Role of Progesterone in Miscarriage

Alokananda Ray*

Senior Consultant Department of OBGYN, Tata Main Hospital Jamshedpur India

Abstract: About 10-15% of clinically recognized pregnancies end in a miscarriage. Recurrent miscarriage defined as loss of three or more consecutive pregnancies complicate about 1-2% of couples trying to conceive. The most common cause of miscarriage is chromosomal aberration in the fetus. However in a vast majority, the cause of miscarriages remain unknown. This makes treatment options difficult and often empirical. It has been postulated that a causative factor in many cases of miscarriage may be inadequate secretion of progesterone during the luteal phase of the menstrual cycle and in the early weeks of pregnancy. Therefore, progestogens have been used, beginning in the first trimester of pregnancy, in an attempt to prevent spontaneous miscarriages. In women presenting with a clinical diagnosis of threatened miscarriage, there is preliminary evidence of a reduction in the rate of spontaneous miscarriage with the use of progesterone. Larger RCTs may help to validate these findings. Initial reports of favourable outcome with use of progesterone in recurrent pregnancy loss (RPL) could not be confirmed uniformly by larger randomized trials. This article aims at reviewing the role of progesterone in treatment of threatened and recurrent miscarriages.

Keywords: Progesterone, Prevention, Threatened, Recurrent, Miscarriage.

INTRODUCTION

Human reproduction is associated with a high risk of pregnancy loss. Almost 60% of fertilized ova do not reach the stage of clinically recognized pregnancy; resulting in occult miscarriage either due to immediate demise of the fertilized ova or failed implantation of the blastocyst [1-3]. In addition to this about 10-15% of clinically recognized pregnancies end in a miscarriage [4].

The term miscarriage refers to spontaneous loss of pregnancy prior to twenty weeks of gestation (*i.e.* prior to the age of fetal viability). Vaginal bleeding in the first twenty weeks of pregnancy: ranging from mild spotting to profuse bleeding along with pain or without pain is known as threatened miscarriage. Pregnancy loss in first 20 weeks, after appearance of fetal cardiac activity affects less than 5% of pregnancies [5]. When bleeding is associated with cervical dilatation miscarriage is inevitable. Recurrent miscarriage defined as loss of three or more consecutive pregnancies complicate about 1-2% of couples trying to conceive [6, 7].

The most common cause of miscarriage (in < 50%) is chromosomal aberration in the fetus [8, 9]. Other risk factors include- advanced maternal age, obesity, multiple gestation and acute infections. Pregnancy loss may be recurrent due to autoimmune factors (such as phospholipid antibodies, lupus anticoagulant and cardiolipin antibodies), genetic disorders, polycystic ovaries, poorly controlled diabetes, thyroid dysfunction, uterine anomalies and thrombophillias. However in more than 50% couples the cause of recurrent miscarriages remain unknown. This makes treatment options difficult and often empirical.

Pregnancies complicated with threatened miscarriage are 2.6 times more likely to miscarry and are often associated with adverse pregnancy outcomes such as- placenta previa, placental abruption, preterm labour, fetal growth restriction, low birth weight, caesarean section and increased risk of perinatal mortality [10]. Research shows that - miscarriage can result in significant emotional and physical stress to both partners [11, 12]. Needless to say the financial impact of miscarriage to any health care system can be substantial.

A considerable body of evidence now suggest that a shift from T-helper 2 (Th2)-dependent anti-inflammatory cytokines to T-helper 1 (Th1)-mediated production of pro-inflammatory cytokines is seen in aborted pregnancies. Studies have indicated an association between Th1 mediated immune responses and reproductive failure [13]. Tumor necrosis factor α(TNFα) which is a Th1-dependent pro-inflammatory cytokine initiates cytotoxic activity resulting in trophoblast apoptosis [14, 15]. An increase in the Th1-dependent production of IL-12 and a decrease in the expression of anti-inflammatory cytokine Interleukin (IL)-10, can activate maternal lymphocytes and result in pregnancy loss. On the other hand a high level of IL-10 production is protective with favourable pregnancy outcome. [16]. Women suffering from repeated spontaneous miscarriages, differ in the Th1/Th2 cytokine ratio compared with women who do not have RPLs; *e.g.*: The ratio of interferon (IFNγ)- /interleukin

*Address correspondence to this author at the Senior Consultant Department of OBGYN, Tata Main Hospital India; Tel: +916572441344;
E-mail: E-mail: alokanandaray@yahoo.com

E-ISSN: 2408-9761/16

(IL)-10 produced by mitogen-stimulated peripheral blood mononuclear cells (PBMC) is 0.5 in women without RPL in the first trimester as compared to 15 in women with RPL [17].

More recent studies have demonstrated that kisspeptin, G - protein coupled receptor 54 (GPR54) and progesterone induced blocking factor (PIBF) expression in both syncytiotrophoblasts and cytotrophoblasts are decreased in women with recurrent pregnancy loss (RPL) as compared to controls ($P<0.05$) [18]. Also, kisspeptin, PIBF and progesterone receptor (PR) expressions in decidua are significantly decreased in women with RPL as compared to controls ($P<0.01$) [18].

PROGESTERONE AND EARLY PREGNANCY

Progesterone, a female sex hormone, causes secretory changes in the endometrium during the second half of the menstrual cycle and improves its receptivity for successful implantation of a fertilized egg. Progesterone is secreted mainly by the corpus luteum, formed in the ovary after the follicle ruptures during ovulation. The window of implantation (day 6-day 10 post ovulation) coincides with maximum progesterone production by the corpus luteum with maximum α2, β2 integrin and osteopontin expression with pinopode activity at the endometrial level. The response of endometrium to progesterone depends not only on optimal progesterone seretion from the corpus luteum but also on adequate induction of progesterone receptors by oestrogen during the follicular phase. A deficient response to adequate levels of progesterone could also result from endometrial pathology like Asherman's syndrome, endometritis or primary endometrial defect- resulting in infertility or miscarriage. Should pregnancy occur, HCG secreted from the implanting embryo rescues the corpus luteum with continuation of progesterone secretion and maintenance of early pregnancy. The leuto-placental shift occurs 36 days after the LH surge (at 7-8 weeks of gestation) when placenta takes over the function of secreting progesterone.

Progesterone has been shown to aid implantation and maintenance of pregnancy by stabilizing the endometrium and inhibiting myometrial contractions [19]. Pregnancy involves a significant decrease in uterine vascular tone and an increase in uterine blood flow, which is mediated partly by steroid hormones, including oestrogen, progesterone, and cortisol. Progesterone induces endothelial nitric oxide synthase expression and activity, nitric oxide production, and expression of enzymes for prostacycline production, thereby altering uterine artery contractility and increasing uterine blood flow during pregnancy [20, 21].

An immune-modulatory role of progesterone has also been suggested- progesterone induced blocking factor (PIBF), promotes a shift from Th1-dependent pro inflammatory cytokines towards Th2-dependent protective cytokines that support pregnancy [22].

It has been postulated that a causative factor in many cases of miscarriage may be inadequate secretion of progesterone during the luteal phase of the menstrual cycle and in the early weeks of pregnancy. Therefore, progestogens have been used, beginning in the first trimester of pregnancy, in an attempt to prevent spontaneous miscarriages.

There is now evidence suggesting that exogenous administration of progestational agents can decrease IFNγ- production by peripheral blood mononuclear cells and shift the immune system toward Th 2-dependent anti-inflammatory cytokines such as IL-4 and IL-6 [22]. Vaginal micronized progesterone treatment in women with threatened miscarriage was likewise shown to cause a potential protective shift in the cytokine concentration of endocervical secretions with signify-cant decrease in IFNγ- and increase in IL10 levels [23].

However a few other studies failed to show similar results with no significant differences in the cytokine expression after administration of progestin (dydrogesterone) in women with threatened or recurrent miscarriages. The authors concluded that dydrogesterone in the study group possibly had a protective effect on pregnancy through a mechanism that did not involve alteration of serum cytokine levels [24, 25].

PROGESTERONE IN THREATENED MISCARRIAGE

Treatment modalities for bleeding in early weeks of gestation are likely be effective only when the fetus is viable, and has no chromosomal abnormality [26]. Ultrasound enables rapid and accurate establishment of viability of a pregnancy, with the ability to predict if a pregnancy is likely to continue when there is bleeding. Identification of fetal heart activity carries a 97% likelihood for the pregnancy to continue beyond 20 weeks [27]. The therapeutic approach to women with threatened miscarriage can therefore be rationalized where ultrasound is available.

Most women with threatened miscarriage are prescribed bed rest and progesterone with limited and conflicting evidence for both treatment modalities [28].

In women presenting with threatened miscarriage, there is now preliminary evidence of a reduction in the spontaneous miscarriage rates, with the use of progestins. This conclusion was drawn from four RCTs which included 411 women. Miscarriage was significantly less in women receiving progestins when compared to placebo or no treatment (risk ratio 0.53; 95% CI 0.35 to 0.79). There was no evidence of increase in the rates of antepartum haemorrhage, pregnancy-induced hypertension, or congenital abnormalities in the treatment group [29]. The authors however cautioned that these evidences were preliminary and additional well designed trials are required to confirm them [30].

A systematic review which included 660 participants from five dydrogesterone trials; also showed a statistically significant reduction of miscarriage rates with dydrogesterone compared to standard care in women with clinical diagnosis of threatened miscarriage. OR 0.47 (confidence interval [CI 0.31–0.7]) [31].

Another meta-analysis of seven studies which included a total of 744 women showed a statistically significant reduction in miscarriage rate with progestogen use (RR 0.53, 95% CI: 0.39 to 0.73) [32]. However these studies (Table **1**) were of small sample size and of poor quality with inadequate methodology [32].

The above mentioned trials, [33-39] although small and of poor quality, suggest benefit with use of progesterone and progesterone analogues in treatment of threatened miscarriage.

Presently a large randomised double-blind, placebo-controlled multicentre study – the PRISM trial [32] is underway which plans to randomize 4,150 women with clinical diagnosis of threatened miscarriage, and USG confirmation of intra-uterine gestational sac into the progesterone arm(400mg of micronized progesterone vaginal suppositories twice daily up to 16 weeks of gestation) and placebo arm. The primary outcome measure that shall be studied is live birth rates beyond 34 weeks, other secondary outcome measures include-gestation at delivery; ongoing pregnancy at 12 weeks ; miscarriage rate; survival at 28 days of neonatal life; chromosomal and congenital abnormalities; adverse events; antenatal complications; birth weight; APGAR

Table 1: Trials of Progestogens Versus Placebo or no Treatment for Threatened Miscarriage [33, 39]

Study	Dose and Route	Duration of Treatment	Compared with	Risk Ratio (M-H fixed 95% CI)
Misto 1967 n=25	20-40 mg oral dydrogesterone	Once daily for 6 to 15 days, or for longer periods	Placebo	0.25 (0.01 4.50)
Ehrenskjold 1967 n=153	20 mg oral dydrogesterone	20 mg BD/20 mg TDS until symptoms ceased/10 mg twice daily for5 days/5 mg twice daily for7 days.	No treatment	0.68 (0.38,1.23).
Gerhard 1987 n=34	25 mg progesterone vaginal suppositories twice daily	Until miscarriage or for 14 days after bleeding stopped.	Placebo	0.33 (0.01,7.65)
Palagiano 2004 n=50	90 mg progesterone (8%) vaginal suppositories	Once daily for five days.	Placebo	0.50 (0.17, 1.45)
Omar 2005 n=154	dydrogesterone 40 mg followed by 10 mg BD	Until bleeding stopped.	No treatment	0.29 (0.09, 1.02).
El-Zibdeh 2009 n=146	10 mg oral dydrogesterone twice daily.	From enrolment until one week after bleeding stopped.	No treatment	0.70 (0.37, 1.32)
Pandian 2009 n=191	dydrogesterone 40 mg oral followed by 10 mg twice daily	Until 16 weeks of gestation.	No treatment	0.44(0.24, 0.82)

scores; need for resuscitation and other neonatal complications (such as infection, respiratory distress syndrome, necrotising enterocolitis).

If effectiveness of progesterone therapy in threatened miscarriage is confirmed by the PRISM trial, women with bleeding in early weeks of pregnancy across the globe will benefit substantially.

PROGESTERONE IN UNEXPLAINED RECURRENT PREGNANCY LOSS (RPL)

Recurrent miscarriage defined as loss of three or more consecutive pregnancies affect about 1-2% of couples trying to conceive. Therapeutic management of RPL aims at correcting the underlying cause, unfortunately in more than 50% the cause of RPL remains unknown. High-quality data on management of RPL are limited; therefore, many recommendations are based upon clinical experience and data from observational studies or RCTs of small sample size [40].

The prognosis for a successful future pregnancy in couples suffering from RPL is generally good with overall live birth rates for unexplained RPL as high as 77% [41]. However Increasing maternal age and a higher number of previous miscarriages are associated with a significant decrease in the likelihood of having a live birth. In women with recurrent early first trimester pregnancy loss, the presence of fetal cardiac activity is reassuring with increased possibility of a subsequent viable delivery, nonetheless risk of fetal loss in these women, remain above that of the general population (losses in women with RPL - 5 to 22 % compared to 7 to 15 % in infertile populations and 3 to 6 % in controls) [42].

Whether progesterone supplementation in the first trimester, increase the live birth rates among women with unexplained recurrent miscarriages, is uncertain. However progesterone is often prescribed to women with unexplained RPL, despite the lack of large randomized trials demonstrating its efficacy [43].

The Cochrane review on progesterone for prevention of miscarriage, [44] included progesterone use in both threatened and unexplained recurrent miscarriage. This meta-analysis of 14 trials which included 2158 women showed no statistically significant difference in miscarriage rates between progestogen and placebo groups (Peto odds ratio 0.99; 95% confidence interval (CI) 0.78 to 1.24). Subgroup analysis on method of administration of progestogen (oral, intramuscular or vaginal) also showed no statistically significant difference between progestogen and placebo groups. The authors therefore concluded that there is no evidence to support the routine use of progestogen to prevent miscarriage in early to mid-pregnancy.

Interestingly, after making provision for previous obstetric history, a subgroup analysis which only included women who had suffered three or more consecutive miscarriages prior to the studied pregnancy, showed a statistically significant difference in favour of progestogen compared to placebo or no treatment.(risk of RPL with progesterone odds ratio 0.4 to 0.5 [44]. However, the authors concluded that; the benefit of progesterone therapy in unexplained RPL require further studies , because of the small sample size , wide confidence intervals in most trials, and significant problems in the study designs [44].

A recently published double blind, randomized, placebo-controlled study on the effect of dydrogesterone on pregnancy outcome in women with a history of RPL, and its correlation with Th1 and Th2 cytokine levels concluded that dydrogesterone significantly reduces the miscarriage rates in women suffering from unexplained RPL ($p = 0.004$) when compared to a placebo, along with significantly improved age of gestation at delivery [25]. However these favourable outcomes were not related to changes in the Th1 and Th2 cytokine levels in the maternal plasma. In this study, 29.3% (12 of 41) miscarriages occurred in the first 4 weeks of recruitment. 24.1% [7 of 29] in the placebo group and 41.7% [5 of 12] in the dydrogesterone group, ($P > .05$). Therefore, the benefit of dydrogesterone was uncertain in women who aborted within 3-4 weeks of starting the drug therapy, in the study group.

Another multicenter, double-blind, placebo-controlled, randomized trial on vaginal micronized progesterone use in women with recurrent miscarriages (PROMISE trial) concluded that progesterone therapy in the first trimester of pregnancy did not result in a significantly higher rate of live births among women with a history of unexplained recurrent miscarriages.(65.8% (MVP) versus 63.3% (placebo) RR 1.04 (95% CI: 0.94, 1.15). Also no significant differences were observed between the treatment and placebo group in terms of: gestational age at delivery, clinical pregnancy (at 6-8 weeks), ongoing pregnancy (at 12 weeks), ectopic pregnancy, miscarriage rates, stillbirths and neonatal outcomes [45].

Study limitations and conflicting results on outcome from different trials on use of progesterone in miscarriage, led to a 2015 committee opinion by the American Society of Reproductive Medicine that - use of supplemental exogenous progesterone in a non-ART cycles beyond the time of expected menses (*i.e*., 2 weeks after ovulation) and after the confirmation of pregnancy is of no benefit [46].

SAFETY ISSUES WITH PROGESTERONE USE IN EARLY PREGNANCY.

Use of any drug or hormone during early weeks of pregnancy *i.e.* during embryogenesis and organo-genesis require caution and a need to consider the risk benefit ratio for its use. There has been concern regarding the use of progestins in pregnancy, with respect to the increased risk of genital and non-genital anomalies. All forms of progestins have been implicated to approximately double the background risk (0.5%) of hypospadias in the male fetus [47]. There are insufficient data on the risk to exposed female fetuses, but these drugs may induce mild virilisation in them. A recent study has described a threefold increase in the risk of congenital heart disease in infants of mothers exposed to the progestogen- dydrogesterone in the first trimester of pregnancy [48].

In contrast to the above studies specific analysis of progesterone and 17-hydroxy progesterone has not shown any significant teratogenic effects in large cohort and case-control studies, involving almost 17,695 women [49-52]. A meta-analysis of 14 studies, involving 65,567 women, likewise concluded that there was no association between first-trimester sex hormone exposure and external genital malformations [53]. Because of the pharmacological heterogeneity of the progestins, the FDA in 1999 revoked its single class labelling [54]. The Australian Drug Evaluation Committee has classified natural micronized progesterone as a Category A drug as there are no proven increase in the frequency of malformations or any other harmful effects on the fetus [54]. Progesterone has been used in several studies for the prevention of preterm birth with no safety issues and was approved in February 2011 for this indication by the FDA.

Concerns have been raised that due to the uterine-relaxant properties of progesterone, there may be a delay in spontaneous miscarriage in women with fertilised defective ova or chromosomal anomaly with continuation of the pregnancy. However the available evidence does not suggest that progesterone support a pregnancy with chromosomally abnormal fetus. In 38 trials (including 5,110 women) using progesterone or its analogues in early pregnancy for various indications, there was no increase in aneuploid neonates [55-57].

PROGESTERONE AND MATERNAL SIDE EFFECTS

There appears to be no safety concerns for use of progesterone in the mother. It may be associated with mild side effects like somnolence, dizziness, light headedness, gastrointestinal disturbances, nausea, vomiting, fluid retention and mastalgia. Injectable forms may be associated with pain, inflammation, rash and abscess formation at the local site. Rarely more serious complications may occur, such as jaundice, thrombosis and pulmonary embolism.

Contraindications for the use of progesterone include-

Liver tumours, breast or genital cancers, severe arterial disease, acute porphyria , history of pregnancy with cholestasis, severe pruritus or pemphigoid gestationalis.

CONCLUSION

10-15% of clinical pregnancies miscarry. In a vast majority the cause of miscarriage remain unknown. Progesterone is crucial for implantation, establishment and continuation of pregnancy. It has been suggested that a causative factor in many cases of miscarriage may be inadequate secretion of progesterone during the luteal phase of the menstrual cycle and in the early weeks of pregnancy. Progesterone and progestogen analogues have often been used, beginning in the first trimester of pregnancy, in an attempt to prevent spontaneous miscarriage.

In women presenting with a clinical diagnosis of threatened miscarriage, there is preliminary evidence of a reduction in the rate of spontaneous miscarriage with the use of progesterone. Larger RCTs may help to further validate these findings. Initial reports of favourable outcome with use of progesterone in RPL could not be confirmed uniformly by larger randomized trials. Study limitations and conflicting results from different trials, led to a 2015 committee opinion that use of supplemental exogenous progesterone in a non-ART cycle beyond the time of expected menses and after the confirmation of pregnancy is of no benefit.

REFERENCES

[1] Grudzinskas JG. Endocrinocolgical and metabolic assesssment of early pregnancy. Chamberlain G editor(s). Tumbull's obstetrics. London: Pearson Professional Ltd, 1995.

[2] Simpson JL. Fetal wastage. Gabe SG, Simpson JL editor(s). Ob-stetrics. Normal and problem pregnancies. New York: Churchill Livingstone 1991.

[3] Howie PG. Abortion and ectopic pregnancy. Whitfield CR editor(s). Dewhurst's textbook of obstetrics and gynaecology for postgraduates. Oxford: Blackwell Science Ltd 1995.

[4] Regan L, Braude PB, Trembath PR. Influences of past reproductive performance on risk of spontaneous abortion. BMJ 1989; 299: 541-5. http://dx.doi.org/10.1136/bmj.299.6698.541

[5] Tongsong T, Srisomboon J, Wanapirak C, Sirichotiyakul S *et al*. Pregnancy outcome of threatened abortion with demonstrable fetal cardiac activity: a cohort study- J Obstet Gynaecol 1995; 21: 331-5. http://dx.doi.org/10.1111/j.1447-0756.1995.tb01019.x

[6] Wyatt PR,OwolabiT,Meier C,HuangT.Age-specific risk of fetal loss observed in a second trimester serum screening population. Am J Obstet Gynecol 2005; 192: 240-6. http://dx.doi.org/10.1016/j.ajog.2004.06.099

[7] Stirrat GM. Recurrent miscarriage. Lancet 1990; 336: 673-5. http://dx.doi.org/10.1016/0140-6736(90)92159-F

[8] Burgoyne PS, Holland K, Stephens R. Incidence of numerical chromosome anomalies in human pregnancy estimation from induced and spontaneous abortion data. Human Reproduction 1991; 6(4): 555-65.

[9] Szabo I, Szilagyi A. Management of threatened abortion. Early Pregnancy 1996; 2(4): 233-40.

[10] Everett C. Incidence and outcome of bleeding before the 20th week of pregnancy: prospective study from general practice. BMJ 1997; 315: 32-4. http://dx.doi.org/10.1136/bmj.315.7099.32

[11] Woods JR, Esposito JL. Pregnancy Loss: Medical Therapeutics and Practical Considerations. Baltimore: Williams and Wilkins, 1987.

[12] Vance JC, Foster WJ, Najman JM, Embelton, Thearle MJ, Hogden FM. Early parental responses to sudden infant death, stillbirth or neonatal death. Medical Journal of Australia 1991; 155(5): 292-297.

[13] Paradisi R, Porcu E, Venturoli S, Maldini-Casadei M, Boni P. Maternal serum levels of pro-inflammatory cytokines in missedand threatened abortion. Am J Reprod. Immunol 2003; 50 (4): 302-308. http://dx.doi.org/10.1034/j.1600-0897.2003.00065.x

[14] Curry AE, Vogel I. Drews. Mid-pregnancy maternal plasma levels of interleukin 2, 6, and 12, tumor necrosis factor-alpha,interferon-gamma, and granulocyte-macrophage colony-stimulating factor and spontaneous preterm delivery. Acta Obstet Gynecol Scand 2007; 86 (9): 1103-1110 http://dx.doi.org/10.1080/00016340701515423

[15] Wilke C, Renz H, Tekesin I, Hellmeyer L, Herz U, Schmidt S. Suppression of IL-2 and IFNgamma production in women with spontaneouspreterm labor. J Perinat Med 2006; 34 (1): 20-27

[16] Yui J, Garcia-Lloret M, Wegmann TG, Guilbert LJ. Cytotoxicity oftumour necrosis factor-alpha and gamma-interferon against primary human placental trophoblasts. Placenta1994; 15: 819-835. http://dx.doi.org/10.1016/S0143-4004(05)80184-5

[17] Raghupathy R, Makhseed M, Azizieh F, Omu A, Gupta M, Farhat R. Cytokine production by maternal lymphocytes during normal human pregnancy and in unexplained recurrent spontaneous abortion. Hum Reprod 2000; 15: 713-8. http://dx.doi.org/10.1093/humrep/15.3.713

[18] Wu S, Zhang H, Tian J, Liu L, Dong Y, Mao T. Expression of kisspeptin/GPR54 and PIBF/PR in the first trimester trophoblast and decidua of women with recurrent spontaneous abortion. Pathol Res Pract 2014 Jan; 210(1): 47-54. http://dx.doi.org/10.1016/j.prp.2013.09.017

[19] Di Renzo GC, Mattei A, Gojnic M, Gerli S. Progesterone and pregnancy. Curr Opin Obstet Gynecol 2005; 17: 589-600. http://dx.doi.org/10.1097/01.gco.0000191899.84567.4d

[20] Chang K, Lubo Zhang. Review article: steroid hormones and uterine vascular adaptation to pregnancy. Reprod Sci 2008 Apr; 15(4): 336-48. http://dx.doi.org/10.1177/1933719108317975

[21] Simoncini T, Caruso A, Giretti MS, Scorticati C, Fu XD, Garibaldi S *et al*. Effects of dydrogesterone and of its stable metabolite, 20-a-dihydrogesterone on nitric oxide synthesis in human endothelial cells Fertil Steril 2006; 86(3): 1235-1242. http://dx.doi.org/10.1016/j.fertnstert.2006.05.018

[22] Raghupathy R, Al Mutawa E, Makhseed M, Azizieh F, Szekeres-Bartho J. Modulation of cytokine production by dydrogesterone in lymphocytes from women with recurrent miscarriage BJOG 2005; 112(8): 1096-1101. http://dx.doi.org/10.1111/j.1471-0528.2005.00633.x

[23] Shohreh Alimohamadia, Pouya Javadianb, Mohammad Hadi Gharedaghic, Nima Javadianb, Hossein Alinia b, Soghra Khazardoustd, Sedigheh Bornad, Sedigheh Hantoushzadehb, Progesterone and threatened abortion: a randomized clinical trial on endocervical cytokine concentrations Journal of Reproductive Immunology 2013 98 : 52-60. http://dx.doi.org/10.1016/j.jri.2013.01.004

[24] Kalinka J, Radwan M. The impact of dydrogesterone supplementation on serum cytokine profile in women with threatened abortion. Am. J Reprod Immunol 2006; 55 (2): 115-121. http://dx.doi.org/10.1111/j.1600-0897.2005.00333.x

[25] Ashok Kumar, Nargis Begum, Sudha Prasad, Sarita Aggarwal, Shashi Sharma, Oral dydrogesterone treatment during early pregnancy to prevent recurrent pregnancy loss and its role in modulation of cytokine production: a double-blind, randomized, parallel, placebo-controlled trial Fertility and Sterility® November 2014 Vol. 102, No. 5: 0015-0282

[26] Lede R, Duley L. Uterine muscle relaxant drugs for threatened miscarriage. Cochrane Database of Systematic Reviews 2005, Issue 3.

[27] Everett CB, Preece E. Women with bleeding in the first 20 weeks of pregnancy: value of general practice ultrasound in detecting fetal heart movement. Br J Gen Pract 1996: 46: 7-9

[28] Alexandros Sotiriadis, Stefania Papatheodorou, George Makrydimas, Threatened miscarriage: evaluation and management BMJ 2004; 329 (7458): 152-156. doi: http: //dx.doi.org/10.1136/bmj.329.7458.152 (Published 15 July 2004).

[29] Wahabi HA, Fayed AA, Esmaeil SA, Al Zeidan RA. Progestogen for treating threatened miscarriage. Cochrane Database Syst Rev. 2011(12): CD005943. http://dx.doi.org/10.1002/14651858.cd005943.pub3

[30] Progesterone support of the luteal phase and in the first trimester. Royal Australian and New Zealand College of Obstetricians and Gynaecologists First endorsed by RANZCOG: November 2009 Current: July 2013 Review due: July 2016

[31] Carp H. A systematic review of dydrogesterone for the treatment of threatened miscarriage. Gynecol Endocrinol 2012; 28: 983-90.) http://dx.doi.org/10.3109/09513590.2012.702875

[32] Arri Coomarasamy Hoda Harb ISRCTN: TBC Eudra CT: 2014-002348-42 PRISM Protocol Version 1.0 (11th September 2014.

[33] Ehrenskjold ML, Bondo B, Weile F. [Treatment of threatened abortion with dydrogesterone]. Ugeskrift for laeger 1967; 129(50): 1678-9.

[34] El-Zibdeh MY, Yousef LT. Dydrogesterone support in threatened miscarriage. Maturitas 2009; 65 Suppl 1: S43-6. http://dx.doi.org/10.1016/j.maturitas.2009.11.013

[35] Gerhard I, Gwinner B, Eggert-Kruse W, Runnebaum B. Double-blind controlled trial of progesterone substitution in threatened abortion. Biological research in pregnancy and perinatology 1987; 8(1 1ST Half): 26-34.

[36] Misto A. [Experiences with 6-dehydro-retroprogesterone int the treatment of placental insufficiency]. Annali di ostetricia, ginecologia, medicina perinatale 1967; 89(2): 102-12.

[37] Omar MH, Mashita MK, Lim PS, Jamil MA. Dydrogesterone in threatened abortion: pregnancy outcome. The Journal of steroid biochemistry and molecular biology 2005; 97(5): 421-5. http://dx.doi.org/10.1016/j.jsbmb.2005.08.013

[38] Palagiano A, Bulletti C, Pace MC, D DEZ, Cicinelli E, Izzo A. Effects of vaginal progesterone on pain and uterine contractility in patients with threatened abortion before twelve weeks of pregnancy. Annals of the New York Academy of Sciences 2004; 1034: 200-10. http://dx.doi.org/10.1196/annals.1335.022

[39] Pandian RU. Dydrogesterone in threatened miscarriage: a Malaysian experience. Maturitas 2009; 65 Suppl 1: S47-50.) http://dx.doi.org/10.1016/j.maturitas.2009.11.016

[40] Togas Tulandi, Haya M Al-Fozan, Management of couples with recurrent pregnancy loss www.uptodate.com ©2015 UpToDate).

[41] Harger JH, Archer DF, Marchese SG, *et al*. Etiology of recurrent pregnancy losses and outcome of subsequent pregnancies. Obstet Gynecol 1983; 62: 574.

[42] Bricker L, Farquharson RG. Types of pregnancy loss in recurrent miscarriage: implications for research and clinical practice. Hum Reprod 2002; 17: 1345. http://dx.doi.org/10.1093/humrep/17.5.1345

[43] Whitley KA, Ural SH. Treatment modalities in recurrent miscarriages without diagnosis. Semin Reprod Med 2014; 32: 319) http://dx.doi.org/10.1055/s-0034-1375185

[44] Haas DM, Ramsey PS. Progestogen for preventing miscarriage. Cochrane Database of Systematic Reviews 2013, Issue 10. Art. No.: CD003511. http://dx.doi.org/10.1002/14651858.CD003511.pub3

[45] Coomarasamy A, Williams H, Truchanowicz E, Seed PT, Small R, Quenby S *et al*. A Randomized Trial of Progesterone in Women with Recurrent Miscarriages, N Engl J Med 2015; 373: 2141-8. http://dx.doi.org/10.1056/NEJMoa1504927

[46] Current clinical irrelevance of lutealphase deficiency: a committee opinion Practice Committee of the American Society for Reproductive Medicine American Society for Reproductive Medicine, Birmingham, Alabama Fertility and Sterility® 2015; 103(4): 0015-0282 Copyright ©2015 American Society for Reproductive Medicine.

[47] Carmichael SL, Shaw GM, Laurent C, Croughan MS, Olney RS, Lammer EJ. Maternal progestin intake and risk of hypospadias. Archives of pediatrics & adolescent medicine 2005; 159(10): 957-62. http://dx.doi.org/10.1001/archpedi.159.10.957

[48] Zaquot M, Emad Aslem, Mazen Abu qamal, Osma Abughazza, Joseph Panzer, Daniel De Wolf. The impact of oral intake of dydrogesterone on fetal heart development during early pregnancy. Pediatric Cardiology 2015; 36(7): 1483-8. http://dx.doi.org/10.1007/s00246-015-1190-9

[49] Michaelis J, Michaelis H, Gluck E, Koller S. Prospective study of suspected associations between certain drugs administered during early pregnancy and congenital malformations. Teratology. 1983; 27(1): 57-64. http://dx.doi.org/10.1002/tera.1420270109

[50] Duan L, Yan D, Zeng W, Yang X, Wei Q. Effect of progesterone treatment due to threatened abortion in early pregnancy for obstetric and perinatal outcomes. Early Hum Dev 2010; 86(1): 41-3. http://dx.doi.org/10.1016/j.earlhumdev.2009.12.007

[51] Katz Z, Lancet M, Skornik J, Chemke J, Mogilner BM, Klinberg M. Teratogenicity of progestogens given during the first trimester of pregnancy. Obstet Gynecol 1985; 65(6): 775-80. http://dx.doi.org/10.1097/00006254-198511000-00016

[52] Resseguie LJ, Hick JF, Bruen JA, Noller KL, O'Fallon WM, Kurland LT. Congenital malformations among offspring exposed in utero to progestins, Olmsted County Minnesota 1936-1974. Fertil Steril. 1985 Apr; 43(4): 514-9. http://dx.doi.org/10.1016/S0015-0282(16)48490-6

[53] Raman-Wilms L, Tseng AL, Wighardt S, Einarson TR, Koren GF *et al*. genital effects of first-trimester sex hormone exposure: a meta-analysis. Obstet Gynecol. 1995 Jan; 85(1): 141-9). Brent RL. Nongenital malformations following exposure to progestational drugs: the last chapter of an erroneous allegation. Birth Defects Res A Clin Mol Teratol 2005; 73(11): 906-18. http://dx.doi.org/10.1002/bdra.20184

[54] AMH. Australian Medicines Handbook 2010.

[55] Haas DM, Ramsey PS. Progestogen for preventing miscarriage. The Cochrane database of systematic reviews 2008; (2): CD003511. http://dx.doi.org/10.1002/14651858.cd003511.pub2

[56] Van der Linden M, Buckingham K, Farquhar C, Kremer JA, Metwally M. Luteal phase support for assisted reproduction cycles. The Cochrane database of systematic reviews 2011; (10): CD009154. http://dx.doi.org/10.1002/14651858.cd009154

[57] Dodd JM, Jones L, Flenady V, Cincotta R, Crowther CA. Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth. The Cochrane database of systematic reviews 2013; 7: CD004947. http://dx.doi.org/10.1002/14651858.cd004947.pub3

Received on 25-06-2016 Accepted on 14-07-2016 Published on 29-07-2016

http://dx.doi.org/10.15379/2408-9761.2016.03.02.02