COMPARISON OF ORAL DYDROGESTERONE AND INTRAMUSCULAR PROGESTERONE IN THE TREATMENT OF THREATENED ABORTION

QING G., HONG Y., FENG X. AND WEI R.
Northwest Women's Hospital, Xian City, Shanxi Province, China

ABSTRACT

Background and Objective: Threatened abortion is a common condition and presents with varied clinical manifestations. The aim of the study was to observe and analyze the efficacy and safety of dydrogesterone in threatened abortion.

Methods: One hundred and seventy two pregnant women with early – threatened abortion diagnosed during prenatal care in Northwest Women's Hospital from January 2012 to December 2013, were selected and randomly divided into dydrogesterone group and the progesterone group. Patients received either oral dydrogesterone or progesterone injected intramuscularly, respectively. The clinical efficacy and safety of both drugs were observed.

Results: There were no significant differences in age, gravidity, parity and gestational age between the two groups (p> 0.05) and there was no significant difference in progesterone levels following treatment (p > 0.05). There were no significant differences in the success rate of fetus protection, abortion rate and treatment time between the groups (p > 0.05).

Conclusion: Dydrogesterone and progesterone have significant beneficial effects in the treatment of threatened abortion, and they are easy to use and safe.

Keywords: Threatened abortion; Dydrogestrone; Progesterone injection.

INTRODUCTION

Threatened abortion is a common condition, and the clinical manifestations are as follows: vaginal bleeding, with or without lower abdominal pain, non-dilatation of cervix, it is likely to develop into complete abortion or incomplete abortion, in particular during the first three months of pregnancy.[1,2] There are a several causes for the threatened abortion, about 20% of threatened abortions are caused by endocrine factors and the rest include chromosomal, genetic, anatomical, immunological, hormonal, infectious and psychological factors.[2] Socio economic and cultural changes have led to changes in eating habits, environment pollution and increase in work and life pressures in the women. The incidence of threatened abortions is increasing year by year. In addition to a small number of genetic and immune factors, maternal endocrine diseases are the common cause in most cases. Low serum progesterone levels may be the leading cause of threatened abortion and progesterone supplements are the conventional treatment for threatened abortion. Luteal phase defect may lead to inadequate endogenous progesterone, which is not conducive to the embryo transfer and the maintenance of pregnancy.[3] Studies have shown that progesterone can promote muscle protein synthesis in utero, improve sensitivity to prostaglandin and estrogen and has a significant role in the prevention of early contractions of the myometrium.[4] It plays a key role in inducing a protective immunomodulatory effect on the embryo. The intramuscular progesterone has a confirmed curative effect, and has been the preferred method for the treatment of threatened abortion. After more than a decade of use across the globe, there has been no report on fetal abnormalities caused by progesterone.[5] Intramuscular HCG and progesterone can sometimes cause severe allergic reactions in patients[6] and their long-term use may easily lead to local reactions such as pain, swelling and in duration at the injection site and the application is painful with poor patient compliance. Dydrogestrone is a highly active oral progestin and has been in use for over twenty years in other countries, and it has been in use in China in the past 10 years. It is synthesized through UV irradiation of dioscin, which is extracted from Chinese yams or soybeans. Its structure is similar to that of the endogenous progesterone and its crooked molecular structure iscompared with the molecular structure of the natural progesterone. In addition to the double bond between 4 – position and 5 – position carbon atoms, a double bond is created between 6 – position and 7 – position carbon atoms. The hydrogen atoms and the methyl group on 9 – position and 10 – position carbon atoms

Corresponding Author: Yuejian Hong
Address: No. 1616, Yanxiang Road, Xian City 710061, China
Tel: +86-029-89550272. Fax: +86-029-89550272. Email: yuejianhong889@163.com

are reversed in comparison to natural progesterone, so that its molecular structure can be transformed from two – dimensional structure into three – dimensional structure. Therefore, it has high selectivity to the progesterone receptor and a high biological activity, and it is easily absorbed with a small hepatic workload. This high selectivity also helps in avoiding the side effects caused by its binding with other hormone receptors. Its metabolite DHD (20-α-dihydrogesterone) has progestin like activity, no aromatization (i.e. no estrogene like effect) and no 17α-hydroxylation (i.e. no androgenic effect), and does not cause masculinization of the female fetus.

In addition to that the dydrogesterone can play the role of supplementing progesterone in the treatment of threatened abortion and fetal protection. Dydrogesterone also has the following effects:

1. It has an induction effect on progesterone-induced blocking factor (PIBF, a protective factor) and is a characteristic of normal pregnancy.[7]
2. The response is greater than Th1 response during normal pregnancy, while Th1 response is predominant in women with threatened abortion. Dydrogestrone can produce non-inflammatory T2 cytokines,[8] can effectively reduce maternal rejection of the embryo and play a role in embryo protection.[9]
3. Nitric oxide can improve uterine blood flow and oxygen supply and is conducive to the growth of the fetus. Dydrogesterone metabolite (20-α-dihydrogesterone) and progesterone can activate human endothelial nitric oxide synthase (eNOS) and enhance the role of nitric oxide synthase.[10]

The most common treatment for threatened abortion include: progesterone injection; oral sustained release preparation: dydrogesterone, micronized progesterone capsules, suppositories: progesterone gel, progesterone soft capsules and progesterone vaginal ring. Intramuscular progesterone provides optimal blood levels but can induce abscesses formation and is extremely painful. Of the oral progestagens, progesterone itself has variable plasma concentrations,[11] and side effects including such as nausea, headache, and sleepiness. The drugs produce different effects due to their different structures, while the drugs of same structure with different dosage will also produce different effects. Dydrogestrone is an oral preparation used in Northwest Women's Hospital, and it has a first pass effect. Dydrogesterone has a good safety and tolerability profile. It is structurally and pharmacologically similar to natural progesterone has good oral bioavailability and few side effects. Dydrogesterone has no androgenic effects on the fetus, and does not inhibit the formation of progesterone in the placenta.[12] The commonly used progesterone injection can maintain the function of corpus luteum, to treat threatened abortion, and it's therapeutic effect has been confirmed.[13] In this study, a comparison of efficacies of oral dydrogesterone and injectable progesterone, used at our hospital between January 2012 and December 2013, was carried out in the treatment of threatened abortion.

MATERIALS AND METHODS

General Information:172 pregnant women with early threatened abortion diagnosed during prenatal care at our hospital from January 2012 to December 2013, were selected, and the study subjects met the following conditions: menstruation stopped for less than 12 weeks, a small amount of vaginal bleeding, no tissues were excreted, B-ultrasound showed a visible gestational sac within uterus and the size was consistent with the gestational age; the pregnant women had no known pathologies, and didn't receive any medications during the pregnancy. The patients were randomly distributed into two groups, one that received oral dydrogesterone and another that received intramuscular progesterone.

Methods: The patients in the dydrogesterone (Figure 1A) group were given dydrogesterone 40 mg, orally as an initial dose, followed by dydrogesterone 10 mg every 12 hours. The patients in the progesterone (Figure 1B) group were injected with progesterone 20 mg, once a day intramuscularly. The drug was continued until the vaginal bleeding stopped, and then the drug was administrated for 1 week at a reduced dose (Use Medicine after vaginal bleeding stopped and discretionary reduced the medicince usage of one week according to the value of progesterone test). The progesterone levels were measured in patients before treatment and at 2 weeks after treatment, and the relevant data were recorded for comparison.

Observational Indices: Progesterone level, ongoing pregnancy rate, abortion and treatment time were compared between two groups of patients.

Curative Effect Evaluation Standard: Following treatment, if the vaginal bleeding disappeared, the abdominal pains was relieved, B ultrasonic examination showed that the embryo survived, and the symptoms didn't reappear within a month, it would be considered as an effective treatment. If the women continued their pregnancy uneventfully, it would be considered that the fetus was successfully protected. Following drug administration, if the signs and symptoms did not disappear, B ultrasonic examination showed no visible fetal bud, and the fetal heart beat disappeared, it would be considered as an invalid treatment.

Statistical Methods: The data were recorded using EpiData software and SPSS 18.0 statistical software was used for statistical analysis. The data are expressed as mean ± standard deviation ($\bar{x}\pm s$). T-test was used and the data were compared using x^2 test, test level $\alpha = 0.05$, $p < 0.05$ was considered statistically significant.

RESULTS

Basic data obtained from the patients: Both groups of patients were compared in age, gravidity, parity, gestational age and clinical symptoms, the differences were not statistically significant ($p > 0.05$), and the samples were comparable (Table 1).

Progesterone Levels: Through analysis and comparison of two groups of patients following treatment, it was found that the progesterone levels in both groups were higher than those before treatment and the difference was statistically significant ($p < 0\ 05.$), however, there was no significant difference between the two groups ($p > 0.\ 05$) (Table 2).

Comparison of Drug Efficacy: There was no significant difference in the treatment time between the two groups ($t = 1.267$, $p > 0.05$). The success rate of fetus protection in the dydrogesterone group was slightly higher than that in the progesterone group, but there was no significant difference ($x^2 = 0.385$, $p > 0.05$) (see Table 3).

Adverse Reactions: The patients in the dydrogesterone group had no significant adverse reactions after taking oral dydrogestrone and 2 patients felt a slight abdominal discomfort. 8 patients in the progesterone group had injection site pain, of whom 6 developed an induration, which was alleviated bylocal hot compress and the patients continued to receive treatment. The routine examinations such as hepatorenal function and blood urine showed no major abnormalities in both groups of patients.

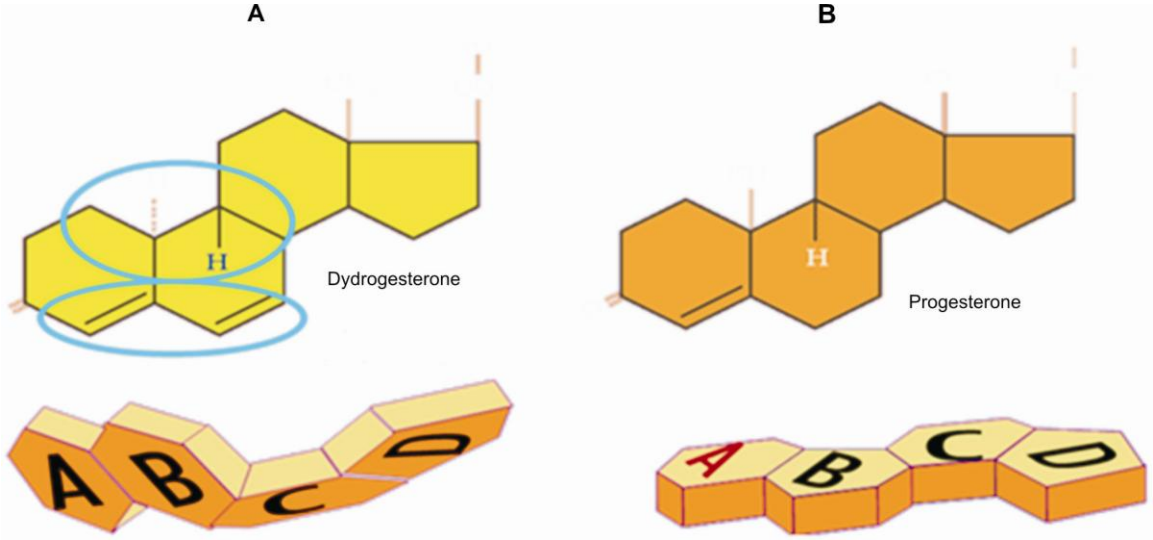

Figure 1: *Schematic showing the structures of (A) Dydrogesterone and (B) Progesterone.*

Table 1: *Comparison of clinical information between two groups of patients ($\bar{x}\pm s$).*

Group	Cases	Age (Year)	Gravidity (Times)	Parity (Times)	Gestational Age (d)	Clinical Symptoms	
						Vaginal Bleeding	Vaginal Bleeding with Abdominal Pain and Low Back Pain
Dydrogesterone	86	26.3 ± 4.6	26.6 ± 4.0	1.1 ± 0.45	54.4 ± 13.5	47 (54.65)	39 (45.35
Progesterone	86	27.7 ± 4.2	27.7 ± 4.2	1.1 ± 0.48	55.6 ± 13.8	45 (52.33)	41 (47.67)

Table 2: *Comparison of progesterone level between two groups of patients (x±s, mmol/L).*

Group	*Cases (n)*	*Before Treatment*	*After Treatment*
Dydrogesterone	86	58.4 ± 19.9	74.5 ± 19.1
Progesterone	86	57.8 ± 21.1	73.8 ± 18.6

DISCUSSION

Threatened abortion is the most common complication, occurring in 20% of all pregnancies. The condition may progress to miscarriage in approximately one – half of cases or may resolve.[14] Moreover, there is an increased risk of subsequent pregnancy

complications, such as pre-term labor or pre-eclampsia, and low birth weight after a threatened miscarriage.[14] There are several factors that contribute to an increased risk include mothers with systemic diseases (such as diabetes or thyroid dysfunction).[15] mothers who have been treated for infertility[16] mothers or fathers with genetic defects[17] and advancing paternal, as well as maternal, age.[18] There are numerous options available to treat threatened abortion including treatment with progesterone or human chorionic gonadotropin.

Table 3: *Comparison of clinical efficacies between two groups of patients.*

Group	*Cases (n)*	*Success Rate of Fetus Protection [Case (%)]*	*Abortion Rate [Case (%)]*	*Treatment Time (d)*
Dydrogesterone	86	76 (88.4)	10 (11.6)	7.2 ± 3.5
Progesterone	86	73 (84.9)	13 (15.1)	8.0 ± 3.2

Several studies have demonstrated that treatment with dydrogesterone has led to a reduction in pregnancy loss in women with threatened abortion. In short, dydrogesterone can modulate the immune status of the mother, and reduce rejection of the embryo.[19] Omar et al., demonstrated that pregnancy success rate, in terms of viable pregnancies at 20 weeks, was 95.9% in the women who were treated with dydrogesterone compared to 86.3% in women who was treated conservatively.[20] A study on women who presented with subchorionic hemorrhage who were treated with oral dydrogesterone 40 mg/day showed a 37% reduction in abortion rate.[21] A study by Kalinka, et al, to evaluate the role of oral dydrogesterone on threatened abortion showed that there was a significant increase in PBIF levels in women treated with dydrogesterone, thereby increasing pregnancy success rates.[22] A double – blind study of 54 women reported a miscarriage rate of 8.3% with dydrogesterone (30 mg/day for 6 weeks) compared with 14.0% with vaginal micronised progesterone (300 mg/day for 6 weeks).[23] Dydrogesterone was also found to reduce the rate of miscarriage compared with standard care alone in women suffering from recurrent miscarriage.[24]

In our study of 172 patients with threatened abortion were selected in this study and randomly distributed into two groups. After both groups of patients were treated with dydrogesterone tablets and injectable progesterone, the success rates of fetal protection were 88.4% and 84.9%, respectively. Although the dydrogesterone tablet had first pass effect, and there was no significant difference in efficacy between two groups ($p > 0.05$), the success rates of fetal protection in the dydrogestrone group was slightly higher. The dydrogesterone tablets are convenient to take with fewer adverse reactions. This helps to improve patient compliance in the long term treatment of threatened abortion. A review of maternal use of dydrogesterone during pregnancy also found no evidence for an increased risk of congenital malformations.[25]

In this study, some patients experienced adverse reactions, such as edema, headache, itching and so on, but usually disappeared slowly.

It is therefore ***concluded*** that dydrogesterone can effectively reduce the incidence of threatened abortion. It has no significant difference in efficacy compared to injectable progesterone. Its unique structure provides multiple modes of action in protecting the fetus. It is also convenient to take orally, with good tolerability and compliance and no significant adverse drug reactions. Therefore, dydrogesterone could play a significant role as a therapeutic option in patients with threatened abortion.

ACKNOWLEDGMENTS
This paper does not have any grant support.

Author's Contribution
G. Q. and Y. H. collected and analysed the data, X. F. and R. W. prepared and wrote the manuscript.

REFERENCES

1. Basama FM and Crosfill F. The outcome of pregnancies in 182 women with threatened miscarriage. Arch. Gynecol. Obstet., 2004; 270: 86-90.
2. Sotiriadis A, Papatheodorou S, Makrydimas G. Threatened miscarriage: evaluation and management. BMJ. 2004; 329: 152-5.
3. Pabuccu R, Akar ME. Luteal phase support in assisted reproductive technology [J]. Curr. in. Ogster. Gynecol., 2005; 17: 277-81.
4. Chakravarty BN, Shirazee HH, Pam P. Oral hydrogesterone versus intravaginal micronized progesterone as luteal phase support in assisted reproductive technology (ART) cycles: results of a randomized study [J]. J. Stero. D. Biochem. Mol. Biol., 2005; 97: 416-20.
5. Szekeres – Bartho J, Balasch J. Progestagen therapy for recurrent miscarriage [J]. Hum. Reprod. up. Date, 2008; 14: 27-35.
6. Tavaniotou A, Smitz J, Bourgain C, Devroey P. Comparison between different routes of progesterone administrations as luteal phase support in infertility treatments [J]. Hum. Reprod. Update, 2000; 6: 139.
7. Polgár B, Nagy E, Mikó E, Varga P, Szekeres-Barthó J. Urinary progesterone – induced blocking factor concentration is related to pregnancy outcome. Biol. Reprod., 2004; 71: 1699-705.
8. Druckmann MA. Progesterone and the immunology of pregnancy [J] J. Steroid. Biochem. Mol. Biol., 2005; 97: 389-96.
9. Wahabi HA, Fayed AA, Esmaeil SA, Zeidan RAA. Progestogen for treating threatened miscarriage [DB]. Co-

chrane. Database. Syst. Rev., 2011; 12: CD005943.
10. Simoncini T, Caruso A, Giretti MS, Scorticati C, Fu XD, Garibaldi S, et al. Effects of dydrogesterone and its stable metabolite, 20-alpha-dihydrodydrogesterone, on nitric oxide synthesis in human endothelial cells. Fertil. Steril., 2006; 86 (4 Suppl.): 01235-1242.
11. Di Renzo GC, Mattei A, Gojnic M, Gerli S. Progesterone and pregnancy. Curr. Opin. Obstet. Gynecol., 2005; 17: 598-600.
12. Schindler AE, Campagnoli C, Druckmann R, Huber J, Pasqualini JR, Schweppe KW, Thijssen JH. Classification and pharmacology of progestins. Maturitas. 2003 Dec 10; 46 Suppl. 1(): S7-S16.
13. Bouchard P, Chabbert –Buffet N, Fauser BC. Selective progesterone receptor modulators in reproductive medicine: pharmacology, clinical efficacy and safety. [J]. Fertil. Steril., 2011; 96: 1175-89.
14. Weiss JL, Malone FD, Vidaver J, Ball RH, Nyberg DA, Comstock CH, et al. Threatened abortion: A risk factor for poor pregnancy outcome, a population – based screening study. Am. J. Obstet. Gynecol., 2004; 190: 745-50.
15. Greene MF. Spontaneous abortions and major malformations in women with diabetes mellitus. Semin. Reprod Endocrinol., 1999; 17: 127-36.
16. Wang X, Norman RJ, Wilcox AJ. Incidence of spontaneous abortion among pregnancies produced by assisted reproductive technology. Hum. Reprod., 2004; 19: 272-7.
17. Warren JE, Silver RM. Genetics of pregnancy loss. Clin. Obstet. Gynecol., 2008; 51: 84-95.
18. Slama R, Bouyer J, Windham G, Fenster L, Werwatz A, Swan SH. Influence of paternal age on the risk of spontaneous abortion. Am. J. Epidemiol., 2005; 161: 816–23.
19. Gruber CJ, Huber JC. The role of dydrogesterone in recurrent (habitual) abortion. J. Steriod. Biochem. Mol. Biol., 2005; 97: 49-50.
20. Omar MH, Mashita MK, Lim PS, Jamil MA. Dydrogesterone in threatened abortion: pregnancy outcome. J. Steroid. Biochem. Mol. Biol., 2005; 97: 421-5.
21. Pelinescu – Onciul D. Subchorionic hemorrhage treatment with dydrogesterone. Gynecol. Endocrinol., 2007; 23 (Suppl. 1): 77–81.
22. Kalinka J, Szekeres – Bartho J. The impact of dydrogesterone supplementation on hormonal profile and progesterone – induced blocking factor concentrations in women with threatened abortion. Am. J. Reprod. Immunol., 2005; 53: 166–71.
23. Czajkowski K, Sienko J, Mogilinski M, Bros M, Szczecina R, Czajkowska A. Uteroplacental circulation in early pregnancy complicated by threatened abortion supplemented with vaginal micronized progesterone or oral dydrogesterone. Fertil. Steril., 2007; 87: 613–8.
24. El-Zibdeh MY. Dydrogesterone in the reduction of recurrent spontaneous abortion. J. Steroid. Biochem. Mol. Biol., 2005; 97: 431-4.
25. Queisser – Luft A. Dydrogesterone use during pregnancy: overview of birth defects reported since 1977. Early. Hum. Dev., 2009; 85: 375–7.