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Insulin Resistance and Homa-Ir Levels in Third-Trimester Normal Obese Pregnant Women: Synergistic Effects of Pregnancy and Obesity

Hermanto Tri Joewono[1]*, Esmond W[2] and Sonny W[3]

[1*]*Dep Obstetrics & Gynecology Faculty of Medicine Universitas Airlangga Surabaya, East Java, Indonesia.*

[2]*Field manager, writing paper Indonesia.*

[3]*Diabetes experts, suggestion, thanks to dr Qurota A in additional statistic calculations Indonesia.*

***Corresponding Author**
Hermanto Tri Joewono, Dep Obstetrics & Gynecology Faculty of Medicine Universitas Airlangga Surabaya, East Java, Indonesia.

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Abstract

Background: *Normal pregnancy is characterized as a diabetogenic state marked by increased anabolism, accelerated starvation, and insulin resistance. Obesity is associated with low-grade inflammation and insulin resistance. The combination of these two conditions is considered synergistic, leading to increased insulin resistance. In recent years, a significant proportion of pregnant women have been classified as overweight or obese. HOMA-IR is one of the markers used to measure the level of insulin resistance. We aimed to assess the level of insulin resistance in third-trimester pregnant women, both obese and nonobese.*

Objective: *To measure and correlate HOMA-IR levels in normal obese and nonobese third-trimester pregnant women.*

Methods: *This cross-sectional study involved 42 third-trimester pregnant women who visited the antenatal clinic at Dr. Soetomo General Hospital after obtaining ethical clearance from the hospital's ethical commission. Exclusion criteria included women with diabetes, preeclampsia, autoimmune diseases, and other metabolic disorders. Body mass index (BMI) was calculated as body weight in kilograms divided by height in square meters. HOMA-IR was calculated using the formula: fasting insulin in uU/ml × fasting plasma glucose in mg/dL / 405. Insulin resistance was confirmed if HOMA-IR > 2.44. Data were analyzed using appropriate statistical methods. Results: among the 42 third-trimester pregnant women, 16 were obese, of which 13 had insulin resistance. In the nonobese group of 26 women, 5 had insulin resistance, a statistically significant difference ($p < 0.05$). HOMA-IR levels in the obese group were 2.99 ± 0.72, while in the nonobese group, they were 1.84 ± 0.57, also showing a statistically significant difference ($p < 0.05$). Pearson correlation analysis revealed a positive correlation between BMI and HOMA-IR with a coefficient value of 0.804 and a significance value of 0.000.*

Conclusion: *Normal Obese third-trimester pregnant women had higher levels of HOMA-IR and a higher incidence of insulin resistance. There was a positive correlation between Body Mass Index (BMI) and HOMA-IR in these women.*

Keywords: Normal Pregnancy, Third Trimester, Obesity, Insulin Resistance, Bmi and Homa-Ir.

1. Introduction

Carbohydrate metabolism in normal pregnancy exhibits distinctive characteristics, including mild fasting hypoglycemia (reflecting accelerated starvation), postprandial hyperglycemia (indicative of facilitated anabolism), and elevated levels of insulin, despite minimal changes in insulin half-life throughout pregnancy. This maternal metabolic adaptation signifies a pregnancy-induced state of peripheral insulin resistance. It is primarily driven by the placental secretion of diabetogenic hormones, including growth hormone, corticotropin-releasing hormone, placental lactogen (chorionic somatomammotropin), prolactin, and progesterone. Notably, insulin sensitivity in late normal pregnancy diminishes significantly, ranging from 30 to 70 percent lower than that of nonpregnant women [1-7].

Overweight and obese women face an increased risk of reduced insulin sensitivity compared to their lean or average-weight counterparts. When coupled with the physiological metabolic changes that occur during a normal pregnancy—most notably, the substantial 60% decrease in insulin sensitivity—overweight and obese pregnant women become particularly susceptible to adverse pregnancy outcomes, such as gestational diabetes,

preeclampsia, and fetal overgrowth [1-3, 7].

Several laboratory tests are available to assess insulin resistance, with the Homeostatic Model Assessment (HOMA) being one of the simplest and widely accepted methods. HOMA has been validated against the euglycemic hyperinsulinemic clamp technique, as demonstrated in the study by Bonora and colleagues [8-10].

In this study, we aim to compare and correlate body mass index (BMI) with insulin resistance in third-trimester normal pregnant women, distinguishing between those who are lean and those who are obese. Our hypothesis posits a synergistic effect of pregnancy and obesity on insulin resistance, as measured by HOMA-IR. By conducting this investigation, we aim to gain a deeper understanding of insulin resistance in pregnant women without metabolic disorders. This research seeks to shed light on the intricate relationship between pregnancy, obesity, and insulin resistance, which holds implications for both maternal health and the well-being of the developing fetus. Ultimately, our findings may contribute to improved clinical management and preventive measures in the context of pregnancy-related metabolic health.

2. Materials and Methods

This cross-sectional study was conducted between August and October 2020 at Dr. Soetomo General Hospital in Surabaya. The study included third-trimester pregnant women (28–40 weeks of gestational age) with singleton pregnancies. Participants were selected through consecutive sampling, and their willingness to participate was a prerequisite for inclusion [8-10]. Exclusion Criteria: Pregnant women with pregestational or gestational diabetes mellitus, hypertensive disorders, chronic kidney disease, autoimmune diseases, or other chronic conditions were excluded. Ethical clearance was obtained from the hospital's ethical commission. BMI was calculated by dividing body weight in kilograms by the square of height in meters (kg/m²) at admission. Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) was calculated using the formula: (fasting insulin in uU/ml) × (fasting plasma glucose in mg/dL) / 405. Insulin resistance was defined as a HOMA-IR result greater than 2.44. The collected data were categorized into lean and obese groups based on BMI and into insulin-resistant (IR) and non-insulin-resistant (non-IR) groups based on HOMA-IR values. Statistical analyses were performed accordingly.

3. Results

Factors	Obesity (+) 16	Obesity (-) 26	Others
Age (years)	31,25±5,88	29,46±6,22	
<20 y.o	0 (0%)	1 (3,8%)	
20-35 y.o	12 (75%)	21 (80,7%)	
>35 y.o	4 (25%)	4 (15,5%)	
Parity			
Nulliparity	6 (37,5%)	4 (15,4%)	
Multiparity	10 (62,5%)	22 (84,6%)	
Gestational age			
28-32 week	10 (62,5%)	9 (34,6%)	19 (45,2%)
33-36 week	5 (31,2%)	12 (46,1%)	17 (40,5%)
37-40 week	1 (6,3%)	5 (9,3%)	6 (14,3%)
BMI(kg/m^2)	34,90±2,9	25,27±2,9	
18,5-24,9		12 (46,1%)	
25-29,9		14 (53,9%)	
30-34,9	9 (56,25%)		
35-39,9	6 (37,5%)		
≥40	1 (6,25%)		
HOMA-IR	2,99±0,72	1,84±0,57	p <0.05
≤2,44(IR -)	3 (18,7%)	21 (80,7%)	p <0.001
>2,44(IR +)	13 (81,3%)	5 (19,3%)	

Table 1: Distribution of Obese and non-obese

From table 1 above can be summarized that Age Distribution: The majority of subjects in this study fell within the age range of 20 to 35 years, comprising 33 subjects, which accounts for 78.6% of the total; Parity: Among the participants, multiparous women constituted the largest proportion in both the obese and non-obese groups; The most common gestational age range was 28 to 36 weeks among the study participants; HOMA-IR Values: The obese group exhibited an average HOMA-IR value of 2.99, whereas the non-obese group had an average value of 1.84. This difference was statistically significant ($p<0.05$); Among obese mothers, there was a significantly higher frequency of HOMA-IR values exceeding the threshold of 2.44, indicative of insulin resistance; Specifically, 13 mothers in the obese group exhibited insulin resistance compared to 5 mothers in the non-obese group ($p<0.01$).

When classifying the distribution according to IR positivity and negativity, as shown in Table 2, we observed that in the

IR-positive group, there was a higher frequency of primiparity, elevated fasting insulin and glucose levels, an almost twofold increase in the average HOMA-IR score, a higher frequency of individuals with a BMI exceeding 30, and no cases of morbid obesity in the IR-positive group.

Factor	Insulin Resistance(+): 18	Insulin Resistance (-): 24	others	
Age	30,83±5,98	29,63±6,23		
<20 y.o	0 (0%)	1 (4,1%)		
20-35 y.o	14 (77,5%)	19 (79,1%)		
>35 y.o	4(22,5%)	4 (16,6%)		
Parity				
Primiparity	8 (44,5%)	4 (16,6%)		
Multiparity	10 (55,5%)	20 (83,4%)		
Gestational age				
28-32 week	10 (55,5%)	9 (37,5%)		
33-36 week	2 (11,1%)	11 (45,8%)		
37-40 week	6 (33,3%)	4 (16,6%)		
Fasting Insulin	13,29±1,9	8,62±1,6		
Fasting Glucose	93,16±12,03	79,29±11,06		
HOMA IR	3,05±0,58	1,69±0,43		
BMI	32,83±3,7	26,03±4,8		
18,5-24,9	0 (0%)	12 (50%)		
25-29,9	5 (27,7%)	9 (37,5%)		
30-34,9	7 (38,8%)	2 (8,3%)		
35-39,9	6 (33,3%)	0 (0%)		
≥40	0 (0%)	1 (4.1%)		
BMI≥30	13 (81,2%)	3 (12,5%)	16	p<0.05
BMI<30	5 (27,7%)	21 (87,5%)	26	

Table 2: Distribution according to Insulin Resistance and non-Insulin Resistance Groups

Additional findings from further analysis: a. the distribution of HOMA-IR values aligned with our initial hypothesis. b. A positive correlation was observed between BMI and HOMA-IR, as indicated by the Pearson correlation test. In other words, higher BMI was associated with higher HOMA-IR values. c. Among the obese women in the study, one in every 1.2 suffered from insulin resistance (IR), whereas among the lean women, the prevalence of IR was lower, with one in every 5.2 being affected. d. Notably, within the obese group, 3 out of 16 individuals did not exhibit insulin resistance, while in the non-obese group, 5 out of 26 individuals had insulin resistance.

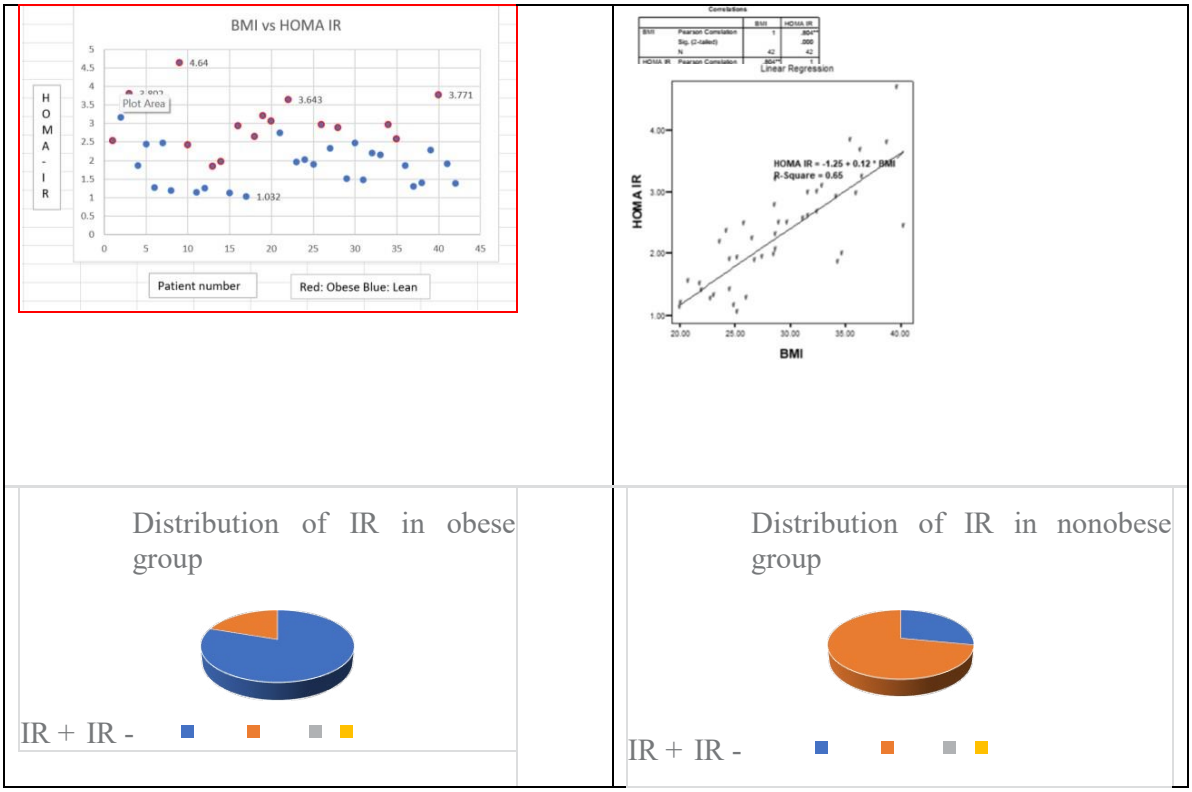

Figure 1: Distribution of HOMA and correlation of BMI and HOMA-IR

4. Discussion

Decreased insulin sensitivity or increased insulin resistance is characterized by a reduced biological response of target tissues, such as the liver, muscle, or adipose tissue, to a given concentration of insulin. As anticipated, our study revealed a significant increase in the number of third-trimester pregnant women with insulin resistance (IR) within the obese group compared to the non-obese group. Furthermore, obese pregnant women exhibited higher levels of IR, and there was a positive correlation between BMI and IR levels. Specifically, one out of every 1.2 obese women suffered from IR, in contrast to one out of every 5.2 lean women. In simpler terms, our results support the hypothesis of a synergistic effect between obesity and pregnancy, where obese pregnant women were 4.3 times more likely to suffer from IR compared to their lean counterparts [11].

Our findings align with those of reported similar conclusions. They compared 30 healthy nonpregnant women with 20 women in each trimester of pregnancy (1st, 2nd, and 3rd trimesters) and found that mean fasting serum insulin (FSI), log FSI, and log Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) were significantly higher in the 2nd and 3rd trimesters, while the Quantitative Insulin Sensitivity Check Index (QUICKI) showed significantly lower values. also noted that pregnancy entails a gradual increase in insulin resistance, serving as a physiologic adaptive mechanism to ensure an adequate supply of glucose to the rapidly growing fetus [11].

Emphasized that pregnancy induces a diabetogenic state, particularly in the third trimester, to adapt maternal physiology to pregnancy's increased nutrient demands, particularly for glucose. This adaptive insulin resistance during pregnancy elevates maternal blood glucose levels, ensuring an adequate glucose supply for the developing fetus. Human pregnancy undergoes a series of metabolic changes, including early gestational adipose tissue accretion, followed by insulin resistance and facilitated lipolysis in late pregnancy. While early pregnancy often sees increased insulin secretion with unchanged or decreased insulin sensitivity, late gestation exhibits a decline in maternal adipose tissue stores, elevated postprandial free fatty acid (FFA) levels, and a 40–60% decrease in insulin-mediated glucose disposal compared to the prepregnancy state [1].

Mechanisms and Factors Contributing to Insulin Resistance during Pregnancy

The exact mechanism of insulin resistance (IR) during pregnancy remains a subject of debate and can be categorized as pre-receptor (involving insulin antibodies), receptor (related to a reduced number of insulin receptors on cell surfaces), or post-receptor (involving defects in the intracellular insulin signaling pathway).

Several Hypotheses Have Been Proposed to Explain This Phenomenon

Multiple Factors: IR during pregnancy is likely multifactorial, involving hormonal, placental, genetic, and epigenetic factors. Other contributing factors include increased visceral adipose tissue, alterations in gut microbiota, and the presence of overweight and obesity. Overweight women with excessive gestational weight gain tend to accumulate fat mass during early pregnancy [1-6]. However, in the third trimester, fat storage decreases or ceases due to enhanced lipolytic activity and

reduced lipoprotein lipase activity. This transition to a catabolic state favors the use of lipids as an energy source by the mother, preserving glucose and amino acids for the fetus.

Placental Hormones and Growth Factors: Placenta-derived hormones and growth factors play a central role in altering pancreatic morphology and function. In pregnant mice, there is an increase in β-cell replication, leading to a 2-3-fold increase in mass, peaking in late gestation. This increase may result from the proliferation of existing β-cells, the differentiation of resident progenitor β-cells, or islet cell transdifferentiation [7-11].

Post-Receptor Defects: During pregnancy, decreased insulin sensitivity is often characterized as a post-receptor defect. This involves a reduced ability of insulin to facilitate GLUT4 mobilization from the cell interior to the cell surface. Contributing factors to this defect include human placental lactogen (HPL), cytokines, elevated lipid concentrations, and TNF-alpha. Insulin resistance during pregnancy is typically compensated for by an adaptive increase in pancreatic β-cell mass and enhanced glucose-stimulated insulin release. Maternal β-cell mass and function increase to meet the higher insulin demand. However, excessive insulin resistance or an inability to increase insulin production accordingly can disrupt the physiological modulation of glucose metabolism during pregnancy. If left uncompensated, it may lead to the development of maternal gestational diabetes (GDM). Research suggests that a failure of β-cells to undergo adaptive changes after the first trimester is associated with the development of gestational diabetes. These multifaceted mechanisms and contributing factors underscore the complexity of insulin resistance during pregnancy and its potential implications for maternal and fetal health. Understanding these processes is essential for effective management and prevention of gestational diabetes and related metabolic disorders [11-14].

Obesity and Insulin Resistance (Ir)

The exact mechanisms through which obesity contributes to insulin resistance are not yet fully understood. Qatanani et al. have emphasized that obesity-associated insulin resistance is a complex disorder involving disturbances in multiple endocrine, inflammatory, and neural pathways. The notion that a single factor is primarily responsible for the link between obesity and insulin resistance is overly simplistic [15-19].

Findings from various studies:

1. through mouse models and human studies, researchers have identified molecules derived from the placenta and islets of Langerhans that likely contribute to metabolic adaptations during pregnancy. These molecules undergo physiological alterations in obese, glucose-intolerant mothers.
2. Obesity stands out as the most common risk factor associated with reduced insulin sensitivity. 3. Ramsey and Schenken have highlighted the active endocrine role of adipose tissue, particularly when present in excess. Excessive adipose tissue can disrupt metabolic, vascular, and inflammatory pathways across multiple organ systems during pregnancy, potentially impacting obstetric outcomes, including conditions like preeclampsia. The correlation between the severity of obesity and the increased incidence of obesity-related pregnancy complications further emphasizes the role of obesity in adverse outcomes.

Obesity, Pregnancy and Insulin Resistance

When obesity coexists with pregnancy, it tends to amplify or synergize insulin resistance, as noted by some authors. This synergy underscores the complexity of the relationship between obesity, insulin resistance, and pregnancy-related metabolic adaptations [2, 3, 6]. Overall, understanding the multifaceted connections between obesity and insulin resistance during pregnancy is crucial for both clinical management and the development of effective preventive measures. Further research in this area is essential for improving maternal and fetal health outcomes. If a woman with obesity becomes pregnant, insulin resistance (IR) can be amplified or synergized, as highlighted by several studies. Table 3 presents evidence of the synergistic effect of obesity and pregnancy based on these studies [14-19].

Writer	Highlight
Catalano	In pregnancy the decreased insulin sensitivity is best characterized as a post receptor defect resulting in the decreased ability of insulin to bring about GLUT 4 mobilization from the interior of the cell to the cell surface
Barbour	…the critical molecular mechanisms involved in increasing maternal lipid flux in obese women throughout pregnancy that may underlie skeletal muscle insulin resistance and increased fetal fuels are just beginning to be investigated
Cunningham	Maternal obesity during pregnancy can create a pro-inflammatory environment that can disrupt the response of the β-cells to the endocrine signals of pregnancy and limit the adaptive changes in β-cell mass and function, resulting in an increased risk of gestational diabetes.
McCurdy	Obesity and pregnancy are associated with a combination of insulin resistance and inflammatory increase insulin resistance and the mechanisms are not completely understood, but involve an unknown post-receptor defect(s), perhaps caused by interaction between inflammation and serine kinases such as p70S6K in skeletal muscle. The majority of these changes are reversible postpartum except in obese GDM women who maintain impaired glucose intolerance.

Table 3: Obese and Pregnancy – a Synergistic Effect According to Some Studies

These findings collectively illustrate the complex interplay of insulin resistance, pregnancy, and obesity, emphasizing the importance of understanding these metabolic changes for maternal and fetal health [2, 3, 6]. Further research in this area may lead to improved strategies for managing insulin resistance in pregnant women, ultimately promoting better health outcomes for both mother and child [14-19].

Proposed Mechanism of IR in Obese Pregnant Women – Synergistic Effect

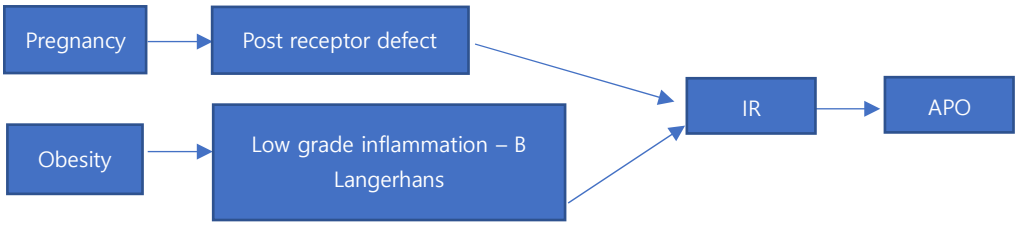

Figure 2: Proposed mechanism of IR in Obese pregnant Women

The Growing Challenge of Obesity in Pregnancy

Obesity has emerged as a significant global concern, with its prevalence nearly tripling worldwide since the 1970s. Wu and Ballantyne reported that in 2016, over 1.9 billion adults, accounting for 39% of the world's adult population, were overweight, and more than 650 million were classified as obese. Alarming statistics revealed that 340 million children and adolescents aged 5 to 19 years, along with 41 million children under age 5, were overweight or obese on a global scale. In the United States, the situation mirrored this trend, with over 93 million adults, or roughly 40% of the adult population, identified as obese in 2015 to 2016. Among children and adolescents aged 6 to 19 years, almost 20% were found to be obese during the same period. In Indonesia, the issue of obesity in pregnancy has not remained unnoticed. The study conducted by. revealed a prevalence of obesity in pregnant women at Dr. Soetomo Surabaya from 2013 to 2015, where 7.4% of births were attributed to obese mothers, with a notable 37.93% of these obese pregnant women experiencing gestational diabetes mellitus [20-22]. Virdayanti et al. reported concerning findings from the Riskesdas data, indicating a significant rise in the prevalence of obese Indonesian women. This prevalence increased from 13% in 2007 to a staggering 32% in 2013. Moreover, a substantial number of maternal obesity cases, accounting for 21.5%, were recorded from 1384 deliveries at Dr. Soetomo General Hospital in 2021 to 2023. From personal observations, it is evident that this issue extends to institutions such as the Universitas Airlangga Teaching Hospital, where the number of pregnant mothers with obesity has witnessed a substantial increase. This surge in cases, both in Surabaya, Indonesia, and worldwide, underscores the pressing need for concerted efforts to address obesity, particularly in pregnant women. It calls for proactive measures to safeguard the health of expectant mothers and their offspring.

Promoting a Proactive Approach to BMI Management during Inter Pregnancy Interval

This study's confirmation of the synergistic effect of obesity and pregnancy underscores the pressing need for a more assertive approach to managing body mass index (BMI) both before and after pregnancy. Numerous studies have unequivocally demonstrated the benefits of weight reduction before and after childbirth in enhancing perinatal outcomes. Additionally, controlling weight gain during pregnancy has evident advantages for both the mother and the unborn child [23-27]. Pregnancy presents a unique window of opportunity to improve the long-term health prospects of both the mother and the child. This hypothesis aligns with the work of Barker (FOAD) and Gluckman Hanson (DOHaD), who have emphasized the profound impact of early-life experiences on adult health. The choices we make during pregnancy can have far-reaching consequences, and as such, it is imperative that we take proactive measures to mitigate insulin resistance, prevent adverse pregnancy outcomes (APOs), and avert long-term complications for both generations [26, 27]. Proposed Conceptual Framework for Reducing Insulin Resistance and Promoting Maternal and Child Health.

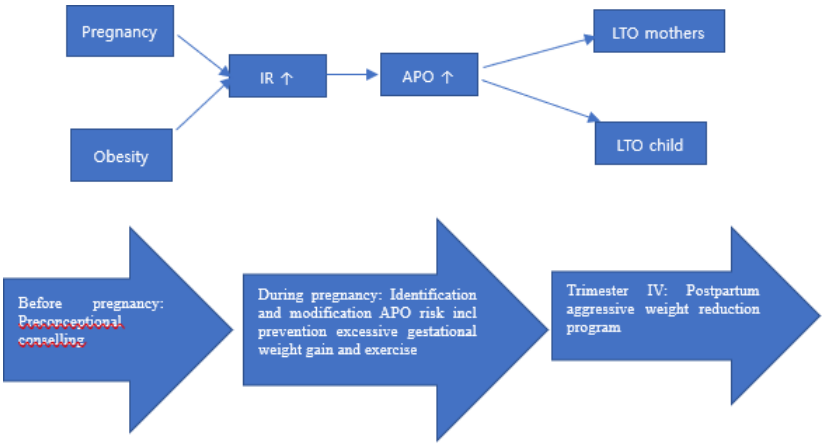

Figure 3. Proposed conceptual framework to manage IR

5. Conclusion

In pregnancies without underlying metabolic or medical disorders, we observed a higher level of Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) and a greater number of mothers with insulin resistance in the obese group. Furthermore, our study revealed a positive correlation between body mass index (BMI) and HOMA-IR among third-trimester pregnant women. Importantly, it's noteworthy that not all obese pregnant women exhibited insulin resistance, and conversely, not all lean pregnant women were exempt from insulin resistance. This suggests that obese pregnancies should be classified as high-risk pregnancies, warranting active measures to reduce insulin resistance before, during, and after pregnancy.

Strengths of the study

1. The inclusion of third-trimester BMI as a variable in our study, despite many patients beginning antenatal clinic visits in the later stages of pregnancy, allowed us to derive practical insights. 2. The study's results contribute new information regarding the synergistic effect of obesity and pregnancy, even though a minority of obese mothers did not exhibit insulin resistance, and some nonobese individuals did. 3. The findings revealed higher HOMA-IR levels in normal obese women, enhancing our understanding of insulin resistance physiology during pregnancy and obesity. This understanding opens up opportunities for preventing adverse pregnancy outcomes, starting from the preconception stage to the postpartum period.

Limitations of the study

1. The study's sample size was relatively small, limiting the generalizability of our conclusions to the broader population. 2. The use of third-trimester BMI, without accounting for weight gain during pregnancy, may not provide a completely accurate representation of fatness degree. Despite these limitations, our study sheds light on the complex relationship between obesity, pregnancy, and insulin resistance, advocating for a proactive approach to managing insulin resistance in pregnant women to improve maternal and fetal health outcomes. Further research with larger and more diverse populations may help corroborate and expand upon these findings.

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