Original Article

Prophylaxis of Preterm Labour with Hydroxyprogesterone Caproate in High Risk Cases: A Pearl for Obstetricians

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Abstract

Objective: to study the effectiveness of hydroxyprogesterone caproate in high risk cases for preterm labour.

Study Design: observational study.

Place and Duration of Study: January 2014-December 2014, Obs/Gynae ward, PAF Hospital Islamabad.

Methodology: the study included fifty seven patients who were high risk for preterm labour and were admitted at obs/gyne ward at PAF hospital Islamabad. They had gestational amenorrhea between 24 – 34 weeks and complaints of pain lower abdomen/ uterine contractions/vaginal infection /urinary infection/previous history of preterm labour/irritable uterus or cervical length less than 3.0 cm. They were treated with hydroxyprogesterone injections once weekly along with protocol of preterm labour. The effects of injection hydroxyprogesterone caproate were studied and patients were followed till delivery. The results were presented in tabulated form.

Results: a total of 57 patients were screened as being high risk for preterm birth. Among them 22 (38.59%) patients were found to have history of one or more preterm deliveries before. Cervical length less than 3.5 cm was calculated in 9(15.78%) women. Among 57 women 37(64.91%) were from low socioeconomic class. Only 5(8.77%) women were tobacco smokers. Irritable uterus was observed in

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41(71.92%) of patients. Most of the patients were anemic. Vaginal, Urinary tract and gingival infection was observed in 21(36.845%), 19(33.33%) and 15(26.31%) women respectively.

After empirical treatment of preterm labour and Progesterone supplementation pain lower abdomen was improved in 29 (68.42%) patients. Feeling of uterine contractions was improved in 26(81.25%) patients. Backache was better in 16(64%) women. Similarly there was marked improvement in vaginal discharge and urinary symptoms.

Out of 57 women 5(8.77%) delivered at 24-27^{+6}, 7(12.28%) at 28-31^{+6} weeks of gestation and 32(56.14%) reached 32-36^{+6} weeks gestation while 13(2.80%) patients reached term.

Conclusion: control of preterm birth is a challenging event for the obstetrician. The use of natural progesterone in the form of hydroxyprogesterone caproate injections in women who are high risk for preterm birth results in marked reduction in preterm birth

Key Words: preterm labour, threatened preterm labour, cervical length, hydroxyprogesterone caproate.

Introduction

Currently preterm birth is the most difficult and important problem in maternal-child health throughout the world as it accounts for over 85% of all perinatal morbidity and mortality.[1-3] Preterm labour includes all deliveries between 24^{+6} and 36 $^{+6}$ weeks gestation. According to aetiology, outcome and risk for recurrence preterm labour is divided into three groups. These are mildly preterm (32-36^{+6} weeks), moderately preterm (28-31^{+6} weeks) and extremely preterm (24-27^{+6} weeks). An obstetrician encounters preterm labour in daily practice and faces challenges to predict, diagnose and treat in order to get best survival outcome for the newborn.[4, 5]

The aetiology of preterm labour is varied from patient to patient. Approximately 20% of preterm deliveries are iatrogenic, 20-30% are due to premature preterm rupture of membranes (PPROM), 20-25% are result of intra-amniotic infections or inflammations and rest 20-25% are due to unexplained spontaneous preterm labour.[6]

A number of risk factors are identified which are responsible for preterm labour. Some of them are non-modifiable and some are modifiable. Several scoring systems have been developed over the past years which are based on history, epidemiological risks, habits and social support for the patient but this risk factor based screening although helpful but fails to identify over half of pregnancies who deliver preterm.[7-10]

Progesterone has a vital role in maintenance of pregnancy. In 1956, Csapso proposed the theory of blockade of myometrial contractility by progesterone and documented that withdrawal of progesterone leads to onset of labour. In most of the mammals' labour is initiated when there is decreased level of progesterone in blood and this mechanism is different in different species. The role of progesterone is thought to inhibit uterine contractions by repressing contraction- associated protein such as gap-junction proteins, oxytocin,

prostaglandin receptors and prostaglandin-metabolizing enzymes.[11-13] Now it is emerging that progesterone imparts a complex role in maintaining myometrial physiology during pregnancy through phenotype modulation of myocytes during the synthetic phase of myometrial differentiation in last trimester of pregnancy which results in myometrial hypertrophy along with synthesis and deposition of interstitial matrix.[14, 15]

The use of progesterone has been in practice in patients with previous history of preterm labour, recurrent preterm labour or high risk for preterm labour. Progesterone is available in two forms. Natural progesterone is usually administered through vaginal preparations and synthetic progesterone, 17-hydroxyprogesterone is administered through intramuscular route. The American College of Obstetrics and Gynecology recommend the use of progesterone preparations in those patients where there is risk of preterm labour with singleton pregnancy or when there is history of previous spontaneous preterm birth.[13, 15]

In case of established preterm labour any intervention as hydration, antibiotics or tocolysis is unable to delay delivery longer than 24-48 hours. Due to failure of intervention more attention has been focused on prevention of preterm labour over the past few years. A number of measures have been proposed but the prevention has mostly failed. Now there is more interest in the use of recent FDA approved progesterone supplementation to prevent preterm labour.[15, 16]

Progesterone inhibits preterm labour by exhibiting a number of actions at different levels. At the level of myometrium and cervix it regulates the two major isoforms of progesterone receptors PR-A and PR-B gene in such ratio that enhance cervical softening and myometrial contractility. It also alters the expression of PR co activators and histone acetylation enhancing contractions of myometrium. At the level of placenta it interferes with cortisol-mediated regulation of placental gene expression which is considered to be placental clock for timing of labour. At the level of amniotic fluid it up regulates the endogenous inhibitors of phospholipase A_2 leading to production of prostaglandins.[7]

It also inhibits apoptosis (programmed cell death) in foetal membranes thereby preventing PPROM. These factors elucidate that how it is possible for progesterone supplementation to maintain uterine quiescence and leads to prevention of preterm labour without altering level of progesterone in maternal circulation by acting directly on uterus, cervix and foetal membranes.[7]

Methodology

The study was conducted at obs/gynae ward PAF Hospital for a period of one year from 1 January 2014 to 31 December 2014. PAF Hospital is a secondary care centre for families of Pakistan Air Force and Army. Written informed consent from the patients and approval from hospital ethical committee has been taken.

Inclusion Criteria: all patients with previous history of one or more preterm labour, cervical

length less than 3.5 cm or irritable uterus were included in study. Patients with vaginal infections, urinary tract infection, gingival infections and anaemia were also included in study. Women who smoke cigarettes or tobacco (huqqa) or have stressful home or work environment or low socioeconomic status were also included in study.

Exclusion Criteria: patients with history of thromboembolic disorders, arterial or cardiovascular disease, and hepatic disorders were excluded from study. Women having multiple pregnancy, preterm premature rupture of membranes, bleeding due to low lying placenta or any cause and cervical cerclage in place were excluded from study.

A total of 57 patients were admitted during this period for prophylaxis/ treatment of preterm labour that fulfilled the inclusion criteria. Patients were counseled in detail about the purpose and benefits of treatment. Gestational age was calculated from the date of last menstrual period when known and earliest dating scans. A biophysical scan was performed on admission and foetal parameters were measured. Cervical length was also measured by transvaginal ultrasound provided in gynae OPD or in radiology department. A detailed history was taken and thorough physical, systemic, obstetric and pelvic examinations were performed. Pelvic examination included speculum examination to see discharge and dilatation of cervix. High vaginal swab was taken from all patients and sent to labouratory for culture. All the patients were given intramuscular injection of hydroxyprogesterone caproate (Proluton Depot) in OPD as an effective measure to prevent preterm birth. This was done in OPD to give early and prompt treatment and to avoid lapse of treatment during the time taken for admission.

The appropriate strategies were adapted for prevention of preterm birth. The patients were advised bed rest and were educated about prenatal care. Those who smoked cigarettes or other forms of tobacco were advised to avoid smoking tobacco. Staff on duty was advised not to do repeated pelvic examination unnecessarily.

All protocol for prevention of preterm labour was followed. Investigations sent were blood complete picture, blood sugar random, hepatitis B and C screening, C reactive proteins, urine complete examination and high vaginal swab (already taken during speculum examination in OPD).

Patients were given Progesterone supplementation i.e injection hydroxyprogesterone caproate (Proluton Depot Bayer Shering Pharma Germany) on weekly basis in alternate buttocks. In addition they were also given oral Progesterone supplements in case of extreme prematurity. They were treated with I/V drips on daily basis to improve hydration and course of corticosteroids for lung maturity of foetus. After taking vaginal swab empirical broad spectrum antibiotic therapy was initiated to treat vaginal as well as urinary tract and gingival infections. Vaginal infections were treated empirically by use of vaginal antifungal and antibacterial pessaries. Patients who were diagnosed to have iron deficiency anaemia were treated for anaemia either with

parental iron therapy, blood transfusions or oral iron.

All patients were monitored for different parameters during treatment in morning and evening rounds or during on call visits. Physical signs and repeat investigations were monitored. Antenatal examination was done repeatedly to see irritable uterus and uterine contractions. Pelvic examination was repeated only when required otherwise avoided. Foetal well-being was monitored by daily cardiotocography and by ultrasound twice weekly. Cervical length and gestational age was reconfirmed by ultrasound from X-ray department by radiologist. Patients were monitored and remained admitted till asymptomatic and were discharged after reassurance.

On discharge they were advised to take rest and avoid sexual intercourse as a prevention of preterm labour. They were advised to have intramuscular injection of Proluton Depot (hydroxyprogesterone caproate) at home weekly. They were also advised to take care of foetal movements and report to hospital in case of any symptom of preterm labour or any other problem. Injection Proluton Depot was continued on weekly basis till 36 weeks and then stopped to allow normal labour.

Statistical Analysis: data had been entered and analyzed using SPSS. The data was presented as tables and figures after calculating percentages and mean values.

Results

There were total 57 patients who were screened high risk for preterm birth as shown in table I. Among them there were 22 (38.59%) patients found to have history of one or more preterm deliveries before. Cervical length less than 3.0 cm was calculated in 9(15.78%) women. Among 57 women 37(64.91%) were from low socioeconomic class with a number of stress factors at home. Only 5(8.77%) women were tobacco smokers either in the form of cigarette or huqqa. Irritable uterus was observed in 41(71.92%) of patients. Most of the patients were anaemic i.e. 45(78.94%). Vaginal infections were the commonest while 21(36.845%). Urinary tract infection and gingival infection were observed in 19(33.33%) and 15(26.31%) of women respectively.

Table I. High Risk Patients Screened For Preterm Birth (n=57)

S. No	Risk Factor	Number of Patients	Percentage
1.	History of one or more preterm deliveries	22	38.59%
2.	Cervical length less than 3.5 cm	9	15.78%
3.	Low Socioeconomic status	37	64.91%
4.	Tobacco Smokers	5	8.77%
5.	Irritable uterus	41	71.92%
6.	Anaemia	45	78.94%
7.	Vaginal Infections	21	36.84%
8.	Urinary tract Infections	19	33.33%
9.	Gingival Infections	15	26.31%

Table II shows the symptoms which were commonly observed in these patients. The most common symptom was pain lower abdomen recorded in 39(68.42%) of patients. Feeling of uterine contractions was observed in 32(56.14%) of women. Backache was observed in 25(43.85%) of patients.

Table II. Symptoms Commonly Observed (n = 57)

S. No.	Symptoms	Number of patients	Percentage
1.	Pain lower abdomen	39	68.42%
2.	Feeling of Uterine contractions	32	56.14%
3.	Backache	25	43.85%
5.	Vaginal discharge	21	36.84%
6.	Urinary symptoms	19	33.33%

Table III shows improvement in symptoms after empirical treatment of preterm labour by Progesterone supplementation. Pain lower abdomen improved in 29 (68.42%) out of 39 patients. Perception of feeling of uterine contractions improved in 26(81.25%) out of 32 women. Backache was better in 16(64%) of women. Similarly there was marked improvement in vaginal discharge and urinary symptoms.

Table IV shows that 5 (8.77%) of patients delivered at 24-27^{+6} in spite of treatment. Similarly 7(12.28%) patients delivered at 28-31^{+6} weeks of gestation. Highest number of patients i.e 32(56.14%) reached 32-36^{+6} weeks gestation. A good number 13(2.80%) patients also reached term.

Table III. Improvement in Symptoms after treatment (n = 57)

S. No.	Symptoms Improved	Number of patients	Percentage
1.	Pain lower abdomen	26/39	68.42%
2.	Feeling of Uterine contractions	26/32	81.25%
3.	Backache	16/25	64.00%
4.	Vaginal discharge	18/21	85.71%
5.	Urinary symptoms	14/19	73.68%

Table IV. Follow up/Delivery (n = 57)

S. No.	Gestational age at delivery	Number of Patients	Percentage
1.	24-27^{+6} weeks	5	8.77%
2.	28-31^{+6} weeks	7	12.28%
3.	32-36^{+6} weeks	32	56.14%
4.	Term	13	2.80%

Prophylaxis of Pre-term labour with hydroxyl progesterone in high risk cases is a Pearl for obstetricians!

Discussion

The effectiveness of hydroxyprogesterone caproate in treatment of preterm labour results in prolonging gestational age which leads to less neonatal morbidity and better survival of newborn.[1,2] Hydroxyprogesterone caproate is a very valuable drug and its safety is also not compromised and can be given to patients at any gestational age.[3]

Several studies have been performed to establish the role of hydroxyprogesterone caproate in prevention of preterm birth. There is increasing data in different studies which demonstrate that progesterone supplementation reduces the rate of

spontaneous preterm birth in patients who are high risk for preterm labour.[4]

In the study conducted by Meis and co investigators it was concluded that weekly 250mg dose of hydroxyprogesterone caproate has a key role in prevention of preterm birth in women with history of spontaneous preterm delivery. In their study they randomly assigned 459 patients with a documented history of preterm delivery to weekly 250mg hydroxyprogesterone caproate injections or placebo beginning from 16 to 20 weeks of gestation and continuing until 36 weeks.[4] It was concluded that women who were given of hydroxyprogesterone caproate weekly injections had significantly reduced risk of recurrent preterm birth as compared to placebo group (36% vs. 55%). The study is comparable to our study results in which 12.28% women reached 28-31^{+6} weeks gestation significant number of patients (56.14%) continued the pregnancy to32- 36^{+6} weeks.

In our study there was a significant reduction in pain lower abdomen, feeling of uterine contractions, backache and vaginal discharge after the treatment. A study conducted by Norwitz Errol R and Aaron B also recommends the use of hydroxyprogesterone caproate on weekly basis. They demonstrated that use of hydroxyprogesterone caproate results in prolonging gestational age significantly and also results in reduction of symptoms of preterm birth.[7] They also verified that the levels of progesterone in maternal circulation do not change in the weeks preceding labour and preterm labour is associated with functional withdrawal of progesterone activity at the level of the uterus.[7] This study also supports the role of hydroxyprogesterone caproate in prevention preterm birth as done in our patients as there was reduction in symptoms of preterm birth as well as reduction in spontaneous preterm birth in high risk women.

The study conducted by Gupta, Simi and Ashley showed that 17-α hydroxyprogesterone caproate is a safe and effective drug used for prevention of preterm birth. In their study they used 250mg hydroxyprogesterone caproate injections weekly in patients with threatened preterm labour or history of one or more preterm births. They concluded that there is 30 to 35% reduction in preterm birth in these high risk patients.[10] This is comparable to our study in which there are also a significant number of women having reduction in symptoms of preterm birth.

Ibrahim and Sherrine in their study demonstrated the Effect of 17-alpha-hydroxyprogesterone caproate injections on rate of cervical length change in women with a history of prior preterm birth. They found that symptomatic women found at mid gestation to have a short cervix are at greatly increased risk for spontaneous early preterm delivery and hydroxyprogesterone injections reduced this risk in such women. Spontaneous delivery before 34 weeks of gestation was less frequent (19.2%) with progesterone supplementation.[17] It was shown that progesterone administration in women who previously delivered prematurely reduced the risk of recurrent premature delivery as it was also

shown in our study. In treating these high risk women with such a cost effective drug (hydroxyprogesterone caproate) not only leads to prevention of preterm labour and also saves efforts, time and costs of hospital staff in case of neonatal morbidity.[18-21]

Asian study conducted by Jayasooriya, G. S. and R. F. Lamont showed the use of progesterone and other progestational agents to prevent spontaneous preterm labour and preterm birth in women who were high risk for preterm labour. They concluded that use of progesterone supplements whether natural or synthetic results in a considerable drop of preterm birth.[11] In our study we demonstrated with weekly injections of hydroxyprogesterone caproate which also show the same results of decline in preterm births.

Conclusion

Preterm birth complicates one in eight deliveries and remains a foremost reason for infant morbidity and mortality. The use of hydroxyprogesterone caproate supplementation results in reduction of risk of preterm labour in high risk patients. Its use can no longer be considered as investigational as much work is done to establish its effectiveness in preterm labour. Hydroxyprogesterone caproate is a pearl for threatened preterm labour. Its usage is safe and helps the obstetrician to take the patient to a better safety margin for the neonate.

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