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Progesterone Therapy for the Prevention of Preterm Labor in Women with Single Risk-factor: A Systematic Review and Meta-analysis

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Background: Preterm labor is a common complication of pregnancy which has become a main health concern around the world due to its negative consequences. **Objective:** To investigate the efficacy of progesterone therapy in the prevention of preterm labor in women with single risk factor. **Search strategy:** A PubMed, Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, Science Direct, Scopus, OVID, EMBASE, SID, Magiran and Google Scholar search (date last searched April 2016) without any time, language and location restriction was done. **Inclusion criteria:** All randomized clinical trials of singleton pregnancies with single risk factor (prior preterm labor without short cervical length or short cervical length without prior preterm labor) which were randomized to progesterone and control groups were included in our meta-analysis. **Primary outcome:** Our primary outcome was gestational age at delivery. **Results:** 13 studies (1259 subjects and 2653 control women) were included in the meta-analysis. Using random effect model showed that mean gestational age at delivery of progesterone group is 0.74 (0.41-1.06) month longer than that of control group with CI=95% which is significant statically. **Conclusions:** Progesterone therapy is an effective intervention for the prevention of preterm labor in women with single risk factor.

Keywords: Preterm birth, Preterm labor, Previous preterm labor, Progesterone, Short cervical length.

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INTRODUCTION

Preterm labor which is defined as the delivery after 20 weeks and before 37 completed weeks of gestation is a common complication of pregnancy worldwide.[1-4]

Reports indicate that between 5 to 25 percent of all pregnancies are resulted in preterm labor.

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The prevalence of preterm labor is different in different populations. In 2010, about 12% of all live births in US, 8% in Canada, 5-15% in developed countries and more than 23% in India has been occurred premature.[6-13]

Preterm birth is a multi-causal condition influenced by various factors.[14-20] Preterm birth has very negative consequences and is the most important cause of infant mortality and long-term disability.[1,2,13]

Respiratory distress syndrome and chronic lung disease which are the most important complications of premature birth and the leading causes of infant mortality, Cerebral palsy, neurological problems and sensory-motor disability, heart defects, increased risk of heart disease (heart attack, stroke and hypertension) and diabetes in adulthood, vision loss and blindness, hearing defects, patent ductus, bronchopulmonary dysplasia, intracranial infections and bleeding, necrotizing enterocolitis, asphyxia, retinopathy of prematurity, sudden infant death syndrome and the long-term mental and developmental disabilities are among the most common complications which premature infants faced with them. Also, the prematurely born babies, often experience cognitive, behavioral and social problems in adulthood and their educational achievements are poor. These problems increase the social costs of preterm birth for premature born babies, their families and societies and lead to an increased need to treatment assistance and psychological disorders with its following negative consequences.[3-17]

Therefore, the preventing from preterm birth has become a top concern of health decision makers and practitioners around the world due to its widespread adverse consequences.[6-8] The first step in the prevention of preterm labor is the sound identification of at risk pregnant women.[13] Several indicators can help to predict preterm labor[3] but most studies have shown that the most powerful predictors of preterm labor are the history of previous preterm labor and short cervix length.[3,6,10,12,13,16] Various studies have shown that the risk of preterm labor in women with a previous history is at least 2.5 times more than that of women without previous preterm labor and this rate increases as the number of previous preterm labor increases.[6] Short cervix length is another good predictor of preterm labor which can help to predict the occurrence of the condition many weeks before labor and can provide an appropriate time interval for preventive interventions.[13] To date, many prospective trials have approved the short cervix length as reliable predictor of preterm labor.[13,16,21] Also, a logistic regression analysis has shown that the short cervix length is the only independent factor which contributes to preterm labor and therefore could be the most reasonable tool to predict the risk of preterm labor.[13] In order to prevent the occurrence of preterm labor, after identification of at risk women, effective preventive interventions should be designed and applied. So far, the treatment with a variety of different drugs has been the first method of treatment.[9] For this, a large number of medicines with different pharmacological formulas have been produced in the past decades but the Progestin had the highest efficacy.[7,8,10,17,20]

The Progestin have introduced as the treatment for preterm labor in about 50 years ago after the introducing of progesterone fluctuation theory by Csaplo et al. (1956) which states that a high level of progesterone prevents the occurrence of labor through Tocolytic (preventing uterine contractions).[22] Now progestin drugs are available in different forms for the prevention of preterm labor and in recent decades a variety of authors have studied the various aspects of this type of medications.[4,6,10,14,17,20]

The aim of this meta-analysis was to analyze the results of previous clinical trials which have been done in order to establish the efficacy of progesterone drugs in the prevention of preterm labor in women with single risk factor (the history of preterm labor or short cervix length).

METHODS

Search strategy

An electronic databases' search including PubMed, Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, Science Direct, Scopus, OVID, EMBASE, SID (Scientific Information Database), Magiran (a Persian scientific database) and Google Scholar (date last searched April 2016) with the use of text search terms preterm birth, preterm delivery, preterm labor, singleton pregnancy, cervical length, prior preterm birth, recurrent preterm birth, progesterone, progestin, vaginal, intramuscular, oral and their Persian equivalents with "Or" and "And" operations in the title and abstract of studies was done. The reference lists of retrieved studies were searched by hand to find publications which may not be retrieved through the databases' search and to increase the sensitivity of study. No time, language or geographical location restrictions were applied. Search was done by 2 researchers independently and the third researcher checked the agreement of retrieved studies with those 2 researchers.

Study selection

All randomized clinical trials of singleton pregnancies with single risk factors (prior preterm labor without short cervical length or short cervical length without prior preterm labor) that were randomized to treatment with progesterone

(intervention group) and placebo or no treatment (control group) were included. For this, Full texts of all articles were retrieved through an advanced search. The repeated or unrelated ones were removed and the investigation of the results of the reminders was done to prevent bias caused by reprint (publication bias of transverse and longitudinal). The remaining results were entered to quality assessment process.

Quality assessment process

All relevant studies were considered to quality assessment by two authors (MA.B and M.M). This process of quality assessment was done using a valid measuring scale (Jadad scale). Jadad scale[23] is a 5-point scale for measuring the quality of randomized trials. In this measuring scale studies which obtain at least 3 or more score are assessed as high quality ones.[24] This scale involves 3 domains related to quality of studies: 1) random sequence generation (0 = no description; 1 = inadequate description; 2 = adequate description); 2) blinding process (2 = double-blinding with adequate description; 1 = double-blinding with inadequate description; 0 = wrong usage of double-blinding), and 3) withdrawal of patients (1 = the number and reasons of patients withdrawal described; 0 = otherwise). Two reviewers independently evaluated the studies. In the cases of disagreement, further discussion and consultation were undertaken involving a third-party opinion.

Data Extraction

The required data from selected studies including the title, first author, publication year, and location of study, sample size of intervention and control groups, the situation of randomized allocation, blinding, number of withdrawals, administered progesterone and the mean and standard deviation of gestational age at delivery in intervention and control groups were extracted and entered to EXCELL.

Inclusion criteria

All randomized clinical trials of singleton pregnancies with single risk factor (prior preterm labor without short cervical length or short cervical length without prior preterm labor) that were randomized to treatment with progesterone (intervention group) and placebo, nursing daily care or other or no treatment (control group) that have reported the sample size and mean and standard deviation of gestational age at delivery for intervention and control groups and passed the quality assessment process successfully were included in the study.

Exclusion criteria

Exclusion criteria included trials involving women with multiple risk factors (prior preterm birth and short cervical length) or trials in multiple pregnancies or trials with preterm labor at the randomization time. Also, the studies which have not reported sample size or the mean and standard deviation of gestational age at delivery for intervention and control groups, case reports, the abstracts of seminars and studies with <3 score of quality assessment process were excluded from study.

Data analysis

We used STATA ver.11 software for data analysis. The heterogeneity index between studies was determined using Cochran (Q) and I-squared tests. Random effect model was used to estimating the standardized difference of mean gestational age at delivery due to the existing heterogeneity. Inverse variance method and Cohen statistics were used for estimation. The point estimation of standardized difference of mean gestational age at delivery was calculated using forest plot and 95% confidence interval. In this plot, the size of square represents the weight of each study and its booth side's lines represent 95% confidence interval. Potential publication bias was assessed by using Egger's test. P value < 0.01 was considered statistically significant.

RESULTS

We found 23100 studies in our initial search from which 21649 studies were removed by limiting the search. From reminding 1451 studies, 864 studies were removed because of overlapping of searched databases. The reviewing of titles and abstracts identified 430 studies as unrelated. The remaining 157 studies were selected for investigation of their full text after that 141 studies were removed from study due to their inappropriateness. The remaining 16 studies were entered to be assessed based on the quality measurement scale and inclusion and exclusion criteria from them all of 2 studies was removed and 14 ones were identified to be appropriate for our study (Fig.1). These 14 studies had investigated the effect of progesterone (intramuscular progesterone

in 7 studies, vaginal progesterone in 5 studies and oral progesterone in 2 studies) on the mean gestational age at delivery in women with one risk factors of preterm labor (previous preterm labor without short cervical length and vice versa). In 9 studies the control groups had been received placebo, in 2 studies the control group subjects received daily nursing care, in 1 study they received ritodrine and in 2 studies they received no treatment. The total subjects were 1259 and 2653 for progesterone and control groups. The mean gestational age at delivery for progesterone group was longer than that of control group in 11 studies, was shorter in 2 studies and was equal to that of control group in 1 study.

The significance level has been reported in 8 studies with a significant difference between mean gestational age at delivery of progesterone and control groups in 6 studies (table1). From 14 studies, 1 study which has not reported standard deviation for gestational age at delivery was not entered into the meta-analysis (Table1).

The results of other 14 studies were combined using meta-analysis. The heterogeneity between these studies was calculated as very high (I-squared=93.1%, Q=173.2, P<0.001). Therefore, using the random effect model the standardized difference between mean gestational age at delivery of progesterone group was estimated to be 0.74 (0.41-1.06) month longer than that of control group with CI=95% which was significant statically. 3 variables including type of risk factor (β=0.54, P-value=0.458), administered progesterone (β=-0.03, P-value=0.931) and intervention of control subjects (β=-0.25, P-value=0.315) were investigated using meta-regression for the identification of heterogeneity which showed that these factors are not the source of heterogeneity.

It seems that the sample size of included trials is one of the heterogeneity sources. The results of standardized difference estimation of mean gestational age at delivery in the subgroups of administered progesterone are shown in figure2.

This figure shows that the mean gestational age at delivery of intervention group in studies in which the case subjects have received intramuscular progesterone is 0.85 (0.31-1.38) months longer than that of control subjects (CI=95%). Also, the mean gestational age at delivery of intervention group in studies in which the case subjects have received vaginal progesterone is 0.73 (0.13-1.34) months longer than that of control subjects (CI=95%). But these observed differences were not statistically significant.

Also, the results of standardized difference estimation of mean gestational age at delivery in the subgroups of intervention type in control subjects are shown in figure3.

This figure shows that the mean gestational age at delivery of intervention group is 1.53 (1.14-1.92) months longer than that of control subjects which have received no treatment (CI=95%). Indeed, figure4 shows that the mean gestational age at delivery of intervention group among women with previous preterm delivery is 0.69 (0.36-1.03) months longer than that of control groups (CI=95%) with preterm history. Also, the mean gestational age at delivery of intervention group among women with short cervical length is 0.95 (-0.04-1.94) months longer than that of control groups (CI=95%) with this risk factor.

We used Egger's test for the investigation of potential publication bias in that the intercept confidence interval was ranged from -77.5 to 49.2 which includes zero value. Also, P value was 0.633 which does not show statistical significance. These results indicate that a considerable bias in the publication of the results has not taken place (Figure 5).

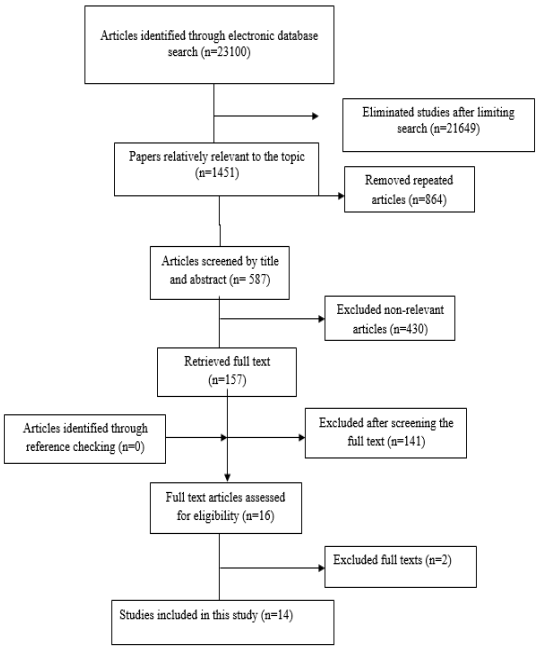

Figure 1
Literature search and review flowchart for selection of studies

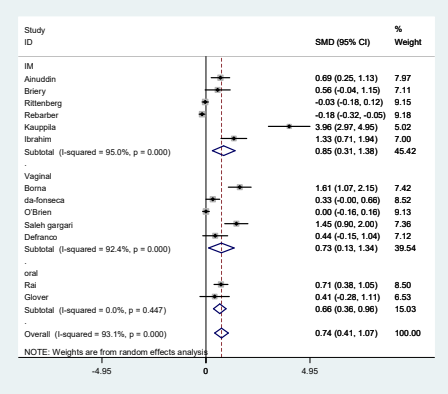

Figure 2
The difference of mean gestational age at delivery of progesterone and control groups (CI=95%) based on the administered progesterone.

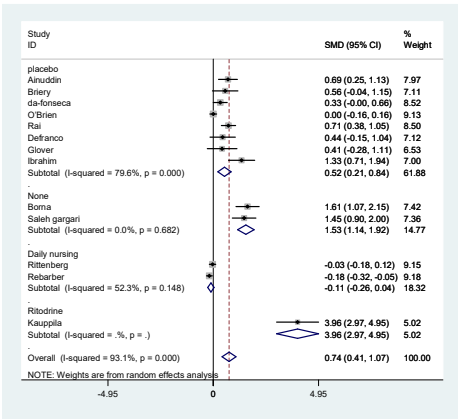

Figure 3
The difference of mean gestational age at delivery of progesterone and control groups (CI=95%) based on the type of intervention of control group

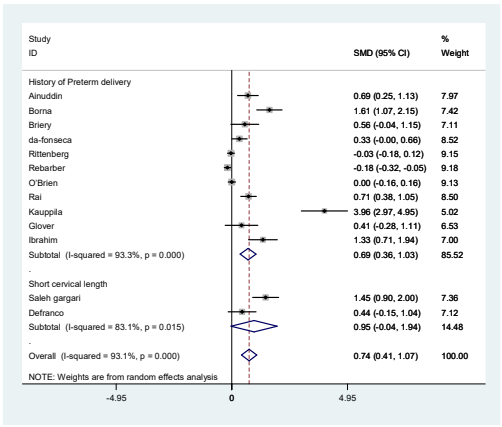

Figure 4
The difference of mean gestational age at delivery of progesterone and control groups (CI=95%) based on the risk factor

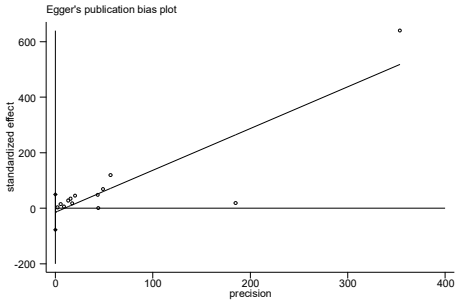

Figure 5
Egger test for investigating the publication bias of results

Table1: Characteristics of primary studies which were included into the meta-analysis

No.	First author	Year	Location	Risk factor*	Administered progesterone	Type of intervention in control group	Sample size		GA at delivery (weeks), case group		GA at delivery (weeks), control group		p-value
							case	control	Mean	SD	Mean	SD	
1	Ainuddin [1]	2009	Pakistan	1	IM	placebo	50	36	36.14	2.63	34.33	2.61	0.004
2	Borna [25]	2008	Iran	1	Vaginal	none	37	33	36.7	1.5	34.5	1.2	0.041
3	Saghafi [26]	2011	Iran	1	IM	placebo	50	50	36.94	-	32.1	-	0.011
4	Briery [27]	2014	USA	1	IM	placebo	22	23	31.8	4.1	29.6	3.8	0.067
5	da-fonseca [28]	2003	Brazil	1	Vaginal	placebo	74	71	37	2.8	36	3.3	-
6	Rittenberg [29]	2009	USA	1	IM	daily nursing	342	342	36.6	3	36.7	2.9	-
7	Rebarber [30]	2008	USA	1	IM	daily nursing	232	1650	35.4	4.7	36	3	-
8	O'Brien [31]	2007	Multinational	1	Vaginal	placebo	309	302	36.6	3.8	36.6	4.2	-
9	Rai [32]	2009	India	1	oral	placebo	74	74	36.1	2.6	34	3.25	-
10	Hartikainen-Sorri [33]	1980	Finland	1	IM	ritodrine	24	24	39.1	0.3	37.7	0.4	-
11	Saleh Gargari [34]	2012	Iran	2	Vaginal	none	32	32	36.2	1.4	34.1	1.5	0.039
12	Defranco [35]	2007	USA	2	Vaginal	placebo	19	27	36.3	2.4	34.6	4.6	-
13	Glover [36]	2011	USA	2	oral	placebo	19	14	37	2.7	35.9	2.6	0.3
14	Ibrahim [37]	2010	Egypt	1	IM	placebo	25	25	37.47	1.559	34.71	2.49	0.001

*** History of Preterm delivery=1, Short cervical length=2**

DISCUSSION

Preterm birth, which has different causes and various negative consequences, is a dramatic event for infants, their families and societies.[4] In recent years, despite improvements in perinatal care, preterm birth rate has increased, to the extent that it has become an important clinical problem and one of the major health concerns in different countries.[1-6] It seems that the reduction of preterm birth rate can have many benefits through the reduction of infants' morbidity, mortality and long term disability.[13] However, despite extensive efforts, the management of preterm labor, continue to be a major challenge for clinicians.[1,7,9] Preventing preterm birth is not possible without doing extensive research on the various aspects of this condition.[7] The high and increasing rate of preterm birth and its widespread negative consequences justify the necessity and importance of more research in this field. In the past decades, a great effort from researchers and clinicians has been done in order to identify the predictors and appropriate prevention and treatment protocols for preterm birth.[1] In this case, many studies have shown that history of previous preterm labor and short cervical length are among the best predictors of preterm labor in pregnant women.[3,6,9,10,11,13,16] Also, in terms of treatment, progesterone therapy has been identified as the most effective intervention.[7,8,10,17,20] Although numerous studies such as Mackenzie et al. (2006), Dodd et al. (2006), Sanachez et al. (2005), a multicenter randomized controlled trial by the US Institute of Child Health and Human Development (NICHD) and a large controlled clinical trial in Brazil (2003) have shown that progesterone therapy is an effective intervention in the prevention of preterm labor.[38-42] However, some studies including a systematic review at the end of the 1980s[17] have concluded that progesterone products are not effective for the management of preterm labor. So, it seems that in this field research still needs to be done. the aim of our study was to analyze the results of studies which have been performed in order to investigate the efficacy of progesterone in the prevention of preterm labor in women with single risk factors (previous preterm labor without short cervical length and vice versa). For this, a broad search of electronic databases without any restrictions of location, language or time was done; many studies were found and evaluated in terms of the quality. Finally, 14 studies (including 12 randomized clinical trials and 2 retrospective cohorts) were included in our meta-analysis. The administered progesterone for the intervention group was intramuscular in 7 studies, vaginal in 5 cases and oral progesterone in 2 ones. Also, the control subjects had received placebo in 9 studies while in they had received daily nursing care in 2 studies, no treatment in 2 other ones and ritodrine in 1 study. The main outcome of our meta-analysis was mean gestational age at delivery. In 13 of 15 studies included in the meta-analysis, mean gestational age at delivery was longer in case group while in one study it was equal in 2 groups and one other study, the control subjects had longer mean gestational age at delivery than progesterone ones. Also, our meta-analysis indicated that mean gestational age at delivery in the progesterone group is 0.74 (0.41-1.06) month longer than the control group and this difference is statistically significant. So in summary, our results suggest that progesterone therapy has sufficient efficacy in the prevention of preterm labor occurrence in women with single risk factor.

CONCLUSION

In brief, our results approved the efficacy of progesterone therapy in the prevention of preterm labor in women with single risk factors. Therefore, it can be considered as an effective intervention in the management of preterm labor.

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