ORIGINAL ARTICLE

COMPARISON OF EFFICACY OF ORAL PROGESTERONE AND MICRONIZED PROGESTERONE PESSARY IN REDUCTION OF INCIDENCE OF SPONTANEOUS PRETERM BIRTHS

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Background: Preterm births are among the leading causes of fetomaternal mortality and morbidity. Progesterone is routinely used for the treatment of preterm births but scarce data is available that compared the efficacy of oral progesterone (dydrogesterone) with micronized progesterone (cyclogest pessary/rectal) to reduce the incidence of spontaneous preterm births in our local population. **Methods:** This randomized controlled trial was conducted at Gynaecology and Obstetrics department of Combined Military Hospital Nowshera from June to November 2018. Patients were divided into two groups. Group A was given oral progesterone (10 mg twice daily) while group B was given cyclogest pessary (400 mg daily) per rectal use. Efficacy of both groups was compared applying chi-square test and p-value ≤0.05 was considered significant. **Results:** Total 152 patients were included in study with 1:1 randomization (76 patients in each group). Mean gestational age was 29.6 weeks±1.5SD. Micronized progesterone cyclogest pessary per rectal usage is associated with reduction in preterm C-section, maternal systemic side effects., tocolysis use, NICU admissions, perinatal mortality, intraventricular haemorrhage, oxygen use at 28th day of life and retinopathy of prematurity (p<0.05). An insignificant association between two interventional groups and reason for delivery, antenatal corticosteroids use, birth weight, respiratory distress syndrome, pneumonia, sepsis (p>0.05). **Conclusion:** Prophylactic micronized progesterone per-rectal use is more effective in reducing preterm birth in patients at high risk of prematurity as compare to oral progesterone (dydrogesterone). Cyclogest pessary 400mg per rectal usage is associated with less maternal and neonatal complications.

Keywords: Cyclogest pessary (micronized progesterone); Dydrogesterone; Preterm birth

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INTRODUCTION

Preterm birth is most important emerging issue in maternal and child health, worldwide.[1] Preterm birth refers to premature births (occurring prior to 259 days of gestation). An estimated 15 million births occur in 2010 globally, out of which 1 million babies died as a result of preterm births and its associated complications.[2] In United States (U.S), 1/8 deliveries are associated with preterm births; however, 85% of them are associated with perinatal mortality and morbidity.[3] An estimated 3.1 million global neonatal deaths are associated with 35% of preterm birth complications.[4] A Meta-analysis reported 18.89% pooled prevalence of preterm births in Pakistan.[5]

An estimated 20% preterm delivery causes are found to be iatrogenic. These deliveries are performed for fetal and maternal indications (preeclampsia, high vertical caesarean delivery, intrauterine growth restriction, placenta previa, cholestasis, non-reassuring fetal testing and monochorionic-monoamniotic twins).[6] Preterm births occur in 20–30% cases due to preterm premature rupture of membrane, 20–25% as a result of intra-amniotic inflammation or infection and 25–30% due to unexplained (spontaneous) preterm labor.[7]

Literature reported that no intervention (including antibiotics, hydration or tocolytic therapy) can delay delivery more than 24–48 hours (once they presented in preterm labour). So, our focus more diverted towards prevention strategies including bed rest, pelvic rest (intercourse avoidance), prenatal care, intensive education, lower genital tract infection screening and management, gingival disease treatment, prophylactic tocolytic therapy, empirical broad-spectrum antibiotic therapy, prevention of multiple pregnancies and cessation of smoking and illicit substance abuse.[8]

Recent literature reported that progesterone has a significant role in uterine quiescence maintenance (during latter half of pregnancy) due to limitation of stimulatory prostaglandins production and contraction associated proteins genes (expression) inhibition. Moreover, term and preterm

labour onset is associated with functional withdrawal of progesterone activity (at uterus level).[9]

Maternal Foetal Medicine Units Network Trial randomized 459 patients to intramuscular injection of 17P (250 mg) weekly or placebo at 20th week of gestation and continued till 36th week of gestation. They reported less perinatal morbidity, need for supplemental oxygen, intra-ventricular haemorrhage and reduced rate of necrotizing enterocolitis.[10] A Brazilian trial randomized 142 women to vaginal progesterone suppositories (100 mg) or oral supplementation from 24–34th week of gestation. They reported significant reduction in recurrent preterm birth at all gestation ages in vaginal group ($p<0.05$).[11] Limited data is available on progesterone efficacy in Pakistan.

Present study aims to compare efficacy of oral progesterone and Micronized progesterone (cyclogest pessary) in prevention of preterm birth among patients with risk of preterm labour.

MATERIAL AND METHODS

A randomized controlled trial (RCT) was conducted at Gynaecology and Obstetrics department Combined Military Hospital, Nowshera. Study duration was 6 months (June to November 2018). A sample size of 152 patients was calculated with 80% power of test, anticipated population (P1) 28.57%, and anticipated population (P2) 48% and 95% confidence interval using WHO calculator.[12] Non probability consecutive sampling was used for selection of patients. Ethical approval was taken from Ethical Approval Board. Consent forms were taken from all patients. Patients of age >18 years, previous minimum 2 c-sections with preterm births, history of prolonged nursery and short cervical length (ranging from 2.5–3 cm) on anomaly scan. Exclusion criteria were based upon multiple gestations and abnormal foetuses. After selection of patients, they were randomly allocated into two groups using lottery method.

Group A was given oral progesterone (10 mg twice daily) while group B was given cyclogest pessary (400 mg daily) per rectal use at bed time. Patients were followed at 32 and 37 weeks of pregnancy. Efficacy of both interventions was measured in terms of maternal(mean weeks of gestation, delivery before 28, 32 or 35 weeks, reason for delivery, caesarean delivery, tocolysis used, antenatal corticosteroids used, maternal systemic complications, and neonatal (perinatal death, respiratory distress syndrome, use of oxygen at 28 days of life, pneumonia, intra-ventricular haemorrhage, neonatal sepsis, retinopathy of prematurity, birth weight, head circumference, and Neonatal intensive care unit admission) outcomes. Data was analysed using SPSS version 24. Mean and percentage was calculated for quantitative variables. Frequency and percentages were calculated for qualitative variables. Chi-square test was applied. p-value ≤ 0.05 was considered significant.

RESULTS

Total 152 patients were included in study with 1:1 randomization (76 patients in each group). Mean gestational age was 29.6 weeks±1.5SD. Reason for delivery was spontaneous in 77 (50.7%) women and indicated in 75(49.3%) women. Out of all deliveries 63 (41.4%) had caesarean deliveries while 89(58.6%) were not undergone C-section. Tocolysis was used in 70 (46.1%) cases while in 82 (53.9%) cases tocolysis was not utilized. Antenatal corticosteroids were used in 88 (57.9%) while not utilized in 64 (42.1%) women. Other descriptive characteristics are given in table-1. Sepsis and respiratory distress syndrome are most common neonatal complications as shown in figure-1.

Majority of patients in oral progesterone group 46 (30.3%) undergone preterm emergency caesarean delivery while in cyclogest pessary 17 (11.2%) undergone preterm emergency C-section (p=0.000). Tocolysis was used in 48(31.6%) and 22 (14.5%) in oral progesterone and cyclogest pessary groups respectively (p=0.000). Majority of maternal complications were reported in oral progesterone group 39 (25.7%) as compare to cyclogest pessary 19 (12.5%) (p=0.001). Frequency of NICU admission was high in oral progesterone group 46 (30.3%) as compare to cyclogest pessary 25 (16.4%) (p=0.001). Majority of neonates in cyclogest pessary group 38 (25%) had head circumference >30 cm as compare to oral progesterone group 56 (36.8%) as shown in table-2. Cyclogest pessary is associated with less perinatal mortality 3 (2%) as compare to oral progesterone group 13 (8.6%) (p=0.01). Oral progesterone group patients require more oxygen at 28th day of life 21 (13.8%) as compare to cyclogest pessary group 9 (5.9%) (p=0.02). Oral progesterone group neonates were more prone to have intraventricular haemorrhage 20 (13.2%) as compare to cyclogest pessary 7 (4.6%) (p=0.01). Oral progesterone group reported more neonates with retinopathy of prematurity 19 (12.5%) as compare to cyclogest pessary 9 (5.9%) (p=0.05) as shown in table-3. An insignificant association between two interventional groups and reason for delivery, antenatal corticosteroids use, birth weight, respiratory distress syndrome, pneumonia, sepsis ($p>0.05$).

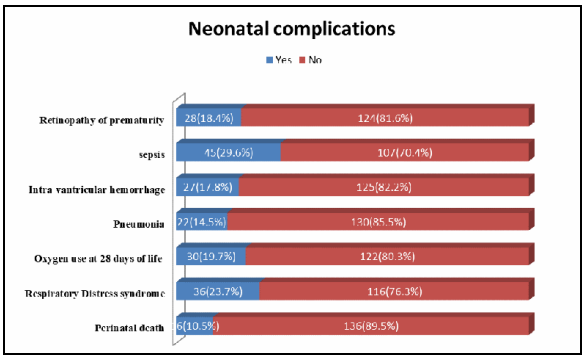

Figure-1: Neonatal complications

Table-1: Descriptive characteristics

Descriptive Characteristics	Frequency (n=152)	Percentage
Maternal Complication		
Yes	58	38.2
No	94	61.8
Systemic side		
No	97	63.8
Yes	55	36.2
NICU admissions		
No	81	53.3
Yes	71	46.7
Birth weight (Grams)		
≤1500	61	40.1
>1500	91	59.9
Head Circumference (cm)		
≤30	58	38.2
>30	94	61.8

Table-2: Association of maternal and neonatal outcomes with interventional groups

Emergency Caesarean delivery	Interventional groups		Total	*p*-value
	Group A (Oral progesterone)	Group B (Cyclogest Pessary)		
No	30 (19.7%)	59 (38.8%)	89 (58.6%)	0.000
Yes	46 (30.3%)	17 (11.2%)	63 (41.4%)	
Tocolysis used				
No	28 (18.4%)	54 (35.5%)	82 (53.9%)	0.000
Yes	48 (31.6%)	22 (14.5%)	70 (46.1%)	
Maternal complications				
No	37 (24.3%)	57 (37.5%)	94 (61.8%)	0.001
Yes	39 (25.7%)	19 (12.5%)	58 (38.2%)	
NICU admissions				
No	30 (19.7%)	51 (33.6%)	81 (53.3%)	0.001
Yes	46 (30.3%)	25 (16.4%)	71 (46.7%)	
Head **circumference**				
≤30 cm	38 (25%)	20 (13.2%)	58(38.2%)	0.004
>30 cm	38 (25%)	56 (36.8%)	94 (61.8%)	
Total	76 (50%)	76 (50%)	152 (100%)	

Table-3: Association of neonatal complication with interventional groups

Perinatal deaths	Interventional groups		Total	*p*-value
	Group A (Oral progesterone)	Group B (Cyclogest pessary)		
No	63 (41.4%)	73 (48%)	136 (89.5%)	0.01
Yes	13 (8.6%)	3 (2%)	16 (10.5%)	
Oxygen use at 28th day of life				
No	55 (36.2%)	67 (44.1%)	122 (80.3%)	0.02
Yes	21 (13.8%)	9 (5.9%)	30 (19.7%)	
Intraventricular haemorrhage				
No	56 (36.8%)	69 (45.4%)	125 (82.2%)	0.01
Yes	20 (13.2%)	7 (4.6%)	27 (17.8%)	
Retinopathy of prematurity				
No	57 (37.5%)	67 (44.1%)	124 (81.6%)	0.05
Yes	19 (12.5%)	9 (5.9%)	28 (18.4%)	
Total	76 (50%)	76 (50%)	152 (100%)	

DISCUSSION

Preterm birth is leading cause of new born mortality, globally. In present study 152 patients were included with 76 patients in each group. Majority of patients in oral progesterone group 46 (30.3%) undergone emergency caesarean delivery while in cyclogest pessary 17 (11.2%) undergone emergency C-section (*p*=0.000). Kramar *et al* reported patients with oral progesterone usage during pregnancy are less prone to undergo emergency C-section (*p*=0.01)[13]. However, Mattison *et al* reported that there is no significant difference in delivery mode of oral and vaginal progesterone usage (*p*=0.176).[14]

In present study, majority of maternal complications were reported in oral progesterone group 39 (25.7%) as compare to cyclogest pessary 19(12.5%) (*p*=0.001). A similar study reported that progesterone is associated with less maternal complications (*p*=0.00).[15] However, Hack *et al* reported that progesterone per rectal usage is more effective for lowering maternal complications (*p*=0.02).[16]

In present study, frequency of NICU admission was high in oral progesterone group 46 (30.3%) as compare to cyclogest pessary 25 (16.4%) (p=0.001). Allen *et al* reported that there is positive correlation in oral progesterone usage during gestation and low frequency of NICU admission (r=0.7).[17]Another similar study reported that vaginal progesterone usage is associated with low frequency of preterm birth and NICU admission.[18]

In present study, Cyclogest pessary is associated with less perinatal mortality 3(2%) as compare to oral progesterone group 13(8.6%) (p=0.01). Elder *et al* reported that per-rectal progesterone leads to lower uterine contraction and reduced preterm birth resulting in perinatal mortality reduction (p<0.05).[19]

In present study, cyclogest pessary group showed significant reduction in oxygen usage at 28th day of life, intraventricular haemorrhage and retinopathy of prematurity (p<0.05). Petrou *et al* reported that neonatal outcomes were found to be better in cyclogest pessary per rectal use as compare to prophylactic vaginal use (p=0.00).[20]

Small sample size and single cantered data collection limits generalizability of study.

CONCLUSION

Prophylactic Micronized progesterone per-rectal is more effective in reducing preterm birth at high risk of prematurity as compare to oral progesterone. Micronized progesterone per-rectal usage is associated with less maternal and neonatal complications.

AUTHORS' CONTRIBUTION

NA: Lit search, Conceptualization of study, Study design, Data analysis, Data collection, Data interpretation and proof reading. UM: Study design, Data analysis, Data collection, Data interpretation and proof reading. SB: Data interpretation, Data analysis and proof reading. SK: Data collection, Proof reading. SK: Data collection, Proof reading.

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