MODERN VIEW ON CHRONIC RESPIRATORY DISEASES IN PREGNANT (review)

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Abstract

Disorders in the fetoplacental complex of pregnant women with chronic respiratory diseases (CRD) include a wide range of problems in modern obstetrics in medical, economic and social aspects. Respiratory diseases in the context of disorders of the fetoplacental complex (FPC) may be a comorbid process, a background to the abnormal pregnancy, or a premorbid condition that contributes to the development of placental dysfunction (PD) or even initiates it; morphophysiological changes characteristic of pregnancy also affect the state of the respiratory system, moderating the course of bronchoobstructive diseases. Respiratory diseases in women, the impact of its treatment and features of the course and medical support of pregnancy in these conditions affect the condition of both the woman and the fetus, and physical and neuropsychological development of the child in future.

Keywords: *angiogenesis factors, bronchial asthma, chronic bronchitis, placental dysfunction, respiratory diseases.*

INTRODUCTION

Extragenital diseases negatively affect the course of pregnancy and childbirth, constantly increasing the rates of maternal and perinatal morbidity. Chronic respiratory diseases of pregnant (bronchial asthma, chronic bronchitis) have recently spread among women of childbearing age and can complicate the course of pregnancy and childbirth.

Respiratory diseases in the context of fetoplacental complex disorders may be a comorbid process, underlie abnormal pregnancy or a premorbid condition that contributes to the development of fetoplacental insufficiency or even initiate it; morphophysiological changes typical for pregnancy also affect the state of the respiratory system, moderating the course of bronchoobstructive diseases [1, 2]. Respiratory disorders in women, the action of agents for its treatment and features of the course and medical support of pregnancy under these conditions are reflected in the condition of the woman and fetus, as well as physical and neuropsychological development of the child in the future [3, 4].

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The aim of the study was to analyze the modern literature on the problem of the influence of chronic respiratory disorders on the course of pregnancy and childbirth, the condition of the mother and newborn.

Physiological changes in the body of a pregnant woman may increase the risk and severity of extragenital diseases, including the respiratory system [5–7]. The processes that take place in a woman's body during pregnancy are aimed at forming reserves and compensating for the energy needs of the pregnant woman and the fetus [8].

Mehta et al. [7] indicate that the physiological and anatomical features of the mother's body during pregnancy affect the respiratory system, sometimes changing the presentation of respiratory disorders. Adaptive changes in the respiratory system in pregnant women, emphasized by researchers [9–11], begin after fertilization under hormonal stimulation, continue throughout pregnancy and can sometimes mask the pathological process or, conversely, be misinterpreted as a disease. Thus, Mehta et al. (2015) believe that vasodilation due to the action of progesterone results in the development of edema and increased vascularization of mucous membranes, which can cause rhinitis and nosebleeds. At the same time, normal partial pressure of CO_2 should be interpreted as the development of respiratory failure, as pregnancy is characterized by a decrease in $PaCO_2$ [7].

Bronchial asthma (BA) is one of the most common pulmonary abnormalities in the general population is [11, 13]. Asthma, by definition, is a chronic recurrent disease that involves airway hypersensitivity, leading to recurrent symptoms, including wheezing, coughing, and shortness of breath [14]. Tamasi et al. [15] add that asthma is an allergic disease caused by the activity of T-helpers type 2 (Th2), which leads to bronchial hyperreactivity, inflammation, respiratory obstruction and remodeling of respiratory tissues. Traditionally, asthma is diagnosed in existing airway obstruction during spirometry with its reversibility (increase in forced expiratory capacity for 1 second by at least 12%) [16].

Asthma symptoms are not specific, and are in particular predominated by cough and shortness of breath, which can result in a misdiagnosis of "shortness of breath of pregnant". In addition, the development of respiratory complications is determined in 8% of cases of mild asthma, 48% of moderate asthma and 65% of severe asthma [17].

In pregnant women, BA is the most common disease of the pulmonary system, the incidence of which varies from 1 to 4% [12, 18]. According to Meakin et al. (2017), in Australia, BA is detected in 12% of pregnant women annually, with an increase in the frequency in pregnant from socially disadvantaged categories [19].

In Europe, the incidence of asthma in pregnant women is estimated at 8% and becomes one of the most common comorbidities during gestation.

According to [20], BA is detected in 15% of pregnant women. According to a study by Alqalyoobi [21], the incidence of asthma among pregnant in the United States is up to 8.8%, with 1–4% developing especially severe pregnancy complications caused by asthma.

BA is known to affect the course of pregnancy with the development of complications, and pregnancy can significantly worsen the course of BA. Alqalyoobi et al. [21] add that BA symptoms peak in the late second and early third trimesters. In 3.7–8.4% of cases, BA complicates the course of pregnancy [22]. Pregnant women with asthma per 500 pregnancies develop severe complications such as preeclampsia, fetal growth retardation (FGR), premature birth, fetal distress and neonatal asphyxia, etc., which determine high rates of perinatal morbidity and mortality and can have long-term consequences, including neurological and other chronic disorders [23].

During pregnancy, depending on the severity, almost 30–50% of pregnant women are found to have complications of BA, which is a significant medical problem [24, 25]. A retrospective study conducted by Ali et al. [12] determined a relationship between asthma complications and pregnancy. Asthma has been shown to be associated with both pregnancy complications and adverse effects on the fetus [1].

Inflammation, hypoxia and stress reactions are the most common pathological processes in BA. Thus, in the case of uncontrolled recurrent course and exacerbations of BA during pregnancy, the level of systemic inflammation, oxidative stress and the development of fetal hypoxia increases. Exacerbations of asthma cause the development of alkalosis in the mother, which impairs uterine blood flow and, consequently, oxygenation of the fetus, leading to hypoxia and hypercapnia, in particularly severe cases, the possible development of acidotic conditions [7].

Pregnant with BA, according to the authors, develop pregnancy complications more commonly, including preeclampsia, gestational diabetes, placenta previa, premature rupture of membranes, postpartum hemorrhage, miscarriage, low birth weight, etc. The course of BA in almost a third of pregnant women deteriorates during pregnancy [26, 27]. Almost 10% of women are diagnosed with exacerbations of asthma during childbirth [28].

Studies on asthma as a risk factor for caesarean section, prematurity, low Apgar score, low gestational age, or intrauterine growth retardation remain relevant today [2, 29]. It should be added that conflicting data from different researchers may be related to differences in research structure, diagnostic aspects and multifactorial nature of the disease, including the impact of asthma on pregnancy and child health [29].

A study [30] showed that women with insufficient asthma control (69.8%) had significantly more ($p<0.001$) pregnancies compared to pregnant women with sufficient asthma control (56.3%). There was no significant difference between the frequency of smoking and alcohol consumption between the groups [30]. At the same time, the social status was higher than the average in 77.9% of women with adequate asthma control than with insufficient (62.5%), $p<0.001$. Significantly ($p=0.01$) higher average daily dosage of inhaled corticosteroids was registered in pregnant women with insufficient asthma control (481.1± ±88.0 ng) than with sufficient (399.3±314.0 ng) [31]. Decreased disease control may be due to a number of factors, including low adherence or

reduced response to treatment, increased severity of pathology, or incorrect choice of treatment strategy. According to the authors [30], insufficient control of asthma and higher frequency of hospitalizations due to asthma were observed in patients with higher doses of glucocorticosteroids (GCS). At the same time, higher doses of corticosteroids in such patients may mean a reduced response to their action or insufficient effect in patients with more severe conditions.

During the treatment of BA in pregnant women, some difficulties are caused by restrictions on the use of certain groups of drugs for the treatment of pulmonary diseases. Bacterial infections can significantly complicate pregnancy. Thus, the treatment of infectious diseases (chronic bronchitis, pneumonia, etc.) is carried out taking into account the systemic effects of antibiotics. The use of mechanical ventilation requires an accurate assessment of the state of oxygenation and hemodynamics of the mother with the support of saturation at the level of at least 95.0% [7].

The authors [22, 32] add that insufficient control of BA significantly increases the risk of fetal growth disorders. In addition, existing obesity has also been associated with an increased incidence of asthma complications during pregnancy and, as a consequence, with a risk of developing other respiratory diseases, including nocturnal apnea [33]. The latter can be explained by the fact that the decrease in immune reactivity during pregnancy may be impaired in obese patients, as the latter detects a greater number of young T cells.

A significant increase in the number of peripheral cells that produce interferon-γ (IF-γ) has been identified [15]. Subsequent assessment found a negative correlation with the number of these IF-γ-positive T cells and the weight of the newborn, which may indicate that intrauterine growth retardation may be associated with immune responses mediated by asthma.

At the same time, Tamasi et al. [15] state that approximately one third of pregnant women with BA are found to have an improvement in the course of asthma, one third are diagnosed with worsening symptoms and one third of pregnant women have a stable course of the condition. In the literature, such features are described as the "rule of thirds" [22]. It was also determined that pregnant women with female fetuses were more often diagnosed with exacerbation of the course of asthma and a higher frequency of fetal growth retardation.

Meakin et al. [19] also emphasize the difference in the adaptation of the placenta to asthma-associated changes depending on the sex of the fetus, with a higher risk of complications in male fetuses, especially in the presence of exacerbations of asthma. The authors note the presence of a gender-specific difference in fetal development and the chances of its survival in pregnant women with asthma. Thus, females are more likely to be underweight at birth (<2500 g) and underweight at gestational age (<10 centiles), while males are more likely to be born prematurely (<37 weeks gestation) and have a higher risk of stillbirth [19].

Pregnant with BA are more likely to require regular medication during pregnancy [11]. In the first trimester, exacerbation of BA increases the risk of congenital malformations. Garne et al. [11] emphasize the increased risk of congenital malformations due to exposure to BA drugs (β-2 agonists, corticosteroids), despite the inhalation route of administration, which reduces the systemic effects on the body. The authors [11] also add that it is currently unknown how the risk of fetal malformations is affected by etiological factors of asthma (systemic chronic inflammation and hypoxia), the use of drugs for its treatment (corticosteroids [31], short β2-agonists, etc.) or a combination of these factors.

In addition, restoring control of BA as early as possible during pregnancy reduces the risk of exacerbations. Thus, according to the authors [34], in an 8-year study 1208 pregnant women were diagnosed with 468 exacerbations of BA, of which 273 (58%) were moderate and 195 (42%) severe. Moreover, 33 (3%) pregnant had more than one complication. It was also determined that the risk of exacerbations of BA was influenced by the age of the mother (OR=1.05; 95.0% CI [1.02–1.08] p=0.003), the absence of a history of childbirth (OR=0.59; 95.0% CI [0.44–0.81] p<0.001), gestational weight gain during the first trimester (OR=1.22; 95.0% CI [1.17–1.28] p<0.01) and total weight gain throughout pregnancy (OR=1.11; 95.0% CI [1.06–1.17] p<0.001). The authors add that these indicators of increasing risk in relation to maternal age and gestational weight gain are, respectively, calculated for each year and kilogram. Moreover, the age of the mother significantly (p=0.02) affects the severity of complications: OR=1.05; 95.0% CI [1.00–1.10]. A similar trend also persists with respect to gestational weight gain during the 1st trimester (OR=1.20; 95.0% CI [1.13–1.27] p<0.001) and total gesta-

tional weight gain (OR=1.11; 95.0% CI [1.06–1.17] p<0.001) [34].

Chronic bronchitis is also one of the common diseases of the respiratory system, which complicates the course of pregnancy and can lead to fatal consequences. The incidence of complications of chronic bronchitis in pregnancy is 1:1000 in the United States and 6.7:1000 in Taiwan. An important aspect that complicates timely diagnosis is the potential teratogenic effects of radiography and therapeutic agents [35]. Physiological changes in immunity, including T-lymphocyte counts, decreased lung volume, and increased oxygen demand may be important risk factors for complications in pregnant [7, 35]. In addition, it is noted that pregnant women have an increased risk of complications of childbirth compared to pregnant without the mentioned pathology [7]. According to the authors [36], chronic bronchitis during pregnancy increases the risk of prematurity, young children of gestational age, and such patients in most cases have a lower average weight of children.

The findings of Chen et al. [36] indicate a higher incidence of pregnancy complications. Thus, according to the obtained data, patients with chronic bronchitis significantly (p<0.001) more often had children with lower birth weight than in the control group: 9.8% and 5.9%, respectively (OR=1.73 [95.0% CI 1.41–2.12], p<0.001). Premature births were almost twice as common: 12.3% and 7.1% in control (p<0.001) (OR=1.71 [95.0% CI 1.42–2.05], p<0.001). The number of children younger in gestational age than in the control group also prevailed: 20.7% and 16.2%, respectively, p<0.001 (OR=1.35 [95.0% CI 1.17–1.56], p<0.001). Besides, caesarean section was performed significantly (p<0.001) more often in pregnant women with respiratory diseases than in the control group: 55.5% and 40.6%, respectively (OR=1.77 [95.0% CI 1.58–1.98], p<0.001). The development of preeclampsia in such pregnant women was observed almost three times more often, the researchers diagnosed the development of preeclampsia: 2.7% compared to 0.8% in the control group (p<0.001) (OR=3.05 [95.0% CI 2.01–4.63], p<0.001) [35]. The authors emphasize that pregnant with respiratory diseases typically have a high risk of pre- and eclampsia.

It should also be added that Tang et al. [35] among diseases of the respiratory system pay special attention not only to chronic bronchitis, but also the development of pneumonia and its course in pregnant. According to the study, 2 patients out of 12 pregnant with pneumonia died of progressive respiratory failure. The main complications of the process were: septic shock (42%), respiratory distress syndrome in adults (42%), liver and kidney failure (33%, respectively), severe preeclampsia (25%) and stress ulcers (17%). At the same time, intrauterine fetal death was determined in 17% of pregnant women, premature birth in 86%, neonatal fetal death in 14%, cesarean section was employed in 71% of cases.

The pathophysiological mechanism of pregnancy complications in women with chronic respiratory disorders involves severe systemic hypoxia, which naturally leads to placental dysfunction. The primary aspect of the development of hypoxia is the physiological elevation of the diaphragm by almost 4 cm with a natural decrease in lung function and increased by 40% oxygen demand [36].

Placental hypoxia is considered to be a trigger for the expression of antiangiogenic and inflammatory factors that adversely affect the maternal endothelium, provoking the development of endothelial dysfunction, hypertension and target organ damage. In addition, the development of pulmonary edema in this case significantly complicates the course of pregnancy due to a significant deterioration in oxygenation [35].

At the same time, there are some contradictions about the exact mechanisms that shape the development of complications during pregnancy [36]. One of the proposed mechanisms is infection of the placenta from the pulmonary focus and subsequent infection of the fetus. The latter is realized through the umbilical vein or aspiration of the affected amniotic fluid [36].

Hung et al. [37] studied the effect of respiratory failure (RF) on pregnancy. The authors determined that the most common obstetric cause of acute respiratory failure is hemorrhage and hypertensive disorders. At the same time, non-obstetric causes include sepsis and pneumonia. According to the data obtained, respiratory failure was diagnosed in 33.3% of bacterial and 22.2% of viral pneumonia in pregnant women. At the same time, acute fetal distress, meconium aspiration and the incidence of sepsis significantly (p=0.001) prevailed in women with non-obstetric RF (33.3%). Unfortunately, there are very few reliable data on the course of pregnancy, the impact on the condition of the fetus and newborn in pregnant women with chronic bronchitis.

Placental dysfunction (PD) is a significant medical and social problem, which is found in 17–35%

of pregnant women. Almost 70% of miscarriage and 35% of preeclampsia are caused by the development of PD. Up to 60% of cases of PD are detected in pregnant women who have suffered a bacterial or viral infection and up to 45% in the presence of other extragenital conditions. A number of extragenital disorders have been identified that increase the risks of developing PD, including pulmonary, endocrine, cardiovascular, infectious, etc. [22].

Disorders in the fetoplacental complex can significantly complicate the course of pregnancy, significantly affecting perinatal morbidity and mortality [38]. Timely determination of fetoplacental insufficiency markers, especially in women with extragenital disorders, still remains an urgent medical problem.

Decreased uteroplacental circulation and placental ischemia may stimulate the release of TNF-α and IL-6 into the mother's systemic bloodstream, leading to generalized endothelial dysfunction and hypertension.

According to Tamasi et al. [15], one of the mechanisms of development of pregnancy disorders is physiological changes in immunity. Physiological immunosuppression during pregnancy is known to protect the fetus from the mother's immune response to antigens expressed in her body. In addition, the activity of type 2 T-helpers predominates during pregnancy. There is also an increase in regulatory T cells, which depends on the trimester. Tamasi et al. [15] add that a decrease in regulatory T cells may lead to fetal rejection due to maternal immunological activity. In addition, inhibition of natural killer cells (NK cells) by regulatory T cells may cause hypersensitivity to viral infections.

Shah et al. [40] add that during physiological pregnancy, the development of the decidual membrane involves remodeling the stromal vessels of the uterus into epithelium-like decidual tissues. It was determined that the degree of decidualization correlates with the concentration of decidual natural killers, which under the influence of IL-15 produce interferon-γ, which is a necessary substance for remodeling of spiral arteries.

During physiological pregnancy, type 2 T-helpers begin to produce IL-10. Its predominant amount is determined in the trophoblast, and anti-inflammatory action helps in the formation of "mother-fetus" tolerance, provides the development of vascular network of the placenta for sufficient blood supply to the fetus and reduces the activity of MMPs. On the other hand, NK cells induce the development of tolerance to the fetus by the main histocompatibility complex type 1 (GCG-1) [40]. Intrauterine NK cells have been shown to produce angiogenesis factors, including vasculoendothelial growth factor, placental growth factor, and tissue growth factor-β. Their activation of GCG-1 partner causes the production of VEGF, which further affects the middle and extravillous trophoblast, causing its adequate invasion.

The authors [41] consider that the activation of the immune response during pregnancy is accompanied by elevated plasma levels of plasminogen activation inhibitor type 1 (IAP-1), tumor necrosis factor-α (FPN-α) and C-reactive protein (PSA). Due to placental ischemia in preeclampsia, the production of tumor necrosis factor-α, interleukin IL-6 and IL-8 is determined. Under the action of TNF-α, vasodilation is reduced and endothelin-1 (ET-1) production is induced by endothelial cells. Further release of free oxygen forms and activation of lipid peroxidation are also caused by the action of TNF-α.

ET-1, which has a potent vasoconstrictor effect, also plays a significant role in the pathogenesis of obstetric complications of preeclampsia. In addition to hypoxia, ET-1 production is affected by a number of cytokines and the presence of autoantibodies to the angiotensin receptor type 1 (AT1-AA) [40]. Concentrations of ET-1 increase up to 2-3 times in plasma, 4-8 times in the umbilical cord and kidney tissue. However, its levels quickly return to normal after delivery [40, 41].

According to [41], the levels of TNF-α and IL-6 increase 2-3 times in patients with preeclampsia as compared with normal pregnancy in the 3rd trimester. It should be added that hypoxia may be a trigger for the production of endothelin-1, a vasoconstrictor synthesized by endothelial cells. It is noted that the concentration of ET-1 in the umbilical cord of pregnant with preeclampsia is approximately 4-8 times higher than in normal pregnancy. Moreover, the concentration of ET-1 is normalized within 48 hours after childbirth in pregnant with preeclampsia [40, 41].

Shah et al. [40] note that pregnancy is characterized by excessive oxidative stress, and reactive oxygen species (ROS) (O2, superoxide, hydrogen peroxide H2O2 and hydroxyl ion OH) produced by the placenta are compensated by the antioxidant system (AOS) [18]. Hypoxia leads to a decrease in the activity of AOS (superoxide dismutase, glutathione peroxidase, catalase, etc.). This causes an imbalance in the direction of oxidative activity, which stimulates lipid peroxida-

tion and loss of glutathione peroxidase activity of the placenta.

Shah et al. [40] add that in obstetric complications, including hypertensive disorders, overexpression of IL-6 alters the differentiation of monocytes into macrophages. The latter produce TNF-α, which alters the activity of placental vascular adhesion molecules, induces metalloproteinase (MMP) production, trophoblast apoptosis, and expression of the plasminogen-1 activator inhibitor. This mechanism inhibits trophoblast invasion, which in turn leads to placental ischemia [40].

Normal placental function is associated with VEGF and PIGF activity. Their sufficient number in mid-pregnancy is associated with normal placental weight [8]. The development of PD is associated with the existing imbalance of antiangiogenic and proangiogenic factors [38, 40, 42]. The former includes soluble receptor type 1 vasculoendothelial growth factor (sVEGFR-1), the latter is placental growth factor. They have been identified as direct markers of changes associated with PD. Tomimatsu et al. [165] emphasize that excessive activity of these antiangiogenic factors reduces the function of VEGF and PIGF, which stimulates the development of generalized endothelial dysfunction in pregnant with obstetric disorders [42].

However, the authors [38] add that although the influence of these factors is a direct trigger in the development of PD and can serve as valuable diagnostic markers, other clinical, laboratory and instrumental indicators remain the gold standard of diagnosis, including hypertension and proteinuria in the second half of pregnancy. Moreover, the latter are not always the cause of complications of PD and cannot serve as a reliable prognostic criterion. At the same time, the diagnosis of FGR is based on Doppler ultrasound (US) data, although these methods do not allow for accurate differential diagnosis with other conditions, such as constitutionally small fetuses.

Herraiz et al. [38] emphasize that all the outlined factors significantly complicate the preliminary diagnosis of PD, and this leads to its detection at a later stage, which worsens the prognosis and complicates the selection of optimal treatment. Other authors add that such diagnostic limitations actualize the study of the vascular factor system, in particular the sVEGFR-1/PIGF ratio, which may be important in the early diagnosis of PD.

Another element of the development of PD is that vascular endothelial disorders are triggered by placental insufficiency. As a result, it causes peripheral vasoconstriction, with a compensatory increase in the systemic blood pressure of the mother to enhance the flow of oxygenated blood to the intervillous space, which further causes the development of preeclampsia [38]. Shah et al. [40] added that an experiment on the pathogenesis of preeclampsia suggested that decreased uteroplacental perfusion pressure, subsequent hypoxia, and placental ischemia contribute to the release of biologically active substances that cause generalized vascular dysfunction and hypertension.

Shah et al. [40] emphasize that in placental ischemia, the action of ROS reduces the amount of L-arginine in platelets, while the activation of arginase stimulates the transition of L-arginine to urea, not nitric oxide. The latter may explain the decrease in nitric oxide concentrations in pregnant with obstetric abnormalities (preeclampsia) [40]. Interaction of nitric oxide with superoxide ion forms peroxynitrite, which reduces NO activity and inhibits trophoblast growth and stimulates endothelial dysfunction in pregnant. Also, according to the authors [40], the action of nitric oxide increases the concentrations of VEGF and PIGF by reducing the activity of sVEGFR-1 in ischemic trophoblast cells. The pathophysiological mechanism is severe systemic hypoxia, in particular pneumonia, which naturally leads to placental hypoxia. It is noted that placental hypoxia is a trigger for the expression of antiangiogenic and inflammatory factors that adversely affect the maternal endothelium, provoking the development of endothelial dysfunction, hypertension and target organ damage. Endothelial dysfunction is a complex process associated with disruption of homeostasis of constrictive and dilated mechanisms, factors of vasculogenesis and their inhibitors, etc. Thus, extragenital pathology, in particular chronic respiratory diseases, can cause impaired remodeling of the spiral arteries, leading to changes in perfusion in the feto-placental complex and placental dysfunction.

Thus, extragenital diseases negatively affect the course of pregnancy and childbirth, constantly increasing the rates of maternal and perinatal morbidity. Chronic respiratory diseases of pregnant (bronchial asthma, chronic bronchitis) have recently spread among women of childbearing age and can complicate the course of pregnancy and childbirth.

Manifestations of BA symptoms reach their apogee in the late second and early third trimesters, leading to complications that manifest themselves in the form of increased systemic in-

flammation, oxidative stress and the development of hypoxia, especially in the case of uncontrolled recurrence. Exacerbations of BA cause the development of alkalosis in the mother, which impairs uterine blood flow and, consequently, oxygenation of the fetus, which leads to hypoxia and hypercapnia, the possible development of acidotic conditions. This develops such severe obstetric complications as preeclampsia, fetal growth retardation, prematurity, increased frequency of surgical delivery. Patients with chronic bronchitis were significantly more likely to have children with a lower birth weight, younger gestational age and FGR [43, 44].

The course of a normal pregnancy causes significant remodeling of the vascular system to ensure metabolism and adequate metabolism in the "mother-placenta-fetus" system.

Conclusion

Timely identification of placental dysfunction markers in women with chronic respiratory disorders remains an urgent task and requires a comprehensive approach with further research to identify specific markers of pathological changes that can predict placental dysfunction.

DECLARATIONS:

Statement of Ethics

The authors have no ethical conflicts to disclosure.

Consent for publication

All authors give their consent to publication.

Disclosure Statement

The authors have no potential conflicts of interest to disclosure, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included.

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