Reproductive and Developmental Toxicology

CHAPTER 17

RABIA AZMAT*, MARYAM JAMEEL, AMARA TAHIR, MUHAMMAD MAKHDOOM JALAL, MUHAMMAD UMAR IJAZ, HAMMAD AHMAD KHAN, MUHAMMAD FAISAL HAYAT, ALI AKBAR

Department of Zoology, Wildlife and Fisheries, University of Agriculture, Faisalabad, Pakistan
*Corresponding author: rabianoorbwn@gmail.com

SUMMARY

There has been a growing concern in recent years regarding the potential for reproductive and developmental toxicity resulting from the excessive use of drugs. There are several gaps in the present understanding of reproductive and developmental toxicity and few validated assays to assess the effects of drugs on various stages of the reproductive and developmental cycle because this area of toxicology had not received much attention before. This chapter provides a closer look at several types of drugs, with particular emphasis on the reproductive toxicity associated with the anticancer drug doxorubicin, the detrimental impacts of methotrexate on rapidly proliferating reproductive cells, and the growing apprehension regarding the possible damage of the reproductive systems by antidepressants. Furthermore, corticosteroids also have adverse effects on the reproductive and developmental cycles. To mitigate potential hazards, this thorough analysis highlights the need for a nuanced knowledge of drug-induced reproductive and developmental toxicity. It also emphasizes the need of more research and a holistic strategy for drug safety assessment.

INTRODUCTION

Reproductive toxicology is defined as a harmful effect on the development of the progeny or the fertility of the parents' generation. Given that developmental toxicology involves the study of adverse impacts on development of organisms from the time of conception to sexual maturation, it can be regarded as a subfield of reproductive toxicology. The issue of reproductive and developmental toxicity is highly intricate due to the constant changes that occur in the mother, placenta, and fetus. A developing organism may be exposed to toxins while still in the womb, through breast milk, or through tainted food. It is generally known that developing organisms are more vulnerable to the adverse effects of drugs than adults because of a restricted defense system and detoxifying systems. Research indicates that early exposure to harmful chemicals may be directly linked to successive rises in the prevalence of most common diseases in humans and the diseases that have grown most rapidly over the past 20 years, such as obesity, premature adolescent (Novikova et al., 2008), infertility, breast and prostate cancer, as well as other disorders (Yaoi et al., 2008).

In recent times, a number of widespread reproductive disorders, such as infertility, suboptimal birth outcomes, pregnancy, fetal growth anomalies and diminished sperm quality among young adult males, have experienced an upward trend in incidence (Stukenborg et al., 2021). The failure to conceive after one year of sexual activity is characterized as human infertility (Kumar and Singh, 2015). Infertility is on the rise in humans, affecting around 12% of couples globally who are of reproductive age, while around 50% of instances of infertility are due to male-related fertility (Borght and Wyns, 2018). Insufficiencies in male prenatal and initial postnatal development have been directly associated with abnormal sperm quality and decreased male fertility (Durairajanayagam, 2018). One aspect of drug effects on fertility following recovery is the effect of chemotherapy on the primordial follicular reserve. These treatments have the potential to cause premature ovarian loss and, in severe cases, primary ovarian insufficiency (POI) due to primordial follicle exhaustion (Han et al., 2009).

The consequences of maternal depression at birth, adverse effects of drug use, such as antidepressants, during pregnancy, chronic pulmonary hypertension in the newborn, infant withdrawal/toxicity syndrome, increased internalizing behaviors in toddler years, and increased risk for autism spectrum disorder have all been documented (Field, 2017).

EFFECTS OF DIFFERENT DRUGS ON FERTILITY, PREGNANCY, AND FETAL DEVELOPMENT

Doxorubicin

Doxorubicin (DOX), commonly known as Adriamycin, is the preferred anticancer drug for the treating different chemo-responsive malignancies, such as lung cancer, lymphomas, ovarian cancer, liver cancer and breast cancer (Vendramini et al. 2010). Its numerous systemic side effects, including as hepatotoxicity, pulmonary toxicity (Guzel & Tektemur, 2021),

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and nephrotoxicity (Qi et al., 2020), are the reason for its extended therapeutic administration. TUNEL (terminal deoxynucleotidyl transferase dUTP nick end labeling) positive cells observed in secondary, pre-antral, and antral follicles during in vivo investigations there are a large number of granulosa cells which are the quickly growing cells, the presence of these cells clearly demonstrate ovarian toxicity caused by the drug (Morgan et al., 2013). DOX may predominantly impair spermatogenesis, which may ultimately result in sterility (Howell & Shalet, 2005). However, due to their extended life expectancy, young cancer survivors are particularly vulnerable to late-onset side effects of effective treatment, including infertility, heart damage and therapy-induced secondary cancers (Jahnukainen et al., 2001). Patients who are fertile should be concerned about the effects of chemotherapy on gamete quality and fertility. A harmful side effect of various tumor treatments that lowers the quality of existence for survivors in their prime years for reproduction or pre-reproduction is infertility (Valli et al., 2014).

Spermatogonia control of mitosis depends on the DOX mTORC1 signaling pathway (Xu et al., 2016), and cell survival depends on the mTORC2 signaling pathway, which regulates Akt phosphorylation. Because mTOR complexes alter the BTB (blood-testis barrier), they are essential to the process of spermatogenesis. Matrix metalloproteinase 9 (MMP-9) synthesis is initiated by mTORC1, which helps BTB relax and allows sperm to move from Sertoli cells to the abluminal chamber for further meiotic division (Mok et al., 2014). Conversely, connexin-33 (Cx33) and connexin-43 (Cx-43), which are necessary for throughout the retightening of the BTB in the process of sperm formation, are produced as a result of mTORC2 signaling. It has been found that the level of MMP-9 was decreased, although the mRNA expression of connexin-43 and mTOR was upregulated. Thus, these findings imply that the injection of doxorubicin disrupts mTOR signaling (Gurel et al., 2019). Albino male doxorubicin was given to two groups of Wister rats at various doses: 0.31 mg/kg per week for five weeks, and 3.2 mg/kg per week for the same duration, detrimental effects on mitochondrial signaling through PGC-1a, uncoupling protein (UCP-1) and uncoupling protein-2 regulation. Impaired azoospermia, spermatogonia and reduced sperm quality leading to oxidative stress (OS) and apoptosis were seen along with elevated levels of apoptotic, mitochondrial damage, and oxidative stress indicators (Renu & Gopalakrishnan, 2019).

However, a variety of negative consequences, including as reproductive toxicity in both humans and experimental animals, are caused by DOX (Damani et al., 2002). Doxorubicin-induced ovarian toxicity has been linked to granulosa cell death in growth, which can affect granulosa cell-to-oocyte transmission and nutrition delivery and consequently cause follicular atresia (Zhang et al., 2017). The depletion of seminiferous epithelium can result from adult mice targeting testicular germ cells, namely A1-A4 spermatogonia (Lu & Meistrich, 1979). Additionally, it can damage primary spermatocytes and type B spermatogonia, cause ultimately lead to testicular failure, germ cell death in the testis (Hou et al., 2005) and alter testicular lipids. Additionally, it has been observed that doxorubicin lowers the weight of the reproductive organs as well as the motility (Kato et al., 2001) and concentration of sperm (Prahalathan et al., 2005). Doxorubicin-induced ovarian toxicity has been linked to granulosa cell death in growth, which can affect granulosa cell-to-oocyte communication and nutrition supply and consequently cause follicular atresia (Zhang et al., 2017).

Male fertility in rats was adversely affected by DOX, as evidenced by reduced sperm motility, decreased sperm count, and morphological deterioration of sperm (Kato et al., 2001) and the primary processes associated with DOX-oxidative stress brought on by the breakdown of lipids and cellular death are major mechanism of induced testicular toxicity (Trivedi et al., 2011). It has been proposed that abnormal sperm motility may come from doxorubicin-induced PARP-1 activation, which enhances ATP consumption (Gungor-Ordueri et al., 2019). Furthermore, abnormalities in the sperm's shape and defects in the head and tail were obvious. Likewise, there was a significant decline in sperm cell motility that was dose- and time-dependent (Kato et al., 2001) there was a notable reduction in sperm counts (Yeh et al., 2009). Leydig cells are the primary location of androgen manufacture, hence the decrease in androgen levels can be used to understand the adverse effect of doxorubicin on these cells (Karna et al., 2019). Doxorubicin has been reported to be ototoxic, to induce premature ovarian follicle, amenorrhea and to impair the ability of female cancer survivors to reproduce (Molina et al., 2005).

Doxorubicin administration reduces the weight of the epididymal gland, which may be the cause of the decreased spermatozoa production (Abdelaziz et al., 2019). The type B spermatogonia within the seminiferous tubules of stage V exhibited the earliest indication of testicular toxicity through apoptosis. The preleptotene and pachytene spermatocytes of stages VIII–IX do not exhibit this impact as strongly (Jahnukainen et al., 2000). Stage V cells are susceptible because they are found within the seminiferous tubule's basement membrane, where the drug can readily enter via the testicular interstitial fluid. In contrast, Sertoli cells conceal the cells in stages VIII–IX, which are present in the intermediate compartment of seminiferous tubules. Unfortunately, because the blood-testis barrier's tight connections are already compromised, Sertoli cells cannot provide the maximum level of protection against drug invasion (Li & Cheng, 2016). Doxorubicin treatment decreased the seminiferous tubules cross-sectional area and immunofluorescence analysis of seminiferous tubules showed that spermatids and spermatozoa were absent (Yang et al., 2017).

The impact of DOX on the formation of ovarian follicles in humans are less well understood. Upon chemotherapy, including DOX the probability of amenorrhea in female cancer patients varies from 20% to 80% (based on the patient age), indicating a loss of developing follicles and a decline in estrogen levels (Lee et al., 2006). In addition, primordial follicles, oocytes and granulosa cells, DOX therapy results in considerable dose-dependent double-strand DNA breaks. This premature aging of the ovaries occurs in both premenopausal and postmenopausal cancer survivors (Soleimani et al., 2011). These results demonstrate that DOX may have a deleterious

effect on GCs and oocytes, which might result in ovarian follicle death, polycystic ovarian follicles, and infertility (Imai et al., 2007).

After receiving chemotherapy for breast cancer, a young woman can frequently experience infertility and early oocyte formation. Furthermore, they also cause reproductive toxicity in females, which manifests as premature ovarian failure (POF) (Jukkala & Meneses, 2009). Follicles and oocytes are directly impacted by doxorubicin. It has certain genotoxic effects that lead to infertility in both humans and animals (Zhang et al., 2016). After receiving doxorubicin treatment, the female loses reproductive function, which is shown by a reduction in the number of primordial follicles, which lowers the availability of oocytes. Apoptosis and oocyte-granulosa cell degradation are other effects of damaged granulosa cell damage that may impact the nutrition supply to oocytes [Thomson et al., 2010 (Fig 1)].

Methotrexate

Methotrexate (4-amino-10-methylfolic acid, MTX), an antagonist and analogue of folic acid, was formerly known as amethopterin. It is frequently employed in the treatment of both malignant and non-malignant diseases (Chan & Cronstein, 2013). In order to cause a folic acid deficit and subsequent cell death in cancer cells, MTX competes with folic acid to produce its chemotherapeutic action. Despite the fact that MTX toxicity has adverse side effects, it has been administered to treat lymphoma, acute leukemia, osteosarcoma, and certain malignancies, including those of the skin, neck, breast and lung cancers (Tousson et al., 2014). Furthermore, testicular injury is a significant possible MTX side effect that might lead to male infertility (Asci and Ozer, 2011). In addition to producing spermatozoa, which are necessary for reproduction, the testes also produce testosterone, a hormone required for auxiliary reproductive gland purposes. Toxic substances that are administered or obtained externally can readily damage this organ (Vardı et al., 2010). One of the main causes of male reproductive system dysfunctions is oxidative stress. When oxidants and antioxidants are not in balance either in favor of oxidants or against them leads to the development of oxidative stress (Turner and Lysiak, 2008). Free radicals are continuously produced throughout cellular enzymatic activities as intermediate products in the active regions of enzymes. Reactive oxygen species (ROS) are produced when enzymes active areas leak free radicals that unintentionally

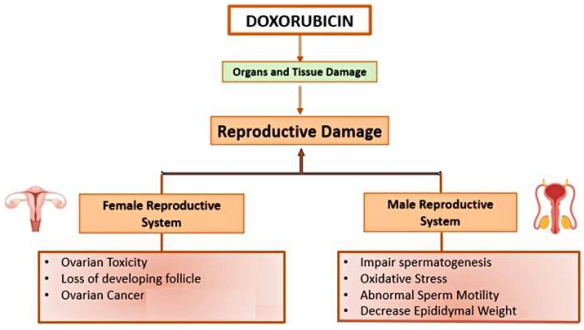

Fig 1. Effect of doxorubicin on the reproductive and development cycle

come into contact with oxygen. Antioxidants eliminate the ROS that the cell produces. Sometimes, antioxidants may not always be able to remove all of the ROS that is produced. This leads to oxidative tissue damage. Cell membranes are first impacted by free radicals, which then combine with them to produce peroxidation products (Saral et al., 2021). A lipid damage marker on oxidative stress induced is malondialdehyde (MDA). Through cross-linking, the resultant MDA polymerizes the membrane lipids. Certain modifications that impact membrane characteristics, such as ion transport and the deterioration of enzyme activity, are brought about by polymerization (Niki, 2008).

A folic acid antagonist called MTX reversibly inhibits the enzyme dihydrofolate reductase (DHFR), which is responsible for converting dihydrofolate to tetrahydrofolate, a necessary cofactor for the production of purine and thymidylate. DNA synthesis and cellular replication are compromised when methotrexate inhibits this process. Methotrexate is especially effective against tissues with high rates of cellular proliferation, such as cancer cells or fetal and trophoblastic cells (Verberne et al., 2019). Methotrexate is widely used to treat neoplasia and autoimmune diseases due to its antineoplastic and immunosuppressive properties. In addition, methotrexate is a well-known substitute for surgery in the treatment of ectopic pregnancy, just like in rheumatoid arthritis. A cytotoxic drug called methotrexate is used to treat both non-malignant etiologies and cancers. In clinical trials, methotrexate has been used to treat rheumatoid arthritis, psoriasis, cancer, and other autoimmune and inflammatory conditions. In case of surgical treatment of ectopic pregnancy methotrexate is a known substitute for misoprostol (Jones et al., 2017). It has also been used in conjunction with misoprostol for voluntary abortion. Folates play a role in several one-carbon transfer reactions, including as the oxidation of formate, the production of purines and thymidylate and amino acids metabolism. DNA and RNA synthesis is dependent on the essential process of purine and thymidylate biosynthesis (Tamura & Picciano, 2006). Maternal health and fetal development depend on these folate-dependent processes (Tamura & Picciano, 2006). Additionally, folic acid might play significant role in other physiological systems that are necessary for angiogenesis (Williams & Wooltorton, 2005), endothelial-dependent vascular relaxation, successful pregnancy including methylation of the homocysteine and antioxidant effect. The development of feto-placental circulation depends on these processes (Ciaccio et al., 2008).

Chromosomal aberration has already been used to report the genotoxic effects of MTX in somatic cells. In male Swiss mice, were used to study the toxicity of MTX to germ cells after repeated exposures. This may result in reduced sperm counts, TUNEL positive cells, sperm DNA damage, increased sperm head abnormalities, and damage to the seminiferous tubules (disorganization and vacuolization). Most cases of male infertility are caused by abnormalities in the motility, morphology, or sperm count (Beltagy et al., 2016). MTX exposure in male Swiss mice showed that morphology index, significant reduction in the sperm count, progressive motility, viability and total motility. On the other hand, unprogressive

and immotile sperm as well as significant increases in sperm defects were observed in MTX. Furthermore, oogenesis and spermatogenesis are defectively caused by MTX (Asci & Ozer, 2011). Since MTX inhibits protein expression in spermatogonia, which is necessary for DNA replication as well as successive proliferation and cell growth, this action may be the consequence of MTX reduction of spermatogenesis through its effects on cell differentiation and multiplication (Eldaim et al., 2019).

It is commonly well-known that methotrexate (oligospermia, asthenospermia) is toxic to the testicles. Suppression of spermatogenesis productivity does not significantly affect the capacity to conceive in the early stages following MTX treatment. Additionally, the prevalence of stillbirths, fertilized egg deaths, and external deformities in offspring did not significantly increase (Gutierrez et al., 2017). MTX accumulates intracellularly and inhibits DHFR, which is why its toxic effects increase with repeated administration. It was found that methotrexate increased the number of sperms and reduced sperm count with malformed heads. Sperm counts are decreased when there is disruption to the spermatogenesis process and subsequent removal of sperm cells at various stages of development (Padmanabhan et al., 2009).

The "fetal methotrexate syndrome," also known as "methotrexate embryopathy," is a congenital malformation condition characterized by limb abnormalities, microcephaly, growth deficit, facial dysmorphic features and craniosynostosis. It was established over the last few decades as a result of multiple instances of congenital defects caused by methotrexate exposure during prenatal development (Lewden et al., 2004). Male rats treated with MTX do not have reduced fertility due to an increased chance of delayed term embryo mortality (beyond the time of spermatogenesis) (Sun et al., 2013). Various experimental studies have investigated the reproductive toxicity of high doses of MTX. The results have included abnormalities in the testicles, including cellular disorganization, a decrease in the height and diameter of the inflammatory cell infiltration, epithelium, atrophy in certain endocrine disruption, seminiferous tubules, impaired function of gamete motility, decreased testosterone levels (Ghafouri-Fard et al., 2021), and sertoli cells (Fig 2).

Antidepressants

Psychiatric disorders are prevalent in adolescents and children; hence antidepressant drugs widely apply for treating a variety of psychological disease states and their use is still increasing constantly among pediatric patients (Zhang et al., 2018). While the most vulnerable population to suffer from depression are women whose vulnerability is more pronounced at around 25-34 years age (Ferrari et al., 2013). In addition, untreated prenatal and also postnatal depression has been associated with the poor mother-infant outcomes including maternal suicide (Khalifeh et al., 2016), relapse in subsequent chronic depressive episodes, preeclampsia (Hu et al., 2015), spontaneous abortion (Mulder et al., 2002), premature birth, worse emotional cognitive behavioral development and impaired mother-child interactions. The administration of antidepressants has beneficial therapeutic effects, but several adverse effects include sexual dysfunction, weight changes as well as sleep disorders that hinder their application (Ferguson 2001).

To pass to the fetus through placenta antidepressants reach amniotic fluid and also cord blood (Schoretsanitis et al., 2021). In the case of fetal exposure, maternal serum levels may reach 80%. Antidepressants can also pervade through the fetal blood-brain barrier (Oberlander et al., 2012). Altered brain development and behavioral abnormalities in offspring have been associated with animal models (Ko et al., 2014). While such studies do not necessarily suggest risk to humans, there is still a possibility of an influence on fetal development following in utero antidepressants due to disrupted serotonergic signaling during early pregnancy (Galbally et al., 2012). Serotonin is a neural growth factor during the fetal brain's critical period and controls processes related to synaptogenesis, neuronal maturation and differentiation of neural crest cells (Sadler et al., 2011). Clinical research also showed that the use of SSRIs was linked to decreased sperm parameters. Male fertility can be decreased by low sperm counts, poor motility, and DNA breakage. SSRIs can also decrease sperm count, restrict sperm motility, and damage the genetic material (DNA) in sperm (Preti et al., 2000).

However, there are many negative outcomes of maternal depression: obstetric complications as a result, impaired growth, prematurity and stillbirths due to it (El-Marroun et al., 2012). AD drugs, particularly members of the SSRIs class, are notorious to permeate human placentas, thereby contributing to some adverse effects on neonatal health (Cantarutti et al., 2017). Recently, scientific community has directed its growing interest on the possible relationship between perinatal AD uptake and occurrence of adverse neonate's outcomes such as preterm birth low weight or congenital malformation (El-Marroun et al., 2012).

The studies with rich data for type of SSRI demonstrate that sertraline was the most commonly prescribed while pregnant, followed by citalopram and fluoxetine. Many guidelines advocate the use of sertraline during pregnancy because it is safe to take in while nursing (Pinheiro et al., 2015). Fluoxetine is not first line due to half-life of 40h and presence in milk. Such a use of paroxetine has been linked with an enhanced risk congenital cardiovascular malformation; however, this remains to be confirmed (Grigoriadis et al., 2013). Overall, however, guidelines warn against switching to non-preferred SSRI even during pregnancy (Molenaar et al., 2018).

5-HT is a monoamine neuromodulator and developmental signaling molecule within the central nervous system. It controls neurogenesis, neuronal cell migration and correct wiring of the brain (Bonnin & Levitt, 2012). Various neurological side-effects have been correlated with changes in fetal brain 5-HT signaling. It is also crucial to the growth and physiological activity of many other organs such as heart, lungs, gastrointestinal tract and hypothalamic–pituitary-axis besides fatty acid metabolism (Maroteaux et al., 2019). Therefore, precisely balanced amounts of 5-HT in the fetoplacental unit during gestation are essential to ensure

optimal conditions for intrauterine growth and appropriate programming (Staud et al., 2018).

As a result, even the slightest insult to 5-HT homeostatic actions during pregnancy may provoke complications or poor outcomes (Liu et al., 2017). A lot of epidemiologic studies have shown a relationship between the use of antidepressants in pregnancy and adverse effects on fetus development, and programming. It is interesting to note that female fetuses seem much more susceptible than male ones towards autism or neurodevelopmental delays after exposure SSRIs (Harrington et al., 2014). Moreover, although the direct teratogenic effects of antidepressants are controversial centers increase risks of lung heart and neural abnormalities have been noted in literature (Gao et al., 2018). At last, it is mentioned that newborn babies whose mothers had taken antidepressants during pregnancy were found to have lower birth weight, preterm delivery; low Apgar scores and withdrawal syndromes (Zhao et al., 2018). In spite of this, the mechanistic origins are still far from being clarified.

Additionally, epidemiological studies have reported increased risks of autism spectrum disorders and mental illnesses associated prenatally to SRI exposure (Kobayashi et al., 2016). There have been previous suggestions that SRIs may affect 5-HT homeostasis in the fetoplacental unit leading to suboptimal levels of 5-HT concentrations inside, but there has not been direct evidence showing underlying molecular mechanisms of these alterations (Kobayashi et al., 2016). Placental uptake of 5-HT is regulated by two distinct membrane transporters: SERT, the high affinity/low-capacity transporter expressed in MVM and OCT3, the low-affinity/high-capacity transporter localized to BM membrane. SRIs are inhibitors of SERT and OCT3 (Zhu et al., 2012).

Corticosteroids

Glucocorticoids are known as “corticosteroids”, a more general terminology that regulates diverse cellular functions such as growth, homeostasis, metabolism, cognition, and inflammation (Rhen & Cidlowski, 2005). Glucocorticoids are some of the most widely marketed drugs because of their profound immunomodulatory properties. These drugs marketed throughout the globe generate over US$ 10bn annually (Schacke et al., 2002).

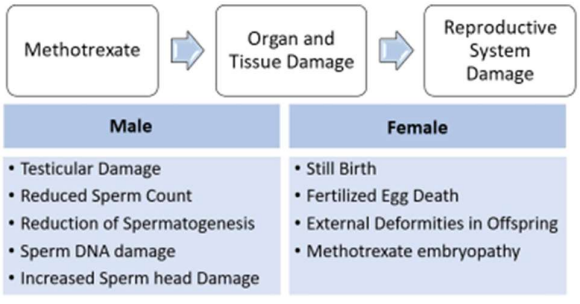

Fig 2. Effect of methotrexate on the reproductive and development cycle

However, due to the fact that excess levels of glucocorticoids caused by stress can probably participate in failure towards fertility status (Whirledge et al., 2013). Across various species, stress related compromises of reproductive functions have been reported. Physical stress has a negative effect on male and female reproduction among mammalian species such as rats, birds, lizards and snakes (DeRensis & Scaramuzzi, 2003). Stress also affects reproduction across the lifespan of humans such as high perceived stress during pregnancy may lead to preterm labor with negative implications in the offspring (Hobel et al., 2008). Lack of regular periods occurs frequently among female athletes who suffer with delayed puberty or menstrual disorders like secondary amenorrhea. Such conditions are common in females performing aesthetic sports like dancing ballet and also among women taking part in endurance sports such as marathon running (Stafford 2005). Such an excessive cortisol associated with physiological and psychological stress on the body can cause this reproductive dysfunction through modification of HPG axis activity. Also, patients with hypo cortisolism (Addison’s disease) or Hypercortisolism (Cushing’s syndrome) usually have delayed onset of puberty (Zadik et al., 1993).

Glucocorticoids play an important role in the optimal development of a fetus during pregnancy. As the fetus approaches term the concentrations of cortisol demanded reduces while the quantity of glucocorticoids permits is increase by the placenta. All mammals have maternal glucocorticoids that facilitate the growth, development, and survival of the fetus (Murphy e al., 2006). The fetus development, however, has a significant medical significance especially, considering its role in lung maturation (Class et al., 2011). It is crucial for the development of most others, including kidney, adrenal, heart, genital, and many more systems. For their part, fetuses may suffer serious developmental effects if exposed to excessively high levels of cortisol, which may result from maternal stress, among many other factors (Murphy et al., 2006). Some of the adverse effects of increased levels of glucocorticoids in pregnancy are a consequence of disturbance of the formation of the placenta whereas others act more directly and concern for example, heart development, the formation of kidneys or immunity. Furthermore, synthetic glucocorticoids are frequently used in pregnant women that can go into pre-mature labor or those suffering from asthma, systemic lupus erythematosus or hyperemesis gravidarum (O’Sullivan et al., 2013). Prolonged exposure to synthetic glucocorticoids during fetal development may affect one’s health across his entire life span (Braun et al., 2014).

An increased level of maternal glucocorticoids has been linked to differential stress response motor delay development and hypertension (Clifton et al., 2015). Research on rodents has also proven that administration of synthetic glucocorticoids to pregnant females can cause sex-specific changes to placental maturation and bad impacts on fetal health outcomes (Cheong et al., 2016). For instance, dexamethasone treatment in the mice resulted to a decreased size of placenta with diminished fetal growth on female placentae (Cuffe et al., 2016).

CONCLUSION

To sum up, this book chapter provides an in-depth look of reproductive and developmental toxicities caused by several drugs such as doxorubicin, corticosteroids, antidepressants, and methotrexate. Concerns for human health emerged when it became evident that chemicals and drugs could cross the placenta, causing irreversible damage to the fetus and reproductive organs. This realization spurred scientists and regulators to deepen their understanding of reproductive and developmental toxicology, aiming to protect future generations and their parents. These findings emphasized the need for a more comprehensive understanding of the potential risks associated with these drugs, particularly for individuals of reproductive age.

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