Thai Journal of Obstetrics and Gynaecology
JULY 2011, Vol. 19, pp. 97-104

OBSTETRICS

Effect of Dydrogesterone on Treatment of Threatened Miscarriage: A Systematic Review and Meta-Analyses

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ABSTRACT

Objectives: We performed a systematic review and meta-analyses to assess the benefits and adverse effects of Dydrogesterone orally in treatment women with threatened miscarriage.

Methods: We searched four online databases including Pub Med and Scopus, Ovid and Science Direct. The key search terms were "threatened miscarriage" or "pregnancy loss" and "dydrogesterone" This study was a systematic review examining pregnant women with threatened miscarriage treated with dydrogesterone orally compared with no treatment without language restriction were included. Studies were evaluated for relevance and methodological quality. The primary outcome was continuing pregnancy beyond 20 weeks gestational age.

Results: Three randomized controlled trials (480 women) were included. For women with threatened miscarriage, dydrogesterone was associated with a significant reduction in miscarriage OR 0.41, 95% CI 0.25 to 0.68, P= 0.0005 I^2=2%, it was more effective than no treatment in treating miscarriage and achieving term deliveries OR 2.07, 95% CI 1.24 to 3.48, P= 0.0006 I^2=17%. No statistically significant benefit was found in preventing preterm labor OR 1.11, 95% CI 0.45 to 2.70, P= 0.82 I^2=2% and incidence of obstetrical complications. However, our review suffered from a small sample- size and the included studies were relatively poor quality.

Conclusions: There is insufficient data on the effect of dydrogesterone on threatened miscarriage, as the result was obtained from pooling together three studies of poor methodological quality,Therefore one needs to be caution in interpreting the results. Large sample-size, double-blind, randomized controlled trials are needed.

Keywords: dydrogesterone, threatened miscarriage, pregnancy loss, continuing pregnancy, adverse effects

Introduction

Threatened miscarriage is a common problem during pregnancy. Approximately 20% of pregnancy women will experience threatened miscarriage and about half of them will eventually suffer from an actual miscarriage[1-4]. In women who have had one prior miscarriage, the rate of spontaneous miscarriage in a subsequent pregnancy is about 20%. Women with three consecutive miscarriage will have up to 50% chance of pregnancy loss[5]. Moreover, the risk of

subsequent pregnancy complications, such as preterm labor, pre-eclampsia, and low birthweight after a threatened miscarriage is also increased[3].

Progesterone plays a crucial role in maintaining pregnancy as well as inducing secretory changes in the endometrium during the luteal phase to promote implantation and to support early pregnancy[6-7]. It modulates the maternal immune response to prevent fetal rejection[8] and relaxes the uterine smooth musculature[9]. Perkins[10] demonstrated that a serum progesterone concentration of less than 45 nmol/L was highly predictive of nonviable pregnancy in spontaneously pregnant patients (88.6%, sensitivity; 87.5%, specificity). This shows the significant impact of progesterone on pregnancy development[11]. However, oral administration of natural progesterone can cause side effects such as nausea, headache, and sleepiness and shows extreme variability in the plasma concentrations because of individual variability in gastric absorption and enteropathic circulation.[12] Dydrogesterone is a retro-progesterone. It is structurally and pharmacologically very similar to natural progesterone with better oral bioavailability. It is suitable for women with threatened miscarriage as it does not have androgenic or estrogenic effects on the fetus nor alter the normal secretory transformation of the endometrium or inhibit the formation of progesterone in the placenta. Hence, it allows administration of lower dose and avoids progestogenic side-effects[13-15].

Three studies have demonstrated the superiority of dydrogesterone to no treatment in the benefit of continuing pregnancy until 20 weeks of gestation[16-18]. Nonetheless, most of them suffered from small sample size with relatively poor quality of study design. This review presents the main findings of the dydrogesterone trials with the aim of assessing the benefits (continuous pregnancy beyond 20 weeks gestational age) and risks (complications of maternal and neonatal such as pre-eclampsia, antepartum hemorrhage, low birthweight, congenital anomaly and intrauterine growth restriction) of dydrogesterone versus no treatment in pregnant women with threatened miscarriage.

METHODS

Study design

We carried out a systematic review and meta-analyses in accordance with the reporting guidelines for health research: a systematic review consensus statement[19].

Types of participants

Pregnant women who were diagnosed as threatened miscarriage with a viable fetus.

Types of interventions

Dydrogesterone orally in threatened miscarriage compared with no treatment, placebo or any other treatment.

Outcome measures

Our primary outcome was continuing pregnancy beyond 20 weeks gestational age. Secondary outcomes were successful term delivery; the incidence of preterm labor, pre-eclampsia, antepartum hemorrhage; low birthweight; congenital anomaly and intrauterine growth restriction. We also reported the outcomes for studies that met the above inclusion criteria and mentioned as continuing pregnancy defined as pregnancy beyond 20 weeks of gestational age.

Search strategies

We searched through four online databases including Pub Med, Scopus, Ovid and Science Direct (1980 to Sept 2010). The key search terms were “threatened miscarriage” or “pregnancy loss” and “dydrogesterone”. Additional eligible studies were sought by reviewing the reference lists of identified articles.

Study eligibility criteria

For the systematic reviews examining pregnant women with threatened miscarriage, we included randomized trials of the pregnant women with

threatened miscarriage using dydrogesterone for treatment of threatened miscarriage. Collected variables were maternal age, gravidity, parity, previous miscarriage in multiparous women, miscarriage, preterm labor, term delivery, adverse effects for the mother or neonate, such as pre-eclampsia, antepartum hemorrhage, low birthweight, congenital anomaly and intrauterine growth restriction. We excluded duplicate publications, on basis of review of title or abstracts and inclusion criteria not met.

Quality assessment and data synthesis

Two reviewers independently assessed studies' quality using the Jadad scale for quality assessments of the RCTs20 as shown in Table 2. The scale includes three items directly related to the validity of RCTs, giving a total score of 0 to 5 points described in detail elsewhere. We used Review Manager, version 5.0 (Cochrane Collaboration), for statistical analyses. For dichotomous data, we meta-analyzed the findings in relation to odds ratio and continuous data were analyzed in term of mean difference. Weighting of the studies in the meta-analyses was calculated on the basis of the inverse variance of the study. The heterogeneity was presented using I2.

RESULT

Study selection

The process of study selection is presented in Fig. 1. After the screening process, 326 citations were selected to undergo review of the full text article; 321 were excluded on basis of review of title and abstracts and then 5 reports retrieved for more detailed evaluation. Later, two were excluded after inclusion criteria not met. The reports included were three randomized controlled trials[16-18].

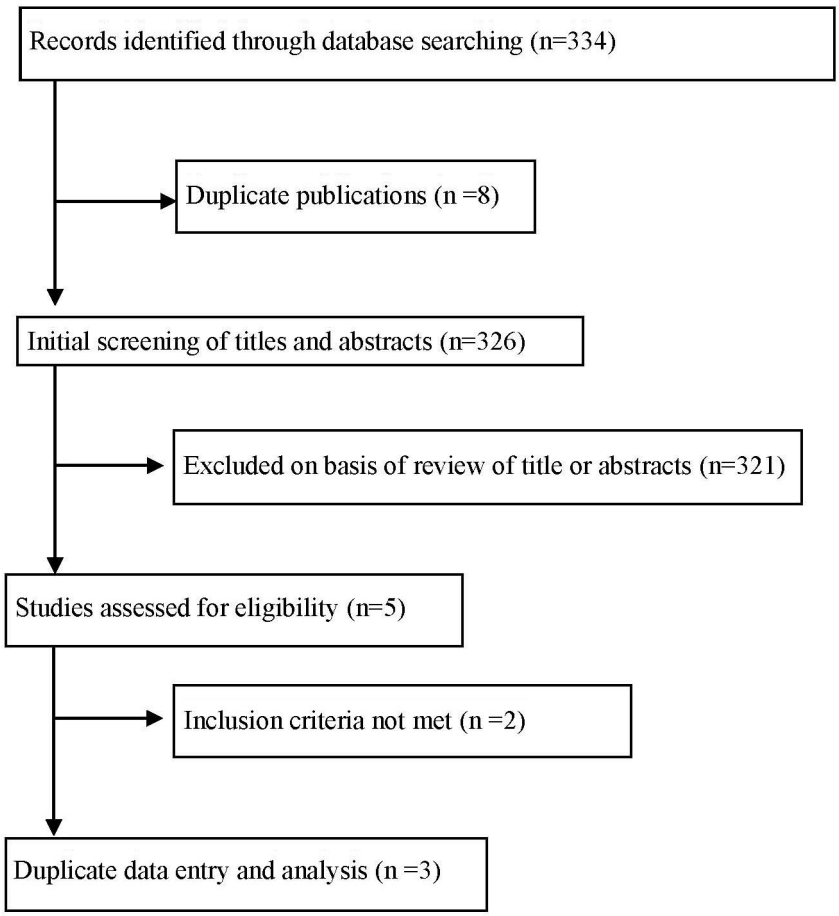
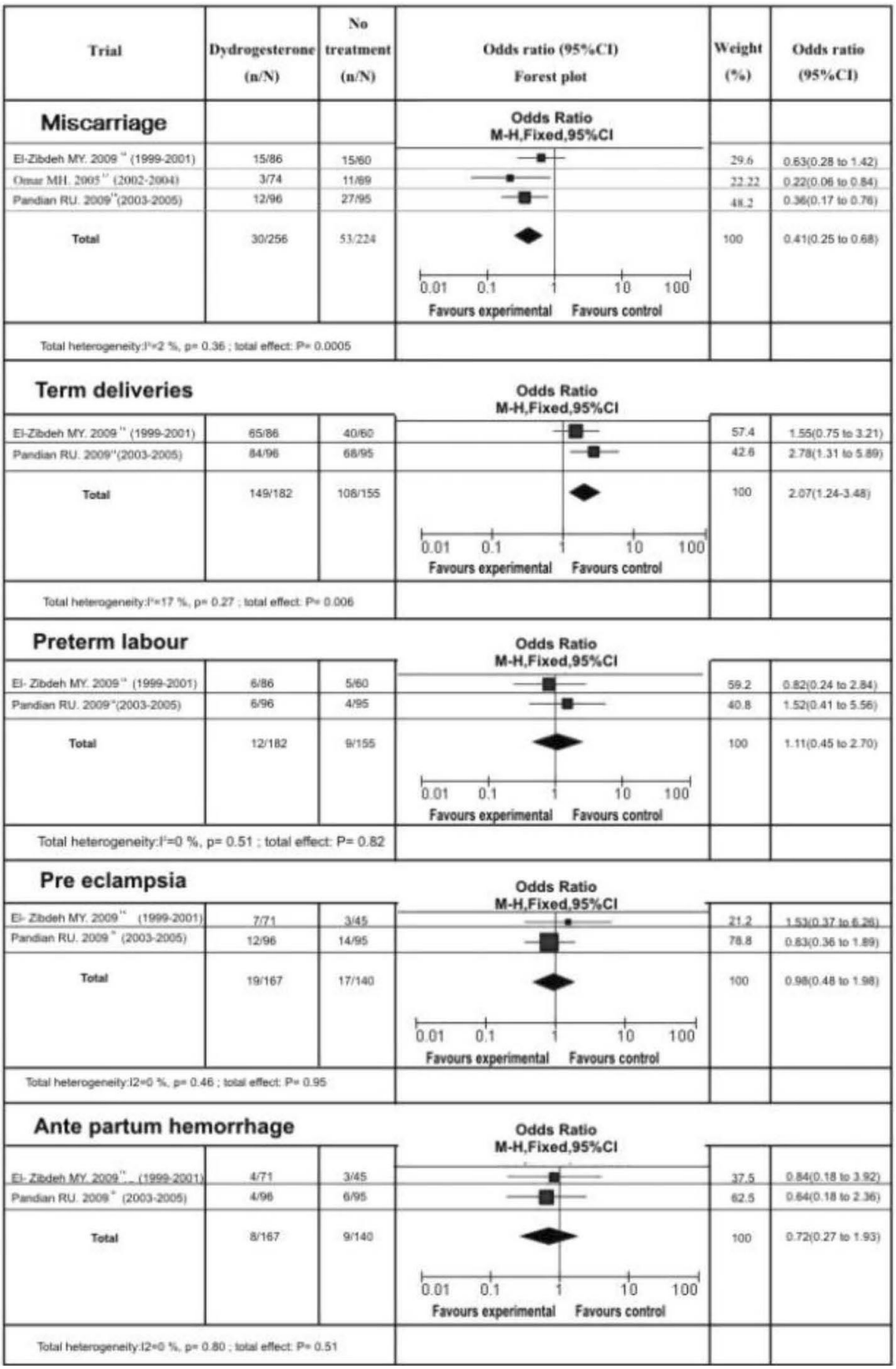


Fig. 1. Flow of article selection in trial


Trial
Dydrogesterone (n/N)
No treatment (n/N)
Odds ratio (95%CI) Forest plot
Weight (%)
Odds ratio (95%CI)
Miscarriage
Odds Ratio M-H,Fixed,95%CI
El-Zibdeh MY. 2009 [14] (1999-2001) 15/86 15/60 29.6 0.63(0.28 to 1.42)
Omar MH. 2005 [17] (2002-2004) 3/74 11/69 22.22 0.22(0.06 to 0.84)
Pandian RU. 2009 [18] (2003-2005) 12/96 27/95 48.2 0.36(0.17 to 0.76)
Total 30/256 53/224 100 0.41(0.25 to 0.68)
0.01 0.1 1 10 100
Favours experimental Favours control
Total heterogeneity:I²=2 %, p= 0.36 ; total effect: P= 0.0005
Term deliveries
Odds Ratio M-H,Fixed,95%CI
El-Zibdeh MY. 2009 [14] (1999-2001) 65/86 40/60 57.4 1.55(0.75 to 3.21)
Pandian RU. 2009 [18] (2003-2005) 84/96 68/95 42.6 2.78(1.31 to 5.89)
Total 149/182 108/155 100 2.07(1.24-3.48)
0.01 0.1 1 10 100
Favours experimental Favours control
Total heterogeneity:I²=17 %, p= 0.27 ; total effect: P= 0.006
Preterm labour
Odds Ratio M-H,Fixed,95%CI
El- Zibdeh MY. 2009 [14] (1999-2001) 6/86 5/60 59.2 0.82(0.24 to 2.84)
Pandian RU. 2009 [18] (2003-2005) 6/96 4/95 40.8 1.52(0.41 to 5.56)
Total 12/182 9/155 100 1.11(0.45 to 2.70)
0.01 0.1 1 10 100
Favours experimental Favours control
Total heterogeneity:I²=0 %, p= 0.51 ; total effect: P= 0.82
Pre eclampsia
Odds Ratio M-H,Fixed,95%CI
El- Zibdeh MY. 2009 [14] (1999-2001) 7/71 3/45 21.2 1.53(0.37 to 6.26)
Pandian RU. 2009 [18] (2003-2005) 12/96 14/95 78.8 0.83(0.36 to 1.89)
Total 19/167 17/140 100 0.98(0.48 to 1.98)
0.01 0.1 1 10 100
Favours experimental Favours control
Total heterogeneity:I2=0 %, p= 0.46 ; total effect: P= 0.95
Ante partum hemorrhage
Odds Ratio M-H,Fixed,95%CI
El- Zibdeh MY. 2009 [14] (1999-2001) 4/71 3/45 37.5 0.84(0.18 to 3.92)
Pandian RU. 2009 [18] (2003-2005) 4/96 6/95 62.5 0.64(0.18 to 2.36)
Total 8/167 9/140 100 0.72(0.27 to 1.93)
0.01 0.1 1 10 100
Favours experimental Favours control
Total heterogeneity:I2=0 %, p= 0.80 ; total effect: P= 0.51

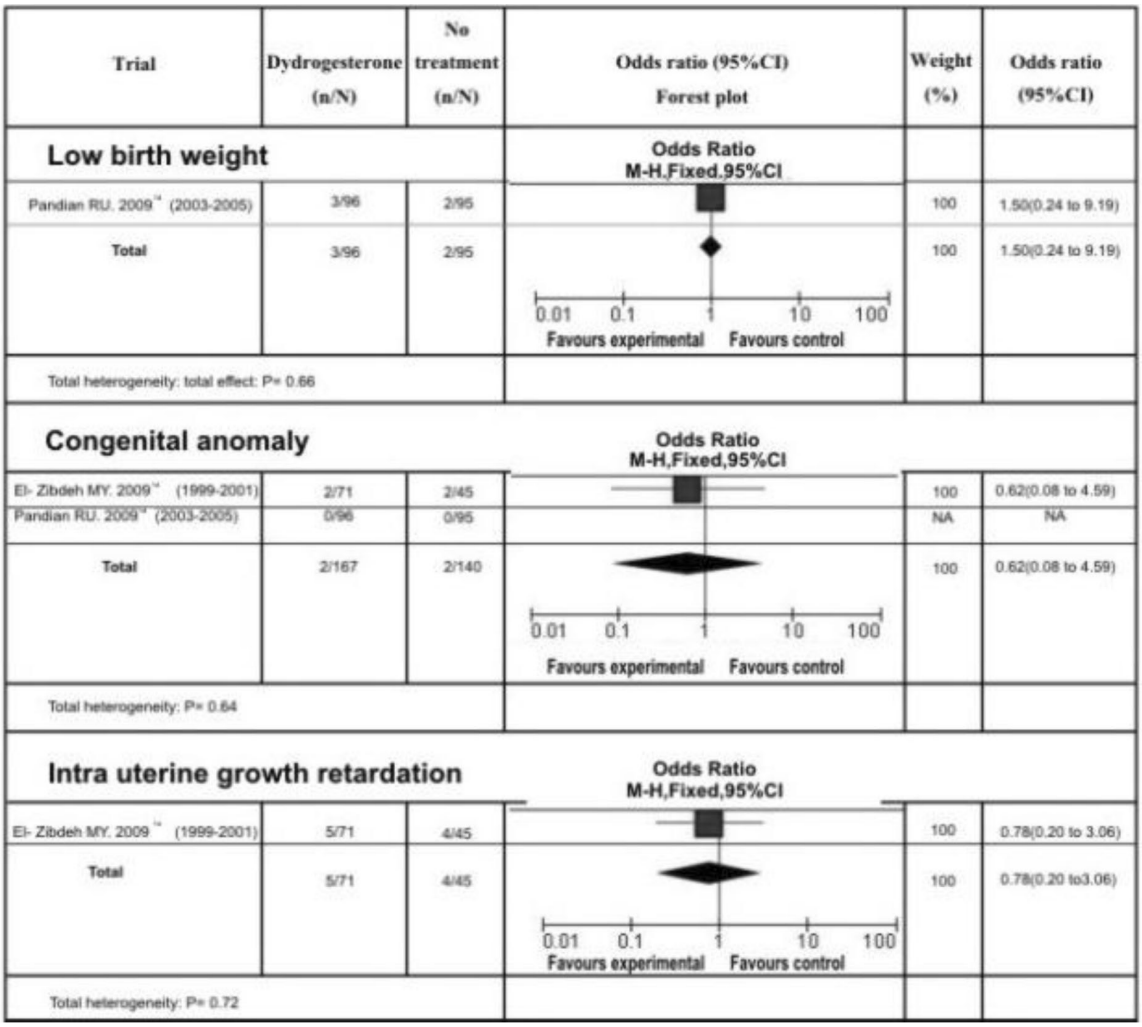


Fig. 2. Forest plot showing meta-analyses of outcomes for trials that compared dydrogesterone with no treatment

Study characteristics

The three studies included 480 participant pregnant women (256 with dydrogesterone and 224 without dydrogesterone) for the analysis (table 1). All of them were randomized controlled trials which examined the effect of dydrogesterone on pregnant women presenting with vaginal bleeding and diagnosed with threatened miscarriage in the first trimester, regardless of age. One study used 10 mg twice daily of dydrogesterone. Two studies used similar dosage with a 40 mg loading dose. One study was prospective open and two studies were randomized controlled trial. One study was no allocation concealment and two were unclear. All three studies was no blinding. The primary outcome of all studies was continuation of pregnancy beyond 20 week gestation. For the secondary outcomes; ie, term delivery, preterm delivery, pre-eclampsia, congenital anomaly, antepartum hemorrhage, were measured in two studies. Low birthweight and intra uterine growth restriction were measured in one study. Table 2 shows the quality of the included studies using Jadad scale. Overall, the study quality was relatively low (score 0-3).

Table 1. Characteristics of randomized controlled study of pregnant women with threatened miscarriage and Dydrogesterone compared with no treatment

Study (period)	population	Allocation Concealment	Dydroesterone treatment	Setting	Methods	Blinding	Dydrogesterone: :N	No treatment: :N
El- Zibdeh MY. 2009 [16] (1999-2001)	pregnant women who consecutively presented with mild or moderate vaginal bleeding during the first trimester	No	10 mg bid. and continuing for 1 week after the bleeding had stopped	Amman Islamic, Jordan.	Randomized, controlled study	No	86	60
Omar MH. 2005 [17] (2002-2004)	All pregnant women who present with vaginal bleeding before 20 weeks gestation.	Unclear	40 mg stat followed by 10 mg twice a day until the bleeding stopped	Kuala Lumpur, Malaysia.	Prospective open study	No	74	80
Pandian RU. 2009[18](2003-2005)	All women presenting with vaginal bleeding up to 16 weeks of pregnancy	Unclear	40 mg stat followed by 10 mg twice daily	Penang, Malaysia	Randomized study	No	96	95

Treatment outcome

Figure 2 presents the outcome of using dydrogesterone for treatment of threatened miscarriage comparing to no treatment of the three studies combined. We found that dydrogesterone was associated with a significant reduction of miscarriage (OR 0.41, 95% CI 0.25 to 0.68, P=0.0005, I^2=2%). In relation to preterm labor and term delivery, two studies with 337 participants were examined. It has been shown that there was no significant differences between the two groups with respect to the women experiencing preterm labor (OR 1.11, 95% CI 0.45 to 2.70, P= 0.82 I^2=0%) but there was an increase in the number of term deliveries in the group using dydrogesterone (OR 2.07, 95% CI 1.24 to 3.48, P= 0.006 I^2=17%). There was also no significant difference between the groups with regard to obstetrical complications such as pre-eclampsia, antepartum hemorrhage, congenital anomaly, low birthweight and intrauterine growth restriction. Moreover, the combined findings from meta-analyses showed relative low heterogeneity in all aspect of the outcomes (I^2 ranged from 0-17%).

DISCUSSION

To our knowledge, this is the first systematic review of a comprehensive evidence base of treatment trials of using dydrogesterone versus no treatment in pregnant women with threatened miscarriage. Although overall, dydrogesterone were found to be more effective in promoting continuing pregnancy beyond 20 weeks gestational age compared with no treatment or conservative treatment but there is insufficient data on the effect of dydrogesterone on threatened miscarriage, as the result was obtained from pooling together three studies of poor methodological quality. Therefore, we need to exercise with caution in interpreting the results.

Strengths and limitations of the review

The current review is the first study assessing the treatment outcome of treating threatened miscarriage with dydrogesterone. Its treatment outcomes of both efficacy and adverse effects were very homogenious with the maximum of I^2 equal to 17%. However, the studies included had small sample-sizes with relatively poor quality study designs. In total, there were fewer than 500 patients included and the Jadad scale was less than three in all three included studies. We only had access to aggregated data. We also suffered from difficulties in retrieving unpublished trial data and were not able to compare the outcome of published and previously unpublished trials which might suggest the potential for publication bias.

Comparison with other studies

The current review demonstrates some benefit of the using dydrogesterone over no treatment in relation to continuing pregnancy beyond 20 week gestation and did not increase the risk of maternal and neonatal complications. However, (Queisser-Luft A[21]) 28 cases were reported with birth defects after maternal dydrogesterone therapy between 1977 and 2005 and were very diverse. Musculo-skeletal system abnormalities and multiple birth defects were the first two most commonly reported. Nonetheless, according to the current literature, there is no evidence to support a proven causal link between dydrogesterone and any of these defects. The data do not provide evidence for congenital malformations associated with dydrogesterone use.

Conclusions and policy implications

Our analysis of a comprehensive evidence base of trials using dydrogesterone compared with no treatment in threatened miscarriage. There is insufficient data on the effect of dydrogesterone on threatened miscarriage, as the result was obtained from pooling together three studies of poor methodological quality and therefore one needs to exercise caution in interpreting the results although appears to indicate some beneficial effects with no potentially harmful maternal and neonatal complications (such as pre-eclampsia, antepartum hemorrhage, low birthweight, congenital anomaly and intrauterine growth restriction), large sample-size,

Table 2. Quality assessment using Jadad scale

Jadad Scale Calculation	El-Zibdeh MY. 2009 [16] (1999-2001)	Omar MH.2005[17] (2002-2004)	PandianRU.2009[18] (2003-2005)
1. Was the study described as random?	1	0	1
2. Was the randomization scheme described and appropriate?	0	0	1
3. Was the study described as double-blind?	0	0	0
4. Was the method of double blinding appropriate? (Were both the patient and the assessor appropriately blinded?)	0	0	0
5. Was there a description of dropouts and withdrawals?	1	0	1
Total	2	0	3

double-blind, randomized controlled trials are essential to confirm these initial findings.

Statement of conflict of interest, there are none to declare.

Acknowledgments

The authors wish to thank Prof. Robert Mills for his English approval.

References

1. Everett C. Incidence and outcome of bleeding before the 20th week of pregnancy: prospective study from general practice. BMJ 1997;315:32-4.
2. Stabile I, Campbell S, Grudzinskas JG. Ultrasonic assessment of complications during first trimester of pregnancy. Lancet 1987;2:1237-40.
3. 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.
4. Sotiriadis A, Papatheodorou S, Makrydimas G. Threatened miscarriage: evaluation and management. BMJ 2004;329:152-5.
5. Stirrat GM. Recurrent miscarriage. Lancet 1990;336:673-5.
6. Cunningham FG, Leveno KJ, Bloom SL, Hauth JC, Gilstrap III LC, Wenstrom KD. Williams's obstetrics. 22 ed. New York: McGraw-Hill Professional; 2005.
7. Schindler AE. First trimester endocrinology: consequences for diagnosis and treatment of pregnancy failure. Gynecol Endocrinol 2004;18:51-7.
8. Szekeres-Bartho J, Barakonyi A, Polgar B, Par G, Faust Z, Palkovics T, et al. The role of gamma/delta T cells in progesterone-mediated immunomodulation during pregnancy: a review. Am J Reprod Immunol 1999;42:44-8.
9. Hidalgo A, Suzano RC, Revuelta MP, Sanchez-Diaz C, Baamonde A, Cantabrana B. Calcium and depolarization-dependent effect of pregnenolone derivatives on uterine smooth muscle. Gen Pharmacol 1996;27:879-85.
10. Perkins SL, Al-Ramahi M, Claman P. Comparison of serum progesterone as an indicator of pregnancy nonviability in spontaneously pregnant emergency room and infertility clinic patient populations. Fertil Steril 2000;73:499-504.
11. Spitz IM. Progesterone antagonists and progesterone receptor modulators: an overview. Steroids 2003;68:981-93.
12. Di Renzo GC, Mattei A, Gojnic M, Gerli S. Progesterone and pregnancy. Curr Opin Obstet Gynecol 2005;17:598-600.
13. Schindler AE, Campagnoli C, Druckmann R, Huber J, Pasqualini JR, Schweppe KW, et al. Classification and

pharmacology of progestins. Maturitas 2008;61:171-80.
14. Tausk M. A general summary of dydrogesterone, a derivative of retro-progesterone. In: Tausk M, ed. International Encyclopaedia of Pharmacology and Therapeutics. Section 48. Pharmacology of the Endocrine System and Related Drugs: Progesterone, Progestational Drugs and Antifertility Drugs. Volume II. Pergamon Press: Oxford, New York 1972:481.
15. Anin SA, Vince G, Quenby S. Trophoblast invasion. Hum Fertil (Camb) 2004;7:169-74.
16. El-Zibdeh MY, Yousef LT. Dydrogesterone support in threatened miscarriage. Maturitas 2009;65 Suppl 1:S43-6.
17. Omar MH, Mashita MK, Lim PS, Jamil MA. Dydrogesterone in threatened abortion: pregnancy outcome. J Steroid Biochem Mol Biol 2005;97:421-5.
18. Pandian RU. Dydrogesterone in threatened miscarriage: a Malaysian experience. Maturitas 2009;65 Suppl 1:S47-50.
19. Moher D, Weeks L, Ocampo M, Seely D, Sampson M, Altman DG, et al. Describing reporting guideline for health research: a systematic review. J Clin Epidemiol 2011 Jan 6.
20. Olivo SA, Macedo LG, Gadotti IC, Fuentes J, Stanton T, Magee DJ. Scales to assess the quality of randomized controlled trials: a Systematic review 2008;88:165-75.
21. Queisses-Luft A. Dydrogesterone use during pregnancy: Overview of birth defects reported since 1997. Early Hum Dev 2009;85:375-7.

ผลของยาไดโดรเจสเตอโรน ในการรักษาภาวะแท้งคุกคาม

ฐิติพร สิริวชิรชัย, ธรรมสรณ์ พิริยสุพงศ์

วัตถุประสงค์ *: เพื่อทำการศึกษาอย่างเป็นระบบถึงประโยชน์และผลข้างเคียงของยาไดโดรเจสเตอโรนในการรักษาภาวะแท้งคุกคาม*
วิธีการศึกษา *: ทำการสืบค้นข้อมูลจากสี่ฐานข้อมูล Pub Med, Scopus, Ovid และ Science Direct โดยไม่มีการจำกัดภาษา คำสำคัญในการสืบค้น "Threatened miscarriage" หรือ "Pregnancy loss" และ "Dydrogesterone" เป็นการศึกษาเชิงระบบที่ทำในสตรีตั้งครรภ์ที่มีภาวะแท้งคุกคามซึ่งรักษาด้วยยาไดโดรเจสเตอโรนแบบรับประทานเปรียบเทียบกับไม่รักษาด้วยยาใดๆ การศึกษานี้มีการประเมินความสัมพันธ์และเกี่ยวกับระเบียบวิธีวิจัยที่มีคุณภาพ ผลลัพธ์หลักคือการตั้งครรภ์ต่อจนอายุครรภ์มากกว่า 20 สัปดาห์*
ผลการศึกษา *: พบว่ามีการวิจัยแบบสุ่มทดลองและกลุ่มควบคุม 3 รายงานเป็นจำนวนสตรีตั้งครรภ์ที่มีภาวะแท้งคุกคาม 480 ราย ที่ได้รับการรักษาด้วยยาไดโดรเจสเตอโรน พบมีการลดลงของภาวะแท้งบุตรอย่างมีนัยสำคัญโดยมี OR 0.41, 95% CI 0.25 - 0.68, P= 0.0005 I2=2%, และมีผลให้การตั้งครรภ์ดำเนินต่อถึงครบกำหนดมากกว่ากลุ่มที่ไม่ได้ยา (OR 2.07, 95% CI 1.24 - 3.48, P= 0.0006 I2=17%.) แต่ไม่พบว่ามีประโยชน์ในการป้องกันการเจ็บครรภ์คลอดก่อนกำหนดอย่างมีนัยสำคัญ (OR 1.11, 95% CI 0.45 - 2.70, P= 0.82 I2=2%)และไม่พบว่ามีการเพิ่มภาวะแทรกซ้อนทางสูติกรรม อย่างไรก็ตามการทบทวนนี้ก็มีจุดอ่อนจากจำนวนตัวอย่างที่น้อยและการศึกษาที่นำมารวบรวมก็มีคุณภาพต่ำ*
สรุป *: มีข้อมูลสนับสนุนไม่เพียงพอในผลของยาโดรเจสเตอโรนต่อภาวะแท้งคุกคาม เพราะผลลัพธ์ที่ได้มาจากการรวมการศึกษาที่มีคุณภาพของระเบียบวิธีวิจัยต่ำ ซึ่งต้องระมัดระวังในการแปลผลการศึกษา ดังนั้นจำนวนตัวอย่างที่มากพอ การสุ่มตัวอย่างอย่างเป็นระบบและถูกต้องมีคุณภาพจึงจำเป็นในการยืนยันผลลัพธ์ข้างต้น*