REVIEW ARTICLE

Review on the Use of Dexamethasone and its Impact on Fertility and Pregnancy

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ABSTRACT

Purpose: Although benefit/risk analysis is usually undertaken prior to starting a treatment, some conditions will inevitably require the use of drugs with known side effects even during pregnancy. This is the case with dexamethasone use in ante natal care. The purpose of this review was to provide an overview of the uses of dexamethasone and its impacts on pregnancy and fertility in humans.

Data source: The review is based on literature searches using PubMed and MeSH and authors' personal manuscript/abstract files and citations of known references.

Study selection: The selection of articles reflects the authors' opinion as to originality and importance in the context of the review. The review included human and some aspects of animal study.

Data extraction: The electronic searches were scrutinized and full manuscripts of all quotes considered relevant to the study were obtained. All the articles whose abstracts were not available were excluded.

Results: Dexamethasone use has evolved over the years to include fertility treatment in both males and females in addition to its use in pregnancy to prevent respiratory distress syndrome in neonates despite its side effects due to the fact that its benefits outweigh the risks.

Conclusions: Dexamethasone use has evolved over the years to include fertility treatment in addition to use in the prevention of respiratory distress syndrome. Low doses have no major adverse effects; however, repeated doses and long-term therapy are associated with more serious sequelae. It is recommended that dexamethasone therapy be incorporated into maternal and neonatal health care services.

KEYWORDS: Dexamethasone, Fertility, Pregnancy, Respiratory disease syndrome

Introduction

The establishment, maintenance and the successful outcome of pregnancy with the birth of a live, healthy offspring is the ultimate goal of the reproductive system. However, it has been estimated that the likelihood of a woman conceiving during a given menstrual cycle is only 30%, and only 50 to 60% of these conceptions survive to 20 weeks of gestation[1,2]. Furthermore, in the United States, 12.5% of live births were delivered premature in 2004 alone with 8.1% of live infants weighing less than 2500g[3]. This represents an increase in the incidence of low birth weight of 11% since 1994. In Australia, 8% of the 250,000 annual births are preterm, defined as delivery prior to 37-week completed gestation[4]. In 2010 alone, it was estimated that there were 14.9 million preterm births, which was 11.1% of live births, worldwide. The rate was 5% in European countries 18% in African countries. Of this, over 60% of the preterm births occurred in Southern Asia and sub-Saharan Africa, which contributes 52% of

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global live births[5]. Hence preterm birth is a global problem as its complications are considered to be the leading cause of neonatal death[6,4]. Thus, along with perinatal death and neonatal disability preterm birth is an important public health problem globally[7,8]. The situation is compounded by equity gap for survival of preterm babies between the developed and underdeveloped countries. As interventions progress more rapidly in the developed regions, other regions like Southern Asia and sub-Saharan Africa contribute an increasing share of preterm and neonatal deaths, with the highest neonatal mortality rate occurring in sub-Saharan Africa[9]. Table 1 presents estimated preterm birth rates and numbers by region.

Table 1: Preterm birth rates and total number of preterm births in 2010 by region

Region	Number of Live births	Mean preterm birth rate (%)	Number of preterm births
Developed regions	14 300 000	8.6% (8.3-9.4)	1 233 200 (1 188 500-1 345 100)
Eastern Asia	17 400 000	7.2% (5.4-9.0)	1 262 200 (943 100-1 564 100)
Latin America	10 200000	8.4% (6.8-11.4)	852 800 (695 500-1 164 000)
Northern Africa	3 543 100	7.3% (4.8-10.9)	259 200 (168 700-387 900)
Oceania	263 200	7.4% (4.5-15.6)	19 500 (11 800-41 000)
Southeastern Asia	11 000 000	13.6% (9.3-18.6)	1 497 500 (1 019 400-2 044 700)
Southern Asia	38 700 000	13.3% (10.1-16.8)	5 159 300 (3 900 100-6 504 200)
Sub-Saharan Africa	32 100 000	12.3% (9.5-15.8)	3 936 800 (3 039 500-5 068 000)
Western Asia	4 855 300	10.1% (6.9-14.3)	488 200 (33 4000-693 700)
Caribbean	682 800	11.2% (7.8-20.8)	76 500 (53 300-142 000)
Caucasus and Central Asia	1 643 000	9.2% (6.0-13.0)	151 300 (99 100-212 800)
Total worldwide	135 000 000	11.1% (9.1-13.4)	14 936700 (12268 200-18 089 700)

Modified from [5]Blencowe *et al.*, 2012

Respiratory distress syndrome (RDS) is a common complication of preterm birth, and is widely considered the primary cause of death among preterm babies[6,10,11]. Hence RDS as a consequence of immature lung development is the principal cause of early neonatal morbidity and mortality and contributes significantly to high costs of neonatal intensive care[12]. The cost of caring for preterm infants is high, gulping as much as $5.8 billion in the USA, representing 57% of the cost of neonatal care in that country[13]. The cost to support a single infant born at 25 weeks of gestation is estimated at $US? 250,000[13,14].

While babies born at 25 weeks gestation in Europe or America have a 50% chance of survival, babies born even in hospitals in relatively poor countries have less than 50% survival even at 32 weeks gestation[15]. Therefore there was dare need for cost effective priority medicines that will have the biggest impact on reducing maternal, newborn and child morbidity and mortality. Thanks to late Sir Graham Liggins whose seminal work in the 1969 revolutionized perinatal medicine and has been responsible for the survival of thousands of preterm infants who would otherwise have died[16].

While examining the contribution of glucocorticoids to provoke parturition in sheep, Liggins serendipitously observed that when fetuses had been exposed to

glucocorticoids, as preterm newborn lambs they unexpectedly survived. Few years later, Liggins and Howie[17] published the landmark paper reporting the first randomized controlled trial (RCT) in human pregnancy in which the synthetic glucocorticoid administered prenatally to mothers improved survival and lung function in preterm neonates. They demonstrated that antenatal corticosteroid could reduce the risk of neonatal RDS from 25.8% to 9.0%, and the rate of neonatal mortality from 15.0% to 3.2%[17]. In addition to reducing the risks of complications of prematurity, dexamethasone has also been reported to increase efficiency of blood circulation in both the mother and the foetuses[17]. Their findings were later confirmed and validated by some other researchers[18-24].

After the first study in 1972 by Liggins and Howie[17], RCTs have established antenatal corticosteroid as a standard of ante natal care recommended by the WHO and the United States National Institutes of Health, among other organizations[25,24]. In 1994, American National Institutes of Health (NIH) professionals' consensus conference recommended that women at risk of preterm birth be routinely given a course of antenatal dexamethasone treatment[25]. Since then, the incidences of respiratory RDS, intraventricular haemorrhage (IVH), perinatal death (PD), necrotizing enterocolitis (NEC), periventricular leukomalacia (PVL), neonatal hyperbilirubinaemia and neonatal death (ND) have been significantly reduced[8,24,26-29].

In the Liggins and Howie[17] innovative trial the regimen for administration was two 12mg injections to the mother, administered 24 hours apart. This has now been modified as four 6 mg doses of dexamethasone given intramuscularly 12 hours apart in pregnancies at risk for preterm delivery[30, 58] which is basically the same as in the original Liggins and Howie[17] trial. However, due to concerns about potential impact on long-term development combined with a lack of adequate data, repeat course of antenatal corticosteroid treatment (ACST) are reserved for rare cases only, although a Cochrane meta-analysis[31] examined the safety and efficacy of repeat courses of dexamethasone indicated strong benefits and found reduced risk in incidence and severity of neonatal lung disease as well as infant morbidity.

Hence ACST for women at risk of preterm delivery is now generally considered to be the most effective intervention for reducing incidence of RDS and resultant death and disability[6,10,11,32]. Therefore, maternal administration of synthetic glucocorticoids is important in the management of pregnant subjects, neonates, women at risk of early preterm birth as well as suspected cases of congenital adrenal hyperplasia (CAH)[10,33,34]. Adoption of ACST in developed regions of the world escalated quickly following 1994 NIH Consensus Statement supporting the use[25, 35]. ACST are now used in nearly 90% of cases of preterm labor in these regions. As interventions progress more rapidly in these regions, there has been considerable reduction in the risks of complications of prematurity such as respiratory RDS, IVH, PD, NEC, PVL, neonatal hyperbilirubinaemia and neonatal death[8,26-29]. Unlike in the developed regions, Southern Asia and sub-Saharan Africa has lowest coverage of ACST interventions and therefore have the highest neonatal mortality rate[9]. ACST coverage was estimated to be less than 10% for although data are generally sparse[36]. This is of particular concern because these regions also have limited resources for neonatal health-care facilities and access to expensive interventions such as surfactant therapy[7,8]. Barriers to ACST coverage may be lack of awareness and knowledge of ACST.

Drug exposures during pregnancy have several impacts on foetal survival and the future of adult fertility[7,8,37,38]. Although the benefit/risk balance is usually assessed before starting a treatment, some pathological

conditions will inevitably require the use of drugs during pregnancy. This is the case for the continual administration and uses of synthetic glucocorticoids, particularly dexamethasone in ante natal care despite its side effects.

Dexamethasone is a synthetic glucocorticoid receptor agonist that mimics the effects of the natural glucocorticoids[39]. 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[40-42]. In pharmacological doses, it plays a major role in the treatment of many diseases in both humans and animals[43,44]. This compound is an anti-inflammatory, immunosuppressive and analgesic agent commonly prescribed in human and veterinary medicine. In human, the drug is commonly used for the treatment of a wide range of disorders which include, but not limited to, endocrine disorders, rheumatic and unresponsive musculoskeletal disorders, collagen diseases, dermatologic diseases, allergic states, ophthalmic diseases, respiratory diseases, haematologic disorders, neoplastic diseases, gastrointestinal disease, spinal cord trauma, cerebral edema and diagnostic testing of adrenocortical disorder[45-51]. Dexamethasone is used clinically for the suppression of inflammation[52] and alleviation of emesis associated with chemotherapy[53]. It is usually incorporated into antibiotics and used topically to treat a variety of skin and eye problems[54].

The importance of dexamethasone is demonstrated by its wide application. Dexamethasone and betamethasone are the two main antenatal corticosteroid drugs. While neither has been definitively shown to be superior to the other, due to supply limitations and higher costs of betamethasone, dexamethasone is much more widely available and widely. This used makes it the lowest-cost and most accessible means of preventing RDS and deaths due to preterm birth. Hence among the antenatal corticosteroid drugs, dexamethasone is considered to be the most inexpensive and cost-effective.

It has been estimated that approximately 27,000 human prescriptions contained dexamethasone as the active pharmaceutical ingredient were dispensed in the United States alone in 2004[55]. It was estimated that about 0.9% of all adult population used dexamethasone as therapy for various ailments at any given time point in the United Kingdom[56]. As mentioned above, data on ACST are generally sparse in Africa and sub Saharan region[37].

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[40]. This property has made it one of the most frequently prescribed drugs worldwide[55,57]. It is now on the World Health Organization (WHO) model list of essential medicines as among the most important medications needed in a basic health care system[58].

Dexamethasone is a glucocorticoid receptor agonist that 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[39,59-61].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[39,61]. Consequently, this steroid exerts a diverse range of functions throughout the body, many of which have important implications on reproduction and fertility[33,42,62]. The purpose of this review was to provide an overview of the uses of dexamethasone and

its impacts on human pregnancy and fertility. The review is based on a comprehensive literature searches between 1966 and 2017. We used electronic searches on PubMed and combination of MeSH and text words indexing the term "dexamethasone use", "pregnancy" and "fertility" as well as authors' personal manuscript/abstract files and citations of known references and discussed according to the multidisciplinary backgrounds of the authors. The selection of articles reflects the authors' opinion as to originality and importance in the context of this review. The electronic searches were scrutinized and full manuscripts of all quotes considered relevant to the study were obtained. All the articles whose abstracts were not available were excluded. Due to ethical restraints of human investigations, many of the pregnancy related effects of dexamethasone were investigated in animals. Hence this review included some aspects of animal study.

Dexamethasone

Dexamethasone is a synthetic glucocorticoid and a potent anti inflammatory, immunosuppressive and analgesic agent commonly used in human and veterinary medical practice[10,17,51,63,64]. 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 $C_{22}H_{29}FO_5$. The chemical structure is presented as follows:

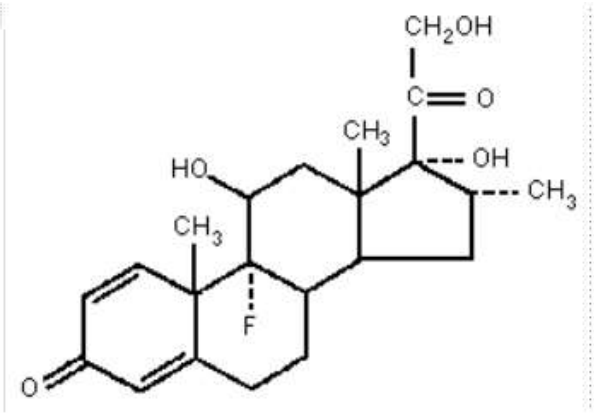

Figure 1: Dexamethasone (Source [65]: Rx-List Inc. Internet Drug Index 2016)

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)

Like all synthetic therapeutic glucocorticoids, 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[64,66]. 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} [51, 66]. This compound has virtually no mineralocorticoid effect, but remains potent anti- inflammatory and analgesic glucocorticoids with wide range of physiological and therapeutic uses[51,66]. The drug has profound effects on nearly all cell types and organ system[42,60]. The compound has effects on several important biochemical pathways and cellular transport mechanisms including, cellular sodium transport, glycogen synthesis and anti-inflammatory responses[39,59-61].

Effects of dexamethasone on some female reproductive structures

The mechanisms by which dexamethasone affects reproduction could be by direct effects on the reproductive target tissues or structures[67].

The uterus

Uterine quiescence during pregnancy is maintained by anti-inflammatory actions of some maternal and foetal hormones and endogenous glucocorticoids, while foetal parturition is associated with an inflammatory response within the maternal uterus and cervix, including stimulation of

macrophage migration to the uterus, release of cytokines or prostaglandins and activation of inflammatory transcription factors[42]. The uterus, endometrium, placenta and the embryo or foetuses are each exposed to physiological glucocorticoids arising from either maternal or foetal adrenal glands.

Exogenous administration of dexamethasone during pregnancy has been shown to have several roles in improving the intrauterine environment. For example, in the uterus, 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[68, 69]. The peri-implantation secretion of human chorionic gonadotrophin (hCG) from human trophoblasts can be stimulated by up to 10-fold by treatment with the synthetic glucocorticoid[70,71].

Ovaries

Throughout the reproductive cycle, the ovary is regulated, partly by endogenous glucocorticoids which exert both agonistic and antagonistic effects on ovarian function[72]. Synthetic glucocorticoids, dexamethasone, plays similar roles. Dexamethasone is able to directly modulate ovarian function in three unique ways[73,74]. 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[73,74]. Glucocorticoids protect the ovary via increased expression of 11β-hydroxysteroid dehydrogenase type-1 (11β-HSD1), increased GR suppression of cyclooxygenase 2 (COX-2) gene expressions and suppression of IL-1α matrix metalloproteinase (MMP) gene expression[39]. This stimulates both expression of the anti-inflammatory signaling protein GR and 11β-HSD1 and serve as the antagonistic substrate for cell remodeling. This suggests a novel mechanism for localizing and limiting proteolytic damage to the ovarian surface during ovulation[75].

The primary regulatory mechanism consists of changes in the expression of the two isoforms of 11β-hydroxysteroid dehydrogenase (11β-HSD) that catalyze 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[76]. 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[73,74]. This single-layered 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[77].

As ovulation is considered to be analogous to an inflammatory event[78], increased generation of endogenous anti-inflammatory glucocorticoids by the reductase 11s-HSD1 may be a physiological mechanism to limit the ovarian inflammatory process[77,78]. Accordingly, glucocorticoid action in the ovary is an integral part of its physiology, which requires precise levels of available

glucocorticoids[73,74,77,78]. The use of exogenous glucocorticoids, like dexamethasone, enhances these processes[79].

Dexamethasone enhances speedy and smooth ovulation[74,75,77]. It acts on the adrenal glands to decrease the production of androgen hormones that interfere with egg growth and development[39,78,]. Further actions of dexamethasone in the ovary include local regulation of steroidogenesis, oocyte maturation, maintenance of the corpora lutea, and luteal regression[74]. 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[74,80]. 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[74,75].

Keayl et al.[81] reported that use of dexamethasone along with ovulation stimulation drugs helps the ovaries be more receptive to treatment and increase clinical pregnancy rates in humans. They suggested inclusion of dexamethasone in stimulation regiments to optimize ovarian response[81]. In recent reports, dexamethasone 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[82]. Interleukin-1β (IL-1β), a cytokine crucial to the ovulatory process also up-regulates basal and luteinizing hormone-stimulated expression of 11β-HSD1 in granulosa cells which may be part of the inflammatory cascade of ovulation[74]. Hence dexamethasone is now increasingly being used as adjuvant treatments in poor responder patients in in vitro fertilization (IVF) program[81,82].

Corpus luteum

In humans and most mammalian animals, the corpus luteum plays significant role in pregnancy maintenance. The corpus luteum is an anatomic endocrine structure on the ovarian surface, consisting of a spheroid yellowish tissue that grows within the ruptured ovarian follicle after ovulation[83]. During each menstrual cycle, corpus luteum is formed after ovulation. It acts as 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[83]. 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[83].

Due to the well documented anti-inflammatory effects of dexamethasone and the expression of the glucocorticoid receptor (GR) in the corpus luteum, dexamethasone affects corpus luteum maintenance or the immune cell mediated processes during luteolysis by inhibiting rather than stimulates the remodeling associated with luteolysis and increase the survival of luteinized granulosa cells[84].

Effects of dexamethasone on pregnancy

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[32]. Dexamethasone has several anti-inflammatory actions required for implantation. In early pregnancy, dexamethasone treatment suppresses the synthesis of the pro-inflammatory interleukins (IL)-1b[85]. It also contributes to prevention of immunological rejection of the foetal semiallograft in the pregnant uterus by inhibiting eosinophil infiltrations[86].

In addition to promoting foetal lung maturation, maternal dexamethasone administration promotes neonatal thermoregulation activity. This activity has been reported to improve significantly in premature foetuses from dexamethasone treated mothers[87,88]. 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[87,88]. Hence current evidences support the use of dexamethasone in treatment of pregnancy related ailments.

Although there are no reported teratogenic effects or serious side effects from single course dexamethasone treatment during human pregnancy, evidence from epidemiological and animal studies suggests increased risk of foetal growth restriction (FGR) and placental mass from repeated long-term treatments[31,58,89-93]. The two 11β-HSD isoenzymes, known as 11β-HSD1 and β-hydroxysteroid dehydrogenase type-2 (11β-HSD2), have been identified and characterized[94]. Foetuses are normally protected from the higher maternal concentrations of glucocorticoids by the placental enzyme, 11β-HSD-2. This enzyme acts as a barrier to prevent inappropriate action at glucocorticoid-responsive tissues during foetal development[95]. Dexamethasone easily crosses the placenta[96,97] and is a poor substrate for 11β-HSD-2[98]. It is poorly metabolized by 11β-HSD-2 and, therefore, most readily crosses the placenta[99]. This may be responsible for reported cases of FGR and decrease birth weight associated with prenatal dexamethasone treatment[31,89-93].

Cases of abortion have been reported following repeated prenatal dexamethasone treatments in animals that depend on placental progesterone source to maintain pregnancy[66,93,100]. The abortions were attributed to decrease progesterone level as a consequence of decreased placental mass. In human progesterone, which is required to support gestation, is also derived initially from the corpus luteum and subsequently from the placenta. Being pregnancy Category C drug, dexamethasone, whose adverse effects on placenta cause abortions in animals whose pregnancies maintenance by progesterone is placental-dependent, could be extrapolated to have similar potential in humans.

Effects of dexamethasone on maternal fertility

Fertility is defined as the ability of the male and female to produce viable germ cells, and successfully mate and conceive and carry the pregnancy to term and give birth to normal living young [101]. Infertility on the other hand is defined as a failure of a couple to achieve a pregnancy after one year of regular unprotected coital exposure[102].

Apart from direct influence on pregnancy, the use of dexamethasone is also known to have some consequences on fertility[38]. The outcome could be adverse or beneficial. Dexamethasone has the potential to increase fertility[33,42]. Dexamethasone can affect female fertility by acting at different levels of the hypothalamo-pituitary-gonadal axis[67,103].

Dexamethasone variably stimulate the release of follicle stimulating hormone (FSH), luteinizing hormone (LH), and prolactin (PLR)[104], enhance FSH action in follicular phase of the menstrual/estrous cycle[105] and may accelerates timing of ovulation and increase in the number of oocytes[104,106]. Recently, glucocorticoid receptors have been identified on ovarian cells and some embryonic structures[73]. In animal studies, dexamethasone has been reported to decrease estradiol, testosterone and progesterone levels by down-regulation of the steroidogenic acute regulatory protein

expression in rats and mouse[103].

Persistent mating-induced endometritis may alter the uterine environment resulting in early embryonic loss[42,107,108]. However, modulation of this inflammatory response may improve fertility in susceptible subjects[32,107,109]. Hence dexamethasone has been recommended for females with habitual or recurrent miscarriages[32,42,55,]. As reviewed above, the drug has also been reported to have some positive effects on uterus, ovaries and corpus luteum[68,69,7374]. In this context, dexamethasone has been reported to inhibit luteolysis and increases the survival of luteinized granulosa cells and plays a role in maintenance of the corpora lutea during maternal recognition of pregnancy[84]. This could be another beneficial effect of dexamethasone treatment on fertility.

Moreover, dexamethasone activates 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. In addition, McDonald et al.[110] 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[111] in rats and Leavitt et al.[112] in humans. In another study, dexamethasone has been reported to increase PR concentration in chick oviduct[113]. 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.

In assisted conception and IVF clinics, dexamethasone is used in the treatment of premature ovarian failure and as adjuvant to improve ovarian responsiveness to gonadotropin stimulating drug used in IVF protocols and to improve ovulation in women with polycystic ovarian syndrome (PcOS)[81].

Apart from the beneficial effects, 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[114]. Low concentrations of progesterone and estrogen have been implicated as a causative factor in low pregnancy rates[115]. In addition, Dexamethasone has been reported to have inhibitory and direct stimulatory effects on placental and CG production in vitro[116,117]. However, it does not appear to affect the circulating or amniotic fluid concentrations of CG[114,118].

Effects of dexamethasone on male reproductive structures and fertility

Infertility affects an estimated 10% of couples worldwide and 50% of these cases are traced to male factor[119]. Precise levels of glucocorticoids are required for proper gonadal function. Where the balance is disrupted by exogenous administration of synthetic glucocorticoids, may fertility. As reviewed above, exogenous synthetic glucocorticoids can affect and modify gonadal functions at multiple levels in hypothalamo-pituitary-gonadal axis and this modulates steroidogenesis and/or gametogenesis[103]. For example, systemic inflammation due to infection or autoimmune diseases inhibits testicular steroidogenesis and spermatogenesis, leading to temporary or permanent fertility

problems[120,121,122]. Due to its profound anti-inflammatory and immunosuppressive effects, dexamethasone is commonly used to treat such disorders in males. On the other hand, high doses of dexamethasone inhibit hypothalamic–pituitary–gonadal axis in both male and female[69,123]. Thus, dexamethasone brings about the inhibition of testosterone by negatively influencing anterior pituitary and testes through hypothalo-pituitary-gonadal axis[124].

Dexamethasone affects testis homeostasis by inducing apoptosis in testis and decreases testosterone level[125,126]. 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[127]. Dexamethasone indirectly affects sperm maturation, transport and metabolism within the epididymis[128], due to the deleterious effect on the testicular function[129]. In addition, expression of glucocorticoid receptor in spermatocytes of discrete stages of spermatogenesis suggests that glucocorticoids can directly influence the spermatogenic cycle in a stage-specific manner[128]. In the developing rodent gonads, other studies have reported that dexamethasone decreased testosterone production in the testis[130]. Another study in bulls has shown that administration of dexamethasone induces a spermiogram that was similar to that of heat stressed bulls[131]. Similar effects may be expected in humans.

Conclusions

Dexamethasone has several consequences on pregnancy and fertility. Although the knowledge of the importance of dexamethasone use in pregnancy and fertility treatment is still rapidly unfolding, its use has evolved over the years to include fertility treatment in both females and males in addition to uses in the prevention of respiratory distress syndrome in neonates. Single or low dose treatments have no records of adverse effects on pregnancy and fertility. However, high or repeated doses and long-term therapy are associated with more serious sequelae. Currently, dexamethasone is on WHO model list of essential drugs. As dexamethasone therapy is relatively inexpensive and cost effective, it is recommended that dexamethasone therapy be incorporated into comprehensive maternal and neonatal health care services, especially in poor developing countries provided skilled health-care providers are available to identify women at risk of preterm birth and administer appropriately. To achieve this, problems arising from barriers to maternal and child care interventions using dexamethasone coverage such as lack of awareness and knowledge of ACST should be promptly and deliberately addressed.

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