SYSTEMATIC REVIEW

The efficiency of 17α hydroxyprogesterone in the prevention of preterm labour irrespective of administration route: Systematic review metanalysis

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Abstracts

Objectives: To verify the benefits of 17 alpha hydroxyprogesterone use throughout the second half of pregnancy in preventing preterm birth among those with an increased risk of preterm birth.

Method: The systematic review was conducted at the University Hospital, Baghdad, Iraq, from June 2020 to July 2021, and comprised search for randomised controlled trials having used progesterone for the prevention of preterm birth among women with a short cervix length <2.5cm. The search, conducted on Cochrane, Medline, PubMed and Scopus databases, was not limited by publication date. Cochrane guideline for conducting systematic review and metanalysis was used.

Results: There were 3 randomised controlled trials comprising 1705 subjects; 860(50.4%) cases and 845(49.6%) controls in the placebo group. Among them, 175(20.3%) cases and 197(23.3%) controls suffered from preterm labour (p=0.116).

Conclusion: Though earlier evidence supported the benefits of locally applied progesterone to a short cervix in pregnancy prolongation, but the current analysis found no significant benefits in this regard.

Keywords: Preterm labour, Prevention, Progesterone, Short cervix.

Introduction

The new millennium has witnessed a new revolutionary approach to both prevention and treatment of preterm labour.[1,2] To date, preterm labour (PL) remains a major cause of neonatal morbidity and mortality, accounting for >50% of all preterm births.[3,4] PL is defined as the occurrence of uterine contractions of sufficient frequency and strength to cause progressive effacement and dilatation of the cervix before completing 37 weeks of gestation.[5] The causes of preterm labour are quite diverse in aetiology.[6] History of preterm birth is the most significant risk factor.[7] High-frequency vaginal ultrasound introduced a new concept of PL pathogenesis as a short cervix <2.5cm in length which is applied in practice as a screening test to detect premature cervical ripening.[8] Progesterone, cervical cerclage, and cervical pessary have all been tried to lower the incidence of preterm delivery in women who are at a higher risk.[9] Progesterone is available in a variety of forms during pregnancy, like natural 17 alpha hydroxyprogesterone (17α-OHP), or other more chemically modified types, like dydrogesterone and micronised progesterone.[10,11] Natural progesterone is offered vaginally, orally, or intramuscularly (IM) and was found to be the best approach for primary prevention of preterm birth and reduction of neonatal death among high-risk women and those with a history of PL.[12] In the course of a normal pregnancy, progesterone is produced initially by the corpus luteum till 8 weeks of gestation, supported by the mounting secretion of human chorionic gonadotropin (hCG) from the placenta. Then the placenta itself will produce this hormone in progressive amounts till the end of the pregnancy. It has a profound uterine muscle-relaxant effect which plays a major role in the prevention of PL.[13]

Hydroxyprogesterone (OHP) acetate, or caproate, is still one of the most reliable drugs used in the support of threatened abortion in the first half of pregnancy. Its role during the second half of pregnancy is still a debated issue.[14,15] Moreover, in the last 10 years, progesterone was introduced in a new locally administered form, like gel, capsule, vaginal pessaries and rectal variant.[16,17]

The current systematic review was planned to assess the benefit of progesterone in the prevention of PL irrespective of the method of administration in high-risk women.

Methods

The systematic review was conducted at the University Hospital, Baghdad, Iraq, from June 2020 to July 2021. Cochrane, Medline, PubMed and Scopus databases were searched using key words 'preterm labour', 'prevention', 'progesterone', '17α Hydroxyprogesterone' and 'short cervix'. The search was not limited by publication date.

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Articles included were randomised controlled trials (RCTs) conducted in a clinical setting on human population and published in the English language. Cross-sectional studies, unpublished studies, posters and articles with limited participants or when the data was not presented were excluded and so were studies involving cases of twins. Three studies were chosen as a primary base for the current meta-analysis.[18-20]

After the extraction of the total number for the intervention and placebo groups in the included studies, the results were analysed for the total fixed and random effect odds ratio (OR) with the calculation of 95% confidence interval (CI) using the Mantel-Haenszel method.[21] Test for heterogeneity was done using Tau statistics. Egger's test and Begg's test were used to assess publication bias. P<0.05 was considered significant. All statistical analyses were done using Medcalc 17. Cochrane guidelines for conducting systematic review and meta-analysis were followed.[22]

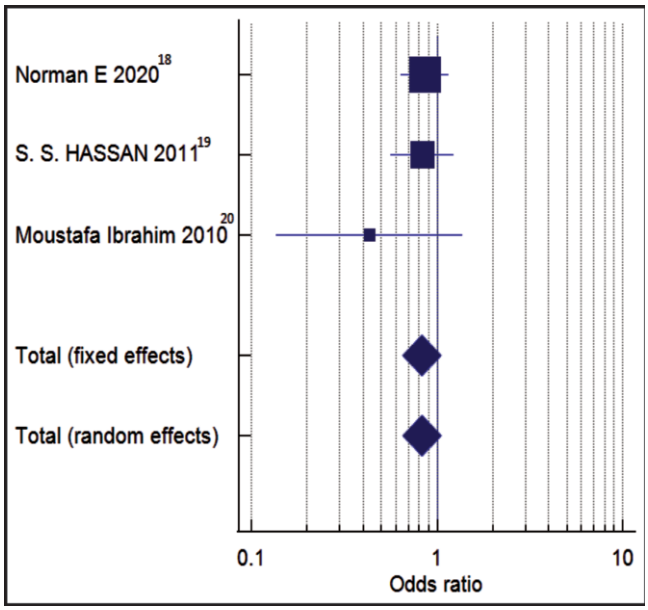

Figure: Forest plot showing the contribution of each study to the overall odds ratio (OR) calculation.

Results

The 3 RCTs included for review together comprised 1705 subjects; 860(50.4%) cases and 845(49.6%) controls in the placebo group. Among them, 175(20.3%) cases and 197(23.3%) controls suffered from PL (p=0.116) (Table).

Among the 3 RCTs, the first, conducted by Norman E. in 2020,[18] included women with a PL history or those treated with a vaginal gel of microionised progesterone with a short cervix in the study group and were given 17α-OHP IM, while the control group received a placebo. The cut-off value of pregnancy duration was 34 weeks of gestation. There were 600 women in the study group versus 597 in the control group.

The second RCT, conducted in 2011 by Hassan et al.,[19] recruited participants based on a short cervix. They were all given a vaginal gel containing natural progesterone 90mg in gel format, starting early in the second half of pregnancy. The cut-off value for pregnancy duration was 37 weeks of gestation. There were 235 women in the study group and 223 in the control group.

The third RCT, conducted by Moustafa et al., published in 2010[20] had women with a history of preterm birth who were given 17α-OHP IM starting from the second trimester till 36 weeks of gestation. Short cervix was not considered. The cut-off value for pregnancy duration was 37 weeks of gestation. There were 25 women in the study group and 25 in the control group.

The cut-off value for pregnancy duration and cervical length were the two sources of bias among the 3 RCTs,

Table: Metanalysis with odds ratio (OR) and 95% confidence interval (CI).

Study	Intervention	Controls	Odds ratio	95% CI	z	P	Weight (%)	
							Fixed	Random
Norman E 2020[18]	96/600	108/597	0.862	0.638 to 1.166			60.26	60.26
S. S. HASSAN 2011[19]	71/235	76/223	0.837	0.565 to 1.240			35.59	35.59
Moustafa Ibrahim 2010[20]	8/25	13/25	0.434	0.138 to 1.371			4.15	4.15
Total (fixed effects)	175/860	197/845	0.829	0.656 to 1.048	-1.570	0.116	100.00	100.00
Total (random effects)	175/860	197/845	0.829	0.656 to 1.048	-1.564	0.118	100.00	100.00
Q	1.2824							
DF	2							
Significance level	P = 0.5267							
I2 (inconsistency)	0.00%							
95% CI for I2	1.0 - 94.77							

and can potentially cause highly biased results in case of a a significant difference between the intervention and control groups in the current meta-analysis. The difference of progestational agent used in the 3 RCTs was well within the aims of the current review, and, as such, was not a source of bias in the context of the meta-analysis.

The risk of publication bias, checked by Egger and Begg's tests, proved to be non-significant (p=0.0991 and p=0.1172, respectively).

Forest plot suggested that the RCT conducted by Moustafa et al.[20] had a negligible contribution to the final OR estimation, while the other 2 RCTs showed a higher contribution, but since all the 3 RCTs were found skewed, they indicated non-beneficial effect of progesterone in the prolongation of a pregnancy threatened by PL (Figure).

Discussion

The current meta-analysis showed that in women with PL history and those with short cervix, confirmed by transvaginal ultrasound, the addition of 17α-OHP had no significant benefit regardless of the way of progesterone administration.

The cervix is a cause of PL. The guidelines published in the Canadian Journal of Obstetrics and Gynecology were based on women with previous PL, short cervix, uterine shape abnormalities, cervical conisation, cervical cerclage, and women with multiple gestations.[23-25] The logical query is whether or not the local application of progesterone preparation to the cervix has any advantage in preventing PL.

Romero et al.[26] concluded that locally-administered progesterone had a beneficial effect in preventing PL as well as improving measures of neonatal morbidity and mortality. The study included 159 subjects who received vaginal progesterone versus 140 in the control group, and investigated the value of vaginally-administered progesterone in asymptomatic pregnant women with twin pregnancies and a sonographic short cervix compared to the placebo group. They recommended progesterone effect in reducing PL in women <33 weeks of gestation (31.4% vs 43.2%). Hassan et al. stated that local application of progesterone reduced PL.[19]

A systematic meta-analysis by Pacora et al. recommended local application of progesterone to be as effective as cervical cerclage in preventing PL and in reducing poor neonate outcomes. The study compared indirectly the local application of progesterone versus placebo, including 265 participants to the effect of cerclage versus none among 504 participants. The reduction in PL was equal in both groups. They advised that the choice of interventions will be that of the physician and the patient depending on preferences based on cost and risk assessment.[27]

In 2019, Jarde et al.[28] discussed the value of oral, vaginal administration of progesterone, pessaries, and cerclage in reducing PL risk and improving neonatal outcomes among high-risk women with singleton pregnancies. Vaginal progesterone was superior to all other interventions in prolongation of pregnancies beyond 37 weeks in the risky women. The study enrolled 11,311 pregnant women and estimated a reduction in PL in gestational age <34 weeks (OR" 0.43, 95% CI: 0.20-0.81) and <37 weeks (OR: 0.51, 95% CI: 0.34-0.74).

Clearly, all the above RCTs and meta-analyses preferred local application of progesterone for preventing PL through systemic administration of the hormone. However, all these RCTs were unregistered, and having no prospective trial registration makes it difficult to prove anything for any individual trial.[29]

A 2017 systemic review and meta-analysis on the benefits of progesterone, whether locally administrated or systemically, cerclage and placebo in twin gestations, included 6,626 women and showed reduction in PL risk at <34 weeks and neonatal outcomes compared to the control group. No intervention was beneficial for the prevention of PL <34 weeks of gestation. A study said vaginal progesterone improved some neonatal outcomes.[12] A review summarising Cochran's database meta-analysis in 2013 had four studies, and all of them supported the theory of beneficial progesterone administration for preventing PL.[18] The review excluded all the biased data from the four trials and showed that progesterone administration, whether systemic or local, did not affect preventing delivery <34 weeks of gestation (p=0.67).

Interestingly, another trial contradicted the results which agreed with the findigs of the current review.[30] The trial was a randomised, double-blind study using vaginal 200mg versus placebo daily, starting early in the second trimester, and did not show any significant advantage in prolonging pregnancy beyond 34 weeks. The trial questioned the universal use of progesterone in PL prophylaxis and discussed its safety on newly born children up to 2 years of age.[30]

In the current meta-analysis, both local and systemic administration of progesterone was non-significant in

preventing PL. This may be explained because the administration of a naturally produced hormone by the placenta through a systemic pathway will naturally not affect the timing of delivery whether before 34 weeks or at 37 weeks.

The evidence on progesterone's efficacy for women at PL risk, its impact on preterm birth rates, and the baby's long-term implications are still inconclusive. Clinicians and pregnant women may evaluate the benefits, risks and side-effects of the intervention they choose. In the future, there might be a reconciliation of the divergent viewpoints on this critical issue.

The limitation of the current systematic review is that one of the RCTs[21] had a small sample size compared to the two other studies.[18,19]

Conclusion

Progesterone was found to be ineffective in preventing preterm birth. The heterogeneity of PL syndrome should modify the universal use of progesterone and offer a tailored treatment option for the high-risk groups.

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