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Impact of Antenatal Steroid Treatment on External Morphological Feature of Newly Born Rats

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Abstract

This paper is about the application of Steroid treatment during pregnancy as practiced in common in practice, in rheumatological and autoimmune diseases, its prolonged use has an adverse effect on fetal growth. The study aimed to assess the effect of prenatal dexamethasone and hydrocortisone treatment on rats' offspring concerning growth parameters, congenital malformation, and survival rate. Sixty pregnant rats were allocated into 12 groups, and administered intraperitoneally either dexamethasone (1mg/kg/day) or hydrocortisone (10 mg/kg/day), and a control group that received normal saline. These were administered in the first week or last week of gestation. Neonatal body weight, length, and gross morphological anomalies were evaluated postnatal at 1 and 15 days. Prenatal dexamethasone treatment in late pregnancy resulted in 27 % neonatal mortality on day 3. Dexamethasone and hydrocortisone significantly reduced body weight and length of neonates compared to the control group, which is more prominent in dexamethasone treatment. However, both glucocorticoids resulted in profound developmental deficits when given in late pregnancy, especially dexamethasone, which causes profound growth retardation and teratogenic effects in neonates. At the same time hydrocortisone has a less severe impact on postnatal malformations and growth retardation. This sheds more light on the timing of steroid administration during the prenatal period, which should be taken into consideration for risk-benefit assessment.

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1. Introduction

Glucocorticoids are steroid hormones secreted from suprarenal cortex that has a potent anti-inflammatory and immunosuppressive effects, they are widely used in clinical practice for the treatment of various maternal conditions during pregnancy, such as systemic lupus erythematosus, rheumatoid arthritis, or urticarial diseases [1]. In addition, glucocorticoids is used in the treatment of arthritis, gastrointestinal disorders, dermatological, and ophthalmological diseases [2]. These hormones have a multi factorial influence on fetal health, with their levels tightly regulated by the placenta through enzymatic inactivation of active glucocorticoids to their inactive metabolites by 11ß-hydroxysteroid type 2 (11ßHSD2), which is fundamental for fetal development, any alteration in their level can increase the risk for fetal development and mortality [3]. Fetal exposure to glucocorticoids occurs by three major possible routes:

a. Elevated transplacental transfer of maternal glucocorticoids occurs due to stress-induced elevations in steroids hormonal level in the mother or reductions in placental 11ßHSD2 activity
b. As a result of fetal exposure to hypoxia or nutrient deficiencies leading to activation of the hypothalamic pituitary adrenal axis (HPA) and,

c. Exogenous treatment with synthetic glucocorticoids can affect various maternal diseases. Animal experimental studies have shown that one of these pathways affects the metabolism of the placenta and fetal tissue [4].

Fetal development is a strictly controlled sequence of organogenesis and cellular differentiation. Alteration in fetal glucose or homeostasis during developmental periods leads to disruption in biological systems, such as endocrine and neuroendocrine systems, and especially the HPA axis [5,6]. The previous changes are associated with an increased life long risk of cardiovascular, metabolic, neurological, and psychiatric disorders [7]. Studies in humans and animals revealed that excessive exposure of the fetus to glucocorticoids from pharmaceutical treatment decreases expected birth weight and alters HPA axis regulation [8,9]. Dexamethasone is a potent synthetic glucocorticoid used in veterinary and human medicine; it readily crosses the placenta and causes intra-uterine growth retardation (IUGR) and affects the metabolism of the placenta and fetal tissues [10]. Neonatal adrenocorticotropic hormone (ACTH) suppression develops during maternal steroid use within 14 days [11]. The degree of HPA axis suppression is directly proportional to potency, timing, and duration of glucocorticoids treatment [12], being more pronounced with dexamethasone, moderate effect with prednisolone, and mild effect with hydrocortisone. Therefore, glucocorticoid treatment must be administered for a short effective duration and with a minimal effective dose. After treatment with glucocorticoids starting the dose tapering to help HPA axis recovery and prevent serious adrenal insufficiency [13]. Prolonged prenatal Hydrocortisone exposure can cause glucose uptake and impaired lipoprotein lipase (LPL) activity in the placenta. These alterations may reduce placental growth, leading to compromise of nutrient supply to the fetus and subsequent fetal growth retardation [14]. Furthermore prenatal glucocorticoid exposure early in pregnancy is associated with teratogenic risk, as shown by an experimental study in mice demonstrating glucocorticoids associated with cleft palate with a 3-6 fold increase in orofacial cleft following early gestational glucocorticoid use [1]. Other experiments suggested a high risk of neural tube defect and neurogenital anomalies, especially with first-trimester exposure [15]. Given these concerns, the current study aims to investigate the effects of prenatal dexamethasone and hydrocortisone administration in rats by evaluating morphological abnormalities, survival rates, and growth parameters through different gestational exposure windows. The results are expected to improve the evidence base on the safety of prenatal glucocorticoids and enrich clinical guidelines for corticosteroid therapy in pregnant women.

2. Materials and Methods

2.1. Experimental animals and treatment

Sixty healthy female rats (*Rattus norvegicus*) at (3-6 months old) chosen from the animal house of Biotechnology Research Center, Al-Nahrain University, Baghdad, Iraq. These animals were acclimatized for one week before the experiments, then, the female and male rats were mated at a ratio of (2:1) and placed overnight in clean plastic cages under controlled climate room under standard conditions (22±2°C and 12 h light/darkness cycle), tap water and rodent pellet were provided ad libitum. After mating vaginal smear was examined in the morning and proving sperms positive results, considered gestational day 0. All procedures complied with the Guide lines for the Care and Use of Laboratory Animals of the Al-Nahrain University, College of Medicine, Iraq, and were approved by the Institutional Animal Care and Use Committee (IRB no. 20250370).

2.2. Drugs used

Dexamethasone phosphate (Decadron, MEDOCHEME LTD, Cyprus) was administered intraperitoneally to pregnant female rats at dose of 1 mg/kg/day [16], Hydrocortisone sodium succinate (E.I.P.I.C.O, Egypt) was administered intraperitoneally to pregnant female rats at dose of 10 mg/kg/day [17].

2.3. Study design

Sixty adult female rats were divided into 12 groups (5 rats each), including control groups treated with intraperitoneal normal saline (early: EC, late: LC) and experimental groups treated with either dexamethasone (early: EDx, late: LDx) or hydrocortisone (early: EHd, late: LHd). Treatments were given either during the first week of gestation (early administration) or from day 15 until the end of pregnancy (late administration). Neonates were evaluated separately at postnatal day 1 and day 15, with each age obtained from different dams within the same treatment group.

2.4. Body measurement.

Following delivery, the neonates were carefully removed from the cage and weighed on postnatal day 1 and 15 after euthanasia. Body length of

neonates at 1 and 15 days of age was measured from the head to the base of the tail. All measurements were taken in millimeters.

2.5. Statistical analysis

Data were analyzed using SPSS version 23 and presented as mean ± SD. One way ANOVA with Tukey test and independent t-test were used for group and age treatment comparisons. Statistical significance was set at $P < 0.05$.

3. Results and Discussion

3.1. General morphology and macroscopic features

A. Pilot study

- Early gestation treatment

At a dose of 1 mg/kg/day of dexamethasone administered intraperitoneally to pregnant rats from the 1st through the 15th day of gestation, all rats became pregnant. Still, they suffered spontaneous abortions before giving birth or resorption of embryos. This is in agreement with Yahi research on rats and humans, thus reported that abortions, IUGR and intrauterine death are due to reduction of upsurge of progesterone hormonal activity with prostaglandin synthetase and generation of F2α prostaglandin in early pregnancy [10]. Similarly Ahmadabad and Lee, who mentioned dexamethasone early gestational treatment increase the resorption rate of embryo significantly, linked to embryonic loss [18,19]. And a study done by Gunberg on rats found that hydrocortisone altered maternal metabolism, and increased the number of resorptions, with reduction in placental size, reduced fetal size, and exerted a detrimental effect on fetal viability, as hydrocortisone can cross the human placenta to the fetus; these findings are likely relevant for humans [20]. While our results do not agree with de Figueiredo Moraes, who reported no malformation, abortion has been observed. This difference is mainly related to the dose and duration of treatment. Dexamethasone duration the treatment for 10 days has no impact on fertility and development on the kidneys, lungs and liver of neonates, but regarding the administration of dexamethasone for 15 days, we totally agree with the results concerning the high maternal mortality [21]. The maternal mortality rate in the (LDx and EDx groups) reached 60%, in addition to features of rapid breathing, irritability, and bleeding in the eyes and nose, which may suggest hypertension. We agreed with de Figueiredo Moraes, that administration for 15 days leads to a high maternal mortality [21].

- Late gestation treatment

Also, when the dexamethasone is given in the early period of gestation from day 7 to the end of gestation, with the same dose as in the early gestation, neonates showed severe gross morphological abnormalities; like failure of abdominal wall development leaving opening in the abdominal wall, stunted growth, cleft lip, inverted foot, and macrocephaly with mortality rate approaching 100% at birth (Figure 1). This conforms with a previous study done by Wangui, who mentioned the effects of antenatal exposure to a wide range of glucocorticoid levels was observed to have negative manifestation to the developing fetus, as left palate and lip, syndactyl, limb Amelia, limb's hypoplasia, mal development of the anterior abdominal wall, microcephaly, and congenital club foot. These are dependent on the gestational period and the dose of dexamethasone administered [22,23]. In another study, glucocorticoids with dexamethasone treatment during pregnancy are associated with postnatal hypertension, postnatal cardiovascular disease, postnatal glucose intolerance, increased postnatal activity in the hypothalamic-pituitary-adrenal axis, and effects on fetal brain development [9]. In addition, the hydrocortisone given in a dose of 10 mg/kg/day to pregnant rats for the same period of gestation resulted in neonates born with cleft palate. This is mentioned by Kemp, who showed a significant association between systemic corticosteroid use and cleft lip and palate [24].

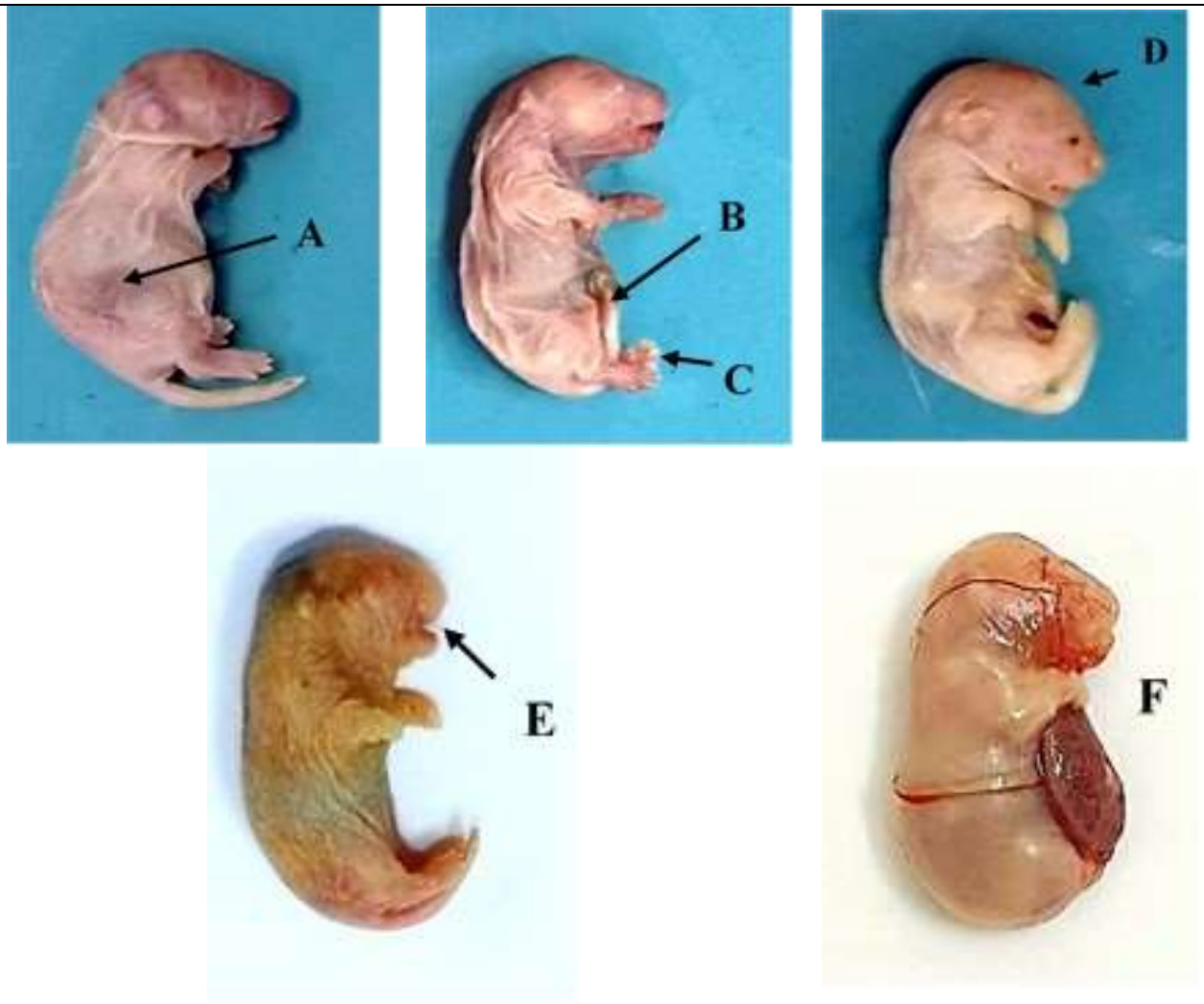


Figure1. Lateral view of congenital anomalies of neonates observed from LDx groups at postnatal day 1 and 15. (A) Undeveloped anterior abdominal wall, (B) Failure of anterior abdominal wall closure, and blood congestion, (C) Congenital club foot, (D) Macrocephaly, (E) Cleft lips, (F) Stunted growth.

B. The protocol after adjustment of the treatment duration

The duration of dexamethasone and hydrocortisone administration was reduced to 7 days in the first week of pregnancy (EDx and EHd groups) and the last 7 days of pregnancy (LDx and LHd groups). The pregnancy success rate was 86.9 % (60 of 69) of female rats became pregnant. A total of 68 neonates in (LDx), including 1st and 15th days age neonates, only 50 were born alive. In comparison, the remaining 18 neonates were stillborn or born with abnormal closed mouth opening, resulting in a 0% survival rate by the 3rd day post hnatal. Regarding LHd, EHd, EDx, and control, all neonates were born alive and healthy. Also, abortions and external congenital malformation were not observed. This is explained in a study done by Agnew, in which dexamethasone reduce glucocorticoid receptor (GR) leading to fetal death in mice during late gestation because of maturational defects that reflect a direct effect on fetal heart maturation by glucocorticoids, which shows that both structural and functional immaturity occur [25]. Furthermore, as the study Cella mentioned, prenatal dexamethasone exposure decreased fetal gain in weight and impair the development of neonates decreasing the survival of pups to almost 0% by day 3 postnatal. This is mainly related to changes in behavioral and emotional state of the mother, disrupting their affection toward the offspring [26]. This high mortality rate during dexamethasone treatment in late gestation is probably related to the prolonged half-life of dexamethasone, since it remains in the body for 3 days after exposure, as mentioned by Selvido, Dexamethasone has a half-life of 100 to 300

minutes and a biological half-life of 36 to 72 hours [27]. Abnormal pregnant rat behavior was noticed during the treatment with dexamethasone in the LDx group, such as anxiety, depression related behavior, stress, reduce food intake during gestation and increase in the amount of time spent immobile, increased the time out of the nest, decrease behavior towards neonates care like carrying and licking and eating their neonates after birth. This was reported by previous research done on gestational dexamethasone treatment that altered maternal behavior that caused a neurochemical alterations during gestation that increase features like depression and anxiety with inappropriate maternal care increased anxiety and depressive-like behaviors, impairing the expression of adequate maternal care [26].

3.2. Body weight

At postnatal day 1, neonates of dams treated with dexamethasone (EDx and LDx) exhibited significantly lower mean body weight compared to both hydrocortisone-treated (EHd and LHd) and control groups, with a highly statistically significant ($P < 0.001$). Also, the hydrocortisone groups showed a significant difference from the control, ($P < 0.01$). Generally, groups treated in the last week of gestation had a significant weight reduction compared to early treatment for dexamethasone and hydrocortisone ($P < 0.001$ and $P < 0.01$, respectively). (Table 1). At postnatal day 15, the neonates of dams treated by dexamethasone and hydrocortisone exhibit significant weight gain reduction ($P < 0.001$ and $P < 0.05$, respectively) compared to controls; Meanwhile, the body weight gain reduction was significantly lower in the dexamethasone-treated groups compared to the hydrocortisone-treated groups ($P < 0.001$. The late gestation treated group by dexamethasone and hydrocortisone (LDx and LHd) showed significantly lower body weight compared to the early gestation treated group (EDx and EHd) at ($P < 0.001$ and $P < 0.05$, respectively) (Table 1). These results are consistent with previous studies which reported that exposure to glucocorticoids in late pregnancy and in mid pregnancy may lead to an unfavorable fetal intrauterine growth retardation (IUGR) [9]. Similarly, Xiao demonstrated that pre natal dexamethasone treatment led to reduced birth weight in neonates and may contribute to long-term health issues such as length osteoporosis, epilepsy, and glomerulosclerosis [28].

Table 1. Comparison of the body weight between pair of groups by ANOVA test with (Tukey test) and Independent-Samples T-Test to determine significant differences in mean values among the experimental and control groups.

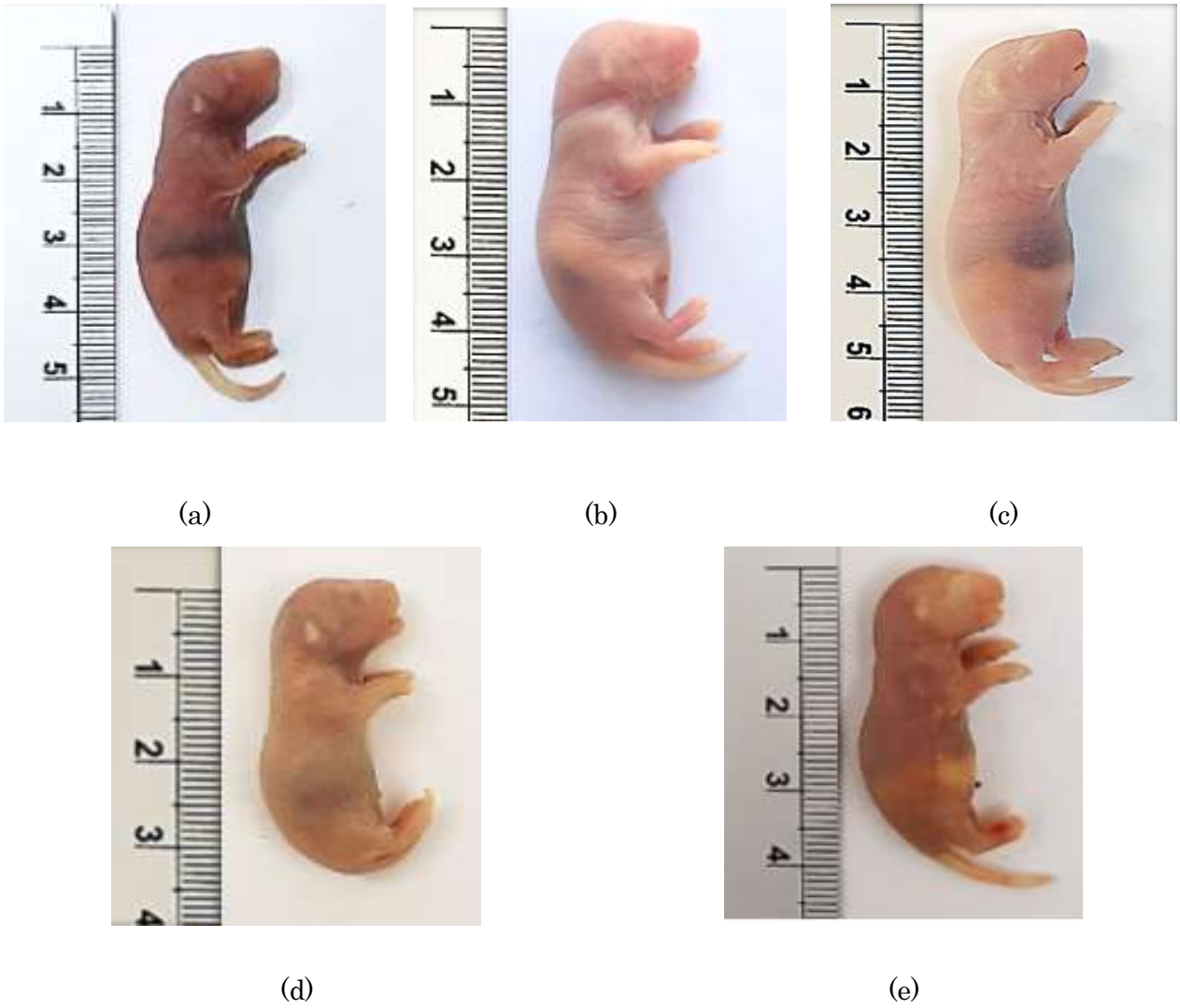
Age	Treatment (Mean ± SD)					
	control		Dexamethasone		Hydrocortisone	
	Early	Late	Early	Late	Early	Late
1d	6.6340 ± 0.5714	6.5663 ± 0.4212	5.4930 ± 0.6391 ***	3.7777 ± 0.4534 *** •••	6.1393 ± 0.5244 ** +++	4.7640 ± 0.3973 *** +++ •••
15d	28.8813 ± 2.5164 ###	28.0823 ± 2.1417 ###	25.2270 ± 2.0507 ***###	21.0827 ± 2.1772 *** •••###	27.4600 ± 1.7558 * ### +++	26.4863 ± 1.4930 ** ### +++ •

Comparison between treatment *vs* control groups: * *P<0.05*; ** *P<0.01*, *** *P<0.001*.
Comparison between 1 day *vs* 15 days age groups: # *P<0.05*; ## *P<0.01*, ### *P<0.001*.
Comparison between Dexamethasone *vs* Hydrocortisone groups: + *P<0.05*; ++ *P<0.01*, +++ *P<0.001*.
Comparison between Early *vs* Late pregnancy treatment groups: • *P<0.05*; •• *P<0.01*, ••• *P<0.001*.

3.3. Body Length

At postnatal day 1, neonates exposed to prenatal dexamethasone and hydrocortisone exhibited a significant reduction in body length ($P < 0.001$) compare to controls. Notably, there was a highly significant decrease in body length in neonates of dams treated with dexamethasone compared hydrocortisone $P < 0.001$. Great reduction in body length is observed significantly more in late gestation exposure than early exposure, late gestation exposure resulted in a greater reduction in body length than early treatment for both

(dexamethasone, $P < 0.001$, and hydrocortisone, $P < 0.001$). (Figure 2), (Table 2). At post natal day 15, neonates exposed to dexamethasone and hydrocortisone pre natally remained to show an obvious significant reduction in body length ($P < 0.001$) compared with controls, with a more significant reduction seen in dexamethasone groups than hydrocortisones groups ($P < 0.01$ in early treatment, and $P < 0.001$ in late treatment). Late gestation treatment remained to produce significantly lower body length than early gestation treatment for (dexamethasone $P < 0.001$ and hydrocortisone $P < 0.05$) (Figure 3), (Table 2). Our observations agree with Cella, who found that dexamethasone treatment during pregnancy reduced birth weight and length, indicating impaired intrauterine growth, also this effect was shown with hydrocortisone treatment [26]. At LDx 15 days postnatal noted the hair growth appeared sparse, particularly on the extremities, face, and abdomen (Figure 3 D). This is probably related to the effect of dexamethasone on androgen receptors on the cells of dermal papillae, *via* triggering glucocorticoids receptor thus increasing androgen receptor activity, and enhancing DDKK-1-mediated inhibition of the WNT/ß-catenin pathway, resulting into follicle recreation with subsequent premature hair fall [29].



(a) (b) (c)

(d) (e)

Figure 2: Comparative variations in body length of neonatal at postnatal day 1. (a) Control, (b) EDx, (c) EHd, (d) LDx, appeared with curved tail, (e) LHd groups.

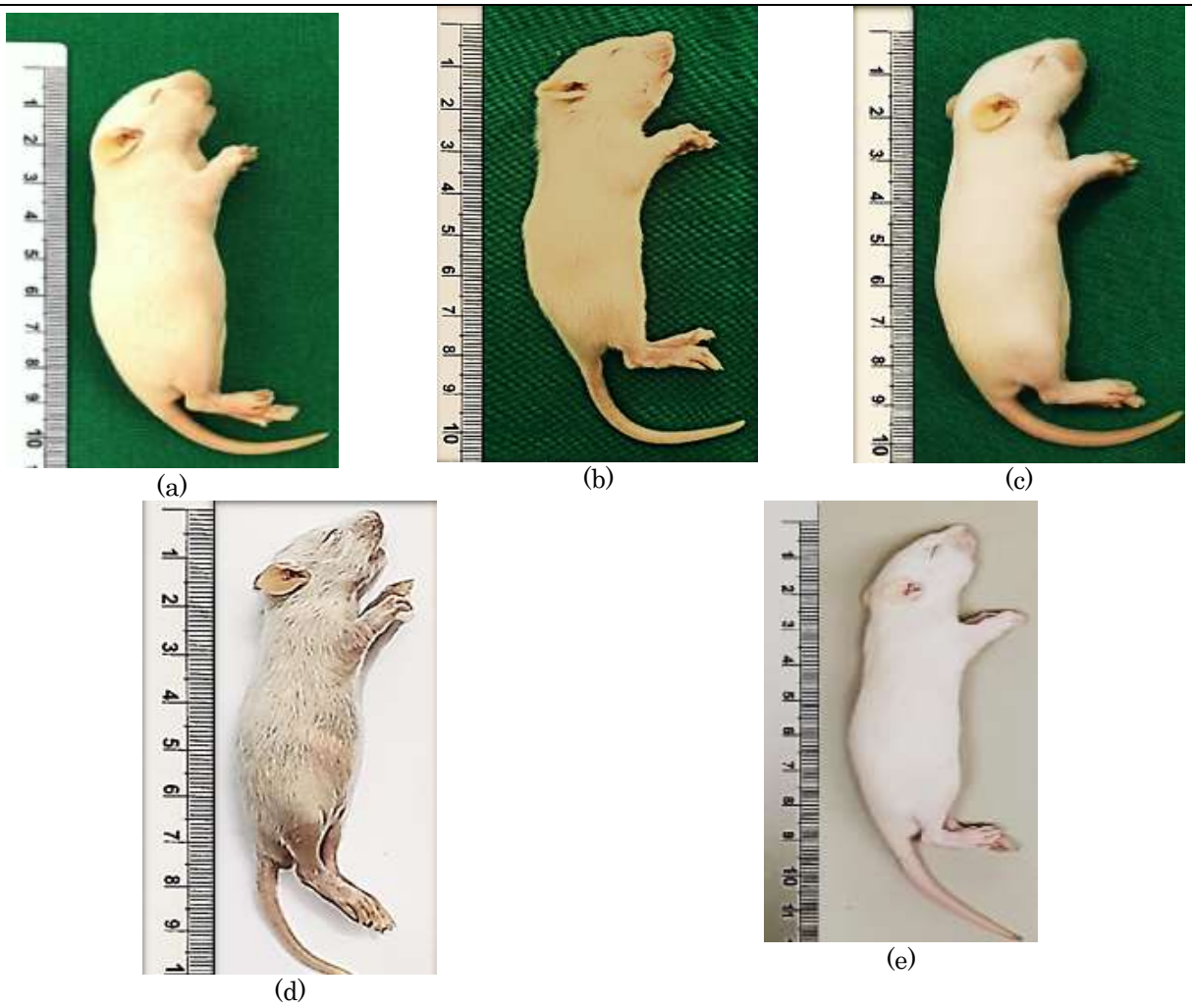


Figure 3: Comparative variations in body length of neonatal rats at postnatal day 15. (a) Control group (b) EDx, (c) EHd, (d) LDx, and show low hair of the body, and (e) LHd groups.

Table 2. Comparison of the body length between pair of groups by ANOVA test with (Tukey test) and Independent-Samples T-Test to determine significant differences in mean values among the experimental and control groups.

Age	Treatment (Mean ± SD)					
	control		Dexamethasone		Hydrocortisone	
	Early	Late	Early	Late	Early	Late
1d	45.8000 ± 5.0814	44.7000 ± 3.6591	38.0333 ± 3.1457 ***	33.5667 ± 2.0625 *** •••	42.3667 ± 3.5475 ** +++	39.1333 ± 3.0141 *** +++ •••
15d	95.9667 ± 8.1726 ###	93.1333 ± 8.3943 ###	83.0333 ± 6.3271 ***###	76.1000 ± 6.0819 *** •••###	89.2667 ± 6.5597 ** ### ++	86.0333 ± 5.3076 *** ### +++ •

Comparison between treatment *vs* control groups: * *P<0.05*; ** *P<0.01*, *** *P<0.001*.
Comparison between 1 day *vs* 15 days age groups: # *P<0.05*; ## *P<0.01*, ### *P<0.001*.
Comparison between Dexamethasone *vs* Hydrocortisone groups: + *P<0.05*; ++ *P<0.01*, +++ *P<0.001*.
Comparison between Early *vs* Late pregnancy treatment groups: • *P<0.05*; •• *P<0.01*, ••• *P<0.001*.

4. Conclusions

This study showed that antenatal glucocorticoids treatment has a prolonged and marked effect on neo natal growth and development. Dexamethasone treatment in late pregnancy profoundly impairs fetal development, significantly increases the risk of congenital anomalies, and reduces the survival rate due to its potency and timing of administration. Hydrocortisone on the other hand has a lesser but still a critical effect on neonatal growth retardation and malformations. Clinically, the above results require cautious weighing of the risk and benefit with reference to the minimally effective dose with the shortest treatment duration, considering the safest gestational stage to minimize the risk of developmental hazards. We recommended that morphological data should be integrated with histological and hormonal analysis with extended postnatal observation period to a sure better comprehensive assessment of the long-term effects of steroids exposure.

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