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# Pregnancy Miscarriage and Intrauterine Growth Restriction Reduce Fetal Survival Rates: Placental Dysfunction

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## Abstract

Adequate rise in UBF maintains the well-being of the fetus and mother during pregnancy. Insufficient rise in UBF during pregnancy often leads to preeclampsia (PE) and intrauterine growth restriction, which are major causes of perinatal morbidity and mortality and also predisposes the mother and her offspring at a greater risk of developing metabolic diseases such as diabetes and cardiovascular diseases later in life.

Preeclampsia, a pregnancy-specific illness that affects 2 - 8% of pregnant women globally, is a primary cause of maternal and perinatal morbidity and mortality. Several animal studies revealed that giving LPS to pregnant rats caused preeclampsia-like symptoms. The LPS-treated rats demonstrated all of the signs and pathological lesions in the placenta that are associated with preeclampsia in humans. In pregnant rats, the LPS induced an instant rise in blood pressure that persisted until the end of pregnancy, as well as disrupting the intrauterine fetal growth. The procedure is identical to the preeclampsia-like illness described in pregnant rats exposed to LPS at late gestational ages. Balanced immune responses are essential for a healthy pregnancy. Preeclampsia is more likely to occur if the immune system is compromised during pregnancy. Pregnancy is a condition of oxidative stress caused by increased placental mitochondrial activity and production of reactive oxygen species (ROS), such as nitric oxide, carbon monoxide and peroxynitrite. These ROS have significant impacts on placental function, as well as trophoblast proliferation and differentiation and vascular reactivity.

***Keywords:*** *Pregnancy; Preeclampsia; Placental Function; Fetal Growth; LPS; Chitosan; Uterine Blood Flow*

## Abbreviations

UBF: Uterine Blood Flow; PE: Preeclampsia; LPS: Lipopolysaccharide; ROS: Reactive Oxygen Species; SA: Spiral Artery; UA: Uterine Artery; NO: Nitric Oxide; AII: Angiotensin II; IUFD: Intrauterine Fetal Death; IUGR: Intrauterine Growth Retardation

## Introduction

Placental dysfunction affects 2 - 8% of all human pregnancies worldwide, and it is still the dominant cause of maternal and fetal mortality and morbidity [1,2]. Although the cause is unknown, mounting evidence suggests a link between placental dysfunction and an abnormal maternal-fetal inflammatory response that results in insufficient spiral artery (SA) remodeling, a key change in the pathophysiology of preeclampsia. The maternal cardiovascular system undergoes dynamic changes after conception, including mild reductions in

systemic blood pressure and vascular resistance. They also include significant increases in blood volume and total cardiac output. These changes result in a marked increase in uterine blood flow (UtBF) to facilitate maternal-fetal exchanges of respiratory gasses ($O_2$ and $CO_2$), exhaust metabolic wastes, and preheat the uterus [3-6].

Restricted UBF is a common denominator in various gestational disorders, including preeclampsia with or without intrauterine low birthweight, affecting both the mother and the fetus during pregnancy and increasing susceptibility for both to a higher risk of metabolic diseases like diabetes and cardiovascular diseases later in life [7]. The peri-implantation time window of pregnancy is critical for the development, implantation, and signaling for the establishment of pregnancy for the conceptus. Embryonic mortality in mammals during the peri-implantation pregnancy period ranges from 20% to 40%, and it is still an unsolved problem in animal production. Most embryonic mortalities during pregnancy's peri-implantation period happen due to defects in conceptus development, pregnancy recognition signaling, or insufficient histotrophic nutrition of uterine secretions and/or transporting nutrients into the uterine lumen from maternal blood [1].

## Uterine blood flow and placental function

Preeclampsia (PE) is a pregnancy-specific disorder characterized by hypertension, proteinuria, and frequently edema after the 20$^{th}$ week of pregnancy. According to the Report of the Working Group on High Blood Pressure in Pregnancy of the National High Blood Pressure Education Program, PE affects roughly 10 million women annually and occurs in 3 to 8% of pregnancies worldwide [8,9]. PE increases perinatal mortality 5-fold, causing the deaths of 45,000 newborns annually in the United States alone and 76,000 pregnant women worldwide [9,10]. PE has a two-stage pathogenesis: 1) a disruption in placentation in the first trimester due to superficial trophoblast invasion and impaired UA remodeling, and 2) restricted UBF causes placenta ischemia/hypoxia, which further provokes placental generation of risk factors that circulate in the maternal bloodstream, leading to inflammation and vascular endothelial dysfunction [11]. Current PE treatments seek to normalize blood pressure rather than target the condition itself, but none of them are effective; hypertension is only temporarily decreased, allowing a cesarean delivery to be scheduled before term. The only current effective treatment for the condition is delivery, demonstrating the disease's severe medical demands. Correcting placental abnormalities after clinical PE is discovered, on the other hand, should be challenging because it may be too late after the 20$^{th}$ week of pregnancy. Improving UBF is an appealing alternative for controlling clinical PE (i.e. hypertension) in order to safely extend gestation and avoid premature birth. Unfortunately, numerous attempts to target all known pathways, including the most studied nitric oxide (NO) pathway, failed miserably [12,13]. These failures must clearly be attributed to a lack of understanding of uterine hemodynamics.

## Lipopolysaccharide and placental function

In response to a wide range of agonists, including angiotensin II (AII) and ATP, the uterine vasculature produces more vasodilators during the pregnancy period. As a result, the vascular resistance decreases, and the uterine blood flow increases to meet the growing fetus's needs [14-16]. Embryonic resorption, intrauterine fetal death (IUFD), intrauterine growth retardation (IUGR), and preterm labor have been all linked to lipopolysaccharide (LPS). LPS-induced developmental toxicity media involves reactive oxygen species (ROS) [17]. Through their ability to produce vasodilators like nitric oxide (NO) and prostacyclin, endothelial cells play a significant role in modulating vascular resistance and blood flow. That is especially noticeable during pregnancy, when several agonists, such as angiotensin II (AII) and ATP, have enhanced effects on UA endothelial vasodilator production and thus increase uterine blood flow [17].

## Chitosan and placental function

Chitosan oligosaccharide is a natural polysaccharide with good water solubility and other biological activities, including immune-stimulant [18], anti-inflammatory [19] and antioxidant properties. Numerous studies have shown that chitosan is an effective agent for reducing oxidative stress [20]. Furthermore, as the primary interface between the mother and the fetus, the placenta performs various

functions, including the production and secretion of hormones and cytokines, and the transfer of nutrients, oxygen, and waste products [21,22]. Nutrients pass from maternal to fetal blood via the syncytiotrophoblast and endothelium of the fetal capillaries; thus, placental nutrient transport is the primary determinant of fetal growth and development [23]. Jansson., *et al*. (2006) discovered that pregnant rats subjected to protein deficiency during pregnancy had a decrease in placental amino acid transport, which may contribute directly to the development of IUGR [24].

Chitosan is a marine-derived linear polysaccharide produced by treating shrimp and crustacean chitin shells with an alkaline substance. Chitosan has gained more attention considering its unique physical and chemical properties, and it has different uses in a variety of medical applications as an antibacterial agent, a drug carrier, and a wound-healing agent. Several chitosan-based biomaterials have been used as drug, cell, and gene delivery vehicles with impressive results [25,26].

## Conclusion

The preeclampsia may be related directly to the placental vascular dysfunction due to the downregulation of the angiogenic proteins. Chitosan oligosaccharide supplementation during late pregnancy increased antioxidant defense capability and facilitated placental amino acid transport, which may improve pregnant women's health and fetal survival. The administration of 0.5 g/kg LPS to pregnant rats on gestational day 5 in rats produced a novel animal model of preeclampsia. This model may help studying the different hypotheses for treatment of the placental dysfunction in women.

## Bibliography

1. Elmetwally MA., *et al*. "Effects of catecholamines on secretion of interferon tau and expression of genes for synthesis of polyamines and apoptosis by ovine trophectoderm". *Biology of Reproduction* 99.3 (2018): 611-628.

2. Elmetwally MA., *et al*. "Dietary supplementation with L-arginine between days 14 and 25 of gestation enhances NO and polyamine syntheses and the expression of angiogenic proteins in porcine placentae". *Amino Acids* 54.2 (2021): 193-204.

3. Sanghavi M and Rutherford JD. "Cardiovascular physiology of pregnancy". *Circulation* 130.12 (2014): 1003-1008.

4. Soma-Pillay P., *et al*. "Physiological changes in pregnancy". *Cardiovascular Journal of Africa* 27.2 (2016): 89-94.

5. Lang U., *et al*. "Uterine blood flow--a determinant of fetal growth". *European Journal of Obstetrics and Gynecology and Reproductive Biology* 110.1 (2003): S55-S61.

6. Gaccioli F and Lager S. "Placental nutrient transport and intrauterine growth restriction". *Frontiers in Physiology* 7 (2016): 40.

7. Zhang H-H., *et al*. "Pregnancy Augments VEGF-Stimulated *In Vitro* Angiogenesis and Vasodilator (NO and $H_2S$) Production in Human Uterine Artery Endothelial Cells". *Journal of Clinical Endocrinology and Metabolism* 102.7 (2017): 2382-2393.

8. "Report of the national high blood pressure education program working group on high blood pressure in pregnancy". *American Journal of Obstetrics and Gynecology* 183.1 (2000): S1-S22.

9. Cousens S., *et al*. "National, regional, and worldwide estimates of stillbirth rates in 2009 with trends since 1995: a systematic analysis". *Lancet* 377.9774 (2011): 1319-1330.

10. Kuklina EV., *et al*. "Hypertensive disorders and severe obstetric morbidity in the United States". *Obstetrics and Gynecology* 113.6 (2009): 1299-1306.

11. Chen D., *et al*. "Global protein expression profiling underlines reciprocal regulation of caveolin 1 and endothelial nitric oxide synthase expression in ovariectomized sheep uterine artery by estrogen/progesterone replacement therapy". *Biology of Reproduction* 74.5 (2006): 832-838.

12. Johal T., *et al*. "The nitric oxide pathway and possible therapeutic options in pre-eclampsia". *British Journal of Clinical Pharmacology* 78.2 (2014): 244-257.

13. Dunn L., *et al*. "Sildenafil in pregnancy: A systematic review of maternal tolerance and obstetric and perinatal outcomes". *Fetal Diagnosis and Therapy* 41.2 (2017): 81-88.

14. Elmetwally M., *et al*. "Noninvasive color Doppler sonography of uterine blood flow throughout pregnancy in sheep and goats". *Theriogenology* 85.6 (2016): 1070-9.e1.

15. Elmetwally MA and Meinecke-Tillmann S. "Simultaneous umbilical blood flow during normal pregnancy in sheep and goat foetuses using non-invasive colour Doppler ultrasound". *Animal Reproduction* 15.2 (2018): 148-155.

16. Elmetwally MA., *et al*. "Uterine blood flow, fetal heart rate, gestational length, and fetal birth weight variability in response to maternal temperament in the goat". *Animal Science Journal* 92.1 (2021): e13563.

17. Chen Y-H., *et al*. "Ascorbic acid protects against lipopolysaccharide-induced intra-uterine fetal death and intra-uterine growth retardation in mice". *Toxicology* 217.1 (2006): 39-45.

18. Xie C., *et al*. "Chitosan oligosaccharide affects antioxidant defense capacity and placental amino acids transport of sows". *BMC Veterinary Research* 12.1 (2016): 243.

19. Mendis E., *et al*. "An *in vitro* cellular analysis of the radical scavenging efficacy of chitooligosaccharides". *Life Sciences* 80.23 (2007): 2118-2127.

20. Anandan R., *et al*. "Dietary chitosan supplementation attenuates isoprenaline-induced oxidative stress in rat myocardium". *International Journal of Biological Macromolecules* 51.5 (2012): 783-787.

21. Rosario FJ., *et al*. "mTOR folate sensing links folate availability to trophoblast cell function". *Journal of Physiology* 595.13 (2017): 4189-4206.

22. Gupta MB and Jansson T. "Novel roles of mechanistic target of rapamycin signaling in regulating fetal growth". *Biology of Reproduction* 100.4 (2019): 872-884.

23. Cindrova-Davies T and Sferruzzi-Perri AN. "Human placental development and function". *Seminars in Cell and Developmental Biology* (2022).

24. Jansson N., *et al*. "Down-regulation of placental transport of amino acids precedes the development of intrauterine growth restriction in rats fed a low protein diet". *Journal of Physiology* 576.3 (2006): 935-946.

25. Okawa H., *et al*. "Effects of Intrauterine Infusion of a Chitosan Solution on Recovery and Subsequent Reproductive Performance of Early Postpartum Dairy Cows with Endometritis: A Pilot Field Trial". *Animals (Basel)* 11.1 (2021): 197.

26. Viudes-de-Castro MP., *et al*. "Antibacterial activity of some molecules added to rabbit semen extender as alternative to antibiotics". *Animals (Basel)* 11.4 (2021): 1178.

**Volume 11 Issue 6 June 2022**