

Does Vaginal Progesterone Affect Fetal Nuchal Translucency in Patients With Threatened Miscarriage: Cohort Study

Thesis

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By

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Introduction

Progesterone is $C_{21}H_{30}O_2$ and it belongs to a group of steroid hormones called progestogens. It is mainly secreted by the corpus luteum in the ovary during the second half of the menstrual cycle and also produced by the placenta, and adrenal gland, It plays important roles in the menstrual cycle and in maintaining the early stages of pregnancy. (*Giorlandino et al., 2015*).

Progesterone is an essential hormone for the continuation of pregnancy and is prescribed in 13–40% of women with threatened miscarriage, according to the literature (*Sotiriadis et al., 2004*).

Progesterone reduce abortion rate in women with *threatened* abortion by releasing certain anti-abortive cytokines, modulation of the maternal immune system (immunological tolerance of the fetus), and with relaxation of uterine muscles (*Halasz and Szekeres-Bartho 2013*).

Data on the use of progesterone for threatened miscarriage remain conflicting. A more recent systematic review suggested lack of evidence to support routine use of progesterone to prevent miscarriage in early to mid-pregnancy (*Haas and Ramsey 2013*).

With the increased use of progesterone, 2 meta analyses evaluated its use in the first trimester of pregnancy for both prevention of miscarriage and for treating threatened miscarriage in a low-risk population and stated that it does not modify the outcome (*Wahabi et al., 2011*).

Miscarriage is a spontaneous loss of a fetus < 20 weeks of gestation. It is a traumatic event, which can have psychological consequences for the parents. Threatened miscarriage, demonstrated by vaginal bleeding with or without abdominal cramps, is a common complication of early pregnancy. It occurs in about a fifth of all pregnancies and approximately half of them will be lost (*Yassaee et al., 2014*).

Nuchal translucency (NT) is a transient subcutaneous collection of fluids behind the fetal neck seen ultrasonographically at 11-14 weeks' gestation by trans abdominal ultrasound or trans vaginal ultrasound, trans abdominal ultrasound is more sensitive and need urinary bladder to be full for good examination .and also is recognized as a sensitive marker for open neural tube defect. (*Nicolaides et al., 1992*)

Despite its important role in the first trimester of pregnancy for open neural tube defect screening the use of NT measurement is still considered controversial (**Mol et al., 1999**). Furthermore, it is well known that increased NT is also present in euploid fetuses (**Bilardo et al., 2010**).

Many pathophysiological theories have been put forward to explain this increase like chromosomal, genetic and structural defect or even heart failure (**Rizzo et al., 2003**), so that Allan described fluid retention after exposure to many environmental factors early in pregnancy. (**Allan 2006**).

Giorlandino speculated that the use of exogenous progesterone in the first trimester of pregnancy could lead to abnormal blood flow patterns that may affect both the expression of the growth factors required for the normal development of the fetus and the deregulation of fetal blood pressure (**Giorlandino et al., 2015**).

Therefore, this investigation was carried out to make a prospective evaluation of NT thickness between 11-14 weeks' gestation among women receiving exogenous progesterone and to compare the findings with controls.

Aim of the Work

The aim of this study was to assess the relationship between 400 mg vaginal progesterone (**Prontogest®**) and thickness of fetal nuchal translucency in 80 women with threatened miscarriage for 1 week treatment duration.

Research hypothesis:

Alternative hypothesis: In women with threatened miscarriage, 400 mg vaginal progesterone (**Prontogest®**) may lead to increase nuchal translucency.

Null Hypothesis: In women with threatened miscarriage, 400 mg vaginal progesterone (**Prontogest®**) may not affect nuchal translucency.

Research Question:

In women with threatened miscarriage does 400 mg vaginal progesterone (**Prontogest®**) affect fetal nuchal translucency?

Threatened Miscarriage

Threatened miscarriage is the commonest complication of early pregnancy and is often associated with anxiety and stress regarding the pregnancy outcome. It occurs in about 20% of recognized pregnancies and about half of these will eventually suffer an actual miscarriage (*Weiss JL et al., 2004*).

These women usually present vaginal bleeding, with or without abdominal pain and cramps, but the cervix is closed. Bleeding during pregnancy can cause maternal anxiety and emerging evidence suggests that it may be associated with poor fetal and maternal outcomes (*Sotiriadis A et al., 2004*).

Furthermore, there is an increased risk of subsequent pregnancy complications, such as Ante- partum hemorrhage (APH), premature rupture of membranes (PROM), intrauterine growth retardation (IUGR) and preterm delivery after a threatened miscarriage (*Dongol A et al., 2011*).

Other factors that contribute to an increased risk include endocrine abnormalities (such as diabetes, PCOS or thyroid dysfunction) and poor life or working environment (*Li DK et al., 2002*).

A number of treatment options are available, including bed rest and a simple wait and watch policy, and treatment

with progesterone or HCG, as well as using uterine muscle relaxant drugs. Unfortunately, these western medicines have some adverse effects. Nausea, headache and sleepiness are common, and high doses may result in drowsiness and liver toxicity (*Li DK et al., 2003*).

For instance, oral administration of progesterone shows several disadvantages including the extreme variability in the plasma concentrations obtained and poor bioavailability. Vaginal administration of progesterone is inconvenient for women with vaginal bleeding, and the absorption is also unreliable (*Alimohamadi S et al., 2013*).

As another option to preserve pregnancy, CAM therapies include acupuncture and Chinese herbs have the superiority of little side effects compared with Western medicine. Within fertility research, acupuncture demonstrated beneficial hormonal responses with decreased miscarriage rates and promoted specific beneficial effects in terms of positive emotion and hormonal responses in early pregnancy (*Betts D et al., 2012*).

Chinese herbs made up of products from plants mostly and some animal and mineral substances have become very popular and are commonly used as an alternative treatment

for threatened miscarriage recently (*Li L et al., 2012*).

So, it is worthwhile to examine the possible treatment benefits of CAM therapies for miscarriage. The aim of this manuscript is therefore to summarize the current knowledge in the threatened miscarriage and to analyze the most updated research and clinical usage, mechanism and side- effects of CAM therapies for threatened miscarriage, in order to guide future researches and clinical applications (*Li L et al., 2012*).

The subject's perception about the amount of bleeding, compared with her normal menstrual period, is important in predicting a failed pregnancy. In general, the greater amount of perceived blood loss, the greater chance of a non-viable pregnancy may have. Threatened miscarriage rarely presents with heavy vaginal bleeding. For abdominal pain, patients may or may not report pain that is similar to periodic pain or cramps. This is due to the contraction of the uterus in response to irritation caused by the bleeding (*Heine and Swamy 2009*)

On vaginal examination, the cervical os is closed and no cervical motion tenderness is found. Diffuse uterine tenderness and/or adnexal tenderness may be present (*Pearlstone and Baxi 1993*).

Anxiety and stress considerably increased the risk of miscarriage up to 2.6 times. And these psychological symptoms could persist for 6 months to 1 year after the miscarriage (Everett C 1997).

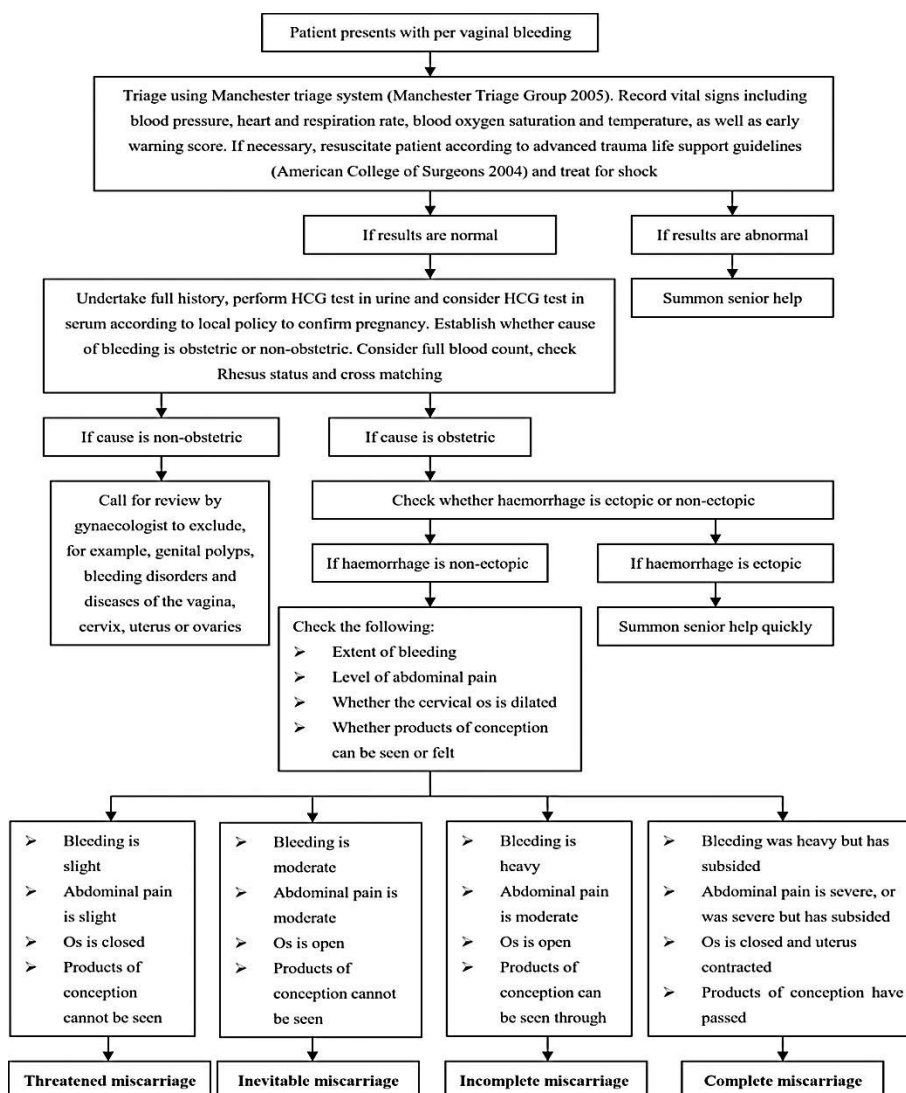


Figure (1): Flow chart for diagnosing women with early pregnancy per vaginal bleeding (Marquardt U., 2011).

Pathophysiology

The pathophysiology of threatened miscarriage is still not understood. Currently the known pathogenesis of threatened miscarriage includes changes in levels of cytokines and placental membranes, maternal immune dysfunction, and endocrine abnormalities. Most women with threatened abortion probably have multiple risk factors for miscarriage (*Sotiriadis A et al., 2004*)

1.1 Abnormal cytokines profiles

The pathophysiology of threatened miscarriage in terms of cytokines involves a change in the T helper (Th) 1/Th2 balance resulting from an increase of uterine Th1 type pro inflammatory cytokines and/or a deficiency of Th2/3 type cytokines, therein increased maternal serum interleukin (IL)-2 receptor and tumor necrosis factor (TNF)- α levels (*Clark DA, et al., 2001*).

1.2 Immunologic dysfunction

Immunologic recognition of pregnancy is crucial to the maintenance of gestation. And inadequate recognition of fetal antigens may cause abortion (*Chen SJ et al., 2012*).

Regards to threatened miscarriage, studies show that the presence of anti-b2-glycoprotein I antibodies is associated with an increased risk of pregnancy loss in women with threatened miscarriage in the first trimester (*Mezzesimi A et al., 2007*).

Evidence suggests that circulating levels of chemokines which are proteins involve in regulation of inflammation and immune response are associated with increased risk of miscarriage and may have a regulatory function in pregnancy. Elevated epithelial cell-derived neutrophil-activating protein-78 (ENA-78) levels, a protein involved in regulation of angiogenesis and leukocyte recruitment, are associated with increased risk of miscarriage as the collection-outcome increased interval (*Whitcomb BW et al., 2007*).

1.3 Oxidative stress

Lipid peroxidation and alterations in antioxidant enzyme activities may be of importance in the pathogenesis of miscarriage. The architecture of the human first trimester gestational sac limits fetal exposure to oxygen (O₂) (*Jauniaux E et al., 2003*).

Placenta and fetus develop in a physiologically low O₂ environment and their metabolisms are essentially anaerobic. O₂ free radicals are generated under hypoxic conditions and confirmed to be a potential teratogenic threat to the fetal tissues and are known to be related to the pathophysiology of common human pregnancy disorders, including miscarriage. *(Gupta S et al., 2007).*

Besides, a modified nitric oxide (NO) pathway might play an important role in the physiological changes of advancing gestation but may also contribute to the pathophysiology of miscarriage. A study showed that serum NO levels clearly decreased compared with non-pregnant patients and patients with regular pregnancy and threatened abortion. The data report implied that a direct functional role of the NO mediator in early embryonic development confirmed its importance in the uterus and cervix during abortion *(Paradisi R et al., 2007).*

Therefore, any factors balancing NO metabolism might be useful in the treatment of miscarriage, reducing the substantial morbidity and associated mortality.

1.4 Endocrine disorders

For most other miscarriages, the causes are unknown, but some may be related to endocrine disorders of mothers. The

most common endocrinologic factors are polycystic ovarian syndrome (PCOS) and obesity. Several factors have been implicated as potential contributors to miscarriage in PCOS. In addition to fetal defects, these include anatomically polycystic ovaries, obesity, endometrial defects, placental thrombosis, and hormonal abnormalities such as insulin resistance or excess androgen secretion. Notably, insulin resistance has been linked to several of the aforementioned contributors to pregnancy loss (*van der Spuy and Dyer 2004*).

In addition, obesity will cause increased risks of congenital anomalies, preeclampsia, gestational diabetes, and still birth (*Dokras A et al., 2006*).

There are also data suggesting the risk of miscarriage is increased among obese women (*Lashen H et al., 2004*).

1.5 Placental membranes

Combining ultrasound and in-vitro experiments have indicated that the maternal circulation inside the placenta is associated with a physiological oxidative stress which can be the trigger for the formation of the placental membranes (*Jauniaux E et al., 2005*).

And there is clear ultrasound evidence for excessive entry of maternal blood inside the intervillous space having a direct mechanical effect on the villous tissue, and an indirect oxidative stress effect that contributes to cellular dysfunction and/or damage (*Jauniaux and Burton 2005*).

The abnormal development of these membranes can lead to sub chorionic hemorrhage which may result in placental separation and threatened miscarriage(*Jauniaux and Burton 2005*).

Additionally, the presence of a hematoma may also be associated with a chronic inflammatory reaction in the decidua, resulting in persistent myometrial activity and expulsion of the pregnancy (*Salafia CM et al., 1995*)

2. Risk factors

Numerous researches have examined the association of miscarriage with some diet, behavior or lifestyle and work environment. Poor dietary intake of vitamins has been confirmed with the association of miscarriage. Supplementing women with vitamins either prior to or in early pregnancy may reduce the risk of miscarriage, but recent review cannot confirm its efficacy. However, taking vitamin supplements before or at the time of conception may more likely lead to a multiple pregnancy. The

impact of different combinations of vitamins needs to be further studied. In addition, it has been shown that caffeine consumption > 300 mg/day may double the risk of miscarriage (*Giannelli M et al., 2003*).

Whereas, there was no evidence that daily consumption of 400 µg of folic acid before and during early pregnancy influenced the risk of miscarriage (*Gindler J et al., 2001*).

Besides, a slightly increased risk was found for dental workers exposed to mercury amalgam, some acrylate compounds, solvents and disinfectants (*Lindbohm ML et al., 2007*).

It is well known that miscarriage risk increases with age of women. Because there is a high risk of pre-gestational, gestational complications and perinatal loss, pregnancy at 40 and over is a high-risk pregnancy (Table 1) (*Miletic T et al., 2002*).

Table (1): Miscarriage rates stratified by maternal age at conception (*Nybo Andersen AM et al., 2000*).

Age (years)	Total number of pregnancies	Miscarriage rate
20-24	350395	9%
25-29	414149	11%
30-34	235049	15%
35-39	93940	25%
40-44	25132	51%
≥ 45	1865	75%