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**REVIEW ARTICLE**

# The Use of Dexamethasone in Animals: Implication for Fertility, Pregnancy and Extrapolation of the Animal data to Humans

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**SUMMARY**

Exposure to dexamethasone causes numerous changes in various biological systems including the reproductive system and this has huge implication on fertility and pregnancy. Maternal dexamethasone administration promotes foetal lung maturation and thermoregulation in premature foetuses. This indication makes dexamethasone a drug of choice in maternal and neonatal human and veterinary health care. In addition, dexamethasone is widely used in human and veterinary medicine as potent anti-inflammatory, immunosuppressive and analgesic drug in all age categories. Although the safety profile of short term dexamethasone treatment has been established, there has been growing concern about the long term effects of dexamethasone therapy and its implication on fertility and pregnancy in animals and humans. Most of the indications or uses in humans are extrapolated from animal data. This necessitates the need to provide review updates of current literature on dexamethasone use in humans and animals as there are many intrinsic differences between humans and animals. The review provides an overview of dexamethasone uses, its merits and demerits on animal pregnancy and fertility and implication on extrapolation of the animal data to humans. The review is based on a comprehensive literature search of relevant materials between 1969 and 2016 as well as authors' personal manuscript/abstract files and citations of known references and discussed according to the multidisciplinary clinical experience of the authors. Although low-dose dexamethasone treatment has been used in veterinary and human clinics for many years and produced no severe effect on vital functions, repetitive high dose or long-term therapy may be associated with more serious sequelae on fertility and pregnancy. While no animal truly recapitulates human pregnancy and fertility, it is recommended that results from animal data be subjected to rigorous preclinical pharmacokinetic scaling processes to justify possible extrapolation to humans.

**Key words:** Animals, Dexamethasone, Fertility, Humans, Pregnancy.

## INTRODUCTION

Dexamethasone is a synthetic glucocorticoid that is commonly used in human and veterinary medical practice as potent anti-inflammatory, immunosuppressive and analgesic agent (Liggins and Howie, 1972; Andrews, *et al*., 1991; Roberts and Dalziel, 2006; Aliu, 2007a; Trine *et al.,* 2008). In pharmacological doses, it plays a major role in the treatment of many diseases in both humans and animals and has heterogeneous effects on reproductive function (Fauci *et al.,* 1976; Yahi *et al*., 2016). Glucocorticoid receptors (GR) have been identified on various segments of reproductive system of both humans and animals (Schreiber *et al*., 1982; Rae, 2004; Shannon and John, 2010). Studies have shown that dexamethasone could alter hypothalomo-pituitary - gonadal axis functions and induce changes in concentrations of some key reproductive hormones and cause systemic paternal/maternal and foetal effects (Suter and Schwartz, 1985; Hardy *et al.,* 2005; Shannon and John, 2010). These effects can be beneficial or adverse.

It is the drug of choice in the treatment of pregnancy related animal diseases such as ketosis, pregnancy toxaemia, mastitis, prenatal foetal lung malformations and management of neonatal diseases (Liggins and Howie, 1972; McDonald, 1990; Crowley, 1995; Aliu, 2007b). In both humans and animals, dexamethasone reduces the incidence of respiratory distress syndrome (RDS) in the new-born (Liggins and Howie, 1972; Crowley, 1995), enhances the efficacy of neonatal surfactant therapy, reduces the associated risk of intravascular haemorrhage (IVH), periventricular leukomalacia (PVL), necrotising enterocolitis (NEC), neonatal hyperbilirubinaemia (NHB) and neonatal death (Sinclair, 1994; Eiman *et al*., 1999; Canterino *et al*., 2001).

However, there has been some concern about adverse maternal effects of dexamethasone therapy with reports of infection due to altered immune response, pulmonary oedema, altered blood glucose control and adrenal suppression (Crowley, 1995). Available evidence indicates that increased exposure of foetuses to glucocorticoids during pregnancy may result in adverse outcomes including intrauterine growth restriction (IUGR), hypertension, glucose intolerance, altered hypothalamo–pituitary–adrenal axis, and decreased foetal and placental weights (Mathews, 2000; Bloom *et al*., 2001; Kranendonk *et al*., 2006; Baisden *et al*., 2007). In males, dexamethasone has been reported to have deleterious effect on the testicular function (Abbaticchio *et. al.,* 1981). Hence, the cumulative effects of dexamethasone treatment have huge implication on both male and female fertility as well as pregnancy. As most of the indications or uses in humans are extrapolated from animal data, there is need to provide review updates of current literature on dexamethasone use in humans and animals. The review also addressed the potential implications of extrapolation of results of animal data from synthetic glucocorticoid studies to human.

## DEXAMETHASONE

Dexamethasone is a synthetic glucocorticoid receptor agonist that mimics the effects of the natural glucocorticoids (Rae, 2004). The molecular weight of dexamethasone is 392.47∂. It is designated chemically as 9-fluoro-11β, 17, 21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione and has empirical formula $C_{22}H_{29}FO_5$. Structurally, dexamethasone differs from cortisol in three positions, namely: extra double bond in the aromatic ring, between carbons 1 and 2, additional fluorine atom on the ninth carbon atom (9-α-fluoro group) and methyl group on sixteenth carbon atom (16-α-methyl substituent)

Dexamethasone is a derivative of corticosteroid, having similar 21 carbon steroid skeleton, similar to hydrocortisone.

Modifications of this skeleton selectively alter the degree of anti-inflammatory, metabolic and immunosuppressive activities, as well as the protein binding affinity of the resultant compound (Aliu, 2007a; Pierre-Louis, 2010). Dexamethasone is a product of such modifications. It is a fluorinated compound derived from corticosteroid and having 21- carbon steroid skeleton with hydroxyl ($OH^-$) or methyl ($CH_3^-$) group attached at $C_{16}$ (Trine *et al.*, 2008; Pierre-Louis, 2010). This compound has virtually no mineralocorticoid effect, but remains potent anti- inflammatory and analgesic glucocorticoids with broad significant physiological and therapeutic uses (Trine *et al.*, 2008; Pierre-Louis, 2010).

**USES OF DEXAMETHASONE**

The drug has profound effects on nearly all cell types and organ system (Shannon and John, 2010; Michael, 2010). It has broad pharmacological and physiological uses in both human and veterinary medical practice. The compound has effects on several important biochemical pathways and cellular transport mechanisms including, cellular sodium transport, glycogen synthesis and anti-inflammatory responses (Adedapo *et al.*, 2004; Michael, 2010). Therefore, it is used to treat and manage several diseases and other medical conditions of both animals and humans (Adedapo *et al.*, 2004; Michael, 2010).

It has a long history of use in veterinary medicine for the treatment of a range of metabolic and reproductive diseases and inflammatory disorders in companion and farm animals (Bette and Kietzmann, 1991). It is also widely used to treat and manage several disease conditions which include, but not limited to, arthritis, autoimmune disorders, pruritis, unresponsive musculoskeletal disorders, osteoarthritis, treatment of thyroiditis, adrenal insufficiency and thyrotoxic crisis as replacement therapy, colitis, canine distemper, meningitis, necrotizing enterocolitis, non-specific skin diseases, shock and stress (Bette and Kietzmann, 1991; Parrot *et al.*, 1997; Adedapo *et al.*, 2004; Chaudhuri and Behan, 2004; Beek *et al.*, 2007; Trine *et al.*, 2008; Pierre-Louis, 2010; David, 2010; Dowling, 2010**).** In dogs, cats and horses, dexamethasone is used systemically in high doses in emergency situations for anaphylactic reactions, spinal cord trauma or shock. It is used to manage and treat immune mediated disease such as immune mediated haemolytic anaemia or thrombocytopenia; some specific cancers; allergic reactions such as asthma, hives and itching; inflammatory diseases and some neurologic diseases.

In pregnant animals, dexamethasone is used to treat pregnancy related and metabolic diseases such as ketosis, pregnancy toxaemia, mastitis, prenatal foetal lung malformations, neonatal diseases, fatty liver syndrome and hepatic lipodosis (Liggins and Howie, 1972; McDonald, 1990; Crowley, 1995; Aliu, 2007b). Hence dexamethasone is usually used as replacement glucose therapy in acute hypoglycaemic conditions during pregnancy like ketosis or acetonaemia. Immediate relief is usually achieved within 8-10 hours following I.V. or I.M dosages of dexamethasone (McDonald, 1990; Aliu, 2007b).

The use of dexamethasone and other important synthetic corticosteroids during pregnancy is considered as one of the best advances in antenatal and neonatal medicine in recent times (Lockwood, 2004). The most common cause of deaths among preterm babies is respiratory distress syndrome (RDS). Antenatal dexamethasone treatment for pregnant women at risk of preterm birth is an established intervention for the prevention of respiratory distress syndrome (RDS). Liggins and Howie first described this indication in 1972, when they demonstrated that antenatal corticosteroid could reduce the risk of neonatal RDS from 25.8% to 9.0%, and the rate of neonatal mortality dropped from 15.0% to 3.2% (Liggins and Howie, 1972). Apart from reducing the incidence of respiratory distress syndrome (RDS) and mortality in the

neonate's dexamethasone has been used prophylactically to impede morbid symptoms associated with preterm delivery, such as RDS and intra-ventricular hemorrhage (IVH) and to increase efficiency of blood circulation in both the dam and the foetuses (Liggins and Howie, 1972; Christer, 1994; Crowley, 1995).

Subsequently, serial studies and leading world medical and other professional bodies have confirmed the effectiveness and recommended antenatal dexamethasone therapy in pregnant subjects (Morrison *et al*., 1978; Ballard *et al*., 1979; Pageorgiou *et al*., 1979; Doran *et al*., 1980; Young *et al*., 1980; Caspi *et al*., 1981). In 1994, American National Institutes of Health (NIH) professionals' consensus conference recommended that women at risk of preterm birth should routinely be given a course of antenatal dexamethasone treatment. Since then, the incidence and mortality rates of respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH), and necrotizing enterocolitis (NEC) in preterm infants have been significantly reduced (Christer, 1994; Crowley, 1995; Crowther *et al.*, 2006; Garite *et al*., 2009). The recommendation was later reviewed and in 2001, the US National Institutes of Health recommends single course of antenatal corticosteroid treatment for foetal lung maturation. Repeated courses of antenatal glucocorticoid may have some benefits for lung function of the preterm newborn, but ongoing concerns for long-term health preclude their use at the present time (Walfisch *et al.*, 2001; Crowther *et al.*, 2006; Crowther *et al.*, 2007). Therefore, maternal administration of dexamethasone becomes an important clinical tool used both in the management of pregnant subjects and neonates and women at risk of early preterm birth and also in suspected cases of congenital adrenal hyperplasia (Hankinson *et al.*, 1999). It has succeeded in reducing neonatal mortality and morbidity from respiratory distress syndrome and also protects female foetuses from virilization (Ritzen, 2001). In addition, dexamethasone is also given pre-conceptually to women with recurrent miscarriages (Kostich and Lazorchak, 2008; Shannon and John, 2010).

The wide range of therapeutic uses and the broad spectrum of pharmacological actions of dexamethasone are not unconnected with its property as glucocorticoid receptor agonists (Schreiber *et al.*, 1982; Rae, 2004; Shannon and John, 2010). Being glucocorticoid receptor agonist, dexamethasone regulates several transcription factors, including activator protein-1, nuclear factor-AT, and nuclear factor-κB, and influence several important biochemical pathways and cellular transport mechanisms including cellular sodium transport, glycogen synthesis and anti-inflammatory responses (Goff 2004**;** Rae, 2004). This leads to the activation and repression of key genes involved in several biological processes and the inflammatory response, eventually culminating in its therapeutic effect as an anti-inflammatory, immunosuppressive and analgesic drug (Goff, 2004**;** Rae, 2004). Consequently, this steroid exerts a diverse range of functions throughout the body, many of which have important implications on fertility (Rabin, 1988; Hankinson *et al.*, 1999; Shannon and John, 2010).

In addition to its use as anti-inflammatory agent it has the potential to increase fertility in females (Hankinson *et al.*, 1999; Shannon and John, 2010). Persistent mating-induced endometritis may alter the uterine environment resulting in early embryonic loss (Denker, 1994; Shannon and John, 2010; Moh *et al.*, 2012). However, modulation of this inflammatory response may improve fertility in susceptible subjects (Denker, 1994; Lockwood, 2004; Thomas and Fuller, 2004). Hence dexamethasone has been recommended for females with habitual or recurrent miscarriages (Lockwood, 2004; Kostich and Lazorchak, 2008; Shannon and John, 2010). The drug has been reported to have some positive effects on uterus, ovaries and corpus luteum (Schreiber *et al*., 1982; Kennedy, 1983; Lopezbernal *et al*., 1995; Tetsuka, 1999)

Despite its important uses, dexamethasone has been found to inhibit some reproductive functions in humans and some domestic animal species (Kauppila *et al*., 1976; Benediktsson *et al.,* 1993; Liptrap, 1993; Sugden and Langdown, 2001). Dexamethasone can affect female reproduction by acting at different levels of the hypothalamo-pituitary-gonadal axis (Suter and Schwartz, 1985; Rockwell and Koos, 2009; Shannon and John, 2010).

Reproductive functions are partly controlled by somatic and mental stresses (Dong *et al.,* 2004). Studies indicate that an increase in stress-induced glucocorticoids results in decrease in serum concentration of some reproductive hormones and cause systemic effects (Hardy *et al.,* 2005). Dexamethasone administration has been shown to suppress maternal and foetal adrenal production of the estrogen precursor, dihydroepiandrosterone sulphate (DHEAS), and so lead to reduced circulating concentrations of estrogen (Ylikorkala *et al*., 1978). Low concentrations of progesterone and estrogen have been implicated as a causative factor in low pregnancy rates (Diskin and Morris, 2008).

Dexamethasone has been reported to have inhibitory and direct stimulatory effects on placental and human chorionic gonadotrophin (HCG) production *in vitro* (Mano and Chou, 1981; Wilson and Jawad, 1982). However, it does not appear to affect the circulating or amniotic fluid concentrations of HCG (Ylikorkala *et al*., 1978**;** Haning *et al.,* 1989).

Glucocorticoid receptors (GR) have been identified on the uterus, ovarian cells, corpus luteum and the placenta (Schreiber *et al.,* 1982; Rae, 2004; Shannon and John, 2010). The expression of the receptors in these organs is consistent during follicular maturation, ovulation and pregnancy (Schreiber *et al.,* 1982; Rae, 2004) indicating that the principal regulatory mechanisms in these cell types is the level of active glucocorticoids (Tetsuka, 1999; Robert, 2012).

Dexamethasone influence on male fertility can be adversely negative or beneficial. In males, dexamethasone administration in male has been shown to have a direct negative effect on testicular functions and could reduce semen quality (Abbaticchio *et al.,* 1981). It has been reported to suppress testosterone (Juniewicz *et al.,* 1987) and luteinizing hormone (LH) production and alter general testicular endocrine functions (Matteri *et al.,* 1984; Fomicheva 1985; Scwannyana *et al.,* 1990; Juh'asz *et al*., 2001). On the other hand, due to its profound anti- inflammatory and immunosuppressive effects, dexamethasone is beneficial in the treatment of testicular dysfunctions associated with systemic inflammation due to infection or autoimmune diseases (Adamopoulos *et al.,* 1978; Cutolo *et al.* 1988; Buch and Havlovec, 1991)

## IMPLICATIONS OF DEXAMETHASONE USE ON FERTILITY AND PREGNANCY

Implications of dexamethasone treatment on fertility and pregnancy are usually mediated through its actions on reproductive structures and on the foetuses themselves. The knowledge of the importance of dexamethasone treatment on fertility is rapidly unfolding. Dexamethasone induced reproductive function impacted hugely on fertility and offspring viability (Rockwell and Kroos, 2009). Dexamethasone variably stimulate the release of follicle stimulating hormone (FSH), luteinizing hormone (LH), and prolactin (PLR) (Brann *et al*., 1991), enhance FSH action in follicular phase of the menstrual/estrous cycle (Huan and Li, 2001) and may accelerate timing of ovulation and increase in the number of oocytes (Degreef and Vandershoot, 1987; Brann *et al*., 1990). In addition, the stimulatory effects of dexamethasone have also been reported in rats (Brann *et al*., 1990). In assisted conception and *in vitro* fertilization (IVF) clinics, dexamethasone is used in the treatment of premature ovarian failure and as adjuvant to improve ovarian

responsiveness to gonadotropin stimulating drug during IVF protocols and to improve ovulation in women with polycystic ovarian syndrome (PcOS) (Keay *et al*., 2001).

**The uterus**

Exogenous administration of dexamethasone during pregnancy has been shown to have several roles in improving the intrauterine environment. Dexamethasone regulates the synthesis of prostaglandins that have been implicated to play critical roles during implantation by increasing stromal vascular permeability and in the initiation of parturition (Kennedy, 1983; Lopezbernal *et al*., 1995). The peri-implantation secretion of human chorionic gonadotropin (hCG) from human trophoblasts can be stimulated by up to 10-fold by treatment with the synthetic glucocorticoid (Guller *et al.,* 1994; Hahn *et al*., 1999). The intracellular enzyme 11β-hydroxysteroid dehydrogenase (11β-HSD) catalyzes the inter-conversion of bioactive glucocorticoids (cortisol and corticosterone) and their inactive metabolites (cortisone and 11-dehydrocorticosterone). Thus, it is an important modulator of glucocorticoid bioavailability in both glucocorticoid and mineralocorticoid target organs (Monder and Shackleton, 1984). The two 11β-HSD isoenzymes (known as 11β-HSD1 and 11β-HSD2) have been identified and characterized (Seckl, 1993).

In addition, dexamethasone has several anti-inflammatory actions required for implantation. In early pregnancy, dexamethasone suppresses the synthesis of the pro-inflammatory interleukins (IL)-1b (Librach *et al.,* 1994). It also contributes to prevention of immunological rejection of the foetal semiallograft in the pregnant uterus by inhibiting eosinophil infiltrations (Tchernitchin *et al.,* 1975). Moreover, dexamethasone activate many of the biochemical processes in uterine tissues such as altering expression of numerous receptors, enzymes, ion channels, transporters, growth factors, cytoskeleton proteins, binding proteins, clotting factors, gap and tight junction proteins and intracellular signaling pathways' components involved in foetal growth. These may produce ultimate functional alterations at the systemic level. McDonald *et al.* (1987) reported that dexamethasone is involved in the heterologous up-regulation of several hormone receptors. The mechanism is probably through regulation of receptor mRNA levels by influencing increase in progesterone receptor (PR) mRNA levels and gene transcription as reported by Kraus and Katzenellenbogen (1993) in rats and Leavitt *et al*. (1977) in humans. Therefore, dexamethasone probably stimulates transcriptional activity of PR and increases total PR expression in the uterus. This provides some windows of possibility of dexamethasone as potential drug for treatment of secondary infertility that might be linked to progesterone receptor deficiency in females.

**Ovaries**

Dexamethasone enhances fertility and fecundity possible through an effect of prolactin on follicle development, or by other direct effects on the ovary (Rockwell and Koos, 2009). Dexamethasone directly modulates ovarian function in three unique ways (Schreiber *et al*., 1982; Tetsuka, 1999). These are by indirectly altering levels of circulating gonadotropins, and by acting on the hypothalamus and pituitary, altering metabolic hormones and growth factors, such as insulin-like growth factor-1 and by directly modulating ovarian functions through the presence of receptors in the ovarian cell types. Beyond control at the hypothalamic and pituitary levels, the ovary is also equipped with local regulatory mechanisms of glucocorticoid action (Schreiber *et al*., 1982; Tetsuka, 1999). The primary regulatory mechanism consists of changes in the expression of the two isoforms of 11β-hydroxysteroid dehydrogenase (11β-HSD) that catalyze the conversion between active and inactive glucocorticoids (Tetsuka, 1999). During follicular maturation, the dehydrogenase

activity of 11β-HSD restricts levels of active glucocorticoids. Meanwhile at ovulation, the 11β-HSD increases levels of active glucocorticoids, which mediates the inflammatory response associated with oocyte rupture of the ovarian surface epithelium. The glucocorticoids receptors are present in the ovarian follicular surface epithelium cells (Schreiber *et al*., 1982; Tetsuka, 1999). The epithelium contains a local system for generating anti-inflammatory glucocorticoids through increased conversion of cortisone to cortisol by 11β-HSD1 as part of the process to minimize injury of the ovarian surface during ovulation (Yong, 2002). The means by which glucocorticoids protect the ovary include increased expression of 11β-HSD1, increased GR suppression of the cyclo-oxygenase 2 (COX-2) gene expressions and suppression of IL-1α matrix metalloproteinase (MMP) gene expression (Rae, 2004). This stimulates both expression of the anti-inflammatory signaling protein GR and 11β-HSD1 and serve as the antagonistic substrate for cell remodeling and that suggests a novel mechanism for localizing and limiting proteolytic damage to the ovarian surface during ovulation (Thurston, 2002).

As ovulation is considered to be analogous to an inflammatory event (Richards and Pangas, 1998), increased generation of endogenous anti-inflammatory glucocorticoids by the reductase 11s-HSD1 may be a physiological mechanism to limit the ovarian inflammatory process (Richards and Pangas, 1998; Yong, 2002). Accordingly, glucocorticoid action in the ovary is an integral part of its physiology, which requires precise levels of available glucocorticoids (Schreiber *et al*., 1982; Richards and Pangas, 1998; Tetsuka, 1999; Yong, 2002). The use of exogenous glucocorticoids, like dexamethasone, enhances this process (Seckl and Walker, 2001).

Dexamethasone enhances speedy and smooth ovulation (Schreiber *et al*, 1982; Tetsuka, 1999; Yong, 2002). It acts on the adrenal glands to decrease the production of androgen hormones that interfere with egg growth and development (Richards and Pangas, 1998; Rae, 2004). In humans, it is used together with clomiphene citrate (Clomid), to achieve ovulation in anovulate females with 80-90% response rate in women who had not responded to clomid alone (Lawrence and Wichita, 2015). Interleukin-1β (IL-1β), a cytokine crucial to the ovulatory process also up-regulates basal and LH-stimulated expression of 11β-HSD1 in granulosa cells which may be part of the inflammatory cascade of ovulation (Tetsuka, 1999). This may find application in assisted conception and *in vitro* fertilization (IVF) protocols.

**Corpus luteum**

The corpus luteum is a temporary endocrine structure that secretes progesterone, which serves to maintain the decidual layer of the uterine endometrium in the richly vascular state necessary for implantation and pregnancy (Gale 2008). If conception occurs, the corpus luteum is maintained and grows and secretes increasing amounts of progesterone to sustain the pregnancy. The corpus luteum continues to produce progesterone until the placenta begins to take over progesterone production (Gale, 2008). Dexamethasone inhibit rather than stimulate the remodeling associated with luteolysis and increase the survival of luteinized granulosa cells and may play a role in maintenance of the corpora lutea during maternal recognition of pregnancy (Myers, 2007). Due to the well documented anti-inflammatory effects of dexamethasone and the expression of the glucocorticoid receptor (GR) in the corpus luteum, dexamethasone pstively affects corpus luteum maintenance or the immune cell mediated processes during luteolysis. Further actions of dexamethasone in the ovary include local regulation of steroidogenesis, oocyte maturation, maintenance of the corpora lutea, and luteal regression (Tetsuka, 1999). At ovulation, the 11β-HSD increases the levels of active

glucocorticoids, which mediates the inflammatory response associated with oocyte rupture of the ovarian surface epithelium (Michael, 1997; Tetsuka, 1999). The 11β-HSD1 expression increases progressively as the cells undergo functional luteinization, which corresponds to increased levels of available glucocorticoids and a switch in expression from mineralocorticoid receptors in the follicle to GR in luteinized cells (Tetsuka, 1999; Thurston, 2002).

**Foetus and placenta**

The foetus is a developing entity in the uterus in the postembryonic period, after attaining some degree of species specific form or resemblance (Bazer *et al.,* 1981). The placenta is an extraembryonic tissue that is situated between maternal and foetal compartments and acts to ensure the normal progression of foetal development (Bazer *et al.,* 1981). This task is achieved through regulating nutrient and waste transport and modulating the maternal environment through the elaboration of an assortment of hormones, growth factors, and other regulatory molecules (Garvey and Scott, 1981). Foetal growth is directly related to placental growth and development (Garvey and Scott, 1981). Excessive levels of foeto-placental glucocorticoid derived from maternal administration of synthetic corticosteroids like dexamethasone or sustained endogenous foetal cortisol production, results in intrauterine growth restriction (Garvey and Scott, 1981; McEwen, 2007). Synthetic glucocorticoid, particularly, dexamethasone, has the ability to cross the placenta thereby increasing the level of movement of glucocorticoid from mother to foetus during pregnancy (Garvey and Scott, 1981; McEwen, 2007). This usually produces undesirable effects on placental formation. Whilst the acute and chronic side effects of pharmacological dexamethasone excess are well-recognized in non- pregnant state, their roles in reproductive physiology are more pronounced. Their roles with balanced homeostatic effects facilitate short-term and long term survival and recovery from challenge of both the foetuses and the dam (Munck *et al*., 1994; McEwen, 2007).

Dexamethasone plays an essential role in normal foetal development and maturation of various foetal tissues including the liver, lungs, gut, skeletal muscle and adipose tissue and surfactants synthesis in preparation for extra-uterine life (Yong *et al*., 1980; Fowden *et al*., 1998). Dexamethasone stimulates surfactant production by the lungs (Liggins, 1969; Liggins and Howie, 1972) and it is for this reason that the synthetic glucocorticoid treatment is so widely used in preterm pregnancies where lung immaturity threatens neonatal viability. In addition to promoting foetal lung maturation, maternal dexamethasone administration promotes thermoregulation, an activity that has been reported to improve significantly in premature foetuses from such dams (Nedergaard *et al*., 2001; Symonds *et al.*, 2003). In particular prenatal dexamethasone treatment enables the premature newborn to initiate non-shivering thermogenesis, an adaptation that is mediated in part by promoting the rapid appearance of the brown adipose tissue specific uncoupling protein (UCP-1) which is uniquely able to generate very large amounts of heat (Nedergaard *et al*., 2001; Symonds *et al.*, 2003)

Although dexamethasone treatment greatly improves foetal and neonatal survival (Liggins and Howie, 1972; Roberts and Dalziel, 2006), they are not without adverse effects. Maternal dexamethasone administration has been reported to induce intrauterine growth restriction (IUGR) in some species of animals and humans (Bloom *et al*., 2001; Langdown and Sugden, 2001). Intrauterine growth restriction is one of the causes of perinatal death and neonatal morbidity and mortality and is associated with placental insufficiency, dysregulation of placental hormone production, and inhibition of placental IGF-II (Langdown and Sugden, 2001).

Placental development is a critical determinant of foetal growth. Glucocorticoids affect growth and development of the foetus indirectly by affecting placental development and functions (Langdown and Sugden, 2001). The size of the foetus is proportional to placental size. When the size of the placenta is restricted, as in compromised placental function, the foetus is also often growth restricted (Price *et al.,* 1992). A poorly developed or inefficient functioning placenta is therefore associated with a reduction in birth weight.

Dexamethasone treatment during pregnancy has been reported to decrease placental weights in rats and humans (McDonald *et al*., 2003; Ain *et al*., 2005; Hewitt, *et al*., 2006). The actions of glucocorticoids on foetal growth are mediated, in part, by changes in the placenta. In sheep, rats, mice and non-human primates, dexamethasone treatment during gestation reduces placental weight (Fowden *et al*., 1998; Langdown *et al.,* 2001). In humans, dexamethasone administration induced intra uterine foetal growth restriction and decreased placental mass by approximately 50 % (Koppe *et al*., 1977; Ain *et al*., 2005). Microarray analysis showed that maternal glucocorticoid administration leads to marked changes in the gene expression profile in the placenta**.** Additionally, glucocorticoids change the production and metabolism of hormones by the placenta, such as prostaglandins, placental lactogen, leptin, corticotrophin-releasing hormone (CRH), estrogens, progesterone and other progestagens (Fowden *et al.,* 2008; Fowden and Forhead, 2009). Glucocorticoids also alter the placental activity of various enzymes involved in the synthesis and inactivation of steroids and thyroid hormones such as 17, 20-lyase, 17α-hydroxylase, aromatase, renin and endothelial nitric oxide synthase (Fowden and Forhead, 2009).

In normal pregnancy, maternal glucocorticoid level is said to be markedly higher than those in the foetal circulation (Malassine and Cronier, 2002). Foetuses are normally protected from the higher maternal concentrations of glucocorticoids by the placental enzyme, 11 β-hydroxysteroid dehydrogenase type-2 (11β-HSD-2). It has been stated that the role of placental 11β-HSD is to protect the foetus from adverse effects of maternal glucocorticoids (Alfaidy *et al.,* 2003). In placenta, 11β-HSD1 protein is expressed specifically in the placental villous endothelial cells, amnion, chorionic and extravillous trophoblasts. The expression of 11β-HSD1 increases throughout pregnancy in response to progesterone (Alfaidy *et al.,* 2003). As the placenta differentiates, there is an up-regulation in the expression of 11β-HSD2 enzyme that becomes the major placental isoenzyme (Hardy and Yang, 2002). The distinct pattern of 11β-HSD1 and 11β-HSD2 localizations may indicate having different physiological functions. 11β-HSD2 is said to be better suitable for this role because of its location, that is, the site of maternal–fetal exchange and its enzymatic properties (Hardy and Yang, 2002). This enzyme acts as a barrier to prevent premature or inappropriate action at glucocorticoid-responsive tissues during foetal development (Alfaidy *et al.,* 2003). It has been suggested that a reduction in the expression or activity of placental 11β-HSD2 leads to increased transplacental passage of active glucocorticoids and reduces foetal growth (Alfaidy *et al.,* 2003). Dexamethasone easily crosses the placenta (Benediktsson *et al.,* 1993; Lindsay *et al.,* 1996) and is a poor substrate for 11β-HSD-2 (Albiston *et al*., 1994). It is poorly metabolized by 11β-HSD-2 and, therefore, most readily crosses the placenta (Siebe *et al.,* 1992) but the extent to which it actually crosses the placenta into the foetal circulation and accesses foetal tissues may vary among species (Dodic *et al*., 2002; Siebe *et al.,* 1992; Kerzner *et al.,* 2002). It has also been suggested that a reduction in the expression or activity of placental 11β-HSD2 by dexamethasone leads to increased transplacental passage of active glucocorticoids and which reduces foetal

growth (Kerzner *et al.*, 2002). Also Ogueh *et al.* (2000) asserted that corticosteroid therapy causes adrenal suppression in foetus and alter glucose tolerance in the dam. Novy and Walsh (1983) who observed decreased adrenal weights in rhesus macaques following maternal dexamethasone treatment even though their observation indicates significant decrease in contrast to the mild decrease in the present study. In addition, placenta is one of the major relaxin-containing tissues during pregnancy, and progesterone has been shown to be responsible for maintaining relaxin levels by suppression of myometrial contractility (Ykijarvinen *et al.*, 1985). Hence, compromised placental function could lead to increased uterine contractility and this may contribute to abortion in placental dependent animal species.

**IMPLICATIONS OF DEXAMETHASONE TREATMENT ON MALE FERTILITY**

Male fertility is an important factor in reproduction (Godfrey and Dodson 2005; Sylla *et al.*, 2007). Successful male reproductive ability is influenced by semen quality (Laing *et al.*, 1988). Dexamethasone indirectly affects sperm maturation, transport and metabolism within the epididymis (Tsantarliotou *et al.*, 2002) due to the deleterious effect on the testicular function (Abbaticchio *et al.*, 1981). Testosterone is usually synthesized in the leydig cells of the testes which are known to have glucocorticoid receptors. Therefore, being glucocorticoid receptor agonist, the first target of dexamethasone activity is testicular tissue (Gametchu and Watson, 2002).

Dexamethasone brings about the inhibition of testosterone by negatively influencing anterior pituitary and testes through hypothalo-pituitary-gonadal axis (Herreraluna *et al.*, 2013). In addition, previous studies in bulls have shown that administration of dexamethasone induces a spermiogram that was similar to that of heat stressed bulls (Barth and Bowman, 1994). On the other hand, dexamethasone has been shown to have beneficial influence on male fertility. Systemic inflammation due to infection or autoimmune diseases inhibits testicular steroidogenesis and spermatogenesis, leading to temporary or permanent fertility problems (Adamopoulos *et al.*, 1978; Cutolo *et al.* 1988; Buch and Havlovec, 1991). Due to its profound anti-inflammatory and immunosuppressive effects, dexamethasone is commonly used to treat such disorders in males

**IMPLICATIONS OF EXTRAPOLATION OF ANIMAL DATA FROM DEXAMETHASONE STUDY TO HUMANS**

The use of animal models to predict drug pharmacological and toxic effects in humans has a long history as the central physiological functions are believed to be similar in all mammals (Jiunn *et al*., 1998). The first seminal work of the late Sir Graham Liggins in the 1969 on synthetic glucocorticoid which revolutionized peri-natal medicine and has been responsible for the survival of thousands of preterm infants, who would otherwise have died, was done on animals (Liggins, 1969). Liggins serendipitously observed that when foetuses had been exposed to synthetic glucocorticoids as preterm newborn lambs they unexpectedly survived. Few years later, Liggins and Howie (1972) published the landmark paper reporting the first randomized controlled trial (RCT) in human pregnancy in which the synthetic glucocorticoid administered pre-natally to the mother and improved survival and lung function in preterm neonates. In this innovative trial, the regimen for administration was two 12mg injections to the mother, administered 24 hours apart.

To this day, the methods of prescribing dexamethasone or betamethasone remain the same as in the original Liggins and Howie trial (NIH, 1994; Gilstrap *et al*., 2000; Roberts and Dalziel, 2006). In this context, dexamethasone is by and large safe to take as prescribed as there is no proven human

teratogenicity or developmental risks to the foetus and the side effects to the dam are infrequent, temporary in nature and reversible on proper withdrawal. Given the benefits of antenatal dexamethasone and other synthetic glucocorticoids therapy in reducing the incidence of respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH), peri-ventricular leukomalacia (PVL) and necrotizing enterocolitis (NEC), overall neonatal mortality and the need for neonatal respiratory support in preterm infants significant decreased in recent years (Crowley, 1995; Crowther *et al.,* 2006; Garite *et al*., 2009). Human and animal studies showed that the benefits of dexamethasone treatments are most obvious when the treatment is given at short term low – dose or single dose regimen (Roberts and Dalziel, 2006). Nevertheless, many obstetricians prescribed multiple long term course treatments to their patients without regard for the adverse effects (Walfisch *et al.,* 2001; Crowther *et al.,* 2006; Crowther *et al.,* 2007). They based the treatments on the premise that multiple course of corticosteroid has adequate benefits to justify the use. However, the justification was based on animal data and inconclusive non randomized controlled trials. Some of the benefits reported include reduction in the incidence of ductus artriosus, RDS and lung disease (Walfisch *et al.,* 2001; Crowther *et al.,* 2006; Crowther *et al.,* 2007).

Animal studies consistently indicate high risk adverse effects with multiple courses. These include foetal growth restriction, poor neurodevelopment, neonatal infection, maternal and fetal adrenal suppression, maternal infection, impaired glucose tolerance, osteoporosis, reduction of neonatal birth weight and head circumference, and increased incidence of neonatal chronic lung disease and deaths (Gross *et al*., 1981; Economides *et al.,* 1988; Tyson *et al*., 1995; Jobe and Ikegami, 2000). When these results were extrapolated to humans, dexamethasone exposure indicated similar side effects. Despite little evidence from either clinical trials or animal studies of improved benefit/risk balance and neonatal outcomes for repeated or multiple long term course treatments as opposed to single doses of glucocorticoid (Newnham and Jobe, 2009), the practice became widespread Recent survey showed that the proportion of women receiving antenatal corticosteroids had increased consistently (Quinlivan *et al*., 1998; Brocklehurst *et al*., 1999). For example, obstetricians in Australia in 1998 (Quinlivan *et al*., 1998) and the UK in 1999 (Brocklehurst *et al*., 1999) reported that due to increase demand for glucocorticoid treatments, in no distant future, 85 and 98% of obstetric units, respectively, would prescribe multiple courses of glucocorticoids.

In 2001, a National Institutes of Health Consensus Group questioned the use of multiple-dose glucocorticoid therapy (Roberts and Dalziel, 2006) as based on animal studies and few studies from non-randomized controlled trials the treatment course indicated consistent high risk adverse effects (Ikegami *et al*., 1997; Pratt *et al*., 1999; Huang *et al*., 1999; Abbasi *et al*., 2000). It was stated that the current data are insufficient to support routine use of the regimen. Despite the warning however, more recently, in 2004 as rightly predicted (Quinlivan *et al*., 1998; Brocklehurst *et al*., 1999), a study determined that 85% of obstetric units continued to prescribe multiple courses of antenatal glucocorticoids, despite the fact that the risk/benefit ratio of multiple doses was not yet known (Empana *et al*., 2004). The widespread use of repeat antenatal glucocorticoid therapy, suggests that the practice is likely to continue to increase. Therefore, more foetuses are likely to be exposed to multiple dose courses of antenatal corticosteroids unduly. It would appear prudent to heed the earlier recommendation that more studies in animals and humans need to be performed to determine the pathophysiological and metabolic consequences of long term repetitive antenatal glucocorticoid treatment

(Gilstrap *et al*., 2000; Roberts and Dalziel, 2006). This is especially important in the more vulnerable subset of special group population including the pregnant and breast feeding or lactating subjects. In view of the growing controversy regarding the inappropriate extrapolation of animal data to humans, particularly from multiple or repeat dose glucocorticoid treatment studies to humans, US-NIH proposed comprehensive randomized clinical trials (RCT) study in 2001 to investigate the benefits/risk ratio of repeat ante natal glucocorticoids regimen. The study has been completed in 2007 and updated and verified on 29th September, 2016 (NIH, 2016), but the outcome has not been made public. If the maxim of "first do no harm" is to be observed strictly, until data from the just completed randomized clinical trials (RCT) establish a favorable benefit-to-risk ratio, repeat courses of synthetic corticosteroids should not be used routinely in humans or animals.

## CONCLUSION

The benefits of antenatal dexamethasone administration in reducing morbidity and mortality in preterm neonates as well as increasing fertility and fecundity are clear and generally outweigh the risks associated with this therapy. The benefits are most obvious when the treatment is single short term dose course regimen compared to multiple dose regimens. Although exposure to dexamethasone causes numerous beneficial changes in various biological systems including the reproductive system, it is not without adverse effects. The high risk adverse effects associated with multiple dose treatment regiments reported in humans could have been averted if the animal data from the corticosteroid study was subjected to series of rigorous preclinical pharmacokinetic scaling processes and randomized clinical trials. Due to many intrinsic differences between animals and humans, the extrapolation data from animals to humans is not direct and straightforward; hence the positive benefits /risk balance in animals may turn out to be negative in humans and *vice versa.* While no animal truly recapitulates human pregnancy and fertility, it is recommended that results from animal data be subjected to serial rigorous preclinical pharmacokinetic scaling processes to justify possible extrapolation to humans.

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