with serum leptin before and during pregnancy while leptin correlated with HOMA-IR identifying a complex interactive role of maternal leptin, adiposity and insulin sensitivity. Although we cannot make conclusive inferences about the composition of excessive GWG based on the results of our study, previous work suggests that high maternal fat content predominates and stimulates fetal growth as evidenced by data showing maternal total body fat [40] and excessive GWG [2] positively relate to birthweight and that neonates born to mothers who gain in excess have higher body fat [41]. Furthermore, the pregnancy-
enhancing effect on the relationship between maternal body fatness and insulin resistance [37] may represent a physiological mechanism predisposing pregnant women to preferentially store body fat as excessive weight is gained. It is now widely accepted that maternal body size affects fetal growth and metabolic homeostasis [3, 42]. Our findings, in addition to others [43], suggest that maternal body size and/or weight gain are important factors determining the amount of dietary energy required by the developing child. Excessive GWG may present a mechanism by which offspring size and/or body composition is regulated via alterations in the IGF axis in response to dietary energy availability in the maternal environment. Although we were unable to comprehensively assess maternal or fetal body composition, we cannot exclude the hypothesis that GWG-induced perturbations in IGF axis function may alter maternal-fetal body composition; a phenomenon thoroughly documented in mother-infant dyads who gain excessively and is exacerbated as pregravid BMI increases leading greater relative fat mass accretion [6]. Therefore, future longitudinal investigations should examine the influence of physical activity energy expenditure and eucaloric dietary intake on IGF axis dynamics and maternal-fetal body composition to confirm our findings in a larger sample.

The limitations of our study include the cross-sectional design, relatively small sample size and inability to control for maternal dietary intake and physical activity patterns. However, we present a novel finding identified with validated methodology, while controlling for the acute effects of postprandial metabolism as all women were fasted for at least 12 hours. Through this design, we also attempted to control for diurnal variation in IGF metabolism
given that all blood was drawn at the same time of day (i.e., the morning upon arrival to hospital admitting and fasting). Further, our study population was homogenous in nature as all women were normoglycemic as defined by clinical standards. In an attempt to avoid a confounding effect of mode of delivery on cord blood IGF profile all women in our study underwent elective caesarean section. Lastly, we used the most recent 2009 evidence-based recommendations for GWG as outlined by the IOM [1].

Our findings provide further support that the GWG recommendations offer tremendous clinical value for primary care as women and providers can track and monitor weight status throughout pregnancy to not only reduce the likelihood of impairing maternal-fetal metabolic signals, but also the incidence of large for gestational age neonates [2]. Specifically, if altering weight pre-pregnancy is not a feasible option, being aware of another modifiable factor, GWG, that may promote down-stream infant health could provide motivation for women to gain weight within the limits. This reinforces the need to optimize GWG for all women as this determinant contributes to postpartum weight retention and infant birth weight; known contributors to the intergenerational obesity cycle. In conclusion, our results align with epidemiological data suggesting that excessive GWG has an independent effect on maternal growth signals during pregnancy. Although it appears that IGFBP-3 attempts to sequester free IGFs and prevent undesired increases in IGF bioactivity with excessive GWG, the potential consequent induction of impaired glycemic control renders excessive gain harmful. Therefore, this study suggests that small deviations in IGFBP-regulated IGF bioavailability, arising from excessive weight gain, may
influence adipocyte differentiation and glycemic control. Adhering to the 2009 IOM recommendations may improve physiological mechanisms designed to optimize growth regulating peptides in the mother during pregnancy.

**Authors’ roles:** ZMF conceived the study, recruited the patients, collected the samples, ran the experiments, analysed the data and lead manuscript drafting. QQ supervised the experiments and assisted with data analysis. AG assisted with study design, helped interpret the data and critically reviewed the manuscript. KBA assisted with study design, data interpretation and critical review of the manuscript. All authors approved the final manuscript.

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Reference List


### Table 1: Patient Characteristics

Unless otherwise specified n=8 ADHERE and n=13 EXCEED. HOMA-IR, homeostasis model of assessment insulin resistance (n=3 ADHERE, n=8 EXCEED); BMI, body mass index; GWG, gestational weight gain; GCT, glucose challenge test (n=5 ADHERE); % exceed IOM, institute of medicine upper limit of GWG based on prepregnancy BMI; placenta weight and fetal-placental weight ratio (n=12 EXCEED); Kruskal-Wallis independent samples t-test used to compare group differences. Data presented mean (standard deviation).

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>GWG Adhere</th>
<th>GWG Exceed</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>33.88(6.6)</td>
<td>32.31(5.0)</td>
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<tr>
<td>Height (m)</td>
<td>1.62(0.9)</td>
<td>1.63(0.7)</td>
<td>0.63</td>
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<tr>
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<td>64.07(20.0)</td>
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<tr>
<td>BMI (kg/m(^2))</td>
<td>24.51(8.7)</td>
<td>32.75(9.8)</td>
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<tr>
<td>Parity</td>
<td>2.38(0.7)</td>
<td>2.08(0.4)</td>
<td>0.38</td>
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<tr>
<td>Gestational age (wks)</td>
<td>38.38(1.1)</td>
<td>38.77(0.9)</td>
<td>0.20</td>
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<tr>
<td>Prenatal GCT (mmol/L)</td>
<td>6.36(1.9)</td>
<td>6.39(1.3)</td>
<td>0.73</td>
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<td>HOMA-IR (log)</td>
<td>0.22(0.1)</td>
<td>0.52(0.3)</td>
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<tr>
<td>Absolute GWG (kg)</td>
<td>11.89(3.6)</td>
<td>14.97(4.5)</td>
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<td>% Exceed IOM upper limit</td>
<td>78.21(18.0)</td>
<td>136.82(33.6)</td>
<td>&lt;0.01</td>
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<td>Infant birth weight (g)</td>
<td>3216.25(505.8)</td>
<td>3547.77(310.1)</td>
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<tr>
<td>Placenta weight (g)</td>
<td>731.00(157.9)</td>
<td>742.83(94.7)</td>
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<td>Fetal-placental weight ratio</td>
<td>4.47(0.5)</td>
<td>4.87(0.6)</td>
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<tr>
<td>Maternal endpoints</td>
<td>GWG Adhere</td>
<td>GWG Exceed</td>
<td>p value</td>
</tr>
<tr>
<td>--------------------</td>
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<tr>
<td>IGF1 exp. (log. % IC)</td>
<td>2.32(0.1)</td>
<td>2.24(0.1)</td>
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<td>IGF2 exp. (log. % IC)</td>
<td>3.03(0.3)</td>
<td>2.95(0.2)</td>
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<td>IGFBP1 exp. (log. % IC)</td>
<td>2.09(0.1)</td>
<td>2.1(0.1)</td>
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<td>IGFBP3 exp. (log. % IC)</td>
<td>1.95(0.2)</td>
<td>2.16(0.3)</td>
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<tr>
<td>IGFBP4 exp. (log. % IC)</td>
<td>2.22(0.1)</td>
<td>2.08(0.1)</td>
<td>0.05</td>
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<tr>
<td>Maternal Insulin (log. pg/ml)</td>
<td>2.67(0.1)</td>
<td>2.81(0.1)</td>
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<td>Glucose (mmol/l)</td>
<td>3.68(0.5)</td>
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<td>Leptin (pg/ml)</td>
<td>16659.50(11300.0)</td>
<td>29560.33(16119.8)</td>
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<th>Fetal endpoints</th>
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<td>IGF1 exp. (log. % IC)</td>
<td>1.87(0.2)</td>
<td>1.67(0.3)</td>
<td>0.31</td>
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<tr>
<td>IGF2 exp. (log. % IC)</td>
<td>1.92(0.1)</td>
<td>1.92(0.0)</td>
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<td>IGFBP1 exp. (log. % IC)</td>
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<td>2.02(0.1)</td>
<td>0.22</td>
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<tr>
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<td>IGFBP4 exp. (log. % IC)</td>
<td>2.11(0.2)</td>
<td>2.04(0.1)</td>
<td>0.39</td>
</tr>
<tr>
<td>Cord Insulin (log pg/ml)</td>
<td>2.61(0.3)</td>
<td>2.83(0.2)</td>
<td>0.16</td>
</tr>
<tr>
<td>Glucose (mmol/l)</td>
<td>3.56</td>
<td>3.01(0.1)</td>
<td>0.14</td>
</tr>
<tr>
<td>Leptin (pg/ml)</td>
<td>18270.71(12319.1)</td>
<td>25837.75(18038.3)</td>
<td>0.35</td>
</tr>
</tbody>
</table>

**Table 2: Maternal and fetal outcome variables for mothers who ADHERE to and EXCEED GWG recommendations.** IGF, insulin-like growth factor; exp, protein expression relative to IC, internal control; IGFBP, insulin-like growth factor binding protein; GWG, gestational weight gain; Kruskal-Wallis independent samples test used to make between group comparisons. Data presented mean (standard deviation). Unless otherwise specified n=8 ADHERE and n=13 EXCEED. Maternal ADHERE glucose n=3; maternal EXCEED n=9, 8, 9 for insulin, glucose and leptin respectively. Fetal ADHERE n=6 for IGF1, IGF2, IGFBP1, -3, -4, n=7 cord insulin, n=1 cord glucose, n=7 cord leptin; Fetal EXCEED n=11 for IGF1, n=12 for IGF2, IGFBP1, -3, -4, n=8 cord insulin and leptin, n=5 cord glucose.
Table 3: Spearman correlations between maternal and fetal outcomes. % exceed GWG, percent exceed upper limit for gestational weight gain based on pre-pregnancy body mass index; HOMA-IR, homeostasis model of assessment insulin resistance; IGFBP4, insulin-like growth factor binding protein-4; Leptin; birth weight; Bonferroni adjustment for multiple comparisons *p≤0.01, for trend ** p=0.02, *** p≤0.05.
**Figure 1:** Excessive gestational weight gain augments maternal IGFBP3 expression. Representative serum expression patterns of glycosylated (g) and non-glycosylated (ng) maternal IGFBP3 isoforms of patients who ADHERE to or EXCEED the 2009 IOM GWG guidelines. IGFBP3, insulin-like growth factor binding protein-3; GWG, gestational weight gain; IOM, institute of medicine.
Figure 2: Maternal leptin levels increase in women who exceed 2009 GWG recommendations.

GWG, gestational weight gain; IOM, institute of medicine; n=8 ADHERE group; n=9 EXCEED group.
Figure 3: Maternal leptin levels positively correlate with A. excessive GWG and B. HOMA-IR.

Leptin (n=20); % Exceed upper limit of gestational weight gain (GWG) target recommendation based on prepregnancy body mass index; HOMA-IR (n=14), homeostasis model of assessment insulin resistance; Bonferroni adjustment for multiple comparisons p<0.01
Following completion of our epidemiological and molecular assessments examining the effects of maternal obesity and excessive gestational weight gain it was clear that both phenotypes independently contribute to aberrant physiology during pregnancy. This finding, coupled with the emergence of data from preliminary intervention trials during pregnancy lead us to hypothesize that many pregnant women are not receiving appropriate recommendations concerning physical activity engagement, appropriate weight gain targets or information about pregnancy-specific caloric intake. Thus we focused our efforts to developing and implementing a healthy eating and physical activity intervention to address the unmet needs of this population. However, despite a plethora of scientific literature telling pregnant women what recommendations are best, little to no patient-centred evidence existed that evaluated the type and utility of advice presented to patients by care providers. Given the role that healthy eating and physical activity play in general health, body weight regulation and chronic disease risk reduction we aimed to determine how knowledge was mobilized from provider to patient. Therefore, we designed and administered a comprehensive lifestyle questionnaire for pregnant women. This allowed us to tailor the design of our intervention to the wants and needs our study population in hopes that it would limit attrition and fill their knowledge gaps.
8.0 MANUSCRIPT V

An assessment of patient information channels and knowledge of physical activity and nutrition during pregnancy

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Z. Ferraro helped conceive the study, lead creation of the questionnaire, recruited the patients, analysed the data and lead manuscript drafting. J. Rutherford helped with the creation of the questionnaire and critically reviewed the manuscript. E. Keely helped with study conception, questionnaire creation and critically reviewed the manuscript. L. Dubois assisted with questionnaire creation and critically reviewed the manuscript. K. Adamo helped conceive the study, assisted with questionnaire creation, critically reviewed the manuscript and supervised the research.
An assessment of patient information channels and knowledge of physical activity and nutrition during pregnancy

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Summary
Background: Excessive weight gain during pregnancy increases the risk for obesity in mother and child. Healthy eating and physical activity may help prevent excessive gestational weight gain and minimize offspring risk of developing obesity, diabetes and cardiovascular disease. Our goal was to determine the information channels used by pregnant women to obtain information on nutrition and exercise.

Methods: We collected information about their knowledge of physical activity and nutrition during pregnancy and assessed their satisfaction with this information to identify factors that may be improved upon when designing a behavioural intervention. An anonymous, voluntary questionnaire was completed by 147 pregnant women to identify the proportion who are currently receiving information about exercise from their care provider.

Results: The primary Caucasian sample (age: 30 ± 4.2, weeks gestation: 21.4 ± 9.4) completed the survey. A total of 86% are willing to participate in a lifestyle intervention trial. Personal health and the health of their child were cited as top reasons for participation. Most women were not informed as to the importance of appropriate pregnancy-specific energy intake or made aware of their own personal healthy gestational weight gain targets. A total of 63% report receiving some form of information on physical activity during pregnancy. Of those who do not, almost all (93%) would like to receive this information from the care provider. Overall, 88% of women consider it safe to exercise when pregnant.

Discussion: Given their responses, nutrition and exercise information offered through a lifestyle intervention during pregnancy may increase healthy behaviours and warrants clinical investigation.

Keywords: obesity, pregnancy, physical activity, nutrition, intervention

INTRODUCTION
In recent years, overweight and obesity in women of reproductive age has emerged as a major public health concern affecting one in every two women. Excessive adiposity during this critical period not only has negative consequences on maternal health, but also poses significant risk to the developing fetus (fetal growth and development). Obesity at preconception (body mass index [BMI] ≥ 30) is a modifiable risk factor that, if left unattended, may lead to a progressive worsening of the obese state if excessive weight is gained during gestation and retained during the postpartum period. Maternal obesity is associated with a myriad of complications including infertility, recurrent miscarriage, spontaneous abortion, gestational diabetes, pre-eclampsia, risk of caesarean section, poor lactation/difficulties breastfeeding, fetal macrosomia and neonatal death. Furthermore, obese children are more likely, than their lean counterparts, to remain obese or develop obesity as adults; perpetuating the vicious cycle of body weight dysregulation.

There is now an abundance of evidence available to suggest that maternal energy balance may alter fetal growth and development. Recently, Stuebe et al.7 reported, for the first time, a link between prepregnancy BMI, gestational weight gain and offspring obesity in adulthood. Their findings, along with those of Okan, strongly suggest that prepregnancy weight and gestational weight gain if modified may reduce the developing child’s risk of obesity.

In an attempt to ameliorate the negative effects of excess adiposity, it is now recommended that all overweight women of reproductive age receive counselling on the beneficial roles of diet and physical activity prior to pregnancy, during gestation and in the interconceptional period. The Institute of Medicine (IOM) echoed this recommendation by revising the gestational weight gain guidelines. Building on the previous 1990 publication, these new recommendations impose both a

narrow range and an upper limit (5–9 kg) of weight gain for obese women (BMI ≥ 30). Furthermore, this report, in addition to others, highlights a need for interventions aimed at promoting a healthy diet and physical activity during pregnancy in an attempt to ensure women optimize gestational weight gain trajectories that balance the risks and benefits of weight change on maternal–fetal health. The need to encourage maternal weight gain targets that stay within the respective gestational weight gain intervals (based on prepregnancy BMI) through lifestyle interventions may provide an avenue by which maternal–fetal health can be optimized. A joint position statement from the Society of Obstetricians and Gynaecologists of Canada and the Canadian Society for Exercise Physiology (SOGC/CSEP) supports this notion. The ‘exercise in pregnancy and the postpartum period’ clinical practice guideline recommends continuation of healthy active living during pregnancy in gravidas without contraindications to exercise. However, despite the academic literature supporting these behaviours there is a need for a greater understanding from the pregnant women’s perspective that identifies where they receive information, their receptiveness to physical activity and nutrition guidance from care providers and whether this content is considered helpful. Given the need for intervention research in the overweight population, the aim of our study was to assess patient knowledge of and determine the information channels used by women to obtain information on nutrition and exercise during pregnancy. Further, we wanted to evaluate their degree of satisfaction with the information they received in order to identify factors that may be improved upon when designing a behavioural intervention. To our knowledge, this is the first study of its kind designed to concurrently assess physical activity and nutrition information channels and satisfaction with these outlets in a pregnant population.

MATERIALS AND METHODS

All pregnant women, of any gestational age, presenting at clinic for obstetrical reasons were potential candidates for this study; those presenting with solely gynaecological problems were not invited to complete a survey. The clinic is affiliated with an academic medical centre (The Ottawa Hospital/University of Ottawa) and provides primary care to a medium-sized urban area in west Ottawa. The ultrasound clinic receptionist briefly informed patients about the study and asked for their participation. Women who expressed interest were directed to the study coordinator who then explained the consent process, the purpose of the survey and was available to clarify any study-related questions. Approximately 175 questionnaires were distributed to consenting pregnant adult women entering an obstetrics/gynaecology clinic affiliated with The Ottawa Hospital between November and December 2008. Twenty-five questionnaires were not returned to the drop box or were incomplete and voided by the participant. This project was approved by the Children’s Hospital of Eastern Ontario and the Ottawa Hospital research ethics board.

Procedures

Women were encouraged to complete the 31-item (~10 minute) self-administered questionnaire consisting mostly of closed-ended questions where participants could select from multiple choices. This included, when appropriate, an ‘other’ category where respondents could input an open-ended response not captured within the listed choices. Participants completed the questionnaire while they waited for their appointment with their care provider; those who were unable to finish prior to being seen by their provider had the option to complete the survey following their appointment. This process continued until approximately 150 anonymous questionnaires were completed. To ensure confidentiality, participants returned completed questionnaires to the clinic receptionist or study coordinator who then put them in a closed drop box, kept under lock and key and delivered them to the primary investigator once all data were obtained. A targeted sample size of 150 completed surveys was selected to appropriately identify the proportion of women currently receiving information about exercise during pregnancy from their care provider. With 150 respondents, a proportion of 0.5 could be estimated to within ±8%, 19 times out of 20. This describes a 95% confidence interval based on 50% prevalence, which provides a conservative estimate of precision when evaluating the women’s responses.

The questionnaire was designed to be used as a non-validated instrument to collect information about nutrition and exercise information channels and satisfaction with these outlets in a sample of pregnant women. Items were chosen following a review of the literature and consensus from our expert group consisting of a clinical methodologist, endocrinologist, clinical psychologist, exercise physiologist, paediatric scientist and dietitian knowing that a validated tool for this specific population and purpose does not exist. A final version of the survey is available upon request from the Children’s Hospital of Eastern Ontario Research Institute’s Healthy Active Living and Obesity Research Group. Data were analysed using the SPSS software version 16.0.

RESULTS

The questionnaire was completed by 147 primarily Caucasian women (age: 30.9 ± 4.2, weeks gestation: 21.4 ± 9.4). All demographic information obtained from consenting women is presented in Table 1. A total of 86.6% of women who completed the survey responded in favour of participating in a lifestyle intervention during pregnancy should a programme of this nature exist. Of those who would elect not to participate, the reasons included already living a healthy lifestyle, lack of time or disinterest. When asked to select from a list of sources from which they could choose more than one option, the 127 women who expressed an interest in a lifestyle intervention reported their motives for participation to include: for the health of their child (87%), their personal health (83%) and to learn more about exercise and nutrition (52%). Use of electronic communication (i.e. email) was reported as the preferential way to receive information about physical activity and nutrition during pregnancy with 56% of respondents choosing this from a list of sources from which they could choose more than one option. Others (40%) stated they would prefer this detailed information to come from an interactive in-person consultation from an exercise or nutrition specialist, while 33% preferred the more traditional avenue of directly receiving all pregnancy-specific advice from their practitioner.
Diet and nutrition

Eighty-two per cent of the sample reported receiving information about healthy eating, diet and nutrition during the perinatal period, although nearly 20% of women did not receive any information of this nature during pregnancy. Of the 121 women who received dietary advice, the primary source of this information was from books, magazines and waiting room material, the Internet and their general practitioner (see Table 2). From these sources the prominent topics of discussion include vitamin/mineral requirements, the importance of balanced macronutrient consumption, knowing which foods to avoid, eating for a healthy pregnancy weight gain and appropriate energy (kcal) intake during pregnancy (see Table 2). The majority (43%) of women who received dietary information from any source found it very useful, while only 22% and 26% reported the information to be extremely and somewhat useful, respectively. Taking into account the entire sample of women, 86% reported they would like to receive information about proper nutrition during pregnancy from a health provider or specialist, while 6% and 8% respectively, said they did not want this information or were unsure if they wanted dietary recommendations from a health provider (see Table 2). When asked if receiving pregnancy-specific nutrition information was important to them, 49% responded with ‘very important’ and 35% ‘extremely important’. This specific dietary advice was perceived by the women as important because of its potential to optimize their child’s growth and development, to promote long-term child health and to help understand ways in which they can manage their weight during and after pregnancy (see Table 2). When asked which type of information would be most helpful, it was reported that being more aware of foods they can eat to improve their baby’s health, having an improved understanding of which foods to avoid, learning healthy meal ideas, receiving infant feeding advice, individualized vitamin and mineral information, and having an awareness of healthy gestational weight gain were valuable topics to be addressed in a pregnant population (see Table 2).

Exercise and physical activity

An unexpected 63% of this population of pregnant women reported receiving information about physical activity during pregnancy (see Table 3). From the 93 women who did obtain this type of information, the primary sources of uptake included book/magazine, their general practitioner, the Internet and their obstetrician/gynaecologist (OB/GYN) (see Table 3). Of those presented with pregnancy-specific information from any source, the main topics covered in the material/discussion were intensity of exercise, the type of activity, the frequency of exercise and the optimal duration of exercise. Encouragingly, of the 54 women who did not receive pregnancy-specific exercise recommendations, 93% would like to have access to this type of information from a health educator (see Table 3). Of the 93 women who did receive physical activity information, 19%,
31% and 34% of women found the information to be extremely, very or somewhat useful, respectively, and a mere 8% found information of this nature to be only slightly useful. However, when asking the entire cohort if receiving pregnancy-specific information about physical activity is important to them, 31%, 35% and 29% perceived this type of information as extremely, very or somewhat important, respectively. For these women, the most frequently cited reasons why exercise was perceived as important were to help prepare their body for delivery; have potential to improve their wellbeing; may optimize their child’s health; may help them maintain an appropriate body weight; may help defend against chronic diseases such as diabetes, cardiovascular disease and cancer (see Table 3). Similarly, the women's perceived benefits of exercise during pregnancy included optimizing both their and their child’s health; they feel it is the “right thing to do”; they want to maintain their current routine and feel this is an opportune time to initiate a new routine (see Table 3). Given the past belief that was propagated among social networks stating exercise and over-exertion during the delicate and fragile time of gestation may harm the unborn child and that women who are uncertain about exercise safety are more likely to stop activity, we felt it necessary to ask women their beliefs about exercise safety. Of all 147 women surveyed, 88% believe it is safe to exercise during pregnancy while 11% reported ‘unsure’ because they either did not know what constitutes ‘safe’ activity or felt that exercise would harm their child. Overall, 53% of the total population surveyed reported that they are currently exercising while pregnant.

Table 3. Exercise results

<table>
<thead>
<tr>
<th>Received information about PA during pregnancy? (%)(n=147)</th>
<th>63.3</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>36.7</td>
</tr>
<tr>
<td>Primary sources of PA information during pregnancy? (%)</td>
<td></td>
</tr>
<tr>
<td>(n=147)</td>
<td></td>
</tr>
<tr>
<td>Books/magazines</td>
<td>62.4</td>
</tr>
<tr>
<td>GP</td>
<td>51.6</td>
</tr>
<tr>
<td>Internet</td>
<td>43.4</td>
</tr>
<tr>
<td>OB/GYN</td>
<td>33.3</td>
</tr>
<tr>
<td>Family</td>
<td>16.1</td>
</tr>
<tr>
<td>Friend</td>
<td>10.1</td>
</tr>
<tr>
<td>Other</td>
<td>9.7</td>
</tr>
<tr>
<td>RN</td>
<td>6.5</td>
</tr>
<tr>
<td>Personal trainer</td>
<td>6.5</td>
</tr>
<tr>
<td>RD</td>
<td>1.1</td>
</tr>
</tbody>
</table>

Did NOT receive PA info but would like to from a health educator? (%) (n=54) | 92.6 |

Preparation my body for delivery | 86.3 |

Improve overall well being | 85.6 |

Improve the health of my child | 76.0 |

Helps maintain body weight during and after pregnancy | 73.3 |

Prevents of chronic disease | 57.5 |

Exercise is perceived as safe and beneficial to pregnant woman | 47.7 |

My and my child’s health | 47.7 |

Feel it is the right thing to do | 20.9 |

Want to stick to routine | 13.9 |

Great time to start new routine | 9.2 |

Other (i.e. stress relief, hope for easier birth, prevent excess weight gain) | 3.9 |

Not sure | 1.5 |

PA = physical activity; GP = general practitioner; OB/GYN = obstetrician/gynaecologist; RN = registered nurse; RD = registered dietitian.

**DISCUSSION**

Despite the consistent plea in the literature for interventions that target excessive weight gain during pregnancy, no study, to our understanding, has concurrently assessed the knowledge, and information channels used to increase awareness, of exercise and nutrition from the pregnant women's perspective. Thus, the purpose of this investigation was to examine a woman’s current knowledge of pregnancy-specific exercise and nutrition recommendations, determine the information channels used to obtain these facts and gauge their satisfaction with the information gathered/provided. Our intent was to use these findings to help aid in the evidence-based development of structured lifestyle intervention arms of a randomized controlled trial.

Overall, willingness to participate in a lifestyle intervention during pregnancy was high with more than 86% of the women surveyed favoring participation should a programme of this nature exist. The top cited reasons for participation were for the health of their child, their personal health and to learn more about exercise and nutrition. Unfortunately, it is hard to draw firm conclusions about the subgroup of women who elected not to participate because of the limited number who selected this option. Another limitation to the current study was that we did not collect information regarding the stage of behaviour change each participant was at and thus do not have a complete understanding of the specific type of lifestyle change patients would consider implementing.

Nonetheless, the overall results suggest that this population of women do have a genuine concern for their and their child’s health and are motivated to participate in programmes that offer maternal–fetal benefit during pregnancy. However, we cannot extend these results to support the notion that women are aware of the beneficial longer-term, intergenerational effects that healthy eating and regular exercise during pregnancy may have on subsequent pregnancies or downstream child health. While an awareness of disease risk factors (i.e. obesity) may confer an advantage in obese pregnancies to help optimize weight regulation, women are seldom given proper gestational weight gain guidance tailored to their pre-pregnancy BMI. Recent evidence suggests that provider-informed patient awareness of their specific gestational weight gain target goal helps to reinforce maintenance of body weight within the IOM guidelines.16-17 This finding is also emphasized by Claesson et al.,15 who reported that the pregnant woman herself must be actively involved with goal-setting and be provided with continuous feedback and reinforcement. When intervening during pregnancy, this type of support was deemed beneficial by trial participants to help optimize gestational weight gain trajectories that may incur greater health benefits to the mother and child.15 Despite this, the vast majority of pregnant women are rarely given gestational weight gain guidance16-17 and if given advice, do not necessarily follow the recommendations2 or are given inaccurate advice that conflicts with the IOM guideline.15 A recent report by the IOM16 revisits these findings and further states that despite efforts to publicize these recommendations women are not made aware of the importance of continual weight monitoring during this critical period and fail to adhere to the specific gestational weight gain ranges as outlined in the revised IOM recommendations.16

In our study, greater than 70% of respondents expressed that they would prefer detailed, pregnancy-specific diet and
physical activity information from an interactive in-person consultation with an exercise/nutrition specialist and/or their physician when asked to choose from a list of options where they could make more than one selection; while 56% preferred electronic communication through the Internet. This finding supports the belief that interaction with multidisciplinary allied health-care teams may play an advantageous role in mitigating the detrimental effect of obesity, especially if follow-up material is available through electronic communications as this counselling strategy has demonstrated success.21

Diet and nutrition

With respect to dietary and nutrition recommendations, nearly 20% of women are not receiving pregnancy-specific information from any source. This is startling as it was anticipated that every woman would have received some degree of information concerning healthful dietary practices from a medical or allied health professional, a form of popular media (e.g. the Internet or television), or a family member and/or friend. However, few studies have examined the content of prenatal care from the patient’s perspective.22 Using data from the National Maternal and Infant Health survey, Kogan et al.23 reported that 93% of women received advice concerning proper food choice during prenatal care from their health provider alone. As far as we are aware the disparity in our study is a novel finding that suggests that the content of prenatal care recommendations are not being met for all women in our population. Moreover, the perceived adequacy and specificity of the dietary information obtained by patients in our sample must be questioned given that their primary sources were books/magazines and the Internet, two channels which may lack individual relevance, be outdated or not evidence-based.

In our study, 84% of the women who received some form of dietary advice were told about vitamin/mineral requirements, but there was a lack of pertinent guidance provided concerning healthy eating for optimal pregnancy weight gain and an awareness of appropriate caloric intake during gestation. This is of little surprise and in agreement with previous findings by Kogan et al.,24 who showed that vitamin recommendations were received by 97% of patients. The discrepant variation in the type of information patients receive illustrates inconsistencies in knowledge exchange between care provider and patient, especially with respect to physical activity and nutrition – two fundamental lifestyle behaviours that should be fully integrated into prenatal care.25 Although we cannot comment on the specific content and quality, which is a limitation of our study, the majority of women surveyed perceived the information they obtained to be very useful. The women sampled in this study expressed an interest in receiving pregnancy-specific nutrition recommendations from a health provider and believe that learning about healthy eating during pregnancy is important. Perceived benefits of initiating healthy eating behaviours reflect an understanding of both the short- and long-term potential of healthful nutrition during pregnancy. Their responses demonstrate an awareness of the immediate effects that may optimize child growth and development in utero as well as the benefits that maternal lifestyle choices have on promoting longer-term child health; albeit to a lesser extent. When the women were asked about helpful information they would like to receive during pregnancy, healthy eating advice aimed at promoting child health and having a greater awareness of which foods to avoid were top cited, whereas those pertaining to learning about healthy gestational weight gain and appropriate caloric intake during pregnancy were less frequently perceived as helpful. Overall, it is difficult to make comparisons with existing literature given our study, as far as we are aware, is novel with respect to assessing specific prenatal care needs from the patient’s perspective. It is therefore important to recognize that women do want to improve their overall health and that of their unborn child, but may lack a true understanding of how body weight regulation and caloric intake during gestation may influence maternal-fetal outcomes. Educating pregnant women about appropriate caloric intake, consuming a variety of healthy macronutrients, providing strategies to promote energy expenditure and emphasizing the importance of optimal weight gain in a primary care setting may provide an avenue by which simple and practical nutrition information may become more available to an at-risk overweight population.

Physical activity and exercise

Regular exercise and physical activity play a pivotal role in improving cardio-respiratory fitness; an outcome that is inversely related to all-cause mortality.26 These behaviours effect energy balance and promote optimal regulation of body weight if practised in conjunction with a healthful caloric intake.27 Given the benefits associated with exercise and its potential to optimize weight gain during pregnancy, the SOGC/CSEP joint position statement on exercise in pregnancy has been developed to promote exercise during pregnancy and the postpartum period in women without specific contraindications.28 Despite the health benefits associated with regular exercise and the consensus that a pregnant population can also engage in and benefit from regular participation, only 63% of our sample population received information about the physical activity during pregnancy from any source (i.e. books, Internet, doctor, etc.). Furthermore, the finding that one in every two women is not receiving information about active living from their general practitioner and that only one in every three women is discussing this with their OB/GYN is disheartening given the known health benefits associated with regular activity. Collectively, these results were lower than what we had anticipated finding, given the strong public messages acknowledging the benefits of exercise as well as the clinical practice guidelines endorsing these behaviours from the physicians’ own professional society.29 Furthermore, our knowledge is far from complete with respect to the quantity and quality of exercise recommendations made during prenatal care delivery from the patient’s perspective. Existing research either fails to integrate this information into the assessment tool30 or acknowledges that the relationship between prenatal care and the adoption of healthy behaviours has received little to no attention.31 Nonetheless, the vast majority (93%) of women surveyed in our study expressed an interest in having access to this type of information from a health educator supporting the need to increase accessibility and provide outlets designed for knowledge dissemination of this nature.32

Encouragingly, there was a common belief among our survey respondents that pregnancy-specific exercise recommendations are important and may help with many of the immediate conditions associated with pregnancy (i.e. improved fitness for labour, increased wellbeing and optimizing child’s health.
in utero). Although to a lesser extent than the acute advantages associated with active living on maternal–fetal health, we can speculate that pregnant women in our population acknowledge a benefit for the potential use of exercise as preventive medicine when defending against longer-term chronic diseases (i.e. type 2 diabetes, cardiovascular disease and cancer), in both mother and child. Thus, both public initiatives and research interventions targeting excessive weight gain during pregnancy may benefit mothers if there is a greater emphasis on the potential intergenerational effects that exercise during pregnancy may have on their health and that of their child.

Lastly, when delivering an exercise intervention during pregnancy, safety of the participants is a primary concern. Of all the women surveyed in our sample, 88% reported that they believe that exercise during pregnancy is safe while some were unsure as to what constitutes ‘safe’ or felt it may harm their child, a belief that aligns with the past medical paradigm. Collectively, these findings demonstrate that the majority of our sample population places high value on pregnancy-specific exercise behaviours as they deem them both safe and beneficial. These findings are in agreement with those of Duncombe et al., in which most (61–83%) in women in their study believe low-intensity, low-impact exercise to be safe, whereas high-intensity and high-impact activities are not. Moreover, 55% of our sample population reported exercising during pregnancy, which is a slightly greater prevalence compared with other investigations reporting 28% and 42% participation. The differences in our findings may be attributed to the lack of a nationally representative sample, variation within individual definitions of what one considers safe and/or selection bias by feeling compelled to select the exercise option given the healthy living focus of the questionnaire.

Nonetheless, our study supports the importance of patient education concerning diet and exercise practices during pregnancy as women both need and want current and practical tools during this time to help defend against excessive weight gain. These findings align with Claesson et al., who assessed obese women’s satisfaction with a weight gain intervention during pregnancy and demonstrated that mental coach- ing in conjunction with weekly didactic sessions about weight maintenance and motivational talk from a midwife, were viewed as positive experiences that were beneficial to them. All women participating in the Claesson intervention would recommend a programme of this nature to a friend and 70% were satisfied with their weight gain supporting a role for interventions in an obese pregnant population.

CONCLUSION

While we cannot make population-level inferences from the present study as the women surveyed are predominantly Caucasian, educated and have some form of immediate social support, as demonstrated by 96% married/common-law and over 85% completing some form of college or university, our results lend support to the notion that women are not receiving adequate information with respect to the long-term benefits that regular physical activity and balanced nutrition may have on both maternal and fetal outcomes. We can speculate, however, from our educated sample of women who have an existing support network during pregnancy, that initiatives targeting visible minorities, such as single, uneducated mothers, may be of greater value; a future area of study that remains to be tested.

To date, much of the research on exercise and nutrition has focused on implementing these behaviours and examining their effects on the prevention and management of obesity and diabetes. Our approach was slightly different. We assessed patient knowledge of, and determined the channels used by pregnant women to obtain, exercise and nutrition information. This approach has helped identify gaps in the type of content delivered in a prenatal care setting and highlights the necessity for inclusion of this information given the rising obesity rates. Furthermore, knowing what type of information women want and view as beneficial may help inform health promotion initiatives provided to expectant mothers. It is not uncommon for pregnant women to receive recommendations from their care provider about the ill-effects of smoking and alcohol consumption, as well as the benefits of vitamin supplementation (e.g. folic acid) and breastfeeding. However, our results suggest a need to incorporate prenatal recommendations on appropriate caloric intake, physical activity and gestational weight gain targets based on preconception BMI.

Similar to women’s perception concerning nutrition recommendations, pregnant women hold the belief that receiving pregnancy-specific exercise recommendations is of utmost importance to them. If care providers capitalize on a mother’s receptiveness to information about this nature and promote an active lifestyle tailored to their individual needs early in gestation, health benefits may become more visible. Additionally, if practitioners believe that providing recommendations about nutrition and exercise is beyond their scope of practice or feel that imparting this type of knowledge is too complex, or unable to provide in a office-based setting, referral to the appropriate allied care provider may optimize short- and long-term outcomes. Our intent is not to assign blame, but rather highlight an emerging area of concern in a primary care setting where health-care providers have the opportunity to educate the patient population about the potential health benefits that may result from optimizing their own healthy behaviours before, during and following pregnancy. Whether pregnant women understand the long-term sequelae associated with excessive gestational weight gain remains to be elucidated. It appears through any intervention or recommendation that confers an immediate benefit during pregnancy is both expressed by the care provider and viewed as important by the patient. However, these findings suggest that physical activity and nutrition recommendations are underemphasized in primary care, despite the abundance of scientific evidence which supports promotion and monitoring these behaviours during pregnancy.

Given the response of the target population, research of this nature demonstrates proof of concept for further testing the efficacy of exercise and dietary initiatives in controlled research settings. The information obtained through this investigation has helped to inform a randomized controlled trial pilot project designed to attenuate maternal gestational weight gain and optimize infant growth trajectory. Overall our findings add support to other investigations that highlight an immediate need for effective clinical interventions aimed at preventing excessive weight gain during pregnancy as a way to halt the intergenerational cycle of obesity. Focusing on a life-course perspective acknowledging the acute benefits of healthful nutrition and exercise during pregnancy itself, but also creating an awareness of the positive longer-term intergenerational effects these behaviours may have on growth, development and disease defence, is warranted.
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(Accepted 14 February 2013)
Preamble: Manuscript VI

The results of the previous study suggested that although pregnant women believe that physical activity during pregnancy is safe, many are not getting proper guidance from their care providers with respect to the maternal-fetal advantages of this behaviour. Thus, we set out to synthesize the existing literature for care providers about physical activity and exercise during pregnancy and examined its influence on maternal-fetal outcomes in a reader friendly narrative intended for continuing medical education. In our review, we describe the seminal works as well highlight novel findings pertaining to the risks and benefits to mother and baby when physically active during pregnancy. Specifically, the following manuscript will focus on the role of a physically active lifestyle in preventing aberrant fetal growth and optimizing maternal-fetal outcomes including risk for several chronic conditions.
The potential impact of physical activity during pregnancy on maternal and neonatal outcomes

Zachary M. Ferraro, Laura Gaudet and Kristi B Adamo

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Z. Ferraro searched the literature, retrieved sources, evaluated the evidence and wrote the manuscript. L. Gaudet critically reviewed the manuscript and provided clinical insight. K. Adamo contributed to the evaluation of the extracted sources, critically revised the manuscript, supervised the research and provided guidance and support.
The Potential Impact of Physical Activity During Pregnancy on Maternal and Neonatal Outcomes

Zachary M. Ferraro, MSc, MD, FRSC; and Kristi B. Adamo, PhD

Introduction: Pregnancy is a critical period of body weight regulation. Maternal obesity and excessive gestational weight gain have become increasingly common and contribute to poor obstetrical outcomes for mother and baby. Regular participation in physical activity may improve risk profiles in pregnant women.

Purpose and Methods: Our objectives were to provide an overview of maternal-fetal exercise physiology, summarize current evidence on the effects of physical activity during pregnancy on maternal-fetal outcomes, and review the most recent clinical practice guidelines. In addition, we summarize the findings in the context of the current obesity epidemic and discuss implications for clinical practice. A literature review was completed in which we queried OVID (Medline), EMBASE, and PSYCHINFO databases with title words "exercise or physical activity" and "pregnancy or gestation" from 1950 to March 1, 2010. A total of 212 articles were selected for review.

Recommendations: Care providers should recommend physical activity to most pregnant women (i.e., those without contraindications) and view participation as a safe and beneficial component of a healthy pregnancy.

Target Audience: Obstetricians & Gynecologists and Family Physicians

Learning Objectives: After participating in this CME activity, physicians should be better able to classify the potential impact of physical activity on maternal glycemic control and fetal growth outcomes. Assess maternal lifestyle and provide recommendations on appropriate gestational weight gain, evaluate pregnant women for contraindications to physical activity participation, make individualized recommendations for exercise participation, and educate patients on the merits of physical activity for health benefit.

THE CASE

Susan, a 35-year-old G1P woman, presented to her family physician for a routine prenatal visit at 25 weeks’ gestation. Her pregnancy was uncomplicated to date, and she had no significant past medical history (including glucose intolerance, hypertension, or hypothyroidism). A 1-hour glucose challenge test (50-g glucose load) had been performed at 24 weeks, with a resulting plasma glucose value of 7.6 mmol/L (normal: <7.8 mmol/L). Because this was below the
screening cutoff value, further testing was not indicated. Susan expressed concern about the impact of her weight on the health of her baby. Detailed history was obtained, and physical examination was performed. Susan described a history of inactivity and steady weight gain since her early 20s and was found to have a body mass index (BMI) of 30 kg/m². No contraindications to exercise participation were identified.

INTRODUCTION

Obesity and excessive weight gain in pregnancy are known to contribute to poor obstetrical outcomes, including hypertensive disorders, glycemic dysregulation, and aberrant fetal growth. Pregnancy is a critical period of body weight regulation. Gestational weight gain (GWG) often exceeds clinical recommendations, a situation that poses an elevated health risk to mother and fetus. Gaining the recommended amount of weight during pregnancy minimizes the incidence of adverse outcomes, including gestational hypertension, cesarean delivery, and birth weight <2500 g or ≥4000 g, independent of prepregnancy BMI. Engaging in healthy active behaviors during pregnancy may offer a useful and economical approach to attenuating excessive weight gain, improving obstetrical outcomes, and promoting optimal fetal growth trajectories. Ideally women should conceive at a healthy body weight (i.e., BMI: 18.5-24.9), taking full advantage of the adage “prevention before conception.” Unfortunately, many individuals currently display poor fitness and increased fitness, making this goal more challenging. Nonetheless, achieving a healthy prepregnancy body weight must still be considered the ultimate and ideal goal. Care providers should help women achieve a healthy body weight or slow the rate of weight gain, before pregnancy, as individuals with excess weight have increased risk of cardiac and pulmonary disease, gestational hypertension, and diabetes as well as obstructive sleep apnea. Routine physical activity during pregnancy may attenuate some of the comorbidities associated with an increased body weight. This is particularly important for overweight and obese women to optimize their health and longevity as well as that of their baby.

There are few randomized controlled trials or systematic reviews specifically addressing the effects of physical activity on maternal and neonatal outcomes, making precise clinical recommendations difficult. Most recommendations are based on observational studies, consensus guidelines, or extrapolations from animal models. A recent systematic review of 14 trials involving 1014 pregnant women evaluated the effect of aerobic exercise on maternal and neonatal outcomes. Although largely inconclusive, the authors noted that those who engage in 2 to 3 episodes of weekly exercise have similar pregnancy duration, risk of cesarean delivery, and infant birth weight, as those who maintain their habitual activity level. The authors felt that they were unable to confidently show whether exercise has other effects on maternal-fetal outcomes due to a lack of available evidence, methodological flaws, and small sample sizes of the included studies. They suggest that the available literature lacks power and consistency to allow evaluation of the potential risks or benefits of physical activity during pregnancy for the mother or infant but concluded that aerobic exercise during pregnancy can maintain or improve physical fitness, a known contributor to reduced cardiovascular morbidity and all-cause mortality. There is presently a need to evaluate the evidence on the impact of a physically active pregnancy on the mother and baby.

Pregnancy is a unique state in which women are often highly motivated to institute behavior change. However, many women are unaware of what constitutes “safe and effective” exercise in pregnancy and have difficulty overcoming common barriers to participation. In addition, health care providers may fail to recognize the benefits of being physically active during pregnancy and may be unaware of available screening tools such as the “Physical Activity Readiness Medical Exam for Pregnancy.” This pregnancy-specific tool, endorsed by several North American obstetrics and exercise societies, considers medical and obstetrical history and provides a list of absolute and relative contraindications to exercise in pregnancy in a check list format. It also includes aerobic and muscular conditioning guidelines, safety considerations, and guidelines to patients as to when to stop exercise and seek medical advice. Providers should be aware of the benefits of non-sedentary pursuits during gestation and in light of the obesity epidemic, ensure their patients attempt to overcome the challenges presented to them in our modern obesogenic environment.

The purpose of this review is to provide a synopsis of the physiology of pregnancy and summarize the evidence concerning physical activity during pregnancy and its effects on maternal and fetal health, incorporating both novel emerging literature and existing practice guidelines in the context of obesity prevention and management.
METHODS

OVID (Medline), EMBASE and PSYCHINFO databases were queried from 1950 to March 1, 2010 with the title search words “exercise,” “physical activity,” “pregnancy” and “gestation.” After limiting the search to studies involving human subjects in the English language, a total of 505 relevant articles were retrieved. Each abstract was screened for relevance to the purpose of the review leaving a total of 212 articles. Each abstract was then systematically reviewed. Reference lists were reviewed to identify additional articles. Relevant studies were grouped according to maternal (i.e., gestational diabetes mellitus [GDM], preeclampsia, pregnancy complications) and fetal outcomes (i.e., small for gestational age [SGA], large for gestational age [LGA], medical complications).

DISCUSSION

Section 1: Overview of Physical Activity in Pregnancy

Exercise Physiology and Pregnancy

Pregnancy and exercise are independently associated with significant physiologic and metabolic changes. It is important to recognize that pregnant women are capable of benefiting from physical activity to a similar extent as nonpregnant women, as the physiological response to physical exertion does not differ significantly compared with the nonpregnant state. Table 1 outlines the activity-induced changes in maternal physiology relative to the pregnant resting state to help the reader understand the basic physiological adaptations to maternal physical activity in pregnancy.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (HR)</td>
<td>↑</td>
</tr>
<tr>
<td>Stroke volume (SV)</td>
<td>↑</td>
</tr>
<tr>
<td>Cardiac output (Q)</td>
<td>↑</td>
</tr>
<tr>
<td>Tidal volume (Vt)</td>
<td>↑</td>
</tr>
<tr>
<td>Core temperature</td>
<td>↓</td>
</tr>
<tr>
<td>Placental perfusion</td>
<td>↓</td>
</tr>
<tr>
<td>Hemoconcentration</td>
<td>↓</td>
</tr>
<tr>
<td>Plasma volume</td>
<td>↓</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>↓</td>
</tr>
<tr>
<td>Absolute energy expenditure for a given work load</td>
<td>↑ (as a result of weight gain)</td>
</tr>
</tbody>
</table>

Pregnancy-induced changes in maternal physiology are primarily designed to protect the developing fetus by ensuring that the metabolic demands of both mother and fetus are met. Recent evidence suggests that the fetus is not deprived of substrate during periods of maternal physical activity in the presence of adequate maternal nutrition. This protective effect may be mediated by changes in substrate delivery across the placenta arising from activity-induced alterations in placental form and function. Jackson et al. compared the histomorphometry of term placentas from women who exercised regularly throughout either the entire or solely the first half of pregnancy and made comparisons with matched controls. Using stereological techniques to assess placental volumetric composition, surface area, and villous and vascular differences between the groups, it was noted that exercise throughout pregnancy increased the parenchymal component of the placenta, the total vascular volume, and site-specific capillary volume, as well as the surface area and other parameters associated with an enhanced rate of placental perfusion, and transfer function. They noted that exercise-induced placental changes were confined to villi >80 μm in diameter and attributed the lack of change in smaller villi to adaptive mechanisms, chiefly increased rates of blood flow in the mid-trimester, that maintain fetal oxygenation and substrate delivery for the remainder of pregnancy. As such, pregnancy-induced, placenta-mediated adaptation occurs to balance the maternal-fetal energy demands during exercise and optimize fetal growth in active mothers. Studies of placental perfusion and function show an improvement in blood flow and gas exchange in the placentas of women who engage in regular physical activity.

Maternal blood glucose levels are also affected by exercise in pregnancy. Seminal work by Clapp and Capeless demonstrated that sustained weight-bearing activity during pregnancy elicits a transient reduction in placental glucose. This occurs, as placental blood flow and maternal blood glucose concentrations are decreased, and blood is redirected to active muscles and skin. This effect was demonstrated to be strongest at moderate intensity exercise, in late pregnancy and shortly after a meal. This effect differs from the nonpregnant state, during which exercise elicits a hyperglycaemic response at the onset of activity. Reduction in blood glucose may be observed, as hepatic glucose output is balanced with increased skeletal muscle uptake due to the demands of physical exertion. Although there are few studies addressing causal mechanisms, these findings sug-
gest that inadequate nutrition or a combination of factors (e.g., contraindications to exercise during pregnancy), rather than simply maternal physical activity, must be present for strenuous physical activity to adversely affect delivery of substrate to the fetus. Adequate ingestion of nutrients throughout the day, ideally several hours before engaging in structured physical activity, may ensure optimal substrate availability for mother and baby.

Methodological constraints make it difficult to predict whether an acute period of fetal hypoglycemia occurs at the onset or during the course of maternal physical activity, and whether this results in any long-term negative consequences. Additionally, there is a paucity of data from well-designed randomized controlled trials examining the long-term effects of maternal physical activity on downstream child health. However, ample experimental data in both humans and sheep have demonstrated that glucose and oxygen delivery to the fetus is not compromised due to maternal exercise in uncomplicated singleton pregnancies. Although an acute period of fetal hypoglycemia may occur at the onset of maternal exercise, fetal glucose delivery is likely to be enhanced by the greater placental surface area available for uptake in active women. This leads one to speculate that the fetus is protected from hypoglycemia as a result of this compensatory mechanism. The physiologic processes responsible for the maintenance of placental blood flow, cord blood oxygen saturation, and glucose delivery during exercise include maternal hemocoencentration (via decreased plasma volume), increased cardiac output, and improved perfusion balance at the placenta. As such, there seem to be protective mechanisms in place that compensate for the theoretical risks associated with hypoglycemia due to physical activity.

A recent clinical study by May et al compared low-risk pregnant women who exercised regularly throughout pregnancy (>30 minutes of aerobic exercise, 3 ×/wk) with healthy nonexercising controls and found, using fetal magnetocardiograms, that the fetal heart rate (HR) at 36 weeks’ gestational age was significantly lower, and the variability was significantly increased during maternal physical activity in the exercise group. This finding counters previous research suggesting that a decrease in fetal HR that occurs during or immediately after maternal aerobic exercise is due to chronic fetal hypoxia; one would expect decreased HR variability indicative of an adverse stress on fetal autonomic nervous system development if chronic hypoxia were present. Previous work examining the effect of regular exercise over the course of pregnancy in largely sedentary patients found that maternal physical activity did not impair uteroplacental blood flow as measured by Doppler ultrasound scans of the uterine and umbilical artery pulsatility index immediately following a graded exercise test in the third trimester. Because serum erythropoietin can be a marker for acute and/or chronic hypoxia, investigators have also looked at these levels in association with maternal exercise. In one study, continuous exercise throughout gestation did not alter maternal serum erythropoietin concentration, although a small acute elevation was observed after exercise in mid and late pregnancy. Other studies have similarly found that markers of fetal stress, such as levels of erythropoietin or cord blood and amniotic fluid, are not increased at the time of delivery in women who exercised throughout pregnancy, suggesting that fetal oxygenation was not impaired.

During the second and third trimesters of pregnancy, the fetal parasympathetic and sympathetic nervous systems are maturing, which leads to increased HR variability and decreased HR. Furthermore, regular maternal aerobic exercise in healthy, low-risk pregnancies seems to positively influence the development of fetal cardiac autonomic control, an effect that has been hypothesized to arise from chronic exposure to norepinephrine and other catecholamines essential for fetal development. This evidence, together with the developmental origins hypothesis, which states that the fetus makes adaptations in response to the in utero environment, suggests that maternal exercise may induce an adaptive response in utero that yields cardiovascular health benefits later in life.

Energy Expenditure During Pregnancy

During pregnancy, energy expenditure is altered, both at rest and with physical activity. Total energy expenditure, quantified by oxygen uptake (VO2), is the sum total of calories used at rest plus those expended when performing a given amount of external work. Pregnancy is generally associated with appreciable weight gain; this added mass contributes to the increase in energy expended at rest and during submaximal weight-bearing activity (i.e., walking, running, stepping, etc.) relative to the nonpregnant state. As such, the metabolic cost of physical activity progressively increases from early to late pregnancy in proportion to the amount of GWG and is independent of maternal physical activity status. Therefore, it is expected that the VO2 values relative to body weight (i.e., mL/kg/min) will remain similar.
or increase slightly when compared with the non-pregnant condition with similar exertion, suggesting that pregnancy does not impair oxidative metabolism but rather impedes activity capacity due to the added weight of pregnancy.

To examine the effect of added pregnancy weight on maternal energy expenditure during submaximal exertion, Carpenter et al. had women perform cycling and treadmill exercise tests at 34 weeks’ gestation and 8 weeks postpartum. Although absolute VO₂ at the same workload was higher during pregnancy than postpartum with both activities, none of the differences persisted when VO₂ was expressed per kilogram body weight. In fact, increased body weight during pregnancy compared with the postpartum period accounted for 75% of the increased VO₂ during submaximal activity. During pregnancy, there is a need to provide a continuous supply of energy to the utero-placental unit and to the developing fetus. The energy demands associated with fetal growth, increasing maternal body weight, and the increased work of breathing, collectively contribute to the overall rise in oxygen consumption (i.e., VO₂) and thus pregnancy-related energy expenditure during physical activity.

Cardiorespiratory Adaptations to Physical Activity During Pregnancy

Pregnancy-related maternal cardiovascular adaptations include an increase in blood volume, HR, stroke volume, and consequently cardiac output (HR × stroke volume). Changes in the anatomy of the chest wall (e.g., increased elasticity, flaring and expansion as well as elevated diaphragm) allow pregnant women to compensate (more so than nonpregnant women) during exercise with an increase in minute ventilation (tidal volume × breaths/min) and tidal volume (inspired volume of air/breath). As the developing fetus presses upward against the diaphragm, breathing may be more labored, resulting in mild discomfort due to dyspnea.

Concern has been raised that the redistribution of blood flow to active muscle during physical exertion could result in inadequate delivery of nutrients and oxygen to the fetus, with potentially lasting negative effects. However, in an uncomplicated pregnancy, moderate-to-vigorous physical activity (i.e., movements that result in the participant feeling quite warm and increasing their respiratory rate) has been deemed acceptable and beneficial for both pregnant women and their developing offspring, provided there are no contraindications (Table 2). How-

| TABLE 2 |
|-------------------------------|-----------|
| **Contraindications for exercise during pregnancy** | **Absolute** |
| Ruptured membranes             | Previous spontaneous abortion |
| Preterm labor                  | Mild/moderate cardiovascular disorder |
| Hypertensive disorders of pregnancy | Mild/moderate respiratory disorder |
| Incompetent cervix             | Anemia (Hb: <100 g/L) |
| Growth-restricted fetus        | Malnutrition or eating disorder |
| High-order multiple gestation  | Twin pregnancy after 28th wk |
| (≥3 fetuses)                   | Other significant medical conditions |


ever, fetal cardiac autonomic control may be affected by the intrauterine milieu, as aberrant measures have been documented in growth-restricted fetuses, signifying that assessing the fetal autonomic response to maternal exertion may be an avenue of research worth pursuing to better understand fetal cardiovascular adaptations to physical activity. As discussed earlier, a prospective longitudinal trial by May et al. found that a decrease in fetal HR and increased HR variability during aerobic exercise are indicative of normal healthy development. This suggests that, in addition to maternal benefits, there may be positive fetal cardiovascular adaptations as a result of regular maternal physical activity because physical conditioning has been demonstrated to improve HR and HR variability measures in previously sedentary adults.

Musculoskeletal Adaptations of Pregnancy and Physical Activity

Physical discomfort is common during pregnancy and has been shown to be attenuated or prevented with routine activity. The anatomical changes that occur during pregnancy include anterior shift in the center of gravity, exaggerated lordosis of the spine, protruding abdomen, rectus diastasis, and altered gait. Discomfort may be caused or exacerbated by ligament laxity from increased progesterone and relaxin that prepare the musculoskeletal system for delivery. Excessive GWG often leads to increased lower back, pelvis, and/or joint pain. Musculoskeletal pain can be attenuated with physical activity in

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Section 2: Impact of Physical Activity on Maternal Pregnancy Outcome

Maternal Physical Activity and Gestational Diabetes Mellitus

Aerobic exercise improves insulin sensitivity in pregnant women. Those who report continuous activity before and during pregnancy have a lower risk of developing GDM, particularly when the physical activity is performed at a moderate-to-vigorous intensity level. These protective effects may be attributed to the regulation of glycemic control. In a randomized controlled trial of treatment of GDM, exercise and diet were compared with insulin therapy and diet, with euglycemia as the primary outcome. There were no significant differences in maternal-fetal outcomes, suggesting that exercise and diet can be a safe and effective alternative treatment for GDM during pregnancy. Physical activity was also examined in a case-control study of 155 pregnant women with GDM compared with 386 healthy pregnant controls. Engagement in physical activity before and during pregnancy was associated with a reduced incidence of GDM, with pronounced benefits especially in those with an increased prepregnancy (BMI ≥ 25). Considerable population and clinical level data indicate that continuous long-term engagement in physical activity optimizes outcomes with respect to glycemic control during pregnancy regardless of glucose tolerance status. Pregnant women with an increased BMI who are physically active during pregnancy have approximately a 50% reduction in risk for developing GDM when compared with sedentary controls, suggesting a protective effect against the development of GDM. To gain the greatest protective benefit, physical activities should be initiated early in life, strongly recommended to all women of childbearing age (particularly those who carry excess weight), and be maintained throughout the life course.

Maternal Physical Activity and Preeclampsia

Several investigators have demonstrated that women who engage in moderate-to-vigorous intensity physical activity before and during uncomplicated pregnancies are at a reduced risk of hypertensive disorders. Physical conditioning and preeclampsia have opposite effects on critical physiological functions, such as placentation and vascularization and susceptibility to oxidative stress and endothelial dysfunction. Evidence suggests that physical activity has the greatest beneficial effects for preeclampsia prevention when performed at a moderate-to-vigorous intensity before and during gestation. Women who are active during pregnancy seem to have roughly a 40% reduction in risk of developing preeclampsia. Thus, appropriate physical activity seems to be a promising preventive strategy. However, one recent observational cohort study did suggest that extreme amounts of aerobic exercise (>270 min/wk) during the first trimester of pregnancy may increase the risk of developing preeclampsia. Although evidence is limited to this one study, it seems reasonable that women should be advised not to exceed physical activity recommendations.

Maternal Physical Activity and Preterm Delivery

Physical activity during pregnancy has been demonstrated to have no or a slight protective effect on gestational age at delivery and incidence of preterm birth (<37 weeks' gestational age). A recent systematic review of aerobic exercise interventions during pregnancy did not show a significant adverse effect of maternal activity on preterm birth or mean gestational age, and concluded that aerobic exercise maintained or improved fitness for women, but that data are insufficient to infer other important risks (such as preterm birth) or benefits for the mother or infant. A large population-level cohort study that used self-report measures of aerobic, resistance, low-, and high-intensity physical activity found that physical activity during pregnancy had no effect on risk of preterm birth and that, when compared with nonexercisers, the 40% of women who participated in some kind of physical activity demonstrated a reduced risk of preterm birth. Another randomized controlled trial suggested that the effects of resistance training during pregnancy on previously sedentary, healthy women carrying singletons did not alter gestational age at delivery when compared with inactive controls. Taken together, these results support the notion that healthy pregnant women, without contraindications to physical activity, are able to engage in these active behaviors without undue risk of preterm birth. Whether such activities confer a benefit in reducing the rate of preterm birth requires further study.

Maternal Physical Activity and Mode of Delivery

Although one prospective study of 800 pregnant women found that sedentary mothers were 4 times more likely to have a cesarean delivery compared with women who exercised regularly, this finding has not been replicated in other investigations.

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Further, light-moderate resistance training during the second and third trimesters had no effect on the rate of normal, instrumental, or cesarean delivery when compared with inactive controls. Although the evidence is limited, maternal physical activity does not seem to impact mode of delivery.

Section 3: Impact of Physical Activity on Neonatal Outcomes

Physical Activity and Fetal Growth

Physical activity during pregnancy seems to be protective against birth weight extremes (i.e., SGA and LGA) and thus increases the likelihood of delivering an appropriate-for-gestational-age infant. Most studies have not shown a significant detrimental effect on birth weight with moderate amounts of exercise.74-76 suggesting that regular physical activity is safe and does not compromise fetal growth. Furthermore, a recently published randomized controlled trial concluded that exercise training may attenuate adverse consequences of excess maternal body weight on infant birth size.78 The optimization of infant birth weight in women who engage in regular physical activity is thought to occur as a result of an increased functional capacity of the placenta to appropriately deliver nutrients via an increase in placental surface area, improvements in blood flow, and an enhanced-perfusion balance.1,3,25 Importantly, physical activity may prove most advantageous for overweight or obese pregnant women as a way to reduce their risk of delivering an LGA infant. Observational data from a large birth cohort demonstrated that routine engagement in exercise during pregnancy protects the developing infant from birth weight extremes (i.e., SGA or LGA).79 Some studies have demonstrated a link between maternal physical activity and low birth weight.73,80-88 In these studies, an important limitation was lack of controlling for dietary intake. Many of these classical studies have focused on lean, healthy active women,138-91 and therefore results may not be generalizable to the other populations. Clapp noted an asymmetric reduction in birth weight of exercising mothers, a difference that was entirely accounted for by a reduction of neonatal fat mass with no changes in lean mass compared with the offspring of matched controls.89

Currently, there is a dearth of evidence from well-designed, appropriately powered randomized controlled trials to address the effects of maternal physical activity on fetal growth outcomes. The inconsistency of results from studies examining the effect of activity on infant birth weight likely arises from differences in the type, frequency, timing, and duration of the activity program imposed. Further, lack of control for confounding variables, including maternal nutritional status (i.e., caloric intake during pregnancy), gestational age at birth, and socioeconomic status may contribute to the discrepancy in the literature.8

Physical Activity and Long-Term Child Health

Recent findings suggest that the downstream effects of maternal physical activity may trigger beneficial adaptations to environmental stressors, which may lead to health benefits later in life.72,82,85 The intrauterine environment plays a critical role in downstream child health and as such, there is a need for strategies aimed at preventing childhood adiposity by managing maternal weight gain during pregnancy.

Human and animal studies have shown that babies born LGA are more likely to be overweight in childhood, adolescence,80 and adulthood.80 In contrast, babies born SGA are more likely to have increased truncal adiposity, develop insulin resistance, type 2 diabetes mellitus, and early onset cardiovascular disease.81 Thus, modifying risk factors and increasing physical activity, which have been suggested to optimize birth weight,84,85 may improve downstream child health. It has been observed that maternal prepregnancy weight, high GWG, and GDM are all positively and independently associated with offspring weight.89 Therefore, intrauterine nutrition, mediated by these factors, may play an important role in subsequent risk for obesity. Recently, Fraser et al91 demonstrated that children of mothers who gained in excess of the GWG recommendations had elevated BMI, waist circumference, greater fat mass, blood pressure, and inflammatory markers in their circulation at age 9 when compared with offspring of mothers who met the recommendations. This preliminary evidence suggests that gaining within the current recommendations may confer health benefits later in life for the child. Overall, physical activity provides an accessible and affordable outlet by which the predisposing factors for the development of obesity may be modified during the course of pregnancy.

Section 4: Recommendations for Physical Activity and Lifestyle in Pregnancy

An ideal physical activity program for pregnancy must ensure that recommendations are appropriate for the individuals’ fitness level, stage of pregnancy, and degree of motivation while anticipating potential risks and identifying necessary pregnancy modifications. Promotion of individualized, activity-specific behaviors may discourage women from adopting ex-
cessively sedentary pursuits during pregnancy. Physical activity may also prevent or manage chronic conditions, such as hypertension, obesity, gestational diabetes, dyspnea, and preeclampsia. Table 3 highlights exercise HR training zones for overweight and obese pregnant women who choose to incorporate physical activity into their lifestyle as a way to manage GWG and improve their overall health. Regular physical activity may help women meet GWG targets and thus positively influence maternal-fetal outcomes.

The known benefits of physical activity on maternal-fetal health obligate healthcare practitioners to provide advice to women regarding best practices for these healthy behaviors throughout pregnancy. To assist in this endeavor, several clinical practice guidelines have been published. In North America, the Canadian Society for Exercise Physiology in partnership with the Society of Obstetricians and Gynecologists of Canada and the American College of Obstetricians and Gynecologists are key organizations who have developed an example of such guidelines that support participation in regular physical activity during uncomplicated pregnancies. Their respective position statements describe the contraindications that would preclude exercise participation as highlighted in Table 2. The guidelines also provide information on the type, frequency, intensity, and duration of routine exercises suitable for women and their developing baby. However, it is important for clinicians to individually assess and monitor each patient and review their history to avoid potentially limiting physical activity in otherwise healthy women who have previously presented with a contraindication to participation.

Table 4 provides a synopsis of recommendations for exercise in pregnancy. Of greatest importance before commencing physical activity during pregnancy is appropriate medical screening. An example of an appropriate useful screening tool is the “Physical Activity Readiness Medical Examination for Pregnancy” or the PARmed-X for Pregnancy. This user-friendly tool was designed to be a guideline for health screening before participation in a prenatal fitness class or any other type of exercise or physical activity during pregnancy. The PARmed-X is endorsed by the Canadian Society for Exercise Physiology, Society of Obstetricians and Gynecologists of Canada, and the American College of Sports Medicine, is readily available free of charge and is encouraged to be reproduced in clinical settings.

Table 4 Sample exercise prescription for pregnant women without contraindications

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Intensity</th>
<th>Duration</th>
<th>Type</th>
<th>Previous Sedentary</th>
<th>Active</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 d/wk</td>
<td>Low-moderate</td>
<td>15 min gradually ↑ to 30 min sessions</td>
<td>Low impact aerobic (swim, walk, cycle)</td>
<td>Resistance/strength training</td>
<td>Resistance/strength training</td>
</tr>
<tr>
<td>4 d/wk</td>
<td>Moderate-vigorous</td>
<td>[≥]30 min per session</td>
<td>Low impact aerobic</td>
<td>Resistance/strength training</td>
<td>Resistance/strength training</td>
</tr>
</tbody>
</table>


Table 5 Target gestational weight gain for singleton pregnancies

<table>
<thead>
<tr>
<th>Prepregnancy Body Mass Index (BMI)</th>
<th>Range in kg</th>
<th>Range in lbs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight (&lt;18.5 kg/m²)</td>
<td>12.5–18</td>
<td>28–60</td>
</tr>
<tr>
<td>Normal weight (18.5–24.9 kg/m²)</td>
<td>11.5–16</td>
<td>25–35</td>
</tr>
<tr>
<td>Overweight (25–29.9 kg/m²)</td>
<td>7–11.5</td>
<td>15–25</td>
</tr>
<tr>
<td>Obese (≥30 kg/m²)</td>
<td>5–9</td>
<td>11–20</td>
</tr>
</tbody>
</table>

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recommended GWG for obese women. “Project Viva,” a large prebirth longitudinal cohort found no increased risk of adverse birth outcomes when comparing adequate versus inadequate GWG in the subgroup of obese women, thereby supporting the revision. Although some interventions aimed at attenuating GWG have been unsuccessful in preventing women from exceeding the Institute of Medicine recommendations, others have had success. In a community-based randomized controlled trial during pregnancy, for example, home-based moderate intensity cycling exercise reduced offspring birth weight and growth promoting factors (i.e., insulin-like growth factor-1 and -2), without alterations in maternal insulin sensitivity. These findings suggest that routine activity yields protective benefits in offspring of overweight women.

FUTURE DIRECTIONS

Our understanding of the influence of maternal physical activity on short- and long-term pregnancy outcomes is far from complete. Further, knowledge of the underlying mechanisms is limited. The physiologic processes driving substrate delivery from mother through placenta to fetus are not known. The extent to which energy is partitioned in utero in the presence of excessive prepregnancy weight, rapid and/or excessive GWG, and maternal exercise at the molecular level remains unclear. Recent advances in our understanding of developmental plasticity and epigenetics are shedding new light on critical molecular pathways, which may provide insight into novel therapeutic targets that may in turn be modified with physical activity.

Historically, the major clinical focus has been protection from fetal undernutrition, yet in today’s society, we must consider prevention strategies for women who have a high prepregnancy weight and are at increased risk for excessive GWG. Promotion of physical activity is one such strategy that must continue to be studied during pregnancy to determine the effects that maternal physical activity has on downstream child growth and development. There is considerable evidence to suggest that lifestyle interventions during pregnancy are safe and may provide both maternal and fetal benefits.

THE CASE REVISITED

Following discussion and prescreening using the PARmed-X for pregnancy, Susan was advised to engage in aerobic activity at low-to-moderate intensity 3 times per week. Given her previous sedentary lifestyle, she was encouraged to exercise for 15 minutes per session for 2 weeks and to increase the duration of activity to 30 minutes per session thereafter. Providing this regimen was well tolerated for 2 weeks, her plan was to increase the frequency of physical activity to 4 times per week. Options for physical activity were discussed, including outdoor walking programs, upright stationary cycling in her home, and/or water aerobics for moderate resistance training. Modification of physical activity for pregnancy was reviewed, as were methods to assess intensity including the “talk test”—a surrogate marker of physical exertion. It was also suggested that a lower-intensity warm-up and cool-down period be included in any type of physical activity. Maintenance of the exercise program in the postpartum period was strongly recommended to help offset the severity of weight retention.

KEY POINTS

- Exercise during pregnancy is safe for pregnant women and their babies in the absence of specific contraindications.
- Being physically active before becoming pregnant and continuing to exercise during pregnancy may help minimize the risk of developing GDM, preeclampsia, and abnormal fetal growth.
- Maternal physical activity may help limit GWG to the recommended targets.
- Emerging evidence suggests that the developing child has the ability to positively adapt to the physiological stress imposed by maternal physical activity and thereby may reduce their risk of excessive and restricted growth; an effect that may confer adaptive benefits for the child later in life. This effect may be more beneficial to overweight or obese women who tend to have larger babies.

ACKNOWLEDGMENT—Authors thank the Ontario Ministry of Research and Innovation whose funding to K.B.A. provides graduate student support for Z.M.F. Additional thanks to the Canadian Institutes for Health Research (CIHR), the University of Ottawa Faculty of Health Sciences, CHEO Research Institute, and the Ottawa Dragon Boat Foundation who provide financial support for this area of research focus.

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REFERENCES

44. Perennicke V, Young G. Interventions for preventing and treating pelvic and back pain in pregnancy. Cochrane Database Syst Rev. 2007;CD001139.
45. Metzger K, Schutz Y, Boulvain M, et al. Physical activity and
Obstetrical and Gynecological Survey

12

10.0 FINAL DISCUSSION

Children born to obese mothers or those who have experienced excessive GWG, have an increased risk of obesity themselves as a result of the likelihood of nutrient overexposure and associated developmental programming in utero as well as environmental exposure to the same obesogenic lifestyle as the mother. Accordingly, the developmental origin of adult disease hypothesis posits that environmental assaults during intrauterine life may alter central regulatory mechanisms of the developing child [4, 8, 71, 106, 131]. Such in utero perturbations may predispose the fetus to limited movement and increased food intake behaviours later in life by compromising physiological thresholds of energy balance regulation. During this critical period developmentally plastic systems may be disrupting homeostatic balance of the oxrexigenic and anorexigenic responses to postnatal environmental stressors [9]. As such, chronic exposure to energy surplus, hormones and growth factors in utero may potentially increase offspring susceptibility to downstream chronic disease [4]. Therefore, it is of paramount importance to identify the underlying physiological factors involved with maternal-fetal obesity transmission to best design effective prevention and management strategies.

The purpose of this dissertation was to help address the knowledge gaps and better understand maternal contributors to fetal growth and energy metabolism, validate population level predictors of excessive fetal growth, evaluate the effects of maternal obesity and/or excessive GWG on IGF axis protein expression in mom and baby, gather
information from a pregnant population that would help design preventive strategies and efficacious weight management interventions during gestation and review the evidence concerning physical activity as a potential modifier of fetal growth. This work provides several contributions including:

i) Identification of independent contributors to excessive fetal growth including maternal obesity and/or excessive GWG with reference to the most recent 2009 IOM GWG recommendations

ii) The discovery of aberrant expression of IGFBP-4 in cord serum from pregnancies complicated by maternal obesity (see below table)

iii) The discovery that excessive GWG augments expression of IGFBP-3 in maternal blood (see below table)

iv) Identification of clinically relevant discussion topics during the prenatal visit that are not being addressed by the care provider. These include a lack of information about pregnancy-specific energy requirements, little to no evidence-based recommendations about appropriate GWG targets and a lack of informed education concerning the beneficial role of physical activity during pregnancy
Conclusion

What can be taken from this series of studies is that pregnancy is a critical period of body weight regulation for the mother and baby where obesity and/or excessive GWG may compromise molecular signals over time leading to subclinical and eventually clinical presentation of obesity-related pathology. However, human resiliency aids in our ability to maintain homeostasis, respond to allostatic loads placed on the body (i.e., overnutrition and sedentarism) and adapt to external stressors including physical. Interestingly, mom and baby may beneficially adapt to the external stimuli of human movement in the same way as non-pregnant individuals would, suggesting that human health may be optimized through lifestyle intervention. Future research should therefore aim to evaluate the effects of a physical activity and nutrition intervention during pregnancy on downstream child health in a randomized controlled trial. Furthermore, understanding the mechanisms underlying the association between the intrauterine milieu and childhood obesity by examining placenta nutrient transporters may enhance our knowledge of placenta form and function and help unravel the complex interactions mediating some of the observed changes in neonatal phenotype that may involve the maternal-fetal interface.

As noted by Charles Darwin in his seminal work[132], given that “man tends to increase at a greater rate than his means of subsistence” we can speculate that this also holds true for those struggling with obesity such that as the global prevalence of this condition rises, a suitable solution for the associated pathology lags behind. And while knowing "In the struggle for survival, the fittest win out at the expense of their rivals
because they succeed in adapting themselves best to their environment” we must therefore acknowledge that “It is not the strongest of the species that survives, nor the most intelligent that survives. It is the one that is the most adaptable to change”. Such eloquent historical principles provide reason to pursue multidisciplinary strategies that optimize the intrauterine milieu as it is well known that “In the long history of humankind (and animal kind, too) those who learned to collaborate and improvise most effectively have prevailed”.

Targeting a suboptimal intrauterine environment with natural therapies including healthy, balanced dietary practices and regular engagement in physical activities may promote beneficial maternal-fetal adaptations that resonate throughout the life-course. Presently, much attention, with respect to developmental origins of adult health and chronic disease, has focussed on the long-term effects of nutrient deprivation or energy deficits during pregnancy suggesting that those who have the most experience with famine may be at greatest risk for disease later in life. This is said to be in part due to a down-regulating adaptation that limits overall fetal size to preserve the function of vital organs and systems including brain and heart. However, this is unlikely to result in the presentation of a diseased state unless the child is born into an environmental mismatch of energy surplus, thus overwhelming intelligently designed ‘thrifty phenotypes’ and predisposing aberrant catch-up growth. However, our present society is rarely forced to overcome such deprivation and is subjected to cope with experiences of nutrient excess and/or positive energy balance during pregnancy. Thus, this changes the way in which we adapt and project
developmental origins of chronic disease risk such that those in our society who may be at the greatest risk are not those with the most historical experience with famine, but those individuals whose ancestors had the least experience with excess. Such a continuum of disease risk based on one’s historical pregnancy experiences and the environment in which the offspring thrives post-natally will ultimately contribute to the major factors dictating the severity of metabolic compromise, if any, later in life.

Overall, further insight regarding the precise regulation of the mechanisms mediating maternal phenotype and behaviours to fetal growth and development will ultimately lead to more effective pharmacological and behavioural interventions during the perinatal period. These advances may have a profound impact on clinical obstetrical practice and medical education as knowledge is disseminated from bench to bedside to optimize maternal-fetal outcomes in the presence of obesity and/or excessive pregnancy weight gain. Such knowledge exchange practices (see APPENDIX J) and fruitful collaboration will have a profound impact on patient triage, diagnoses, the implementation of weight management strategies, will lead to enhanced monitoring of phenotype throughout the life course and eventually will transform clinical and public health practices ultimately reducing the intergenerational burden obesity.
11.0 REFERENCES


June 13, 2011

NRC Research Press

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12.2 APPENDIX B – Tri-council policy statement (TCPS) certificate for research ethics involving humans

Certificate of Completion

This is to certify that

Zach Ferraro

has completed the Interagency Advisory Panel on Research Ethics' Introductory Tutorial for the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS)

Issued On: January 15, 2010
APPENDIX C - Consent form for placenta dysfunction (IGF-related) studies

Patient Information and Consent Form

MECHANISM OF PLACENTAL DYSFUNCTION IN OBESE MOTHERS

WHY ARE YOU BEING GIVEN THIS FORM?

This form will provide information about the study. This form will also (1) Allow your obstetrician to run additional tests on your blood and take blood from your umbilical cord after delivery; (2) Allow your obstetrician to conduct ultrasounds during your pregnancy and to collect and examine your placenta after delivery (3) Allow you to decide if you would like to participate in the study described below.

PROJECT TEAM

Dr. A. Gruslin (Maternal-Fetal Medicine Specialist), Ottawa Hospital-General Campus
Dr. Q. Qiu (Research Scientist), Ottawa Hospital
Mylène Gagné (3rd year Medical Student), University of Ottawa
Kristina Arendas (Postgraduate Year 2), Ottawa Hospital-General Campus
Sharon Lafrenière (Research Nurse) Ottawa Hospital-General Campus
Lindsay Patrick (Research Assistant) Ottawa Hospital-General Campus
Zachary Ferraro (3rd year PhD Student), University of Ottawa

WHY IS THE STUDY BEING DONE?

In the past decade, obesity has greatly increased in the general population, and doctors are seeing more and more obese pregnant women in their clinics. This is important because many reports explain that obesity during pregnancy increases the risk of pregnancy complications.

When a woman is obese certain changes can occur in her body that may cause changes to a vital tissue during pregnancy, the placenta. The placenta, the connection between the mother and baby, is essential to both fetal growth and health. If the placenta is dysfunctional (because of obesity for example), the baby and mother can suffer serious complications.

Our knowledge is very limited as to the link between obesity and fetal complications. We know that in order to have a healthy placenta and baby the mother needs a certain protein called insulin growth factor II (IGF-II). This

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Updated on September 23, 2010
Patient Information and Consent Form

protein is made by the body and is present normally in all women but we believe that obesity might cause it to decrease. A decrease in IGF-II may lead to placental dysfunction and pregnancy complications. The overall objective of this study is to examine whether changes in IGF-II may be involved with observed placental dysfunction and pregnancy complications.

WHAT WILL YOU BE ASKED TO DO?
If you agree to participate
(1) three blood tests (5mL each), two during your pregnancy and one at delivery
(2) three ultrasounds during your pregnancy
(3) taking cord blood (5mL)
(4) sending your placenta to the laboratory for analysis after delivery
(5) have a small sample of placenta tissue stored and subsequently analyzed for non-clinical genetic markers of metabolism (i.e., IGF axis protein expression).
(6) record your baby’s weight as well as the weight of the placenta.

Results from the genetic component of this study will be preliminary and the clinical implications of any findings may not be understood for many years. These genetic markers have NO clinical diagnostic value and thus no individuals, other than study researchers, will have access to these samples or information gained from the samples. Because no information will be provided to participants or others from the examination of this sample, the risk is minimal.

We are NOT screening for genetic abnormalities but rather potential relationships that exist as a result of excess body weight. Therefore, the use of the term non-clinical genetic markers refers to testing ONLY FOR gene variations which may provide insight on how nutrients are transferred from mom to baby during pregnancy.

We will conduct our study using all of these results. Blood samples provided will only be analyzed for the purposes of this study and no further testing will be done without your written consent. This will, in no way, interfere with your care. In addition, we will also record whether you have any characteristics that may affect our research project (e.g., diabetes, hypertension). That information will be given a code for research, and any papers with your identity will be kept in a locked cabinet by the senior physician (Dr. A. Gruslin).

POTENTIAL HARMs

There is no risk to you or your baby.
Patient Information and Consent Form

RISKS OF INSURABILITY AND EMPLOYABILITY

We will take all reasonable steps to keep your research information confidential. Should someone not involved in the research find out that you took part in this research study, or if you choose to share your results (if they are provided to you), there is a possibility that this could affect your insurance or employment.

BENEFITS

Our study will help us determine if maternal obesity is related to placental dysfunction and if this dysfunction is associated with changes in IGF-II. This study could provide information for the development of useful clinical screening tools to better understand and therefore better treat obese pregnant women. Although this may not benefit you directly, this knowledge will benefit others in the future.

ALTERNATIVES TO PARTICIPATING IN THE PROJECT

You do not have to participate in this research study to receive standard of care.

PRIVACY AND CONFIDENTIALITY

All information provided regarding you and your baby, including blood and placenta tissue, will be coded with a numeric identifier, will not contain your name and will be kept under lock and key. A list of names and matching codes will be stored separately in the office of Dr. Gruslin so that no identifying information will be present in research files. Only the staff involved in this research study will have access to the records. Overall results may be published for scientific purposes, but participant identity will remain confidential. All results of the study will be kept confidential and will not be communicated to any third parties such as employers, governmental organizations or insurance companies unless you provide specific authorization, or where the law requires, or a court order has been obtained. This includes your spouse, other members of your family and your physician. These results will not appear in your medical chart.

The placenta tissue samples will become property of Dr. A. Gruslin and used for academic research purposes only. The results of this study will not be exploited for commercial use.

No identifiable information will leave the Ottawa Hospital. All information relating to this study will be kept in Dr. Gruslin’s office in a locked cabinet for 15 years. After this time, the papers copies will be shredded and the electronic files will be deleted to ensure that all information is destroyed. All tissue and blood samples taken will be kept until termination of the study under lock and key and stored in

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Updated on September 23, 2010
Patient Information and Consent Form

a -80 freezer in the laboratory of a member of the project team. Following completion of the study all unused samples will be disposed of as medical waste by the University of Ottawa’s usual method.

All the information regarding you or your baby will be kept confidential at the Ottawa Hospital unless release is required by law. Representatives of the Ottawa Hospital Ethics Board (OHREB) and the Ottawa Health Research Institute (OHRI) may review your relevant records for audit purposes under the supervision of Dr Gruslin’s staff, for audit purposes.

COMPENSATION FOR INJURY, LEGAL RIGHTS

You are not waiving your legal rights by agreeing to participate in this study. The doctors and the hospital still have their legal and professional responsibilities.

REIMBURSEMENT OF EXPENSES/PAYMENTS FOR PARTICIPATING

There are no expenses or payments associated with the participation in this project.

YOU HAVE THE RIGHT TO CHANGE YOUR MIND

Your participation in this study is entirely voluntary. You may choose not to participate or to withdraw from the study at any time without providing the investigator with a reason. Your decision will not affect the care you and your baby receive at this institution now or in the future.

NEW INFORMATION DURING THE STUDY?

If any new information during the study becomes available that might affect your willingness to participate, you will be informed as soon as possible.

WHO TO CONTACT IF YOU HAVE ANY FURTHER CONCERNS OR QUESTIONS

If you have any concerns or questions regarding the study, you may reach Dr. A. Gruslin at

ETHICS REVIEW

If you have any questions about your rights as a research participant, you may contact the Chairperson of the Ottawa Hospital Research Ethics Board at 613-798-5555, extension 14902.

Updated on September 23, 2010
Patient Information and Consent Form

STATEMENT OF CONSENT – PRINT AND SIGN NAME

I, ____________________________, (__________________________) have read, or have been read the information given in this 4-page informed consent and all my questions have been answered to my satisfaction. I have had sufficient time to consider whether to participate in this study. My participation in this study is entirely voluntary and I may withdraw from the study at any time without penalty.

I voluntarily consent to participate in this study and allow my placental tissue to be sampled. I will receive a signed copy of this form for my records.

TEAM MEMBER WHO INTERACTED WITH THE SUBJECT – PRINT AND SIGN NAME

To the best of my knowledge, the information in this consent form, and the information that I, ____________________________, (__________________________) have provided in the response to any questions, fairly represents the project. I am committed to conducting this study in compliance with all the ethical standards that apply to projects that involve human subjects. I will ensure that the subject receives a copy of this consent form.

Participant’s name

Participant’s signature ____________________________ Date ____________________________

Investigator/Delegate’s name ____________________________

Investigator/Delegate’s signature ____________________________ Date ____________________________

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Updated on September 23, 2010

(Valid until April 14, 2011)
12.4 APPENDIX D – Research ethics board approval for questionnaire study

The Ottawa Hospital L'Hôpital d'Ottawa

Research Ethics Board Conseil d'éthique en recherches

Monday, November 17, 2008

Dr. Erin Keely

Dear Dr. Keely:

Re: Protocol # 2008565-01H Prenatal Lifestyle Intervention Study - Willingness to Participate Questionnaire

Protocol approval valid until - Monday, November 16, 2009

Thank you for the e-mail from Z. Ferraro dated November 7, 2008. I am pleased to inform you that this protocol underwent expedited review by the Ottawa Hospital Research Ethics Board (OHREB) and is approved. Approval is for the English Prenatal Lifestyle Intervention Study-Willingness to Participate Questionnaire. No changes, amendments or addenda may be made to the protocol or the consent form without the OHREB’s review and approval.

If the study is to continue beyond the expiry date noted above, a Renewal Form should be submitted to the OHREB approximately six weeks prior to the current expiry date. If the study has been completed by this date, a Termination Report should be submitted.

The Ottawa Hospital Research Ethics Board is constituted in accordance with, and operates in compliance with the requirements of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans; Health Canada Good Clinical Practice: Consolidated Guideline; Part C Division 5 of the Food and Drug Regulations of Health Canada; and the provisions of the Ontario Health Information Protection Act 2004 and its applicable Regulations.

Raphael Saghir, M.D.
Chairman
Ottawa Hospital Research Ethics Board

/cb
12.5 APPENDIX E – Research ethics board approval for birth cohort (OaK) analysis

Ottawa Hospital Research Ethics Boards / Conseils d'éthique en recherches

Wednesday, March 03, 2010

Dr. Mark Walker
Ottawa Hospital – General Campus

Dear Dr. Walker:

Re: Protocol # 2010109-01H The Effect of Gestational Weight Gain on Maternal and Neonatal Outcomes: Support for Obstetrical Weight Management?

Protocol approval valid until - Wednesday, March 02, 2011

Thank you for the letter from Zach Ferraro dated February 18, 2010. I am pleased to inform you that this protocol underwent expedited review by the Ottawa Hospital Research Ethics Board (OHREB) and is approved. No changes, amendments or addenda may be made to the protocol without the OHREB's review and approval.

If the study is to continue beyond the expiry date noted above, a Renewal Form should be submitted to the OHREB approximately six weeks prior to the current expiry date. If the study has been completed by this date, a Termination Report should be submitted.

The Ottawa Hospital Research Ethics Board is constituted in accordance with, and operates in compliance with the requirements of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans; Health Canada Good Clinical Practice: Consolidated Guideline; Part C Division 5 of the Food and Drug Regulations of Health Canada; and the provisions of the Ontario Health Information Protection Act 2004 and its applicable Regulations.

Yours sincerely,

[Signature]

Chairman
Ottawa Hospital Research Ethics Board

/ob
12.6 APPENDIX F – Research ethics board approval for placental dysfunction study

Ottawa Hospital Research Ethics Boards / Conseils d’éthique en recherches

Tuesday, June 08, 2010

Dr. Andree Gruslin

Dear Dr. Gruslin:

Re: Protocol # 2008450-01H Mechanism of Placental Dysfunction in Obese Mothers

Thank you for your letter dated May 12, 2010. The protocol amendment report dated May 12, 2010 is approved.

Approval is for the following:
- revised English Patient Information and Consent Form dated May 12, 2010
- revised French Patient Information and Consent Form dated May 12, 2010

Zachary Ferraro has been added as study staff on this file.

Ethical approval remains in effect until April 14, 2011.

Yours sincerely,

Raphael Saginur, M.D.
Chairman
Ottawa Hospital Research Ethics Board

Encl.

All
12.7 APPENDIX G – Copy of the willingness to participate questionnaire

Information and Consent Form
Prenatal Lifestyle Intervention Study - Willingness to Participate Questionnaire

Background
The obesity epidemic among women in their childbearing years is becoming a major public health concern. The number of overweight women between the ages of 20-39 years has doubled in the last two decades. Women with a high pre-pregnancy weight are at the greatest risk of excessive weight gain during pregnancy, which can lead to problems during pregnancy and delivery. In the longer term, the risk for obesity in both the mother and the child is greatly increased with excessive weight gain during pregnancy.

Purpose
Developing healthy eating behaviours and engaging in regular physical activity not only prevent excessive weight gain in pregnancy, it can also minimize your and your child’s risk of developing obesity, heart disease and diabetes. Our research team believes there is a need for a program for pregnant women to learn how to prevent excessive weight gain in pregnancy through healthy eating and physical activity. This program would be specific to, and safe for, pregnant women. We need your input to help us develop this program. We are asking approximately 150 women to complete this survey to understand what your needs are, and whether you would participate in such a program should it exist.

Description of Questionnaire
We are asking pregnant women attending obstetrics clinics to complete our one-time survey with the goal of assessing their willingness to participate in a medically supervised program involving ‘gender and pregnancy specific’ physical activity and nutrition sessions from a certified professional. The information gathered from the survey will allow us to effectively design and offer a program that will benefit future pregnant women by preventing excessive weight gain and helping to prevent future health problems in both the mother and child.

You may skip any question you do not feel comfortable answering. Participating in this 15 minute survey may or may not benefit you, but information gained might benefit future pregnant women.

Voluntary Participation
It is important for you to know that you are under no obligation to participate in this questionnaire. If you choose not to complete this survey, your future care at this clinic, CHEO or the Ottawa Hospital will not be affected in any way. We will not be contacting you about participating in future planned study.
Questions about your Participation

This questionnaire has been reviewed and approved by the Ottawa Hospital Research Ethics Board. The Research Ethics Board is a hospital committee that includes individuals from

this person cannot provide any health-related information about the questionnaire.

Confidentiality
The data collected in this study is completely anonymous and will be kept under lock and key in a safe place at CHEO in Dr. Adamo’s secure filing cabinet. This information will be used for research purposes only and after fifteen years of storage, all records will be destroyed. Overall results may be published for scientific purposes.

Consent
I have read the 2-page Information Sheet and Consent Form (or have had this document read to me). My questions and/or concerns have been answered to my satisfaction and I agree to participate in this survey. A copy of the Information sheet and Consent Form will be provided to me should I want to review the information at a later date. I hereby consent to take part in this survey. My participation is voluntary and I am free to withdraw from participation at any time.

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Prenatal Lifestyle Intervention Study - Willingness to Participate Questionnaire

To begin, we are interested in knowing whether a medically supervised physical activity and healthy eating program would be of interest to you if it were available. The program would be taught by trained experts who have the exercise and dietary knowledge and experience to help pregnant women develop healthier lifestyle habits during pregnancy and beyond. Your responses here will help us develop the program to ensure it will meet the needs of pregnant women.

1. Would you consider participating in a physical activity and healthy eating program during pregnancy?  
   □ Yes  
   □ No  
   □ Not sure

   **IF YES, why would you participate? (Please check all that apply)**
   □ To learn more about nutrition and exercise
   □ For the health of my child
   □ For my personal health
   □ I feel it is important to contribute to research (Altruism)
   □ I would, but don’t know why
   □ Other: __________________

   **IF NO, why would you NOT participate? (Please check all that apply)**
   □ I don’t have the time
   □ I have no way to get there
   □ I cannot afford childcare
   □ I’m afraid that this would cost too much
   □ I’m not interested
   □ I’m already living a healthy lifestyle
   □ Other: __________________

Continued on next page...
2. Would you be more likely to participate if the program was provided FREE of charge?

☐ Yes
☐ No
☐ I would participate no matter what
☐ It wouldn’t matter. I would never choose to do something like this
☐ Not sure

3. If you were going to receive information about healthy eating and physical activity during pregnancy what form of communication is best for you?

☐ Interactive in-person setting (i.e., face to face consult, group sessions etc.)
☐ Email
☐ Telephone
☐ Facebook
☐ During doctor’s appointment
☐ Mail
☐ Other: _______


Healthy Eating and Pregnancy:

The second section of this questionnaire will address your current lifestyle habits with a focus on nutrition during the perinatal period (the time around the birth of your child). Your valuable input will help us understand ways in which to improve information given to pregnant women.

1. Have you received information about nutrition/healthy eating during pregnancy?
   - Yes
   - No (skip to question #4)

2. If yes, from where? (Please check all that apply)
   - Family Physician
   - Obstetrician/Gynecologist
   - Nurse
   - Family Member
   - Dietician
   - Friend
   - Personal Trainer
   - Internet
   - Books, magazines, waiting room material (i.e., pamphlets)
   - Other ____________

Continued on next page...
3. A. Specifically, what was discussed: (please check all that apply)
   □ ‘Extra’ calorie consumption during pregnancy
   □ Balanced food selection (i.e., choosing foods from a variety of different groups)
   □ Vitamins/Mineral requirements
   □ Importance of healthy pregnancy weight gain
   □ Foods to avoid (i.e., Caffeine, artificial sweeteners, etc.)
   □ None of the above
   □ Other: ______________

3B. Was the information you received useful? (Please check one)
   □ Extremely useful
   □ Very useful
   □ Somewhat useful
   □ Slightly useful
   □ Not useful at all
   □ Not useful at all
4. Is receiving specific dietary advice and/or pregnancy-specific nutrition information important to you? (Please check one)
   - Extremely important
   - Very important
   - Somewhat important
   - Slightly important
   - Not important at all
   - Not sure

   **IF YES, why? (Please check all that apply)**
   - Help me gain a healthy amount of weight during pregnancy
   - Help me return to a healthy weight after the baby is born
   - Improve the long-term health of my child
   - Improve the growth and development of my baby
   - Improve my long-term health by preventing chronic disease (e.g., diabetes)
   - Not sure
   - Other: ___________

   **IF NO, why not? (Please check all that apply)**
   - I don’t want to hear it
   - I don’t think it will make a difference with my health
   - I don’t think it will make a difference to my baby
   - I don’t think I need to change
   - I don’t think I can change
   - Other: _______________
5. Would you like to receive information about proper nutrition during pregnancy from a health provider?
   □ Yes
   □ No
   □ Not sure

6. What type of information would be most helpful? (Please select all that apply)
   □ Healthy meal ideas
   □ Ways to work ‘healthy eating’ into my busy life
   □ Importance of foods I eat and the health of my baby
   □ Vitamins and Mineral information
   □ Learn which ‘foods to avoid’
   □ Reading food labels
   □ How many calories should I be eating
   □ Infant feeding advice (i.e., breastfeeding, solid foods, etc.)
   □ Balancing your budget to eat well
   □ Healthy weight gain during pregnancy
   □ Other: ________________
   □ I would not benefit from information like this

Continued on next page...
Physical Activity and Pregnancy:

This section of the survey is looking for your thoughts on physical activity and pregnancy. Your answers will help our team to educate other professionals to ensure pregnant women receive the information they have an interest in learning.

1. Have you received information about physical activity during pregnancy?
   □ Yes
   □ No

If YES, from where? (Please select all that apply)
   □ Family Physician
   □ Obstetrician/Gynecologist
   □ Nurse
   □ Family Member
   □ Dietician
   □ Friend
   □ Personal Trainer
   □ Internet
   □ Books and magazines
   □ Other____________

If NO, would you like to receive information about exercise and pregnancy from a health educator?
   □ Yes
   □ No

Continued on next page...
2. If physical activity was discussed with you, what information was brought up? If it wasn’t, skip to Question #4. (Please select all that apply)

☐ How often I should exercise (i.e., frequency)

☐ Appropriate levels of intensity during exercise (i.e., how hard I should be working)

☐ How long I should exercise each time I do (i.e., duration of each activity session)

☐ Appropriate exercise types

☐ Other__________

3. If you did receive information about exercise and pregnancy, was it useful? (Please check one)

☐ Extremely useful

☐ Very useful

☐ Somewhat useful

☐ Slightly useful

☐ Not useful at all

☐ Not sure

4. Is receiving pregnancy specific exercise/physical activity information important to you? (please check one)

☐ Extremely important

☐ Very important

☐ Somewhat important

☐ Slightly important

☐ Not important at all

☐ Not sure

Continued on next page...
If YES, why do you think exercising during pregnancy is important? (Please select all that apply)

- Prevents chronic diseases such as diabetes, heart disease and obesity
- Improves my overall wellbeing (I just feel better!)
- Prepares my body for delivery
- Improves the health of my child
- It will help me maintain a healthy body weight during and after pregnancy
- Other: ________
- I don’t think it is important, so this question doesn’t apply to me

5. Are you currently exercising now that you are pregnant?

- Yes
- No

6. Do you think it is safe for women to exercise during pregnancy?

- Yes
- No
- Not sure

Continued on next page...
If YES, why do you think it is beneficial to exercise when pregnant? (Please select all that apply)

☐ It’s important for my and my child’s health
☐ I want to stick with my current routine
☐ This is a great time to start a new routine
☐ I feel like it would be the right thing to do
☐ Not sure
☐ Other: ______________

If NO, why don’t you think exercising when pregnant is beneficial? (Please select all that apply)

☐ I feel it is unsafe to exercise when pregnant
☐ Exercise may harm my child
☐ It will cause me discomfort (e.g., it will hurt my lower back, hurt my feet, etc.)
☐ I’m too busy to exercise
☐ I do not know what is considered ‘safe activity’
☐ I don’t have the confidence to go out in public to exercise
☐ I am too tired
☐ Other: ______________
Personal Information:

The final section of the questionnaire will ask you for demographic and personal information to help us identify if the people who completed our questionnaire are similar to our pregnant population in general.

1. Date of Birth (MONTH YEAR): _______ Month / _______ Year
2. Height: _______________ (e.g., 160 cm) or _______________ (e.g., 5'6")
3. Weight: _______________ (kg) or _______________ (lbs)
4. When is your due date?

5. How many children currently live at your home?
   □ 0
   □ 1
   □ 2
   □ 3
   □ 4
   □ 5+

6. How many times have you have carried a child to term?
   □ First
   □ Second
   □ Third
   □ Fourth
   □ 5+

Continued on next page...
7. My current level of education is:
   □ Have not finished High school
   □ Completed High school
   □ Some College/University
   □ Completed College/University
   □ Obtained a Graduate degree (e.g., Master’s)
   □ Completed a Professional degree

8. Marital status (current):
   □ Single
   □ Married/Common law
   □ Divorced
   □ Widow

9. My current employment status is: (choose what is applicable)
   □ Fulltime
   □ Part-time
   □ Unemployed
   □ Self-employed
   □ On leave (sick or early maternity)

Continued on next page...
10. I most closely associate myself with the following ethnic group(s):

☐ White
☐ Chinese
☐ Aboriginal Peoples of North America (North American Indian, Metis, Inuit/Eskimo)
☐ Black
☐ South Asian (e.g., East Indian, Pakistani, Sri Lankan, etc.)
☐ Filipino
☐ Arab
☐ Latin American
☐ Southeast Asian (e.g., Cambodian, Indonesian, Laotian, Vietnamese, etc.)
☐ West Asian (e.g., Afghan, Iranian, etc.)
☐ Japanese
☐ Korean
☐ Other (please specify): ____________________

THE END

Please ‘drop’ your completed questionnaire into the designated box in the waiting area

Thank you for completing this survey. Again, all of your responses will be kept strictly confidential. We greatly appreciate your time and effort. This questionnaire will be used to improve the quality and type of information women receive during pregnancy in the future. Thank you for helping to better the future health of women and children.
12.8 APPENDIX H - Published abstracts during PhD tenure


**Ferraro ZM, Q. Qiu, A. Gruslin, KB. Adamo.** Maternal obesity is associated with increased activators of MAPK/ERK signaling in fetal circulation. *The Obesity Society Annual Scientific Meeting.* Orlando, Florida. October 1-5, 2011. Published in *Obesity* (19) S89.


12.9 APPENDIX I - Canadian Society for Exercise Physiology (CSEP) Certified Exercise Physiologist (CEP) Certification

CSEP Certified Exercise Physiologist®

Zach Ferraro

March 31, 2011

Expiry Date: Date d'expiration

CSEP President (Président) de la SCPE

SOCIÉTÉ CANADAINE DE PHYSIOLOGIE DE L'EXERCICE

SCPE

CANADIAN SOCIETY FOR EXERCISE PHYSIOLOGY

SCIENCE AND PERSONAL TRAINING

HAVING SUCCESSFULLY COMPLETED ALL REQUIREMENTS AS

AVANT RÉPONDU À TOUS LES EXIGENCES ÉTABLIES PAR LE

PROGRAMME: SANTÉ ET CONDITION PHYSIQUE (CEP) DE LA

SOCIÉTÉ CANADAINE DE PHYSIOLOGIE DE L'EXERCICE (SCPE)

Cette délivrance est reconnue

REGISTERS RECONNAIT

AS A LE TITRE DE

PHYSIOLOGISTE DE L'EXERCICE CERTIFIÉ(E)-SCPE

Certified Exercise Physiologist (CEP) Certification
Dear Zach,

Thank you for submitting your renewal application for the 2011-2012 membership year, effective April 1st, 2011 through March 31st, 2012. You must renew your CSEP certification annually in order to maintain your valued status as a CSEP Certified Exercise Physiologist® (CSEP-CEP).

Your renewal forms and payment have been processed by the Ontario Society for Health and Fitness (OSHF) membership office.

Please accept this letter as confirmation that your CSEP-CEP certification and insurance policy have been renewed for the 2011-2012 membership year, and will expire on March 31, 2012.

Please find enclosed your March 31, 2012 renewal sticker or CSEP-CEP certificate (if purchased), and official receipt of payment. Information regarding your CSEP insurance policy will be mailed to you by the CSEP National Office in the coming weeks.

It is important to keep records of any documents related to your certification for up to 7 years. The OSHF may request an audit at any time during your certification period.

In order for your CSEP-CEP status and insurance policy to remain active throughout the year, you must ensure that your CPR training is current at all times. To remain current, CPR must be updated every 12 months. CSEP insurance will not cover any incidents that occur beyond 12 months of your last CPR update.

For more information about your CSEP certification, including recent member communications, visit www.oshf.ca. Please feel free to contact the OSHF office with any questions.

The Ontario Society for Health and Fitness thanks you for your continued support.

Sincerely,

[Signature]

Ontario Society for Health and Fitness
12.10 APPENDIX J – Knowledge translation initiatives during PhD tenure

**Ferraro ZM.** The past, present and future of trainee and young professional involvement within the Canadian Obesity Network (CON). Invited oral address to CON-Student and new professional delegates. *Canadian Obesity Network 2nd National Obesity Summit*. Montreal, Quebec. April 26-30, 2011.


**Ferraro ZM.** Improving student involvement in knowledge translation initiatives. State University of Maringá, Paraná, Brazil. December 3-10, 2010. (Invited lecture series)

**Ferraro ZM.** The intergenerational effects of maternal obesity: Managing chronic disease in mom while preventing it in baby. State University of Maringá, Paraná, Brazil. December 3-10, 2010. (Invited lecture series)

**ZM Ferraro.** Champlain Maternal Newborn Regional Program, *Perinatal Perspectives summer newsletter ‘Maternal Obesity Management’* invited editorial, June 2011

**ZM Ferraro.** School Equipment and Injuries. *Active Healthy Kids Canada*. Canada’s Annual Report Card on Physical Activity for Children and Youth (School infrastructure and equipment section), 2011

KB Adamo and **ZM Ferraro.** Healthy active moms, healthy active kids. *Active Healthy Kids Canada*. Canada’s Annual Report Card on Physical Activity for Children and Youth (Maternal-fetal health section), 2010

Canadian Obesity Network Guest Speaker Grant for Knowledge Translation. ‘Neurobiology of energy balance, energy balance and obesity-related pathology’. S. Yasai & **Z. Ferraro** $1000. September 2009 (awarded) Hosted Dr Barry Levin.

CIHR Institute for Community Support grant. K. Chechi, X. Ramos-Salas and the Canadian Obesity Network Student and New Professional National Executive (which **Z. Ferraro was Chair and lead the initiative**) $15000 (awarded). ‘CON- Student and New Professional: community development and knowledge translation’ 2011.

Canadian Obesity Network Guest Speaker Grant for Knowledge Translation. ‘Forks versus Feet: The role of exercise and diet in obesity treatment and management’ **Z. Ferraro** & T. Saunders $1000. February 2011 (awarded) Hosted Drs Robert Ross and Yoni Freedhoff to address diverse audience at the University of Ottawa Health Sciences Complex

CIHR Cafe Scientific Knowledge Translation Grant for ‘Obesity: Disease or result of our modern environment?’ **Z. Ferraro** & T. Saunders. August 2011. $3000 (awarded)
In recognition of completion of the 4th Annual Human Placenta Workshop held by Queen's University, Kingston, Ontario, Canada - July 10-25, 2000.

This certificate is presented to: Zach Ferraro
This document certifies that the above-named person registered for and attended the
Exercise is Medicine Symposium.

ZACH FERRARO

June 9, 2009 13:00 – 17:00
Kingston, Ontario
Queen's University

CERTIFICATE OF ATTENDANCE

EXERCISE IS MEDICINE SYMPOSIUM
APPENDIX M - Canadian Obesity Network educational ‘boot camp’ certificate

August 2008

Zach Ferraro
PhD Candidate

Dear Mr. Ferraro,

This letter certifies that Zach Ferraro participated in the Canadian Obesity Network/Université Laval Obesity Summer Boot Camp 2008 (3rd edition) held in Duchesnay, Quebec on July 27 – August 3, 2008. The Boot Camp qualifies for 40 educational hours of scientific sessions on obesity, from epidemiology and complications for health to adipose tissue biology, energy balance regulation, treatment and prevention.

This award is valued at approximately $2500.00.

With our best regards to you.

Sincerely,

Arya M. Sharma, MD, FRCPC
Scientific Director
Canadian Obesity Network

Denis Richard, PhD
Director, Merck/Frosst/CIHR Research
Chair in Obesity
Université Laval
12.14 APPENDIX N – Canadian Perinatal Surveillance System birth weight for gestational age growth curves
## Birth Weight (in g) for GA in Completed Weeks
### Canadian Male Singletons

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Please feel free to make copies of these sheets, or you can download them from Health Canada’s website: http://www.hc-sc.gc.ca/pxhp-dgpsp/rhs-ssg/index.html
Birth Weight for Gestational Age (GA)

Female Singletons

Gestational Age (completed weeks)

Birth Weight (g)

- 3%ile
- 5%ile
- 10%ile
- 50%ile
- 90%ile
- 95%ile
- 97%ile

Health Canada

Canada
## Birth Weight (in g) for GA in Completed Weeks

### Canadian Female Singletons

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Please feel free to make copies of these sheets, or you can download them from Health Canada’s website: http://www.hc-sc.gc.ca/pphb-dgspsp/rhs-ssg/index.html
# TABLE S-1 New Recommendations for Total and Rate of Weight Gain During Pregnancy, by Prepregnancy BMI

<table>
<thead>
<tr>
<th>Prepregnancy BMI</th>
<th>Total Weight Gain</th>
<th></th>
<th>Rates of Weight Gain&lt;sup&gt;6&lt;/sup&gt;</th>
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<tbody>
<tr>
<td></td>
<td>Range in kg</td>
<td>Range in lbs</td>
<td>2nd and 3rd Trimester</td>
<td>Mean (range) in kg/week</td>
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<tr>
<td>Underweight (&lt; 18.5 kg/m²)</td>
<td>12.5-18</td>
<td>28-40</td>
<td>0.51 (0.44-0.58)</td>
<td>1 (1-1.3)</td>
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<td>Normal weight (18.5-24.9 kg/m²)</td>
<td>11.5-16</td>
<td>25-35</td>
<td>0.42 (0.35-0.50)</td>
<td>1 (0.8-1)</td>
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<tr>
<td>Overweight (25.0-29.9 kg/m²)</td>
<td>7-11.5</td>
<td>15-25</td>
<td>0.28 (0.23-0.33)</td>
<td>0.6 (0.5-0.7)</td>
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<tr>
<td>Obese (≥ 30.0 kg/m²)</td>
<td>5-9</td>
<td>11-20</td>
<td>0.22 (0.17-0.27)</td>
<td>0.5 (0.4-0.6)</td>
</tr>
</tbody>
</table>

* Calculations assume a 0.5-2 kg (1.1-4.4 lbs) weight gain in the first trimester (based on Siega-Riz et al., 1994; Abrams et al., 1995; Carmichael et al., 1997).