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Inteleukin-6 secretion during pathophysiological events of pregnancy – preterm birth, preeclampsia, fetal growth restriction, gestational diabetes mellitus

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ABSTRACT

Cytokines play a role in nearly all reproductive and pregnancy processes. These proteins are expressed in various body fluids and tissues related to reproduction. Interleukin-6 (IL-6) stands out as one of the best-characterized members of the cytokine family. This protein has an immense and imperfectly understood impact on both normal and pathological aspects of human pregnancy. IL-6 exerts a wide range of effects on the immune system, and it plays crucial roles in regulating inflammation processes and homeostasis. Herein, we summarize current knowledge on IL-6 secretion during pathophysiological events of pregnancy: preterm birth, preeclampsia, fetal growth restriction and gestational diabetes mellitus. Cytokines, particularly interleukin-6, play crucial roles in regulating pregnancy physiology. Maintaining IL-6 homeostasis is essential for the health of both the mother and fetus. IL-6 supports pregnancy by influencing uterine receptivity, trophoblast function, and immune interactions at the feto–maternal interface. Disrupted IL-6 expression may contribute to various pregnancy complications. A deeper understanding of IL-6 regulation can help detect dysregulation and potentially optimizing pregnancy outcomes. Addressing knowledge gaps identified in this review is vital for improving current practices and enhancing pregnancy outcomes.

Introduction

Cytokines are a huge group of proteins involved in almost all processes in the human body. Most, if not all, cells in the human body both produce and respond to cytokines of one sort or another. Interleukin-6 (IL-6) is one of the most multifunctional proteins of the cytokine family. Inter-

leukin-6 is a glycoprotein which is produced by blood monocytes, activated T lymphocytes, tissue macrophages and fibroblasts [1,2]. Cytokine pathways in pregnancy have been intensively investigated, with most studies examining the cytokines in maternal serum, cervicovaginal or amniotic fluid in women who present with preterm labor or had preterm prelabor rupture of membranes (PPROM) [3]. A newly released study showed that IL-6 values are higher in the amniotic fluid than in maternal serum in healthy women and that they are independent of gestational age, maternal age, body mass index, ethnicity, smoking status, parity, method of conception and delivery [4,5]. These data show that interleukin-6 may be a valuable diagnostic tool in pregnancy complications because it is not related to maternal factors. It is well known that interleukin-6 plays an important role in several pregnancy complications such as preterm delivery, chorionamniotitis, preeclampsia and fetal growth restriction [6].

This article is an overview of current knowledge and provides guidance on the further capabilities of this protein in obstetrics.

Methodology

Herein, we summarize current knowledge on IL-6 secretion during pathophysiological events in pregnancy: preterm birth, preeclampsia, fetal growth restriction and gestational diabetes mellitus. This study was a narrative review of the English literature using PubMed database. We analyzed and drew conclusions from more than sixty scientific papers. The keywords that we used were "pregnancy", "interleukin-6", "inflammation", "preterm labor", "fetal growth restriction", "preeclampsia", "gestational diabetes mellitus". The inclusion criteria were as follows: articles in the English language that were clinical studies. The excluded articles comprised studies written in languages other than English, case reports, and those in which the study design did not include statistics. Additionally, we explore the potential role of IL-6 in studies aimed at developing new strategies for diagnosing and treating pregnancy-related disorders.

Preterm birth

Pregnancy occurs as a state of maternal-fetal bidirectional immunological tolerance and requires adaptational changes in both the systemic and local immune interface. Loss of this balance may manifest in the onset of preterm labor [1]. The onset of labor is a complex process that involves communication between the fetus and mother at the cellular and molecular levels. Preterm delivery is defined as labor between 22 and 37 weeks of gestation; it is a major cause of neonatal morbidity and mortality worldwide [7,8] and affects approximately 10% of all pregnant women [6]. Preterm birth may begin spontaneously or be induced for medical reasons (iatrogenic preterm labor) [9]. Spontaneous preterm birth can start with PPROM or occur with intact amniotic membranes (preterm labor, PTL) [10]. Another category of spontaneous preterm birth is idiopathic preterm birth, which is initiated with a breakdown of maternal-fetal tolerance and leads to maternal inflammatory response occurring with an elevation in cytokine concentration [11]. Although the etiology of preterm labor is multifactorial, it has been proven that spontaneous preterm labor most often begins with an ascending infection of the genital tract and microbial invasion of the amniotic cavity and leads to maternal inflammatory response, which involves an elevation in cytokine concentrations [6,11–14]. Even in a healthy pregnancy, the fetus

Table 1. The table shows the most common bacteria detected in amniotic fluid in women with healthy pregnancy, in women in preterm labor with intact membarnes and in women with preterm premature rupture of the membranes (15–19)

Women in non-complicated pregnancies	Women in preterm labor with intact membranes	Women with preterm premature rupture of the membranes
– *Ureaplasma* – *Mycoplasma* – *Acinetobacter*	– *Fusobacterium* – *Ureaplasma* – *Mycoplasma* – *Bacteroides* – *Group B streptococci*	– *Ureaplasma* – *Streptococcus* – *Staphylococcus* – *Mycoplasma* – *Fusobacterium*

does not develop in a sterile environment. It is well known that bacterial invasion of the uterus as a consequence of ascending infection from the lower urogenital tract of the mother may affect pregnancy and lead to miscarriage or preterm birth. Novel findings describe bacteria whose presence does not cause fetal infection; they simply colonize the amniotic cavity and placental tissues [15–19]. The most common bacterial culprits detected in amniotic fluid, depending on the membrane status, are presented in the table (see **Table 1**). About one-third of patients in preterm labor develop intra-amniotic inflammation (IAI) which develops into two different pathways: increased levels of pro-inflammatory markers in amniotic fluid without microbial invasion (sterile intra-amniotic inflammation) or inflammation with microbial invasion of the amniotic cavity (intra-amniotic infection) [6,11]. This causes the activation of inflammatory reactions and the secretion of a range of cytokines. The severity of intra-amniotic inflammation is closely related to increased IL-6 concentration in amniotic fluid and to adverse pregnancy outcomes such as preterm delivery, lower gestational age at delivery, lower infant birth weights and lower Apgar scores at delivery, respiratory distress syndrome, congenital sepsis and perinatal deaths [6]. Patients with severe IAI have histologic chorioamnionitis more frequently [6]. Data highlight the ability to use cervicovaginal fluid samples instead of invasively collecting amniotic fluid for the discovery of protein biomarkers, including IL-6, for IAI or spontaneous preterm delivery in women with preterm labor [20].

Maternal plasma IL-6 level itself may predict intra-amniotic infections in patients with preterm labor, but it has worse diagnostic value than IL-6 concentrations in amniotic fluid – IL-6 has its cut-off value to expect occurrence of delivery within 48 hours [21]. It is worth mentioning, that the concentration of Interleukin-6 changes in response to stress factors and it is associated with various diseases. IL-6 is produced in response to stress, triggering host defense mechanisms. However, dysregulated IL-6 production can lead to disease development. Examples include cardiac myxoma, rheumatoid arthritis, Castleman's disease, myeloma, autoimmune diseases, and cancers [22]. Therefore, it should be remembered that infectious factors are not the only contributors to the increase in the production of interleukin-6.

Investigating the exact pathomechanism of preterm delivery is essential for the early identification of patients at risk, which allows the implementation of proper therapy and preventing infant prematurity. In clinical practice, ultrasonographic measurement of cervical length, gynecological examination and risk stratification based on the patient's past medical history are commonly used. It has recently been demonstrated that in intrauterine infection, the secretion of pro-inflammatory cytokines in cervicovaginal fluid increases dramatically [10]. The prompt identification of such patients may be useful in clinical practice because it makes it possible to propose appropriate medical intervention (both pharmacologic and nonpharmacologic), which allows the implementation of proper therapy and prevention of infant prematurity. These interventions include the use of tocolytic drugs, antibiotics, corticosteroids, magnesium sulfate and cervical cerclage. However, these medications are not inert and, when administered unnecessarily, can be potentially harmful. Therefore, more diagnostic strategies, particularly those which are non-invasive, are needed in order to identify these patients with truly high risk for preterm birth. There are many reports of a positive correlation of certain biochemical markers with the occurrence of preterm labor, such as fetal fibronectin, tumor necrosis factor α, matrix metalloproteinase-8, interleukin-8, interlukin-10, interleukin- 17α, interleukin-27 and interleukin-6 [8,20,23–26]. In this study, we aimed to assess current knowledge of interleukin-6 as a biochemical marker of preterm delivery. To date, no single universal and clinically useful tool has been identified and put into practice to stratify risk for preterm delivery successfully.

Many studies have shown increased interleukin-6 concentration in cervicovaginal fluid and in amniotic fluid in pregnancies which ended in preterm delivery or were complicated with states prior to it, such as intrauterine inflammation and chorioamnionititis [6,20,26,27]. Data show that the presence of microbes together with increased concentrations of IL-6 in amniotic fluid are strongly associated with preterm delivery [11]. One of the most studied biochemical markers used to predict preterm birth is fetal fibronec-

tin (fFN). Normally, cervicovaginal fluid does not contain this protein from the 24th gestational week until near the delivery term. Hadži-Lega et al. evaluated the usefulness of measuring cervicovaginal pro-inflammatory cytokine IL-6 and fetal fibronectin (fFN) levels as predictors of preterm delivery in patients with symptoms of preterm labor. They hypothesized that adding cervicovaginal IL-6 determinations as an additional marker to fFN will improve the positive predictive value of fFN testing for preterm birth. In this study, vaginal swabs for fetal fibronectin (fFN) and CVF IL-6 were taken from 58 patients with symptoms suggestive of preterm labor. The results showed that combined fFN and CVF IL-6 tests resulted in an 86.7% risk of delivering prematurely if both tests were positive. This study proved that combination of both tests performed better than the individual fFN tests and decreased the false positive rate, which in turn reduced the chances for inappropriate patient treatment [28].

An interesting hypothesis is that the interleukin-6 level peak in amniotic fluid precedes the rupture of the fetal membranes [2,29]. Lee et al. investigated the presence and activation of interleukin-6 in amniotic fluid and reproductive tissues of pregnancies complicated by intrauterine inflammation and preterm birth. They studied 301 women during the second and third trimesters and preterm labor with intact membranes or with preterm premature rupture of membranes. Their research confirmed that interleukin-6 is a regular component of amniotic fluid in pregnancies with normal outcomes and absent infection and is expressed in fetal membrane and placental tissues. They hypothesized that interleukin-6 has a dual role, acting as both a pro-inflammatory and anti-inflammatory agent. The anti-inflammatory function involves reducing the expression of pro-inflammatory cytokines (i.e., TNF-α, interferon-γ) and inducing antagonists for certain receptors. These actions affect various biological processes in the placenta and amnion, potentially impacting fetal development. However, they found that patients with intra-amniotic inflammation but intact fetal membranes had higher IL-6 levels than women with PPROM and intra-amniotic infection [29]. Holmström et al. made similar observations in their study. They evaluated the correlations of cervical and amniotic fluid matrix metalloproteinase-8 (MMP-8) and IL-6 concentrations and investigated whether the levels of these amniotic inflammatory biomarkers could be assessed with noninvasive cervical swab samples. They observed a trend in which women with microbial invasion of the amniotic cavity (MIAC) and intact membranes showed higher median concentrations of amniotic fluid IL-6 than women with MIAC and PPROM. Unfortunately, a statistical difference was not reached, perhaps due to the small sample size. Nevertheless, this outcome may reflect a possible progression in the IAI sequence: the initial IL-6 peak in amniotic fluid followed by PPROM [2].Marcellin et al. investigated a group of women with spontaneous delivery before 37 weeks of gestation and compared them with women who gave birth at or after 39 weeks. They used only amniotic fluid without stigmata of infection. Their research revealed that amniotic fluid levels of interleukin-6 did not differ between these two groups [30].

Together, these data support the argument that IL-6 is instrumental in regulating the timing of delivery in normal gestation and in infection-induced preterm birth. Measurement of amniotic fluid IL-6 has potential relevance as a biomarker to stratify the risk of preterm birth in patients with preterm labor. There is a need to assess the potential role of AF (amniotic fluid) IL-6 in the management of these women. Further prospective studies are required to determine whether the cut-off value of IL-6 concentration in cervical secretions and in amniotic fluid is optimal in larger populations in preterm labor. In conclusion, the occurrence of increased IL-6 concentration in cervical secretions and in amniotic fluid is associated with higher risk of infection of the amniotic cavity, leading to preterm delivery.

Hypertension and preeclampsia:

Hypertension is the most common medical problem encountered during pregnancy, causing complications in 5–10% of pregnancies [31]. Hypertensive disorders complicating pregnancy (HDP) are classified into four categories: chronic hypertension, preeclampsia–eclampsia, preeclampsia superimposed on chronic hypertension and gestational hypertension. Preeclampsia (PrE) is a multifactorial heterogeneous disorder unique to pregnancy, with a frequency ranging

from 2 to 8% worldwide [32]. Preeclampsia can lead to a number of adverse maternal and perinatal effects, including the death of both the mother and the fetus/infant. Preeclampsia is defined as maternal hypertension associated with proteinuria after 20 weeks of gestation. However, preeclampsia can also manifest in the absence of proteinuria with some additional diagnostic criteria such as thrombocytopenia, impaired hepatic function, epigastric pain, renal insufficiency and pulmonary edema. It causes significant maternal and perinatal morbidity and mortality [32]. The exact etiology of preeclampsia has not been elucidated completely; however, the systematical immunoactivation and downregulation of the immunoregulatory system seem to be the core of preeclampsia development. Patients with preeclampsia are characterized by chronic inflammation and enhanced production of autoantibodies. It is postulated that during preeclampsia, placental ischemia occurs due to insufficient trophoblast invasion [33]. Data show that placentas from preeclamptic women exhibit vascular abnormalities and increased inflammatory markers compared to healthy patients, confirming a potential link between inflammation and this disease [34]. This is associated with an immune imbalance, characterized by an increase in pro-inflammatory CD4+ T cells and a decrease in T regulatory cells [35]. This state leads to chronic inflammation marked by oxidative stress and increased levels of pro-inflammatory cytokines and autoantibodies. Evidence suggests that the placenta plays a crucial role in preeclampsia, although the specific pathomechanisms altering placental function are not fully understood. Endothelial cells and circulating neutrophils are major components of the systemic response to inflammation in the vascular system. Preeclampsia is additionally marked by the activation and dysfunction of endothelial cells [35]. High levels of maternal plasma IL-6 may cause damage to vascular endothelial cells and lead to increased blood pressure. The inflammatory component of preeclampsia is characterized by elevated cytokine levels and activated leucocytes as well as stimulation of the angiotensin II type 1 receptor, leading to vasoconstriction. Levels of pro-inflammatory cytokines such as tumor necrosis factor (TNF)-alpha, interleukin-6 and interleukin-8 are elevated, while anti-inflammatory factor levels such as interleukin-10 are decreased in a state of preeclampsia [36,37].

The data suggest that levels of interleukin-6 are higher in patients with preeclampsia and increases with the progression of its severity [37–42]. M. Tosun et al. observed that there were higher levels of inflammatory cytokines (specifically IL-6, IL-8 and TNF-α) in both maternal and umbilical cord samples from women with preeclampsia when compared to healthy pregnant women. Additionally, the study revealed that elevated levels of maternal serum IL-8 and TNF-α were associated with the severity of preeclampsia [37]. Preeclampsia may occur before the 34th week of gestation – classified as early-onset preeclampsia – or after the 34th week – classified as late-onset PE. Maternal blood concentrations of IL-6 were found to be higher in late-onset PE than in healthy pregnancy or early-onset preeclampsia [43]. In contrast, M.I. Lumbreras-Marquez et al. compared the levels of interleukin-6 in maternal venous samples and umbilical venous samples of patients with preeclampsia versus normotensive controls and they did not find a significant difference [40].

Nzelu et al. examined the differences between the serum level of inflammatory mediators in women with chronic hypertension who developed superimposed preeclampsia compared to those who did not and normotensive controls. They measured IL-6, TNF-alfa, vascular cell adhesion molecule (VCAM) and endothelin levels at 11+0 to 13+6 weeks of gestation [44]. In their study, there were no significant differences in the levels of IL-6 between women in the first trimester with chronic hypertension and normotensive controls. In the group of women with chronic hypertension who later developed superimposed preeclampsia, compared with those who did not, there were no significant differences in the levels of IL-6. Among the women with chronic hypertension who developed superimposed preeclampsia, those who delivered before 37 weeks and those who delivered at term had also similar levels of IL-6. This research shows that further studies evaluating first-trimester serum cytokines are required to find an effective diagnostic tool for the early detection of women at high risk for developing preeclampsia.

Ayse Ekin Kara et al. investigated serum levels of interleukin-6, high-sensitivity C-Reactive Pro-

tein (hs-CRP) and sialic acid (SA) in pregnancies complicated with preeclampsia and compared them with healthy pregnancies. No significant differences between these groups were observed in this study [45].

Early atherosclerosis-like lesions have been observed in the spiral arteries of pregnancies complicated by preeclampsia [41]. The inflammatory cascade involving inflammatory mediators such as interleukin-6 is implicated in the development of endothelial dysfunction and atherosclerosis outside of pregnancy [37]. It is suggested that in preeclampsia, an increase in these inflammatory mediators contributes to the formation of similar lesions within the fetal–placental circulation, and this systemic effect results in the clinical symptoms of the disease [46]. However, it has not yet been definitively established whether this inflammatory process precedes placental impairment or if it occurs as a consequence of it—further research on this topic is required to clarify it. M.L. Martinez-Fierro et al. examined the profile of 34 proteins in plasma and urine in women at 12, 16 and 20 gestational weeks. They compared patients who developed preeclampsia to normotensive women. They found that urine levels of interleukin-6 in women at 12 weeks of gestation demonstrated a predictive value for the development of preeclampsia, indicating an increased risk of preeclampsia within the study population. The ROC analysis of the significant markers showed that the PPV for the IL-urine levels was 0.71 with the NPV 0.81. The specificity of the IL-urine levels was 0.937 with the sensitivity 0.583 [47]. Aggarwal et al. found that the expression of interleukin-6 in placental tissues and in maternal serum was increased in women who developed preeclampsia as compared to healthy pregnant patients [36]. Their data showed also that preeclamptic placental tissues and maternal serum interleukin-6 levels correlated positively with tumor necrosis factor-alfa levels and negatively with interleukin-4 and interleukin-10 levels. These findings confirmed that these cytokines exhibit mutual correlations in both the placenta and serum of mothers with preeclampsia throughout pregnancy.

In conclusion, the exact etiology of preeclampsia has not been elucidated completely. Inflammatory factors definitely play a crucial role in the processes leading to the development of preeclampsia. The progression of preeclampsia is closely related to mother and fetal health. It is necessary to predict the risk of developing preeclampsia in healthy women and rate the severity of preeclampsia to assess the benefits and risks of continuing the pregnancy. Further studies identifying the role of interleukin-6 in the development of hypertension during pregnancy are critical to improve decisions affecting patient care in women with preeclampsia. These studies are crucial for enhancing decision making in the healthcare of women dealing with preeclampsia. The outcomes of such investigations will significantly benefit our understanding of the physiological consequences linked to preeclampsia and advance the development of therapeutic approaches for this condition.

Fetal growth restriction:

Fetal growth restriction (FGR), also known as intrauterine growth restriction (IUGR), is a medical condition that occurs during pregnancy when a developing fetus does not reach its genetic and biologic growth potential and is a consequence of several causes. It is typically defined as a fetus that is smaller in size than expected for its gestational age, often indicated by a measurement below the third percentile on growth charts or below the tenth percentile with evidence of uteroplacental dysfunction. Fetal growth restriction is associated with signs of abnormal fetoplacental function and poorer perinatal outcome in contrast to constitutional small-for-gestational age characterized by a near-normal perinatal outcome. Fetal growth restriction increases the risk of fetal morbidity and mortality and it is linked to perinatal complications such as prematurity, cerebral palsy and intrauterine fetal death, and also to adult diseases such as obesity, hypertension and type 2 diabetes. Two commonly recognized phenotypes of suspected FGR are early and late, typically distinguished by the timing of diagnosis—early being diagnosed before 32 weeks of gestation, and late after 32 weeks of gestation [48]. Categorizing FGR into early- and late-onset helps distinguish the two phenotypes based on differences in severity, their association with preeclampsia, and the progression of fetal deterioration over time. Early-onset FGR represents 20–30% of

all FGR and it presents an association with early preeclampsia in up to 50% [49]. Early-onset FGR is closely linked to severe placental insufficiency and chronic fetal hypoxia. In early-onset FGR, placental insufficiency is linked to signs of abnormal early implantation [48]. However, it remains unclear whether late FGR results from a mild form of abnormal placental implantation during early pregnancy or if it involves placental damage occurring in the second half of pregnancy. Fetal growth restriction occurs when the fetus receives inadequate nutrients and oxygen due to maternal vascular malperfusion and/or inefficient extraction of substrates by the placenta. FGR is a multifactorial disorder and it is often the result of one or more maternal, placental and fetal causes that interfere with the normal mechanisms regulating fetal growth. The pathogenesis of fetal growth restriction involves many causal pathways, such as placental insufficiency and maternal conditions (chronic illnesses, anemia, undernutrition, smoking, drug use disorder, poor weight gain), as well as fetal issues, including chromosomal abnormalities, malformations and congenital infections. Placental failure limits the transfer of nutrients from the mother to the fetus. In these cases, FGR can be viewed as a model of chronic fetal hypoxia, which results in hypoxic–ischemic tissue injury with inflammatory features, including the production of pro-inflammatory cytokines and acute-phase proteins [50]. Consequently, FGR caused by placental insufficiency is marked by an amplified inflammatory response. However, the relationship between pro-inflammatory markers and FGR requires further investigation. It is essential to identify the biomarkers of FGR for better diagnosis and early identification of patients at risk for this condition. Several studies have shown that numerous cytokines and inflammatory markers are responsible for endothelial damage leading to placental dysfunction and, as a result, fetal growth restriction, but the results are conflicting and no consensus has yet been reached on which markers may be better predictors in this condition.

In the literature, there are few studies investigating the relationship between these pathologies and IL-6 levels, which is a marker of cellular immune response. Ayse Ekin Kara et al. investigated serum levels of interleukin-6, high-sensitivity C-Reactive Protein (hs-CRP) and sialic acid (SA) in pregnancies complicated with FGR and compared them with healthy pregnancies. No significant differences between these groups were observed in this study [45]. Yue et al. studied the correlation between several blood biomarkers measured at delivery and shortly after birth and development of fetal growth restriction. They found that FGR was associated with significantly higher levels of interleukin-6 measured in cord blood [51]. U. Lausten-Thomsen et al. investigated the levels of inflammatory markers in umbilical cord blood from neonates who were born small for gestational age (SGA) and comparing them to neonates who were born appropriate for gestational age (AGA). They found a significant elevation in interleukin-6 levels in the SGA group compared to the AGA group [50]. Alfian I. et al. investigated inflammasome gene expression profiles characterized by real-time PCR on human placental tissues collected from third-trimester fetal growth restriction and control pregnancies. They found that placental mRNA expression of interleukin-6 was doubled in FGR compared with healthy pregnancies [52]. M. Al-Azemi et al. measured cytokine production using maternal peripheral blood lymphocytes from women with fetal growth restriction and from healthy pregnant women. They found that IL-6 levels were increased in FGR pregnancies with placental insufficiency and that IL-6 acts as a potential marker of the inflammatory process [53].

Studies show that the increase in pro-inflammatory cytokines and activation of the components of the inflammasome cascade is consistently reported in pregnancies associated with placental inflammation leading to fetal growth restriction. Interleukins may be involved in a common pathway contributing to the development of growth restriction, though more research is needed to determine the extent to which IL-6 contributes to disease progression. Taken together, the upregulation of IL-6 may be associated with the pathogenesis of placental dysfunction in FGR pregnancies.

Gestational diabetes mellitus

Gestational diabetes mellitus (GDM) is a metabolic disorder characterized by glucose intolerance first identified during pregnancy, marked

by hyperglycemia and insulin resistance. It commonly occurs in the second trimester of pregnancy. Its global prevalence, currently estimated at 7% to 10%, is challenging to ascertain due to variations in screening and diagnostic criteria [54]. GDM increases the risk of adverse health outcomes for both the mother and child, manifesting during and after pregnancy. Substantial evidence indicates that pregnancies affected by GDM face an elevated likelihood of cesarean section, preeclampsia, macrosomia and neonatal hypoglycemia. Additionally, GDM has been associated with an increased long-term risk of metabolic complications, including type 2 diabetes mellitus (T2DM), obesity and cardiovascular diseases for both the mother and child [54]. We can divide gestational diabetes risk factors into modifiable and non-modifiable ones. Non-modifiable risk factors for predisposition to GDM include advanced maternal age; ethnicity; experience of previous adverse pregnancy outcomes, such as congenital abnormalities, miscarriages and stillborn births; macrosomic deliveries; displaying persistent glycosuria and proteinuria; and history of GDM in previous pregnancies [54]. Obesity is a major modifiable risk factor in gestational diabetes mellitus [55]. With the incidence of obesity worldwide reaching epidemic levels, the number of pregnant women diagnosed as having gestational diabetes mellitus is still growing. Throughout pregnancy, there is a notable alteration in metabolic state that significantly influences insulin action and sensitivity. This impact becomes more pronounced in the latter half of pregnancy, due to insulin resistance and the ensuing development of hyperglycemia. While the etiology of GDM is not entirely understood, it is well known that GDM is a temporary form of glucose intolerance caused by insulin resistance and pancreatic β-cell malfunction during pregnancy. The increase in insulin resistance is attributed to increased maternal adiposity and placental hormones [56,57]. Numerous studies have concentrated on exploring potential mediators of insulin resistance, including adipokines, such as leptin, tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), derived from adipose tissue and the placenta [58,59]. Zhang, Jie et al. investigated the levels of serum and placental tissue biomarkers from 140 women with GDM and 140 women with healthy pregnancies. They found that serum IL-6 levels were significantly associated with GDM. By detecting the metabolic indexes, they also found that the inflammatory biomarkers in placental tissues, including IL-6, had significantly higher levels between GDM and healthy pregnancies [60]. This observation indicated that the placentas of women with GDM were exposed to an inflammatory environment, and the heightened levels of inflammatory mediators could potentially trigger intraplacental inflammatory cascades through specific gene transcription or translation. Moreover, adipose tissue contributed to this by generating numerous adipokines, further fostering the production of inflammatory cytokines and thereby exacerbating the GDM condition. Francis EC, Li M, Hinkle SN et al. prospectively investigated the association of a panel of adipokines in early- and mid-term pregnancy with GDM risk. They measured a panel of 10 adipokines, including interleukin-6, in plasma among 107 GDM patients and 214 healthy controls. They found that at 10–14 weeks of gestation, IL-6 levels were generally positively related to subsequent fasting glucose metabolism markers. They observed that higher IL-6 concentrations throughout pregnancy were consistently higher among women who developed GDM compared with controls [61]. Zhao, Xiaolei et al. measured circulating inflammatory cytokines in 102 pregnant patients in 24 to 28 weeks of gestation. They calculated correlation coefficients between inflammatory cytokines and BMI, HbA1c, insulin or 1hGCT. Their findings indicate a substantial upregulation in the circulating levels of hs-CRP, IL-6, and IL-18 among pregnant women with GDM or glucose intolerance. In this study, elevated inflammatory cytokines were associated with an increased risk of GDM between 24 and 28 weeks of gestation. They also found that BMI was significantly and positively correlated with hs-CRP, IL-6 and IL-18; these cytokines are also positively correlated with the upregulation of HbA1c, insulin and 1hGCT [62]. These findings suggest that hs-CRP and IL-6 may serve as potential serum markers for the early screening of glucose intolerance in pregnancy. Siddiqui, Samreen et al. analyzed the association of inflammatory mediators like IL-6 and CRP with the development of GDM in Indian females. Their study included 53 patients with GDM and 50 pregnant women with Normal Glucose Tolerance (NGT) between 24 and 31 weeks

of gestation. They found that serum IL-6 levels were significantly higher in GDM patients as compared to control patients. Serum IL-6 levels in their study population were strongly correlated with pre-pregnancy BMI. IL-6 levels correlated also with fasting blood sugar (FBS) and postprandial sugar (PPBS) [63]. Other studies support the hypothesis that an elevated level of IL-6 may be implicated in the pathogenesis of GDM and their evaluation should be part of prenatal care routines [64–66].

Inflammation has now been recognized as one of the key mechanisms that can disrupt insulin signaling and cause gestational diabetes. Interleukin-6 could be implicated in the pathogenesis of GDM and used as a potential biomarker for assessing GDM risk. Additional longitudinal studies with large sample sizes are needed for a further evaluation of these findings.

Conclusions

Cytokines are ubiquitous proteins with multidirectional regulatory functions. Several lines of evidence suggest that homeostasis of IL-6 must be maintained to ensure the health of the mother and fetus. According to the reviewed literature, interleukin-6 clearly plays multiple functional roles in pregnancy physiology and disturbances. It appears to play roles in supporting pregnancy establishment and maintenance by facilitating uterine receptivity, trophoblast function during implantation and parturition. It also contributes to immune interactions at the feto-maternal interface and other ongoing processes. The evidence presented in our review suggests that disrupted expression of IL-6, either at the feto-maternal interface or systemically, may contribute to the development of various pregnancy complications. With a deeper understanding of the regulation of IL-6, as well as its effects on various cell types, we can better detect dysregulation of the levels of this protein and associated immunopathology during gestation. We may then modulate IL-6 signaling in the uterus to optimize outcomes of pregnancy. Consequently, targeting the IL-6 pathways could potentially modify certain pregnancy outcomes and prevent or alleviate associated issues. Addressing the knowledge gaps identified in this review could contribute to optimizing current practices and improving pregnancy outcomes.

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