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The Efficacy of Progesterone Therapy for the Prevention of Preterm Labor in Women with Mixed Risk-factors: A Systematic Review and Meta-analysis of Randomized Clinical Trials

Running title: Progesterone for the Prevention of Preterm Birth

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Abstract

Background: Preterm birth is a worldwide concern which has widespread negative consequences. Therefore, prevention of preterm birth has become a top priority of health managers and clinicians in recent decades.

Objective: To evaluate the efficacy of progesterone therapy in the prevention of preterm labor in women with mixed risk factors.

Search strategy: An extensive search of electronic databases was done (date last searched April 2016). No restrictions of language, time, or geographic location were applied.

Inclusion criteria: All randomized clinical trials of singleton pregnancies with multiple risk factors (including prior preterm birth and short cervical length) that were randomized to treatment with progesterone (intervention group) and placebo or no treatment (control group) were included in meta-analysis.

Primary outcome: Our primary outcome was gestational age at delivery.

Results: Three RCTs (521 subjects and 37823 control women) were included. Random effect model showed that mean gestational age at delivery of progesterone group is 0.18 (-0.41-0.77) month longer than that of control group with CI=95% but this difference is not statically significant.

Conclusions: Progesterone therapy has not sufficient efficacy in the prevention of preterm labor in women with multiple risk factors. However, further investigation is required to unequivocally establish this result.

Keywords: Recurrent preterm birth, Preterm labor, Progesterone, Short cervical length

Introduction:

According to the World Health Organization, the birth after 20 weeks and before 37 completed weeks or 259 days of gestation is said preterm birth which is a common complication of pregnancy. Preterm birth can be classified based on the birth weight, clinical presentation or the gestational age at delivery. In the latest classification, birth at before 28 weeks of gestation is said extremely or severe premature birth which accounts for less than 5% of all preterm births. The birth at 28-31 weeks is defined as the very premature birth which accounts for less than 1% of all deliveries and about 10% of all preterm births and the birth at 32-33 and 34-36 weeks of gestation are called mild and moderate preterm birth, respectively which account for the majority (85%) of all preterm births [1-9]. Annually, about 13 million babies are born as premature worldwide.

Preterm birth has very negative consequences. It is the main cause of infant mortality and long-term disability. While this type of birth includes smaller part of all births but it is accounted for more than 85% of perinatal deaths and more than 35% of all neonatal deaths. Studies show that the risk of death in preterm infants is more than 40 times higher than other babies. [5] Although advances in recent decades has increased the survival chance of premature infants, but the survived prematurely born babies is more likely to experience the long-term health problems during their lives until old ages [7-14]. Also, the financial burden of preterm birth is another important negative consequence. For instance, in an estimation of preterm birth costs in US at 2005, the economic costs related to preterm birth including those costs of caring from the premature infants for health system, educational costs and the loss of labor force productivity has been estimated to be more than 26.2 billion dollars [3,12].

Preterm birth is a multifactorial event which is affected by various factors including such as social, physiological, biological, demographic, anthropometric, ergonomic and socio-economic ones, medical and midwifery conditions, lifestyle, psychosocial profile and life events during pregnancy [15-18].

In recent decades, prevention of preterm birth has become a top priority of health systems in all countries due to its widespread negative consequences [16-18]. Thus, the search for effective approaches for the prevention and control of preterm delivery is one of the major research topics among clinicians. The first step in the prevention of preterm birth is the correct identification of women who are at risk of preterm delivery [10]. Several indicators can help to predict preterm delivery, [1] but studies have shown that the most powerful predictors of preterm delivery are the history of previous preterm delivery and the short cervix length during pregnancy [9,10,13]. After identifying of at risk pregnant women the effective interventions should be applied to treat and prevent preterm delivery. So far, the treatment with a variety of different drugs has been the first method of preventing from preterm delivery occurrence among at risk women [7]. For this, in the past decades a large number of different drugs with different pharmacological formulas has been introduced but the progestin drugs

has been the most effective ones in the prevention of preterm labor [7,14,18]. So, today Progestins which are available in various forms are the first prescription of clinicians for the women who have the risk factors of preterm delivery. Therefore, in the recent decades, a much studies have been done to evaluate the efficacy, side effects and other aspects of Progestins in the management of preterm birth [1,3,7,11,14,18]. Although in many cases the efficacy of these drugs has been approved but many researchers and clinicians believe that the efficacy of these drugs in the prevention of preterm birth in women with single risk factor is different from that of women with multiple risk factors. Also, the efficacy of Progestins in the management of preterm birth in singleton pregnancies is highly different from the multiple pregnancies. In this systematic review and meta-analysis we attempted to analyze the results of published clinical trials regarding the efficacy of Progestins in the prevention of preterm birth in singleton pregnancies with multiple risk factors (history of preterm delivery and short cervix length). .

Methods:

Search strategies:

This meta-analysis was performed according to a recommended protocol for systematic reviews. We searched MEDLINE, Science Direct, Scopus, Cochrane Central Register of Controlled Trials, OVID, ClinicalTrials.gov, EMBASE, SID (Scientific Information Database), Magiran (a Persian scientific database) and Google Scholar (date last searched April 2016) with using keywords and text words preterm birth, preterm delivery, preterm labor, singleton pregnancy, cervical length, prior preterm birth, recurrent preterm birth, progesterone, Progestins, vaginal, intramuscular, oral and their Persian equivalents with "Or" and "And" operations in the title and abstract of studies. Also, the reference lists of retrieved studies were searched manually. No restrictions for time, language or geographical location were placed. Search was conducted 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 multiple risk factors (including prior preterm birth and short cervical length) 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. After removing repeated studies, the unrelated ones were identified by reviewing the title, abstract and full text which then removed, also. The results of the reminders were investigated to prevent bias caused by reprint (publication bias of transverse and longitudinal). The reminder ones were entered to quality assessment process.

Quality assessment:

Two authors (MA.B and M.M) evaluated the quality of the included trials. This process was done using Jadad [19] scale. This scale 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 [20]. The scale includes 3 domains related to quality of clinical trials: 1) random sequence generation description (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 event 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, progesterone which administered and the mean and standard deviation of gestational age at delivery in intervention and control groups were extracted.

Inclusion and exclusion criteria:

All randomized clinical trials of singleton pregnancies with multiple risk factors (including prior preterm birth and short cervical length) that were randomized to treatment with progesterone (intervention group) and placebo or no treatment (control group) and passed the quality assessment process which have reported the sample size and mean and standard deviation of gestational age at delivery for intervention and control groups were included in the study. Exclusion criteria included trials involving women with prior preterm birth without short cervical length and vice versa 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, the abstracts of seminars without full text, case reports and studies which didn't obtain the minimum required score of quality assessment process were excluded from study.

Data analysis:

Data analysis was done using STATA ver.11 software. The index of heterogeneity between studies was determined using Cochran (Q) and I-squared tests. Given that the existing heterogeneity between studies random effect model was used to estimate the standardized difference of mean gestational age at delivery. 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 sides lines represent 95% confidence interval. Potential publication bias was assessed by using Egger's test. P value < 0.01 was considered statistically significant. Also, we investigated the factors related to

heterogeneity using meta-regression and analysis was done in subgroups based on the administered progesterone (IM, vaginal, oral) and risk factor (previous preterm labor or short cervical length).

Results:

We found 23500 studies in our initial search from which 22876 studies were removed by limiting the search. From reminding 714 studies, 328 studies were removed because of overlapping of searched databases. The reviewing of titles and abstracts identified 321 studies as unrelated. The remaining 67 studies were selected for investigation of their full text after that 64 studies were removed from study due to their inappropriateness. The remaining 3 studies were entered to be assessed based on the quality measurement scale and inclusion and exclusion criteria from them all of 3 studies were found to be appropriate for our study (Fig.1). These 3 studies had investigated the effect of progesterone (intramuscular progesterone in 2 studies and vaginal progesterone in 1 study) on the mean gestational age at delivery in women with multiple risk factors of preterm labor (including previous preterm labor and short cervical length). In 2 studies the control subjects had been received placebo and in 1 study no treatment. The total subjects were 521 and 37823 for progesterone and control groups. The mean gestational age at delivery for progesterone group was longer than that of control group in 2 studies (Johnson and Cetingoz) and was shorter in 1 study (Dudas). The results of these 3 studies were combined using meta-analysis. The heterogeneity between these studies was very high (I-squared=90.8%, Q=21.8, 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 0.18 (-0.41-0.77) month longer than that of control group with CI=95% but this effect was not significant statically (Fig.2). We used Egger's test for the investigation of potential publication bias in which the intercept confidence interval was ranged from -67.6 to 50.4 which includes zero value. Also, P value was 0.316 does not show statistical significance. These results indicate that a considerable bias in the publication of the results has not taken place. It is notable that the low number of studies is one of the limitations of publication bias investigation and a main cause of high value of intercept confidence interval of Egger test. Also, the number of studies was not enough to assess the factors related to heterogeneity but it seems that the high differences between sample size of intervention and control groups of studies is a main cause of the heterogeneity of results.

Figure1. Literature search and review flowchart for selection of studies

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

Figure2. The difference of mean gestational age at delivery of progesterone and control groups (CI=95%)

Discussion:

Preterm birth, which is a common complication of pregnancy, is a major concern of health systems around the world (19-1) this phenomenon has widespread negative consequences (12).

That's why many specialists and researchers have tried to find effective interventions in order to prevent it. These efforts have been led to the identification of risk factors of preterm labor as a part of efforts to identify those women who at risk of preterm labor for treatment (3).

Although, various factors have been identified as preterm labor risk factors but many studies have shown that the previous preterm labor and short cervical length during pregnancy are the strongest risk factors of preterm labor [3,9,10]. These risk factors can predict the preterm labor for weeks before delivery and give enough time to clinicians for intervention in order to prevent from its occurrence [10]. Now the most common intervention for the prevention of preterm labor is the prescription of progesterone drugs which are available in various forms [4,5,7,14,18,24]. In recent years several studies have been done to evaluate the efficacy of these drugs in the management of preterm labor [1,3,7,11]. The results of these studies are very different. It seems that the different underlying risk factors of women which have been studied are one of the main reasons of such diversity in the results of these studies. For examples, it is said that the women with mixed risk factors may response to progesterone therapy poorer than those who have only one risk factor. With this hypothesis, the aim of our study was to analyze the results of studies which have been done in order to investigate the efficacy of Progestins in the prevention of preterm labor in women with mixed risk factors (previous preterm labor and short cervical length). For this, an extensive search of electronic databases without any location, language or time restrictions was done; many studies were retrieved and evaluated in terms of the quality. Finally 3

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randomized clinical trials were found to be eligible to include in meta-analysis. All of these studies were randomized clinical trial and the used drug for the case subjects was intramuscular progesterone in 2 studies and vaginal progesterone in one study.
Also, placebo has been administered for control subjects in 2 studies while in 1 study they have not received any treatment. The main outcome of our meta-analysis was mean gestational age at delivery. In 2 of 3 studies included in the meta-analysis (an intervention with intramuscular and an intervention with vaginal progesterone) mean gestational age at delivery is longer in case group while in one study which conducted with a relatively large sample (Duddas, 2006) mean it is longer in control group. Also, our meta-analysis showed that mean gestational age at delivery in the progesterone group is 0.18 (-0.41-0.77) month longer than the control group, but this difference is not statistically significant. So in summary, our findings suggest that progesterone therapy has not sufficient efficacy in the prevention of preterm labor occurrence in women with multiple risk factors. However, due to the low number of studies on the efficacy of progesterone in the prevention of preterm labor among women with mixed risk factors (probably due to the rarity of pregnant women with multiple risk factors simultaneously) Further studies in this field is essential.

Conclusion: In brief, our results showed that progesterone has not sufficient efficacy in the prevention of preterm labor in women with mixed risk factors.

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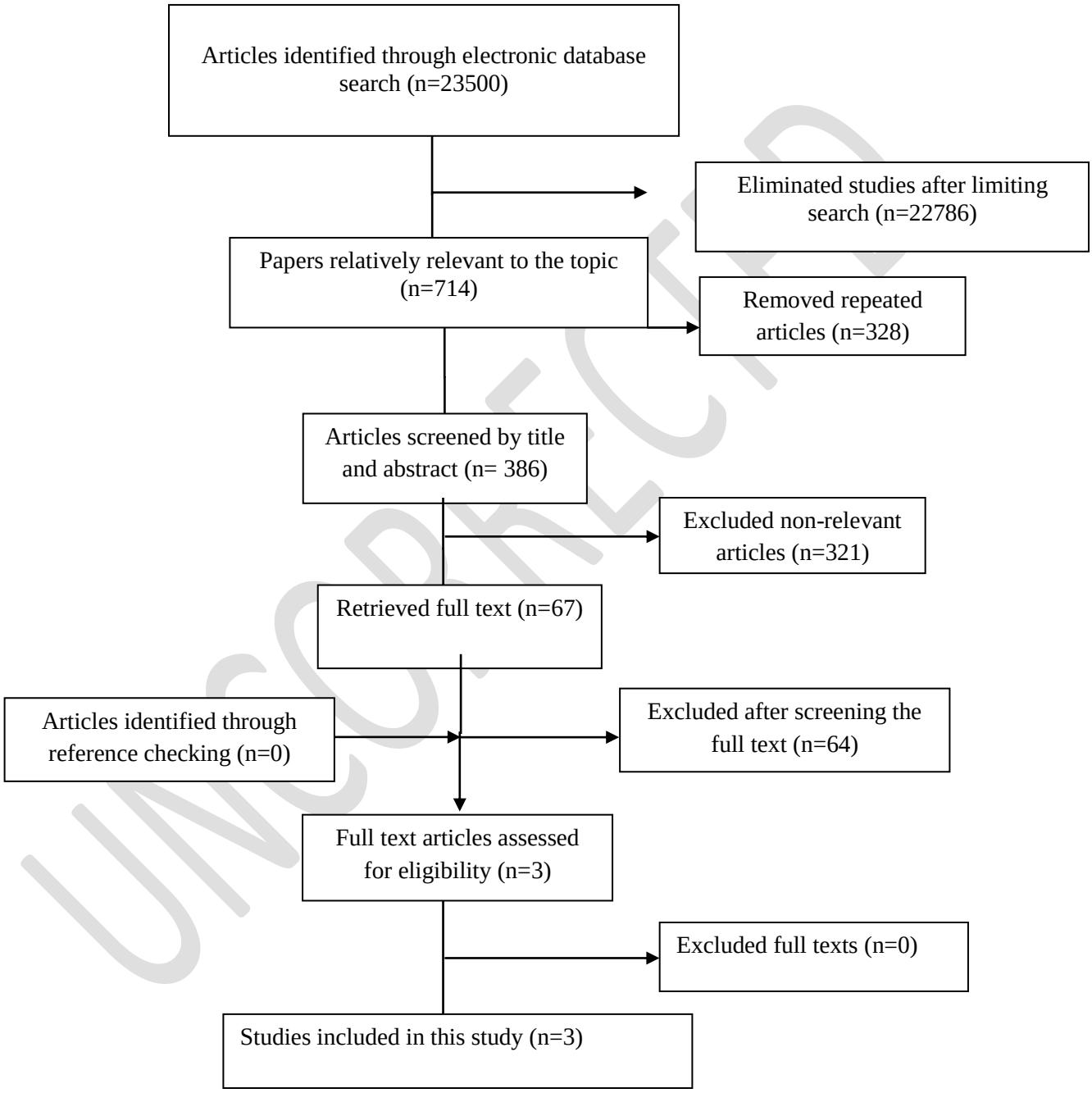

Figure1. Literature search and review flowchart for selection of studies

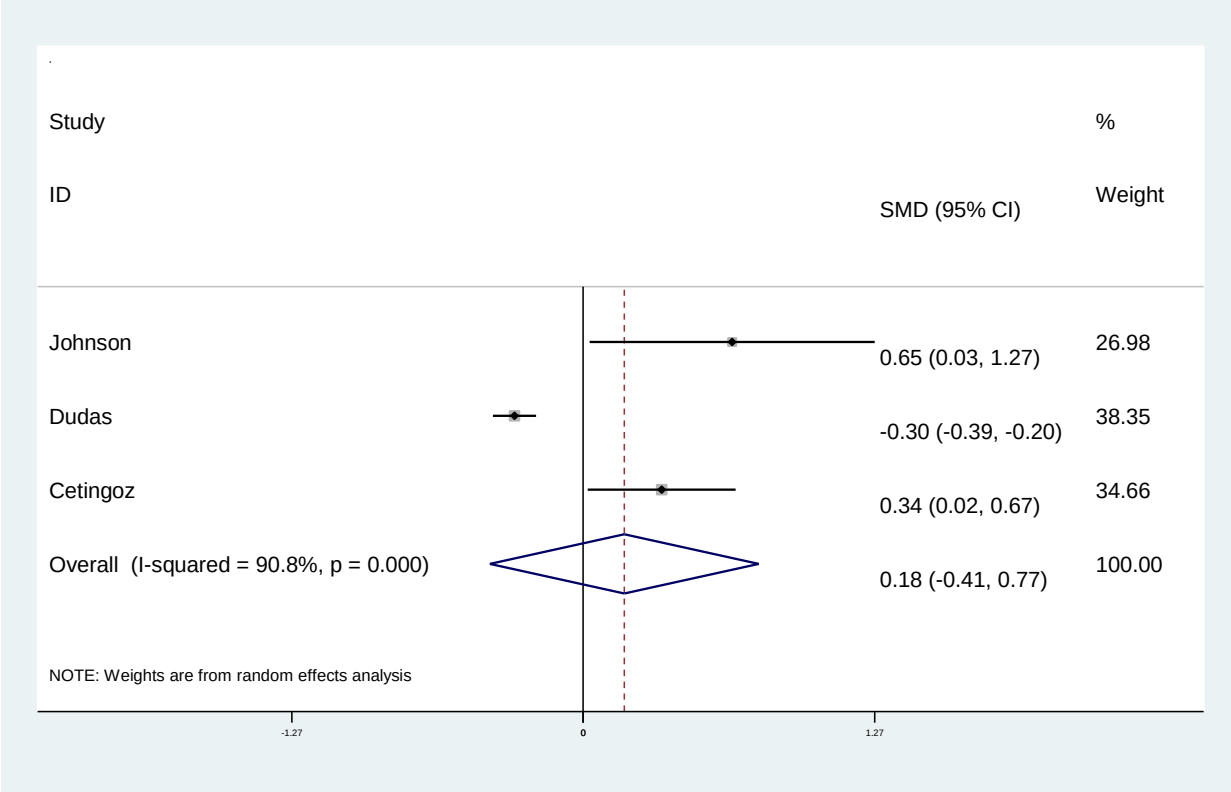

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Table1: Table1. Characteristics of primary studies which were included into the meta-analysis

No.	First author	Publication year	Country	Sample size		GA at delivery (weeks), case group		GA at delivery (weeks), control group		Administered progesterone	type of intervention in control group
				Case	Control	Mean	SD	Mean	SD		
1	Johnson [21]	1975	USA	18	25	38.6	1.6	35.2	6.7	IM	placebo
2	Dudas [22]	2006	Hungary	433	37718	38.8	2.4	39.4	2	IM	none
3	Cetingoz [23]	2011	Turkey	70	80	36.9	2.4	35.9	3.3	Vaginal	placebo