THE ROLE OF MATERNAL NUTRITIONAL STATUS AND INFLAMMATORY MARKERS ON POSTNATAL WEIGHT RETENTION AND INFANT GROWTH FROM A COHORT STUDY IN UNITED ARAB EMIRATES

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by

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TABLE OF CONTENTS

LIST OF TABLES

Page

LIST OF FIGURES

Page

LIST OF ABBREVIATIONS

AAP	American Academy of Pediatrics
Acrp30	Adipocyte Complement–Related Protein Of 30 Kda
ADFCA	Abu Dhabi Food Control Authority
dipoR1	Adiponectin Receptor 1
AdipoR2	Adiponectin Receptor 2
ADPN	Adiponectin
ANOVA	Analysis of Variance
BAZ	Body Mass Index–For–Age–Z–Score
BMI	Body Mass Index
CRP	C–Reactive Protein
CV	Coefficients of Variability
DFE	Dietary Folate Equivalence
EBF	Exclusive Breast Feeding
ELISA	Enzyme–Linked Immunosorbent
GDM	Gestational Diabetes Mellitus
GWG	Gestational Weight Gain
HDL–C	High Density Lipoprotein Cholesterol
HMW	High–Molecular–Weight
Hr	Hour
IGF–1	Insulin–Like Growth Factor 1
IOM	Institute of Medicine
IPAQ	International Physical Activity Questionnaire
IQR	Interquartile Range
Kg	Kilogram
LAZ	Length–For–Age Z–Scores
Lb.	Pound
LDL–C	Low Density Lipoprotein Cholesterol

LGA	Large–For–Gestational Age
MET	Metabolic Equivalent Task
MISC	Mother Infant Sharjah Cohort
MLR	Multiple Linear Regression
MPR	Multiple Pass Food Recall
NCEP	National Cholesterol Education Program
NHLBI	National Heart, Lung, And Blood Institute of The National Institute of Health
NICE	National Institute for Health and Care Excellence
PBF	Predominant Breast Feeding
PIH	Pregnancy–Induced Hypertension
PPWR	Postpartum Weight Retention
RAE	Retinol Activity Equivalent
REC	Ethical Research Committee
SD	Standard Deviation
SGA	Small–For–Gestational–Age
SOP	Standard Operating Procedures
SPSS	Statistical Package for Social Sciences
T2DM	Type 2 Diabetes Mellitus
TC	Total Cholesterol
TG	Triglycerides
TNF–α	Tumor Necrosis Factor Alpha
UAE	United Arab Emirates
UNICEF	United Nations International Children's Emergency Fund
USDA	U.S. Department of Agriculture
USM	Universiti Sains Malaysia
WAZ	Weight–For–Age Z–Scores
WGR	Weight Gain Rate
WHO	World Health Organization
WLZ	Weight–For–Length Z–Scores

PERANAN STATUS PEMAKANAN DAN PETUNJUK INFLAMASI IBU TERHADAP PENGEKALAN BERAT BADAN POSNATAL DAN PERTUMBUHAN BAYI DARI KAJIAN KOHOT DI EMIRIAH ARAB BERSATU

ABSTRAK

Emiriah Arab Bersatu (UAE) telah mengalami kepesatan ekonomi yang mencetuskan perubahan terhadap pemakanan dan gaya hidup, menyebabkan peningkatan prevalens berat badan berlebihan dan kegemukan, terutamanya bagi wanita dalam tempoh usia subur. Kehamilan adalah tempoh berisiko bagi kenaikan berat badan dan keradangan metabolik sistematik yang akan mempengaruhi penyesuaian janin pada peringkat awal kehidupan, dan berkemungkinan memberi kesan jangka panjang pada anak. Perspektif ini membawa kepada Kajian Kohort Ibu dan Bayi (MISC) yang menumpukan amalan pemakanan ibu dan bayi dan kaitannya dengan penanda metabolik. MISC dijalankan selama dua tahun bermula Disember 2015 sehingga Jun 2016 di Emirates of Sharjah, Dubai dan Ajman dari UAE. Seramai 256 wanita Arab hamil dan sihat berusia 19 hingga 40 tahun dengan kehamilan tunggal direkrut semasa trimester ketiga. Peserta ditemuramah sekali semasa kehamilan, semasa kelahiran, pada 2 dan 6 bulan selepas kelahiran di klinik rawatan kesihatan primer. Data yang dikumpulkan untuk ibu termasuk ciri-ciri sosio-demografi, gaya hidup, pengambilan makanan, dan antropometri semasa merekrut dan semasa lawatan selepas bersalin manakala untuk bayi, pengukuran antropometri, dan amalan pemberian makanan. Sampel darah dan susu ibu dikumpulkan semasa kelahiran dari

ibu dan pada 6 bulan selepas bersalin untuk ibu dan bayi. Ini termasuk Gula Darah Berpuasa (FBS), Insulin, Profil Lipid dan Adiponektin Manusia Berat Molekul Tinggi (HMW); Tumor Nekrosis Faktor-alpha (TNF-α) Interleukin-6 (IL-6), dan C Reaktif Protein berkepekaan tinggi (hs-CRP). Selain profil susu adiponectin dan hs-CRP. Analisa deskriptif menunjukkan prevalens peningkatan berat badan kehamilan (GWG) yang ketara iaitu (39.1%) di kalangan peserta, tinggi dalam kalangan ibu berlebihan berat badan dan obes (53.9% dan 48.7%). Selain itu, skor indeks kualiti makanan peserta kurang daripada tahap optimum. Analisa regresi linear berganda (MLR) menunjukkan adiponektin susu (ADPN) semasa lahir berkadar negatif berbanding serum (hs-CRP) dan menurun 9 kali ganda dengan peningkatan 1kg dalam GWG (β = -9.22, $p = 0.01$). Seterusnya, MLR menunjukkan pengekalan berat badan postpartum (PPWR) menurun dengan peningkatan Indeks Jisim Tubuh (IJM) pra kehamilan (β = -.43, $p < 0.01$) dan meningkat dengan peningkatan GWG (β=.391, $p < 0.001$), sementara hanya FBS serum parameter metabolik yang mengaitkan dengan pengekalan berat badan ($\beta = 0.113$, $p < 0.05$). Serum ibu menunjukkan penurunan adiponektin ketara ($p < 0.01$) dan peningkatan keradangan sitokin dan insulin yang tinggi di kalangan wanita obes berbanding normal. Pada usia bayi 6 bulan, penilitian skor Z parameter pertumbuhan, tiada perubahan signifikan ($p > 0,05$) di antara amalan penyusuan yang berbeza (penyusuan susu ibu atau makanan campuran (MF)). Insulin serum bayi (MF) melebihi 3 kali ganda (9.60 μIU / ml), tahap yang direkodkan pada amalan pemberian makanan lain ($p < 0.05$). Model MLR menunjukkan apabila serum BG bayi meningkat, diramalkan berat badan bayi lebih rendah ($\beta = -0.024$, $p = 0.044$). Kelahiran bayi BAZ dan adiponektin serum ibu adalah peramal positif bagi skor BAZ 6 bulan ($\beta = 0.336$, $p = 0.05$) dan ($\beta = .241$, $p < 0.05$). Kesimpulannya, berat badan ibu yang berlebihan yang ditunjukkan dalam IJT sebelum kehamilan yang tinggi, GWG dan PPWR yang

berlebihan adalah petunjuk biasa bagi hasil kajian utama. Ini dianggap faktor risiko yang berpotensi dapat diubah umtuk menjamin pengembangan perubahan sosial dan perundangan yang mendasar untuk mengurangkan kesan transgenerasi kehidupan wanita.Walaupun manfaat penyusuan terhadap berat badan bayi merosot setelah penyesuaian bersama, mempromosikan penyusuan susu ibu merupakan usaha proaktif supaya dapat menyumbang kepada pengaturcaraan metabolik bayi terhadap obesiti dalam jangka masa panjang.

THE ROLE OF MATERNAL NUTRITIONAL STATUS AND INFLAMMATORY MARKERS ON POSTNATAL WEIGHT RETENTION AND INFANT GROWTH FROM A COHORT STUDY (MISC) IN UNITED ARAB EMIRATES

ABSTRACT

The United Arab Emirates (UAE) has experienced rapid economic growth that provoked a shift in diet and lifestyle factors which triggered a marked increase in the prevalence of overweight and obesity particularly among women during their reproductive years. Pregnancy is a vulnerable period for increased weight gain and systematic metabolic inflammation that can dictate fetal adaptations at the earliest stages of the life, with possible long-lasting effects on offspring. These perspectives geared the initiation of Mother and Infant Study Cohort (MISC) to address maternal nutrition, infant feeding practices and its associations with metabolic markers. The current study which stems from (MISC) cohort was conducted from December 2015 and ended in June 2016 in the Emirates of Sharjah, Dubai and Ajman of United Arab Emirates (UAE). A total of 256 healthy pregnant Arab women aged 19 to 40 years with singleton pregnancy were recruited during the third trimester of pregnancy. Participants were interviewed once during pregnancy, then at delivery, at two and 6 months postpartum in the primary health care clinics. The data collected for the mothers included socio-demographic characteristics, lifestyle, dietary intake, and anthropometry upon recruitment and during the postnatal visits while for infants, anthropometric measurements, and feeding practices. Further, blood and breast milk samples were collected at birth from the mothers and at 6 months postpartum for the mothers and the infants. These included fasting blood sugar (FBS), insulin, lipid profile as well as High Molecular Weight Human Adiponectin (HMW) ADPN; Tumor

Necrosis Factor-alpha (TNF-α) Interleukin-6 (IL-6), and High Sensitivity C Reactive protein (hs-CRP). In addition to the breast milk profile of adiponectin and hs-CRP. Descriptive analysis revealed a marked prevalence of excessive gestational weight gain (GWG) (39.1%) among the participant mothers and was prominent among overweight and obese mothers (53.9% and 48.7%) respectively. Besides, their diet quality index score was less than the optimum. At 6 months, multiple linear regression (MLR) revealed that postpartum weight retention (PPWR) decreased with increasing pre pregnancy body mass index (BMI) (β=-.43, $p<0.01$) and increased with increasing gestational weight gain (GWG) (β=.391, $p<0.001$), while serum FBS was the only metabolite parameter associated with retaining weight (β= 0.113, $p<0.05$). The maternal serum demonstrated significantly ($p<0.01$) elevated inflammatory cytokines and insulin among overweight/obese women compared to leaner mothers. At 6 months of infants' age, examining the Z score growth parameters, no significant changes ($p>0.05$) have been encountered among the different feeding practices (exclusive, predominant breast feeding or mixed feeding (MF)). The serum insulin of the (MF) infants significantly exceeded 3 times (9.60 μIU/ml), the recorded levels in other feeding practices ($p< 0.05$). MLR models showed that as infants' serum BG increased, lower infant body weight was predicted (β=-0.024, $p=0.044$). Infant birth BAZ and maternal serum adiponectin were positive predictors for the 6 months BAZ score (β=0.336, $p=0.05$) and (β=.241, $p<0.05$) respectively. In conclusion, excessive maternal weight represented in high pre-pregnancy BMI, excessive GWG and PPWR was the common denominator for the major study outcomes. These considered potentially modifiable risk factors which warrants developing culturally specific legislation to lessen the transgenerational impact of obesity. Though breastfeeding beneficial effects on infants' weight fades after cofounder adjustments, nevertheless,

promoting breastfeeding is a proactive endeavour that may contribute to infants' metabolic programming against obesity in the long run.

CHAPTER 1

INTRODUCTION

1.1 Background

Maternal nutritional status before and during pregnancy dictates fetal adaptations at the earliest stages of the life-which can induce both short-term and long-lasting effects on offspring (WHO, 2016). Much of human growth and development is completed during the first 1000 days extending from the intra-uterine life until two years of infancy (Groer et al., 2014; S. Robinson, 2015). A period of a child's life is viewed as a critical "window of opportunity" for the acquisition of optimal growth, health, and curbing non-communicable disease (NCD). The Developmental Origins of Health and Disease (DoHaD) hypothesis was developed by Barker (Barker, 2007) and colleagues. It highlighted the link between prenatal, perinatal, and early postnatal exposure to certain environmental factors and subsequent development of obesity and non-communicable diseases. This epigenetics area has become one of the widespread and most complex areas of biological science (Patro et al., 2013; S. M. Robinson et al., 2015).

There is an escalating prevalence of overweight and obesity worldwide (Afshin et al., 2015) and across all age groups (WHO, 2016). Recently, the World Health Organization (WHO) had reported that obesity prevalence tripled between 1975 and 2016. The number of overweight adults worldwide has surpassed one billion, an estimated 39% of adults aged 18 years and over were overweight (39% of men and 40% of women), about 13% of the world's adult population (11% of men and 15% of women) were obese. The WHO had revealed that 41 million children under the age of

5 years as overweight or obese in 2016 (WHO, 2016) in high-income countries and low-and middle-income countries. Further, the global prevalence of childhood obesity has increased by more than 8 folds during the last four decades and continues to rise (Alshaikh et al., 2017).

The Gulf Cooperation Council countries (GCC), including the United Arab Emirates (UAE), share this global obesity epidemiology. According to the WHO 2016-country profile of the UAE, obesity prevailed among 27% and 39% of males and females, respectively, 65 % and 13% of adolescent boys and girls. Accumulating epidemiological studies have identified excess weight as a risk factor for expanding the set of chronic diseases, including cardiovascular diseases, diabetes mellitus, chronic kidney disease, and many cancers (Mokdad et al., 2014).

It is essential to highlight that women are more affected by obesity than men, as revealed by the WHO report (2016). Maternal obesity constitutes one of the most important women's health issues and significant obstetric problems (Huda et al., 2010; Patro et al., 2013; Gaillard et al., 2016). Many systematic reviews ascertained that women who were overweight at conception, have nearly twice the risk of excessively gaining gestational weight compared to those with normal pre-pregnancy weight (E. A. Nohr et al., 2008; Vidakovic et al., 2015). Furthermore, excessive GWG increases the risk of greater postpartum weight retention (PPWR) (Riz et al., 2009; Goldstein et al., 2017) and gestational diabetes mellitus (GDM). Consequently, it increases the risk for life-long obesity, metabolic syndrome (MetS), cardiovascular diseases (R. Gaillard et al., 2016) and Type 2 diabetes mellitus (T2DM) (Kiel & Dodson, 2007; Schmatz et al., 2010). Consistent reports arise from GCC, a cross-sectional national study from Qatar (Al Thani et al., 2015) revealed the same high-risk behaviors of elevated odds of MetS among Qatari women in their reproductive ages. At the same time, a recent

systematic review among women from the GCC showed that obesity and physical inactivity were part of the commonly reported risk factors for cardiovascular disease and T2DM, MetS and hypertension (Alshaikh et al., 2017).

Furthermore, maternal adiposity in the antenatal period is associated with excessive placental nutrient transfer (Catalano & Shankar, 2017) and fetal over nutrition and fat accretion, which would be a major contributor to metabolic disturbances and macrocosmic babies. The effects of the maternal diet during pregnancy and lactation are critical for the mother and her infant's future metabolic health. They may be the key to attenuating the transgenerational risk of childhood obesity. In its position statement, the Academy of Nutrition and Dietetics (2014) recommended adherence to healthful dietary patterns, including the alternate Mediterranean Diet, Dietary Approaches to Stop Hypertension (DASH), and Alternate Healthy Eating Index, which has been associated with a 24% to 46% lower risk of GDM.

The obesity epidemic is not merely a consequence of positive energy balance, but a multi-factorial condition of environmental, societal, biological, and genetic roots. Nevertheless, enlargement in fat white deposits triggers an inflammatory response associated with a higher metabolic rate. In the same context, pregnancy per se represents a physiological mild maternal systemic inflammatory state associated with oxidative stress and free radicals' formations (Loy, S. L. & Jan Mohamed, 2014), which eventually becomes exaggerated in obese pregnant women (Bautista-Castaño et al., 2013). This ultimately leads to adipocyte dysfunction resulting in the dysregulated release of inflammatory modulator adipokines.

Adipokines are a group of protein hormones secreted by maternal adipose tissue. Some like adiponectin are found to be produced by the placenta (D'Ippolito et al., 2012) during pregnancy and umbilical plasma. They hence suggest a possible role on fetal development and metabolism. In adults, the circulating concentration of these proteins and hormones is linked to an individual's body weight and BMI; leptin is secreted primarily by adipocytes in proportion to the total amount of body adipose tissue, therefore positively correlated with BMI (Eriksson et al., 2010).

In contrast, adiponectin correlates negatively with adiposity and BMI and exhibits insulin-sensitizing, anti-atherogenic, fat-burning, and anti-inflammatory properties (Arroyo-Jousse et al., 2020). Serum interleukin (IL-6), C-reactive protein (CRP), and tumor necrosis factor-α (TNF-α) are among the important and frequently examined proinflammatory cytokines in clinical settings, which are associated with excess fat mass (Pendeloski et al., 2017).

Human milk, apart from the already known constituents of different nutrients, other biological compounds are uniquely expressed with the potential to influence infant growth and development. Examples of these cytokines and metabolic hormones are adiponectin, leptin, and insulin (Lönnerdal, 2010; Fields & Demerath, 2012). Of interest, adiponectin was detected in human milk (Martin L. J. et al., 2006) in concentrations higher than in circulation (F Savino et al., 2008). Further, CRP is a newly investigated breast milk component marker for obesity mediated inflammatory effects (McLachlan et al., 2006). When adiposity and pre-pregnancy BMI are taken into account, obese pregnant women exhibit higher levels of colostrum and serum CRP but lower levels of serum adiponectin (Whitaker et al., 2017).

The above-mentioned facts open breakthroughs in understanding the breast milk metabolic patterns and beneficial effects of breastfeeding arising from these biological compounds. These facts taken together, breastfeeding is beneficial through an epigenetic mark that is demonstrated to be dose-dependent (Mazzocchi et al., 2019; The Lancet's Series, 2016). A surplus of epidemiological evidence supports the possible protective role of breastfeeding in the prevention of childhood overweight and adult obesity (Kramer & Kakuma, 2002; Perez-Escamilla, 2016). "Breastfeeding is an unequaled way of providing ideal food for the healthy growth and development of infants" (WHO, 2007) and "one of the most highly effective preventive measures a mother can make in protecting the health of her infant and herself is to breastfeed" (Shawar & Shiffman, 2017).

Breastfeeding benefits extends to the mother as well. Women who consistently breastfeed have decreased visceral adiposity (intra-abdominal fat depots) and hence fewer risks of diabetes, cardiovascular disease, and metabolic syndrome (Zhu et al., 2014; Castillo et al., 2016).

1.2 Rationale

During the past decades, UAE has witnessed profound socioeconomic transition and modernization in lifestyle, which fashioned food consumption patterns and lifestyle that led to obesity epidemics in the population (Al Dhaheri, S. et al., 2016; Aljefree & Ahmed, 2015). Physical inactivity and obesity are among the leading risk factors for CVD (38%, 30%), respectively (WHO, 2016). Besides, the population's tendency to develop obesity after marriage is evident, where more than 50% of the Emirati married population is obese (WHO, 2016).

The UAE's 2021 vision has taken on the prevalence of diabetes, the majority of obesity amongst children, and the number of deaths due to cardiovascular diseases per 100,000 population, as its leading national performance indicators for world-class health care to guide targeted interventions and public health efforts (UAE Vision, 2020). In 1992, the Ministry of Health in UAE had adopted the international recommendations of UNICEF/WHO to meet the "Baby-Friendly" standards for optimal breastfeeding-related to maternity care in all maternity hospitals.

Pregnancy is a vulnerable period for increased weight gain, usually followed by higher postpartum weight retention, which initiates a vicious cycle of obesity among women during their reproductive years (Nehring et al., 2011). Consequently, it might contribute to adverse health trajectories recognized in offspring-early life and may have long-term consequences. Accordingly, exploring pregnant women's nutritional status is of precedence in the UAE and geared one of the study's aims.

Given that obesity and pregnancy share metabolic patterns of systematic inflammation, it is interesting to explore the associations of circulatory inflammatory cytokines and adiponectin with maternal and infants' adiposity.

In addition, many authors and cohorts investigated the breast milk bioactive components and, in particular, the role of milk adiponectin in infant metabolic development. Yet, no study to date has examined breast milk components in the UAE.

Considering the cumulative evidence of the possible protective aspect of breastfeeding in preventing childhood overweight and adult obesity (Horta et al., 2007), and the current status of suboptimal breastfeeding feeding practices in the UAE (Radwan, 2013) investigating the link of adipokines among Emirati and Arab mothers and their infants is of great interest.

1.3 Significance of the Study

Amidst these ongoing societal shifts and developments, this study aimed to address maternal and child nutrition and its associations with metabolic markers. A few cohorts have addressed antenatal nutrition and early life exposures and their impact on health outcomes in the Arab region. There is an undoubted need to identify early determinants of obesity in the Arab region (Al-Rifai et al., 2018). Obesity has significant health implications across multiple ages and populations and creates a substantial financial burden worldwide (Afshin et al., 2015). In the UAE, the cost of illness for diabetes per patient was estimated at $2,015 (adjusted for the year 2015), and it became twice and 6 times higher in patients with vascular complications (Radwan et al., 2018). Nevertheless, the Ministry of Health and Prevention, MoHAP, has acknowledged the country's health challenges and recently released the National Nutrition Guideline (*The National Nutrition Guidelines - The Official Portal of the UAE Government*, 2019). This endeavor was part of the country's efforts to achieve the Sustainable Development objectives 2030 and find radical solutions to health situations—the Ministry of Health and Prevention. (2019, October 1).

This study included a rich collection of predictors and confounding factors related to pregnant and lactating women, such as dietary intake and lifestyle as well as infant feeding practices. In addition, numerous maternal and infants' biochemical variables were assessed, and their relationship with mothers' postpartum weight and infant growth patterns were investigated. Collectively, this will serve as a primary database of pregnant and lactating mothers' status that will pave the way for national culture-specific interventions for the health of pregnant women and young children. From this perspective, it is hoped that revealing the potential role of pre-pregnancy overweight, breast milk adiponectin, and the duration of breastfeeding through this

study may help identify its relation to regulation of adiposity development among women and children through this study.

1.4 Objectives

1.4.1 General

To investigate the role of maternal nutritional status and inflammatory markers on postpartum weight retention and on infant growth development during the first 6 months of life through a prospective study.

1.4.2 Specific

i. To evaluate maternal nutritional status (pre-pregnancy BMI), dietary intake, lifestyle factors and gestational weight gain during pregnancy.
ii. To investigate the associations of maternal breast milk adiponectin and C reactive protein (hs CRP) levels and maternal serum adipocytokines levels within the postpartum period.
iii. To compare maternal serum lipid and glycemic profiles and adipocytokines with maternal weight status at 6 months postpartum.
iv. To assess the associations of maternal factors (dietary intake, lactation status, serum adipocytokines) with mothers' (PPWR) at 6 months postpartum.
v. To compare infants' anthropometry and serum adipocytokines levels with infants' different feeding patterns at six (6) months of age.
vi. To investigate the associations between infant's feeding patterns, maternal serum and breast milk adipocytokines levels with infant adiposity at six (6) months of age.

1.5 Research Questions

What is the maternal nutritional status, dietary intake, lifestyle factors, and gestational weight gain during pregnancy?

Is there any association between maternal breast milk adiponectin and C reactive protein (hs CRP) levels with maternal serum adipocytokines levels within postpartum period after controlling the cofounders?

Is there are any association between maternal factors (dietary intake, lactation status, serum adipocytokines) with mothers' (PPWR) at 6 months postpartum after controlling the cofounders?

Is there any difference in maternal lipid, glycemic profiles and serum adipocytokines among maternal different weight status at 6 months postpartum?

Is there any difference in infants' anthropometry and serum adipocytokines among infants with different feeding patterns at six (6) months of age?

Is there an association between infant's feeding patterns, maternal serum and breast milk adipocytokines with infant adiposity at 6 months of age after controlling the cofounders?

1.6 Alternative Hypothesis

Ha: Mothers who gained weight excessively during pregnancy would experience greater postpartum weight and body fat retention.

Ha: Mothers with lower postpartum weights would have lower serum proinflammatory cytokines profile.

Ha: Infants with different feeding patterns will exhibit different growth patterns.

Ha: Infants who are breastfed will have lower serum proinflammatory cytokines profile.

Ha: Maternal breast milk adiponectin levels are associated with reduced infant adiposity development within 6 months of infants' age.

1.7 Conceptual Framework

The conceptual framework depicted in Figure 1.3 presents the study background and the hypothesized exposures, covariates, and outcomes.

At the prenatal environment, this includes maternal pre-pregnancy adiposity, faulty dietary intake, sedentary lifestyle, dyslipidemia as well as excessive gestational weight gain. These conditions, consequently, prejudice metabolic dysregulation in the mothers and fetuses such as elevated maternal pro-inflammatory markers, insulin and depressed serum adiponectin. Knowing the role of adiponectin in glucose and fatty acids metabolism and in insulin sensitivity, the suppressed levels of maternal serum as well as the breast milk adiponectin, might promote adverse effects to the mothers and fetus, through alterations in insulin sensitivity and adiposity for both the mother during postpartum period and for the offspring later in life.

Meanwhile, breastfeeding practices may also play a significant protective role against adiposity development in infants as well as controlling maternal postpartum weight retention.

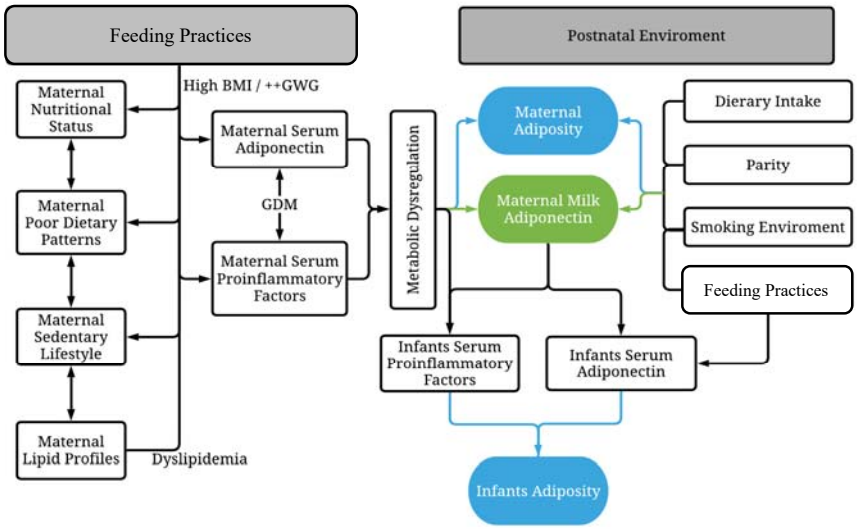

Figure 1.1 Conceptual Framework

1.8 Operational Definitions

- **Adipokines-**Proteins that are secreted from (and synthesized) by adipocytes (include adiponectin and leptin).
- **At Birth-**A follow-up visit, within (median=3, IQR=1-4) days after delivery; for the milk collection, within (median=3, IQR=1-5) days after delivery.
- **Cesarean Delivery-**A delivery by a surgical procedure, in which one or more incisions are made through the mother's abdomen and uterus.
- **Excess Weight** (prepregnancy BMI category)-Mothers with overweight and obese prepregnancy BMI status.
- **Gestational Age-**A measure of the age of pregnancy in weeks, from the first day of the mother's last menstrual cycle to the current date.
- **Healthy Pregnancy-**A pregnancy in the absence of pre-existing or currently diagnosed chronic medical condition and pregnancy complications.

- **History of Chronic Diseases**: diabetes, hypertension, kidney disease, cancer, or other chronic diseases), autoimmune disorders, or infections with the human immunodeficiency virus, or hepatitis in preconception.
- **Macrosomia**-The birth weight of more than 4000g.
- **Low birth Weight** (LBW)-The birth weight of less than 2500g.
- **Normal Delivery-**A delivery through the vagina.
- **Parity-**The number of >20 weeks birth, including stillborn.
- **Postpartum/ Postnatal Period-**A period after delivery or birth; (postpartum is the term used for the mothers, while postnatal is the term used for the infants).
- **Prenatal factors** Include maternal nutritional status, dietary intake, physical activity, physical discomforts, and lipid profiles.
- **Prenatal Period-**A period during pregnancy before delivery or birth.
- **Term Delivery-**A delivery between 37 and 42 weeks of gestation.
- **Third Trimesters of Pregnancy-**Covers week 27 to the end of gestation.

LITERATURE REVIEW

2.1 Maternal Obesity

Obesity is well defined by the World Health Organization as " a clinical condition defined by an increase of adipose tissue that has a major impact on health and is one of the main risk factors for a variety of chronic diseases such as diabetes, hypertension, cardiovascular disease, and cancer" (WHO, 2011).

It is essential to highlight that maternal obesity has the potential to cause an impact on the health of future generations (Moussa et al., 2016; Morais et al., 2019) whether through metabolic changes transmitted to the fetus during pregnancy or through the alterations in an infant's nutritional programming (Bowen et al., 2002). Besides, obesity among pregnant women is a well-documented risk for mothers strongly associated with developing various maternal morbidities such as gestational hypertension and gestational diabetes (Arabin & Stupin, 2014; Erliana & Fly, 2019). On the other hand, higher placental transfer of the maternal nutrients and subsequent programming of offspring adiposity or potential cardiovascular and metabolic development originating from fetal life until adulthood (Arabin & Stupin, 2014). Apart from the metabolic complications, subfertility has also been recognized to be joined with obesity. Simultaneously, the increased likelihood of conception was correlated with weight reduction trials in obese infertile women (Moussa et al., 2016).

Accruing evidence has shown that adiposity in pregnancy is the leading cause of maternal and fetal morbidity, excess gestational weight gain (GWG), metabolic dysregulation, especially gestational diabetes, risk of hypertension. In a contemporary study, maternal prepregnancy overweight and obesity were associated with offspring

earlier adiposity rebound 6-7 years of age (OR=1.07, 95% CI=1.02-1.11) and growing childhood obesity (Moussa et al., 2016).

It is well documented that the drives towards obesity are much more complicated and multifactorial; these include an abundance of cheap, processed, energy-rich foods, oversized portions, and lifestyle factors characterized by reliance on technology. All these encourage less physical activity and reduce energy expenditure and promote an obesogenic environment.

2.1.1 Prevalence of Obesity: the extent of the problem

The growing dominance of maternal obesity worldwide to almost epidemic proportions in the last 20 years constitutes one of the most important women's health issues. Besides, one of major obstetric problem of woman's life in the antepartum, peripartum and postpartum periods (Huda et al., 2010; Poston et al., 2011). Among Westernized societies, data from Australia, America, and the United Kingdom reveals half of the women enter pregnancy with a BMI exceeding 25 kg/m^2 (Li, NanLiu, et al., 2013). In the USA, the prevalence of obese women of childbearing age increased four-fold from 1976 to 2014, approaching 27.5% (Flegal & Larkin, 1990), while in the UK more than half of the deaths during late pregnancy or labor directly or indirectly occurring among overweight or obese women (Poston et al., 2011)

Women of the Gulf countries have also been affected. Alhyas and colleague (Alhyas et al., 2011) explored 45 studies published between 1987 and 2010 that exposed high incidence of risk factors for diabetes and diabetic complications (hyperglycemia, hypertension and dyslipidemia in the GCC region and found the prevalence of overweight and obesity was relatively high in women with advancing age beyond 30 year. A latest review by Mashael K. Alshaikh (2017) identified 11

systematic reviews about women from GCC and reported alarming facts of female obesity approaching the highest global rates; ranges from 29 to 45.7%. The author linked the reasons for lifestyle changes such as physical inactivity (45 to 98.7%) and higher consumption of unhealthy foods. In this sense, pre-gravid overweight is also escalating to render it a common high-threat obstetric situation in the Gulf (Moussa et al., 2016). Married Saudi women (33.7%) has increased risk of obesity with age (Memish et al., 2014); further four years later, in the RAHMA cohort (Fayed et al., 2017), the rate inflated and 65% of the nondiabetic women were either obese or overweight. GDM continued to be a risk factor for all adverse maternal and neonatal outcomes. In Qatar, another Gulf country, within 10 years period, women who had entered pregnancy with a pre-pregnancy BMI>25 Kg/m^2 increased from 42.1% (Abu Yaacob et al., 2002) to 58% (Abdulmalik et al., 2019) MINA cohort.

2.1.2 Obesity and Inflammation

Obesity and pregnancy have been contemplated as a physiological low-grade systemic inflammation status characterized by enlargement in white fat deposits. During pregnancy, the placenta produces a range of immunomodulatory hormones and cytokines. Maternal obesity with expanded adipocyte size upsurges pro-inflammatory cytokines; interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α) (insulin resistance) and C-reactive protein (CRP) (Zavalza-Gómez et al., 2008); as well as decreased expression of adiponectin (insulin sensitivity), alterations in glucose and lipid metabolism, and energy balance and control of appetite (leptin) (Schmatz et al., 2010).

As such, the underlying pathophysiology linking adiposity and adverse pregnancy outcomes is complicated but is likely to involve cellular dysfunction and

dysregulated release of adipokines, which adversely affect placental and fetal development and long-term offspring cardio-metabolic health outcomes (Romy Gaillard et al., 2016) or increased mortality from cardiovascular events (Reynolds et al., 2013).

Studies have demonstrated that metabolic changes due to maternal obesity can lead to changes in the constituents of colostrum and human milk, thereby modifying the different concentrations of hormones regulating appetite and metabolism, such as adiponectin and leptin, through breastfeeding (Bronsky et al., 2011; Fujimori et al., 2017; Kugananthan et al., 2018).

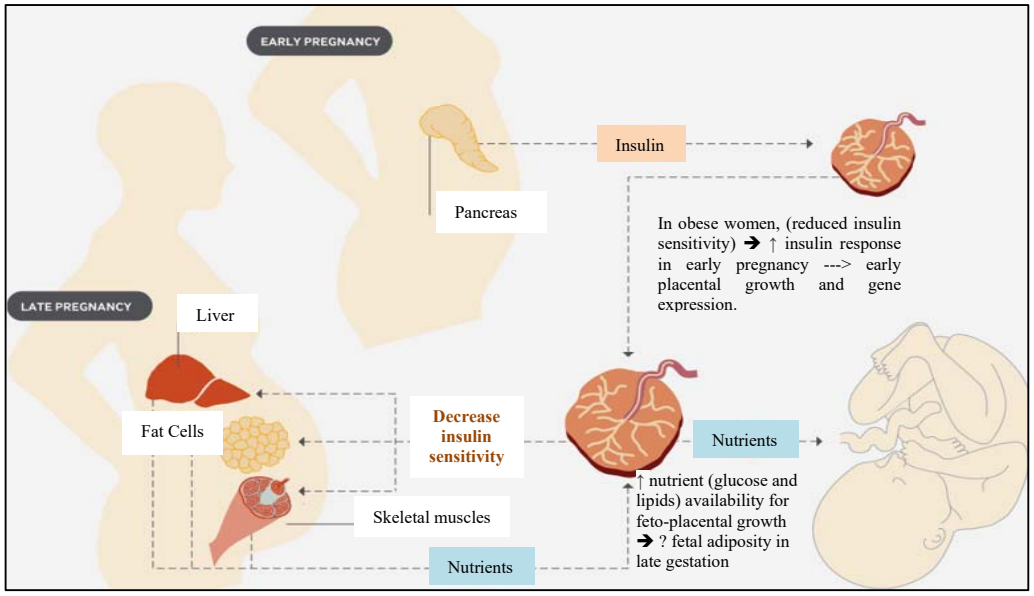

Figure 2.2 Maternal-Placental crosstalk and fetal growth adopted from Catalano, P. M., & Shankar, K. (2017). Obesity and pregnancy: mechanisms of short-term and long-term adverse consequences for mother and child. Bmj, 356, j1.(Catalano & Shankar, 2017).

Despite comprehensive research in this area, the relationship between obesity in pregnancy or “maternal obesity” and inflammation to the moment is still unclear. This may be partly be due to the investigation of different inflammatory mediators in different periods of pregnancy. For instance, while several studies disclose possible association between depressed adiponectin levels in obese women compared to

normal-weight women in the different trimester of pregnancy, others contradict these findings (Anderson et al., 2016; Pourvaghar et al., 2016; Fazeli Daryasari et al., 2019).

2.2 Nutritional status during pregnancy

2.2.1 Dietary intake during pregnancy

Dietary behavior, energy and nutrient intakes during pregnancy are crucial for maternal and child health (Kominiarek & Peaceman, 2017; Richard I. Lowensohn, Diane D. Stadler, 2016) to support the growth of maternal and fetal tissues and to accumulate reserves for lactation. A substantial body of evidence ascertains maternal epigenetic influence on fetal programming, which describes the chemical communication between the mother and the fetus and the transgenerational influence which persist across the life course (Barker et al., 2002; Douglas et al., 2007).

Most of the recent studies' interest in dietary intake during pregnancy stems from its direct relation with the global rise in obesity among women of reproductive age (Koletzko, Demmelmair, et al., 2019). Experts insist that there is no need to increase caloric intake in pregnancy, but rather to shift from energy-dense into more nutrient-dense calories nourishment is of particular importance (Kominiarek & Peaceman, 2017).

There has been growing interest in examining the overall maternal diet quality, in exploring associations between whole foods and health status, rather than just nutrients (Doyle et al., 2017; Shapiro et al., 2016). Some authors used healthy adults' diet indices to assess the diet quality of pregnant women, such as the “Healthy Eating Index” (HEI-2005) and (HEI)-2010) (Shin et al., 2014). At the same time, authors modified the concept to suit the pregnancy population like “Alternate Healthy Eating

Index for Pregnancy (AHEI-P)"(Rifas-Shiman et al., 2009) and "Diet quality Index-pregnancy" (DQI-P) (Crivellenti et al., 2018). The (HEI-SGP), of the Asian cohort study: Growing Up in Singapore Towards healthy Outcomes (Chia et al., 2018; Han et al., 2015). Most of these specific indices have focused on certain nutrient adequacies such as folate and iron since their requirements are elevated before and during pregnancy to satisfy their own needs and optimize birth outcomes (Koletzko, Demmelmair, et al., 2019).

An updated systematic review and meta-analysis (Schwingshackl et al., 2018) revealed high scores from Healthy Eating Index, the Alternate Healthy Eating Index, and the Dietary Approaches to Stop Hypertension were associated with a significantly lower risk of no communicable diseases in the long run. While other studies explored the relation of diet quality (DQ) with weight status and reported inverse association between pre-pregnancy weight status and diet quality, the Project Viva by (Rifas-Shiman et al., 2009) (AHEI-P) and the Asian cohort study (Chia et al., 2018) where older women had significantly higher AHEI-P scores.

Further, adherence to a Mediterranean diet pattern during pregnancy was associated with lower incidence of GDM and better degree of glucose tolerance among women without GDM (Cucó et al., 2006) and adequate intake of fruits and vegetables were associated with birth size and length (See Ling Loy et al., 2011) while lower weekly intakes of vegetables was observed among overweight or obese Egyptian pregnant (Hassan et al., 2016).

On the other hand, some studies revealed inadequacy in key nutrients such as folate, vitamins A and D, iron, calcium, and zinc among Iranian pregnant (Esmaillzadeh et al., 2008) and in food group servings like milk and alternatives, vegetables and fruit, and meat (Fowles et al., 2006) (Fowler et al., 2012) , which are

sources for these essential micronutrients. Consistent to Western findings, of the scarce studies in Arab pregnant, the DEPOSIT cohort, in adequacy of complete protein, dietary fiber, Zn, was among 50% of Palestinian Bedouin women's usual dietary intake and almost 95% had inadequate of vitamin A, calcium and folate (Abu-Saad et al., 2012).

2.2.2 Gestational weight gain

Weight gain is crucial for optimal outcomes for both mothers and infants (Merchant et al., 1999). Many factors influence variation in pregnancy weight gain, however, impact of pre-pregnancy body mass index (BMI), remained a major predictor. With this conception the Institute of Medicine (IOM), (now renamed as the National Academy of Medicine) has set the guidelines for GWG according to pre-pregnancy BMI in 1990 and revised it in 2009 (Siega-Riz et al., 2009). Previous systematic narrative reviews (Marchi et al., 2015), and meta-analysis (Ma et al., 2015), confirmed the predicting effects of excessive gestational weight gain; such as gestational diabetes, pre-eclampsia, gestational hypertension, depression, instrumental and caesarean birth compared with healthy weight women. On the other hand, excessive GWG during early pregnancy was associated with an increased risk of gestational hypertension and preeclampsia, caesarean delivery, macrosomia, and postpartum weight retention after delivery (Ferraro et al., 2012; Ma et al., 2015; Yeşilçiçek Çalik et al., 2018).

Furthermore, excessive GWG was found to exacerbate the generational impact of obesity, whereby women who exceed the recommended weight gain during pregnancy are more likely to retain weight post-partum and to enter the next pregnancy with a higher BMI (Goldstein et al., 2017, 2018a). Most probably will deliver heavier

babies, who have higher odds to become overweight or obese adults later in life (Goldstein et al., 2017).

On the other hand, limited GWG less than the recommendations were found to be associated with stillbirth, infant death, and child impaired neurocognitive or development behavior (Bodnar & Siega-Riz, 2002). At the infant level, maternal obesity and or underweight is also linked to greater risk of large for gestational age babies, and preterm birth or small for gestational age (SGA) and sometimes perinatal death, (Xie et al., 2016) . Another obstetric issue is retention of the excess body weight gained with each pregnancy as revealed in many systematic and meta-analysis reviews (Nehring et al., 2011;Ma et al., 2015), and might be associated with the added burden of chronic diseases (Rong et al., 2015). Besides, the increased maternal fat deposition may lead to the higher placental transfer of nutrients, and consequently, significantly higher infants BMI Z-score (Li, NanLiu et al., 2013).

The mechanisms of these associations remain unclear, as gestational weight gain reflects both maternal nutritional status as well as tissue expansion during pregnancy, because of fat storage and fluids (Siega-Riz et al., 2009). GWG is comprised of the accretion of water, protein fat free mass (FFM) and fat mass (FM) in the fetus as well as the placenta, uterus and amniotic fluid, expansion of maternal blood volume, mammary gland and maternal adipose tissue (Brown, Judith. E. ,Murtaugh, Maureen. A.,Jacobs Jr.David, R., and Margellos, Helen, 2002; Potdar et al., 2014). The fat that is gained during pregnancy is preferentially deposited on the trunk and thighs.

2.3 Adipocytokines

Adipokines and cytokines , collectively are group of bioactive adipokines and cytokines produced mainly by adipocytes are recently gaining researches observation (D'Ippolito et al., 2012; Ohashi et al., 2012; Sahin-Efe et al., 2012). The most

frequently investigated adipokines are adiponectin and leptin; while inflammatory mediated cytokines are tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6), plasminogen activator inhibitor-1, and Resistin. They are secreted by maternal tissues, umbilical plasma and cord blood (Ohashi et al., 2014).

2.3.1 Adiponectin

Adiponectin is an adiposecreted proteins termed adipocytokine, a hormone produced predominantly by adipose tissue, initially discovered and described by Scherer et al. (1995) as ACRP (adipocyte complement-related protein of 30 kDa). It is a 224 amino acid peptide, expressed in adipose tissue and has two different receptors: Adipo-R1 is abundantly expressed in skeletal muscle, while Adipo-R2 is predominantly expressed in the liver (Kubota et al., 2007). Adiponectin (ADPN) circulates in very high concentrations in human serum and it is present as three main isomeric forms: trimeric low molecular weight (LMW), hexameric medium molecular weight (MMW) and high molecular weight (HMW). The high molecular weight multimers accounts for approximately 50% of the total ADPN in human circulation, available in the micrograms per milliliters range (plasma concentration is 5–10 μg/mL) (Halberg et al., 2009) and considered as the most active forms of protein in control of metabolic processes (Halberg et al., 2009; Ohashi et al., 2014; Steinberg & Kemp, 2007). In humans, it has been consistently shown that low circulating levels of ADPN are associated with obesity, type 2 diabetes mellitus (T2DM), and cardiovascular disease (CVD) (Arita et al., 1999; Calle & Fernandez, 2012; Falahi et al., 2015).

Adiponectin demonstrates a vital role in regulating energy metabolism, improve insulin sensitivity, stimulate glucose uptake and fatty acid oxidation and inhibit liver gluconeogenesis (Pfützner et al., 2010). At the peripheral level, such as in

skeletal muscle, adiponectin enhances AMP-activated protein kinase (AMPK) activity, and directly stimulates the glucose uptake in muscle and adipocytes and stimulates fatty acid oxidation. Consequently, this process increases mitochondrial β-oxidation and decreases the circulating free fatty acids which results in decreased triglyceride concentration in muscle and hence leads to improvement in insulin sensitivity (Hoffstedt et al., 2004). While in the liver, triggered (AMPK) activity leads to the suppression of hepatic gluconeogenesis (Maiorana et al., 2007).

It was also revealed that adiponectin has anti-atherogenic properties (Arita et al., 1999; Ouchi et al., 2003; Skrabal et al., 2011) and attenuates adhesion of monocytes to surface of activated endothelial cells (Kubota et al., 2007). In a study by (Ohashi et al., 2012) among Japanese men, low concentration of plasma adiponectin (<4.0 g/mL) exhibited an independent risk factor with a 2-fold increase in coronary artery disease. Furthermore, circulating adiponectin demonstrated significant negative association with some metabolic syndrome components (Kubota et al., 2007; Weyermann et al., 2006) documenting its anti-inflammatory preventive role. Several lines of evidence and recent systematic reviews (Torre-Villalvazo et al., 2018), suggested that low HMW adiponectin described as (hypoadiponectinemia, <2.5 mg/ml) is considered as the most reliable biomarker for MetS diagnosis criteria. Adiponectin levels are mainly inversely associated with visceral fat, total body fat, body mass index (BMI), and waist circumference (Fuglsang et al., 2010). Hence there is reduced release of adiponectin by the abdominal visceral adipocytes (VAT) the metabolically active adipose tissue despite fact that it is abundantly and solely synthesized in adipose tissue (Hocking et al., 2013). Hoffstedt et al (2004) measured adiponectin adipose tissue secretion rate per weight unit in obese subjects and noticed reduced secretion rate by 30% ($P<0.05$) (Hoffstedt et al., 2004). In support of the

clinical findings, some experimental studies with mice have exhibited that adiponectin deficiency contributes to the development of obesity related diseases including insulin resistance, and cardiac diseases.

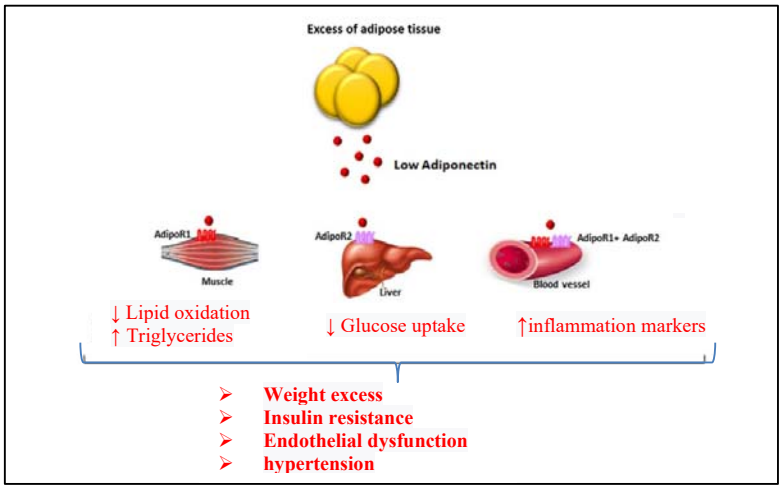

Figure 2.3 Adiponectin Sites of Action (This figure summarizes the main actions of ADPN and their receptors (Adipo-R1and Adipo-R2) in different tissues) (Orlando et al., 2019).

Consistent with adults, studies among children and adolescents of different ethnicity in Chinese (Wen et al., 2014) and Italian cohorts (Nigro et al., 2017) and Brazilian adolescents (Sparrenberger et al., 2019) findings revealed lower adiponectin concentrations are associated with metabolic risk factors (atherosclerosis, waist circumference, triglycerides, total cholesterol, LDL-cholesterol, fasting glucose levels, and insulin resistance)(Medina-Bravo et al., 2011).

The trajectory of adiponectin concentrations throughout pregnancy and in the postpartum period has been explored by several authors (Lacroix et al., 2013; McLachlan et al., 2006; Noureldeen et al., 2014). As reported in previous literature, pregnancy is a naturally mild maternal systemic inflammation state, that shares a pattern of insulin resistance with obesity (Catalano & Shankar, 2017; Romy Gaillard et al., 2016; Hrolfsdottir et al., 2016; Poston et al., 2011). As pregnancy progresses elevated secretion of inflammatory adipokines from maternal adipose tissue and placenta in late pregnancy along with the placental hormones such as human placental

lactogen and placental growth hormones, (Fuglsang et al., 2010; Valsamakis et al., 2010) furnish an insulin resistance environment in an attempt to enhance the availability of glucose for fetal needs. Longitudinal studies during pregnancy, among healthy pregnant mothers documented the decreasing pattern of ADPN concentration with advancing gestation, and generally accompanied by a decreased insulin sensitivity. Other authors reported hypoadiponectinemia to be more pronounced among GDM pregnant at their third trimester compared to(Vitoratos et al., 2008) normal (Fujimori et al., 2017; Noureldeen et al., 2014; Siddiqui et al., 2018;) pregnancy (Fujimori et al., 2017; Noureldeen et al., 2014; Siddiqui et al., 2018; Vitoratos et al., 2008).

The production of adiponectin in the placenta and the fetus has suggested that adiponectin might have an important role in fetal and postnatal development (Weyermann et al., 2006). Some authors found a positive association between cord blood adiponectin levels with infant birth outcomes (weight, BMI percentiles, and lean body mass) (Cekmez et al., 2011; Jacques et al., 2016), while others have not (Bozzola et al., 2010; Lindsay et al., 2003). Lower adiponectin levels were found in the umbilical cord blood of neonates born to diabetic mothers (Cekmez et al., 2011) and in newborns born with large for gestational age (LGA) weights (29.4 ± 13.8 vs 35.0 ± 9.9 μg/mL, $P < .04$) compared to newborns with weights adequate for gestational age (AGA) (Challa et al., 2005). However, earlier studies failed to show differences at two years of children age (Iñiguez et al., 2004).

2.3.2 Adiponectin in breast milk

Adiponectin apart from the main secretion source, evidence demonstrated its synthesis in salivary gland and mammary epithelial cells. In 2006 adiponectin was