COMPARISON OF MICRONIZED PROGESTERONE (CYCLOGEST PESSARY) AND PLACEBO IN PREVENTION OF PRE-TERM BIRTH IN TERTIARY CARE HOSPITAL

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ABSTRACT

Objective: To compare efficacy of micronized per rectal progesterone (cyclogest pessary) and placebo in prevention of preterm birth in tertiary care hospital.

Study Design: Randomized controlled trial (RCT).

Place and Duration of Study: Study was conducted at department of gynecology and Obstetrics, Combined Military Hospital Nowshera, Khyber Pakhtunkhwa, from Jan 2018 to Jun 2018.

Methodology: A sample size of 140 patients was calculated using WHO calculator. Non probability consecutive sampling was used for recruitment of participants. Ethics approval and consent forms were taken. Women were divided into two groups randomly. Group A was given micronized progesterone (cyclogest pessary) per rectal usage and group B was given placebo. Patients were followed for maternal and neonatal outcomes. Data was analyzed using SPSS version 23. Independent t-test was applied. *p*-value ≤0.05 was considered significant.

Results: Total 140 patients were included in study. Mean age of women was 29.4 years ± 4.6SD. Patients in micronized progesterone (cyclogest pessary) was more effective in increasing birth weight (*p*=0.00), Apgar score maintenance at 1st (*p*=0.00) and 5th minute (*p*=0.000) and reduction in length of hospital stay (*p*=0.000) as compared to placebo. Patients were more satisfied with micronized progesterone (cyclogest pessary) per rectal as compared to placebo (*p*=0.00).

Conclusion: Preterm birth is remained as significant issue in health care system of Pakistan. However, micronized progesterone (cyclogest pessary) per rectal usage had positive impact in improving maternal and neonatal health outcomes. Effective strategies for prevention of preterm birth in Pakistan are required.

Keywords: Cyclogest pessary, Preterm birth, Progesterone.

INTRODUCTION

Preterm birth is leading cause of death under five years of children, globally[1]. An estimated 15 million preterm babies born per year, Worldwide[2]. According to World Health Organization (WHO), one million children die each year due to preterm birth complications. Preterm birth is defined as birth (alive) before 37 weeks of pregnancy. WHO divided preterm birth into three categories; extremely preterm (<28 weeks), very preterm (28-37 weeks) and moderate to late pre term (32-37 weeks)[3]. Africa and South Asia are suffering with more than 60% preterm births[4]. Prevalence of preterm birth is 12% in low income countries and 9% in high income countries[5]. Pakistan is ranked 4th in latest global listing of preterm births (750000 preterm births in 2010)[6].

An estimated weekly cost of preterm birth is 10000 U.S dollars, in United States in 19907. However, recent literature suggests annual cost of preterm birth is 26 billion U.S dollars. Moreover, the cost is increasing with earlier gestational ages[8]. The cause of preterm birth is multifactorial (with social, biological, psychological factors playing significant role). Most common risk factor for preterm birth is previous history of preterm birth[9].

Progesterone had significant role in prevention of preterm birth through anti inflammatory properties. Progesterone is associated with raising possible links between inflammatory

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processes leading towards progesterone receptor expression alteration and preterm labor onset[10]. Pharmacokinetics of progesterone is associated with its use in menopausal, assisted reproduction, use in post menopausal women, and endometrial carcinoma. Pharmacokinetics of progesterone is dependent upon route of administration. Literature reported that per rectal or vaginal use is more effective than oral administration[11].

Literature reported that vaginal pessaries are more effective in prevention of preterm birth as compared to placebo (RR: 1.95, C.I: 95% and *p*=0.00). However, progesterone use is associated with antenatal tocolysis reduction[12]. Another similar study reported that intramuscular and per rectal progesterone usage is effective in preterm birth prevention as compare to oral progesterone (*p*=0.01)[13]. Limited data is available on per rectal usage of progesterone in Pakistani settings. Present study aims to compare efficacy of micronized per rectal progesterone (cyclogest pessary) and placebo in prevention of preterm birth in tertiary care hospital.

METHODOLOGY

A randomized controlled trial was conducted at department of Gynaecology and Obstetrics, Combined Military Hospital Nowshera KPK, from January 2018 to June 2018. Ethical approval was taken from ethics review board. Consent forms were taken from all participants. A sample size of 140 patients was calculated with 5% level of significance, 80% power of study, P1=95.5%, P2= 80% and absolute precision 5% using WHO calculator[14]. Non probability consecutive sampling was used for recruitment of participants. Inclusion criteria include women in reproductive age (20-45 years), minimum two C-section previously resulting in preterm birth, short cervical length on anomaly scan ranging from 2.5cm to 3cm and history of prolonged nursery stay. Patients with abnormal fetuses, multiple gestations, uterine malformation and patients with cervical cerclage were excluded. Patients were divided into two groups using computer generated random number table. Group A was given micronized progesterone per rectal (cyclogest pessary) 400 mg daily while group B was given oral multivitamins (Placebo). Patients were undergone through following test urine culture and sensitivity test, high vaginal swabs and C-reactive proteins (CRP) blood test. All patients were delivered before 37 weeks. Primary outcomes of study were mean gestational age, rate of pre term delivery and time of delivery in both groups. Secondary outcomes include infant (birth weight, Apgar score at 1st and 5th minute, length of hospital stay) maternal (adverse effects of drugs and patients satisfaction with drugs). Data was analyzed using SPSS version 23. Quantitative (Mean ± standard deviation) and qualitative (frequency and percentage) were analyzed. Independent t-test was applied. *p*-value ≤0.05 was considered significant.

RESULTS

Total 140 patients were included in study with 1:1 randomization (70 patients in each group). Mean age of women was 29.4 years ± 4.6 SD. Mean Body mass index (BMI) was 30.5 kg/m 2 ± 3 SD. Mean number of previous pregnancies were 2.8 ± 0.7 SD. Mean Number of previous preterm deliveries was 2.9 ± 0.9 SD. Mean length of cervix was 21.5 mm ± 0.92 SD. Mean gestational age at beginning of treatment was 15.8 weeks ± 0.92 SD. Mean gestational age at delivery was 33.8 months ± 1.7 SD. Mean birth weight of infants was 2491 grams ± 2.7 SD. Mean Apgar score at 1st minute was 7.1 ± 1.3 SD. Mean Apgar score at 5th minute was 7.7 ± 0.99 SD. Mean length of hospital stay was 6.8 days ± 1.8 SD.

Mean age of mother was 29.08 ± 4.7 SD in cyclogest pessary group while 29.8 ± 4.6 SD in placebo group (*p*=0.35). Mean BMI was 30.47 ± 3.2 SD in cyclogest pessary group while 30.61 ± 2.9 SD in placebo group (*p*=0.78). Mean number of previous pregnancies were 2.9 ± 0.7 SD while 2.7 ± 0.7 SD in placebo group (*p*=0.100). Mean number of previous pre term deliveries were 3.1 ± 1.05 SD and 2.6 ± 0.6 SD in placebo group (*p*=0.002). Mean length of cervix was 21.5 ± 0.91 SD in cyclogest pessary group while 21.6 ± 0.93

SD in placebo group (p=0.715). Mean gestational age at beginning of treatment was 15.9 ± 0.95 SD and 15.8 ± 0.90 SD in placebo group (p=0.650).

Mean birth weight was significantly high in progesterone (cyclogest pessary) 2583 ± 2.2 SD as compared to placebo 2399 ± 1.9 SD (p=0.000). Mean gestational age at delivery was 34 years ± 1.7 SD in progesterone group while 33 years ± 1.7 SD in placebo group (p=0.103). Mean Apgar scores at 1st minute were significantly lower in progesterone (cyclogest pessary) group 5.9 ± 0.67 SD as compared to placebo 8.2 ± 0.7 SD (p=0.00). Apgar scores at 5 minute were significantly lower in progesterone (cyclogest pessary) group 6.9 ± 0.6 SD as compared to placebo 8.6 ± 0.4 SD (p=0.00). Mean length of hospital stay was significantly lower in progesterone (cyclogest pessary group) 5.7 ± 0.7 SD as compared to placebo 8.5 ± 0.86 SD (p=0.000). Patients in (cyclogest pessary) progesterone per rectal use were more satisfied than placebo, as shown in fig-1.

Table-I: Mother parameters in progesterone (cyclogest pessary) and placebo.

Mother Parameters	Interventional Group		*p*-value
	Progesterone Cyclogest Pessary (N=70)	Placebo (N=70)	
Age of mother	29.08 ± 4.7SD	29.8 ± 4.6SD	0.35
Body Mass Index	30.47 ± 3.2SD	30.61 ± 2.9SD	0.78
No. of previous pregnancies	2.9 ± 0.7SD	2.7 ± 0.7SD	0.100
No. of previous pre term deliveries	3.1 ± 1.05SD	2.6 ± 0.6SD	0.002
Length of cervix	21.5 ± 0.91SD	21.6 ± 0.93SD	0.715
Gestational age at beginning of treatment	15.9 ± 0.95SD	15.8±0.90SD	0.650

Table-II: Infant outcome in both progesterone (cyclogest pessary) and placebo group.

Infant Outcomes	Interventional Group		*p*-value
	Progesterone Cyclogest Pessary (N=70)	Placebo (N=70)	
Birth weight	2583 ± 2.2 SD	2399 ± 1.9 SD	0.000
Gestational age at delivery	34 ± 1.7 SD	33 ± 1.7 SD	0.103
Apgar score at 1st minute	5.9 ± 0.67 SD	8.2 ± 0.7 SD	0.000
Apgar score at 5th minute	6.9 ± 0.6 SD	8.6 ± 0.4 SD	0.000
Length of hospital stay	5.7 ± 0.7 SD	8.5 ± 0.86 SD	0.000

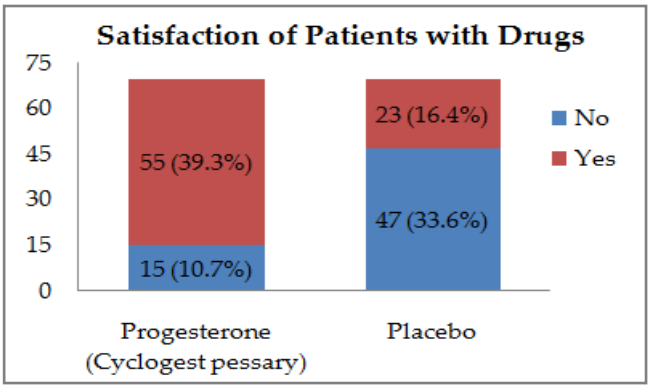

Figure-1: Satisfaction with interventional drugs.

DISCUSSION

Preterm births had significant contribution in infant mortality and morbidity, worldwide. In present study, total 140 patients were included. Mean birth weight was significantly high in progesterone (cyclogest pessary) 2583 ± 2.2 SD as compared to placebo 2399 ± 1.9 SD (p=0.000). Mattisonet al reported that birth weight in infants after preterm delivery is significantly increased with progesterone dose during pregnancy (p= 0.01)[15]. Another similar study reported that female infants were more weighed as compared to males when mothers were treated with oral progesterone in pregnancy (45% vs 20%, p=0.05)[16].

In present study, Mean Apgar scores at 1st minute were significantly lower in progesterone (cyclogest pessary) group 5.9 ± 0.67 SD as compared to placebo 8.2 ± 0.7 SD (p=0.00). Hack *et al*, reported no significant difference in Apgar scores of oral progesterone and placebo was found (p>0.05)[17]. However, Allen *et al*, found out

that vaginal progesterone used during pregnancy had significantly reduced Apgar scores after birth (p=0.00)[18].

In present study, Apgar scores at 5 minute were significantly lower in progesterone (cyclogest pessary) group 6.9 ± 0.6 SD as compared to placebo 8.6 ± 0.4 SD (p=0.00). Kilpatrick *et al*, reported that a positive correlation was found in apgar scores and progesterone used during pregnancy (r=0.9)[19].

In present study, mean length of hospital stay was significantly lower in progesterone (cyclogest pessary group) 5.7 ± 0.7 SD as compared to placebo 8.5 ± 0.86 SD (p=0.000). Elder *et al*, reported that length of NICU admissions was significantly lower in per rectal progesterone group as compared to vaginal group[20]. Moreover, Petrou *et al* reported that mean hospital stay is significantly high in placebo as compare to oral progesterone (RR; 1.7, 95% CI; p=0.01)[21].

In present study, patients in cyclogest pessary progesterone per rectal use were more satisfied than placebo (p=0.00). Hack *et al*, reported that patients were more satisfied with oral progesterone as compare to vaginal progesterone (p=0.01)[22]. Another similar study reported that more satisfaction with rectal usage of progesterone was reported in women as compared to vaginal (p=0.02)[23].

LIMITATION OF STUDY

Study conducted at single center limits generalizability of study.

CONCLUSION

Preterm birth remained as significant issue in health care system of Pakistan. However, progesterone (cyclogest pessary) per rectal usage had positive impact in improving maternal and neonatal health outcomes. Effective strategies for prevention of preterm birth in Pakistan are required.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

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