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The Significance of Supplementing Small Doses of Folic Acid before Pregnancy and Early Pregnancy on Pregnant Women and Fetuses

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Abstract: Pregnancy, as a special physiological process, not only threatens the health of pregnant women, but also has a certain impact on the growth, development and birth conditions of newborns. In recent years, with the further development of medical technology, the survival rate of newborns has improved, but the number of premature babies and low birth weight newborns has also increased. How to effectively improve the nutrient intake of pregnant women and prevent adverse pregnancy outcomes is a key focus of obstetrics. Folic acid is an important nutrient for maintaining body health and plays an important role in the process of glucose and lipid metabolism. "Taking folic acid during pregnancy can reduce the incidence of adverse pregnancy outcomes such as preeclampsia" has been proven by many studies. However, recent research reports indicate that excessive folic acid supplementation will have harmful effects on mothers and offspring, increasing the risk of abnormal neuronal development and metabolic disorders in offspring. Therefore, this article briefly reviews the necessity of folic acid supplementation during pregnancy and the effects of folic acid on pregnant women and fetuses.

Keywords: Pre-pregnancy; Early pregnancy; Folic acid; Pregnancy outcome

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1. Introduction

In recent years, with the further development of medical technology, infant and child mortality rates have been on a downward trend, and related infectious diseases that threaten the health of infants and young children have also been effectively controlled. However, problems such as birth defects still exist, posing a certain threat to children's health [1]. Birth defects refer to metabolic, body structure and functional abnormalities that exist before birth in infants and young children, including physical malformations, inherited metabolic diseases, chromosomal abnormalities, etc. More and more research data confirms that birth defects are closely related to folic acid metabolism. Folic acid, as a type of B vitamin, is an important nutrient during embryonic development. Pregnant women have a sharply increased demand for folic acid. Folic acid deficiency may occur in individual metabolic disorders, which can easily cause pregnancy complications. For example, gestational hypertension, megaloblastic anemia, and placental abruption increase the risk of fetal neural tube defects to a certain extent [2]. In order to effectively prevent birth defects, folic acid supplementation is often used in

clinical practice at this stage. However, birth defects in newborns still exist. In order to further explore more scientific and reasonable folic acid supplementation methods, this article provides a review. The reports are summarized as follows.

2. Folic acid

Folic acid serves as an important coenzyme in the DNA synthesis stage and is widely found in food, such as animal livers, green vegetables, citrus fruits, etc. The human body does not have the ability to directly synthesize folic acid and cannot store it. To supplement folic acid, it needs to rely on exogenous food supplements. Under normal circumstances, adults maintaining a normal diet can effectively meet the body's tissue needs for folic acid. However, folic acid in natural foods is not stable enough and is easy to decompose. During food cooking and storage, 50–70% of folic acid is damaged. Moreover, folic acid in natural foods mostly exists in the form of polyglutamic acid, which is difficult to be directly absorbed and utilized by body tissues, and its bioavailability is less than 50% [3]. Folic acid is involved in DNA repair, synthesis, and amino acid methylation cycle processes. It is also an essential component in intracellular nucleic acid synthesis. However, to have a direct effect on the comfort of body tissues, it also needs the action of folic acid reductase to participate in the metabolic transformation and biosynthesis of important substances in the form of tetrahydrofolate activity.

Pregnant women have further increased demand for folic acid. The reasons for folic acid deficiency in pregnant women are complex, including increased demand for folic acid by body tissues, decreased gastric acid secretion and intestinal motility during pregnancy, and reduced folic acid absorption. In addition, pregnant women's own renal blood flow increases during pregnancy, which accelerates intrarenal folic acid clearance, reduces renal tubular reabsorption, and increases folic acid excretion in the urine. For this reason, effective folic acid supplementation is required. At this time, we can only rely on exogenous intake to ensure that the body's folic acid intake is sufficient. Worldwide, the recommended supplementation dose of folic acid during pregnancy is 400 μg per day to prevent maternal anemia, premature birth, and low birth weight [4].

3. Effects of maternal folic acid levels on fetal development

3.1. Birth defects

Birth defects, also known as fetal malformations, refer to structural and chromosomal abnormalities that occur during fetal development in the womb, including abnormalities in functional metabolism and morphological structure. The causes of birth defects are complex and involve many factors such as chromosomal abnormalities, genetic abnormalities, adverse maternal factors, and childbirth injuries [5]. Our country is an area with a high incidence of birth defects. According to relevant survey and research data, the number of new children with birth defects in our country is as high as 900,000 every year, accounting for up to 4–6% of the birth population. It has a serious impact on fetal survival and quality of life, and will also increase the burden on families and society. Supplementing folic acid is currently a key measure to prevent birth defects. Folic acid is a water-soluble B vitamin that participates in the synthesis of nucleic acids and amino acids and the transfer of methyl groups. It is also an indispensable nutrient during the intrauterine development stage of the embryo. In the body of pregnant women, folic acid is actively absorbed and expanded. It is present in tissues such as the liver, intestinal wall, and bone marrow. It is an essential substance in cell division, proliferation, and metabolic activities.

Neural tube malformations are serious congenital anomalies. Research has confirmed that the fetal nervous system shows symptoms after 18 days of pregnancy. The neural tube gradually closes between 22 and 28 days. This is the basic condition for promoting the normal development of the fetal spinal cord, brain, spine, and skull. If the body's folic acid intake is insufficient before and after conception, fetal DNA synthesis will be inhibited, and folic acid deficiency in early pregnancy is an important cause of neural tube malformations [6]. China's guidelines for perinatal folic acid

supplementation to prevent neural tube defects suggest that women of childbearing age without high-risk factors need to supplement with 0.4/0.8 mg of folic acid daily during the first 3 months of pregnancy until the first 3 months of pregnancy. For women with a history of childbearing with neural tube defects and patients with both husband and wife suffering from neural tube defects, 4 mg of folic acid should be supplemented daily at least 1 month before pregnancy until 3 months of pregnancy. Women who suffer from congenital hydrocephalus, congenital heart disease, cleft lip and palate, limb defects, or have a family history of the above-mentioned defects, or have a history of neural tube defects in first- or second-degree immediate relatives, should take a daily supplement of 0.8 to 1.0 mg of folic acid starting from the possible pregnancy or 3 months before pregnancy until the third month of pregnancy. Women with diabetes, obesity or epilepsy should take a daily supplement of 0.8 to 1.0 mg of folic acid from the time they are likely to become pregnant or at least 3 months before pregnancy until they are 3 months pregnant. Women who are taking drugs that increase the risk of fetal neural tube defects, such as oral carbamazepine, valproic acid, phenytoin, primidone, phenobarbital, metformin, sulfasalazine, trimethoprim, triamterene, cholestyramine and other drugs, should take a daily supplement of 0.8 to 1.0 mg of folic acid starting from the time of possible pregnancy or at least 3 months before pregnancy until 3 months of pregnancy. Women suffering from gastrointestinal malabsorption diseases should take a daily supplement of 0.8 to 1.0 mg of folic acid starting from the time when they may be pregnant or at least 3 months before pregnancy until they are 3 months pregnant. This is of great significance in reducing neural tube defects. Combined with previous retrospective analysis data, it is shown that appropriate supplementation of folic acid can reduce the incidence of birth defects by 28.1%. It can be seen that supplementing folic acid before pregnancy and early pregnancy can effectively reduce the risk of adverse maternal and fetal outcomes. It can promote the synthesis of nitric oxide in vascular endothelial cells, while improving the antioxidant capacity and conducive to giving full play to the protective effect of placental blood vessels. Taking folic acid regularly can keep the concentration of folic acid in the blood in a stable state, which can effectively reduce the risk of neural tube defects.

3.2. Fetal growth restriction

Body weight is an important indicator for fetal growth and development assessment, and is mainly used to assess whether the fetus is at risk of growth restriction. Most growth-restricted fetuses develop serious complications because their birth weight is lower than that of healthy newborns. Folic acid participates in the regulation of folic acid by consuming one carbon unit, and has ideal effects in promoting RNA metabolism and regulating DNA. Not only that, folic acid also participates in the amino acid metabolism process, which in turn has a direct impact on fetal growth and development. Maintaining a balanced intake of nutrients during pregnancy and following the doctor's advice to properly supplement folic acid can prevent the occurrence of low-weight premature babies and can also effectively reduce fetal growth restriction [7].

Although the preventive effect of reasonable folic acid supplementation on fetal growth restriction has been confirmed, it is difficult to draw definite conclusions on the impact of folic acid intake and folic acid levels on pregnancy outcomes. In addition, there is currently a lack of systematic evaluation of the relationship between maternal folic acid levels and fetal birth weight. Therefore, the prevention of intrauterine growth restriction by folic acid supplementation during pregnancy is still controversial. In order to clarify the correlation between the two, in-depth research is needed and more effective data are needed to support it.

3.3. Neonatal diseases

In addition to problems such as fetal growth restriction, birth defects, and low birth weight during pregnancy, problems such as neonatal ischemic hypoxic encephalopathy and neonatal asphyxia have also attracted widespread clinical attention to a certain extent.

3.3.1. Neonatal asphyxia

Clinically, neonatal asphyxia is called perinatal asphyxia. The main cause of the disease is pulmonary gas and placental

exchange disorders. Low folic acid levels in newborns may also cause neonatal asphyxia. Folic acid deficiency and lack of folic acid activity cause abnormal elevation of homocysteine levels. Especially after hyperhomocysteinemia, endothelial cells are damaged, causing neonatal pulmonary blood vessels to contract and tissue hypoxia.

3.3.2. Neonatal brain injury

This disease also mostly occurs in newborns. After birth, due to abnormal nervous system function, the clinical manifestations are epilepsy and decreased reflexes and muscle tone levels. Studies have shown that the occurrence of brain damage is affected by the increase in homocysteine levels in the body. Hyperhomocysteinemia, as an independent risk factor for arteriosclerosis, may induce venous thrombosis. Low serum folic acid levels increase the incidence of neonatal hypoxic-ischemic encephalopathy.

4. The effect of folic acid on the pregnancy process

4.1. Gestational diabetes

At this stage, serum folate and red blood cell folate levels are commonly used to reflect maternal folate levels during clinical research. Serum folate levels are used to reflect an individual's recent folic acid intake, while red blood cell folate concentrations are often used to reflect the folic acid intake in the past three months. They are key evaluation indicators of long-term nutritional status. Due to the rapid growth of the placenta, fetus, and maternal tissues during pregnancy, pregnant women's demand for folic acid increases by 5–10 times compared to non-pregnant women. Since 2009, the National Health and Family Planning Commission of my country has implemented a folic acid supplementation project, requiring women of childbearing age to take a daily supplement of 0.4 mg of folic acid in the first three months of pregnancy and in the third trimester of pregnancy. This is of great significance in reducing the risk of gestational diabetes. There are controlled research data showing that folic acid supplementation before pregnancy and early pregnancy is a protective factor for gestational diabetes. However, some studies have shown that folic acid supplementation of more than 0.8 mg before pregnancy and early pregnancy may increase the risk of gestational diabetes. This is because excessive folic acid supplementation may aggravate the depletion of vitamin B12, have a negative impact on homocysteine concentration and fat production, and increase the risk of gestational diabetes and insulin resistance to a certain extent. Therefore, it is forbidden to blindly supplement folic acid, and the dosage must be reasonably controlled [8]. So far, the effect of folic acid supplements on gestational diabetes is still unclear. This may be related to the dose, time and metabolic level of folic acid supplements. In-depth research is needed to determine the relationship between the two.

4.2. Preeclampsia

Preeclampsia is an important cause that affects the health of mothers and infants. This complication occurs in about 5% of pregnant women. According to US research data, the occurrence of preeclampsia and eclampsia leads to the risk of disseminated intravascular coagulation, thrombocytopenia, placental abruption, aspiration pneumonia and pulmonary edema. The occurrence of this complication is closely related to the dietary intake of nutrients and nutrient supplements during pregnancy. In order to effectively prevent the occurrence of preeclampsia and eclampsia, pregnant women should be given a diversified diet during pregnancy and supplemented with folic acid, which has ideal effects.

4.3. Spontaneous abortion

Folic acid is one of the raw materials for nucleic acid synthesis and is also a key material needed in the body's Hcy metabolism. Because Hcy is embryotoxic, it directly penetrates the placenta and affects fetal growth and development. Therefore, abnormally elevated Hcy levels can cause unexplained recurrent miscarriage. Studies have confirmed that compared with healthy women, Hcy levels in women with recurrent miscarriage are significantly higher.

In recent years, with in-depth research on folate metabolism enzyme genes, it has been found that maternal folate

metabolism gene mutations are closely related to recurrent miscarriage. The inability to utilize folic acid after regular dose supplementation or poor drug absorption can easily lead to spontaneous abortion, recurrent miscarriage and other adverse maternal and childbirth outcomes. Therefore, early monitoring of Hcy levels in early pregnancy has certain clinical significance in identifying high-risk groups and taking personalized supplementary measures in the future.

4.4. Anemia

Pregnant women show varying degrees of folic acid deficiency, limited DNA synthesis, resulting in stagnant development of red blood cell nuclei, a large amount of RNA accumulated in the cytoplasm, and an imbalance in the ratio of DNA and RNA. As the duration of this state increases, the volume of red blood cells increases. Affected by the incomplete development of red blood cell nuclei, megaloblastic red blood cells are subsequently formed and symptoms of anemia occur.

4.5. Premature birth

According to epidemiological research data, as many as 15 million premature infants are born every year around the world, which is also an important factor in neonatal death. One million infants and young children die from complications of premature birth every year. Taking folic acid before pregnancy can help reduce the incidence of premature birth, but supplementing with folic acid after pregnancy has no significant impact on the risk of folic acid. A survey by domestic preconception health care service agencies found that folic acid supplementation before pregnancy is a protective factor against premature birth and has an interactive effect with prenatal BMI.

Some research results show that supplementing iron and folic acid during pregnancy is a risk factor for preterm birth, which may be related to iron-induced macrocytosis increasing blood viscosity and damaging uteroplacental blood flow, resulting in reduced placental perfusion, which in turn increases the risk of placental infarction and causes premature birth.

5. Summarize

To sum up, surveys and statistics show that in my country, a high proportion of pregnant women do not take folic acid during pregnancy. This is related to factors such as economic conditions, education level, unplanned pregnancy, and lack of awareness of folic acid. Regular supplementation of small doses of folic acid before pregnancy and early pregnancy has a positive effect on preventing adverse maternal and infant outcomes and maintaining maternal and infant health. It can improve blood Medium folic acid concentration, in order to ensure the compliance of pregnant women with regular folic acid supplementation, it is recommended to strengthen the publicity and education of small-dose folic acid supplementation within the scope of community services, strengthen the awareness of folic acid supplementation among women of childbearing age, improve the impact of regular folic acid supplementation, maintain normal plasma folic acid concentration in the body, and prevent adverse maternal and infant outcomes.

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Disclosure statement

The author declares no conflict of interest.

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