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Inflammation in Maternal Obesity and Gestational Diabetes Mellitus

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Abstract

The prevalence of maternal obesity is rising rapidly worldwide and constitutes a major obstetric problem, increasing mortality and morbidity in both mother and offspring. Obese women are predisposed to pregnancy complications such as gestational diabetes mellitus (GDM), and children of obese mothers are more likely to develop cardiovascular and metabolic disease in later life. Maternal obesity and GDM may be associated with a state of chronic, low-grade inflammation termed “metainflammation”, as opposed to an acute inflammatory response. This inflammatory environment may be one mechanism by which offspring of obese women are programmed to develop adult disorders. Herein we review the evidence that maternal obesity and GDM are associated with changes in the maternal, fetal and placental inflammatory profile. Maternal inflammation in obesity and GDM may not always be associated with fetal inflammation. We propose that the placenta ‘senses’ and adapts to the maternal inflammatory environment, and plays a central role as both a target and producer of inflammatory mediators. In this manner, maternal obesity and GDM may indirectly program the fetus for later disease by influencing placental function.

Keywords

Metainflammation; obesity; gestational diabetes mellitus; placenta; cytokines

1. Introduction

Obesity in pregnancy is rapidly becoming more common worldwide and constitutes a major medical problem. In the United States, 35% of women of reproductive age are obese (body mass index, BMI>30kgm/m^2) [1]. Maternal obesity has a significant economic impact,

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estimated to cost $106.8 million annually in the US alone [2]. Obesity during pregnancy is associated with increased mortality and morbidity for both mother and offspring. Obese women are at greater risk for developing pregnancy complications such as preeclampsia, thromboembolism, and gestational diabetes mellitus (GDM), as well as cardiovascular and metabolic disorders in later life [3, 4]. The risk of developing GDM is increased 1.3–3.8 times in obese women compared to women of normal BMI [5], and ~70% of women with GDM may go on to develop type 2 diabetes up to 28 years post-partum [6].

Infants of obese mothers have a higher incidence of congenital abnormalities and are more likely to be large for gestational age (LGA) at birth [4, 7, 8]. Children of obese mothers, in particular if they are born LGA, are prone to develop metabolic disease [9–12]. The hypothesis that the fetal environment may influence the development of disease in adulthood, now termed the ‘developmental origins of adult disease’, was proposed by Barker and based on the observation that low birth weight correlated positively with the development of cardiovascular disease in later life [13]. Considerable epidemiological evidence has accumulated demonstrating that maternal obesity is predictive for the development of obesity [14], cardiovascular disease [15], and type 2 diabetes in offspring [10]. Children of obese women with GDM are more likely to have increased adiposity and be insulin resistant, propagating the vicious cycle of metabolic disorders into the next generation [16]. There are currently limited options for early prevention of the metabolic syndrome in children born to obese women. Improving the metabolic environment of the obese pregnant mother to break this vicious cycle may be an attractive approach to decrease the future economical, societal, and personal burden of obesity. However, to make progress in this area, better understanding of the mechanisms linking obesity in pregnancy to adverse outcomes in the infant is necessary.

In recent years, there has been increased interest in the role of inflammation as a mediator of programming of metabolic disorders following exposure to the adverse intrauterine environment in maternal obesity. In the non-pregnant state, obesity is associated with a chronic, low-grade inflammatory state, termed ‘metainflammation’, or metabolically induced inflammation [17]. Metainflammation is distinct from an acute pro-inflammatory response and is triggered primarily by metabolites and nutrients, leading to systemic insulin resistance [17].

Placental inflammation has been observed in pregnancies complicated by obesity [18] and GDM [19], and may play a central role in determining the fetal environment in these pregnancies. Normal pregnancy is associated with a highly regulated inflammatory response that is vital to the process of placentation, from implantation through to labor at term [20]. Maternal obesity and GDM have been associated with changes in placental nutrient transporter expression and activity [21, 22]. These changes in placental function may be caused by altered inflammatory profiles in the mother, placenta and fetus in obesity and GDM, leading to the co-morbidities observed in these pregnancies [23, 24]. This article summarizes the literature reporting inflammatory profiles in the maternal, placental and fetal compartments in association to maternal obesity and GDM. Unless otherwise stated, we have focused specifically on studies documenting inflammation in women. While vascular and endothelial changes, oxidative stress, and tissue damage do occur in response to

inflammation, we have focused on primary changes in inflammatory mediators and immune cells and pathways in obese pregnancies and GDM. A better understanding of how maternal obesity and metainflammation relates to the fetal intrauterine environment may lead to the development of better therapeutic interventions to prevent the development of metabolic disorders in later life.

2. Metainflammation, Obesity and Insulin Resistance in the Non-Pregnant State

The acute inflammatory response induced by infection or trauma is typically a rapid response, characterized by vasodilation, infiltration of tissue by neutrophils, accumulation of macrophages and lymphocytes, and resolution. Acute inflammation is also characterized by an increased basal metabolic rate due to the focused and rapid response to the insult. Once the insult is neutralized, inflammation subsides. Inflammation induced by obesity in non-pregnant individuals is distinct from the classical inflammatory response in that (1) it is metabolically induced by excessive consumption of nutrients; (2) it is a modest and low-grade response; (3) it alters the profile of immune cells favoring a pro-inflammatory environment in tissues such as adipose, liver and pancreas; (4) it is chronically maintained by metabolic cells such as adipocytes without resolution, and (5) it is associated with a reduced metabolic rate [17]. For these reasons, the term ‘metaflammation’ or ‘metainflammation’ was coined to describe this particular profile associated with obesity [17].

The link between adiposity, inflammation and insulin resistance was first identified when it was observed that levels of the proinflammatory cytokine TNF-α were increased in adipose tissue of obese individuals, and that TNF-α antagonism led to increased insulin sensitivity [25]. Weight-loss is associated with a reduction of TNF-α and reversal of insulin resistance [26]. It is now evident that, in the obese state, several adipokines, chemokines, and cytokines released from adipose tissue and immune cells may interact in an autocrine and paracrine network, causing impaired insulin sensitivity in the metabolic syndrome. Adipose tissue thus behaves as one of the largest endocrine organs in the body [27].

Insulin resistance is a primary feature of the metabolic syndrome, caused by reduced insulin sensitivity in adipose tissue, muscle and liver. Pancreatic β-cells increase insulin secretion, but when the demand for insulin exceeds the secretory capacity of the β-cells, hyperglycemia and diabetes may ensue. Insulin exerts its actions on muscle, liver and adipose tissue by binding insulin receptors, which leads to tyrosine kinase phosphorylation of insulin receptor substrates (IRS). IRS binds the regulatory subunit of phosphoinositide 3-kinase (PI3K), activating protein kinase 1 (PDK1) which in turn phosphorylates Akt, resulting in translocation of GLUT4 (glucose transporter 4) to the plasma membrane in adipose tissue and muscle to facilitate glucose uptake. Insulin-stimulated Akt phosphorylation also activates glycogen synthase and glycogen synthesis. Mitogen activated protein kinase (MAPK) and mammalian target of rapamycin complex (mTORC) pathways downstream of insulin signaling play a role in promoting protein synthesis and cell growth and differentiation [28]. In obesity, nutrients or inflammatory signals cause activation of the kinases Janus kinase (JNK) and Iκβ kinase (IKK), leading to serine phosphorylation of

IRS-1 and inhibition of the insulin receptor-signaling cascade, thus causing insulin resistance [17]. Knockout mouse models have highlighted the importance of inflammatory signaling in the development of insulin resistance, as deletion of IKK2 and JNK-1 prevents insulin resistance, while deletion of suppressor of cytokine signaling 1 (SOCS1) or PPAR-γ causes insulin resistance [28, 29].

The immune cell profile is altered in obesity. An increase in macrophages, neutrophils, T cells, B cells and mast cells is observed in visceral adipose tissues (VAT) in non-pregnant mice with diet-induced obesity. Conversely, adipose tissue T-helper cells, regulatory-T cells and eosinophils are decreased. In the non-obese state, macrophages comprise 10–15% of the VAT immune cell population, while 40–50% of all immune cells in VAT are macrophages in obese humans and mice. Macrophages may be activated by the classical or the alternative pathway (M1 and M2 respectively) [30]. In non-obese individuals, IL-4 and IL-13 maintain macrophages in the M2 state, resulting in the secretion of the anti-inflammatory cytokines IL-10 and IL-1Ra. In obesity, the M2 phenotype switches to M1, a proinflammatory state, leading to the secretion of TNF-α and IL-6. IFN-γ and endogenous Toll-like receptor (TLR) ligands maintain the M1 state [31]. Obesity in pregnancy and GDM have been linked to the disruption in several inflammatory mediators in the maternal and fetal compartments. These will be discussed below.

3. Maternal and Fetal Inflammation in Obesity in Pregnancy and GDM

Maternal Inflammation

Pregnancy itself is characterized by an altered inflammatory profile compared to the non-pregnant state. A tightly regulated balance between pro- and anti-inflammatory cytokines may be necessary for normal implantation, trophoblast invasion and placentation. A pro-inflammatory response localized to the uterine site of implantation may be necessary for this process [32]. In contrast, the post-implantation period is associated with an ‘immunosuppressive’ bias towards producing Th2 cytokines, which is believed to be necessary to prevent immune rejection of the fetus [33]. Normal pregnancy is also characterized by a state of insulin resistance, with a 50% reduction in insulin-mediated glucose clearance, and a ~250% increase in insulin production to maintain maternal euglycemia [34]. Pregnant women with obesity or GDM are insulin-resistant compared to normal pregnant women. However, the widely accepted dogma that increased adiposity equates to increased maternal inflammation may not be as evident during pregnancy as in the non-pregnant state.

Evidence from Longitudinal Studies of Maternal Obesity—Longitudinal studies have provided information on the temporal changes in maternal cytokine profiles during normal pregnancy, and alterations of this profile in obesity. Recently, Christian et al. comprehensively measured proinflammatory cytokines IL-6, IL-8, CRP, TNF-α and IL-1β in a total of 57 women of normal BMI, overweight and obese women in the first, second and third trimesters as well as 4–6 weeks post-partum [35]. In normal pregnant women, levels of IL-6 and TNF-α increased at each visit and postpartum, while IL-8 and IL-1β decreased from the first to the third trimester, and increased postpartum. CRP decreased throughout pregnancy and post-partum. In obese women IL-6 and CRP were elevated during pregnancy

and postpartum compared to controls. While the patterns of change in cytokines were similar in normal, overweight, and obese women, the women with higher BMI did show a trend towards elevation in some (CRP, IL-6), but not all inflammatory markers [35]. Similarly, in a study by Stewart et al., an elevation in CRP was observed in obese women at each trimester, while IL-6 was significantly increased only in the second and third trimester compared to controls. TNF-α did not differ at any time-point measured in obese women compared to controls [36].

Friis et al. determined the levels of CRP, MCP1, IL-6 and IL-1Ra in maternal plasma of 240 overweight and obese women using enzyme-linked immunosorbent assay (ELISA). It was found that while levels of these circulating inflammatory mediators were increased with increasing BMI in early to mid-pregnancy, this elevation was not evident towards the end of pregnancy [37]. The authors speculate that perhaps increased adiposity during pregnancy is not associated with enhanced inflammation, as opposed to the widely held belief.

TNF-α, IL-6 and CRP in Obesity and GDM—TNF-α is arguably the most extensively studied cytokine in relation to inflammation and the development of insulin resistance in obesity and GDM. Given the relationship between increased adiposity, TNF-α, and insulin resistance, it would be expected that levels of TNF-α correlate with adiposity in pregnancy, similar to obesity in the non-pregnant state. However, this may not be the case. While increased circulating TNF-α in maternal serum correlate with increasing BMI in some studies [18, 38], several other studies do not report a significant increase in circulating TNF-α in obesity with [39] or without GDM [35, 36, 40–43]. In fact, one study documented a decrease in TNF-α production by T-cells isolated from obese women without GDM [44]. An increase in TNF-α mRNA levels in maternal stromal vascular cells [40] as well as TNF-α mRNA and protein in the placenta of obese women has been observed, but this may not correlate to increased circulating TNF-α levels in maternal blood [40, 41, 45]. Increased circulating TNF-α may be related to the development of GDM, and several groups have therefore postulated that circulating maternal TNF-α levels are an independent predictor for the development of GDM regardless of BMI [46–48].

In contrast, elevated circulating levels of IL-6 in maternal plasma and serum have been consistently observed in maternal obesity as well as in GDM in the presence or absence of obesity [47, 49–52]. An increase in IL-6 mRNA in subcutaneous adipose tissue (SAT) of women with GDM has also been reported [19]. IL-6 induces the acute-phase response, which is characterized by the release of CRP from the liver [35]. Increased CRP levels have frequently been observed in conjunction with increased IL-6 in obesity in pregnancy [36, 40, 41, 53].

Changes across gestation in maternal serum TNF-α and CRP, two inflammatory markers that are most commonly assessed in relation to obesity and insulin resistance, are summarized in Figures 1A and B. These representative schematics show the trends in these two cytokines in women of normal BMI and obese non-pregnant women, compared to normal and obese pregnant women and obese women with GDM. In Figure 1A, levels of TNF-α in obese and normal non-pregnant individuals are presented as an average across three studies in women [54–56]. TNF-α levels are reduced in the pregnant state compared to

non-pregnancy, in both obese and normal women. That TNF-α levels are lower in pregnancy compared to non-pregnant obese women and non-pregnant women of normal BMI, is consistent with the Th1/Th2 paradigm of pregnancy, which postulates that a lower Th1:Th2 cytokine ratio is necessary for the maintenance of pregnancy. Recurrent spontaneous abortion is frequently associated with high levels of Th1 cytokines, such as TNF-α, in early pregnancy [57]. During pregnancy, TNF-α levels are lower in the first and second trimester, and modestly elevated in the third trimester. In Figure 1A, TNF-α values across the first, second and third trimesters in obese and normal women are averaged across three studies [35–37]. TNF-α levels may be elevated in GDM, consistent with the long-standing hypothesis that TNF-α is involved in propagating insulin resistance leading to GDM [46, 58, 59].

In contrast, CRP levels in normal, non-pregnant individuals are low, and are slightly raised in obese non-pregnant individuals. Levels of CRP in normal, non-pregnant women are averaged across 2 studies [55, 60], while levels in non-pregnant obese women are averaged across three studies [55, 60, 61]. CRP increases when women of normal BMI or obese women become pregnant (Figure 1B). Levels of CRP, albeit higher than in normal pregnant women, tend to decrease when an obese woman becomes pregnant and may decrease further at the end of pregnancy [35, 36], while in GDM CRP may increase at the end of pregnancy [62].

Lack of concordance in the profile of inflammatory mediators circulating in maternal serum in obese and/or GDM pregnancies between different studies can be attributed to several factors. (1) Some studies do not exclude other comorbidities related to obesity and the inflammatory mediators observed may be related to other pathologies of pregnancy apart from obesity alone or obesity with GDM. (2) Different study designs (cross-sectional or longitudinal) make it more difficult to directly compare levels of inflammatory mediators between studies. (3) The exact time of sampling, the type of sample (plasma or serum, SAT, VAT, immune cell subsets) as well as assay method may influence the levels of inflammatory mediators measured in each study. (4) Selection of subjects according to race and ethnicity and age may play a role in the responses observed in maternal obesity and GDM. (5) These studies may be confounded by a ‘negative publication bias’, with many studies showing no changes in inflammatory mediators never being published. Further well-designed, appropriately controlled large studies are required to more definitely establish the maternal inflammatory profile in obesity and GDM. Table 1 summarizes the studies investigating inflammation in the maternal, fetal, and placental compartments in obesity with and without GDM. Changes in maternal serum cytokines levels across gestation have not been presented in this table. The representative schematics in Figures 1A and B provide an indication of the differential inflammatory changes that occur in maternal circulating cytokine levels across gestation in obesity and GDM.

Fetal Inflammation

Alterations in maternal inflammatory markers may not be reflected by similar changes in the fetal circulation. In one study, levels of inflammatory proteins were investigated 1, 7 and 14 days after delivery in a total of 939 infants born to non-obese, overweight, and obese

mothers showed that the levels of IL-6, IL-8, ICAM3, TNFR1 and VEGFR2 were positively correlated to maternal BMI. However, day-14 concentrations were not elevated in the obese group [63]. Ategbo *et al.* investigated circulating levels of cytokines and adipokines in 59 women with GDM and their macrosomic infants, compared to 60 age-matched controls [47]. Maternal serum levels of adiponectin and Th1 cytokines (IL-2 and IFN-γ) were decreased, while in their macrosomic neonates, adiponectin was decreased and Th1 cytokines were increased (Table 1). Leptin, IL-6, TNF-α, and IL-10 were increased in GDM mothers, while in their neonates, leptin, TNF-α and IL-6 were decreased (Table 1). Birthweights were significantly increased in neonates born to obese women with GDM [47]. Previous work by our group has also shown that umbilical vein cytokine levels were unaffected by maternal obesity [18]. Birthweight was also increased in the obese group in this study [18]. It is therefore possible that the placenta acts as a mediator and an adaptor in pregnancy, sensing and responding to the maternal inflammatory environment in order to maintain pregnancy. Several studies have assessed inflammation in the placenta in obesity and GDM.

4. The Placenta as an Inflammatory Organ: Not just a Silent Observer

It is well established that placental cytokine production is critical for the maintenance of pregnancy. Cytotrophoblasts, syncytiotrophoblast and Hofbauer cells are known to secrete cytokines necessary at various stages of pregnancy from implantation to delivery [20]. It has been suggested that the placenta plays an active role in mediating inflammation in women with obesity and GDM. Placental structure and function may be altered in an adaptive response to obesity, and the placenta may act as a target and a source of inflammatory cytokines in these pregnancies. Challier at al. have reported a 2–3-fold increase in the number of placental macrophages in obese women, characterized by an increase in IL-1, TNF-α and IL-6 mRNA expression [41]. One study comparing the transcriptome of active monocytes isolated from the placenta, maternal venous, and umbilical cord blood, found that monocytes isolated from maternal blood and the placenta showed 73% homology, suggesting an inflammatory phenotype at the placental interface [64].

Placental mRNA and protein expression of inflammatory mediators in obesity and GDM have been explored in a number of studies. Saben and coworkers sequenced placental RNA and found that levels of *IL-12RB2*, *IL-21R*, and *CX3CR1* were increased, while *IL-1R1*, *IL-1RAP*, *CXCR2*, *CXCR1*, *CCR3* and *ADIPOR1* were decreased in placentas from obese women compared to placentas from women with normal BMI [65]. A number of studies have documented an increase in IL-6 [41] and TNF-α [41, 66] in placentas from obese women, and an increase in IL-8 [67] and leptin [68] in placentas from women with GDM. Other studies found limited indications of inflammation [18].

Some of the changes observed in the placenta in maternal obesity may represent an adaptation, which could contribute to limit exposure of the fetus to inflammation and oxidative stress. For example, Lappas and co-workers reported that exposure of placental tissue from women with and without GDM to oxidative stress resulted in the release of only 3 out of 16 cytokines (IL-1β, TNF-α, M1P1B) and no changes in antioxidant gene expression. This was in contrast to women with normal BMI who exhibited an increase in 13 out of 16 cytokines and alterations in antioxidant genes in placenta exposed to oxidative

stress [69]. Collectively, these studies highlight the importance of the placenta as a source of inflammatory mediators, a site of inflammation and an adaptive mediator.

Cytokines produced by the placenta may be responsible for the elevated levels observed in the maternal circulation in GDM, as 94% of TNF-α produced by *in vitro* perfused placental cotyledons is released to the maternal side and only 6% to the fetal side [46]. In cultured primary human trophoblasts, inflammatory cytokines IL-6 and TNF-α have been shown to upregulate amino acid transporter system A activity [23], while IL-1β down-regulates insulin-stimulated system A transport in primary trophoblasts [70]. This may be one mechanism by which inflammatory mediators influence placental nutrient transport, thereby linking inflammation in maternal obesity to changes in fetal growth.

Previous work by our laboratory has shown that while maternal serum MCP1 and TNF-α is increased, and placental p38-MAPK and STAT3, but not NFκB are activated in maternal obesity, levels of inflammatory markers in umbilical blood are unaltered [18]. It has therefore been suggested that maternal inflammation in obese women or women with GDM may influence fetal development by impacting placental function, rather than directly influencing the fetal inflammatory profile [18].

5. Inflammation and Developmental Programming

Inflammatory mediators may act *in utero* to program fetal adipose tissue, liver and skeletal muscle for insulin resistance later in life. Because it is not possible to examine fetal and neonatal tissues in humans, animal models have been utilized to investigate inflammation in specific tissues in offspring of obese dams. Maternal obesity is associated with adipogenesis, increased adiposity and insulin resistance in fetal tissues in several animal models [71]. In one study, activation of the NF-κB pathway was observed in skeletal muscle from fetuses of obese ewes. Increased adipogenesis, intramuscular adipocytes and insulin resistance were also observed, constituting one mechanism by which maternal obesity may predispose to metabolic diseases in offspring [72]. Fetuses of mice fed a high fat diet display higher levels of TNF-α, CD68 and MCP-1 mRNA in adipose tissue, suggesting that maternal obesity may cause inflammation in fetal adipose tissue [73]. Maternal over-nutrition has been reported to be associated with elevated triglyceride levels, increased inflammatory markers and fatty livers in offspring [74]. The effects of maternal obesity and inflammation on the fetus in animal models have been reviewed recently [71]. More detailed studies are required to investigate the exact mechanisms by which localized inflammation in fetal tissues is linked to metabolic disease later in life.

Conclusions and Future Directions

In conclusion, metainflammation, or chronic, low-grade metabolically induced inflammation may play a role in maternal obesity and GDM, leading to developmental programming *in utero*. The maternal inflammatory profile associated with GDM may be more pronounced than in obese women pregnant women without GDM. Studies investigating inflammatory mediators in the maternal, placental and fetal compartments in obesity and GDM are not always concordant. There is insufficient evidence that maternal inflammation equates to

inflammation in fetal serum. Circulating cytokines may not be truly reflective of inflammatory status, and more data is required detailing cytokine production from specific maternal and fetal tissues. The placenta may play a role as a mediator in inflammation in obesity and GDM. Further, adequately powered, well-designed studies are required to help us better understand (1) the placental mechanisms by which inflammation may be involved in developmental programming, and (2) the effects of inflammation on fetal tissues *in utero*. It is necessary to understand these processes in order to develop treatments to reverse the effects of maternal obesity on the developmental programming of metabolic and cardiovascular diseases.

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Highlights

- Inflammation occurs in maternal obesity and gestational diabetes mellitus (GDM)
- The placenta plays a key role in inflammation in obesity and GDM
- Maternal inflammation may not equate to fetal inflammation

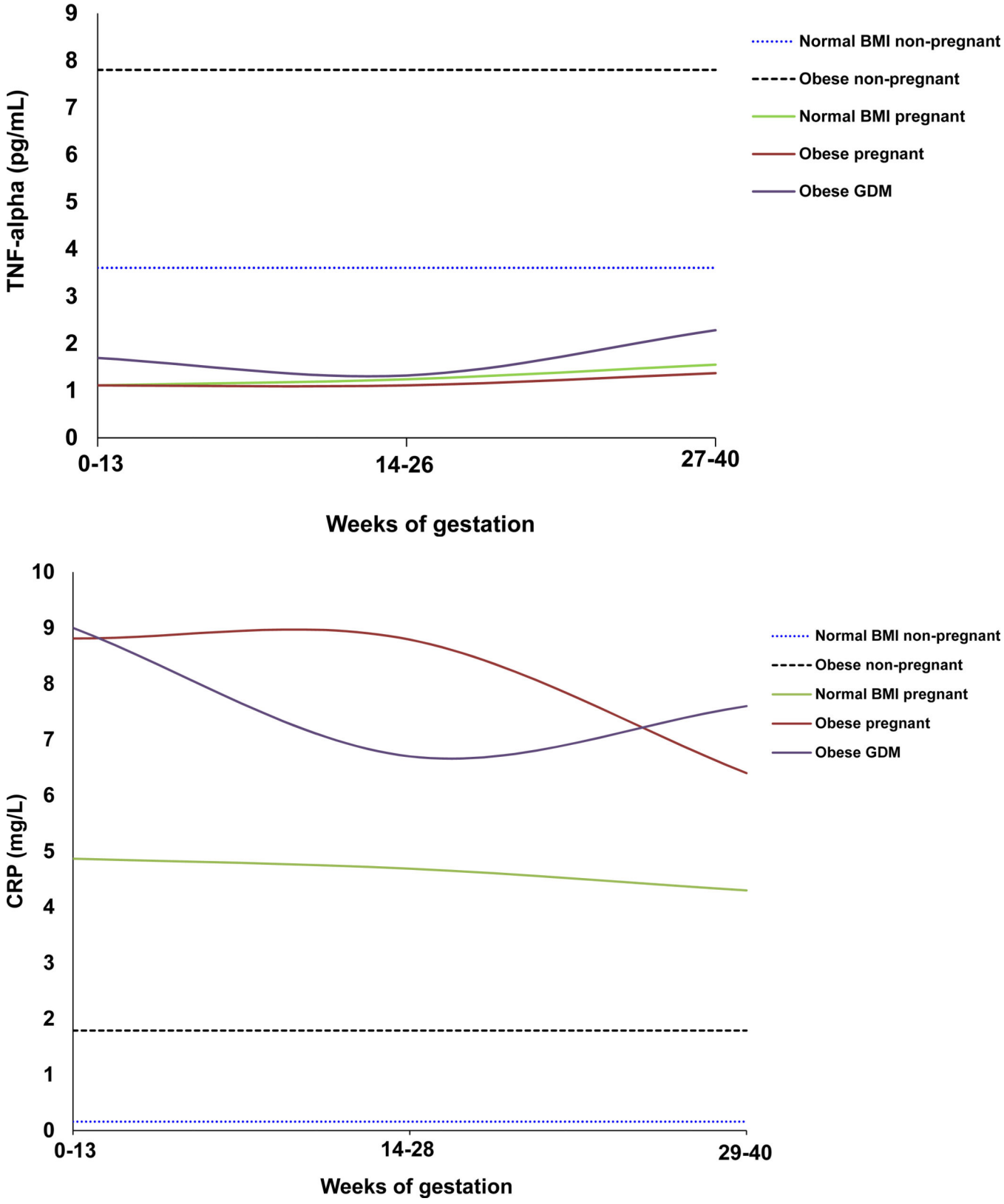

Figure 1.

A: Representative schematic of changes in maternal serum TNF-α levels throughout pregnancy in obesity and GDM, compared with normal pregnant, normal non-pregnant, and obese non-pregnant individuals. TNF-α levels are decreased in normal pregnant women compared to non-pregnant individuals, and appear to increase from the first to third trimester. In obese women, TNF-α levels may be lower than in normal pregnant women, and are increased in GDM. TNF-α is highest in non-pregnant obese individuals. Data represents absolute TNF-α levels in pg/mL in (1) normal and obese non-pregnant individuals averaged across three studies in women [54–56]; (2) normal and obese pregnant women averaged across 3 longitudinal studies measured in the first, second and third trimester [35–37]; and (3) women with GDM (BMI≥30kg/m^2) in the first [46], second [57] and third [46, 57, 58].
B: Representative schematic of changes in maternal serum CRP levels throughout pregnancy in obesity and GDM, compared with normal pregnant, normal non-pregnant, and obese non-pregnant individuals. CRP levels are increased in normal pregnant women compared to normal non-pregnant and obese individuals, and appear to decrease slightly from the first to third trimester. In obese women, CRP levels are increased compared to normal pregnant women and decrease in late pregnancy. The opposite pattern is observed in GDM, with a decrease in mid-gestation and a rise at term. Data represents absolute CRP levels in mg/mL in (1) normal and obese non-pregnant women averaged across 2–3 studies in women [55, 59, 60]; (2) normal and obese pregnant women averaged across 2 longitudinal studies measured in the first, second and third trimester [35, 36]; and (3) women with GDM (BMI≥30kg/m^2) in the first [74], second [75] and third [61, 75] trimester.

Table 1

Overview of changes in cytokines in the maternal and fetal/placental compartments in obese and GDM pregnancies.

Reference	**Criteria**	**TNF-α**	**CRP**	**IL6**	**IL1β**						
Basu et al. [40]	Obese	↔	↑	↑	-						
Challier et al. [41]	Obese	↔	↑	↑	-						
Christian et al. [35]	Obese	↔	↑	↑	↔						
Farah et al. [42]	Obese	↔	-	↑	↔						
Ramsay et al. [53]	Obese	-	↑	↑	-						
Stewart et al. [36]	Obese	↔	↑	↑	-						
Stone et al. [38]	Obese	↑	-	↔	-						
Korkmazer et al. [76]	GDM	↑	↔	-	-						
Kuzmicki et al. [52]	GDM	-	↑	↑	-	***Fetal/placental cytokines***					
Friis et al. [37]	Obese and GDM	-	↑	↑	-	**Sample studied**	**TNF-α**	**IL6**	**IL10**	**MCP1**	**Birthweight in obese/GDM (kg)**
Vega-Sanchez et al. [43]	Obese	↔	-	↔	-	Cord blood	↔	-	↔	-	*
Aye et al. [18]	Obese	↑	-	↔	↔	Cord blood	↔	↔	↔	↔	3.45±0.05 (↑)
Ategbo et al. [47]	Obese and GDM	↑	-	↑	-	Cord blood	↓	↓	↑	-	4.35±0.6 (↑)
Van der Burg et al. [62]	Obese neonates	-	-	-	-	Neonatal blood spots	↔	↑	-	↔	*
Roberts et al. [77]	Obese	↔	-	↑	↔	Placenta (mRNA)	↔	↔	-	↑	3.38±.48 (↔)
Oliva et al. [45]	Obese	-	-	-	-	Placenta (protein)	↑	↑	-	-	3.78±.106 (↑)
Kleiblova et al. [19]	GDM	-	-	-	-	Placenta (mRNA)	↔	↔	-	-	3.47±0.27 (↔)

Note: (↑) indicates cytokines that were increased in obese/GDM pregnancies compared to pregnancies with normal BMI; (↓) indicates cytokines that were decreased compared to normal pregnancies; (↔) indicates no significant difference in cytokine levels compared to normal pregnancies; (-) denotes cytokines that were not measured in that study. Birthweights are indicated as mean weight of neonates born to obese and/or GDM mothers in kilograms. (↑) indicates an increase; (↓) indicates a decrease; and (↔) indicates no change in birthweights of neonates compared to neonates born to control mothers.

(*) indicates studies that did not provide mean birthweight values. All changes indicated are significant ($P<0.05$). Only studies in which ≥2 cytokines were measured have been presented. Changes in maternal serum cytokine levels across gestation are not presented.