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Study of Role of Oral Microzed Progesterone for Management of Preterm Labour, Maternal Out Come

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I. Introduction

Preterm[1] is defined as babies born alive before 37 weeks of pregnancy are completed. Preterm labour is increasing perinatal morbidity and mortality in constant manner.There are sub-categories of preterm birth, based on gestational age:extremely preterm (<28 weeks),very preterm (28 to <32 weeks),moderate to late preterm (32 to <37 weeks).

Preterm labour refers to the onset of uterine contractions of sufficient strength and frequency to effect progressive dilatation and effacement of cervix between 20 and 37 weeks of gestation.[2]Preterm delivery affects11% of pregnancies in US or even greater in developing countries(23.3% in India) [3]

Oral micronized progesterone[4] :

Oral micronized progesterone was first marketed in France in 1980. It is synthesized from a naturally occurring precursor extracted from yams (Dioscorea sp) and is chemically identical to proges- terone of ovarian origin (empiric formula, C2iH3a02; molecular weight, 3 14.47). The micronized (formulation provides optimal progesterone bioavailability, which is de- pendent on both the size of the proges- terone particles in suspension and the na- ture of the oily excipients30 After oral administration of micronized progesterone, 50% to 60% of the dose is absorbed.

Oral Micronized Progesterone. Micronizing is a process designed to increase the half-life of progesterone and reduce its destruction in the gastrointestinal tract. Micronization decreases particle size and enhances the dissolution of progesterone.Maximal serum concentrations are achieved more rapidly with orally administered micronized progesterone (Prometrium) than with injected progesterone. Absorption of micronized progesterone is enhanced twofold when the hormone is taken with food.[5]

AIMS AND OBJECTIVE

1. To determine the efficacy of oral micronized progesterone for the management of preterm labour

II. Material And Method:

The study was a hospital based Randomised controlled study and was carried out in the department of obstetrics and Gynaecology, a tertiary hospitalZMCH, DAHOD,The study Titled as" ROLE OF ORAL MICRONIZED PROGESTERONE IN THE MANAGEMENT OF PRETERM LABOUR"was conducted in obstetrics and Gynaecology Department of 144 preterm patients,as management of preterm labour with oral micronised progesterone.It was conducted between oral micronized progesterone treated group of preterm labour as cases(72) and without oral micronized treated progesterone group as a control(72). Out of them seventy two patients were taken as a cases for giving oral micronized progesterone and seventy two for controls for comparision. The particulars, investigations, treatment, examinations, history etc. were recorded at the relevant time.

INCLUSION CRITERIA: Women with gestational age between 28 weeks to less than 37th completed weeks,Presenting with pain in abdomen,Four uterine contractions in 20 minutes with Cervical dilatation more than 1 cm & effacement more than 80 %,History of previous preterm birth and recurrent miscarriage.

EXCLUSIONCRITERIA

Diabetes,Hypothyroidism,Cardiacds,Severepreeclampsia,Eclampsia,antepartemhaemmrhage,Chorioamnitis,Hydroamnios,Cervical dilation greater than 3 cm, PROM, fetal distress,Women with a history of cervical insufficiency and a cerclage in place.**Study variables :**Maternal profile with respect to age, religion, parity,

obstetric history, type and mode of delivery, POG at the time of delivery and associated morbidity and mortality.

Outcome variables : Gestational age at delivery. latency period , recurrence of preterm labor**.**A informed consent was taken from the subject or subject's informant willing to participate in the study and were screened for inclusion and exclusion criteria.Details of patient's history was taken and a thorough general examination, systemic examination, abdominal examination, per vaginal examinationwas done.Ethical approval was obtained.

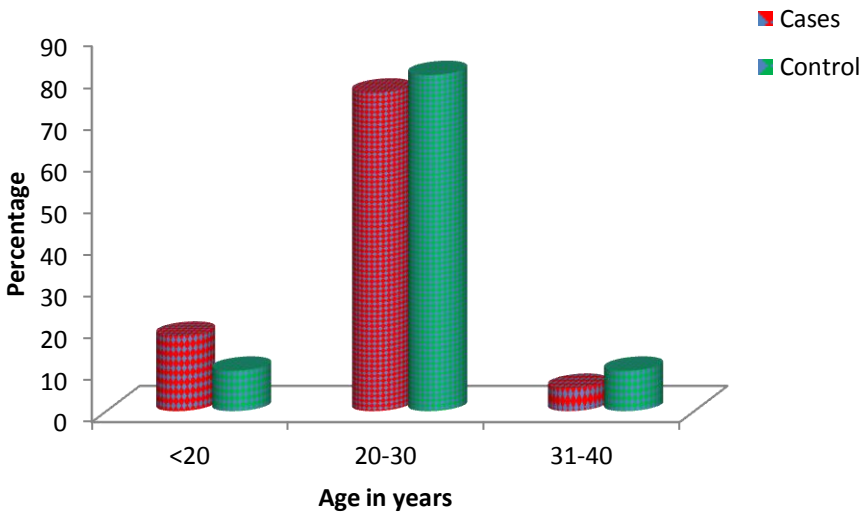
Statistical Methods: Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean ± SD (Min-Max) and results on categorical measurements are presented in Number .Student t test (two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups (Inter group analysis) on metric parameters. Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups, Non-parametric setting for Qualitative data analysis.**Significant figures** + Suggestive significance (P value: 0.05<P<0.10)* Moderately significant (P value:0.01<P ≤ 0.05)** Strongly significant (P value : P≤0.01).**Statistical software:** The Statistical software namely SAS 9.2, SPSS 21.0, Stata 10.1, MedCalc 9.0.1 ,Systat 12.0 and R environment ver.2.11.1 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc**.**

III. Results And Observation.

Table 1: Age distribution of patients studied. Table depicts.the age distribution ranges from 20 to 40 years,with mean age of 23.24+_3.88weeks Among CASES and 24.5+_4.25 weeks CONTROLS.Graph (a) depicts graphical presentation of cases and controls shows that most of cases and control from 20 to 30 years

Age in years	Cases	Control	Total
<20	13(18.1%)	7(9.7%)	20(13.9%)
20-30	55(76.4%)	58(80.6%)	113(78.5%)
31-40	4(5.6%)	7(9.7%)	11(7.6%)
Total	72(100%)	72(100%)	144(100%)
Mean ± SD	23.24±3.88	24.50±4.25	23.87±4.11

Samples are age matched with P=0.100



Graph (a)

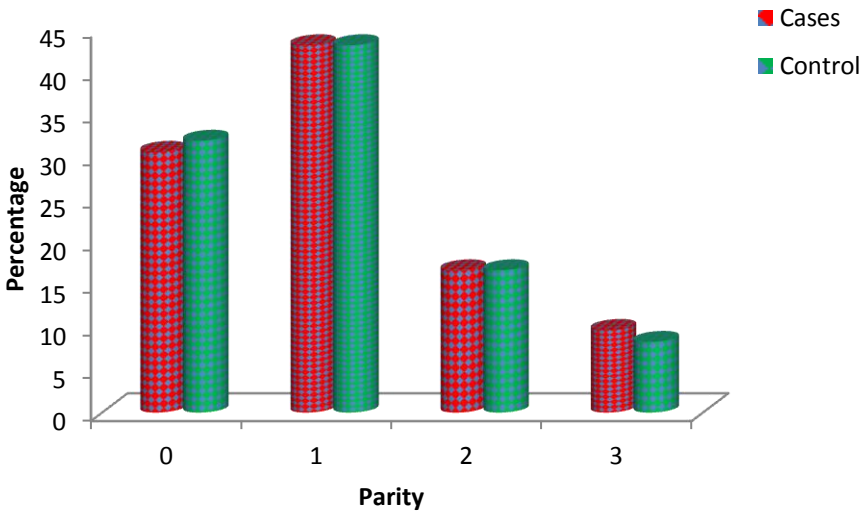
Above graphs depicts the age distribution of patients.Most of the patients from 20 to 30 years age groups.

Table 2: Parity distribution in case-controls studied…

Shows the patients according to parity.The parity distribution ranges from primiparous to parity three.Maximum patients belongs parity one group .

Parity	Cases	Control	Total
0	22(30.6%)	23(31.9%)	45(31.3%)
1	31(43.1%)	31(43.1%)	62(43.1%)
2	12(16.7%)	12(16.7%)	24(16.7%)
3	7(9.7%)	6(8.3%)	13(9%)
Total	72(100%)	72(100%)	144(100%)

P=0.992, Not significant, Chi-Square test



Graph Depicts parity wise distribution
Graph (b)

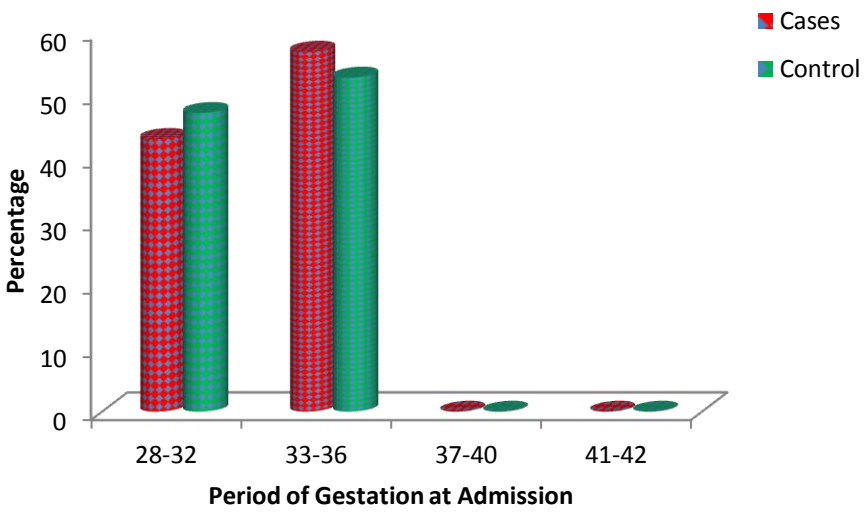
Graph(b) shows that parity one women in cases as control are in maximum number .

Table 3: Period of Gestation at Admission distribution in case-controls studied

Given below table and graph Shows different gestational age group at time of admission .The gestational age on admission ranges from 28 weeks to 36 weeks.Mean GA for cases 32.97+_2.01 and for control 32.89+_2.05 weeks.
Majority of cases and control were from 33 to 36 weeks.

Period of Gestation at Admission	Cases	Control	Total
28-32	31(43.1%)	34(47.2%)	65(45.1%)
33-36	41(56.9%)	38(52.8%)	79(54.9%)
37-40	0(0%)	0(0%)	0(0%)
41-42	0(0%)	0(0%)	0(0%)
Total	72(100%)	72(100%)	144(100%)

P=0.615, Not significant, Chi-Square test



Graph(c)

Table 4: Period of Gestation at delivery distribution in case-controls studied

Given below table and graph Shows period of gestation at delivery .Mean GA of delivery for cases 36.41+_1.88weeks and for control 33.84_+2.06 weeks.It was more in study group compare to controls.(P<0.001**, Significant, Chi-Square test)

Period of Gestation at delivery	Cases	Control	Total
28-32	4(5.6%)	21(29.2%)	25(17.4%)
33-36	30(41.7%)	47(65.3%)	77(53.5%)
37-40	38(52.8%)	4(5.6%)	42(29.2%)
41-42	0(0%)	0(0%)	0(0%)
Total	72(100%)	72(100%)	144(100%)

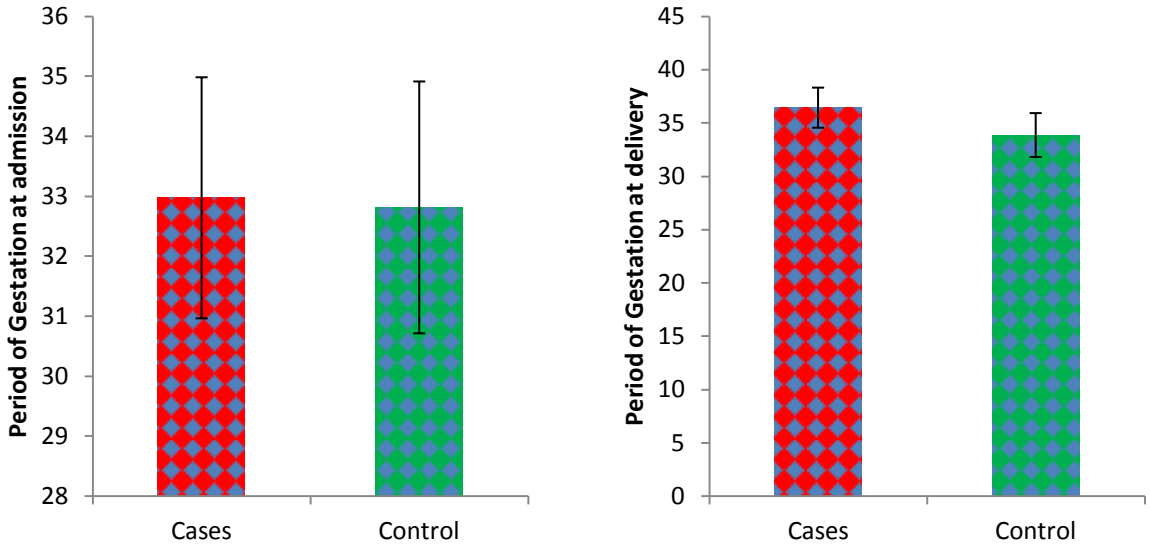
P<0.001**, Significant, Chi-Square test

Graph(d)

Table 5: Comparison of Period of gestation at admission and delivery in case-controls studied
Given below table and graph shows Pregnancy was significantly prolonged in study group compare to control.There was significant prolongation of weeks .(Student t test, <0.001**)

Gestation age in weeks	Cases	Control	Total	P value
Period of Gestation at admission	32.97±2.01	32.81±2.10	32.89±2.05	0.654
Period of Gestation at delivery	36.41±1.88	33.84±2.06	35.12±2.35	<0.001**

Student t test



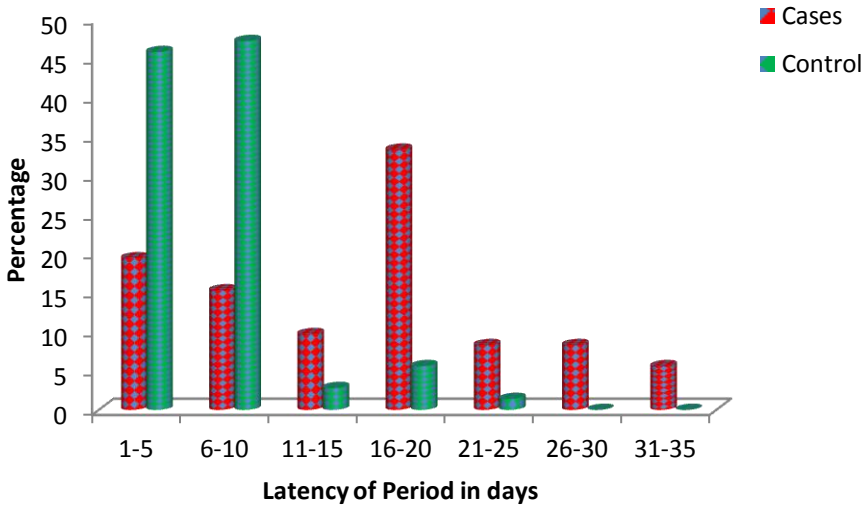
Graph (e)

Table 6: Latency of Period in day's distribution in case-controls studied

Shows latency period in days ranges from one day to 35 days.Mean latency period in study group was 15.07±8.76 Days and6.41±4.10days for control(P<0.001**, Significant, Fisher Exact test)

Latency of Period in days	Cases	Control	Total
1-5	14(19.4%)	33(45.8%)	47(32.6%)
6-10	11(15.3%)	34(47.2%)	45(31.3%)
11-15	7(9.7%)	2(2.8%)	9(6.3%)
16-20	24(33.3%)	4(5.6%)	28(19.4%)
21-25	6(8.3%)	1(1.4%)	7(4.9%)
26-30	6(8.3%)	0(0%)	6(4.2%)
31-35	4(5.6%)	0(0%)	4(2.8%)
Total	72(100%)	72(100%)	144(100%)
Mean ±SD	15.07±8.76	6.41±4.10	10.75±8.09

P<0.001**, Significant, Fisher Exact test



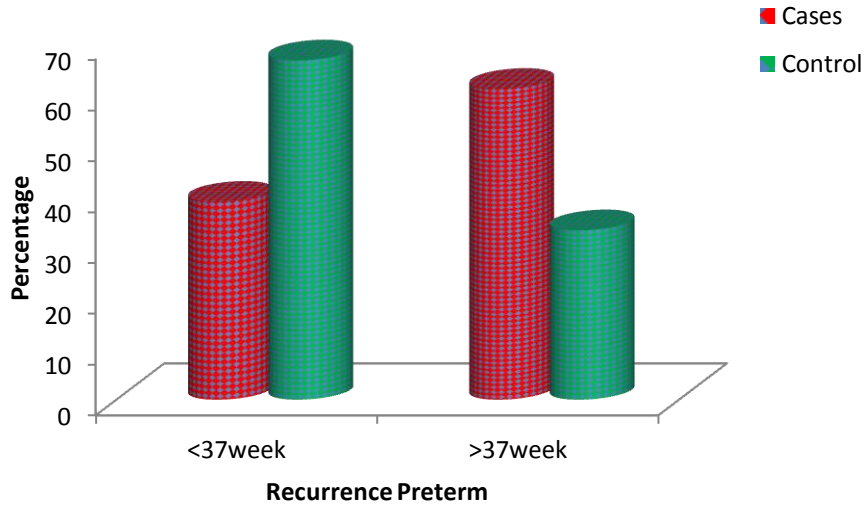
Graph (f)

Table 7: Recurrence Preterm labour.

Shows recurrence of preterm .Recurrence of preterm <37 weeks for cases 38.9% and for control 52.8%.Recurrence of preterm >37 weeks for cases 61.1% and control 33.3 %. Incidence of recurrent preterm labour was reduced .Which is statistically significant.(P=0.001**, Significant, Chi-Square test)

Recurrence Preterm	Cases	Control	Total
<37week	28(38.9%)	48(66.7%)	76(52.8%)
>37week	44(61.1%)	24(33.3%)	68(47.2%)
Total	72(100%)	72(100%)	144(100%)

P=0.001**, Significant, Chi-Square test



IV. Discussion

Preterm birth is the major cause of neonatal mortality and morbidity. In developing countries, it's a major health issue. Natural progesterone has been used in pregnancy without demonstrable effect on fetal development or on the risk of congenital anomalies.The beneficial effect of oral micronized progesterone on prolongation of pregnancy was shown by in the present study, which depicted significantly larger numbers of undelivered women in the progesterone group at each specific time point until delivery compared with controls.Preterm birth (PTB) is a leading cause of infant mortality and morbidity across the globe.It is responsible for huge negative impact on mankind both in terms of lives and economy,in pursuit of understanding the aetiology ,related factors and definite management of preterm labour the study has been carried out using micronized progesterone for better compliance and absorption. According to Blencowe et al[1] Incidence of preterm labour is 23.3% and preterm delivery is 10-69% in India.Chnandraharan E et al [2]found that Prematurity contributes to 75% of all neonatal deaths and 50% of long term neurological neonatal morbidity. A diagnosed 144 patients of preterm labour were taken ,72 patients were taken as control and 72 as cases . Oral micronized progesterone 200 mg twice daily was given to cases till delivery or 37 weeks completed.The efficacy off tocolytic agent and obstetrical out comes were then studied.In our study mean age for cases was 23.24±3.88 and for control 24.50±4.25 years,which was comparable each other .Age of patient is important variable for any type of study.In present study majority of cases and controls from 20 to 30 years age group.Mohan C. Regmi et al[6]found compare results in their study . Their latency period till delivery and recurrence of preterm labour were compared. There was significant reduction in recurrence of preterm labour and increase in latency period in progesterone group. They depicted that Progesterone is useful in reducing the recurrence of preterm labour in a patient who had preterm labour. In their study Age in years(mean) for cases was 23.24 ± 3.47 and 22.81 ± 3.73 years for controls.In an another similar study da Fonseca EB(2003) et al [7] in their study recorded mean age 27.6 year.In our study maximum patients were parity one(43.1%) and primigravida(30.6%) in both cases and controls. Our results were favoured by M chaudhary et al . Mean age of admission in our study was for cases 32.97±2.01 and for controls 32.81±2.10 weeks. In preterm cases period of gestation is an important factor.It was comparable with Chaudhry M et al as their study period of gestation was 31.91 ± 2.09 weeks for cases and for control 32.42 ± 1.65 weaks.Our results were similar with Chaudhary M et al[8].In our study, delivery of cases postponed up to(36.41±1.88)weeks and of controls up to (33.84±2.06)weeks. It was more in study group compare to controls.(P<0.001**, Significant, Chi-Square test) .Our results have been supported by many similar studies. In the study done by Johnson et al[9] and Da Fonseca et al[7] delivery of cases occurred at 38.6 weeks and 35.2 weeks, respectively while that of controls, occurred at 37 weeks and 36 weeks, respectively.

Study done by Cases (weeks) Controls (weeks) like.

Name	Cases(POG) at delivery	Control(POG) at delivery
Johnson et al	38.6 week	35.2 week
Da Fonseca et al	37 week	36 week

Rai et al[10] found that use of oral micronized progesterone was associated with an increase in the mean gestational age at delivery (36.1 ± 2.66 vs. 34.0 ± 3.25 weeks, P < 0.001).In our series results were comparable with Rai et al.It reflect that oral micronized treated group will be having prolongation of pregnancy .This result strongly support use of progesterone as tocolytic agent in preterm labour.In the present study, the mean latency period was significantly longer among women treated with progesterone compared with the controls. In our study we found mean latency prolongation(15.07±8.76) days for cases and (6.41±4.10) days for controls with(P<0.001**, Significant, Fisher Exact test). This is consistent with results from other studies . Borna and Sahabi **[11]** showed significant prolongation of mean latency period with progesterone (36.1 ± 17.9) days in pro-gesterone group vs (24.5 ± 27.2) days in control group; P = 0.037).A randomized controlled trial by Sharami et al.[12]also showed that pro- gesterone therapy resulted in a longer latency period (23.88 ± 18.01 vs 16.67 ± 12.9 days; P = 0.004). An another study Chaudhary M et al conducted that with tocolsis with oral micronized progesterone for prevention of preterm birth after arrested preterm labour.OMP significantly prolonged the latency period (33.29±22.16 vs 23.07 ± 15.42 days; P=0.013). Our study was similar with chaudhary et al for prolongation of latency by oral micronized progesterone.Prolongation of latency period with progesterone can be supported by various mechanisms resulting in uterine quiescence. Progesterone relaxes myometrial smooth muscle, blocks the action of oxytocin, in- hibits the formation of gap junctions and prostaglandin synthesis, and has anti-inflammatory properties[13].Our study also found decreased rate of recurrent preterm labour in OMP treated group. In Our series Recurrence of preterm was <37 weeks for cases 38.9% and it was 52.8%. for controls .Recurrence of preterm >37 weeks for cases was 61.1% and control 33.3 %Which is statstically significant. In the study Borna and Sahabi et al found decrease recurrence rate of preterm labour before 37 weeks in progesterone treated group.Rai et al also found decreased recurrence rate of preterm labour.Our results

are comparable with Rai et al. Hassan SS et al [14] and Andersen HF et al al [15] studied that short cervical length preterm patients were benifited by progesterone. Nageotte MP[16] and Hincz P[17] at el found that fetal fibronectin as predictor for preterm. Mohamed Anwar Al Nory (2011)[18] found that Progesterone therapy for pregnant had recurrent irregular painful uterine contractions provided prolongation of pregnancy with success rate of 43% and continuation with ritodrine therapy allowed successive tocolysis for failed prophylaxis. Deepti s shrivastava et et al[19](2012) studied that micronized progesterone is effective with fewer side effects than isoxsuprine in prevention of preterm labour. Noblot G[20] (1991) et al observed the The mean duration of hospital stay was also significantly reduced (P less than 0.05). David M Haas(2012)[21] et al found that Prostaglandin inhibitors and calcium channel blockers had the highest probability of delaying delivery and improving maternal outcomes. How HY[22] et al suggested that Perinatal death and morbidity are not only strongly related to early gestational age. Judith Mwansa-Kambafwile [23]et al concluded that based on high-grade evidence, antenatal steroid therapy is very effective in preventing neonatal mortality and morbidity . Meis et al[24] studied that treatment with 17P significantly reduced the risk of delivery at less than 37 weeks of gestation .Sanchez-Ramos, et al.[25] found those who received progestational agents had lower rates of preterm delivery .Dodd et al[26] conduced that for all women administered progesterone, there was a reduction in the risk of preterm birth. O'Brien et al[27.] Found that administration of vaginal progesterone reduces the risk of preterm. Tita and Rouse [28] found that intramuscular 17-alpha-hydroxyprogesterone effectively reduces the incidence of recurrent PTB.Caritis et al.[29] found that treatment with 17 alpha- hydroxyprogesterone caproate did not reduce the rate of preterm birth in women with triplet gestations. In present study mean age of admission in our study was for cases 32.97±2.01 and for controls 32.81±2.10 weeks. In our study maximum patients were parity one(43.1%) and primigravida(30.6%).In the study mean age for cases was 23.24±3.88 and for control 24.50±4.25 years, delivery of cases postponed up to(36.41±1.88)weeks and of controls up to (33.84±2.06)weeks.Mean latency of prolongation was (15.07±8.76) days for cases and 6.41±4.10days for controls.

V. Conclusion.

Preterm delivery is challenge in perinatal health care. We should try to reduce numbers of preterm labour in women.In developing country like india, it is better to prevent preterm labour. This study depicts that oral micronsed progesterone can be utilised as useful drug in the treatment of preterm labour.Oral micronized progesterone has few side effects,is affordable , and is likely to be acceptable to women,who face the threat of preterm labour .Thatswhy use of micronized form of progesterone should be encouraged for preterm labour women.

Clinical significance. oral micronized progesterone helps in increasing period of gestation of delivery , reduce recurrence of preterm and increase latency duration in days.Oral micronized progesterone is helpful for better out come for preterm labour and economically cheaper as better alternative in developing country.

Conflict interest NA

Financial assistance NA

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