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Is 17 alpha-hydroxyprogesterone Effective for Preventing Preterm Labor in High Risk Women?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

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ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not "Is 17-alpha hydroxyprogesterone effective for preventing preterm labor in high risk women?".

STUDY DESIGN: Review of one randomized, double blind, controlled trial, one randomized, double blind, placebo controlled trial and one randomized controlled trial published in English between 2015 and 2018.

DATA SOURCES: All three studies were gathered from peer- reviewed journals and found using PubMed.

OUTCOMES MEASURED: Preterm delivery defined as birth less than 37 weeks gestation for Facchinetti et al., Shadab et al. and Winer et al.[6,7,8]

RESULTS: The RCT performed by Facchinetti et al. showed no statistically significant reduction in rates of preterm labor in the patients treated with 17 alpha-hydroxyprogesterone in comparison with the control group ($p = 0.949$). The preterm birth rate in the progesterone group was 23% vs. 22% in the control group.[6] Similarly, Winer et al. found that progesterone supplementation was not effective in reducing rates of preterm labor with $p>0.99$. The preterm birth rate in the progesterone group was 45% vs 44% in the control group.[8] Conversely, Shadab et al. found significant reduction of preterm birth rates treating with 17-alpha hydroxyprogesterone compared to a control group ($p<0.05$). The preterm birth rate in the progesterone group was 28.79% vs 59.09% in the control group.[7]

CONCLUSIONS: The three RCTs utilized for this review did not hold consistent data in determining whether 17 alpha-hydroxyprogesterone supplementation is effective in reducing rates of preterm birth. Facchinetti et al. and Winer et al. demonstrated no statistically significant reduction in preterm birth rates whereas Shadab et al. found a statistically significant reduction in rates.[6,7,8] The research utilized for this review held inconclusive results and revealed limitations within each study. Further research is needed to better evaluate the effects of 17 alpha hydroxyprogesterone supplementation in reducing preterm birth rates.

KEYWORDS: 17 alpha-hydroxyprogesterone, premature birth

INTRODUCTION

Premature labor is defined as birth before 37 weeks gestation. It is the number one cause of infant death, and despite major medical advancements, the rates are continuing to rise.[1] Prematurity is attributed as a cause in more than 75% of deaths during the neonatal period.[2] It is closely linked to various developmental disabilities as well as major health conditions and chronic defects.[2]

Preterm labor occurs in up to 10% of labors in the US and up to 25% of labors in developing countries.[3] About 6% of premature infants die due to secondary complications associated with being premature.[2] Premature labor accounts for healthcare costs up to $26.2 billion annually.[1] Although the exact number is not estimated, it is known that preterm labor is strongly linked to many long term disabilities, resulting in an unreportable number of health care visits through the rest of the baby's life.[1]

There are many iatrogenic conditions known to contribute to rates of preterm labor including kidney disease, preeclampsia, and gestational diabetes.[3] There are also many spontaneous and infectious etiologies including preterm premature rupture of membranes (PPROM), multiple pregnancy, and cervical dysfunction.[3] Prematurity rates rise in underweight mothers, with BMIs below 18 kg/m^2.[3] It is thought that these women are too malnourished to support the fetus long term. Globally, major risk factors include infectious diseases like malaria, HIV, and tuberculosis.[3]

Conventional therapies to prevent preterm labor are limited and lack efficacy in long term prevention. A common therapy utilized is cervical cerclage, a procedure that surgically sutures a women's cervix closed to prevent preterm dilation and to prolong the time until labor.[4] Studies have been shown that cervical cerclage greatly lacked efficacy in women with a shortened cervix

of less than 25mm. Short term therapy includes administering magnesium sulfate to laboring mothers to delay contractions.[4] This therapy is completely ineffective at delaying labor long-term. Lifestyle modifications have been shown to drastically improve rates of preterm labor. These modifications include cigarette smoking cessation, decreased alcohol consumption, and bedrest.[4]

Although there are major medical initiatives to treat and prevent the complications arising from preterm labor, it still affects 1 in 10 US babies.[3] Advanced mid-level providers, including physician assistants, who specialize in areas such as OB/GYN and neonatology commonly encounter preterm labor and it's subsequent consequences regularly. With more efficient prevention therapies, providers will be better able to treat preterm labor and prevent infant mortality and morbidity.

Progesterone is a hormone that is imperative in a women's ability to become pregnant and maintain a pregnancy. Research evidence has suggested that labor is associated with a preceding withdrawal of progesterone action at the site of the uterus.[5] There are many mechanisms proposed to explain the direct physiology in how progesterone affects labor. It has been shown that progesterone levels directly coincide with myometrial contractility, cervical effacement, placental corticotropin releasing hormone, and amniotic fluid production. It has also been shown that progesterone can directly prevent apoptosis of term fetal membranes, preventing PPROM and subsequent preterm birth.[5] Many studies have shown that progesterone may block unwanted contractions before reaching term and subsequently can help retain a pregnancy.[7]

Progesterone therapies including suppositories and injections, have been shown to greatly reduce rates of preterm birth and neonatal death. There is a vast amount of research on the effects progesterone has on preventing preterm labor. Particularly, progesterone therapy is especially

useful for patients in which cervical cerclage is not indicated or is ineffective.[4] It is known that preventing preterm birth is favorable over trying to treat the adverse outcomes that arise from prematurity.[4] This paper evaluates three randomized controlled trials (RCTs) evaluating efficacy of 17-alpha hydroxyprogesterone to prevent preterm labor in women considered to be high risk.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not "Is 17-alpha hydroxyprogesterone effective for preventing preterm labor in high risk women?".

METHODS

Three randomized controlled trials (RCTs) were selected for this review. The key words utilized to search for these studies included 17 alpha-hydroxyprogesterone and premature births. All three articles were published in peer-reviewed journals, in English, between 2015-2018. The RCTs were found utilizing PubMed search engine, and articles were selected based on their ability to answer my clinical question with my patient-oriented outcome of rates of preterm birth. Inclusion criteria consisted of studies that were RCTs published before 2014 and utilized human subjects. Exclusion criteria consisted of studies published before 2014 that were not RCTs. The statistics utilized to analyze these outcomes included p-value, relative risk ratio (RRR), absolute risk ratio (ARR), and numbers needed to treat (NNT).

The population of interest included women with high risk for preterm labor. Although "high risk" was defined differently by each study, generally it included women with singleton pregnancies with cervical length of 25mm or less, who have had an arrested preterm labor, who have a previous history of preterm birth, who have a history of cervical surgery or uterine malformation or have had prenatal exposure to DES[6,7,8]. All three randomized controlled trials utilized a 17-alpha hydroxyprogesterone intra-muscular injection as the intervention of study. In

the study conducted by Facchinetti et al, the intervention utilized was a 341mg intramuscular injection of 17 alpha-hydroxyprogesterone caproate given weekly until 36 weeks gestation. This group was compared to a control group.[6] In the study conducted by Shadab et al, the intervention utilized was a 250mg intramuscular injection of 17 alpha-hydroxyprogesterone caproate given weekly until 37 weeks gestation. This was compared to a group given a placebo of Neurobion, a combination B vitamin.[7] The study conducted by Winer et al, utilized an intervention of 500mg intramuscular injection of 17 alpha-hydroxyprogesterone caproate given weekly until 36 weeks gestation or until preterm birth. This was compared to a control group.[8] The outcome measured in all three RCTs was rates of preterm labor defined as less than 37 weeks gestation.

OUTCOMES MEASURED

This EBM review utilized the outcome of rates of preterm labor. All three RCTs utilized had identical definitions of preterm labor, birth before 37 weeks gestation.

RESULTS

Facchinetti et al. conducted a double blind, RCT utilizing obstetric units from five tertiary care-level university hospitals in Northern Italy. [6] Women were eligible who had singleton pregnancies between 22 and 31 6/7 weeks gestation who had been admitted to the hospital because of a first threatened preterm labor episode. That was defined as the simultaneous presence of contraction at greater than six in 30 minutes and had cervical changes consistent with shorting, softening or dilating on manual exam. [6] Of these women, those who were given tocolysis and corticosteroids for fetal lung maturation and remained at risk for preterm birth due to shortened cervical length (<25mm) were eligible to participate in the study.

Table 1. Demographics & Characteristics of Included Studies

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Facchinetti[6] (2017)	RCT	254	31.8 ± 5.4	Singleton pregnancies with cervical length of 25mm or less, who have had an arrested preterm labor, and no past history of preterm births	Hx PTB, multiparity, PROM, fetal and maternal conditions indicating delivery, Mullerian malformations, prior cervical surgery, presence of regular uterine contractions at discharge	19	341mg IM 17 alpha-hydroxyprogesterone caproate weekly until 36 weeks gestation
Shadab[7] (2018)	RCT	132	>20 years	Singleton pregnancies who have a previous history of preterm birth	Correctable causes including patients with a history of delivery somewhere else, first trimester	13	250mg IM 17 alpha-hydroxyprogesterone caproate weekly until 37 weeks gestation
Winer[8] (2015)	RCT	105	>18 years	Women with a history of spontaneous preterm birth or of cervical surgery, a uterine malformation or prenatal exposure to DES	Cervical dilation greater than 3 cm, chorioamnionitis, PROM, placenta previa, multiparity, severe IGR, major structural or chromosomal fetal abnormality, maternal or fetal disease requiring induced PTB, progestogen therapy before inclusion, ongoing anticonvulsant treatment or participation in other treatment trial	2	500mg IM 17OHP-C weekly until 36 weeks gestation or PTB
Table Note: PTB = Preterm birth, PROM = Premature Rupture of Membranes, IGR = Intrauterine Growth Restriction							

The women in this study could not have a history of previous preterm birth. Refer to Table 1 for exclusion criteria.[6] There were 257 eligible women, 254 opted to participate. Subjects were randomized and 87 women were allocated to the 17 alpha-hydroxyprogesterone caproate group and 81 were allocated to the control group. Of the 168 women who participated in either the IM progesterone or control groups, 8 dropped out and 3 more were excluded from the data analysis due to incomplete data collection. In total, 80 women in the IM progesterone group and 77 women in the control group were analyzed.[6] In the IM progesterone group, 23% (18/80) of mothers had preterm deliveries and in the control group 22% (17/77) of mothers had preterm deliveries. There was no statistically significant difference between groups with $p=0.949$. Statistical significance is noted as $p<0.05$ (Table 2). The relative risk reduction (RRR) was -0.013, the absolute risk reduction (ARR) was 0.01 and the numbers needed to treat (NNT) was -100 (Table 3).[6] An independent data monitoring committee reviewed the data for patient safety. This study was prematurely discontinued due to interim analysis revealing unexpected lack of efficacy associated with a safety concern regarding another treatment group utilized within the study. No safety concerns were noted within the study regarding the IM 17 alpha-hydroxyprogesterone caproate treatment group.[6]

A study conducted by Shadab et al. in an obstetrics outpatient department included women with singleton pregnancy at less than 20 weeks gestational age with a previous preterm birth.[7] Refer to Table 1 for exclusion criteria. Of the 145 patients who opted to participate in the study, 13 were excluded from data analysis due to incomplete records or lost to follow-up. A total of 132 patients were included. Patients were randomized to group A or group B. Group A subjects received IM progesterone weekly while group B received a placebo of Neurobion.[7] The progesterone group had a preterm delivery rate of 28.79% (19/66) and the placebo group had a

rate of 59.09% (39/66). There was a statistically significant difference between groups with a $p<0.05$ (Table 2). The RRR was 0.741, the ARR was 0.303, and the NNT was 4 (Table 3).[7] The study did not address any specific safety concerns but does note that they did not compare any side effects of the drug. The researchers do report that there was no complaint regarding adverse effects or complications secondary to the progesterone injections.[7]

A study conducted by Winer et al. assessed patients from 11 university hospitals in France who were between 20 and 31 weeks of gestation and were considered to be high risk for preterm birth.[8] Inclusion criteria included women with an asymptomatic singleton pregnancy with a history of either preterm birth or cervical surgery, uterine malformation or prenatal DES exposure. Women had to be at least 18 years old, agree to regular follow-up and provide written informed consent. Refer to Table 1 for exclusion criteria.[8] A total of 105 women who met inclusion criteria were randomized into 2 groups. Fifty-one women were allocated to the IM progesterone group while 54 women were allocated to the control group. A total of 2 subjects were lost to follow up. In this study, if a women was admitted before 34 weeks gestation with preterm labor, they were given tocolysis and a course of 12mg betamethasone IM.[8] Women were allowed to remain in the study if labor did not occur. The progesterone group had a preterm delivery rate of 45% (23/50) and the control group had a rate of 44% (24/53). There was no statistically significant difference between groups with a $p>0.99$ (Table 2).[8] The RRR was -0.018, the ARR was -0.01, and the NNT was -100 (Table 3). The study did not discuss any adverse effects of the treatment utilized or safety concerns.[8]

Table 2. Premature Birth Rate and p-value by Study

Study	Progesterone Group	Control Group	P-value
Facchinetti et al.[6]	18 (23%)	17 (22%)	0.949
Shadab et al.[7]	19 (28.79%)	39 (59.09%)	$p<0.05$
Winer et al.[8]	23 (45%)	24 (44%)	$p>0.99$
Statistical significance as $p<0.05$			

Table 3. Calculations for Treatment from Facchinetti et al, Shadab et al., Winer et al.

Study	EER	CER	RRR	ARR	NNT
Facchinetti et al.[6]	0.77	0.78	-0.013	-0.01	-100
Shadab et al.[7]	0.7121	0.4091	0.741	0.303	4
Winer et al.[8]	0.55	0.56	-0.018	-0.01	-100

DISCUSSION

Globally, prematurity is the leading cause of death in babies less than 1 month old and the second leading cause of death in children less than 5 years old.[8] It is evident that preventing premature births will prevent millions of deaths and many major neonatal complications. This systemic EBM review was created to better understand the effects of 17 alpha-hydroxyprogesterone caproate in preventing preterm labor in high risk women. Due to the conflicting evidence of the three randomized, controlled trials utilized, there is still not a clear stance on this topic.

The numbers needed to treat (NNT) values calculated for each of these studies varied from -100 to 4.[6,7,8] Facchinetti et al. and Winer et al. surprisingly had the exact same value for NTT of -100. This value indicates a very insignificant effect of progesterone supplementation at

preventing preterm birth.[6,8] However, Shadab et al. had a NNT of 4, indicated a very strong and large treatment effect and clinical significance.[7]

Facchinetti et al. addressed limitations of their study including it's premature discontinuation due to lack of efficacy and some safety concerns regarding another treatment group they utilized.[6] They report that the likelihood of the study supporting evidence that the progesterone treatment group decreased rates of preterm birth was extremely unlikely after the interim data analysis. The study reports that utilizing women with a previous preterm birth would have overestimated the efficacy of progesterone because they acknowledge the many established studies supporting the efficacy of progesterone for women with that significant history.[6] Shadab et al. notes their limitations include their lack of comparing side effects of the drugs. They recommend further studies to evaluate possible adverse effects or complications that may arise from utilizing 17 alpha-hydroxyprogesterone.[7] Lastly, Winer et al. recognizes multiple limitations of their study. The first is the high rate of cerclage placement among their subjects. They report that 38% of their control group and 45% of their treatment group had a cerclage placed prior to their enrollment in the study.[8] Another limitation discussed is their early discontinuing of the study due to futility noted at interim analysis.[8] They also note that the progesterone injections were initiated around 24 weeks gestation in their subjects, potentially too late in pregnancy to have observed the full treatment effect progesterone injections had the potential to achieve. Finally, Winer et al. notes that neither the investigators of the study nor the participants were blinded to the allocation. The researchers remark that they believe the data analysis revealed no bias associated with their lack of blinding due to their insignificant difference in data.[8] Limitations within this literature review include selection of articles with varying inclusion criteria. Two studies, Shadab et al. and Winer et al. utilized women with a

history of preterm birth as inclusion criteria into their studies, however Facchinetti et al. used it as exclusion criteria. Reviewing literature with more cohesive inclusion and exclusion criteria may be a future consideration to enhance the validity of the data. Overall, these studies all exhibited various limitations that may have contributed to their outcomes.

Although the use of progesterone in preventing preterm labor is not considered to be a new therapy, there is still a great amount of conflicting thought on its use. The US Food and Drug Administration (FDA) approved progesterone supplementation for reducing the risk of recurrent preterm birth in women with a history of at least one prior spontaneous preterm delivery in 2011.[5] Although it is approved, there is still major controversy over the optimal formulation, dosing, and route of administration.[5]

CONCLUSION

This EBM review of three RCTs has provided conflicting evidence as to whether 17 alpha-hydroxyprogesterone is effective in preventing preterm labor in high risk women. Facchinetti et al. and Winer et al. failed to provide sufficient evidence that there is a statistically significant effect of progesterone injections.[6,8] Conversely, Shadab et al. did provide evidence that progesterone injections have a large treatment effect in preventing preterm labor.[7]

Future study is warranted to evaluate the generalizability of IM progesterone supplementation in preventing preterm labor among women. The RCT that revealed strong clinical significance of progesterone injections to prevent preterm labor was the study with the lowest dose of progesterone administered and the most generalized patient population. To better evaluate the effect of this treatment, more studies should be conducted utilizing a more general population such as any women who have previously had a preterm birth.

The inconsistency of these study results indicates that more research should be done to better understand the true effects of progesterone supplementation. Because preterm labor is so prevalent and rates continue to rise despite major medical advancement, it is imperative that more therapies are explored to better prevent preterm labor and/or treat its subsequent consequences.

REFERENCES

1. Premature Babies. Marchofdimes.org. https://www.marchofdimes.org/complications/premature-babies.aspx. Updated 2020. Accessed October 10th, 2020.

2. Glass HC, Costarino AT, Stayer SA, Brett CM, Cladis F, Davis PJ. Outcomes for extremely premature infants. *Anesth Analg*. 2015;120(6):1337–1351. doi:10.1213/ANE.0000000000000705

3. Steer P. The epidemiology of preterm labour. *BJOG.* 2005 Mar;112 Suppl 1:1-3. doi: 10.1111/j.1471-0528.2005.00575.x. PMID: 15715585

4. Keelan JA, Newnham JP. Recent advances in the prevention of preterm birth. *F1000Res*. 2017;6:F1000 Faculty Rev-1139. Published 2017 Jul 18. doi:10.12688/f1000research.11385.

5. Norwitz ER, Caughey AB. Progesterone supplementation and the prevention of preterm birth. *Rev Obstet Gynecol*. 2011;4(2):60-72.

6. Facchinetti F, Vergani P, DiTommaso M, et al. Progestogens for maintenance tocolysis in women with a short cervix. *Am J Obstet and Gynecol*. 2017; 130 (1),64-70. doi: 10.1097/AOG.0000000000002065.

7. Shadab W, Riaz S, Aftab F et al. Efficacy of 17alpha-hydroxyprogesterone in prevention of preterm labour in high risk pregnant women. *J Ayub Med Coll Abbotabad*. 2018;30(2),209-12.

8. Winer N, Bretelle F, Senat MV. 17 alpha-hydroxygprogesterone caproate does not prolong pregnancy or reduce the rate of preterm birth in women at high risk for preterm delivery and a short cervix: a randomized controlled trial. *Am J Obstet and Gynecol*. 2015;212:485.el-10.