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MATERNAL OBESITY CAUSES CHANGES IN THE REPRODUCTIVE SYSTEM OF THE MOTHER AND OFFSPRING

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ABSTRACT

Introduction: In utero nutrition is a crucial period for establishing and maintaining epigenetic landmarks of the offspring, as well as impacting the reproductive system of the mother and offspring. **Objective:** To conduct a literature review on the changes that maternal obesity causes in the maternal and offspring reproductive system. **Methodology:** A systematic review was carried out with the search for articles published in the last five years, based on Pubmed, Scielo and Lilacs databases. Review articles, studies with humans or studies that have performed drug interventions and / or exposure to cigarettes, and / or that has not worked with a hyperlipidic or obesogenic diet were excluded. **Results:** A total of 110 articles were found in the databases, from such 20 articles were selected. **Conclusion:** maternal obesity affects the fertility and the reproductive physiological functions of the offspring, consequently impacting oogenesis, spermatogenesis and embryogenesis.

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INTRODUCTION

Exposure during the first 1000 days of life, which refer to the moment from conception to the second year of life, causes persistent effects on the metabolic health of the offspring and generations to come.It means that maternal nutrition has a transgenerational effect, transmitted to the second and third generation of children, regardless of their lifestyle and genetic factors, resulting in multigenerational impacts of health deficits.This demonstrates the importance of nutrition in the womb, a crucial period for establishing and maintaining epigenetic landmarks (DESAI *et al* 2015; FRIDEMAN, 2018). Maternal obesity and / or a high-fat diet during pregnancy are associated in addition to gestational complications, such as increased triglyceride levels, glucose intolerance, increased liver enzymes, postpartum weight retention, urinary tract infection, diabetes pregnancy and pre-eclampsia.There is alsoassociations with DNA methylation in the umbilical cord and increased methylation of the leptin gene in the placenta and histone modifications (DESAI *et al* 2015; POKON 2015; PANCHENKO *et al*., 2016).

The mother's nutrition also impacts the development of the offspring, since the offspring phenotype is mediated by epigenetic mechanisms in response to the maternal environment. Thus, the intrauterine environment can impact adaptations and / or metabolic complications in the offspring, such as glucose intolerance, obesity, increased serum triglyceride levels and metabolic syndrome (CHEN *et al*., 2014; SOARES *et al*., 2018), besides changes in reproductive capacity, such as reduced motility and sperm count, and increased testicular reactive oxygen species in males (BAUTISTA *et al*., 2017; WANG *et al*., 2018). A diet high in fat and sugar has been shown to alter the function of the circadian cycle in the cells of the ovary, uterus and placenta. In turn, the contribution of the circadian cycle clock gene to reproductive physiology and steroidogenesis is well known. This suggests that maternal nutrition can modify the genetic or epigenetic information carried by germ cells (CHAMBERS *ET AL*., 2016). In such context, it is already well established that fetuses and neonates are vulnerable to maternal nutrition, resulting in changes in the programming and development of organs, cellular response and gene expression, and impacting

the metabolic physiology of the offspring immediately, or even only in childhood or adulthood (DESAI *et al*., 2015). However, what are the impacts of the in-uteroenvironment on the ovary and uterus of the mother and offspring, as well as on the testicles and sperm production? Therefore, this research aimed to investigate how maternal obesity impacts the reproductive system of the mother and offspring.

METHODOLOGY

The systematic review of articles was carried out in the following databases: Scielo, Medline (PUBMED) and Virtual Health Library (BVS). Articles available online in full text, in English, published between 2015 and 2020were used. They also had to have been performed only on animals, containing the following descriptors: maternal obesity, fertility, reproductive system, gonadal white adipose tissue, ovary, pregnancy. The maternal descriptor "obesity" was crossed with each descriptor mentioned above, using the word "and". The authors independently evaluated the summary of each publication. Original articles in Portuguese, English or Spanish, published in the last 5 years (2020-2015), that were carried out on rats or mice and that were exposed to the Hight fat diet (HFD) or obesogenic diet were included. Studies with systematic review methodology, articles that were not in Portuguese or English, studies that have been carried out on humans or not published in the last five years, studies that have used any medication intervention or with cigarette exposure, or with nutritional supplements were excluded. The ethical aspects were contemplated, maintaining the original ideas and concepts of the researched authors.

RESULTS

A total of 110 articles were found in the databases. 20 articles were selected after removing the redundant cross-references, contained in more than one base, and following the inclusion and exclusion criteria. The 20 selected articles were organized according to the author, sampling, objective, intervention and main findings, as shown in the table 1.

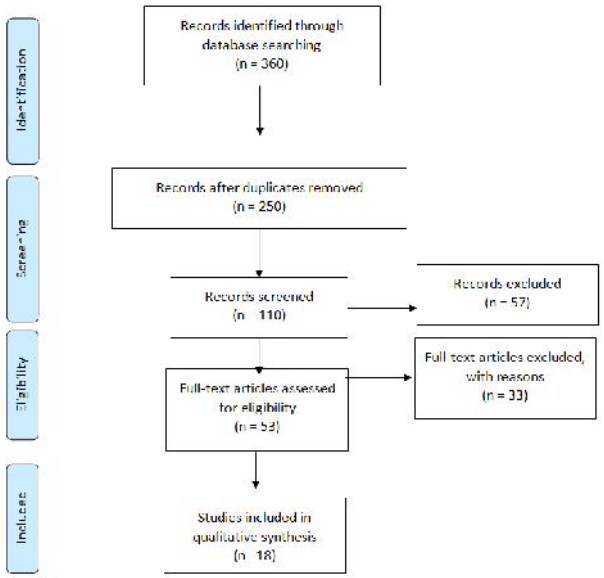

Figure 1. Flow diagram for the literature search process Adapted from: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009)

DISCUSSION

Impacts of maternal obesity on the mother's reproductive system: The maternal reproductive system is affected by exposure to the obesogenic environment, as it has been observed by experimental studies the impact on the quality of oocytes (HAN *et al*., 2018), reduction in fertilized eggs (FIGER *et al*., 2015); mitochondrial dysfunction, oocyte chromosomal abnormalities (YUN *et al*., 2019), and oxidative stress, also impacting oogenesis and embryogenesis.Oogenesis is the sequence of events in which oogonies (primordial germ cells) are transformed into mature oocytes. Figer *et al*., (2015) observed consequences of obesity in this process, such as a reduction in the width of the plush zone in the pronucleated oocyte stage of obese mice, as well as increased levels of aneuploidy, stress in the mitochondrial and endoplasmic reticulum, and apoptosis. Oxidative stress is a link between maternal obesity and the quality of oocytes, as it may be associated with meiotic defects in oocytes. In this context, Wang *et al*. (2018) identified a significant reduction in TIGAR (Regulator of TP53-induced glycolysis and apoptosis) in matured oocytes of obese mice. TIGAR is an essential mitochondrial protein for cellular redox homeostasis, modulates the PPP pathway, a metabolic pathway that determines the quality of mammalian oocytes, and resides mainly in the cytoplasm of oocytes.

Then when they go into miosis, TIGAR is concentrated in the spindle region. Thus, due to its location, TIGAR is essential in regulating the maturation and meiotic division of oocytes. Therefore, the reduction of this protein may be one of the factors that compromises the quality of oocytes in obese mice, since TIGAR could protect oocytes of obese mice against oxidative stress and meiotic defect (WANG *et al*., 2018). The impacts of the maternal obesogenic environment are sometimes similar to a "domino effect", where consequences on oogenesis also affect embryogenesis.

Han *et al*. (2018) demonstrated this possible effect, in which the reduction of STELL in oocytes of obese mice impacted the development of embryos that showed changes in development, especially in the two-cell and blastocyst phase, demonstrating developmental delay and cytoplasmic fragmentation,as well as reduced hypomethylation of DNA during the development of the zygote, which caused embryonic loss, fetal defects in the offspring and a delay in the growth of mice exposed to HFD. Yun *et al*. (2019) also noted that the quality of the oocytes was impacted by maternal obesity, with chromosomal abnormalities, such as deterioration of cohesion, leading to an increase in the termination of the chiasma metaphase I, causing an increase in premature separation of the sister centromeres and an increase in the inter-kinetochore distance. The possible mechanism of these changes is due to oxidative stress induced by maternal obesity, which directly or indirectly influences the damage of cohesins and their instabilities. Thus, it was possible to observe that obesity induced by HFD, mimics and / or aggravates the deterioration of cohesion observed during maternal aging.

Impacts of maternal obesity on the mother's reproductive system in offspring (females): Died-induced excessive maternal weight clearly affects the sexual development of the offspring, particularly in the reproductive system of females (GALARZA et a., 2016; FREY *et al*., 2019).

Table 1. Studies that analyzed the impacts of maternal obesity on the reproductive system of the mother and offspring, published between 2015-2020

Author/year	Sample	Objective	Intervention	Main findings
Finger et al. (2015)	Mouse	To check if the parents' obesity has an effect on the quality and development of the embryo, as well as its implantation	High-fat diet (21% fat)	↓ number of oocytes ovulated by obese females; ↓ number of fertilized eggs in obese couples; The consumption of glucose and lactate was not different between groups; ↑ GLUT-1 expression in obese couples
Rodriguez-Gonzalez (2015)	Rat	To assess whether maternal obesity during pregnancy and lactation increases oxidative stress in the testes and sperm and impacts on the fertility of the offspring	Obesogenic diet	There is no difference between groups in testicle weight; ↓ LH and testosterone in the offspring of obese mothers; ↑ SOD, GPX-1 and nitrotyrosine; ↓ spermatogenesis
Mcpherson (2015)	Mouse	To evaluate the influence of a maternal hyperlipidic diet on the reproductive tract and fetal health	High-fat diet	Parents exposed to HDF had lesser fetuses, ↓ blastocysts ↓ embryo development, altered mitochondria in embryos, and changes the expression of genes in the placenta when compared to control.
Ambroseti (2016)	Rat	To characterize the effect of maternal obesity at the beginning of puberty and on the follicular development of adult rat offspring	High-fat diet(60% fat)	The offspring of obese mothers showed ↑ body weight at all ages and precocious puberty, ↑ estradiol levels, ↓ CYP3A2 expression and ↓ antral follicle health
Chambers (2016)	Rat	Investigate whether feeding mice with HFD results in metabolic or reproductive changes in subsequent generations	High-fat diet(45% fat)	HFD induced obesity but did not alter the glucose tolerance of exposed animals; There were no differencesbetween groups in the dosage of triglycerides, testosterone and luteinizing hormone; ↑ weight gain of HFD mother puppies; The grandparents' diet affects the metabolic physiology of the offspring of the pups;
Galarza (2016)	Rat	To check the effects of maternal overweight and obesity on ovaries, follicle development, and ovulation of offspring	High-fat diet	The offspring of obese mothers showed ↓ number of primary and healthy follicles. However, they had ↑ ovulation rate. They also showed morphological changes such as a larger perivitelline space and a pellucid zone when compared to control animals.
Panchenko (2016)	Mouse	To investigate the effects of chronic maternal obesity on fetal placental growth, and its adjacent epigenetic mechanisms. Also, if preconception weight loss could alleviate these effects	High-fat diet	The fetuses of obese females showed fetal growth restriction and small fetuses for gestational age. The liver and placenta were more responsive to maternal obesity. Genes involved in the histone acetylation pathway were particularly altered
Pinto-Fochi et al. (2016)	Rat	To examine the effects of excessive consumption of a high-fat diet during the different stages of development of the rat, associated or not with maternal obesity, on the cellular organization of the interstitial tissue of the testis and on the steroidogenic capacity of leyding cells	High-fat diet(20% unsaturatedfat)	Reduction of steroidogenic capacity of Leydig cells and testosterone levels; Mitochondrial dysfunction of Leydig cells; Metabolic status, serum and intratesticular content of sex steroid hormones; ↑ elevated leptin levels
Tsoulis et al. (2016)	Rat	To determine the impact of excessive weight gain during pregnancy on ovarian follicle function and growth	High-fat diet(45% fat)	Body weight and insulin and leptin concentrations do not differ between groups; Maternal HF diet impacts the total number of oocytes, the size of secondary follicles and ↑ follicular atresia in the offspring
Lecoutre (2016)	Rat	To examine whether maternal obesity is able to "program" the morphology and number of adipocytes of rats fed with HFD during pregnancy and lactation. And if there is a difference in the gene expression of gonadal and perirenal adipose tissue of offspring, of both sexes	High-fat diet	Neonates from mothers exposed to HFD showed glucose intolerance, hyperinsulinemia and hypercholesterolemia, hyperleptinemia and ↑ weight gain during lactation. In males, this weight gain persisted for three months. Only the perirenal AT showed adipocyte hypertrophy and hyperplasia

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Appel et al. (2017)	Mouse	To investigate whether maternal adipose tissue contributes to an increase in the inflammatory state before labor begins. And if the adipose and placental tissue react in the same way	High-fat diet	Obese mothers ↑ TNF-α, IL-6, MCP-1 and ↓ GPX and catalase in the placenta and adipose tissue
Bautista (2017)	Rat	To evaluate the effects of maternal obesity during pregnancy and lactation, on the antioxidant enzymes of the testicles of the offspring	Obesogenic diet	↑Expression of catalase in the offspring of obese mothers; ↑Chemical expression of SOD-1; ↓ chemical expression of GPx-1/2 in the youngest offspring (p110 and 450), ↓ GPX-4 immunoreactivity
Lin (2017)	Rat	To assess the impact of maternal and post-weaning HFD consumption on ovarian follicular development and steroidogenesis in adult females	High-fat diet(58,5% fat)	↓ the number of small follicles (including primary and secondary) in the offspring's ovaries; ↑ estradiol and ↓ LH in the offspring of mothers fed with HFD; ↑ Igf2, Clock, Per1, Per2, Per3 expression in descending ovaries
Sirotkin (2017)	Mouse	To understand the endocrine mechanisms (the role of progestogens, androgens and IGF-I and their response to FSH) in mediating the influence of the metabolic state or of adipose tissue on ovarian functions	Hypercaloric diet (“ensure plus” add)	↑ accumulation of abdominal and peri-renal AT in the groups that received a high calorie diet; ↑ progesterone and testosterone release in the ↑ AT group; There was no significant difference in the number of embryos between the groups; ↑ AT was associated with ↓ quality of embryos ↓ fertility
Han et al. (2018)	Mouse	To identify what possible mechanisms such as maternal obesity can impair embryonic development and the health of offspring	High-fat diet(60% fat)	↓ STELLA protein in mature oocytes of obese mice; ↑ STELLA expression suppressed oocyte embryo defects in obese mothers
Mao et al. (2018)	Mouse	To assess the in-utero and postnatal impact of exposure to a hyperlipidic and hyperglycidic diet and its effects on spermatogenesis of offspring	High-fat and hyperglycidic diet	HFHS diet during pregnancy ↓ testosterone levels and sperm count. The postnatal HFHS suppressed sperm apoptosis, ↓ weight of the epididymis and sperm count
Muir et al. (2018)	Rat	To investigate the effects of the HFHC diet on the induction of maternal obesity, and its impacts on the plasma, hepatic, and uterine fatty acid (FA) composition during labor, with a focus on FA prostaglandin pathways	High-Fat, High-Cholesterol diet (HFHC)	↑ visceral fat and ↓ hepatic and plasma w-3 and w-6 from HFHC-exposed rats; ↓ uterine w-3 concentrations in HFHC- exposed rats; ↑ synthesis of prostaglandins and dysfunction of myometrial activity in HFHC- exposed rats
Wang (2018)	Mouse	To perform proteomic analysis to identify whether there is a significant reduction in TIGAR protein in matured oocytes of obese mice	High-fat diet(35% fat)	↓ TIGAR expression in oocytes of mice submitted to HFD; NAC ↓ ROS levels in oocytes of mice submitted to HFD and TIGAR knockout; Overexpression of TIGAR improves oocyte meiotic defects in HFD mice
Ferey (2019)	Mouse	To investigate how maternal obesity induces cardiac and oocyte mitochondria in offspring by transgenerational inheritance	High-fat and hyperglycidic diet	↑ left ventricle mass of male and female offspring. Male puppies from obese mothers also transmitted their effects to their offspring
Yun (2019)	Mouse	To check the associations of maternal obesity, chromosomal abnormalities and age-dependent exhaustion	High-fat (60% fat)	Maternal obesity did not affect oocyte maturation; The HF diet was associated with chromosomal abnormalities in metaphases I and II of meiosis of oocytes;

Galarza *et al*. (2016) observed that exposure to a hyperlipidic diet during the gestational period caused a smaller follicular reserve, less follicular development and less number of primary and healthy follicles in the offspring. However, they had a higher ovulation rate. They also showed changes in oocyte morphology, such as greater peri-vitelline space and plush zone, when compared to control animals. The oocytes of the offspring affected by maternal obesity present a mitochondrial dysfunction, inherited by the mother, which will impact the next generations. So, exposure to a hyperlipidic diet can program transgenerational mitochondrial defects, according to Ferey *et al*. (2019). Mitochondria are inherited by the maternal germline, as the sperm's mitochondria are degraded shortly after fertilization. If similar effects occur in humans, maternal and grandparent and great-grandparent obesity can be a risk factor for the development of chronic diseases in the offspring.

Impacts of maternal obesity on the mother's reproductive system in offspring (male): Experimental studies with animals have shown the impacts of maternal obesity on the reduction of reproductive capacity (RODRIGUEZ-GONZALEZ *et al*., 2015), changes in spermatogenesis (MAO *et al*., 2018), reduction in the functional capacity of Leydig cells (PINTO-FOCHI *et al*., 2016), quality and quantity of sperm (KATIB, 2015; MAO *et al*., 2018), epididymisweight (MAO *et al*., 2018), fertility problems (DAVIDSON *et al*., 2015) , testosterone levelsreduction (PINTO-FOCHI *et al*., 2016) and changes in testicular antioxidant capacity (BATISTA *et al*., 2017) of males from the offspring of an obese mother or from a mother who was exposed to a hyperlipidic diet during pregnancy. According to MAO *et al*. (2018,) spermatogenesis is altered with exposure in-utero to a hyperlipidic diet, affecting the fertility of the offspring and reducing sperm cell death, consequently reducing sperm count. Rodriguez-Gonzalez *et al*. (2015) demonstrated in testicular histological analysis a reduction in the number of spermatocytes and spermatogonia, as the main cause of the reduction in sperm concentration. It is known that an exposure to hyperlipidic diet there reduces insulin receptorexpression. Thus, reducing insulin sensitivity can also be a mechanism for reducing sperm count, since insulin plays an important role in regulating the number of Sertoli cells, testis size, and sperm count (MAO *et al*., 2018).

Pinto-Fochi *et al*. (2016) showed that, regardless of the time of exposure to hyperlipidic diet, there is a reduction in the functional capacity of Leydig cells of the offspring of obese mother rats, together with low levels of serum testosterone and high levels of leptin in experimental groups that were exposed to HFD during pregnancy and lactation. This deregulation of leptin is the main factor related to the steroidogenic impairment of Leydig cells, such as the reduction of the 17β-HSD steroidogenic enzyme that catalyzes final stages of sex steroid production, converting them into biologically active forms.Structural changes in Leydig's cell mitochondria have also been observed, with the accumulation of vesicles in the mitochondrial matrix with a structure similar to autophagosomes. Thus, in addition to disturbances in the action of leptin, mitochondrial changes can contribute to the damage of steroidogenic functions. The accumulation of total and gonadal fat of the offspring is one of the consequences of the maternal intrauterine environment, which impacts on the decline in testosterone and LH levels, causing testicular damage and reduced spermatogenesis, both associated with oxidative stress. Obesity itself is characterized by an imbalance in the production of reactive oxygen species and antioxidant enzymes, and, in the gestational period, prenatal hypoxia, super nutrition and / or gestational malnutrition, furtherly favor the offspring to oxidative stress. Such implies testicular dysfunction, abnormal semenand infertility, justified by the damage caused by oxidative stress to DNA in sperm and apoptosis, impacting its quality (RODRIGUEZ-GONZALEZ *et al*., 2015).

The testicles contain antioxidant enzymes, such as catalase, SOD and GP-X, which try to protect the sperm and the steroid process, from ROS.Also, the cell aging process and the oxidative stress are capable of affecting testicular physiological functions. Batista *et al*. (2017) showed a greater immunoreactivity of catalase in the lumen of seminiferous tubules, of SOD-1, as a result of the accumulation of gonadal fat. Also, physiological reduction of GPx-1/2 GP due to its loss of catalytic function and of GPx-4 isoform, due to the increase in oxidative stress, in the offspring of obese rats when compared to control. Rodriguez-Gonzales *et al*. (2015) also noted the increased activity of SOD and GPx-1, as well as an increase in nitrotyrosine, an indicator of cell damage. So, it is evident that maternal obesity affects the antioxidant defense system of male offspring, consequently their testicular physiological functions, leading to premature aging of male reproductive capacity, negatively impacting male fertility.

Conclusion

Exposure to a hyperlipidic diet during pregnancy affects fertility and the reproductive physiological functions of the offspring, programming transgenerational effects, consequently impacting oogenesis, spermatogenesis and embryogenesis. If similar findings would occur in humans, maternal, grandparent and great-grandparent nutrition can be a risk factor for the fertility and the development of diseases in the reproductive system of the next generations.

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