European Journal of Medical and Health Sciences
www.ejmed.org

Obesity in Pregnant Women and Its Impact on Maternal and Neonatal Morbidity

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ABSTRACT

Obesity in pregnancy is currently a health problem that is associated with increased maternal and neonatal morbidity. Along with the times and lifestyles that are more modern, the incidence of obesity is also increasing. Clinically, obesity is defined as the condition of having excess adipose tissue. Obesity is related to insulin resistance and chronic inflammation. This makes obesity a risk factor for various non-contagious diseases such as cardiovascular disease, hypertension, diabetes mellitus, and cancer. The health consequences of maternal obesity are based on low-grade, chronic (meta-inflammatory) inflammation that occurs as a result of changes in the immune system and proinflammatory cytokines in maternal obesity and pregnancy. Obesity can have a negative impact on maternal, neonatal and labor outcomes. Several maternal complications that can occur due to obesity (BMI 30-34.9) and morbid obesity (BMI ≥ 35) are hypertension during pregnancy (10.2-12.3%), preeclampsia (3-6.3%), gestational diabetes (6.3-9.5%). Risks that can occur to the fetus, such as the occurrence of macrosomia (15.4-17.2%), preterm birth (4-5.5%) and impaired fetal growth (1-0.8%). Maternal obesity is also associated with an increased risk of neural tube defects (NTD) in babies, as well as a higher risk of abortion (1.70-3.11%). Obesity also has an impact on the delivery process. Mothers with obesity have a higher rate of vaginal operative procedures (8.5-11.1%), labor induction and longer duration of labor. The increase in caesarean section deliveries is caused by the occurrence of complications due to maternal obesity, namely the occurrence of preeclampsia, fetal distress, macrosomia, and induction failure.

Keywords: Inflammation, maternal, obesity, preeclampsia, pregnancy, preterm.

Submitted : December 12, 2022

Published : June 2, 2023

ISSN: 2593-8339

DOI: 10.24018/ejmed.2023.5.3.1625

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I. Introduction

Obesity in pregnancy is currently a health problem that is associated with increased maternal and neonatal morbidity. The number of obesity is increasing, especially from 1975 to 2016. The prevalence of obesity in the adult population (aged over 18 years) in 2016 according to the World Health Organization (WHO) was 13% worldwide, with 39% of the adult population experiencing overweight. The WHO also estimates that there are 650 million people who are clinically obese. The 2018 Riskesdas data shows that the prevalence of obese women in Indonesia is 29.3% and the Bali province itself has a prevalence of 26.4% [1], [2].

Clinically, obesity is defined as the condition of having excess adipose tissue. Obesity is related to insulin resistance and chronic inflammation. This makes obesity a risk factor for various non-contagious diseases such as cardiovascular disease, hypertension, diabetes mellitus and cancer [3].

Normal pregnancy is associated with a highly regulated inflammatory response and a balance between anti-inflammatory and proinflammatory factors. Given the underlying inflammatory condition of the pregnancy process, obese patients will experience a drastic increase in pro-inflammatory factors which can lead to various health consequences [4], [5].

The health consequences of maternal obesity are based on low-grade, chronic inflammation (meta-inflammation) that occurs due to alterations in the immune system and proinflammatory cytokines in maternal obesity and pregnancy. Meta-inflammation is an inflammatory condition that is different from the acute inflammatory response, namely excessive nutrient consumption, low-grade response, changes in immune cells, adipocytes, and decreased metabolic rate. With inflammatory conditions being excessively increased in obese pregnant women, a proinflammatory environment also exists in the placenta [6], [7].

Obesity can have a negative impact on maternal, neonatal and labor outcomes. Several maternal complications that can occur due to obesity (BMI 30-34.9) and morbid obesity (BMI ≥ 35) are hypertension during pregnancy (10.2-12.3%), preeclampsia (3-6.3%), gestational diabetes (6.3-9.5%). Risks that can occur to the fetus, such as the occurrence of macrosomia (15.4-17.2%), preterm birth (4-5.5%) and

impaired fetal growth (1-0.8%). Maternal obesity is also associated with an increased risk of neural tube defects (NTD) in babies, as well as a higher risk of abortion (1.70-3.11%). Obesity also has an impact on the delivery process. Mothers with obesity have a higher rate of vaginal operative procedures (8.5-11.1%), labor induction and longer duration of labor. The increase in caesarean section deliveries is caused by the occurrence of complications due to maternal obesity, namely the occurrence of preeclampsia, fetal distress, macrosomia, and induction failure [8]-[16].

Based on the explanation above regarding the adverse effects that occur in obese pregnancies, the authors would like to discuss obesity in pregnant women and its impact on maternal and neonatal morbidity.

II. Discussion

Obesity is defined as a condition of excessive accumulation of fat in adipose tissue, which causes significant health impacts. According to the World Health Organization (WHO), obesity is defined as BMI > 30 kg/m^2. Maternal obesity is defined as a condition when a pregnant mother has a body mass index (BMI) > 30 kg/m^2 according to the Royal College of Obstetricians and Gynecologists (RCOG). Obesity was then subdivided into: class 1 25-29.9 km/m^2, class 2 35-39.9 kg/m^2, class 3 (morbid obesity) > 40 kg/m^2, super-morbid obesity > 50 kg/m^2 [17].

In recent decades, the incidence of maternal obesity has increased in women of reproductive age, especially in middle and developed countries. Obesity in women has a higher incidence rate (33.6%) compared to obesity in men (27.8%), especially in married women (33.8%). Meanwhile, Riskesdas data for 2018 shows that the prevalence of obese women in Indonesia is 29.3% and the province of Bali itself has a prevalence of 26.4%. Risk factors for maternal obesity include sociodemographic factors, obstetric history, antenatal physical activity, food intake during pregnancy, distance between pregnancies, body mass index before pregnancy, breastfeeding history, and weight gain during pregnancy [2], [18]-[20].

Pregnancy is a physiological state that puts pressure on the body that requires dynamic changes to allow for sufficient maternal weight gain, development of fetal adipose mass, and growth and development of the placenta. During pregnancy, two metabolic phases are important. First, in the anabolic phase, maternal adipose tissue expands, facilitated by the increased availability of lipids, which primes the maternal metabolism to meet the increased energy demands of the fetus in later stages and to anticipate lactation. The second phase requires mobilization of energy stored in maternal adipose tissue, facilitated by the development of the physiological insulin resistance observed during normal pregnancy [21].

Subcutaneous adipose tissue plays an important role in energy balance and is the major location for energy storage in the body in the form of fat or triglycerides. In addition to functioning as an energy store, adipose tissue also detects energy needs and produces factors such as adipokines and cytokines to regulate other metabolic networks. In obesity, excess nutrition leads to accumulation of fat in mature adipocytes leading to cell hypertrophy and ectopic distribution of fat stores to visceral locations in the body [22].

Adipose tissue secretes cytokines which are known as adipocytokines (adipokines). Some of these adipokines have metabolic functions including adiponectin, leptin, TNF-α, IL-6, resistin, visfatin, klipin, vascular endothelium growth factor (VEGF), lipoprotein lipase, and insulin-like growth factor (IGF). The main adipokine is adiponectin, which promotes increased insulin sensitivity, inhibits hepatic glucose release, and has a cardioprotective effect on circulating plasma lipids. Adiponectin deficit is associated with diabetes, hypertension, endothelial cell activation and cardiovascular disease [17].

Obesity can lead to an inflammatory reaction with different characteristics from acute inflammation. Inflammatory reactions that occur in obesity are chronic with a low degree known as meta-inflammation. Various effects of meta-inflammation lead to decreased protective factors (adiponectin), increased levels of pro-inflammatory cytokines (IL-6, TNF-α), and changes in metabolism in the body [23].

A. Obesity and Pregnancy

Normal pregnancy is associated with a highly regulated inflammatory response and there is a balance between pro-inflammatory and anti-inflammatory factors. This inflammatory response is essential for proper implantation, trophoblastic invasion, and proper placental function. Conversely, the post-implantation period is associated with immunosuppression to prevent immune rejection of the fetus [24].

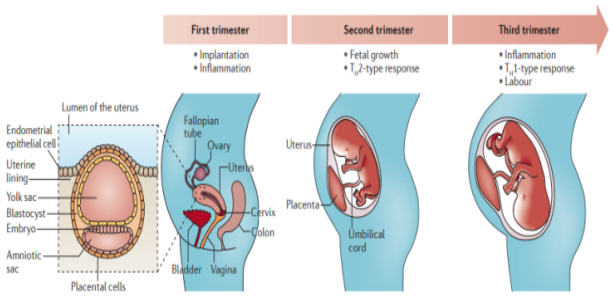

Fig. 1. The three immunological phases of pregnancy [25].

Increased inflammation in obesity is caused by inflammation in adipose tissue. Adipose tissue, apart from being composed of adipocytes, is a host of immune cells such as macrophages and T lymphocyte cells. The inflamed adipocyte tissue responds by releasing cytokine secretions. Pendeloski's study explains that there are different serum IL-6 levels depending on the stage of pregnancy. They found an association between these mediators and maternal obesity but only in the first trimester. Tinius' study also stated that pregnant and obese women have lower metabolic flexibility than normal-weight pregnant women, and underlying IL-6, IL-8 and CRP levels in obese pregnant women were significantly higher. In addition, the Bravo-Flores study stated that visceral adipose tissue in pregnant women has different sizes and different adipocyte numbers depending on BMI before pregnancy. This change is dependent on the presence of CD45 and CD14 markers [26]-[28].

Macrophages are the main inflammatory cells composed in adipose tissue. Number of macrophages and adipocytes in adipose tissue is directly proportional. In addition, in obesity, macrophages undergo changes in the M1-type macrophage

subtype which increases the secretion of proinflammatory cytokines (TNF-α, IL-6, and IL-1β). Macrophages in obese adipose tissue express CD11c (an integrin on the surface of macrophages) which also plays a role in the expression of MHC II which increases the inflammatory reaction [29].

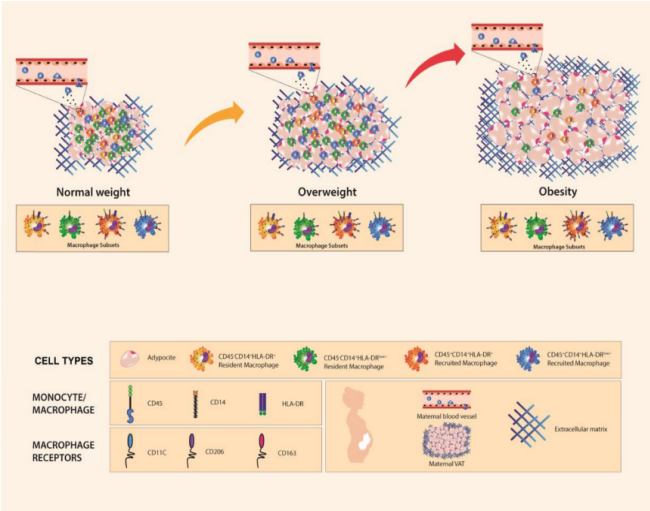

Fig. 2. Effect of BMI on adipocytes and macrophages [27].

B. *Effect of Maternal Obesity on Maternal Outcomes*

Maternal obesity provides several pregnancy complications on the mother's health. Several complications in the mother that can occur due to obesity in pregnancy are hypertension in pregnancy, preeclampsia, and gestational diabetes. Maternal obesity increases the risk of hypertension in pregnancy two to three times compared to non-obese pregnant women. This risk increases linearly with increasing body mass index (BMI). Each increase in BMI of 5 to 7 kg/m^2 increases the risk of preeclampsia by twofold [8], [30].

TNF-α causes a decrease in insulin sensitivity and an increase in plasma levels of free fatty acids. Insulin plays a role in regulating the occurrence of glucose uptake in peripheral tissues such as myocytes and adipocytes through the insulin receptor. The mechanism for the occurrence of insulin resistance in maternal obesity is the inhibitory effect of the IRS-1 protein on serine residues, thereby inhibiting peripheral uptake of glucose [31], [32].

The presence of insulin resistance in maternal obesity also causes a link between maternal obesity and an increased risk of diabetes, both pregestational diabetes and gestational diabetes mellitus (GDM). Compared with women with normal weight (BMI <25 kg/m^2), a recent meta-analysis of 20 studies showed that the OR of DMG occurrence in pregnant women was overweight (BMI 25-30 kg/m^2), obese (BMI > 30 kg/m^2), and pregnant women with severe obesity (BMI > 40 kg/m^2) respectively were 2.14 (95% CI, 1.82-2.53), 3.56 (95% CI, 3.05-4.21), and 8.56 (95% CI, 5.07-16.04). In addition to BMI before pregnancy, several other demographic factors also affect the incidence of GDM [33], [34].

Witteveen's study stated that low-grade chronic systemic inflammatory response accompanied by increased proinflammatory cytokines and CRP levels and endothelial dysfunction in obese pregnant women is associated with placental insufficiency which can cause preeclampsia. Maternal obesity causes meta-inflammation and increased proinflammatory cytokines (TNF-α and IL-6). Pro-inflammatory cytokines lead to maternal and placental endothelial dysfunction. Hyperleptinemia is also reported in maternal obesity. Leptin causes reduced proliferation of cytotrophoblasts in the uterus which triggers placental hypoxia [35]-[37].

C. *Effect of Maternal Obesity on Neonatal Outcomes*

Maternal obesity was associated with risks to the fetus, such as the occurrence of macrosomia ($P < 0.01$), increased care in perinatology ($P < 0.01$), and increased fetal death ($P = 0.03$), and impaired fetal growth. Obese mothers can have fetuses that experience excess nutrition (over-nutrition). Obese pregnant women have an impact on the occurrence of macrosomia in the fetus which appears to increase 2 to 3 times in obese pregnant women. Macrosomia as a result of maternal obesity occurs due to maternal insulin resistance. Maternal resistance provides high glucose and insulin levels in the maternal circulation. In addition, placental lipase metabolizes maternal triglycerides thereby providing free fatty acids for transfer to the growing fetus. Fetal macrosomia associated with maternal obesity is also thought to occur as a result of increased placental transfer of nutrients and is partly related to dysregulation of adiponectin levels. Circulating adiponectin levels in obese individuals who are pregnant are found to be lower [11], [12], [16], [38].

Obesity is known to be associated with an increased risk of preterm birth, particularly very preterm birth; together, these conditions cause an estimated 3 million neonatal deaths worldwide. The increased incidence of obesity-related neonatal death in preterm and spontaneous birth can be attributed to a compromised cardiometabolic profile resulting from dyslipidemia, increased leptin concentrations, insulin resistance, hyperglycemia, low-grade infections, endothelial dysfunction, and increased blood pressure, which all worsen with the severity of the obesity. In addition, maternal obesity is also associated with an increased risk of neonatal death [22], [39].

Maternal obesity is also associated with an increased risk of neural tube defects (NTDs) in babies. The study by Watkins and colleagues concluded that a 1 kg/m^2 increase in BMI was associated with a 7% increased risk of having a baby with an NTD. Several meta-analyses have also reported a relationship between maternal obesity and the risk of congenital heart defects in offspring. The increased risks associated with maternal obesity include a variety of defects in the heart, such as septal defects, aortic arch defects, persistent ductus arteriosus, left ventricular outflow tract obstruction, and right ventricular outflow tract defects. Additionally, the risk of pulmonary valve defects is increased in fetuses of mothers with a BMI of 30 to 35 kg/m^2 [13], [40, [41].

D. *Effect of Maternal Obesity on Delivery Outcomes*

Several complications of maternal obesity can cause complications in the delivery outcomes. Obese women have a higher rate of labor induction, longer duration of labour, increased cesarean section. Available evidence also indicates that the rate of cervical dilation decreases in nulliparous and obese women [15].

The increase in cesarean section deliveries is caused by complications due to maternal obesity, such as preeclampsia, fetal distress, macrosomia, and failed induction. In addition, the Zembala-Szczerba study stated that the majority of

pregnancies in obese women undergoing vaginal delivery will experience shoulder dystocia, an increased amount of bleeding during delivery, and the risk of infectious complications during the puerperium [15], [24], [42].

Obese women also experience problems with anesthesia, namely difficulty placing epidural or spinal analgesia and complications due to difficulty or failure of intubation. Regional analgesia for very obese women is associated with a longer neuraxial procedure and a greater number of failed attempts at insertion. The incidence of thrombosis and embolism is also higher in obese patients due to a longer operating time and a longer postoperative immobilization period [43].

Several retrospective studies have reported a higher rate of wound complications in patients with vertical incisions (35-46%) than transverse incisions (9–21%). Patients who weigh less than 181 kg, lifting the panniculus and pulling it upward allows access for a low transverse incision (e.g., Pfannenstiel) or a lower midline (vertical) incision. Whereas patients who weigh more than 181 kg, and especially those who are more than 272 kg, a supraumbilical transverse incision has several advantages: it has strong transverse traction, avoids burying the wound under a large panniculus, and provides excellent abdominal exposure. A vertical supraumbilical incision is another option, when the panniculus is displaced caudally. Pfannenstiel incision is preferred due to its cosmetic results. In closing vertical incisions, some surgeons recommend layered closure with the addition of through-and-through retention sutures. Others prefer to use the internal retention suture of the Smead-Jones variation. Postoperative complications include a longer recovery period, wound infections, wound dehiscence, atelectasis, pulmonary embolism or deep vein thrombosis, increased maternal morbidity and mortality rates [43]-[47].

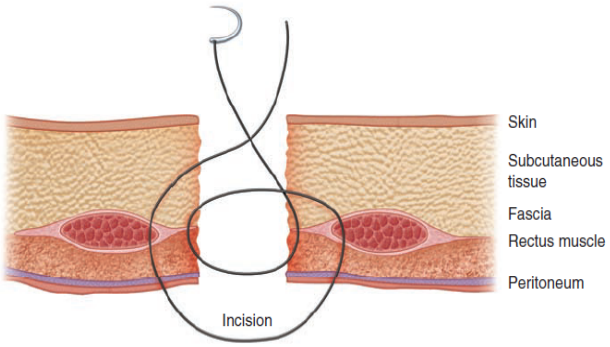

Fig. 3. Smead-Jones suture [43].

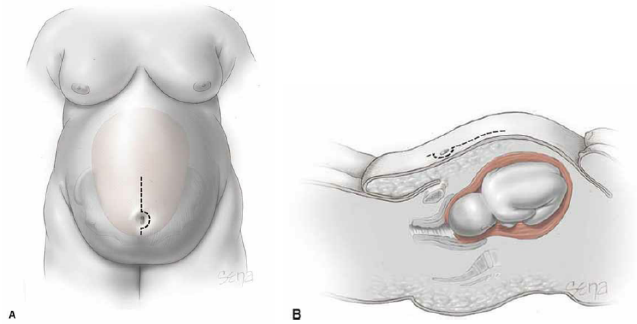

Fig. 4. Abdominal incision for obese mothers. A. Frontal view. Dotted lines indicate skin incisions suitable for entry into the abdomen relative to the panniculus. B. Sagittal view [17].

Some prevention can be done to reduce the incidence of surgical wound infections. The subcutaneous adipose layer should be closed when the layer thickness is ≥ 2 cm, 3-0 absorbable sutures are usually used. In a meta-analysis of randomized trials, covering the subcutaneous adipose layer reduced the risk of wound infection by one-third in patients with a subcutaneous tissue depth of ≥ 2 cm (RR 0.66), but not in patients with a thickness < 2 cm (RR 1.01). For prophylactic antibiotics in patients weighing more than 120 kg, Cefazolin 3 grams given intravenously within 60 minutes before incision. For patients weighing less than 120 kg, Cefazolin 2 grams given intravenously within 60 minutes before incision. If the patient is in labor and/or has ruptured membranes, azithromycin 500 mg intravenously is added. A randomized, double-blind, clinical trial in over 400 obese patients (BMI 30 kg/m^2) comparing oral Cephalexin 500 mg plus Metronidazole 500 mg versus placebo every 8 hours for 48 hours after cesarean section (both already given prophylaxis of 2 grams of Cefazolin preoperative intravenous injection) reported a reduction in surgical wound infection of 6.4% compared to 15.4% [48]-[51].

III. Conclusion

Maternal obesity that occurs can have a negative impact on maternal, neonatal, and delivery outcomes. Obesity causes chronic low-grade inflammation, which leads to an increase in pro-inflammatory cytokines like IL-6 and TNF-. Obesity can have a negative impact on maternal outcomes by increasing the risk of hypertension in pregnancy, preeclampsia, gestational diabetes, and infection. The impact on neonatal outcomes can be macrosomia, increased care in the perinatology room, increased fetal death, impaired fetal growth, and increased congenital abnormalities. While the impact of obesity on labor outcomes is an increase in the need for induction of labor, the need for a cesarean section, and postoperative wound infections.

Conflict of Interest

Authors declare that they do not have any conflict of interest.

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