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Original Article

Does Progesterone Prevent Preterm Labor in Complicated Monochorionic Twin Pregnancies after Radiofrequency Ablation of One Fetus?

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Abstract

Background: Twin pregnancies have a higher risk of preterm labor than singletons. Otherwise, progesterone using to reduce the risk of preterm labor in twin pregnancies remains controversial. Therefore, this study evaluated the effect of intramuscular progesterone to prevent preterm labor in complicated monochorionic diamniotic twin pregnancies after Radiofrequency Ablation (RFA) of one fetus.

Methods: Pregnant women with monochorionic diamniotic twin pregnancies of 16 to 26 weeks of gestational age in an academic center were randomly assigned to receive intramuscular 17-hydroxy progesterone caproate weekly until 36 weeks of gestational age after RFA of one fetus and a control group who did not receive intervention after RFA. Demographic and obstetrical characteristics, as well as maternal, fetal and neonatal outcomes were compared between groups.

Results: In total, 79 participants were recruited in the study. The mean±SD of gestational age at delivery in case and control groups were 34.6±3.8 and 34.6±5.1 with no significant difference (p=0.967). Neonatal outcomes including birth weight (p=0.870), intensive care unit admission (p=0.415), premature preterm rupture of membrane (p=0.115) and pregnancy outcome (live birth, fetal demise or neonatal death) (p=0.524) were not different either. Indeed, gestational age at delivery was inversely related to cervical length at the time of procedure and maternal body mass index, but these differences were not statistically significant. Also, there was no significant difference in terms of gestational diabetes, which was a worrying complication of 17-hydroxy progesterone caproate.

Conclusion: Although 17-hydroxy progesterone caproate seems to be safe with no apparent maternal and neonatal side effects, it does not prolong pregnancy after RFA. Further studies with longer follow up and larger sample size are suggested.

Keywords: 17-Hydroxy progesterone caproate, Monochorionic diamniotic twin pregnancies, Radiofrequency ablation

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Introduction

Over the past decades, following the increase in the use of Assisted Reproductive Techniques (ARTs), the prevalence of twin and multiple pregnancies has increased significantly (1). Multiple pregnancies are associated with higher rates of obstetric complications including preterm delivery, premature rupture of membranes, stillbirth, and structural abnormalities (2). Meanwhile, Monochorionic (MC) twin pregnancies put women at risk for specific complications such as twin reversed arterial perfusion sequence (TRAPS), Twin Anemia-Polycythemia Sequence (TAPS), Twin-Twin Transfusion Syndrome (TTTS) as well as selective Intrauterine Growth Restriction (IUGR) or fetal anomalies (3).

The management of these twins are serial amnioreduction or laser ablation (4). Moreover, in newer methods such as Radiofrequency Ablation (RFA), the umbilical cord of the affected twin is blocked by radiofrequency ablation (5) that seems to be a reasonable option and the survival rate of the neonates is promising (6). However, RFA is associated with a number of known complications including miscarriage, Preterm Labor (PTL), premature rupture of membranes, and intrauterine death of the unaffected fetus (7,8). Among these, PTL is the most important cause of morbidity and mortality (9). Various methods to prevent preterm delivery in twin pregnancies have been studied, which include best rest (10), prophylactic tocolysis (11), using intramuscular or vaginal progestin (12), cerclage (12) and pessaries (13) and totally, it seems that using vaginal progesterone to reduce the risk of preterm labor in twin pregnancies remains controversial.

Complicated twin pregnancies that undergo invasive procedures, including RFA, are at increased risk of preterm delivery compared to other twin pregnancies with normal cervical length. These pregnancies would be managed as a single pregnancy after diminishing the affected twin. Therefore, it seems taking 17-hydroxyprogesterone caproate supplements may inhibit preterm delivery and therefore prevent the consequences of neonatal preterm birth. In this study, we aimed to evaluate the effect of 17-hydroxy progesterone caproate in complicated monochorionic twin pregnancies that undergo RFA procedure to selectively fetal reduction with normal cervical length and compare the maternal and neonatal outcomes in the control group for which progesterone supplement was not used.

Materials and Methods

Study setting

This randomized clinical trial study was conducted in an academic center affiliated to Tehran University of Medical Sciences from January 2019 to January 2021.

Ethical considerations

This study was recruited according to declaration of Helsinki. All participants agreed to participate in the study submitted the informed consent. This study was registered in Iranian Registry of Clinical Trials (IRCT) with reference number: IRCT20200215046496N1.

Eligibility criteria

The inclusion criteria were the women with monochorionic diamniotic (MCDA) pregnancies between 16 and 26 weeks of gestational age with anomaly or severe fetal growth restriction (sFGR) of one twin or acardiac twin who were candidates for fetal reduction by RFA with Cervical Length (CL) more than 25 *mm* before the procedure. Allergy to progesterone compounds, history of preterm delivery, cervical length less than 25 *mm* in transvaginal ultrasound before the procedure, history of cervical insufficiency or recurrent second trimester abortion, having cervical cerclage and TTTS cases were excluded from the study. Also, the cases of threatened abortion or rupture of the membrane were excluded either.

Sample size calculation

The sample size was calculated with a 95% confidence interval and according to the formula below 80 cases were randomly selected into two groups of 40 participants.

$$n = \frac{\left(Z_1 - {}^{\alpha}/_{2} + Z_1 - \beta\right)^2 (\sigma_1{}^2 + \sigma_2{}^2}{(\mu_1 - \mu_2)^2}$$

$$\alpha_1 = 0.05$$

$$\beta = 0.2$$

$$\sigma_1 = \sigma_2 = 3\ weeks$$

$$\mu_1 - \mu_2 = 2$$

RFA procedure

Before the operation, an exported perinatalogist performed a targeted sonography and Doppler study to confirm RFA indication. About 30 *min* before the procedure, Amoxicilline as prophylactic antibiotics 1 *g* orally and Indomethacin 50 *mg* as rectal suppositories were administered (6). RFA was performed by the same perinatalogist by radiofrequency generator (manufactured by RF Medical Co., South Korea). The site of needle insertion was locally disinfected and anesthetized. The site of intra-abdominal umbilical vein was determined under ultrasound guide. After that, a 17-gage needle was inserted to cauterize the umbilical vein for approximately 2 *min*. If the blood flow was not ceased, the procedure was repeated.

Medical Intervention

The cases were randomly divided into two equal groups including case and control. The intervention group by default of survival of the healthy twin and normal middle cerebral artery peak systolic velocity (MCA PSV) on ultrasound the day after RFA, received intramuscular 250 *mg* 17-hydroxy progesterone caproate weekly up to 36 weeks of gestational age. The control group was discharged without further intervention after RFA. Maternal data such as demographic information, past medical, surgical and drug history were gathered. Also, the maternal and neonatal outcomes were evaluated and compared between groups. Obstetrical data including cervical length (measured by transvaginal ultrasound) and amniotic fluid volume of each fetus were evaluated too.

Follow up

All pregnant women were evaluated by Doppler ultrasound for fetal heart activity and MCA PSV measurements 24 *hr* after RFA. The follow-up by telephone calls by a trained midwife to collect potential maternal, fetal and neonatal complications were continued until delivery.

Statistical analysis

The data was analyzed by SPSS 22 (IBM Corp, Armonk, New York, USA) version 22. Frequency (%) was calculated for the qualitative variables and the mean±standard deviation (SD) was calculated for the quantitative variables. T-test was applied to compare quantitative variables between the two groups and chi square test was used to compare qualitative variables. In this study, $p<0.05$ was considered significant.

Results

Eighty participants (40 in each group) were recruited in the study. One case in the intervention group, was omitted due to the early severe preeclampsia. Therefore, the results were analyzed among 79 patients. RFA procedure was successful in all cases. The indications for RFA were sFGR in 50 (63.3%), anomaly in 21 (26.6%), and acardia in 8 (10.1%) cases, respectively. The demographic and obstetrical data were not significantly different between groups except gestational age at procedure that is not clinically significant (Table 1). The comparison of maternal and neonatal outcomes between two groups is summarized in table 2.

The mean gestational age at delivery in both case and control groups was 34 weeks and 4 days, but no significant difference was observed between the two groups. NICU admission was slightly lower in the progesterone group, but was not statistically significant. The mean birth weight was 2350 *g* and in the control group, it was 2310 *g*, but no significant difference was found between the two groups. Also, there was no significant difference between the case and control groups in terms of gestational diabetes, which was a worrying complication of 17-hydroxy progesterone caproate.

In this study, gestational age at delivery was inversely related to cervical length at the time of procedure and maternal body mass index, but these differences were not statistically significant (Table 3).

Discussion

In this study, the administration of weekly 17-hydroxy progesterone caproate had no significant effect on increasing the gestational age and other pregnancy and fetal adverse outcomes in the single pregnancies which endured RFA for selective fetal reduction.

Twin pregnancy is a risk factor for preterm birth, with more than 50% preterm labor. However, the administration of progesterone does not appear to reduce the risk of preterm birth or improved neonatal outcomes (14). Also, in a study by Ward

Table 1. Comparison of the demographic and obstetrical data in progesterone and control groups

Variables	Progesterone	Mean	SD	p-value
Maternal age (year)	Yes	32.21	5.09	0.081
	No	30.08	5.61	
BMI (kg/m^2)	Yes	28.24	4.21	0.087
	No	26.58	4.35	
Gravidity	Yes	2.21	.923	0.314
	No	1.95	1.280	
Parity	Yes	0.87	0.695	0.217
	No	0.63	1.030	
Abortion	Yes	0.33	0.621	0.955
	No	0.33	0.694	
GA at procedure (week)	Yes	21.94	2.59	0.047
	No	20.77	2.56	
Cervical length (*mm*)	Yes	32.56	4.15	0.513
	No	33.18	4.12	

BMI: Body Mass Index, SD: Standard Deviation, GA: Gestational Age.

Table 2. Comparison of maternal and neonatal outcomes between two groups

Variables		Progesterone n(٪)		p-value
		Yes	No	
Fertility type	Spontaneous	33 (85)	33 (82)	0.800
	IVF/Induction	6 (15)	7 (18)	
RFA indication	Anomaly	9 (23)	12 (30)	0.780
	Acardia	4 (10)	4 (10)	
	sFGR	26 (67)	24 (60)	
GDM	Yes	4 (10)	3 (7)	0.666
	No	35 (90)	37 (93)	
Pregnancy outcome	Live	36 (92)	34 (86)	0.524
	IUFD	2 (5)	3 (7)	
	Neonatal demise	1 (3)	3 (7)	
PPROM	yes	14 (36)	8 (20)	0.115
	no	25 (64)	32 (80)	
Delivery type	C/S	27 (69)	21 (52)	0.128
	NVD	12 (31)	19 (48)	
NICU admission	Yes	13 (33)	10 (25)	0.415
	No	26 (67)	30 (75)	
GA at delivery	-	34.62±3.8*	34.67±5.1*	0.967
Fetal weight	-	2351.2±832.7*	2317.75±968.7*	0.870

* mean±SD.

RFA: Radiofrequency ablation, NICU: Neonatal Intensive Care Unit, PPROM: Preterm Premature Rupture of Membrane, IVF: In Vitro Fertilization, sFGR: selective Fetal Growth Restriction, IUFD: Intra Uterine Fetal Demise, C/S: Cesarean Section, NVD: Normal Vaginal Delivery, GA: Gestational Age, GDM: Gestation Diabetes Mellitus.

Table 3. Correlation between the obstetrical characteristics including gestational age at procedure and delivery with maternal age, body mass index and cervical length

Variables		GA at procedure	GA at delivery	Cervical length	BMI	Maternal age
GA at procedure (week)	r	1	0.073	0.077	0.243	0.058
	p-value		0.521	0.502	0.031	0.613
GA at delivery (week)	r	0.073	1	-0.110	-0.047	0.046
	p-value	0.521		0.334	0.682	0.688
Cervical length (*mm*)	r	0.077	-0.110	1	0.013	-0.072
	p-value	0.502	0.334		0.912	0.528
BMI (kg/m^2)	r	0.243	-0.047	0.013	1	0.197
	p-value	0.031	0.682	0.912		0.082
Maternal age (year)	r	0.058	0.046	-0.072	0.197	1
	p-value	0.613	0.688	0.528	0.082	

GA: Gestational Age, BMI: Body Mass Index.

et al, weekly intramuscular progesterone did not prevent spontaneous preterm labor or morbidity in twin pregnancies with a prior singleton spontaneous preterm birth [15]. In these studies, however, the studies in the field of fetal reduction by radiofrequency or laser were not included and therefore this study was the first trial to investigate the progesterone effect after RFA procedure.

Despite the fact that our study could not show a significant effect of progesterone to increase the duration of pregnancy between the two groups, these hypotheses can be suggested for future studies. The effect of progesterone supplementation may also vary if the procedure is performed before and after 18 weeks. In our study, considering that the number of cases performed at the age of less than 18 weeks in each group was less than 5 people, this analysis was not statistically significant which can be considered as a suggestion for future studies. Although a small sample size was the main weakness of the current trail, the strength of this study is its novelty that to the best of our knowledge, this is the first study on 17-OHPC efficacy in twin pregnancies with a prior RFA.

Conclusion

17-hydroxy progesterone caproate had no significant effect on increasing the gestational age and other pregnancy and fetal outcomes in the single pregnancies which endured RFA for selective fetal reduction. Further studies with larger sample sizes or by using progesterone supplementation may yield significant results.

Ethics approval and consent to participate

The ethical committee of Tehran University of Medical Sciences approved this study.

Availability of data and materials

The datasets used during the current study are available from the corresponding author on reasonable request.

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Conflict of Interest

The authors declare no conflict of interest.

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