Effect of Intravenous Dexamethasone on the Duration of Labor Induction: A Randomized Controlled Trial

Thesis

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By

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Amany Abd El Mageed Mohammed

List of Contents

List of Abbreviations

Abbrev.	Full-term
11β-HSD1	**:** 11β-hydroxysteroid dehydrogenase
ACOG	**:** American College of Obstetricians and Gynaecologists
ACTH	**:** Adrenocorticotropic hormone
ARM	**:** Artificial Rupture of Membranes
BPM	**:** Beats per minute
CBP	**:** CREB-binding protein
COX2	**:** Cyclo-oxygenase-2
CRH	**:** Corticotropin-releasing hormone
CRR	**:** Corticotrophin-Releasing Hormone
CS	**:** Caesarean Section
CTG	**:** Cardiotocography
CYPl7	**:** Cytochrome P450 17alpha-hydroxylase/17, 20-lyase
DCs	**:** Dendritic cells
DHEA	**:** Dehydroepiandrosterone
EASI	**:** Extra-amniotic Saline Infusion
FDA	**:** Food and Drug Administration
FHR	**:** Fetal heart rate
GA	**:** Gestational age
GR	**:** Glucocorticoid receptor
GRE	**:** Glucocorticoid responsive elements
HFA	**:** Human fetal adrenal
HSD3B2	**:** Hydroxysteroid dehydrogenase type II
IOL	**:** Induction of labor
IUFD	**:** Intrauterine Fetal Death
LMP	**:** Last Menstrual Period
MMP	**:** Metalloproteinase

NICE : National Institute of Health Excellence
NKT : Natural killer T
NO : Nitric oxide
PGDH : 15-Hydroxyprostaglandin Dehydrogenase
PGE2 : Prostaglandin E2
PGs : Prostaglandins
PR : Progesterone receptor
PROM : Premature rupture of membranes
RCOG : Royal College of Obstetricians and Gynaecologists
RCTs : Randomized controlled trials
RNA : Ribonucleic acid
SD : Standard deviation
SGA : Small-for-Gestation-Age
siRNA : Small interfering RNA
SP-A : Surfactant protein-A
SPSS : Statistical package for social science
TNF- α : Tumor necrosis factor alpha
WHO : World Health Organization

List of Tables

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. **Aim of the work:** to establish whether Dexamethasone plays a role in shorting the duration interval between initiation of labor induction and beginning of true contraction of labor in post-term pregnancy, so shorting the duration of labor. **Patients and Methods:** This randomized controlled trial study was conducted in the labor ward of Ain Shams University Maternity Hospital on one hundred thirty five pregnant women with full term pregnancy divided into the following: Group I (Dexamethasone group) injected with 2 ml (8 mg) of the product (dexamethasone) 4 hours before initiation of labor induction and Group II (Control group) received 2 ml saline (as a placebo). Results: There was a non-significant statistical difference between the two studied groups as regards the age, gestational age on admission, body mass index (BMI), Bishop Score, mode of delivery and Apgar score. There was a high significant statistical difference between the two studied groups as regards Induction- delivery interval, induction-contraction, contraction – delivery interval were shorter in cases of study than control. **Conclusion:** From the above data we can conclude that the intravenous administration of dexamethasone appear to shorten labor duration.

Key words: intravenous dexamethasone, labor induction, post-term pregnancy

List of Figures

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 **(*Hoffman et al., 2012)*.**

The placenta may play a role in this process because it produces a lot of corticotropin-releasing hormone (CRH). 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, a particularly sterol ***(*Ellinger *et al., 2018)***.

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 ***(Kim et al., 2018)***, stimulation of the membranes to produce more prostaglandins ***(Pace et al., 2017)***, stimulation to produce C steroids from placental adrenaline ***(Napso et al., 2018)***, and increase in the estrogen content ***(Raeside et al., 2017)***.

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 (***Hoffman et al., 2012)***.

Although administrating corticosteroids is a suggested method to shorten labor duration, the role of these agents in the process of labor is not well understood ***(McEvoy et al., 2018).***

These findings have led to the hypothesis that corticosteroids also had an effect on the labor of women ***(Bandoli , et al., 2017).***

Different studies have shown the paracrine and autocrine effects of corticosteroids on the human uterus, and receptors for these agents have been detected on the human amniotic membrane ***(Mendes et al., 2019).***

(Kalantaridou et al., 2007) have suggested that the 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. ***New , et al. (2017)*** reported that a prolonged gestation is more likely to occur when the fetus

has congenital adrenal hyperplasia caused by 21-hydroxylase deficiency, which may be due to an impaired cortisol production.

All of these studies show the probable effects of corticosteroids on the labor process. Corticosteroids have been administered intravenously, intramuscularly, and by extra-amniotic infusion in various clinical trials ***(Marik, 2018).***

Aims of the Work

The aim of this work is to study the efficacy and safety of intravenous Dexamethasone on the duration of labor induction.

Glucocorticoids and Human Parturition

Hormones normally produced by the adrenal cortex include hydrocortisone (cortisol) and some androgens and estrogens; the synthesis and release of which is controlled by the hypothalamic-pituitary system, and aldosterone, whose biosynthesis is largely dependent on the renin-angiotensin system ***(Diana et al., 2012).***

The glucocorticoids have widespread actions on intermediate metabolism, affecting carbohydrate and protein metabolism as well as a potent regulatory effect on our endogenous 'defense' reactions such as the innate and acquired immune response. The adrenal gland secretes a mixture of glucocorticoids, but the main hormone in humans is hydrocortisone (also, confusingly, called cortisol), but in rodents corticosterone predominates ***(Joëls et al., 2018).***

Positive feedback loop involving glucocorticoids, pro-inflammatory cytokines, prostaglandins (PGs), surfactant protein-A (SP-A) and 11β-hydroxysteroid dehydrogenase (11β-HSD1) is formed locally in human fetal membranes towards term or in preterm labor. This positive feedback loop would produce abundant biologically active glucocorticoids and PGS in fetal membranes or amniotic fluid, which would ultimately promote fetal organ maturation and initiate parturition ***(Ellinger et al., 2018).***

Synthesis:

The hormones of the adrenal cortex are steroids derived from cholesterol. The rate-limiting step in adrenal hormone biosynthesis is the modification of cholesterol to pregnenolone by side-chain cleavage enzyme. From this step, pregnenolone metabolism can be directed toward the formation of aldosterone, cortisol, or androstenedione. The flux of metabolites through each of these pathways depends on the tissue-specific expression of enzymes in the different cell types of the cortex and on the relative activity of the different synthetic enzymes ***(Dubinsky , 2017).***

Note that several enzymes are involved in more than one pathway and the defects in these enzymes can affect the synthesis of more than one hormone. This overlap of synthetic activities also contributes to non-selective action of glucocorticoid synthesis inhibitors such as trilostane ***(Rendic et al., 2018).***

Enzymes are shown as numbers: steroid 17α-hydroxylase; steroid 21-hydroxylase; steroid 11β-hydroxylase. Amino-glutethimide and high levels of ketoconazole inhibit side-chain cleavage enzyme. Ketoconazole also inhibits 17,20-lyase. Trilostane inhibits 3β-hydroxysteroid dehydrogenase. Metyrapone inhibits steroid 11β-hydroxylase ***((Stefanachet al, 2015)*. (Fig. 1).**

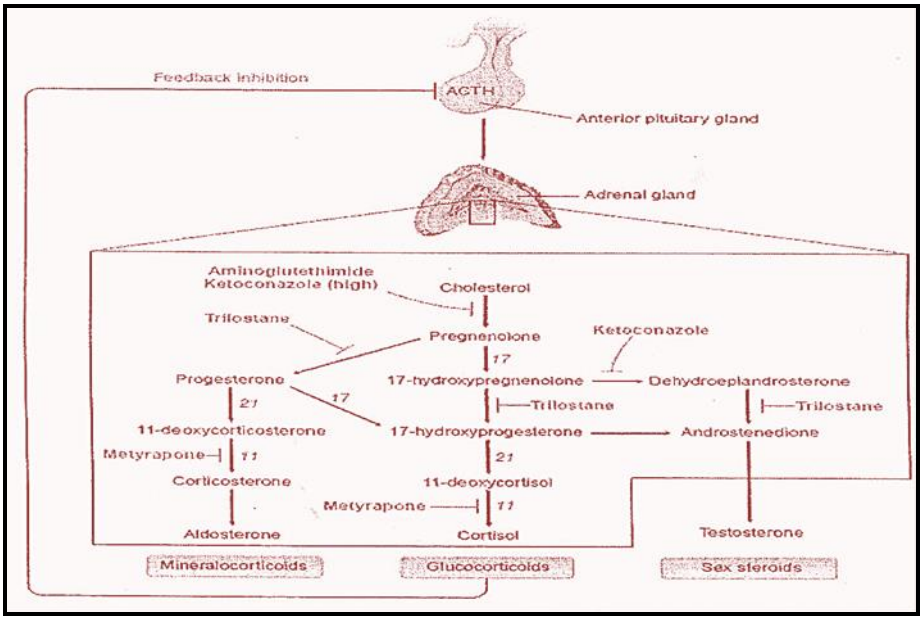

Figure (1): Hormone synthesis in the adrenal cortex***(Adler and Garg, 2012)***

Fetal-pituitary-adrenal axis

The cells of the human adrenal cortex arise from the intermediate mesoderm the earliest recognizable manifestation of the adrenal gland is called "the adrenal blastema" or "the adrenal primordium", which appears distinct from surrounding structures at 33 days post-conception, lying posteromedial to the urogenital ridge ***(Willenberg , Bornstein ,2017)***.

Morphologically and physiologically, the human fetal adrenal glands are remarkable organs. At term, they weight the same as adult adrenal glands and represent the largest endocrine glands in the fetus. The daily production of steroids in the fetal