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The Role of Oxidative Stress and Maternal Multiple Micronutrient Supplementation in Pregnancy Outcomes: Literature Review

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ABSTRACT

Oxidative stress occurs due to an imbalance between oxidants and antioxidants cause damage at the molecular level. An increase in metabolic activity and a decrease in anti-oxidative activity in pregnancy causes excessive oxidative stress leading to complications of pregnancy outcome. Some micronutrients act as antioxidants can stabilize oxidative stress. Maternal Multiple Micronutrient supplementation can improve pregnancy outcomes through its role in preventing oxidative stress. This study summarizes the role of oxidative stress and maternal Multiple Micronutrient supplementation in pregnancy outcomes. Using literature review from various internationally reputed literature sources indexed by Scopus, Pubmed, EBSCO, Elsevier, Proquest, Google scholar published in the last 10 years (2009- 2019). Literature is chosen based on the research objectives. Results: From several literature studies it was found that oxidative stress affects the occurrence of pregnancy complications, including: miscarriage, preterm birth, Intra Uterine Growth Restriction (IUGR) and stillbirth. Factors that influence oxidative stress include exposure to environmental pollution, unhealthy life style and deficiency of some antioxidant micronutrients. Some studies also showed that Multiple Micronutrient supplementation in pregnant women plays a role in reducing oxidative stress in pregnancy and improves pregnancy outcomes. Oxidative stress leading in poor pregnancy outcomes, and it is needed to prevent an increase in oxidative stress in pregnancy by giving Multiple Micronutrient supplementation to pregnant women.

Keywords: Oxidative stress, Multiple Micronutrient, Pregnancy Outcomes
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INTRODUCTION

Oxidative stress is a condition caused by an imbalance between oxidants and anti-oxidants. Oxidative stress is the result of excessive production of free radicals and/or failure of defense mechanisms from anti-oxidants that produce a product called reactive oxygen species (ROS) and reactive nitrogen species (RNS) that can interfere with the signaling and control mechanism and cause damage to the level molecular include lipid peroxidase, protein and nucleic acid(1). Oxidative stress is associated with poor pregnancy outcomes. An increase in metabolic activity and a decrease in anti-oxidative activity during pregnancy leads to excessive oxidative stress resulting in complications in pregnancy outcomes including pre-eclampsia, hypertension in pregnancy, gestational diabetes mellitus, misscariage, preterm birth, intra uterine growth restriction (IUGR), low birth weight (LBW) and stillbirth (2).

Some micronutrients such as ascorbic acid, α-tocopherol, carotenoids and selenium can stabilize oxidative stress thereby preventing damage to the biomolecular due to ROS and RNS. Antioxidant diet plays an important role to protect cells from damage due to increased ROS(3, 4). Protein, macro and micronutrient deficiencies can cause a decrease in antioxidant capacity because protein provides amino acids needed for the synthesis of antioxidant enzymes. In addition, many micronutrients in active form are needed to help the function of antioxidant enzymes or act as cofactors in the regulation of antioxidant enzymes (5). This research aims to analyze the effects of oxidative stress on pregnancy outcomes and the effect of various micronutrients incorporated in Multiple Micronutrients (MMN) on pregnancy outcomes through their role in reducing or preventing increased oxidative stress during pregnancy.

METHODOLOGY

This study summarizes the role of oxidative stress and maternal Multiple Micronutrient supplementation in pregnancy outcomes. Using literature review from various internationally reputed literature sources indexed by Scopus, Pubmed, EBSCO, Elsevier, Proquest,

Google scholar published in the last 10 years (2009-2019). Literature is chosen based on the research objectives.

RESULTS AND DISCUSSION

Oxidative Stress and Preterm Birth

Preterm birth is defined as birth that occurs before 37 weeks' gestation which can cause mortality and morbidity in infants. Most preterm births occur spontaneously. Spontaneous premature labor or PROM is triggered by premature placental aging caused by oxidative stress that induces damage to intrauterine tissue, especially fetal membranes from the placenta, vascular, endocrine and immune system dysfunction (6). Preterm birth is also related to ROS which causes a redox imbalance (balance between pros and antioxidants). At preterm birth there is an increase in oxidation metabolites in the placental and maternal serum (malondialdehyde) accompanied by a decrease in antioxidant levels (GSH, selenium, GSH-T) compared to term birth (7).

Oxidative Stress and Intra-Uterine Growth Restriction

Intra-Uterine Growth Restriction (IUGR) is defined when the weight of the fetus is below the 10th percentile of gestational age. The most common cause of IUGR is uteroplacental dysfunction due to reduced maternal uteroplacental blood flow (2, 8). Placental insufficiency starts in the early stages of gestation when the trophoblast reaches the spiral arteries in the placenta. This process requires high energy for cell growth, proliferation and metabolic activity which can produce ROS and oxidative stress. The incomplete development of spiral arteries causes ischemia / hypoxia worsens oxidative stress and contributes to damage to placental tissue (9).

MDA and xanthine oxidase levels (XO are enzymes that are a generation of ROS) are high in maternal plasma, cord plasma and placental tissue in patients with IUGR compared to healthy pregnant women which reinforces that oxidative stress plays an important role in IUGR (2).

Oxidative Stress and Misscariage

The incidence of miscarriage is around 25% of all pregnancies, the majority of which occur in the first trimester of pregnancy. Increased free radicals and ROS have implications for the pathophysiology of miscarriage. A sharp increase in oxygen pressure before 10-11 weeks' gestation causes syncytiotrophoblast damage by oxidative stress leads to a miscarriage includes spontaneous miscarriage and recurrent miscarriage (2, 10).

Oxidative stress in early pregnancy can interfere with the function of various cells including matrix remodeling, angiogenesis, proliferation of cytotrophoblasts, migration, fusion and endocrine function that can cause miscarriage. Increased ROS in blood granulocytes is also found in women who experience recurrent miscarriage compared to control. (2, 10).

Oxidative Stress and Stillbirth

Stillbirth is one of the complications in pregnancy defined as intrauterine fetal death after 20 weeks' gestation. Most stillbirth cases are still not clearly explained although there are several risk factors for stillbirth that have been identified including maternal age, obesity, smoking and IUGR. Oxidative stress causes changes in placental protein, lipids and DNA which can induce further aging, causing placental insufficiency which in turn leads to fetal death (2). Other studies have shown that there is a significant decrease in telomere length in the placenta in unexplained stillbirths which indicates that premature aging of the placenta and placental dysfunction result in fetal death. (11).

Multiple-Micronutrient, Oxidative Stress and Pregnancy Outcomes

To resolve the problem of various micronutrient deficiencies during pregnancy, the United Nations Children's Fund (UNICEF), United Nations University (UNU) and Word Health Organization (WHO) in 1999 approved the composition of the Multiple-micronutrient (MMN) tablet. The composition of this tablet is in accordance with the recommended daily allowance (RDA) for vitamin A, vitamin B1, vitamin B2, niacin, B6, B12, folic acid, vitamin C, vitamin D, vitamin E, copper, selenium and iodine with 30 mg of iron and 15 mg zinc for pregnant women (12).

Providing MMN supplementation during pregnancy can improve pregnancy outcomes. In a meta-analysis of 12,953 pregnant women in 17 studies examining MMN supplementation in pregnant women compared to controls who received only iron and folic acid there was a decrease in the incidence of stillbirth, low birth weight, premature birth, small gestational age and mortality (13). Analysis the Cochrane Review on the use of MMN during pregnancy evaluating the effect of MMN compared to iron-folic acid on pregnancy outcomes shows that MMN significantly decreases the number of newborns with low or small birth weight during pregnancy (12).

MMN supplementation can improve pregnancy outcomes through its role in preventing and reducing oxidative stress during pregnancy. The components contained in MMN can optimize the function of mitochondria in pregnant women, protection from the oxidative stress damage and can improve pregnancy outcomes (14). The following are the components contained in MMN that function as antioxidants which can prevent oxidative damage, among others:

Folic Acid and Vitamin B12

Folic acid is an essential vitamin that is involved in the process of redox and metabolism of one carbon that is needed in amino acid metabolism and synthesis of purines and pyrimidines. Changes in micronutrient levels in pregnant women (folic acid and vitamin B12) increase homocysteine and oxidative stress levels which cause epigenetic modifications that can contribute to the mechanism of preterm birth and poor pregnancy outcomes (3). The protective effect of folic acid on oxidative stress and homocysteine during pregnancy has been known from previous studies. The key in the one carbon cycle (folic acid, vitamin B12 and DHA) plays an important role in reducing oxidative stress and inflammation in preeclampsia (15).

Vitamins C and E

As an antioxidant, vitamin C can stabilize ROS, RNS and protects tissues from oxidative damage. Vitamin C can reduce oxidative cell death, prevent apoptosis and protect genes from ROS. While Vitamin E (α-tocopherol) is a fat-soluble vitamin that works on the lipid membrane and interacts synergistically with vitamin C. The main

function of vitamin E as an antioxidant that prevents lipid peroxidase effect (16, 17). In pregnant women there is an increase in oxidative stress which is marked by an increase in lipid peroxidase (Malondialdehyde / MDA) levels compared to non-pregnant women. Administration of vitamin C to pregnant women significantly reduces MDA levels during pregnancy (18).

Zink

Zinc works as a cofactor of important enzymes that contribute to the antioxidant defense system. Zinc can protect cells from oxidative damage by stabilizing the membrane, preventing the enzyme nicotinamide adenine dinucleotide phosphate oxidase (NADPH-Oxidase) which is a pro- oxidant enzyme, and induces the synthesis of metallothionein. Metallothionein plays a role in reducing hydroxyl (OH) and ROS free radicals (19, 20-22). Zinc is a structural component of the enzyme superoxide dismutase found in the cytoplasm. Superoxide dismutase has an active center with copper and zinc ions. This enzyme promotes the conversion of two superoxide radicals to hydrogen peroxide and oxygen molecules, reducing the toxicity of ROS by changing the reactive form to another less harmful form (19, 23-25).

Copper

Copper is a cofactor of a number of enzymes involved in metabolic reactions, oxygen transport, angiogenesis and antioxidant protective effects consisting of catalase, superoxide dismutase (SOD) and cytochrome oxidase. About 96% of copper in plasma is bound to ceruloplasmin which is a protein with an antioxidant effect. The presence of Copper deficiency in pregnant women can cause complications in both short-term pregnancies including fetal death in the uterus and abnormalities in body structure and long-term effects which include an increased risk of cardiovascular disease and reduced fertilization rates (16, 26, 28).

Selenium

Selenium is a trace element that plays an important role during pregnancy. Selenium plays a role in fetal development and placental function. Low levels of selenium are associated with poor pregnancy outcomes. Sialoprotein plays a role in preventing oxidative stress in the placenta, stabilizes the trophoblast endoplasmic reticulum and plays a role in thyroid hormone production and thyroid gland function (16). There are several studies that have reported low selenium levels during pregnancy associated with poor pregnancy outcomes. In a meta-analysis study that included 33 studies showed that there was a relationship between low selenium status and an increased risk of spontaneous abortion, preeclampsia, preterm labor and gestational diabetes (4).

Iodine

Iodine is an important nutrient for regulation of growth, development and metabolism through thyroid hormone biosynthesis including thyroxine (T4) and triiodotironin (T3). Iodine can work directly as antioxidants or indirectly regulate antioxidant enzymes such as SOD (17, 29). A study found that pregnant women with optimal iodine levels have optimal antioxidant status and low levels of oxidative stress compared to pregnant women with iodine deficiency. This indicates that iodine plays a significant role in the balance of antioxidant status and that iodine supplementation is beneficial in preventing oxidative stress during pregnancy (20, 30).

CONCLUSION

Various studies have shown that oxidative stress is associated with poor pregnancy outcomes including premature birth, IUGR, misscariage and stillbirth. Providing MMN supplementation containing various micronutrient components that act as antioxidants can reduce oxidative stress and improve pregnancy outcomes.

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CONFLICT OF INTEREST

All authors declare that there is no conflict of interest in this study.

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