# Human Chorionic Gonadotropin in Treatment of Preterm Labour

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## ABSTRACT:

**BACKGROUND:**

Preterm labour is a major healthcare problem throughout the world, it is a major cause of perinatal morbidity and mortality, that is not significantly altered by the current drug therapies, most of which are associated with significant maternal or fetal side effects.

**OBJECTIVE:**

To evaluate the role of human chorionic gonadotrophin (HCG ) in the treatment of preterm labour.

**METHODS:**

Fifty-seven women with preterm labour were enrolled in this clinical trial at Al- Yarmouk Teaching Hospital/ department of Obstetrics and Gynaecology – Baghdad /Iraq during the period from April, 1st 2006 till November, 30th 2006, and were assigned to receive a single intramuscular injection of 5000 units of *HCG* followed by a drip of 10000 units of *HCG* in 500 ml 5% dextrose over 6 hours. 30 women continued the study and the mean prolongation of the pregnancy was calculated for all of them.

**RESULTS:**

The mean prolongation of pregnancy was 32.97 ± 17.6 days and it was highest among gestational ages of 29-30 weeks ( 43.3± 19.85 days ), with the mean gestational age at birth was 35.7 ± 2.8 weeks.

All babies born to these women had weight appropriate for their gestational age at birth with a mean birth weight of 2.7 ± 0.64 kg and 60% of babies weighed > 2.5 Kg at birth.

**CONCLUSION:**

It was shown through this trial that human chorionic gonadotropin was effective in exhibiting potent tocolysis and prolonging pregnancy in preterm labour without causing adverse effects to the mothers or their babies. This can make a major contribution to the management of this common obstetrical complication.


***KEY WORDS*:** HCG, preterm labour, treatment.

## INTRODUCTION:

Preterm birth refers to a birth that occurs before 37 completed weeks (<259days) of gestation [(1)].The incidence of preterm birth in the developed word is between 7 and 12%. The rate of preterm birth prior to 32 weeks has remained relatively stable at 1-2% [(2)]. The incidence of preterm birth in India, which can reflect the incidence in the developing countries, is 20.9% [(3)].

The preterm birth accounts for over 85% of perinatal morbidity and mortality . The mobidity, mortality and costs of preterm delivery are higher at lower gestational ages[(4)].

There are no evidence based guidelines for when to initiate treatment of preterm labour, nor universally agreed upon criteria for making this diagnosis[(5)]. Treatment of preterm labour is undertaken to delay delivery so that corticosteroids can be administered, to allow safe transport of the mother, if indicated, to a facility that can provide an appropriate level of neonatal care if the patient delivers preterm, and to prolong pregnancy when there are underlying, self-limited causes of labour, such as pyelonephritis or abdominal surgery, that are unlikely to cause recurrent preterm labour[(6)]. These fetuses could potentially benefit from prolongation of pregnancy and the non-pulmonary benefits of glucocorticoid therapy. Inhibition of preterm labour, is less effective when cervical dilatation is advanced (>3 cm), but tocolysis can still be considered in these cases[(5)].

Human chorionic gonadotropin (HCG) is a heterodimeric glycoprotein produced primarily in the placenta and has multiple endocrine, paracrine and immunoregulatory actions [(7)]. Although the

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importance of HCG in maintenance of early pregnancy has been widely accepted, reports have highlighted a potential role of *HCG* in maintaining uterine quiescence in the third trimester. The HCG exerts a potent concentration dependent inhibitory effect on human myometrial contractions[8]. The *HCG* receptors in human myometrium are down-regulated following the onset of labor, in both term and preterm deliveries[7,8]. The exact mechanism, of the inhibitory effect of *HCG* in myometrial smooth muscle are unknown, but direct reduction in intracellular calcium availability[10] and down-regulation of gap junctions have previously been suggested [11].

Following I.M. injection, peak concentration of *HCG* occurs about 6 hours after a dose. It is distributed primarily to the gonads. Blood concentrations decline in a biphasic manner, with a half life of between about 6 and 11 hours and 23 to 38 hours respectively. About 10 to 12% of an intramuscular dose is excreted in urine within 24 hours[12].

*HCG* is being evaluated as an inhibitory drug of preterm labor[13].

## METHODS:

Fifty-seven women with established preterm labour between 24-36 weeks of gestation, were included in this study at the beginning. Patients with ruptured membranes, chorioamnionitis, dead, compromised or grossly abnormal fetus, pre-eclampsia, eclampsia or gestational hypertension, diabetes mellitus and cardiac disease, vaginal bleeding consistent with abruptio placentae and cervical dilatation more than 3 cm were excluded from the study.

Patients with significant uterine contractions and cervical dilatation $\leq$ 3 cm with cervical effacement (40-90%) and with no contraindications to inhibition of preterm labor were candidates for HCG administration.

Gestational age was determined by last menstrual period and first trimester ultrasound dating. Informed written consent was obtained from all patients for participation in this trial.

All patients were admitted to the labor room and hemoglobin concentration, urine analysis and microscopical examination, blood group and Rh, blood sugar and high vaginal swab were done for all of them. They were positioned in the left lateral position. Two doses of 12 mg of dexamethasone 24 hours apart were administered with antibiotics given in presence of urinary tract infection. *HCG* was given to all participants in a dose of 5000 units I.M. injection followed by a drip of 10000 units in 500 ml of 5% dextrose, 20 drops/min lasting for 6 hours. Half-hourly assessment of uterine contractions, maternal vital signs, with continuous fetal heart rate monitoring by cardiotocography continued till the end of the drip, then hourly for the rest of the 24 hours.

Patients were kept in the labor ward 24 hours after cessation of uterine contractions and arrest of labor. Follow up was performed by a weekly visit to the antenatal clinic. At each visit blood pressure, pulse rate and fetal heart rate were checked and recorded, signs and symptoms of preterm labor were reviewed and ultrasound examination was performed fortnightly to assess fetal wellbeing and growth. All patients were readmitted to the hospital if any recurrence of uterine contractions happened and reassessment was done and if the membranes were not ruptured, cervical dilatation $\leq$ 3 and normal maternal and fetal conditions, we repeated the medication in the same regimen and calculated the prolongation of pregnancy from the second administration.

At delivery neonatal weight, weeks of gestation and APGAR score were determined.

Twenty seven women were dropped-out from the study: 7 women did not continue the treatment and left the hospital, 13 women did not attend the antenatal clinic for follow up, and 7women were not delivered by Nov. 30$^{th}$ (the end of the study), although they reached a reasonable maturity ( range from 35week + 4days to 37week + 5days), but they were ruled out of the study because the outcome was not known. So at the end 30 women were enrolled in the statistical analysis.

### Statistical analysis

Using computer facilities by EPI-Info Soft Ware ( World Health Organization Adapted ), data presented in simple statistical measures of frequency distribution, means and standard deviation.

## RESULTS:

The demographic characteristic of the study group regarding age, parity, weight and weeks of gestation are shown in table 1.

The mean maternal age was 25.4$\pm$4.81 years (range 16-35 years), the mean parity was 1.17 (range 0-5), the mean maternal weight was 64.3 kg (range 44-82 kg), and the mean gestational age was 30.97 weeks (range 24-34 weeks).

**Table 1: The demographic characteristics of patients in the study**

| Characteristics | Variable | Numbers | Percentage |
|---|---|---|---|
| Age ( years ) | ≤16 | 1 | 3.3% |
| | 17-20 | 5 | 16.7% |
| | 21-25 | 11 | 36.7% |
| | 26-30 | 8 | 26.6% |
| | >30 | 5 | 16.7% |
| Means ± SD= 25.40 ± 4.81 | | Range = 16-35 | |
| Parity (number ) | 0 | 15 | 50.0% |
| | 1 | 6 | 20.0% |
| | 2 | 3 | 10.0% |
| | 3 | 3 | 10.0% |
| | ≥ 4 | 3 | 10.0% |
| Means ± SD = 1.17 ± 1.56 | | Range = 0-5 | |
| Gestational age (weeks) | ≤ 28 | 4 | 13.3% |
| | 29-30 | 8 | 26.7% |
| | 31-32 | 9 | 30.0% |
| | 33-34 | 9 | 30.0% |
| Means ± SD = 30.97 ± 2.33 | | Range = 24-34 | |

The characteristics of preterm labor regarding frequency and duration of uterine contractions, dilatation and effacement of the cervix are shown in table 2.

**Table 2: The characteristics of preterm labor**

| Characteristic | Mean ± SD | (range) |
|---|---|---|
| Frequency of contractions/ 10 min. | 4.02 ± 1.04 | (2-5) |
| Duration of contractions (seconds) | 38.83 ± 5.36 | (30-50) |
| Dilatation of the cervix (cm) | 2.47 ± 0.73 | (1-3) |
| Effacement of the cervix (%) | 70.90 ± 15.45 | (40%- 90%) |

After injection of 5.000 unit I.M. and infusion of 10.000 unit in 500 ml 5% dextrose water in a drip, there was no change in maternal blood pressure, pulse rate or fetal heart rate. All patients included in this study had no further injections of HCG in the same day as uterine contractions subsided after 1-2 hours, three patients needed further repetition of the total dose of HCG after 10 days.

The mean prolongation of pregnancy was 32.97 ± 17.69 days (range 1-71 days). The prolongation of pregnancy was greatest at the gestational age between 29 and 30 weeks, where the mean prolongation of pregnancy was 43.4 days ± 19.85 (range 18-71 days ) as shown in figure 1.

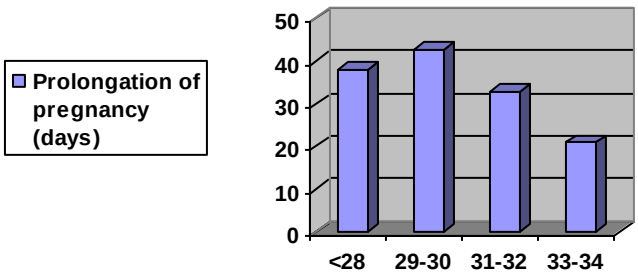


**Figure 1: The prolongation of pregnancy for the patients included in the study according to the gestational age at presentation**

The babies born to mothers showed no adverse cardiovascular or other effects and they were all correspondent to their gestational age.
As shown in table 4, The mean age at birth was 35.7 ± 2.8 (weeks). Out of 30 babies 14 (46.7%) were ≥ than 37 weeks, 13 (43.3%) were 33-36 weeks, 2 (6.6%) were 29-32 weeks, and 1 baby (3.3%) was ≤ 28 weeks.

**Table 4: Birth age of babies delivered to patients included in this study**

| Birth age (weeks ) | Number | Percentage |
|---|---|---|
| ≤28 | 1 | 3.3% |
| 29-32 | 2 | 6.6% |
| 33-36 | 13 | 43.3% |
| ≥37 | 14 | 46.7% |

The mean birth weight of the babies delivered by the patients included in this study was 2.79 kg ± 0.69. Of the delivered 30 babies 18 (60%) had birth weight more than 2.5 kg as shown in table 5.

**Table 5: Birth weight of babies delivered to patients included in the study**

| Birth weight (kg) | Number | Percentage |
|---|---|---|
| < 1 | 1 | 3.3% |
| 1-2.5 | 11 | 36.7% |
| 2.6-3.5 | 15 | 50.0% |
| > 3.5 | 3 | 10.0% |

## DISCUSSION:

Spontaneous preterm labor is responsible for more than half of preterm birth [14].Half of all preterm babies weighing between 500 and 1000 g surviving delivery have a wide range of related short-term and long-term handicaps. Despite the use of a wide variety of drugs, the incidence of preterm labor has remained constant for decades, and some of the drugs used, such as prostaglandin synthesis inhibitors, beta-adrenoreceptor agonists, and calcium channel antagonists, have potentially serious side effects on both mother and infant [15]. The selection of an appropriate labor inhibiting agent should be based upon efficacy and safety[6].
Although the total number of patients in this study was not high, It has been shown that *HCG* is beneficial for relaxation of human myometrium, suppression of preterm labor and prolongation of pregnancy with no maternal, fetal or neonatal side effects.
Carlo et al, observed that many studies conducted worldwide in recent years indicate that *HCG* may play a significant role in maintaining pregnancy well after the first trimester. Emerging evidence suggests that different biomolecular and physiologic effects of *HCG* are concordantly directed toward inhibition of myometrium contractility to maintain pregnancy. These studies have prompted preliminary human testing of *HCG* for the prevention of preterm birth[7].
Slattery et al, recently demonstrated that *HCG* exerts a significant relaxant effect on human myometrial tissue in the third trimester of pregnancy, and this effect is concentration dependent. These findings raise the possibility of its potential use as a tocolytic[8].
Kurtzman et al, Reported that the role of *HCG* in the maintenance of early pregnancy is well known and data suggests that *HCG* may play a role in the maintenance of the later stages of pregnancy as well, by directly and indirectly promoting uterine quiescence. If *HCG* acts as an endogenous tocolytic in normal pregnancy, then it may be an ideal candidate for therapy of preterm labor as well[16].
Ali et al, observed that the mean prolongation of pregnancy was 28.8 days in *HCG* traeted group and 15 days in placebo group and there was statistically significant difference between the two groups regarding the delivery before 37 weeks and the proportion of infants weighing less than 2.5 kg. They stated that *HCG* exhibits potent tocolysis, with no fetal side effects[13].

The mean prolongation of pregnancy in our study was 32.97 days which was found to be more effective at gestational age of 29-30 weeks where the mean prolongation was 43.5 days. All babies born to our patients were of appropriate weight for their gestational ages at delivery with 60% of babies were > 2.5 kg at birth. The mean birth age was 35.7 weeks with 46.7% of babies were ≥ 37 weeks. This is in agreement with Ali et al[13].

We did not find adverse maternal and fetal side effects from this form of therapy as weren't found by Ali et al[13].

## CONCLUSION:

Given the limited effectiveness of tocolytic therapies available at the time, *HCG* may provide a promising pharmacological approach in arresting preterm labour and prolonging pregnancy with no maternal or fetal adverse effects. This can make a major contribution in the management of preterm labor.

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