Chapter 9

USE OF PROGESTERONE AND ITS CLINICAL EFFECTS IN EARLY PREGNANCY

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INTRODUCTION

Progesterone (PG) is a hormone that plays a highly important role in the development and maintenance of pregnancy in addition to its essential role in the menstrual cycle [1]. It is necessarily required to achieve sufficient decidualization in early pregnancy and in the implantation stage [2]. Moreover, PG can also be defined as an immunoregulator that prevents rejection of the fetus by controlling the maternal and fetal immune responses [3]. PG, with the aforementioned roles, is one of the leading hormones that are essential for the healthy establishment and maintenance of pregnancy.

BACKGROUND

PG was first isolated from the corpus luteum (CL) in 1929 by Corner and Allen, who underlined the importance thereof in pregnancy [4]. Later on, Wenning and Browne demonstrated that the placenta exhibited PG synthesis [5]. In another study, Van Wagenen showed that PG had placental and/or maternal origin. In 1945 maternal cholesterol was a substrate of placental PG by demonstrating the presence of deuterium-labeled pregnanediol in the urine of pregnant women who were given deuterium-labeled cholesterol [6]. In the light of these studies, it was acknowledged that PG has extremely important functions in the pregnancy process.

EFFECTS OF PROGESTERONE IN PREGNANCY

PG has an integral role in every stage of pregnancy. It is referred to as the "pregnancy hormone" by many people. It is a steroid hormone secreted by the CL, especially between gestational weeks 7 and 9, after which the placenta starts PG synthesis as a result of the increase in placental weight. CL takes part in PG synthesis until week 10, and placenta takes over the entire PG synthesis as of

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pregnancy in pregnant women with a short cervix [31, 32]. Considering all these, use of PG due to a number of different conditions that lead to preterm labor is still debated and studied in the literature.

ROUTES OF PROGESTERONE ADMINISTRATION

PG preparations are administered through three main routes, i.e. oral, vaginal and intramuscular. Different preparations are preferred depending on the route of administration and side effects may vary, based on the same.

Oral route: Natural micronized progesterone is administered orally. The mean daily dose is 200-400 mg, which may be increased up to 600 mg when necessary. Side effects such as drowsiness, headache and nausea have been identified [33].

Vaginal route: Natural progesterone and micronized progesterone are mainly administered through the vaginal route. The vaginal route is more commonly preferred compared to the oral route due to high bioavailability and fewer side effects. However, vaginal irritation can be observed as a side effect of vaginal administration. Vaginally administered PG has two forms, i.e. vaginal tablets and vaginal gel. Studies have shown that such administration of PG is safe in the first trimester [34, 35].

Intramuscular administration: hydroxyprogesterone caproate is an intramuscularly administered preparation of PG. It can be administered in doses ranging from 250 mg twice a week to 500 mg three times a week. Side effects include injection site reactions due to the route of administration. There are numerous studies on the safety of intramuscular PG administration in pregnancy [34, 36, 37].

CONCLUSION

PG has many roles in various important stages of pregnancy. Today, PG is used in high-risk patients by many physicians and clinics, since numerous studies have shown that PG therapy or supplementation has no significant side effects in pregnancy and a better treatment procedure is yet to be developed. However, PG is best used in suitable patient profiles, considering the benefit-risk balance, since such an intervention is not utilized as a standard procedure.

REFERENCES

1. Piette, P.C.M., *The pharmacodynamics and safety of progesterone.* Best Pract Res Clin Obstet Gynaecol, 2020. **69**: p. 13-29.
2. Wahabi, H.A., et al., *Progestogen for treating threatened miscarriage.* Cochrane Database Syst Rev, 2018. **8**: p. CD005943.

3. Schindler, A.E., *Progestogens for treatment and prevention of pregnancy disorders.* Horm Mol Biol Clin Investig, 2010. **3**(3): p. 453-60.
4. Allen, W.M., *The Chemical and Physiological Properties, and Clinical Uses of the Corpus Luteum Hormone, Progesterone.* Bull N Y Acad Med, 1941. **17**(7): p. 508-18.
5. Browne, J.C., *Placental Insufficiency.* Scott Med J, 1963. **8**: p. 459-65.
6. Hellig, H., et al., *Steroid production from plasma cholesterol. I. Conversion of plasma cholesterol to placental progesterone in humans.* J Clin Endocrinol Metab, 1970. **30**(5): p. 624-31.
7. Peyron, R., et al., *Early termination of pregnancy with mifepristone (RU 486) and the orally active prostaglandin misoprostol.* N Engl J Med, 1993. **328**(21): p. 1509-13.
8. Pritts, E.A. and A.K. Atwood, *Luteal phase support in infertility treatment: a meta-analysis of the randomized trials.* Hum Reprod, 2002. **17**(9): p. 2287-99.
9. Cicinelli, E., et al., *Direct transport of progesterone from vagina to uterus.* Obstet Gynecol, 2000. **95**(3): p. 403-6.
10. Potdar, N. and J.C. Konje, *The endocrinological basis of recurrent miscarriages.* Curr Opin Obstet Gynecol, 2005. **17**(4): p. 424-8.
11. Duan, L., et al., *Effect of progesterone treatment due to threatened abortion in early pregnancy for obstetric and perinatal outcomes.* Early Hum Dev, 2010. **86**(1): p. 41-3.
12. Norwitz, E.R., J.N. Robinson, and J.R. Challis, *The control of labor.* N Engl J Med, 1999. **341**(9): p. 660-6.
13. Lockwood, C.J., et al., *Human labor is associated with reduced decidual cell expression of progesterone, but not glucocorticoid, receptors.* J Clin Endocrinol Metab, 2010. **95**(5): p. 2271-5.
14. Lim, C.E., et al., *Combined oestrogen and progesterone for preventing miscarriage.* Cochrane Database Syst Rev, 2013(9): p. CD009278.
15. Walch, K.T. and J.C. Huber, *Progesterone for recurrent miscarriage: truth and deceptions.* Best Pract Res Clin Obstet Gynaecol, 2008. **22**(2): p. 375-89.
16. Luo, G., et al., *Progesterone inhibits basal and TNF-alpha-induced apoptosis in fetal membranes: a novel mechanism to explain progesterone-mediated prevention of preterm birth.* Reprod Sci, 2010. **17**(6): p. 532-9.
17. El-mashad, A.I., et al., *Role of uterine artery Doppler velocimetry indices and plasma adrenomedullin level in women with unexplained recurrent pregnancy loss.* J Obstet Gynaecol Res, 2011. **37**(1): p. 51-7.
18. Osol, G. and M. Mandala, *Maternal uterine vascular remodeling during pregnancy.* Physiology (Bethesda), 2009. **24**: p. 58-71.
19. Norman, J.E. and I.T. Cameron, *Nitric oxide in the human uterus.* Rev Reprod, 1996. **1**(1): p. 61-8.
20. Maul, H., et al., *Nitric oxide and its role during pregnancy: from ovulation to delivery.* Curr Pharm Des, 2003. **9**(5): p. 359-80.
21. Czajkowski, K., et al., *Uteroplacental circulation in early pregnancy complicated by threatened abortion supplemented with vaginal micronized progesterone or oral dydrogesterone.* Fertil Steril, 2007. **87**(3): p. 613-8.
22. Ghosh, S., et al., *Assessment of sub-endometrial blood flow parameters following dydrogesterone and micronized vaginal progesterone administration in women with idiopathic recurrent miscarriage: a pilot study.* J Obstet Gynaecol Res, 2014. **40**(7): p. 1871-6.
23. Schindler, A.E., *Immunology and progestins in pregnancy.* Gynecol Endocrinol, 1999. **13 Suppl 4**: p. 47-50.

24. Choi, B.C., et al., *Progesterone inhibits in-vitro embryotoxic Th1 cytokine production to trophoblast in women with recurrent pregnancy loss.* Hum Reprod, 2000. **15 Suppl 1**: p. 46-59.
25. Piccinni, M.P., et al., *Progesterone favors the development of human T helper cells producing Th2-type cytokines and promotes both IL-4 production and membrane CD30 expression in established Th1 cell clones.* J Immunol, 1995. **155**(1): p. 128-33.
26. Basak, S., et al., *Expression of pro-inflammatory cytokines in mouse blastocysts during implantation: modulation by steroid hormones.* Am J Reprod Immunol, 2002. **47**(1): p. 2-11.
27. Dong, Y.L., et al., *Regulation of inducible nitric oxide synthase messenger ribonucleic acid expression in pregnant rat uterus.* Biol Reprod, 1998. **59**(4): p. 933-40.
28. van der Linden, M., et al., *Luteal phase support for assisted reproduction cycles.* Cochrane Database Syst Rev, 2015(7): p. CD009154.
29. Daya, S., *Issues in the etiology of recurrent spontaneous abortion.* Curr Opin Obstet Gynecol, 1994. **6**(2): p. 153-9.
30. Stray-Pedersen, B. and S. Stray-Pedersen, *Etiologic factors and subsequent reproductive performance in 195 couples with a prior history of habitual abortion.* Am J Obstet Gynecol, 1984. **148**(2): p. 140-6.
31. Stephenson, M.D., K.A. Awartani, and W.P. Robinson, *Cytogenetic analysis of miscarriages from couples with recurrent miscarriage: a case-control study.* Hum Reprod, 2002. **17**(2): p. 446-51.
32. Raghupathy, R., *Th1-type immunity is incompatible with successful pregnancy.* Immunol Today, 1997. **18**(10): p. 478-82.
33. Thornton, J.G., *Progesterone and preterm labor--still no definite answers.* N Engl J Med, 2007. **357**(5): p. 499-501.
34. O'Brien, J.M., et al., *Progesterone vaginal gel for the reduction of recurrent preterm birth: primary results from a randomized, double-blind, placebo-controlled trial.* Ultrasound Obstet Gynecol, 2007. **30**(5): p. 687-96.
35. Fonseca, E.B., et al., *Progesterone and the risk of preterm birth among women with a short cervix.* N Engl J Med, 2007. **357**(5): p. 462-9.
36. da Fonseca, E.B., et al., *Prophylactic administration of progesterone by vaginal suppository to reduce the incidence of spontaneous preterm birth in women at increased risk: a randomized placebo-controlled double-blind study.* Am J Obstet Gynecol, 2003. **188**(2): p. 419-24.
37. Meis, P.J., et al., *Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate.* N Engl J Med, 2003. **348**(24): p. 2379-85.