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Original Research Article

Compare safety and efficacy of intramuscular progesterone versus vaginal progesterone in prevention of preterm labour

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ABSTRACT

Introduction: Currently preterm labour is one of the most challenging problem faced by both obstetricians and perinatologists, this episode in the course of woman's pregnancy takes a heavy tool for perinatal mortality which accounts for approximately 50-75%. The incidence of preterm labour is estimated to be 5-10% of all pregnancies.

Materials and Methods: It was a prospective randomize control study. All the cases with inclusion and exclusion criteria were selected during the study period. The subjects were randomized into two groups with group A received vaginal micronized progesteron and group B intramuscular 17a hydroxyprogesteron caproate. Total of 100 cases were included in this study.

All preterm pregnancy of more than 20 weeks were considered in this study. Initial nefidipine 10 mg, 4 tablets 15 min apart was given for tocolytic activity for 48 hours. Injection bethamethasone 12 mg I.M 2 doses in a duration of 24 hours apart is given for fetal lung maturity.

One group will receive weekly intramuscular 17a hydroxyprogesteron (250 mg) injection while other group will receive daily micronized vaginal progesteron suppository (200mg).

Subsequently compare the safety and efficacy of intramuscular progesterone versus micronized progesterone as a maintenance therapy in preventing preterm labour and analyse maternal and fetal factors. Subsequently compared the safety and efficacy of intramuscular progesterone versus micronized progesterone as a maintenance therapy in preventing preterm labour.

Results: This analysis showed that women who randomized to progesterone prophylaxis had a significantly increase in duration of pregnancy. The mean ± SD of birthweight in Group A and Group B was 2784.2 ± 490.7 gm and 2813.9 ± 363.3 gm respectively which confirmed the positive effects of progesterone on increasing infants' weights at birth.

Conclusions: Authors concluded that progesterone therapy had acceptable efficacy in the prevention of preterm labor in terms of prolongation of delivery and by increasing gestational age at delivery.

1. Introduction

Currently preterm labour is one of the most challenging problem faced by both obstetricians and perinatologists, as this episode in the course of woman's pregnancy takes a heavy tool for perinatal mortality which accounts for approximately 50 -75%.[1]

The incidence of preterm labour is estimated to be 5-10% of all pregnancies, but there are some difference with different population and variable on socioeconomic status.[2]

Preterm birth (PTB) is the leading cause of perinatal mortality and morbidity in industrialized world. Approximately, 50% of all preterm births occur after 35 weeks gestation and almost all the mortality and morbidity of preterm birth occurs before this time. At 24

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weeks of gestation, perinatal mortality is nearly 80% and 30 weeks of gestation mortality declines below 10%.[3]

Prematurity is a major cause of perinatal mortality and morbidity and it leads to greater risk for both short and long term complications which includes disability and impedinents in growth and mental development.[4] Its contribution to overall perinatal mortality and morbidity is more than 50% of cases. About 40% of all preterm births occur before 34 weeks and 20% before 32 weeks. Majority of morbidity and mortality occurs among those who delivered before 34 weeks.[5]

Wide varieties of tocolytic agents are being advocated since decades for the prevention of Preterm labour[6,7] and also been tried for the management of threatened preterm labour[8,9] Above all, there are insufficient data on long term follow up for reliable conclusion about the effects on the baby of these tocolytic drugs. (RCOG Green top guidelines, 2011)[10] Progesterone is essential for the maintenance and prolongation of pregnancy.[11,12] Delaying delivery reduces the rate of long term morbidity by facilitating maturity of vital organs, helps in optimum action of the administered glucocorticoids, helps in transfer to higher centre with NICU facilities. So different trials have been done to show the efficacy and safety of progesterone in prevention of recurrent preterm birth since 1960.[13,14]

Progesterone can be administered via oral capsule, vaginal gel or suppository, or intramuscularly.[15,16] Oral administration has better patient compliance but there are variability in the plasma concentrations of the drug due to personal variation in gastric filling and enterohepatic circulation, also this route can be associated with side effects such as nausea, headache, sleepiness, etc.[17,18]

The vaginal route results in higher local concentrations in uterus but its blood levels are low, while progesterone administered intramuscularly has optimal blood levels.[19,20] On 3rd February' 2011 injectable form of 17α hydroxyl progesterone (Mekena) has been approved by FDA to reduce the risk of preterm labour before 37 weeks of gestation.[21,22]

On February 3, 2011, the US Food and Drug Administration (FDA) approved the use of progesterone supplementation (hydroxyprogesterone caproate) during pregnancy to reduce the risk of recurrent preterm birth in women with a history of at least one prior spontaneous preterm delivery. This is the first time that the FDA has approved a medication for the prevention of preterm birth, and represents the first approval of a drug specifically for use in pregnancy in almost 15 years. This article reviews the evidence behind the use of progesterone for the prevention of preterm birth, and provide guidelines for the use of progesterone supplementation in clinical practise. The aim of this study was to compare between vaginal and intramuscular progesterone in the prevention of Preterm labour in women at high risk for preterm delivery.

Presently 17 hydroxyprogesterone caproate (intramuscular) is the only FDA approved product for the prevention of recurrent preterm birth, however recent studies suggest that vaginal progesterone may be used for this purpose, and may be even superior.

The American College of Obstetrics and Gynecology does not specify the optimal route of progesterone administration for the prevention of recurrent preterm birth. So it is our intention to compare vaginal and intramuscular progesterone to see if one is superior.

2. Aims and Objectives

Compare the safety and efficacy of intramuscular progesterone versus vaginal progesterone as maintenence therapy to prevent preterm labour in singleton pregnancy.

2.1. Inclusion criteria

All preterm patients (<37 weeks) visiting ANC OPD or admitted in labour room in spontaneous labour showing features of

1. Singleton pregnancy.
2. Live fetus
3. Presence of one of the preterm delivery risk factors.

2.2. Exclusion criteria

All patients with

1. Severe liver and renal disease.
2. Multiple pregnancy.
3. Major fetal anomaly, incompatible with survival.
4. Pregnancies complicated with diabetes mellitus.
5. Patient not giving consent.

2.3. Methods

It was a prospective randomize control study. All the cases with inclusion and exclusion criteria were selected during the study period. The subjects were randomized into two groups with group A received vaginal micronized progesteron and group B intramuscular 17a hydroxyprogesteron caproate. Total of 100 cases were included in this study.

All preterm pregnancy of more than 20 weeks were considered in this study. Initial nefidipine 10 mg, 4 tablets 15 min apart was given for tocolytic activity for 48 hours. Injection bethamethasone 12 mg I.M 2 doses in a duration of 24 hours apart is given for fetal lung maturity.

One group will receive weekly intramuscular hydroxyprogesteron (250 mg) injection while other group will receive daily micronized vaginal progesteron suppository (200mg).

Subsequently compare the safety and efficacy of intramuscular progesterone versus micronized progesterone

as a maintenance therapy in preventing preterm labour and analyse maternal and fetal factors that consists of

2.4. Maternal factors

1. Prolongation of pregnancy
2. Rate of preterm delivery
3. Gestational age at delivery
4. Mode of delivery Normal versus LSCS
5. Satisfaction of the participants
6. Adverse effects of the drugs

2.5. Fetal factors

1. Birth weight
2. Mortality
3. NICU admissions
4. APGAR score
5. Neonatal mortality or morbidity
6. No of days of admission is evaluate

Patients are followed up on OPD basis at regular interval on antenatal visits, by thorough history taking, laboratory investigations, regular antenatal examination. Serial Ultrasonography to monitor gestation age and growth.

2.6. Statistical data analysis

The data on categorical variables is shown as n (% of cases) and the data on continuous variables is presented as Mean and Standard deviation (SD) across two study groups. The inter-group statistical comparison of distribution of categorical variables is tested using Chi-Square test or Fisher's exact probability test. The inter-group statistical comparison of means of continuous variables is done using independent sample t test. The underlying normality assumption was tested before subjecting the study variables to t test. All results are shown in tabular as well as graphical format to visualize the statistically significant difference more clearly.

In the entire study, the p-values less than 0.05 are considered to be statistically significant. All the hypotheses were formulated using two tailed alternatives against each null hypothesis (hypothesis of no difference). The entire data is statistically analyzed using Statistical Package for Social Sciences (SPSS ver 22.0, IBM Corporation, USA) for MS Windows.

3. Results

3.1. Following section shows the detailed statistical analysis of the available data

50 cases studied in Group A, 7 (14.0%) had age between 18 – 20 years, 18 (36.0%) had age between 21 – 25 years, 17 (34.0%) had age between 26 – 30 years and 8 (16.0%) had age between 31 – 35 years. Of 50 cases studied in Group B, 7 (14.0%) had age between 18 – 20 years, 19 (38.0%) had age between 21 – 25 years, 16 (32.0%) had age between 26 – 30 years and 8 (16.0%) had age between 31 – 35 years. The age distribution of cases studied did not differ significantly between two study groups (P-value>0.05).

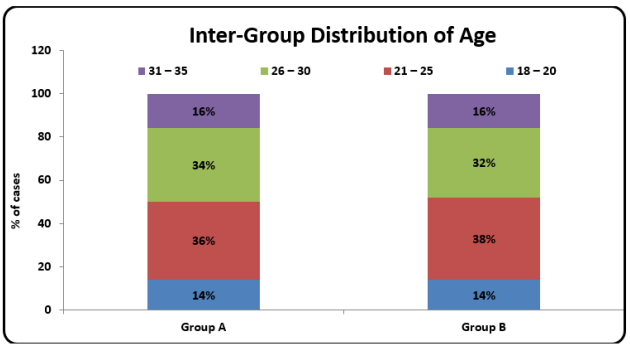

Fig. 1: Inter-Group Age distribution of cases studied.

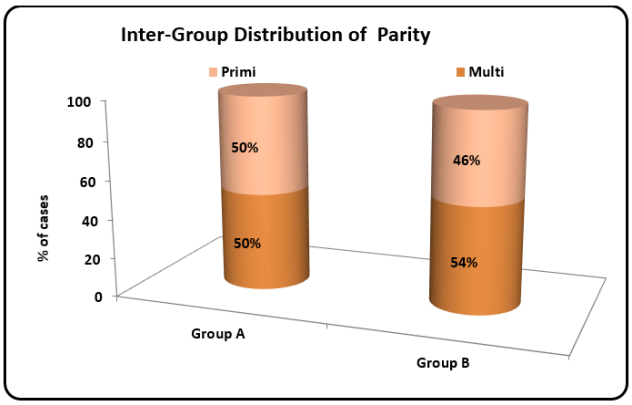

Fig. 2: Inter-Group distribution of parity of cases studied

Of 50 cases studied in Group A, 25 (50.0%) are primigravida, 25 (50.0%) are multigravida. Of 50 cases studied in Group B, 23 (46.0%) are primigravida, 27 (54.0%) are multigravida. The distribution of parity of cases studied did not differ significantly between two study groups (P-value>0.05).

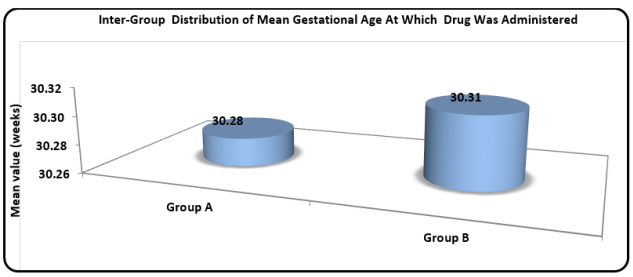

Fig. 3: Inter-Group comparison of mean gestational age at which drug was administered

The mean ± SD of gestational age at which the drug was administered among the cases studied in Group A and Group B was 30.28 ± 2.21 weeks and 30.31 ± 2.19 weeks respectively.

Distribution of mean gestational age at which the drug was administered among the cases studied did not differ significantly between two study groups (P-value>0.05).

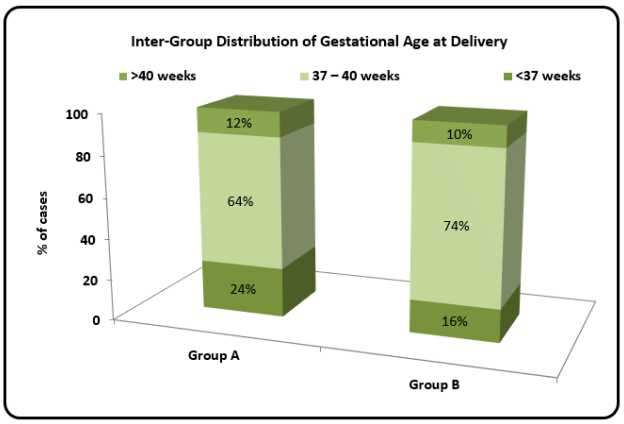

Fig. 4: Inter-Group distribution of gestational age at the time of delivery

Of 50 cases studied in Group A, 12 (24.0%) had gestational age less than 37 weeks, 32 (64.0%) had gestational age between 37 – 40 weeks and 6 (12.0%) had gestational age more than 40 weeks.

Of 50 cases studied in Group B, 8 (16.0%) had gestational age less than 37 weeks, 37 (74.0%) had gestational age between 37 – 40 weeks and 5 (10.0%) had gestational age more than 40 weeks.

Distribution of gestational age at the time of delivery among the cases studied did not differ significantly between two study groups (P-value>0.05).

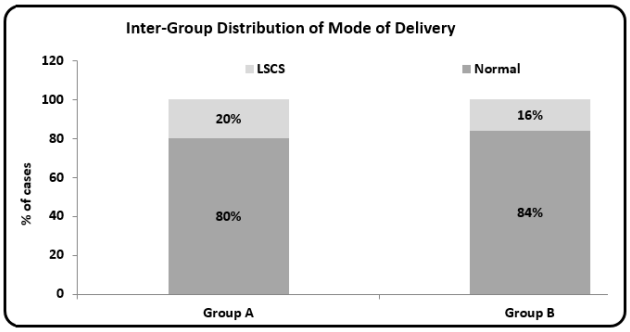

Fig. 5: Inter-Group distribution of mode of delivery

Of 50 cases studied in Group A, 40 (80.0%) had normal delivery and 10 (20.0%) had LSCS delivery.

Of 50 cases studied in Group B, 42 (84.0%) had normal delivery and 8 (16.0%) had LSCS delivery.

Distribution of mode of delivery among the cases studied did not differ significantly between two study groups (P-value>0.05).

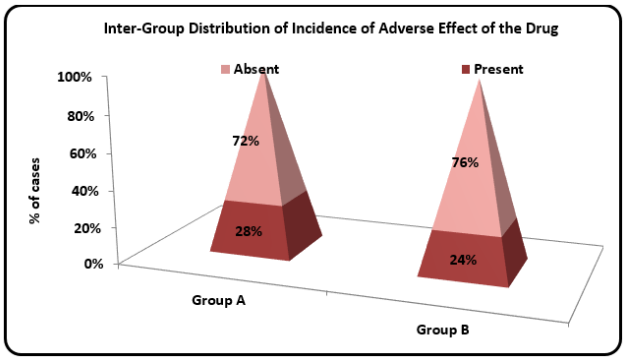

Fig. 6: Inter-Group distribution of incidence of adverse effect of the drug

Of 50 cases studied in Group A, 14 (28.0%) had adverse effect and 36 (72.0%) did not have any adverse effect of the drug.

Of 50 cases studied in Group B, 12 (24.0%) had adverse effect and 38 (76.0%) did not have any adverse effect of the drug.

Distribution of incidence of adverse effect of the drug among the cases studied did not differ significantly between two study groups (P-value>0.05).

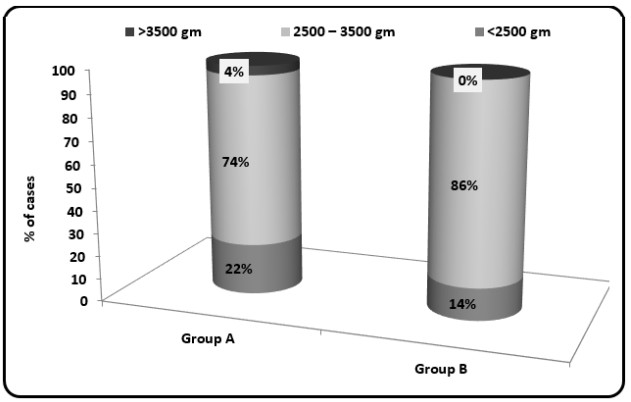

Fig. 7: Inter-Group distribution of birthweight

Of 50 babies born in Group A, 11 (22.0%) had birthweight less than 2500 gm, 37 (74.0%) had birthweight between 2500 – 3500 gm and 2 (4.0%) had birthweight more than 3500 gm.

Of 50 babies born in Group B, 7 (14.0%) had birthweight less than 2500 gm, 43 (86.0%) had birthweight between 2500 – 3500 gm and none had birthweight more than 3500 gm.

Distribution of birthweight did not differ significantly between two study groups (P-value>0.05).

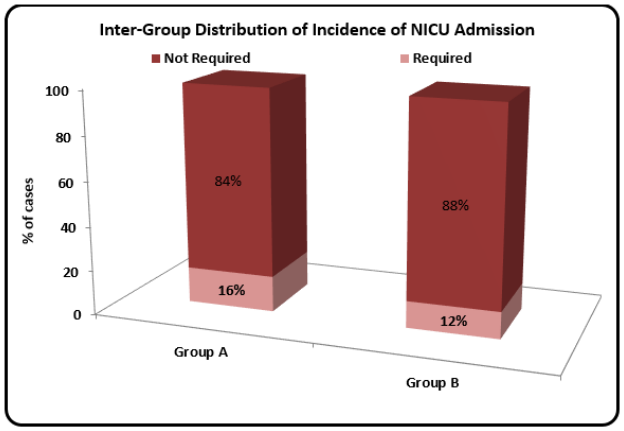

Fig. 8: Inter-Group distribution of incidence of NICU admission

Of 50 babies born in Group A, 8 (16.0%) required NICU admission and 42 (84.0%) did not require NICU admission.

Of 50 babies born in Group B, 6 (12.0%) required NICU admission and 44 (88.0%) did not require NICU admission.

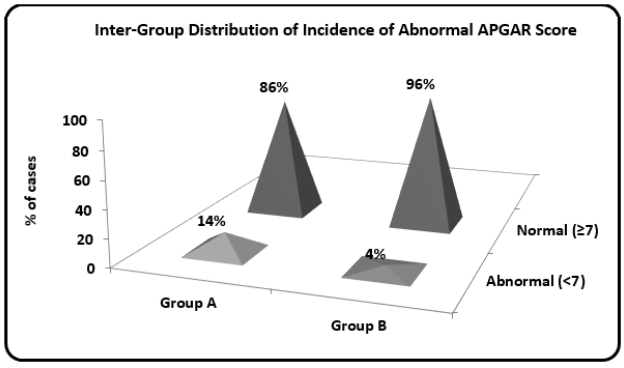

Fig. 9: Inter-Group distribution of APGAR Score

Of 50 babies born in Group A, 7 (14.0%) had abnormal APGAR score and 43 (86.0%) had normal APGAR score.

Of 50 babies born in Group B, 2 (4.0%) had abnormal APGAR score and 48 (96.0%) had normal APGAR score.

Of 50 babies born in Group A, 8 (16.0%) required mechanical ventilation and 42 (84.0%) did not require mechanical ventilation.

Of 50 babies born in Group B, 6 (12.0%) required mechanical ventilation and 44 (88.0%) did not require mechanical ventilation.

Of 50 babies born in Group A, 2 (4.0%) expired and 48 (96.0%) survived. Of 50 babies born in Group B, 1 (2.0%) expired and 49 (98.0%) survived.

4. Discussion

In our study there is no significant difference between vaginal and intramuscular progesterone groups regarding

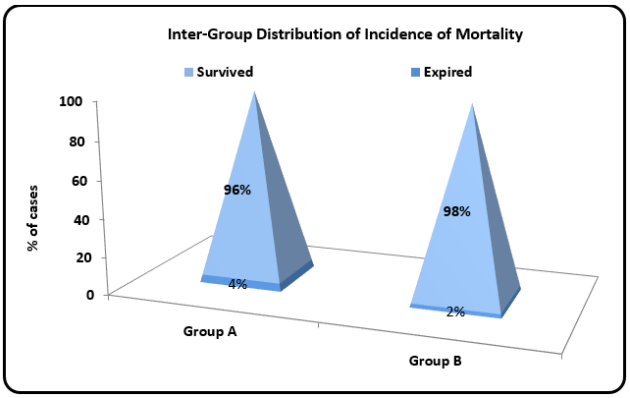

Fig. 10: Inter-Group distribution of incidence of neonatal mortality

baseline characteristics like maternal age, parity, gestational age at admission, cervical dilatation, and risk factors.

According to Meis et al and coinvestigator[23] study, women randomized to 17 hydroxycaproate prophylaxis had a significant reduced risk of preterm birth at all gestational ages .Moreover infants born to group treated with 17 hydroxycaproate (250 mg) has less perinatal morbidity and mortality.

In a present study efficacy findings showed that in case of Intramuscular progestron group out of total 100 cases studied (24.0%) had gestational age less than <37 weeks, 3 (64.0%) between 37–40 weeks and (12.0%) more than >40 weeks.

According to Fonseca et al. and coinvestigator[19] study, women randomized to progesterone prophylaxis had a significantly reduced risk of recurrent preterm labour at all gestational ages.

In a present study in the case of vaginal progesterone group (16.0%) had gestational age less than <37 weeks, (74.0%) between 37–40 weeks and (10.0%) more than >40 weeks. These results confirmed that progesterone therapy have acceptable efficacy in the prevention of preterm labor Distribution of mean gestational age at which the drug was administered among the cases studied was 30.28 ± 2.21 weeks and 30.31 ± 2.19 weeks respectively which did not differ significantly between two study groups (P-value>0.05).

Our results indicates that the frequency of preterm delivery and mean gestational age at delivery were not statistically different between the vaginal progesterone and intramuscular progesterone group. This indicated that these two modes of administering progesterone had essentially the same efficacy in preventing preterm delivery.

Out of total 100 cases studied total (28.0%) had adverse effect in intramuscular progesterone group and (24.0%) in vaginal progesterone group. Incidence of adverse effect of the drug among the cases studied did not differ significantly between two study groups (P-value>0.05).

According to the result Vaginal progesterone has more of local minor side effects like vaginal discharge, itching, pruritis, irritation, yeast infection. Side effect of synthetic injectable progesterone are also mild and restricted to injection site, like pain, swelling, itching, bruising and systemic side effects like nausea, vomiting, pain abdomen, diarrhea, bloating, headache

The studies of Khandelwal et al., Hassan et al. and O'Brien et al. indicated that the rate of adverse effects of vaginal progesterone was similar to that of the placebo.[24] Maher et al. showed that the rate of side effects in women treated with vaginal progesterone was lower than in the case of intramuscular progesterone, i.e., 7.5% as opposed to 14.1%.[25]

Therefore, this study concluded that the use of vaginal progesterone was safer than the use of intramuscular progesterone.

In this study, in addition to comparing the efficacy and safety of vaginal progesterone and intramuscular progesterone in the prevention of preterm delivery, we assessed their effects on some infant outcomes. Based on the results, the birth weights of the two intramuscular progesterone versus vaginal progesterone group was 2784.2 ± 490.7 gm and 2813.9 ± 363.3 gm respectively. Distribution of mean birth weight did not differ significantly between the two study groups (P-value>0.05) confirmed the positive effects of progesterone on increasing infants' weights at birth.

Abd El Hameed[24] studied three groups, i.e vaginal progesterone, intramuscular progesterone, and control groups, and confirmed the positive effect of both vaginal progesterone and intramuscular progesterone on birth weight . In this study, similar to our results, the birth weight of newborns of the vaginal progesterone and intramuscular progesterone groups was not significantly different.

Out of total 100 babies born in intramuscular progesterone group (16.0%) required NICU admission and in vaginal progesterone group (12.0%) and 14.0% had abnormal APGAR score in intramuscular progesterone Group and 4.0% in vaginal progesterone group. Out of that 4 babies in intramuscular group and 3 babies in vaginal progesterone group needs mechanical ventilation.

Distribution of incidence of abnormal APGAR score did not differ significantly between two study groups (P-value>0.05) which shows positive effects of progesterone on reducing admissions to NICU and reducing perinatal mortality and morbidity.

De-Franco et al. confirmed the positive effects of progesterone on reducing admissions to the NICU.[26] The studies of Edwards et al. Conde -Agudelo et al., Abd El Hameed, Hassan et al. and Berghella, et al. confirmed the positive effects of progesterone on reducing perinatal mortality and morbidity.[24,27–29]

In a present study Neonatal mortality are seen in (4.0%) of babies in intramuscular progesterone group and in (2.0%) of the patient with vaginal progesterone group. Distribution of incidence of mortality did not differ significantly between two study groups (P-value>0.05). This confirmed the positive effect of progesterone on reducing neonatal mortality.

In this study, we also assessed the satisfaction of the pregnant women with the drug they received in terms of convenience of use. The findings showed that 100% of participants had a satisfaction level of moderate or better. Also, satisfaction scores were not significantly different between the two groups that were studied. In this regard, Khandelwal et al. in their study in 2012 found that vaginal progesterone was acceptable to women due to its ease of use.[30]

5. Conclusion

Preterm birth remains a significant problem in obstetric care, affecting women and babies world-wide. There are considerable health consequences for infants born preterm, as well as economic consequences for the health care system, individuals, and their families.

Based on our results, we can conclude that progesterone therapy had acceptable efficacy in the prevention of preterm labor in terms of prolongation of delivery and by increasing gestational age at delivery. Both Vaginal progesterone and intramuscular progesterone can be equally useful in the prevention of preterm delivery. Our study indicated that both the two modes of administering progesterone had essentially the same efficacy and safety in preventing preterm delivery with lesser side effects. Present study also indicates positive effect of progestron in decreasing neonatal morbidity and mortality as it had a positive impact on NICU stay, APGAR score, birth weight as the ultimate purpose of interventions designed to prevent preterm delivery is the improvement of infant outcomes. We also assessed the satisfaction of the pregnant women with the drug they received in terms of convenience of use. The findings showed that 100% of participants had a satisfaction level of moderate or better.

6. Source of Funding

No funding sources.

7. Conflict of Interest

None declared.

8. Ethical Approval

The study was approved by the Institutional Ethics Committee.

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