University of Thi-Qar Journal of Science (UTJsci)
E-ISSN: 2709-0256, P-ISSN: 1991-8690, Vol. 10, No. 2, Dec. 2023

Role of Folic Acid, Vitamin D, and Progesterone in Pregnancy and Threatened Abortion

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Received: 2023-07-02, Revised: 2023-08-14, Accepted: 2023-08-14, Published: 2023-12-22

***ABSTRACT*—The most frequent early pregnancy problem threatened abortion, affects 20% of pregnancies. Vaginal bleeding may be present, together with or without abdominal cramps. Women who are getting older, smoking, being overweight or obese, having PCOS, and having had an abortion in the past are danger signs for a potential abortion. The Physiology of the disease has been linked to alterations in cytokine concentrations or weakened maternal immunity. By taking the clinical history into account, determine the therapy options and provide crucial information for the prognosis, the physical examination, the biochemistry of the mother's serum, and the results of the ultrasound. The most popular advice is to stay in bed, but its usefulness is not well supported. Progesterone, vitamin D, and folic acid are further alternatives.**

Keywords*: Pregnancy; Threatened abortion; Folic acid; Vitamin D; Progesterone.*

1. INTRODUCTION

The most frequent early pregnancy problem, threatened abortion, is frequently accompanied by stress and worry over the pregnancy's outcome. About half of them will eventually experience an actual abortion, which happens in about 20% of known pregnancies [1-4]. Although the cervix is closed, these women frequently have vaginal bleeding with or without cramping and abdominal pain. Emerging research indicates that bleeding during pregnancy may be linked to poor fetal and maternal outcomes [2, 5], which can contribute to mother worry. The risk of following pregnancy difficulties, such as antepartum hemorrhage (APH), early membrane rupture (PROM), intrauterine growth restriction (IUGR), and preterm birth following an attempted abortion, is further increased [6-8]. Older women and those who have had abortions in the past are at higher risk of being threatened with one. For instance, in a study of 182 women who had an abortion threatened, the abortion rates between the ages of the women were 31–40, 16–20, and 21–30 years, respectively[9]. Endocrine abnormalities [10] (such as diabetes, PCOS, or thyroid dysfunction) and a poor quality of life or work environment [11–13] are other factors that raise the risk. Treatment.

There are several available treatments for threatening abortion. It is vital to consider the clinical history and examination, maternal serum biochemistry, and ultrasound findings to choose prospective treatment choices and maybe improve the prognosis. The most popular piece of advice is to stay in bed, but its usefulness is not well supported. Progesterone, HCG, and muscle relaxants are other choices. According to studies, bed rest and uterine relaxants are effective Treatments that improve prognosis include hormone therapy and folic acid supplements in situations of threatened abortion with or without subchorionic hematoma . The outcomes of a different study examining the effectiveness of bed rest during pregnancy to prevent abortion, on the other hand, were distinct. The chance of abortion was the same whether the woman was resting in bed or not, and whether she was resting at home or at a hospital . Additionally, the bed rest group had a greater risk of miscarriage than the HCG therapy group that did not receive any bed rest. To verify whether bed rest truly has a therapeutic benefit, a prospective randomized trial is required. The patients must be made aware that there was not sufficient evidence that bed rest had an impact on the result. If a pregnant woman cannot or does not relax and then miscarries, she can be at fault .

A. Folic acid B9

Pteroylglutamic acid (PGA, commonly known as folic acid), the most popular and stable component of the folate

https://doi.org/10.32792/utq/utjsci/v10i2.1066

vitamin family, is referred to as "folate" for a variety of its derivatives. The three main subunits of PGA are glutamic acid, p-aminobenzoic acid, and pteridine. The term "folic acid" is used in this assessment to refer to the parent compound, pteroylglutamic acid, and the term "folate" is used generically to refer to one or a mixture of pteroylglutamates, per the recommendations of the advisory panel of the International Union of Pure and Applied Chemistry and International Union of Biochemistry and Molecular Biology (IUPAC-IUB).There are negligible amounts of folic acid (PGA) per capita in food or the human body. Reduced folates, primarily The PGA derivatives most common in the human body and food , are 5,6,7,8-tetrahydrofolates (THF) and 7,8-dihydrofolate (DHF)—originating from plants and animals. There are also more changes. The majority of natural foods contain folates. Particularly rich sources include liver, yeast extract, beans, certain fruits, and green leafy vegetables. Whenever food is stored, processed, or cooked, they degrade to monoglutamates. Because it is more stable than other vitamin forms, a synthetic pharmaceutical form of the vitamin called folic acid (PGA) is used in supplements and fortifying foods. Folic acid is commonly available as a dietary supplement in daily amounts up to 0.80 mg, independently or as a component of B complex or multivitamin supplements. Preparations that deliver a daily dose of 5 mg are only accessible with a prescription.

B. Folic Acid and Pregnancy

Folic acid is a B vitamin that is necessary for growth since it is crucial for a variety of activities, such as cell division, production of amino and nucleic acids, and cell division [14]. It is crucial for the proper growth of the fetus's spine, brain, and skull, especially during the first four weeks of pregnancy. The mother's blood volume, the placenta's growth, and the embryo's metamorphosis into a fetus all affect the rate of erythrocyte and cell division creation substantially rises throughout pregnancy [15]. Additionally, the mother's body transfers folate to the developing fetus [14], raising the need for folate beyond just her own needs. [16–19] Among the women at risk for poor folate status

• Those who do not take the necessary dosage of folic acid supplements;
• Those who follow restrictive (Chronic Dieters) diets
• Those who have less socioeconomic position;
• Those whose access to nutritious and secure food is restricted or uncertain.

A decreased prevalence of neural tube defects, such as malformations of the spinal column (spina bifida) and the skull (anencephaly), is associated with increased maternal folate intake and greater maternal red blood cell folate concentration (more than 906 nmol/L) [15]. During the third and fourth weeks of pregnancy, neural tube anomalies can develop even before a woman knows she is pregnant. These flaws include the neural tube's incorrect closing. When the woman takes a daily multivitamin with folic acid three months before conception, this risk decreases. conception and keeps taking it through the sixth week after the start of her last period [20]. Folic acid is now well known to be essential for females who are either pregnant or of reproductive age. Given this information and the realization that not all pregnancies are healthy, it is now widely accepted that throughout pregnancy. (See Section 6.3 under Safe Intake Recommendations) Planned.In certain nations, like Canada [20] and New Zealand [21], dietary fortification is either required or voluntary. Additionally, folate supplementation is encouraged for all women who might become pregnant. Folic acid is still not commonly used in the general population worldwide, despite the fact that it is widely recognized as being necessary to avoid neural tube abnormalities. For instance, in 2008 suggestions were madebased on a thorough analysis of important studies carried out to expand the use of folic acid supplements in the UK, particularly among young women and those with low incomes, research was conducted between 1989 and May 2006 across Europe, the USA, Canada, Australia, and New Zealand. There were 18 studies examining the efficacy of preconception therapies, 26 systematic reviews and/or meta-analyses that were uncovered in the larger body of public health literature.. The findings revealed that just half of the target group's women took dietary supplements, even after successful public relations programs to promote use [22]. The Institute of Medicine [15] states that 400 g/day of folic acid should be included in a woman's diet if she is of reproductive age. These guidelines are based on the dietary folat equivalents required to keep appropriate levels of red blood cells. 400 g of folic acid in a multivitamin per day should also be taken by all women who may get pregnant in order to lower the chance of neural tube abnormalities. These guidelines are acknowledged and supported on a global scale [20,21,23-26]. Some nations offer supplemental advice, such people who reside Women in New Zealand at low risk of a neurological To lower the incidence of neural tube abnormalities, it is advised that women who desire conception take 800 g of folic acid daily for 12 weeks after conception and for at least four weeks before conception[21]. There are no known health risks connected with dietary folate consumption. Consuming folic acid through supplements and/or meals that have been fortified carries a negligible risk of toxicity [27]. Any excess ingestion is normally eliminated in the urine because it is a water-soluble vitamin. Before taking folic acid, anyone taking anti-convulsant medication is advised to consult a doctor because there is some evidence that excessive doses of the vitamin can cause seizures in people taking them [28]. Folic acid supplementation was not linked to twin According to a 2009 meta-analysis of 1083 publications investigating the risks of folic acid supplementation included case-control studies, randomized controlled trials, and systematic reviews., two concerns that had previously been raised in the literature were masking vitamin B12 deficiency or preventing pregnancies. One reasonably well-designed study proposed that confounding by infertility medication explains the previously documented relationships between folic acid and twin pregnancy. The retrospective cohort examination included 176,042 Norwegian women who delivered birth with December 1998 and December 2001 to determine the association between prenatal multivitamin or folic acid consumption and risk for twins. Age, parity, and inadequate folic acid reporting consumption, and in vitro fertilization have all been taken into account, and the OR for twin delivery,

periconceptional supplementation had a pregnancies rate of 1.02 (CI, 0.85 to 1.24) that was equivalent to those who did not take folic acid [29].

C. Vitamin D

Vitamin D, a fat-soluble vitamin that may also be generated in the skin when exposed to ultraviolet B rays from natural light, is abundant in fish and eggs. . The maintenance of pregnancy, the growth of the skeleton, and appropriate brain development all depend on vitamin D. Evidence suggests that many people have subclinical vitamin D insufficiency, which is made worse by lengthy workdays spent indoors and sun avoidance to lower the risk of skin cancer [30, 31]. Different types of vitamin D, including D1, D2, D3, D4, and D5, which have varying structures. The two major forms are vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol), collectively known as calciferol. Vitamin D3 is crucial for maintaining the health of the immune, skeletal, and integumentary systems. It is produced naturally when the skin is exposed to sunlight and can also be obtained through dietary sources [32].Vitamin D is not abundant in most foods. While oily fish such as herring, mackerel, pilchards, sardines, and tuna are good sources, many individuals do not consume them regularly. Other sources include fortified yogurts and certain breakfast cereals, which contain vitamin D as required by law in some countries. However, recent research indicates that vitamin D intake is often insufficient due to poor dietary habits, vegetarianism, low fish consumption, and a lack of supplementation. The circulating levels of 25-hydroxyvitamin D, an indicator of vitamin D status, are particularly low in countries without mandatory fortification of staple foods [32].In some countries, vitamin D supplementation accounts for 6% to 47% of the recommended daily intake. Data from 2005 revealed that the average dietary intake of vitamin D in various countries, including the United States, Canada, the United Kingdom, Ireland, Scotland, Australia, Europe, Japan, and others, ranged between 3 and 9 ng/day. Less than 25 to 50 nmol/L of serum 25-hydroxyvitamin D is considered indicative of vitamin D deficiency, and it is estimated that nearly one billion people worldwide have insufficient vitamin D levels, with higher rates observed in regions like China, Japan, the Middle East, and Europe [33,34]. Among women, 9.2% are deficient, with pregnancy being a particularly high-risk period [31]. Furthermore, pregnant women with darker skin pigmentation are more likely to have inadequate vitamin D levels compared to those with lighter skin pigmentation [35]

D. Vitamin D and Pregnancy

A pregnant woman needs vitamin D to:

1. Build sturdy bones. To guarantee that the fetus receives calcium for the development of strong bones, vitamin D must be present, notably In the skulls. Brain injury is quite risky in people with severe hypocalcemia [36]. Perinatal growth restriction and vitamin D deficiency have been linked to decreased bone mineral content in the offspring [37, 38].

2. Keep pregnant—by the third trimester's end, the circulation's content of maternally active vitamin D has doubled [39]. This happens because of an increase in the first trimester. The mother's immune adaption, crucial to maintaining a normal pregnancy ,is thought to be made possible by the early increase [39]. The mother's Vitamin D modifies the immune system, preventing miscarriage [31,39].

3. Encourage healthy brain growth. According to preliminary studies, vitamin D deficiency during pregnancy has been associated with adult mental health issues, particularly schizophrenia [40], and abnormal brain development [35]. Furthermore, observational studies have shown evidence that adequate vitamin D intake throughout childhood may delay the development of immunological illnesses . Evidence suggests that adequate vitamin D intake during childhood may delay the onset of immunological diseases such as Type 1 diabetes [41], allergic diseases [39], lower respiratory tract infections, wheezing, and asthma [42] in children. Vitamin D deficiency can have severe consequences for newborns, including an increased risk of brain damage due to weakened skull bones, as well as various long-term health issues. A recent Cochrane Review evaluated the effects and safety of vitamin D supplementation during pregnancy, including whether it could enhance pregnancy outcomes when taken alone or combined with calcium and other vitamins and minerals [43].The review included studies of 623 women comparing the effects of vitamin D supplementation to no supplementation or placebo, and 400 women comparing the effects of vitamin D + calcium to no supplementation. The results were diverse and heterogeneous, but data from four trials consistently showed that pregnant women taking vitamin D supplements had higher serum vitamin D concentrations at term than those who received no therapy or placebo. In three trials, women who took vitamin D supplements had fewer babies with birth weights ≤ 2500 g compared to those who received no treatment or placebo. There were no significant differences in the incidence of newborn fatalities, stillbirths, or nephritic syndrome between women who were supplemented with vitamin D and those who received no treatment or placebo. The researchers found that supplementing with vitamin D during pregnancy increased serum vitamin D concentrations. However, due to limited high-quality research, the therapeutic significance of these findings and the safe use of this intervention in regular prenatal care have yet to be confirmed by rigorous randomized trials.Toxicity has been observed in very few cases at vitamin D concentrations as high as 10,000 IU/day (250 µg/day), with symptoms typically appearing at levels above 20,000 IU/day (500 µg/day) [44–46]. A study involving 350 pregnant women between 12 and 16 weeks gestation compared daily doses of 400 IU (10 µg), 2000 IU (50 µg), and 4000 IU (100 µg) of vitamin D until delivery. Maternal and neonatal levels of circulating 25-hydroxyvitamin D [25(OH)D] were measured as primary and secondary outcomes. There were no differences between the groups in terms of safety measures, and no adverse events were associated with vitamin D supplementation or blood levels of 25(OH)D. The authors concluded that a daily dose of 4000 IU of vitamin D is safe

and effective in achieving sufficiency in all women and their neonates, regardless of race. This contrasts the current average requirement, which is relatively ineffective at achieving adequate circulating 25(OH)D concentrations, especially in African Americans [47].

E. Progesterone

Professor Willard Allen's discovery and separation of progesterone, which resulted in the publication of the first report on the corpus luteum's progesterone extraction on September 23, 1929, marked the beginning of the hormone's modern history.[48]

The so-called "pregnancy hormone," progesterone, aids in a variety of ways, including:

- Modulating the mother's immune response;
- Suppressing the inflammatory response;
- Decreased uterine contractility, to assist in preparing the secretory endometrium for implantation and maintenance of early pregnancy.
- A better uteroplacental blood flow.
- Support for the luteal phase.

It is well known that genetic factors account for the bulk of early pregnancy losses, and that immunological responses mediated by cytokines bring on 40–60% of idiopathic recurrent spontaneous miscarriages. We now know that a critical factor in boosting fetal survival in pregnancy is the mother's immunological tolerance of the fetus. Progesterone balances both during pregnancy maintenance by assisting human T-cells in producing Th2 cytokines and inhibiting Th1 cytokines. Both natural and synthetic progesterone are available as progesterone. The roots of Mexican yams and soybeans are the sources of natural progesterone.[49] The following qualities are conferred by natural progesterone that has been micronized:[50]

1.It is natural progesterone (increased bioavailability and absorption with smaller particle size) .
2.It is possible to elevate serum progesterone in a dose-dependent manner.
3.After eating, absorption is at its highest level compared to fasting.
4. Needs numerous dosages and has a short half-life.
5.Lipid-supportive.

F. PROGESTERONE AND PREGNANCY

Threatened miscarriage is characterized as vaginal bleeding with a closed cervix that occurs before the gestational when a fetus would be viable outside of the womb .It affects about one in five pregnant women.[51] Unluckily, roughly half of them will ultimately experience a real miscarriage.

Progesterone production in the corpus luteum is essential for pregnancy maintenance until the placenta takes control at 7 to 9 weeks of gestation. In fact, abortion can be easily induced before 7 weeks (49 days) of gestation by removing the corpus luteum[52] or administering a progesterone receptor antagonist[53].

The uterine lining undergoes secretory changes brought on by progesterone that are crucial for the implantation of the fertilized ovum.[54] Due in part to small sample sizes, a variety of progestin kinds, administration methods, and outcomes measured, it has been challingings to determine whether additional progestin therapy benefits women at risk of abortion. Progesterone therapy administration during the first trimester, a big RCT known as the PRISM (progesterone in spontaneous miscarriage) experiment found no meaningful difference between the treatment group and placebo regarding the likelihood of live babies , which included 4,153 women.

According to the number of prior miscarriages, twice-daily administration of 400 mg of vaginal micronized progesterone was linked to higher live birth rates. Live birth rates were 75% (689/914) with progesterone against 70% (619/886) with placebo in a subgroup analysis of women who had a history of one or more miscarriages and bleeding in the current pregnancy (Risk ratio = 1.09, 95% confidence interval: 1.03-1.15; p = 0.003; rate difference 5%). The advantage was larger for the subset of women who had previously miscarried three or more times and were currently bleeding during pregnancy.[55]

Progestogens may have advantages on live birth rate and miscarriage rate. According to a recent meta-analysis, women who are about to miscarry by Li et al. on the topic. The meta-analysis included 10 trials and 5,056 participants. No statistically significant improvements were observed with vaginal progesterone, suggesting that these advantages may only be associated with the use of oral progestogen.[56]

G. Muscle Relaxants

Drugs that relax the uterine muscle have been used in situations where a miscarriage is imminent to reduce the chance of a miscarriage. Among the uteri relaxants, beta agonist was tested on 170 women in one low-quality experiment to see if it could reduce miscarriage compared to a placebo. The results showed that the beta agonist group had No change in preterm delivery, but a lower risk of intrauterine mortality (miscarriage and stillbirth) (average risk ratio (RR) 0.25, 95% confidence interval (CI) 0.12 to 0.51). There has not there hasn't been enough data to determine whether uterine muscle-relaxing medications can stop threatening miscarriage. It is necessary to conduct more studies about how to treat an approaching miscarriage using uterine muscle relaxants.

CONFLICT OF INTEREST

Authors declare that they have no conflict of interest.

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