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Potency of Dexamethasone in Labor Induction

Abd Elazeem Mohamed Ahmed, Osama Mohamed Deif and Mohamed Aly El-Saftawy*
Department of Obstetrics and Gynecology, Faculty of Medicine, Al-Azhar University
***Corresponding author:** Mohamed Aly El-Saftawy; **Mobile:** (+20)01064420247,
Email: mohamedsofyomar@hotmail.com

ABSTRACT

Background: Induction of labor is one of the most common interventions practiced in modern obstetrics. In the developed world, the ability to induce labor has contributed to the reduction in maternal and perinatal mortality and morbidity.

Objective: The aim of this study is to establish whether dexamethasone plays a role in shortening the duration interval between initiation of labor induction and beginning of the active phase of labor in post-term pregnancy, so shortening the duration of labor.

Methodology: This case-controlled trial study was conducted in the labor ward of El Hussein University Hospital and El-Shiekh Zaid Specialized Hospital to evaluate the effect of dexamethasone infusion administration on the duration of induction of labor. This study comprised 100 pregnant women with full term pregnancy, who admitted to the labor ward for induction of labor because of full-term pregnancy (gestational age ≥40 weeks).

Results: There was a high significant statistical difference between the two studied groups as regards duration between labor induction and active phase of labor being shorter in case group. Active phase and second stage of labor were shorter in duration in cases of study than control. No significant statistical difference between the two studied groups as regards mode of delivery, neonatal outcome (birth weight, Apgar score at 1 minute, Apgar score at 5 minutes and fetal complications (meconium stained liquor and admission to NICU).

Conclusion: Intravenous infusion of two ml (8 mg) of dexamethasone appears to shorten labor duration.

Keywords: Dexamethasone, Labor induction

INTRODUCTION

The process of childbirth starts from the axis of the hypothalamus, the pituitary gland, and the adrenal glands. Steroid substances produced in the adrenal glands of the human fetus affect the placenta and the membranes and transform the myometrium from the static to the contractile state[(1)]. The placenta may play a role in this process because it produces a lot of CRH (Corticotrophin releasing hormone). The adrenal glands of the fetus do not produce a considerable amount of cortisol until the third trimester. During the last weeks of pregnancy, the cortisol and DHEA –S (Dehydroepiandrosterone sulfate) contents of the fetus rise and this leads to an increase in maternal estrogens; particularly sterol[(2)].

Placental CRH is not under the influence of negative feedback from cortisol. The concentration of CRH in the fetus rises during the last 12 weeks of pregnancy. This results in modification of the contractility of the uterus [(2)], stimulation of the membranes to produce more prostaglandins, stimulation to produce C steroids from placental adrenaline [(3)], and increase in the estrogen content [(4)].

This will disturb the ratio of estrogen to progesterone and will cause expression of contractile proteins. In fact, the increase in CRH near the end of pregnancy confirms the presence of a placental-fetal clock [(2)].

Although administrating corticosteroids is a suggested method to shorten labor duration, pCRH concentrations predicted the likelihood of delivering within one week of corticosteroid treatment. Current findings suggest that pCRH may be a diagnostic indicator of impending preterm delivery. Increasing the precision in predicting time to delivery could inform when to administer antenatal corticosteroids, thus maximizing benefits and reducing the likelihood of exposing fetuses who will be delivered at term [(5)].

Several animal studies have shown the importance of corticosteroid secretion by the fetal adrenal glands on the beginning of labor [(6)], and infusing glucocorticoids in the lamb fetus was also shown to induce preterm labor [(1)].

These findings have led to the hypothesis that corticosteroids also has an effect on the labor of women [(3)].

Kalantaridou *et al.* [(7)] have suggested that the corticotrophin-releasing hormone (CRH), which has been identified in various organ systems, including the female reproductive system, is the principal regulator of the hypothalamic–pituitary–adrenal axis. Circulating placental CRH is responsible for the physiologic hypercortisolism of the latter half of pregnancy and plays a role in the onset of labor. **O'Sullivan *et al.*** [(8)] reported that a prolonged gestation is more likely to occur when the fetus has congenital adrenal hyperplasia caused

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by 21-hydroxylase deficiency, which may be due to an impaired cortisol production.

Induction of labor is one of the most common interventions practiced in modern obstetrics. In the developed world, the ability to induce labor has contributed to the reduction in maternal and perinatal mortality and morbidity [9].

AIM OF THE WORK

The purpose of the present study was to evaluate the effect of intravenous drip infusion administration of dexamethasone on the duration of induction of labor, cervical ripening and its possible adverse effects.

PATIENTS AND METHODS

This prospective clinical interventional randomized case-controlled trial was conducted at EL-Husein University Hospital and El-Sheikh Zaid Specialized Hospital during the period from April 2018 to January 2019. It included 100 participants who were admitted for labor induction by syntocinon (Novartis co.).

Methodology (plan):

The participants were randomly assigned by computer list into group I (dexamethasone group) N=50 and group II (control group) N=50.

The participants of group I (primigravida = 50) received a prefilled syringe with two milliliters (8 mg) of dexamethasone (Sigmatec co.) infusion drip, and the participants of group II received placebo (2 ml saline)

No cervical ripping agent was used for induction of labor in either group.

After approval of health committee in both hospitals, a verbal consent was obtained from each candidate after explanation of the procedure in details.

- ***The studies were conduct as follows:***

I- Clinical history was obtained.

II- Monitoring for maternal wellbeing: Pulse rate, blood pressure, temperature, random blood sugar and any other maternal complaint i.e. nausea, vomiting, palpitation, headache, etc. was noticed.

III- Monitoring of fetal well-being: Application of CTG half an hour to all participates before starting any intervention.

a) **Per vaginal examination to assess:** Cervical dilatation and effacement at the beginning, state of fetal membranes, station of fetal head, position of fetal head and pelvic adequacy.

V. Each participant received a prefilled syringe with two milliliters of colorless solution infusion drip [either dexamethasone (8 mg) or placebo] randomly assigned by computer list.

IV- After six hours of the initial dose, the labor induction started via Oxytocin using the following protocol [10]:

a) Initial dose of oxytocin..... 1 to 2 mIU/min.

b) Increase interval..... 30 minutes

c) Dosage increment.....1 to 2 mIU.

d) Usual dose for good labor..... 8 to12 mIU/min.

e) Maximum dose…….....30 mIU/min.

V- The interval between the initiation of induction and the beginning of the active phase of labor was recorded (a cervical dilatation of 4 cm plus 3 forceful contractions over a 10-minute span each last from 40-60 sec).

VI- Partographic representation for progression of active phase labor: Frequency and duration of uterine contraction, cervical dilatation was record every two hours by per vaginal examination, station and position of fetal head was noted at the same time, fetal heart rate was recorded every 10 minutes and maternal vital signs of blood pressure, pulse, temperature and random blood sugar every hour .

VII- After delivery: The duration of the first stage of labor was recorded. Partographic representation was done for each participant. The duration of the second stage of labor was recorded. The duration of the placental separation was recorded. The neonatal outcome was recorded by APGAR score and any postpartum maternal adverse effect was noted (e.g. vital sing abnormality and any maternal postpartum hemorrhage).

Primary outcomes: The interval between the initiation of induction and the beginning of the active phase of labor was recorded (a cervical dilatation of 4 cm plus 3 forceful contractions over a 10-minute span each last from 40-60 Sec).

Secondary outcomes: (Partographic representation was done for each participant and Bishop score including station, cervical position, consistency, dilatation and effacement).

(a) The duration of the first stage of labor was recorded
(b) The duration of the second stage of labor was recorded.
(c) The duration of the placental separation was recorded.
(d) The neonatal outcome was recorded by APGAR score.
(e) Any postpartum maternal adverse effect was noted (e.g. vital sing abnormality and any maternal postpartum hemorrhage).
(f) Vital signs (blood pressure, pulse, temperature and random blood sugar) at three occasions (before induction, during induction and after labor).

Statistical methods

The collected data were coded, tabulated, and statistically analyzed using IBM SPSS statistics (Statistical Package for Social Sciences) software version 22.0, IBM Corp., Chicago, USA, 2013.

Descriptive statistics were done for quantitative data as minimum and maximum of the range as well as mean±SD (standard deviation) for quantitative normally distributed data, while it was done for qualitative data as number and percentage. Inferential analyses were done for quantitative variables using independent t-test in cases of two independent groups with normally distributed data and paired t-test to compare the results of the same group. In qualitative data, inferential analyses for independent variables were done using Chi^2 test. The level of significance was taken at P value < 0.05 is significant, otherwise is non-significant.

RESULTS

The studied groups described as:

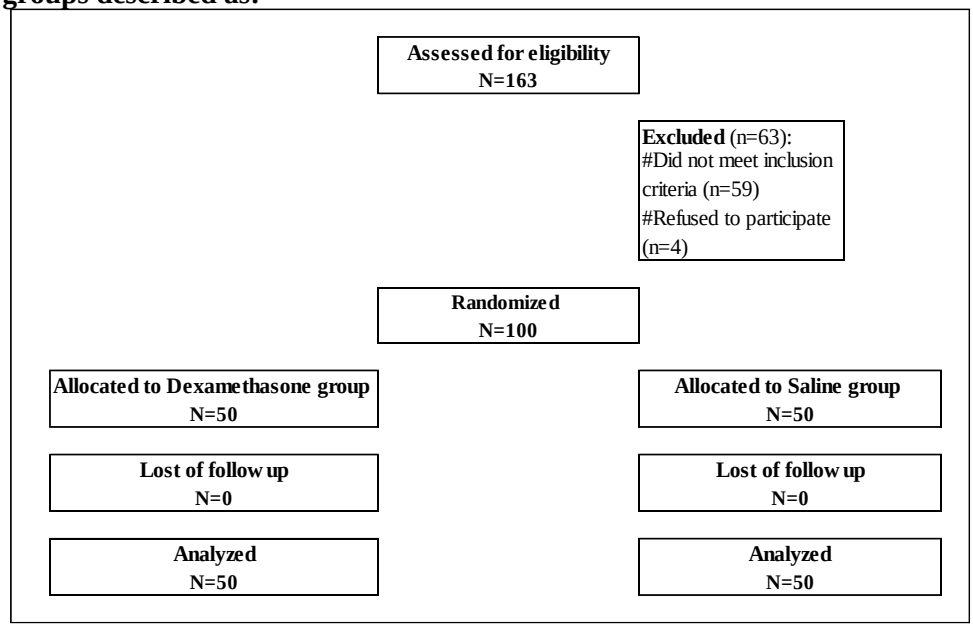

Figure (I): Flow chart of the studied cases

Table (1): Basal maternal and fetal characteristics among the studied groups

Variables		Dexamethasone (N=50)	Saline (N=50)	P
Age (years)	**Mean±SD**	26.5±2.3	25.8±2.9	^>0.05
	Range	22.0–31.0	20.0–33.0	
BMI (kg/m^2)	**Mean±SD**	25.7±2.2	25.6±1.8	^>0.05
	Range	19.9–30.2	20.7–29.0	
GA (weeks)	**Mean±SD**	40.5±0.5	40.7±0.7	^>0.05
	Range	40.0–41.0	40.0–42.0	
ROM, (n, %)		29 (58.0%)	31 (62.0%)	#0.683

^Independent t-test, #Chi square test

Table (1) shows no significant difference between **dexamethasone** and **saline** groups regarding **basal maternal and fetal characteristics.**

Table (2): Bishop score among the studied groups

Variables		Dexamethasone (N=50)	Saline (N=50)	P
Basal	**Mean±SD**	2.9±0.7	2.8±0.6	^>0.05
	Range	2.0–4.0	2.0–4.0	
Induction	**Mean±SD**	6.4±0.9	4.8±0.9	^**<0.001***
	Range	5.0–8.0	4.0–7.0	
Increase	**Mean±SD**	3.4±0.5	1.9±0.6	^**<0.001***
	Range	3.0–4.0	1.0–3.0	
#P (Basal/Induction)		**<0.001***	**<0.001***	
Value of dexamethasone in advancing ripening				
Item		**Mean±SD**	**95% CI**	
BISHOP score increase		1.48±0.11	1.26–1.70	

^Independent t-test. # Paired t-test. CI: Confidence interval. *Significant

Table (2) shows that there was no significant difference between dexamethasone and saline groups regarding basal Bishop score (start assessment). Induction Bishop score *(Bishop 1)* and active stage Bishop score *(Bishop 2)* elevation were significantly higher among dexamethasone group than among saline group.

Table (3): Labor durations (hours) among the studied groups

Variables		Dexamethasone (N=50)	Saline (N=50)	^P
Induction-Active	**Mean±SD**	2.6±0.7	4.1±1.3	**<0.001***
	Range	1.6–4.8	1.8–7.6	
Active-Second	**Mean±SD**	3.5±1.1	3.8±0.8	^>0.05
	Range	1.5–5.8	1.0–5.5	
Induction-Second	**Mean±SD**	6.1±1.3	7.8±1.7	**<0.001***
	Range	3.6–9.0	5.0–12.1	

Value of dexamethasone in shortening labor durations		
Phases	**Mean±SD**	**95% CI**
Induction-Active	1.48±0.21	1.06–1.89
Active-Second	0.25±0.19	-0.12–0.63
Induction-Second	1.72±0.30	1.13–2.31

^Independent t-test. CI: Confidence interval. *Significant

Table (3) show that: **Induction-active, active-second and induction-second durations** were shorter among **dexamethasone** group than among **saline** group, but the differences were statistically significant only in **induction- active and induction-second durations**. **Rate of delivery** was significantly higher among **dexamethasone** group than among **saline** group.

Table (4): Neonatal condition among the studied groups

Indications		Dexamethasone (N=50)	Saline (N=50)	P
APGAR1	**Mean±SD**	7.3±0.6	7.1±0.5	^>0.05
	Range	6.0–9.0	6.0–8.0	
APGAR5	**Mean±SD**	8.4±0.7	8.2±0.4	^>0.05
	Range	8.0–10.0	8.0–9.0	
Birth weight (kg)	**Mean±SD**	3.3±0.1	3.3±0.2	^>0.05
	Range	3.1–3.6	2.9–3.7	
NICU admission		0 (0.0%)	0 (0.0%)	--

^Independent t-test.

Table (4) shows that there was no significant difference between **dexamethasone** and **saline** groups.

Table (5): Systolic blood pressure (mmHg) among the studied groups

Variables		Dexamethasone (N=50)	Saline (N=50)	P
Basal	**Mean±SD**	113.8±7.0	113.4±6.9	^>0.05
	Range	100.0–130.0	100.0–130.0	
During	**Mean±SD**	116.5±10.2	115.8±8.2	^>0.05
	Range	95.0–135.0	95.0–130.0	
After	**Mean±SD**	111.7±8.8	110.8±10.0	^>0.05
	Range	95.0–125.0	95.0–125.0	
#P (Basal/during)		>0.05	>0.05	
#P (Basal/after)		>0.05	>0.05	

^Independent t-test. # Paired t-test. *Significant

Table (5) shows that there was no significant difference between dexamethasone and saline groups regarding systolic blood pressure (SBP).

Table (6): Diastolic blood pressure (mmHg) among the studied groups

Vatiables		Dexamethasone (N=50)	Saline (N=50)	P
Basal	**Mean±SD**	75.0±5.6	74.4±5.7	^>0.05
	Range	65.0–80.0	65.0–80.0	
During	**Mean±SD**	77.0±7.6	76.6±6.6	^>0.05
	Range	65.0–85.0	65.0–85.0	
After	**Mean±SD**	73.4±6.6	73.1±5.3	^>0.05
	Range	60.0–80.0	60.0–80.0	
#P (Basal/during)		>0.05	>0.05	
#P (Basal/after)		>0.05	>0.05	

^Independent t-test. # Paired t-test. *Significant

Table (6) shows that there was no significant difference between **dexamethasone** and **saline** groups regarding **diastolic blood pressure (DBP)**.

Table (7): RBG (mg/dL) among the studied groups

Variables		Dexamethasone (N=50)	Saline (N=50)	P
Basal	**Mean±SD**	97.1±12.8	96.9±14.8	^>0.05
	Range	80.0–123.0	70.0–120.0	
During	**Mean±SD**	93.9±20.9	93.6±24.6	^>0.05
	Range	60.0–130.0	60.0–130.0	
After	**Mean±SD**	91.9±20.3	92.9±21.3	^>0.05
	Range	60.0–120.0	60.0–120.0	
#P (Basal/during)		>0.05	>0.05	
#P (Basal/after)		>0.05	>0.05	

^Independent t-test. # Paired t-test. *Significant

Table (7) shows that there was no significant difference between **dexamethasone** and **saline** groups regarding **RBG**.

DISCUSSION

It is well known that glucocorticoids accelerate lung maturation by enhancing surfactant synthesis in the pulmonary alveolar cells. Evidence was obtained from early studies that the phospholipid content of surfactant provides a source of arachidonic acid that can be used by the amnion for prostaglandin synthesis. More recently there is direct evidence pointing to surfactant protein A (SP-A) as the key link between the maturing fetus and the initiation of parturition in the mouse[(11)].

Glucocorticoids derived from the maturing fetal hypothalamus-pituitary-adrenal axis play a crucial role in, triggering parturition [(12)]. The placenta synthesizes corticotrophin-releasing hormone (CRH), and the exponential rise of this hormone in maternal plasma correlates with the timing of birth [(13)].

The corticotrophin-releasing hormone (CRH), which was identified in various organ systems, including the female reproductive system, is the principal regulator of the hypothalamic-pituitary-adrenal axis. Circulating placental CRH is responsible for the physiologic hypercortisolism of the latter half of pregnancy and plays a role in the onset of labor [(7)].

Cortisol increases the production of prostaglandins in the fetal membranes by either up regulating prostaglandin synthesis levels or down regulating 15-hydroxy prostaglandin dehydrogenase (PGDH) [(14)].

Our findings are in agreement with those observed by **Laloha *et al.*** [(9)] who conducted a study of total number of 172 patients composed of 86

women in the experimental group who received intravenous dexamethasone infusion and the same number in the control group were infused with saline. The average Bishop score at the start of induction in the experimental group was significantly higher than that of the control group Bishop Score at entrance; in cases (2.95 ± 0.9) and control groups (2.82 ± 0.9). It was also found that the mean interval from the start of induction to the beginning of the active phase in the experimental group was shorter than that of the control group (P<0.001). It appears that prescription of dexamethasone can play a role in improving the preparation of the cervix and in speeding up labor induction, and that it may be possible to use dexamethasone to help speed up the childbirth process and improve cervix preparation.

Hajivandi *et al.* [15] performed clinical trial on 100 eligible nulliparous women in their 40 to 42 weeks of gestation in 2009 who were admitted to Amir Hospital in Ahvaz. For the case group, 8 mg dexamethasone was administered intramuscularly 12 hours before induction and the controls were given 2 ml of normal saline at the same intervals.

There was no significant difference between the two groups in terms of age, demographic characteristics, initial Bishop score, first and fifth minute Apgar score, and meconium difference. There was a significant difference between the two groups (p =0.001) concerning the mean-time interval between the induction and the onset of active phase in the case group (3.1±0.68 hours) and in the control group it was (4.2±1.3 hours). They concluded that intravenous dexamethasone reduces the time duration from the induction to the onset of labor phase [15].

In another study, conducted by ***Ziaei et al. (2003)*** [16], that aimed to determine the effect of intramuscular injection of dexamethasone on induction of labor. Women in 41 weeks gestational age and Bishop score greater than or equal to 7 received intravenous infusion of 10 mg dexamethasone in two doses with 12 hours interval, and the next day, induction was carried out using oxytocin. These patients were compared with patients in similar conditions, but receiving oxytocin.

In this study, more of the patients from dexamethasone group entered active phase than that in control group, and interval between induction and onset of active phase was shorter in this group than in control group. They reported that intramuscular injection of dexamethasone before labor induction reduced the time between the induction and the active phase of labor [16].

In another study conducted by **Barkai *et al.*** [17] with the aim to investigate the effect of extra-amniotic normal saline with dexamethasone for induction of labor, the interval between induction and onset of active labor in dexamethasone group was shorter than that in the group that received extra-amniotic normal saline only.

Also, 90.25% of dexamethasone group entered active phase, and 88.37% of control group, but the difference was insignificant. Mean onset of oxytocin to delivery was 7.25±2.86 hours in the case group, and 9.76±3.91 hours in the control group, with a significant difference between the two groups (p =0.002). Results of this study showed that injection of extra-amniotic normal saline was a suitable and inexpensive method for cervical ripening and response to induction. The addition of dexamethasone could help to shorten delivery process and that inducing labor by means of an extra-amniotic infusion of corticosteroids through an intra-cervical Foley balloon catheter reduced the time between induction of labor and delivery. This may indicate a possible role for corticosteroids in the parturition process [17].

Lin *et al.* [18] found that induction of labor using extra-amniotic Foley's catheter and dexamethasone reduces the ripening and induction delivery times; this may indicate a possible role for corticosteroids in the parturition process.

This is mimic to **Zafarghandi and Baghaii** [19] who challenged the possible role of corticosteroids in induction of labor by extra-amniotic injection through an inflated intra-cervical Foley balloon catheter. This randomized trial was conducted on 44 women with a single pregnancy, intact membranes, and an unfavorable cervix. They concluded that the intra-cervical Foley balloon catheter with extra-amniotic corticosteroids was more efficient in reducing the induction-to-delivery interval for termination of mid-trimester pregnancies than the same Foley catheter with saline solution only. Cervical ripening with extra-amniotic corticosteroids possesses the advantages of simplicity, low cost, lack of systemic or serious side effects.

CONCLUSION

Intravenous infusion of two ml (8 mg.) of dexamethasone appears to shorten labor duration.

RECOMMENDATIONS

- More studies are needed to find out the maximum infusion dose of dexamethasone that could be used with induction of normal delivery and its possible side effects .
- Larger randomized controlled studies should be carried out for longer duration to reach the safest regimen of dexamethasone before induction of labor.

- Using of different methods of induction of labor unlike oxytocin.

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