Implications of inflammation and insulin resistance in obese pregnant women with gestational diabetes: A case study

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Abstract

Background: Obesity is one of the leading pregnancy risks for both the mother and the neonate. The prevalence of gestational diabetes mellitus has been increasing, especially with the increase in obesity in reproductive-aged women. A high body mass index, a sedentary lifestyle, a previous macrosomic infant, polycystic ovary syndrome and hypothyroidism are the main risk factors for gestational diabetes mellitus. Early gestational diabetes mellitus detection in high-risk individuals is a useful method for preventing further complications and/or preventing this disease by improving the patient’s lifestyle.

Case presentation: A morbidly obese woman with a high body mass index (>36) at 24 weeks gestational age presented with several gestational diabetes mellitus risk factors. Her glucose tolerance test verified gestational diabetes mellitus, and, incidentally, her C-reactive protein level was elevated without obvious reason. Her plasma levels of inflammatory cytokines had also been assessed and were exaggerated. After lifestyle intervention, including weight management, the patient’s inflammatory mediators, including her C-reactive protein level, dropped. Therefore, this study aimed to identify the relationship between the patient’s inflammation and obesity.

Conclusion: Antenatal C-reactive protein screening could be used throughout pregnancy to predict inflammation from high-risk pregnant women. This case scenario describes the interrelationships between inflammation, insulin resistance and adipokines, as well as the contributions of hypothyroidism and polycystic ovary syndrome. Further research should emphasise the relationships between inflammation and obesity in pregnancy.

Keywords

Inflammation, pregnancy, obesity, adipocytes, C-reactive protein, cytokines, thyroid stimulating hormone, insulin resistance

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Background

Obesity rates have increased worldwide, and women have been affected more than men.1 Obesity complicates a woman’s pregnancy, not only affecting her health but also threatening her foetus.2 Pre-pregnancy obesity is considered to be an independent risk factor for macrosomia, but it does not necessitate abnormal glucose tolerance test (GTT) results.3 However, mothers with higher pre-pregnancy body mass indices (BMIs) are predisposed to gestational diabetes mellitus (GDM).4 A mother with a history of GDM has a greater risk of evolving type 2 diabetes mellitus (T2DM) after pregnancy.3 Moreover, a foetus exposed to maternal hyperglycaemia has greater risks of obesity and glucose intolerance later in life.6

Inflammation and hormone disturbances are considered hallmarks in the pathophysiology of maternal obesity.7–9 Both animal and in vitro models have clearly shown metabolic inflammation changes in obese mothers and their offspring. A model involving obese pregnant mice has proven association with abnormal placentation, cellular inflammation and dys-vascularisation,10 and suggested that maternal obesity might lead to hippocampal insulin resistance in offspring.11 In addition, an in vitro model for skeletal muscle extraction from obese pregnant women demonstrated increased insulin resistance and inflammation.12 Previously, it has been shown that, in human placenta, there is an extreme

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inflammatory response with heterogeneity of macrophages and pro-inflammatory mediators, resulting from obesity in pregnancy.\textsuperscript{9} Taken together, the pathophysiology of maternal obesity induces immunological and inflammatory changes, but this requires clarification.

Circulating biomarkers in the maternal blood could be indicators for metabolic disorders in obesity and GDM. Recently, it was found that multi-inflammatory biomarkers could be safely used as diagnostic or prognostic indicators during pregnancy, including C-reactive protein (CRP), adipokines and inflammatory cytokines, like tumour necrosis factor alpha (TNFα), interleukin 1 beta (IL-1β) and interleukin 6 (IL-6). Some of these biomarkers, such as leptin and CRP, have been identified as playing roles in maternal obesity.\textsuperscript{13}

The current study’s aim was to characterise several inflammatory biomarkers in diabetic, obese pregnant women — placing the studied patient in optimum intervention with better lifestyle choices in addition to insulin therapy and observing her progress to determine whether such intervention would stabilise inflammation and insulin resistance.

### Case presentation

A 26-year-old, Caucasian, Saudi woman presented at her antenatal screening with her third pregnancy (Table 1). She has one daughter and had one previous abortion. Her body weight was 95.2 kg, height was 159 cm, BMI was 36 and blood pressure was 120/85 mm Hg. Her past obstetric history indicated an emergency caesarean section for a macrosomic

Table 1. Timeline table.

| Dates            | Summaries of visits                                                                 | Diagnostic tests                                                                 | Interventions                                                                                     |
|------------------|------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|
| 24 January 2018  | Obese women with an unplanned pregnancy with risk factors for GDM, presented at 20 weeks GA at antenatal clinic | US                                                                                | OGTT requested and transferred to GDM clinic                                                       |
|                  |                                                                                    | Single, viable foetus, with normal motions and anatomy                             |                                                                                                   |
|                  |                                                                                    | FHR = 170 BPM                                                                     |                                                                                                   |
|                  |                                                                                    | EFW = 337 ± 49 g                                                                  |                                                                                                   |
|                  |                                                                                    | GA = 20 weeks ± 1 day                                                             |                                                                                                   |
|                  |                                                                                    | RBG = 6.5 mmol/L                                                                  |                                                                                                   |
| 22 February 2018 | Patients transferred from antenatal to GDM clinic                                    | OGTT                                                                              | - Lifestyle, structured dietary regimen with supplements for pregnancy under medical nutrition therapist and daily moderate exercise for at least 30 min |
|                  | Diagnosed with GDM and insulin therapy was started                                  | FBG = 5.8 mmol/L                                                                  | - Health education on glucose telemonitoring                                                       |
|                  |                                                                                    | 2 h PPG = 8.3 mmol/L                                                              | - 0.7 units/kg/day, divided twice daily, from 100 units/mL insulin (NovoRapid FlexPen)             |
| Weekly           | Follow-up visits                                                                   |                                                                                  |                                                                                                   |
|                  | High glucose readings were reviewed, insulin therapy was adjusted                   |                                                                                  |                                                                                                   |
|                  | Weight scaling every week at clinic                                                |                                                                                  |                                                                                                   |
| 13 June 2018     | Elective caesarean section at 38 weeks of GA                                       | OGTT                                                                              | - 0.9–1.5 units/kg/day insulin, 3 times/day                                                        |
|                  | Baby measurements                                                                  |                                                                                  | - Lifestyle: dietary and activity were encouraged                                                  |
|                  | Weight = 3.6 kg                                                                    |                                                                                  | - Glucose telemonitoring                                                                           |
|                  | HC = 35.5 cm                                                                       |                                                                                  | - 20IU of Insulin was given for 3 days peripartum                                                  |
|                  | Height = 50.5 cm                                                                  |                                                                                  | - Insulin therapy is discontinued when patient discharged home                                     |
| 26 July 2018     | 6 weeks post delivery                                                               | OGTT                                                                              | Lifestyle: intensive dietary plan and aerobic exercises were encouraged post weaning              |
|                  | T2DM was excluded                                                                  |                                                                                  |                                                                                                   |
|                  |                                                                                    | FBG = 4.6 mmol/L                                                                  |                                                                                                   |
|                  |                                                                                    | 2 h PPG = 7.1 mmol/L                                                              |                                                                                                   |
|                  |                                                                                    | HbA1c = 5.1 mmol/L                                                                |                                                                                                   |

BMI: body mass index; PCOS: polycystic ovary syndrome; GDM: gestational diabetes mellitus; GA: gestational age; US: ultrasound; FHR: foetal heart rate; BPM: beats per minute; EFW: estimated foetal weight; RBG: random blood glucose; OGTT: oral glucose tolerance test; FBG: fasting blood glucose; PPG: postprandial glucose; HC: head circumference; T2DM: type 2 diabetes mellitus; HbA1c: haemoglobin A1c.
infant (4.6 kg), and she reported that her 4-year-old daughter was overweight. Her family history indicated that her mother had GDM and, later, T2DM. This patient was previously diagnosed with hypothyroidism (taking levothyroxine) and polycystic ovary syndrome (PCOS).

**Clinical findings**

Multiple GDM risk factors were associated with this case, including previous macrosomia, a first-degree family history of GDM, obesity, hypothyroidism and PCOS. Therefore, a random blood sugar test was recommended before the patient left the antenatal clinic, and she was transferred to the GDM clinic for intensive follow-up. At 24 weeks gestational age (GA), she returned to the GDM clinic, and a 75 g oral glucose tolerance test (OGTT) was requested for her next screening (Table 1). Her blood glucose failed to return to normal levels within 2 h after the OGTT, and such failure is mostly indicative of insulin resistance. Thus, the GDM diagnosis was confirmed, consistent with the guidelines of the International Association of Diabetes and Pregnancy Study Groups (IADPSG). In addition, the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) test was used as a marker for insulin resistance, with the equation HOMA-IR = (glucose × insulin)/22.5 (Table 2).15

Because of this patient’s history of hypothyroidism, the thyroid hormone levels were also tested. She had high thyroid stimulating hormone (TSH) and normal free thyroid hormone levels (Table 2). To further analyse the inflammation in such conditions, CRP testing was recommended. Infection was excluded by this patient’s medical history, which was negative for flu-like symptoms, gastroenteritis, urinary tract infection (UTI) and poor dental hygiene. A negative UTI status was confirmed by urinary dipstick testing.

![CRP: C-reactive protein; TNFα: tumour necrosis factor alpha; IL-6: interleukin 6; IL-1β: interleukin 1 beta; HOMA-IR: Homeostatic Model Assessment of Insulin Resistance; TSH: thyroid stimulating hormone; T3: triiodothyronine; T4: thyroxine.](image)

![Figure 1. Structured dietary regimen.](image)

A low-carbohydrate (CHO) intake, especially early in the morning, and a high-protein diet are encouraged for pregnant diabetic women.

Also, a nasopharyngeal and stool analysis was investigated to rule out other sources of infection.

Surprisingly, the CRP level was extremely high, reaching almost 23.5 mg/dL, whereas normal levels are usually below 3 mg/dL. Consequently, the patient’s blood was drawn, upon her consent, for further analysis of inflammatory mediators, including TNFα, IL-6 and IL-1β, and hormonal levels, including oestradiol, testosterone and leptin (Table 2).

This patient received follow-up care at the GDM clinic and was placed on insulin therapy (Table 1). For consistency purposes, a structured dietary regimen was created, with three meals and two snacks (Figure 1), and a nutritionist carried out the patient’s dietary structure assessment.

In addition, this patient was educated about glucose telemonitoring, and she was asked to take daily measurements – one taken while fasting and one taken 2 h after each meal.
of her three meals, for a total of four. The healthcare provider was automatically alerted if the fasting sugar level overpassed 5.1 mmol/L (≥92 mg/dL) or the 2-h postprandial level overpassed 5.8 mmol/L (≥120 mg/dL), at least three readings per week. Accordingly, the patient was seen weekly in the clinic to adjust her insulin dosage, as shown in Table 1. In addition, her weight gain during pregnancy was an issue, and she was advised not to increase her weight more than 6 kg for the entire pregnancy, which was measured during her visit each week. She began mild to moderate exercise, such as walking – starting at 15 min and grading up to 30 min at least four times a week. At 30 weeks GA, after maintaining good control of her blood glucose and weight gain, the patient’s CRP and inflammatory cytokine tests were repeated. The results showed a subsidence of the inflammatory mediators, as depicted in Table 2.

This patient had an elective caesarean section, delivering a 3.6 kg infant, with no complications or metabolic disorders. Six weeks post delivery, the patient’s OGTT was repeated, and T2DM was excluded (Table 1). Also, her inflammatory mediators (except IL-6) had returned to their basal levels but were still near the upper limit. This patient was advised to manage her weight during lactation by avoiding a high-fat diet. Post weaning, she was advised to do aerobic exercises to avoid metabolic dysfunction and lower her risk for future T2DM.

**Discussion**

The young, obese woman in this case had multifactorial risks for GDM based on her high pre-pregnancy BMI, PCOS and hypothyroidism, which can lead to insulin resistance that may predispose the patient to prediabetes or gestational diabetes. The pathophysiology of GDM is not entirely clear; however, as pregnancy progresses, insulin resistance develops as a result of pregnancy hormones and metabolic inflammation. Failure to physiologically adjust to the decline in insulin sensitivity results in glucose intolerance and GDM.16

Pregnancy is considered a state of inflammation.17 Moreover, obesity is a chronic condition associated with a low grade of inflammation.18 Pregnancy with obesity will exacerbate the inflammatory status that reaches the in utero life.9 Inflammation is cross-linked with the energy haemostasis of the adipose tissue via different mediators, including pro- and anti-inflammatory cytokines and IκB kinase (a regulatory molecule for inflammation).19,20 Human adipose tissue is a vital origin for the systematic release of inflammatory cytokines and other mediators – such as IL-6 and IL-1β, plasminogen activator inhibitor–1, TNFα and CRP19 – for regulating inflammation and insulin resistance.21 IL-6 is a potent inflammatory biomarker, which increases in complicated pregnancies, such as in cases of pre-eclampsia22 and maternal obesity.9 IL-6 and insulin action are negatively correlated via adiposity.23 TNFα acts as a lipid haemostatic factor.24 Previously, it has been shown that TNFα is strongly related to insulin resistance in human adipose tissues from obese subjects, and following weight management programmes can cause insulin sensitivity to increase as a result of dropping TNFα levels.25 A group of researchers recently found that circulating TNFα is increased, with the impairment of T-regulatory and natural killer cells, in overweight women with GDM,26 which verifies that such a case has a state of obesity-related inflammation. CRP is a protein produced in response to inflammation to control it via activating the complementary immune system. In the studied case, an infection was ruled out as the
CRP source, but an overstated level of inflammatory cytokines confirmed the patient’s inflammatory status. Furthermore, CRP levels are reduced in obese pregnant females after lifestyle interventions involving additional physical activity and food intake enhancements.27 Altogether, abnormal elevation of these cytokines reflects their definitive roles in the pathophysiology of insulin resistance. However, their depression after lifestyle intervention leads to improved insulin sensitivity. This might be due to immunological mechanisms – for example, cell-mediated immunity28 – that require further study.

Energy haemostasis of the adipose tissue induces the remodelling and alteration of numerous factors that are implicated in the physiology of the human body. The adipose tissue has recently been recognised as an endocrine organ that produces hormones called adipokines.29 Adipokines have been implicated in energy balance, appetite control, haemostasis, insulin sensitivity, lipid metabolism and insulin excretion from the $\beta$-cells of the pancreas.29 Moreover, adipokines – for example, leptin, chemerin and adiponectin – which are mainly produced via maternal adipose tissue have been implicated in the pathogenesis of insulin resistance.30,31 Similar to the studied case, a recent study demonstrated that circulating leptin and chemerin are increased in obese women with GDM, while the ratio of adiponectin to leptin is decreased, when compared to non-obese women.30 The same researchers also found that leptin and chemerin messenger-RNA expressions were highly expressed in the visceral adipose tissue of obese mothers with or without GDM, when compared to non-obese mothers.30 A recent prospective cohort study demonstrated that healthy dietary patterns throughout pregnancy improve serum adipokine levels.32 Taken together, it is evident that abnormal adipokine levels secreted from adipose tissue are complicated with the establishment of insulin resistance and inflammation.21

Hypothyroidism and PCOS are both risk factors for obesity, and the high pre-pregnancy BMI in this case study highlights the role of inflammation. There is considerable evidence about the elevation of TSH, eventually mediated by leptin,33,34 and its positive relationship with BMI.35 It is believed that TSH is produced by the anterior pituitary gland; however, a variant has been shown to be secreted by the myeloid/monocyte lineage of bone marrow cells, giving it a potential role in inflammation and immune system functions.36 Moreover, high concentrations of TSH are associated with systemic inflammation in premature infants.37 In addition, women with subclinical hypothyroidism exhibit high CRP levels, which are correlated with a high BMI and fat mass.38 However, the high CRP levels in adolescent women are not correlated with PCOS, so they might, instead, be directly linked to the fat mass from these women with high BMI.39 Finally, hypothyroxinaemia is correlated with adverse metabolic outcomes in obese mothers, including insulin resistance.40

**Conclusion**

In pregnant, obese women presenting with inflammatory conditions with abnormal regulation of insulin sensitivity, the source of inflammation is mainly from adipose accumulation in the body mass (Figure 2). Therefore, further investigations should be conducted to explore the relationship between inflammation and obesity in pregnancy.

**Recommendations**

Maternal obesity alone should be considered a highly critical disorder that requires further medical investigation. Moreover, lifestyle interventions should begin during pregnancy and be included in any follow-up plans.

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**Consent for publication**

The purpose of the case report was explained to the patient, and she gave her written consent for publication of the case’s clinical and demographic features, without identifying information (i.e. her name, initials or hospital numbers).

**Declaration of conflicting interests**

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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