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Rafaianne Queiroz de Moraes Souza

Repercussões bioquímicas e reprodutivas de mães e descendentes após o consumo materno de dieta hiperlipídica em roedores: Revisão Sistemática

Tese apresentada à Faculdade de Medicina, Universidade Estadual Paulista "Júlio de Mesquita Filho", Campus de Botucatu, para obtenção do título de Doutora em Ginecologia, Obstetrícia e Mastologia.

Orientadora: Profa. Dra. Débora Cristina Damasceno
Coorientador: Prof. Dr. Gustavo Tadeu Volpato

Botucatu
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"Sou feita de retalhos.
Pedacinhos coloridos de cada vida que passa pela minha e que vou costurando na alma.
Nem sempre bonitos, nem sempre felizes, mas me acrescentam e me fazem ser quem eu sou.
Em cada encontro, em cada contato, vou ficando maior...
Em cada retalho, uma vida, uma lição, um carinho, uma saudade...
Que me tornam mais pessoa, mais humana, mais completa.

E penso que é assim mesmo que a vida se faz: de pedaços de outras gentes que vão se tornando parte da gente também.
E a melhor parte é que nunca estaremos prontos, finalizados...
Haverá sempre um retalho novo para adicionar à alma.

Portanto, obrigada a cada um de vocês, que fazem parte da minha vida e que me permitem engrandecer minha história com os retalhos deixados em mim. Que eu também possa deixar pedacinhos de mim pelos caminhos e que eles possam ser parte das suas histórias.

E que assim, de retalho em retalho, possamos nos tornar, um dia, um imenso bordado de nós".

Cris Pizzimenti

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"Porque dEle e por Ele, e para Ele, são todas as coisas; glória, pois, a Ele eternamente" (Romanos 11:36)

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"*A família é o amor de Deus nos oferecendo um pouquinho do céu aqui na Terra*." (Autor desconhecido)

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Sumário

Capítulo 1

1. CONSIDERAÇÕES INICIAIS

Este estudo faz parte de um projeto mais amplo intitulado “Avaliação de descendentes expostas ao diabetes moderado intrauterino, submetidas à dieta hiperlipídica no período pós-natal e tratadas com mistura de cálcio e vitamina D durante a prenhez” (Protocolo CEUA 1218/2017). Obteve financiamento da FAPESP (Processo número 2016/25207-5, vigência de 01/07/2018 a 30/06/2020).

No primeiro projeto elaborado como sendo o doutorado de Rafaianne Queiroz Moares Souza, a metodologia contemplava os estudos sobre o útero materno e parâmetros fetais referente os animais do projeto completo descrito acima. Para obtenção de filhas de diabéticas (FDmod) com idade adulta, são necessários pelo menos 180 dias (meio ano). Ao longo deste experimento, foi observado que as ratas FDmod apresentaram dificuldades para acasalamento, o que retardou o tratamento desses animais, bem como o experimento como um todo. Após o segundo ano de tentativas frustradas para obtenção de ratas prenhes, advindas de ambiente intrauterina hiperglicêmico e alimentadas com dieta hiperlipídica, a aluna obteve uma pequena amostragem de animais prenhes. Estes animais foram tratados, mas durante o experimento, todos os animais prenhes e não-prenhes foram a óbito em virtude de uma contaminação bacteriana, confirmada por exames específicos realizados no Laboratório Clínico do Hospital Veterinário da FMVZ – Unesp. Desta forma, a aluna precisou reiniciar todo o experimento para obtenção de todos os grupos experimentais. No entanto, como a aluna ainda está coletando os dados novamente

para apresentação desta tese foi realizada uma revisão sistemática a respeito deste assunto. Os resultados sobre prenhez e tratamento com vitamina D e/ou cálcio continuam em andamento e estarão sob a responsabilidade desta aluna e de outras estudantes envolvidas no projeto completo para que sejam tabulados, analisados, discutidos e, posteriormente, publicados em revista de âmbito internacional.

2. ATIVIDADES EXECUTADAS DURANTE O DOUTORADO

A aluna iniciou o Doutorado em março de 2015, durante todo esse período participou das atividades desenvolvidas no Laboratório de Fisiologia de Sistemas e Toxicologia Reprodutiva (FISIOTOX) da Universidade Federal do Mato Grosso (UFMT) e no Laboratório de Pesquisa Experimental em Ginecologia e Obstetrícia (LAPGO), pertencente ao Programa de Pós-graduação em Ginecologia, Obstetrícia e Mastologia da Faculdade de Medicina de Botucatu, Universidade Estadual Paulista (UNESP).

2.1 Artigos Publicados

2.1.1. Soares TS, Andreolla AP, Miranda CA, Klöppel E, Rodrigues LS, **Moraes-Souza RQ**, Damasceno DC, Volpato GT, Campos KE. Effect of the induction of transgenerational obesity on maternal-fetal parameters. Syst Biol Reprod Med. 2018; 64(1):51-59.

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RESEARCH ARTICLE

Effect of the induction of transgenerational obesity on maternal-fetal parameters

Thaigra Sousa Soares [a,b], Ana Paula Andreolla[a], Carolina Abreu Miranda [a,b], Eduardo Klöppel[a,b], Luhara Silva Rodrigues[a], Rafaianne Queiroz Moraes-Souza[a,b], Débora Cristina Damasceno [b], Gustavo Tadeu Volpato [a,b], and Kleber Eduardo Campos [a,b]

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ABSTRACT

Maternal obesity can cause complications for both women and their offspring for generations. Therefore, we intended to verify the repercussions of induction of transgenerational obesity on biochemical parameters, reproductive performance, and congenital anomaly frequency in Wistar rats. Female rats were used from successive generations. The female rats of parental generation (F_0, n=10) were mated to obtain their offspring (F_1 generation). F_1 female rats received a monosodium glutamate (MSG) solution to induce obesity (n=07) or vehicle (control, n=06) during the neonatal period. These adult female rats were classified as normal or obese using the Lee Index, mated, and delivered offspring (F_2 generation), which were also evaluated for obesity using the Lee Index in adult life (F_2MSG, n=13, born from obese dams) or non-obesity status (F_2Control, n=12, born from control dams), and were mated in adulthood. During pregnancy, glycemia and an oral glucose tolerance test (OGTT) were analyzed. At term pregnancy, the females were sacrificed for serum biochemical profile, maternal reproductive outcomes, and fetal development. In F_2MSG rats, body weight gain at early pregnancy, glycemia by OGTT, total cholesterol, high-density-lipoprotein, and alanine transaminase activity were higher compared with those of F_2Control rats. F_2MSG rats also presented a lower implantation number and gravid uterus weight, increased pre-implantation loss and anomaly frequency in their fetuses (F_3 generation) compared with those of F_2Control rats. Therefore, even without significant changes in body weight gain, obesity was established at the end of pregnancy of Wistar rats using other biomarkers. Additionally, these rats showed multiple adverse reproductive outcomes, confirming the deleterious effects that lead to obesity.

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Fetus; obesity; rat; transgenerational

Introduction

Obesity and its related comorbidities have become one of the main conditions negatively impacting public health, representing an alarming global problem. The epidemic proportions of obesity are mainly resulting from lifestyle changes, including increased high calorie intake and decreased physical activities [Flegal et al. 2015]. Obesity and being overweight have also increased in women of reproductive age [McDonald et al. 2010], and have increased strongly in populations with low and average incomes, especially in urban areas of developed countries [Nelson et al. 2010]. During pregnancy, obesity can cause complications for both women and their offspring, which may result in stillbirth and congenital anomalies [Begum et al. 2011]. The impaired maternal intrauterine environment may induce critical changes in fetal growth and development, contributing to the risk of developing disease in later life [Barker 2007; Gluckman et al. 2008].

Clinical and experimental studies show that maternal obesity induced intrauterine changes may influence the fetal organism leading to metabolic adaptations and/or complications [Gluckman et al. 2008], such as glucose intolerance, obesity, and metabolic syndrome in adult life [Barker 2007; Campos et al. 2007; Desai et al. 2013]. Obese women present an increased risk of birth defects in their offspring [Stothard et al. 2009]. In experimental models, obesity is related to an abnormal biochemical profile, with obese rats presenting with increased serum triglyceride levels and glucose intolerance in their offspring [Chen et al. 2014].

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2.1.2. Afiune LAF, Leal-Silva T, Sinzato YK, **Moraes-Souza RQ**, Soares TS, Campos KE, Fujiwara RT, Herrera E, Damasceno DC, Volpato GT. Beneficial effects of *Hibiscus rosa-sinensis* L. flower aqueous extract in pregnant rats with diabetes. PLoS One. 2017; 12(6):e0179785.

PLOS ONE

RESEARCH ARTICLE

Beneficial effects of *Hibiscus rosa-sinensis* L. flower aqueous extract in pregnant rats with diabetes

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Abstract

Purpose

The *Hibiscus rosa-sinensis* flower is widely used in Brazilian traditional medicine for the treatment of diabetes and has shown antifertility activity in female Wistar rats. However, there is no scientific confirmation of its effect on diabetes and pregnancy. The aim of this study was evaluate the effect of aqueous extract of *H. rosa-sinensis* flowers on maternal-fetal outcome in pregnant rats with diabetes.

Methods

Diabetes was induced by streptozotocin (STZ, 40 mg/kg) in virgin, adult, female Wistar rats. After diabetes induction, the rats were mated. The pregnant rats were distributed into four groups (n minimum = 11 animals/group): non-diabetic, non-diabetic treated, diabetic, and diabetic treated. Oral aqueous extract of *Hibiscus rosa-sinensis* was administered to rats in the treatment groups during pregnancy. At term pregnancy, maternal reproductive outcomes, fetal parameters, and biochemical parameters were analyzed.

Results

The non-diabetic treated group showed decreased high density lipoprotein cholesterol, increased atherogenic index (AI) and coronary artery risk index (CRI), and increased preimplantation loss rate compared to the non-diabetic group. Although treatment with *H. rosa-sinensis* led to no toxicity, it showed deleterious effects on cardiac and reproductive functions. However, the diabetic treated group showed increased maternal and fetal weights,

2.1.3. **Moraes-Souza RQ**, Reinaque AP, Soares TS, Silva AL, Giunchetti RC, Takano MA, Akamatsu MA, Kubrusly FS, Lúcio-Macarini F, Raw I, Iourtov D, Ho PL, Bueno LL, Fujiwara RT, Volpato GT. Safety evaluation of a vaccine: Effect in maternal reproductive outcome and fetal anomaly frequency in rats using a leishmanial vaccine as a model**.** PLoS One. 2017; 12(3):e0172525 **(Publicação referente à Dissertação de Mestrado).**

PLOS ONE

RESEARCH ARTICLE

Safety evaluation of a vaccine: Effect in maternal reproductive outcome and fetal anomaly frequency in rats using a leishmanial vaccine as a model

Rafaianne Q. Moraes-Souza[1☯], Ana Paula Reinaque[2☯], Thaigra S. Soares[1], Ana Luiza T. Silva[2], Rodolfo C. Giunchetti[3], Maria A. S. Takano[4], Milena A. Akamatsu[4], Flávia S. Kubrusly[4], Fernanda Lúcio-Macarini[4], Isaias Raw[4], Dmitri Iourtov[4], Paulo Lee Ho[4], Lilian L. Bueno[2], Ricardo T. Fujiwara[2], Gustavo T. Volpato[1]*

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Abstract

While the immunogenic potential of the vaccination against infectious diseases was extensively shown, data on the safety assessment of recombinant proteins in vaccine formulations administered during pregnancy are still scarce. In the current study, the antigenicity of a vaccine against leishmaniasis (based on *Leishmania braziliensis* recombinant protein peroxidoxin) during pregnancy and possible maternal reproductive outcomes and fetal anomalies after immunization with a leishmanial vaccine or adjuvant alone (*Bordetella pertussis* derived MPLA adjuvant) were assessed. Rats were mated and allocated in three groups: **Control**—rats received saline; **Adjuvant**—rats received the adjuvant MPLA, and **Vaccine**—rats received the combination of MPLA and peroxidoxin. The administration was subcutaneously at the dorsal region, three times (days 0, 7, 14 of pregnancy). On day 21 of pregnancy, all rats were bled for biochemical and immunological measurements. The gravid uterus was weighed with its contents, and the fetuses were analyzed. The immunization with peroxidoxin induced a significant production of circulating IgG levels compared to other groups but caused a significant in post-implantation loss (14.7%) when compared to Control (5.0%) and Adjuvant (4.4%) groups. Furthermore, a significantly high rate of fetal visceral anomalies, such as hydronephrosis and convoluted ureter, was also observed in animals that received vaccine when compared to Control or Adjuvant groups. These data indicate the importance of safety evaluation of vaccines during pregnancy and the limited use of peroxidoxin administration during pregnancy. More importantly, the safety monitoring of immunization with MPLA derived from *Bordetella*

2.1.4. Pinheiro MS, Rodrigues LS, S L Neto, **Moraes-Souza RQ**, Soares TS, Américo MF, Campos KE, Damasceno DC, Volpato GT. Effect of *Bauhinia holophylla* treatment in streptozotocin-induced diabetic rats. An Acad Bras Cienc. 2017; 89(1):263-272.

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Effect of *Bauhinia holophylla* treatment in Streptozotocin-induced diabetic rats

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ABSTRACT

Bauhinia holophylla, commonly known as "cow's hoof", is widely used in Brazilian folk medicine for the diabetes treatment. Therefore, the aim of this study was at evaluating the aqueous extract effect of *Bauhinia holophylla* leaves treatment on the streptozotocin-induced diabetic rats. Diabetes was induced by Streptozotocin (40 mg/Kg) in female Wistar rats. Oral administration of aqueous extract of *Bauhinia holophylla* leaves was given to non-diabetic and diabetic rats at a dose of 400 mg/kg during 21 days. On day 17 of treatment, the Oral Glucose Tolerance Test was performed to determine the area under the curve. At the end of the treatment, the animals were anesthetized and blood was collected for serum biochemical parameters analysis. After treatment with *Bauhinia holophylla* extract, non-diabetic and diabetic rats presented no glycemic changes. On the other hand, the plant treatment decreased body weight and increased ALT and AST activities. In conclusion, the treatment with aqueous extract of *B. holophylla* leaves given to diabetic rats presented no hypoglycemic effect in nondiabetic animals and no antidiabetic effect in diabetic animals with the doses studied. In addition, the diabetic animals treated with the *B. holophylla* extract showed inconvenient effects and its indiscriminate consumption requires particular carefulness.

Key words: *Bauhinia holophylla*, diabetes, lipid profile, medicinal plants, rats.

INTRODUCTION

Diabetes mellitus is the name given to a group of disorders with different etiologies. It is characterized by disarrangements in carbohydrates, proteins and fat metabolism caused by complete or partial insufficiency of insulin secretion and/or insulin action (ADA 2016, Reece et al. 2004).

Several drugs are used to control diabetes, however, perfect glucose control is rarely achieved (Cooppan 2005). Moreover, plants have been used as an alternative therapy for the diabetes treatment. Many plants present hypoglycemic activity, which were demonstrated experimentally in animals and humans, but some still require further investigation (Volpato et al. 2002, Damasceno and Volpato 2008). Although several plants were tested for diabetes treatment, many of them were not evaluated, including species of the genus *Bauhinia*, popularly known as "cow's hoof" (Lorenzi and Matos 2002). These species typically present a wide distribution

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2.1.5. **Moraes-Souza RQ**, Soares TS, Carmo NO, Damasceno DC, Campos KE, Volpato GT. Adverse effects of *Croton urucurana* B. exposure during rat pregnancy. J Ethnopharmacol. 2017;199:328-333 **(Publicação referente à Monografia).**

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Adverse effects of *Croton urucurana* B. exposure during rat pregnancy

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ABSTRACT

Ethnopharmacological relevance: Several women often use plant extracts during pregnancy without any concern about its possible toxic effects. The plant effects have been experimentally confirmed in animals and humans, while others require additional investigations.
Aim of study: To evaluated the effect of aqueous extract of *Croton urucurana* latex on the maternal-fetal repercussions in rats.
Methods: Pregnant rats were randomly distributed into four experimental groups: Control=treated with water (vehicle); Treated 200=treated with a dose 200 mg/kg; Treated 400= dose 400 mg/kg and; and Treated 800= dose 800 mg/kg. The rats were orally treated by *gavage* with *Croton urucurana* or vehicle (water) during whole pregnancy. At term of pregnancy, all rats were killed to obtain maternal blood and tissues samples and fetal weight and anomaly analyses.
Results: C. urucurana treatment (Treated 400 and Treated 800) showed elevated liver enzymatic activities, reduced fetal body weight and placental efficiency. The Treated 800 group presented increased maternal total protein and cholesterol levels, and heart relative weight. All treated groups presented reduced maternal body weight and food intake, and increased pre-implantation loss rate compared to those of Control group. In addition, the treatment contributed to increased skeletal and visceral anomalies with higher doses.
Conclusion: Croton urucurana treatment caused maternal toxicity, which contributed for impairment embryo fetal development. These results showed that the indiscriminate use of plants during pregnancy should be avoided to prevent potential risk on maternal health as well as their offspring.

1. Introduction

Medicinal plants have been widely used to treat a variety of diseases. However, the use of these plants during pregnancy may present health risks to the woman and also to her fetus (Moreira et al., 2014). Certain herbs, used as abortifacients can induce embryotoxicity, fetotoxicity and/or teratogenicity when embryonic death does not occur. *Croton urucurana* Baillon, popularly known as dragon blood, blood water, capixingui, urucuana, lucurana, tapexingui and tapixingui, is considered an abortive plant (Gurgel et al., 2002). *Croton* is a large and diverse genus of Euphorbiaceae that comprises at least 800 species of the tropics and subtropics (Webster, 1993). *C. urucurana* is widespread in wetlands and riparian areas and is commonly found in southern Brazil, northern Argentina, Paraguay and Uruguay. The *C. urucurana* tree has an open canopy and bright stem, and reaches up to 15 m (Babieri et al., 2014).

The indigenous culture believe that *C. urucurana* shows remarkable healing properties. This plant has been extensively used in folk medicine for treatment of cancer, rheumatism, lesions, ulcers, diarrhea infections (Rao et al., 2007). Three different products from *C. urucurana* species are primarily used - the red sap or latex, stem bark and the gum exudate (Simionatto et al., 2007). In male rats, Esmeraldino et al. (2005) found that the stem bark of *C. urucurana* aqueous extract showed anti hemorrhagic activity. Also in male rats, was observed an anti-diarrheal response after treatment with 600 mg/kg of *C. urucurana* latex (Gurgel et al., 2001), and antifungal activity against five different dermatophytes when using *C. urucurana* sap in an in vitro study (Gurgel et al., 2005). Cordeiro et al. (2012), testing the acute toxicity of this plant, demonstrated that a single dose of 2000 mg/kg of *C. urucurana* bark methanol extract produced no toxicity signs in female rats, whereas doses at 50, 100 and 250 mg/kg caused reduced gastric lesions in male rats. In 2016, these same

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REVIEW ARTICLE

Medicinal Plants for Diabetes Treatment During Pregnancy

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Abstract: *Diabetes mellitus* is a syndrome of great importance that affects an increasing number of people every day. In particular, diabetes is a common and important disease during pregnancy and is marked by complications, both fetal and maternal, that increase the risks of morbidity and mortality for diabetic pregnant women and their offspring. Drugs such as insulin and hypoglycemic drugs are given to treat diabetes, but regular exercise and adequate diet have also been indicated. Furthermore, coadjutant therapies such as medicinal plants are popularly used to reduce diabetes-induced hyperglycemia, either within or outside the context of pregnancy. However, studies examining plant use for diabetes treatment are necessary to confirm its possible effects and its safety for the mother and fetus. The objective of this literature review was to conduct a survey of plant species that are utilized worldwide and their stated therapeutic uses. A literature search was performed using the terms "diabetes and pregnancy", which resulted in the identification of 31,272 articles. Of these studies, only 12 (0.0038%) were related to medicinal plants, demonstrating that there has been little investigation into this issue. Of the papers analyzed in this review, half evaluated plant leaves, indicating that these scientific studies attempted to reproduce the preparations commonly used by various populations, i.e., in the form of tea. Additionally, more than 90% of studies utilized experimental animals to evaluate the maternal-fetal safety of medicinal plant substances that may potentially be dangerous for humans. Thus, once confidence levels for plant-derived substances are established based on toxicological analyses and safety is confirmed, it is possible that plants will be used to complement conventional diabetes therapies.

Keywords: *Diabetes mellitus*, pregnancy, medicinal plants, herbs, treatment, review.

1. DIABETES BY THE NUMBERS

Diabetes mellitus is a complex and chronic disease that requires continuous medical care to reduce blood glucose and multifactorial risks. It presents multiple etiologies characterized by the chronic elevation of fasting and/or post-prandial glucose due to absolute or relative defects in insulin synthesis or decreased effects of insulin [1, 2].

Diabetes is a crucially important syndrome that is becoming the epidemic of the century. Globally, an estimated 422 million adults were living with diabetes in 2014, compared to 108 million in 1980. The global prevalence (age-standardized) of diabetes has nearly doubled since 1980, rising from 4.7% to 8.5% in the adult population [3]. In the Americas, the number of individuals with diabetes was estimated at 35 million in 2000 and projected to be 64 million in 2025 [4]. However, as of 2011, that number reached 62.8 million and is expected to reach 91.1 million in 2030 [5]. Diabetes is among the ten major causes of death in Western countries, and despite progress in clinical management, its lethal consequences still cannot be prevented. In

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2.2 Apresentação de pôsteres em congressos nacionais e internacionais

2.2.1. MORAES-SOUZA, R. Q.; CRUZ, L. L.; SOARES, T.S.; PAULA, V. G.; SINZATO, Y. K.; DAMASCENO, D. C.; VOLPATO, G. T "Effects of *Curatella americana* treatment on complications of diabetic pregnancy". In: 6th International Symposium on Metabolic Programming and Microbiome and 3rd Meeting of Ibero-American DOHaD chapter, 2018, Cancun. Book of abstracts, 2018. v. 1. p. B60008.

2.2.2. MORAES-SOUZA, R.Q.; REINAQUE, A. P. B.; SOARES, T.S.; BUENO, L. L.; FUJIWARA, R. T.; VOLPATO, G. T. "Repercussões maternas de ratas vacinadas com proteína peroxidoxina recombinante de *Leishmania braziliensis* durante a prenhez". In: I Workshop do Programa de Imunologia e Parasitologia Básicas e Aplicadas, 2015, Barra do Garças. Livro de Resumos, 2015. v. 1. p. 11-11.

2.2.3. MORAES-SOUZA, R.Q.; NETO, L.S.; ALVES, D. G.; SOARES, T.S.; CAMPOS, K. E.; AMERICO, M.F.; DAMASCENO, D. C.; VOLPATO, G. T. "Effect of *Hancornia speciosa* aqueous extract treatment on biochemical parameters in diabetic pregnant rats". In: XX Congresso da Sociedade Brasileira de Diabetes, 2015, Porto Alegre. Diabetology & Metabolic Syndrome, 2015. v. 7. p. A76.

Além das apresentações e participações em congresso, a aluna foi coautora de outros 36 resumos publicados em anais.

2.3 Participações em bancas de trabalhos de conclusão de curso

2.3.1. Participação em banca de Thalita Bohnen Carneiro. Efeitos materno-placentário-fetais em diferentes intensidades glicêmicas no início da prenhez dentro do modelo experimental

de diabete moderado, 2016 (Enfermagem) Universidade Federal de Mato Grosso.

2.3.2. Participação em banca de Bruno Stephano Ferreira da Silva. Repercussões fetais do tratamento com *Curatella americana* em ratas prenhes com diabete de intensidade moderada, 2018 (Enfermagem) Universidade Federal de Mato Grosso.

2.4 Coorientações concluídas de alunos

2.4.1. Vanessa Caruline Araujo da Silva.Repercussões maternas e fetais de ratas tratadas com Micofenolato de Sódio antes da prenhez. 2016. Orientador: prof. Dr. Gustavo Tadeu Volapto. Nível: iniciação científica.

2.4.2. Cristielly Maria Barros Barbosa. Efeitos adversos do tratamento com Ciclosporina antes e durante a prenhez. 2016. Orientador: prof. Dr. Gustavo Tadeu Volapto. Nível: Iniciação Científica.

2.4.3. Mário Cezar Fiuza Carlos. Repercussões maternas e fetais de ratas tratadas com Tacrolimo antes da prenhez. 2015. Orientador: prof. Dr. Gustavo Tadeu Volapto. Nível: Iniciação Científica.

2.5 Atividades de ensino

Atuação como professora convidada para ministrar o tema “Placentação e Anexos embrionários”. Disciplina de Histologia e Embriologia, cursos de Graduação Enfermagem e Biomedicina. Carga horária: 4 horas. Período: 2016, 2018 e 2019.

Capítulo 2

REPERCUSSÕES BIOQUÍMICAS E REPRODUTIVAS DE MÃES E DESCENDENTES APÓS O CONSUMO MATERNO DE DIETA HIPERLIPÍDICA EM ROEDORES: REVISÃO SISTEMÁTICA

BIOCHEMICAL AND REPRODUCTIVE REPERCUSSIONS OF MOTHERS AND THEIR OFFSPRING AFTER MATERNAL CONSUMPTION OF HIGH-FAT DIET IN RODENTS: A SYSTEMATIC REVIEW

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ABSTRACT

Maternal exposure to the high-fat diet (HFD) during gestation or lactation can be harmful to both mother and offspring. The objective of this systematic review was to synthesize the available data on the effects of maternal HFD on the reproductive parameter and biochemical profile in rodents. The electronic search was performed in the PUBMED (Public/Publisher MEDLINE), EMBASE (Ovid) and Web of Science databases. Data from 76 studies showed that change in biochemical and reproductive parameters is dependent on the experimental design. Furthermore, the heterogeneity found in the studies makes it impossible to comparisons. In addition, studies often omit or neglect important information, such as a description of the diet or methodological details. These factors make it difficult to affirm the true effect of maternal HFD consumption for both mother and offspring.

Keywords: high-fat diet, pregnancy, triglycerides, cholesterol, oxidative stress, descendants.

I. INTRODUCTION

During gestation, the developing fetus is totally dependent on the maternal environment for nutrition (Barker, 1998). The intrauterine environment is a crucial determinant in the fetal programming of chronic diseases in adulthood. This concept is called Fetal Origin of Adult Diseases - FOAD (Barker, 2007). However, after several studies, this term has been extended to DOHaD (Developmental Origins of Health and Disease) (Gillman *et al.,* 2007), which refers to a larger critical period of development, ranging from the original fetal period of Barker's proposal to the pre-gestational, embryofetal and postnatal periods. The range of life periods that the DOHaD hypothesis covers is still controversial. There is evidence that the critical period of development occurs from the phase encompassing meiosis and gametogenesis to the entire period of postnatal development and maturation from childhood to adolescence (Suzuki *et al.,* 2018). There is also other evidence about periods the DOHaD covers, disseminated worldwide through the “First 1000 Days” campaign, that affirms the importance of the nutritional status of infants and nursing mothers in the fetal and neonatal period until two years after birth comprising between 280 days before birth and approximately 730 infantile days after birth (Organization 1,000 Days). Although there is no single consensus, research-involving DOHaD thematic purposes to raise awareness about nutrition and health have been investigated (Suzuki *et al.,* 2018).

According to the World Health Organization (WHO), malnutrition refers to deficiencies, excesses or imbalances in a person’s intake of energy and/or nutrients (WHO, 2016), leading to undernutrition or overnutrition (Academy of Nutrition and Dietetics, 2018). The

population is abandoning traditional diets that are rich in fibers and grain for diets that include increased levels of sugars, oils, and animal fats (WHO, 2002). There are five times more obese than malnourished adult people worldwide (WHO, 2016). Maternal consumption of high-fat diet (HFD) is an important factor that causes harm to both mother and her offspring (Yu *et al.,* 2013a; Kim *et al.,* 2016). In the last decades, epidemiological evidence has shown that intrauterine life conditions influence growth, body composition and the risk of developing chronic diseases (Langley-Evans, 2015). Animal studies also indicates that overnutrition during pregnancy induces phenotypic changes can enhance susceptibility to diseases in adult offspring (Parlee *et al.,* 2013; Williams *et al.,* 2014), such as hyperglycemia (Li *et al.,*2015), obesity (White *et al.,* 2009; Franco *et al.,* 2012; Desai *et al.,* 2014) and metabolic syndrome (Desai *et al.,* 2014).

Epidemiological studies in humans are limited in their ability to assess the diet influence during pregnancy to offspring phenotype, as it is difficult to separate the effects of intrauterine and post-natal maternal exposure and genetic factors (Friedman, 2018). Therefore, research involving adequate experimental models is relevant, not only for ethical reasons but also due to uncontrollable variables, such as lifestyle, socioeconomic, nutritional and genetic factors. Hence, the objective of this systematic review was to identify and evaluate the studies with animal models (rodents) that were exposed to the HFD content in the pregnancy and/or lactation period to investigate biochemical and reproductive repercussions of mothers and offspring.

II. METHODS

(1) Literature search

This systematic review was undertaken in accordance with the

PRISMA (Liberati *et al.,* 2009) and registered on PROSPERO - International Prospective Register of Systematic Reviews (Protocol number CRD42019120418). The literature search was performed from inception to December 13th, 2018, on titles, abstracts, and keywords, in PUBMED (Public/Publisher MEDLINE), EMBASE (Ovid) and Web of Science databases. The following Medical Subject Headings (MeSH) and their synonyms were used in different combinations and variations with the Boolean operators "OR" and "AND" to yield a sensitive and comprehensive, yet relevant collection of possible articles “high-fat diet”, “oxidative stress", "triglyceride", "cholesterol", "low-density lipoprotein", "high density lipoprotein", "Alanine transaminase", "alanine aminotransferase" and "rodent" (See Appendix Supplementary S1 for complete search strategy). Besides the electronic search, other sources were used, such as hand searching and screening of reference lists.

Additional records were included from review articles and author-based searches. The searches were restricted to original studies that were published in the English language in scientific journals that were submitted to the peer-review process, without year restriction. After screening of titles and abstracts, three reviewers (RQMS, VPG, and DCD) independently examined full-text articles. Disagreements were resolved in consensus discussions.

(2) Inclusion and exclusion criteria

Studies were included in the data set only if they fulfilled the following criteria: *(i)* All rodent models. Non-rodents, spontaneously obese, genetically modified animals; *ex vivo* and *in vitro* studies involving human subjects were excluded; *(ii)* Studies on rodents being dams were subjected to an HFD around gestation (before and/or

during the whole or any part of pregnancy), or lactation. HFD was considered as chow-based HFD from any fat type (e. g., lard and vegetable oils). Custom-made diet (i.e. cafeteria), high-fiber diet, high-calorie diet, high-glucose diet, low-fat diet in short, and any other diet than non-high-fat diet were excluded. *(iii)* For comparison, animals that were fed a standard diet were included. The evaluation of articles that used to nutritional manipulation (i. e., surgery, drugs, stress, and exercise) was not considered. *(iv)* The primary outcomes were included lipid profile, oxidative stress of the dams and offspring and maternal reproductive outcomes.

- Lipid profile: Triglyceride (TG), Total Cholesterol (TC), High-density lipoprotein (HDL), Low-density lipoprotein (LDL) concentrations,
- Alanine aminotransferase (ALT) and Aspartate aminotransferase (AST) activities.
- Oxidative stress status: Malondialdehyde / Thiobarbituric acid reactive substances (MDA/TBARS) (lipid oxidation), Superoxide dismutase (SOD), Catalase (CAT) and Glutathione peroxidase (GPx) activities, 8-hydroxy-2' -deoxyguanosine (8-OHdG - DNA oxidation), quantification and scavenging reactive oxygen species (ROS).
- Reproductive outcomes: Litter size, maternal and offspring weight.

(3) Data extraction

For studies presenting eligibility criteria, relevant data were extracted such as publication year, animal strain, study design, and intervention, maternal and offspring outcomes were all collected.

(4) Qualitative assessment

Risk of bias for animal studies was assessed using the Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE's tool), which was evaluated in ten steps: three of selection (random group allocation, group similar at baseline and blinded group allocation), two of them on performance (random housing and blinded intervention), two of detection (random and blinded outcome assessment), one of attrition bias (reporting of drop-outs), one reporting (selective outcomes), one to other potential bias (Hooijmans *et al.,* 2014). Included studies were assessed independently by two reviewers (RQMS and GV) and any discrepancies were solved by discussion. The items were classified as low, unclear or high risk of bias. The score of all the articles was defined as the percentage of 0 to 100% and each category (Hooijmans *et al.,* 2014). We did not exclude studies based on high risk of bias.

III. RESULTS

(1) Description of the data set

Initial electronic searching across three databases yielded a number of 2007 citations. In addition, 32 articles were added from other sources. The removal of 676 duplicates resulted in 1363 individual articles to be subjected to inclusion and exclusion criteria. Firstly, the inclusion and exclusion criteria were imposed on title and abstract (removal of 1229), and secondly on study design and methods (removal of 58). Finally, 76 citations were selected for review (Figure 1).

(2) Study characteristics

Figure 2A shows the year of publication of the studies. Only eight (11%) articles had more than ten years of publication, and 33 (43%) have been published from 2009 to 2014, 35 (46%) were published in the last five years.

Among of the rodent strains, 26 (34%) were C57Bl/6 (mice), two (3%) Swiss (mice), four (5%) were Institute of Cancer Research- ICR (mice), 26 (34%) Sprague-Dawley (rats) and 18 (24%) Wistar (rats) (Figure 2B).

Figure 2C shows the characteristics of the maternal diets, which were shown as chow fat content ranged from 16 to 64.5% calories. Twelve studies, (approximately 15%) use of less than 39%Kcal. 46 studies, (approximately 59%) use of 40 – 49% Kcal and 20 (26%) employ more than 50% Kcal. Furthermore, from the 76 articles included in this review, 49 used the as source the animal-derived fats (mainly lard) and eight used vegetal oils, two articles used mixed (one used lard and corn oil and other used vegetable shortening, milk fat, soybean oil) and 17 did not identify the source of fat (Figure 2D).

After analyzing the included papers, 12 studies assessed litter size, of these 10 papers (83.34%) presented no change, one study (8.33%) showed greater litter size and one study (8.33%) with decreased litter size (Figure 3A). Furthermore, 12 studies (52%) presented higher maternal body weight and other 11 studies (48%) showed no abnormal weight (Figure 3B). There were 33 assessment the offspring's weight, 22(67%) presented no offspring weight changes, six (18%) evaluations had greater offspring weight and five (15%) showed lower weights (Figure 3C).

Table 1 shows the period of maternal exposure to diet and the biochemical biomarker assessments of mothers. The HFD exposure

ranges from 19 to 141 days. The biochemical parameters were TG, TC, HDL, LDL, ALT, and measurements of oxidative stress status. In the 21 studies that investigate the maternal TG level, 16 (76%) presented higher levels, four (19%) no change and one (5%) of them showed a decrease. The maternal TC had ten evaluations, eight (80%) of which increased, one (10%) did not change and another (10%) decreased. There were four maternal HDL evaluations [two (50%) increased and others two (50%) did not change]. The two articles (100%) about maternal LDL assessments showed higher levels of this biomarker. The only maternal analysis of ALT did not change. Regarding the oxidative stress status in this systematic review, the results of the studies were included according to the quantification of pro-oxidants (MDA, 8-OHdG, and ROS) and antioxidant enzymes (SOD, CAT, and GPx). In four (100%) maternal evaluations, the MDA levels increased, there was only one maternal analysis of ROS and was increased. The maternal SOD antioxidant enzyme was evaluated in only one study and this was increased. Maternal GPx was also observed higher in only one study. The maternal scavenging capacity on reactive oxygen species was verified to be decreased in two assessments.

Table 2 shows the period of maternal exposure to diet, characteristics of offspring (sexes and death age) and biochemical measurements of the biomarker of the offspring. The HFD exposure ranges from 19 to 154 days. In relation to sex, thirty-one articles verified both sexes; thirty studies analyzed males, fourteen evaluated females and another reported no explanation. The age that the offspring killed ranged between one day after birth up to 650 days old. The observed biochemical parameters were TG, TC, HDL, LDL, ALT, AST and oxidative stress status. Of the 139 articles about TG, 65

(47%) verified higher levels, others 69 (50%) showed no change and five (3%) presented lower levels. Of all 84 articles about TC, 22 (26%) showed an increased level, 54 (64%) verified no change and eight (10%) observed lower concentrations. There were 30 HDL assessments in the offspring, of these four (13%) were increased, 21 (70%) presented no abnormal HDL levels and five (17%) showed decreased concentrations. Furthermore, in 20 papers with LDL analysis in offspring, seven (35%) verified higher levels, 12 (60%) of them showed no change and one (5%) observed low level. The activity of the liver AST enzyme in the offspring was increased in one article (12.5%) and in other seven (87.5%) there was no change. In 11 studies about ALT measurements, in four (36%) was showed higher activity, in six of them (55%) no change and in one paper (9%) a decrease was verified.

In relation to oxidative stress status in offspring, there were 21 studies on MDA analysis, of these 14 (67%) confirmed high concentrations and seven (33%) showed no change. There were three ROS evaluations, two of them (66.67%) verified high values and one (33.33%) no change. The studies showed determinations of oxidative DNA damage, such as 8-OHdG, which three papers (75%) observed high levels and one (25%) no change. There were 18 articles about fetal SOD activity, three (16.67%) of which were increased, one (5.56%) presented no change and 14 (77.77%) articles showed low SOD activity. There were 11 investigations measured CAT activity, one (10%) paper presented no change and ten (91%) of them observed a decreased activity. The offspring GPx activity was evaluated in 17 papers, 3 (18%) of which had high activity, 4 (23%) no change and 10 (59%) showed a decrease. In the two studies using thiol measurements, one (50%) showed no change and another (50%)

verified a decreased level. (Table 2).

The most commonly used sample was blood with approximately 65% (34 analyses used the serum and 31 contained plasma samples). Other samples were also used, 21 (20%) used liver, three (3%) sampled mesentery, two (2%) used kidneys, one (1%) reported milk, one (1%) placenta, one (1%) used sperm, one (1%) testis, one (1%) studied femoral artery, two (2%) used muscles, one (1%) sampled cardiomyocytes, and another (1%) reported islet (Figure 4).

(3) Analysis of bias

The assessment of the SYRCLE risk of bias tool to assess the quality of animal studies indicated a high or unknown risk of bias for the studies in the majority of categories (Figure 5). Although the majority of included studies reported the baseline characteristics (64 studies - 84% were low risk), and 12 studies omitted this information (16% were high risk), there was unclear information about the methods used to generate allocation sequence in 32 studies (42% were unclear risk and 44 studies no description. 58% were at high risk. No description about concealment of the allocation sequence (76 studies - 100%). Information about performance bias, such as animals randomly housed (21 studies - 28% were high risk), care and blinded investigation of intervention/exposure of each animal was deficient (75 studies - 99% of them were high risk). Furthermore, detection bias was assessed as high risk due to no description of random selection for outcome assessment (74 studies - 97%) and blinded assessor about outcomes was 100%. While more than 53% (40 studies) of the included studies reported high attrition bias, the remaining two categories were classified as low risk of bias, which were reporting bias (75 studies - 99%) and other potential bias (76 studies - 100%).

IV. DISCUSSION

The objective of this study is to perform a systematic review on animal models submitted to a maternal high-fat feeding compared to standard diet to identify the experimental design and the most suitable biomarkers of the dams and offspring that were influenced by inadequate diet. After analyzing several full-text (paper), it was demonstrated that there was a lack of uniformity in the methodologies and diet composition. This led to the difficulty of comparing the studies, especially with regard to biomarkers for the definition of risks and injury for both mother and offspring after the maternal consumption of an HFD.

Systematic reviews are commonly used for human studies (Tajali *et al.,* 2010; Santos *et al.,* 2017). However, reviews using an animal model predominantly rodents have been highlighted (Ainge *et al.,* 2011; Lagisz *et al.,* 2015; Besson *et al.,* 2016; Ribaroff *et al.,* 2017). Rodents (mice and rats) are ideal models to induce metabolic alterations (Ramalho *et al.,* 2017) and suitable for investigating the mechanisms related to DOHaD (Chavatte-Palmer *et al.,* 2016). Considering these and other advantages, rodents were employed in this review.

To establish a complete search, there was no year limitation of the included studies. In this context, the majority of the articles are related to the last five years and this might be explained because the investigations on developmental plasticity and fetal programming have been started in these last years (Barker *et al.,* 1993; Gillman *et al.,* 2007). In this review, only articles that used diets with a higher fat content than the control group were evaluated. The major source was

lard, which mainly consists of non-essential fatty acids (Tellechea *et al.,* 2017). Some studies have used plant-originated fat, which contains essential fatty acids (polyunsaturated) (Sasidharan *et al.,* 2013, Jurgoński *et al.,* 2014). According to Tellechea *et al.* (2017), maternal exposure to the diet rich in lard is directly related to metabolic syndrome-related phenotypes in offspring rats. Besides that, essential fatty acids contain fundamental nutrients to fetal and postnatal development and normal cell function (Mennitti *et al.,* 2015). However, an excess may harm and have adverse consequences for offspring (Mennitti *et al.,* 2015). The different sources, concentrations and exposure periods of HFD can be responsible for the heterogeneity of results on reproductive and biochemical parameters (Lagisz *et al.,* 2015). Several authors presented the energy from fat (% Kcal) and others in centesimal composition. To facilitate such comparisons, the values were standardized in % Kcal in this review. Considering that carbohydrate provides four calories/gram, protein provides four calories/gram and fat provides nine calories/gram, these values were used in our review (United States Department of Agriculture - USDA, 2019).

The HFD model in animals has shown to be effective in producing maternal obesity by increasing body weight (Tellechea *et al.,* 2017). Some studies present greater maternal body weight (Khan *et al.,* 2005; Férézou-Viala *et al.,* 2007; Jungheim *et al.,* 2010; Yamaguchi *et al.,* 2010; Krasnow *et al.,* 2011; Masuyama & Hiramatsu, 2012; Cheong *et al.,* 2014; Masuyama & Hiramatsu, 2014; Masuyama *et al.,* 2015; Kim *et al.,* 2016; Lecoutre *et al.,* 2016; Mdaki *et al.,* 2016). However, this parameter presents no change depending on the experimental design (Koukkou *et al.,* 1998; Ghosh *et al.,* 2001; Zambrano *et al.,* 2010; Cerf *et al.,* 2011; Lin *et al.,* 2011; Yang *et al.,*

2012; Yu *et al.,* 2013[b], Desai *et al.,* 2014; Brenseke *et al.,* 2015; Umekawa *et al.,* 2015; Albert *et al.,* 2017).

While one study showed that the HFD maternal consumption during pregnancy can interfere with reproductive parameters such as lower litter size (Cheong *et al.,* 2014), other study verified greater litter size (Krasnow *et al.,* 2011). The result found about decreased litter size might be due to increased FoXO3a levels and, consequently, a reduction in the number of primordial follicles in the ovaries and oocyte apoptosis (Liu *et al.,* 2009; Cheong *et al.,* 2014). Such differences might be justified by the short period of diet exposure (28 days), despite the high-fat concentration (60% Kcal) (Krasnow *et al.,* 2011). After analysis of the full-text, we observed that most of the experimental models related to the included studies caused no change in litter size (Guo & Jen., 1995; Férézou-Viala *et al.,* 2007; Nasu *et al.,* 2007; Cerf *et al.,* 2011; Lin *et al.,* 2011; Masuyama & Hiramatsu, 2012; Ornellas *et al.,* 2013; Brenseke *et al.,* 2015; Masuyama *et al.,* 2015 Mdaki *et al.,* 2016; Albert *et al.,* 2017).

Maternal overnutrition is a risk factor for fetal growth, which might be increased or decreased (Christians *et al.,* 2019). This complex process depends on the fetal genotype and epigenetics, such as intrauterine insults and a variety of growth factors and proteins. The fetal growth depends not only on the maternal organism but also on fetuses and placenta, as well as the availability of oxygen and nutrients to the fetus (Bequer *et al.,* 2018). Although, most rodent studies report that offspring exposed to HFD during pregnancy and/or lactation present no abnormal body weight (Koukkou *et al.,* 1998; Ghosh *et al.,* 2001; Khan *et al.,* 2005; Zambrano *et al.,* 2010; Franco *et al.,* 2012; Yang *et al.,* 2012; Hou *et al.,* 2015; Umekawa *et al.,* 2015; Zhou *et al.,* 2015; Lecoutre *et al.,* 2016; Albert *et al.,* 2017; Sheen *et al.,* 2018),

some studies show that maternal HFD consumption results in lighter offspring (Melo *et al.,* 2014; Zheng *et al.,* 2014; Reynold *et al.,* 2015; Mdaki *et al.,* 2016; Huang *et al.,* 2017; Kunle-Alabi *et al.,* 2018). Other studies demonstrated heavier fetuses (Masuyama & Hiramatsu, 2012; 2014; Masuyama *et al.,* 2015). The phenotypes of offspring body weight are unclear and it seems to be due to differences in the HFD consumption period, fat source, and animal strain (Sullivan *et al.,* 2010).

The consumption of a high-fat diet with animal or plant-derived fats leads to increased TG (triglyceride) levels (Buettner *et al.,* 2007), as observed in most studies included in this review, in which the majority of TG measurements has been increased in the mother (Lin *et al*., 2011; Franco *et al*., 2012; Masuyama & Hiramatsu, 2012; Ornellas *et al*., 2013; Masuyama & Hiramatsu, 2014; MacPherson *et al*., 2015; Masuyama *et al*., 2015; Kim *et al.,* 2016; Mdaki *et al*., 2016; Albert *et al*., 2017; Rahman *et al*., 2017). Although these findings are similar in several studies, the results using diet vary in different laboratories due to animal strain and diet variety (Buettner *et al.,* 2007). It is important to emphasize that even though maternal TG does not change; the maternal consumption HFD may cause metabolic alterations in offspring (Desai *et al*., 2014).

The TG determinations analyzed in offspring showed an increase (approximately 47% of included studies), (Guo *&* Jen*.,* 1995; Ghosh *et al.,* 2001; khan *et al.,* 2003; Chechi *et al.,* 2009; Tokuza *et al*., 2009; Yamaguchi *et al*., 2010; Zambrano *et al*., 2010; Dong *et al*., 2011; Emiliano *et al.,* 2011; Ashino *et al.,* 2012; Chen *et al.,* 2012; Li *et al*., 2012; Masuyama & Hiramatsu, 2012; Yang *et al*., 2012; Ornellas *et al*., 2013; Resende *et al*., 2013; Chen *et al.,* 2014*[b];* Desai *et al.,* 2014; Masuyama & Hiramatsu, 2014; Melo *et al*., 2014; Yokomizo *et al*.,

2014; Bringhenti *et al.,* 2015; MacPherson *et al*., 2015; Masuyama *et al*., 2015; Reynold *et al*., 2015; Seet *et al.,* 2015; Umekawa *et al.,* 2015; Vega *et al*., 2015; Zhou *et al.,* 2015; Bringhenti *et al.,* 2016; Ito *et al.,* 2016; Mazzucco *et al.,* 2016; Tsuduki *et al*., 2016; Zambrano *et al*., 2016; Albert *et al.,* 2017; Huang et al., 2017; Moussa *et al.,* 2017; Nguyen *et al.,* 2017; Lomas-Soria *et al*., 2018; Miranda *et al*., 2018) as expected since the HFD-induced nutrient overload is necessary for the development of metabolic alterations (Hariri & Thibault, 2010; James *et al.,* 2012). Consequently, there are increased serum TG levels (Gheibi *et al.,* 2017). A possible mechanism involved is the AcsI3 gene (acyl-CoA synthetase long-chain family member 3), which is lower after HFD exposure (Huang *et al.,* 2017). Moreover, suppression of this gene is related to the reduced lipid synthesis and TG storage due to the lower cellular uptake of fatty acids (Bu *et al.,* 2009; Poppelreuther *et al.,* 2012). However, other authors observed no change in serum TG levels (approximately 50% of included studies) (Guo & Jen., 1995; Kokkou *et al.,* 1998; khan *et al.,* 2003; khan *et al.,* 2004; khan *et al.,* 2005; Férézou-Viala *et al.,* 2007; Chechi *et al.,* 2009; Tokuza *et al*., 2009; Yamaguchi *et al.,* 2010; Cerf *et al.,* 2011; Zhang *et al*., 2011; Ashino *et al.,* 2012; Chen *et al.,* 2012; Yang *et al.,* 2012; Rajja *et al.,* 2013; Ornellas *et al*., 2013; Chen *et al.,* 2014ª; Chen *et al.,* 2014b; Desai *et al.,* 2014; Yokomizo *et al.,* 2014; Zheng *et al.,* 2014; Brenseke *et al.,* 2015; Gray *et al.,* 2015b; Hou *et al.,* 2015; Umekawa *et al.,* 2015; Vega *et al.,* 2015; Ito *et al.,* 2016; Kim *et al.,* 2016; Lecoutre *et al.,* 2016; Mazzucco *et al.,* 2016; Mdaki *et al.,* 2016; Tsuduki *et al*., 2016; Zambrano *et al*., 2016; Moussa *et al.,* 2017; Glastras *et al.,* 2017; Moussa *et al.,* 2017; Sheen *et al.,* 2018; Tanaka *et al.,* 2018; Zhao *et al.,* 2018; Kunle-Alabi *et al.,* 2018; Miranda et al., 2018; Zhao *et al.,* 2018). Approximately 3% of included studies

observed decreased TG concentrations (Seet *et al.,* 2015; Tsuduki *et al.,* 2016; Mousavi *et al.,* 2017). The most analyses that showed no change or all decrease in TG concentration were performed in the blood samples. This fact may have contributed to the results presented in this review. A higher TG transfer to the liver due to the HFD consumption may have occurred and contributed to the development of non-alcoholic fatty liver diseases, leading to changes in the TG synthesis and transport. (Bugianesi *et al.,* 2005; Fabbrini *et al.,* 2010).

The HFD exposure is associated with dyslipidemia, which involves higher total cholesterol and LDL levels, as well as a reduction in HDL-cholesterol levels (Adiels *et al.,* 2008; Klop *et al.,* 2013). The results found in this review show that few articles evaluated these biomarkers in the mother and were divergent in offspring analyses. This suggests that such biomarkers are not efficient to reveal the injury induced by high-fat consumption, which depends on the experimental model employed.

The excess of common nutrients in HFD may exceed the adipose tissue capacity to process excessive energy and this excessive fat might be deposited in the liver (Despres & Lemieux, 2006). Overload in the liver results in increased ALT and AST activities (Sultan, 2008; Fraulob *et al.,* 2010). Despite the diet influence on the liver, few studies evaluated ALT and AST levels. The studies included in this review showed unchanged maternal ALT levels, but there were higher ALT and AST activities in the offspring (Tsuduki *et al.,* 2016; Kunle-Alabi *et al.,* 2018; Tanaka *et al.,* 2018).

The redox status, nutritional and environmental factors play an important role in the susceptibility to oxidative stress and other metabolic alterations (Luo *et al.,* 2006). Oxidative stress occurs due to increased production of reactive oxygen species (ROS) and/or failure

of the antioxidant system (Bringhenti *et al.,* 2015). This imbalance was observed in the full papers evaluated in this review both for mother (Lin *et al.,* 2011; Vega *et al.,* 2015; Kim *et al.,* 2016) and offspring (Tokuza *et al.,* 2009; Emiliano *et al.,* 2011; Lin *et al.,* 2011; Zhang *et al.,* 2011; Torrens *et al.,* 2012; Resende *et al.,* 2013; Yokomizo *et al.,* 2014; Bringhenti *et al.,* 2015; Rodriguez-Gonzalez *et al.,* 2015; Glastras *et al.,* 2016; Ito *et al.,* 2016; Kim *et al.,* 2016; Mdaki *et al.,* 2016; Glastras *et al.,* 2017; Miranda *et al.,* 2018; Tanaka *et al.,* 2018), most of which show changes in pro or antioxidant biomarkers. Malondialdehyde (MDA) and 8-hydroxy-2 '-deoxyguanosine (8-OHdG) were the pro-oxidants or lipid peroxidation products included in this review. MDA is a final product of lipid peroxidation measured by the quantification of thiobarbituric acid reactive substances (TBARS) (Lee *et al.,* 2012). 8-OHdG is one of the major products of DNA oxidation and may be modified (Hasan, *et al.,* 2017). These biomarkers represent a detrimental environment for both mothers and their offspring (Eriksson *et al.,* 2003; Hjort *et al.,* 2018; Reece *et al.,* 2004). The association of HFD and increased pro-oxidants can be explained by endothelial dysfunction (Mdaki *et al.,* 2016) and increased inflammatory process (Zhang *et al.,* 2011, Glastras *et al.,* 2017).

The enzymatic antioxidant system composed of superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx), the three main endogenous antioxidants, is triggered according to the organism requirement to protect itself against the oxidative insult caused by maternal HFD exposure (Emiliano *et al.,* 2011). The lower antioxidant profile observed in several studies (Emiliano *et al.,* 2011; Lin *et al.,* 2011; Resende *et al.,* 2013; Rodriguez-Gonzalez *et al.,* 2015; Bringhenti *et al.,* 2015; Miranda *et al.,* 2018) may be due to the enzymatic rapid consumption and depletion (Noeman *et al.,* 2011).

The higher antioxidant defenses verified in two of the studies are related to the compensation against the increase of oxidants (Rodriguez-Gonzalez *et al.,* 2015; Vega *et al.,* 2015). Both the increase and reduction of antioxidants represent an attempt to stabilize ROS (Birben *et al.,* 2012).

It is important to note that several papers tested blood samples for biochemical analysis (plasma or serum) (Guo *&* Jen*.,* 1995; Kokkou *et al.,* 1998; Ghosh *et al.,* 2001; Khan *et al.,* 2003; Khan *et al.,* 2004; Khan *et al.,* 2005; Férézou-Viala *et al.,* 2007; Nasu *et al.,* 2007; Chechi *et al.,* 2009; Elahi *et al.,* 2009; Tokuza *et al*., 2009; Jungheim *et al.,* 2010; Yamaguchi *et al*., 2010; Zambrano *et al*., 2010; Cerf *et al.,* 2011; Dong *et al*., 2011; Emiliano *et al.,* 2011; Lin *et al.,* 2011; Zhang *et al*., 2011; Ashino *et al.,* 2012; Chen *et al.,* 2012; Li *et al*., 2012; Masuyama & Hiramatsu, 2012; Yang *et al*., 2012; Yu *et al.,* 2013[a; b]; Ornellas *et al*., 2013; Rajja *et al*., 2013; Resende *et al*., 2013; Yu *et al.,* 2013[a] , Chen *et al.,* 2014[*a*]; Chen *et al.,* 2014[*b*]*;* Desai *et al.,* 2014; Hou *et al*., 2015; Masuyama & Hiramatsu, 2014; Zheng *et al.,* 2014; Brenseke *et al*., 2015; Gray *et al.,* 2015[*b*]; Masuyama *et al*., 2015; Reynold *et al*., 2015; Seet *et al.,* 2015; Umekawa *et al.,* 2015; Vega *et al*., 2015; Bringhenti *et al.,* 2016; Ito *et al.,* 2016; Kim *et al.,* 2016; Lecoutre *et al.,* 2016; Mazzucco *et al.,* 2016; Mdaki *et al*., 2016; Tsuduki *et al*., 2016; Zambrano *et al*., 2010; Albert *et al.,* 2017; Elahi & Matata, 2017; Glastras *et al*., 2017; Huang *et al*., 2017; Mousavi *et al*., 2017; Moussa *et al.,* 2017; Nguyen *et al.,* 2017; Rahman *et al.,* 2017; Kunle-Alabi *et al*., 2018; Lomas-Soria *et al*., 2018; Miranda *et al*., 2018; Sheen *et al.,* 2018; Tanaka *et al*., 2018; Zhao *et al.,* 2018). Blood is an effective material for the evaluation of biochemical profile because it informs the health state at the collection time (Liu *et al*., 2010). The second type of sample most used was the liver (Lin *et al.,* 2011; Zhang *et al*., 2011;

Ashino *et al*., 2012; Chen *et al.,* 2012; Ornellas *et al*., 2013; Yokomizo *et al*., 2014; Chen *et al.,* 2014[a;b]; Melo *et al*., 2014; Bringhenti *et al.,* 2015; Zhou *et al.,* 2015; Vega *et al*., 2015; Ito *et al.,* 2016; Kim *et al.,* 2016; Tsuduki *et al*., 2016; Huang *et al*., 2017; Lomas-Soria *et al*., 2018; Miranda *et al*., 2018; Tanaka *et al*., 2018; Zhao *et al.,* 2018). The hepatic tissue undergoes maturation stages during late gestation and early postnatal life. Hence, the liver is highly susceptible to inadequate nutrition maternal (Bruce *et al.,* 2016). There were also few determinations in other samples, such as mesentery (Emiliano *et al.,* 2011; Gray *et al.,* 2015[a]; Resende *et al.,* 2013), kidney (Glastras *et al.,* 2016; 2017), muscle (MacPherson *et al.,* 2015), placenta (Lin *et al.,* 2011), milk (Franco *et al.,* 2012), islet (Yokomizo *et al.,* 2014), sperm and testis (Rodriguez-Gonzalez *et al.,* 2015), cardiomyocytes (Mdaki *et al.,* 2016), and femoral artery (Torrens *et al.,* 20112). The non-uniformity of the samples is related to the objectives of each research. The difference in sample type also caused variation in the results, as for example in TG measurements that even with the same methodology was found increased in liver or muscle and without alterations in blood samples (Ashino *et al.,* 2012; Yang *et al.,* 2012; Ornellas *et al.,* 2013; Chen *et al.,* 2014[b]).

An inadequate feeding during the prenatal period likely increases the risk of chronic diseases, such as diabetes and metabolic changes during adult offspring (Ganu *et al.,* 2012; Ross & Desai, 2013). The overnutrition during pregnancy is a risk factor for the mother and their offspring, corroborating the DOHaD theory (Gillman *et al.,* 2007).

The selected articles were evaluated with an appropriate bias risk assessment instrument applied to experimental models (Hooijmans *et al.,* 2014). A good design describes the process of randomization, such as bias origin and their influence in the results (Festing, 2014). Most

articles only cite randomization of animals; however, they do not correctly describe the process. The blindness of researchers and data analysis are also an argument for bias, which was neglected in the studies. This probably occurs because of the difficulty for blinding during management with animals and with diet. From the implementation of more appropriate methodologies could reduce the bias, contributing to improving the reliability and interpretation of results (Ribaroff *et al.,* 2017).

In this review, there are methodological limitations of the included studies that culminated in the lack of consensus of results. Firstly, the description of diet composition, both in the control and HFD groups, sometimes is ignored by the authors or not clearly reported. However, by neglecting this information, the investigators hinder the interpretations and make the impractical reproducibility of these studies (Kilkenny *et al.,* 2010). Secondly, the articles selected present a variability of the standard diet (control group) characteristics, which causes difficulty for comparison among the experimental groups and control groups from different studies, showing that there is no consensus in the researches involving high-fat diet. The American Institute of Nutrition (AIN) published the formula use to standard chow for experimental rodents, AIN-93G, which shows all the necessary nutrients to be used during the early growth phase and during reproduction (Reeves, 1997). Thirdly, the fact that we have not restricted the strains, fat concentration, and source, offspring sex, period and number of days of maternal consumption of the HFD, age at which pups were analyzed are factors that contribute to the heterogeneity of the found results. Despite limitations, this review presents strengths, such as an extensive view of the literature. We used different databases with a large number of terms and keywords

to increase the number of searches. In addition, we showed the consequences for both mothers and their offspring.

V. CONCLUSION

In conclusion, this systematic review shows that maternal HFD consumption can change the material parameters and cause damages to their descendants depending on the experimental design. The heterogeneity found in the studies makes the comparisons impossible. In addition, studies often omit or neglect important information, such as a description of the diet or methodological details. These factors make it difficult to affirm the true effect of maternal HFD consumption for both mother and offspring.

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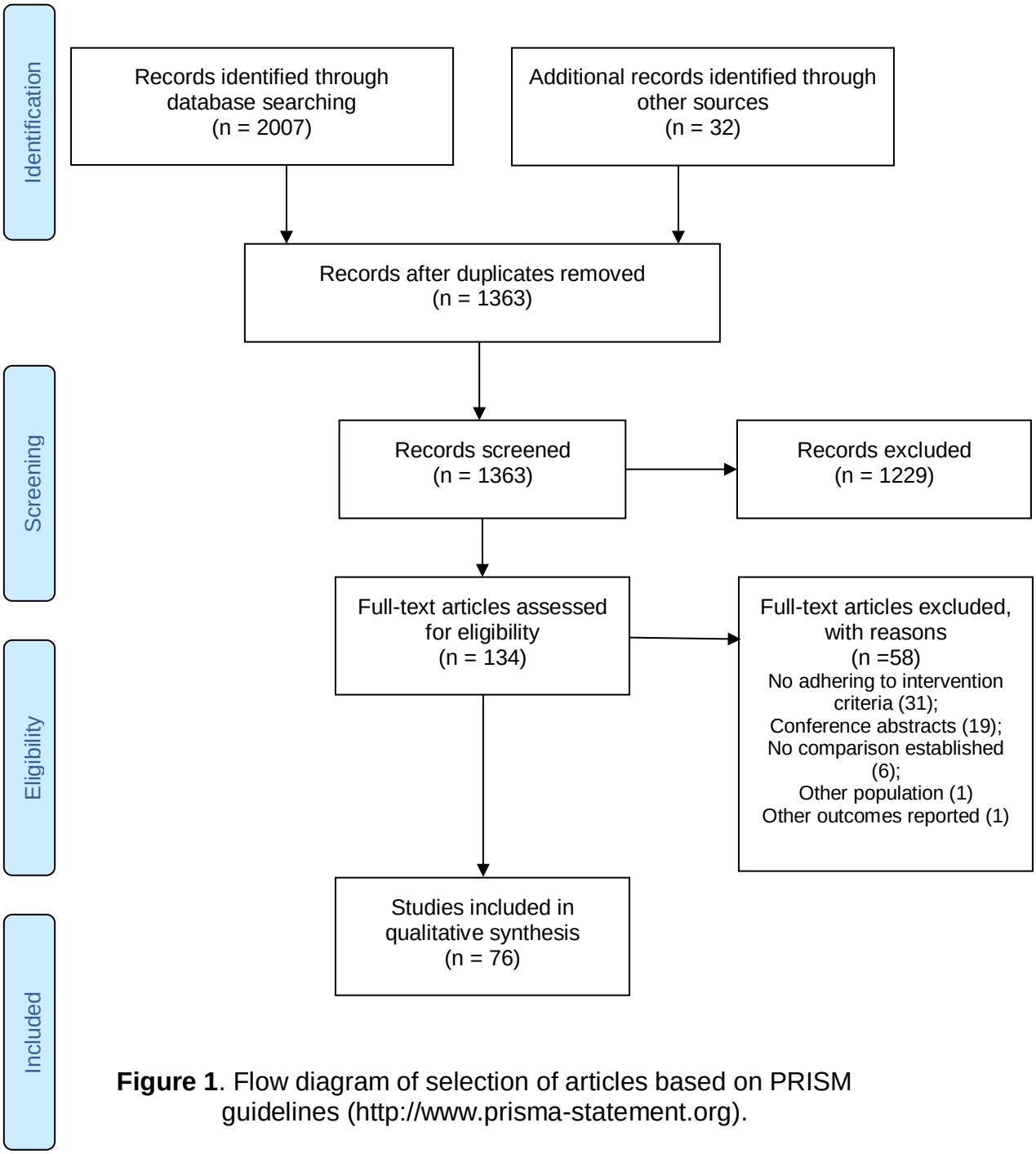

Figure 1. Flow diagram of selection of articles based on PRISM guidelines (http://www.prisma-statement.org).

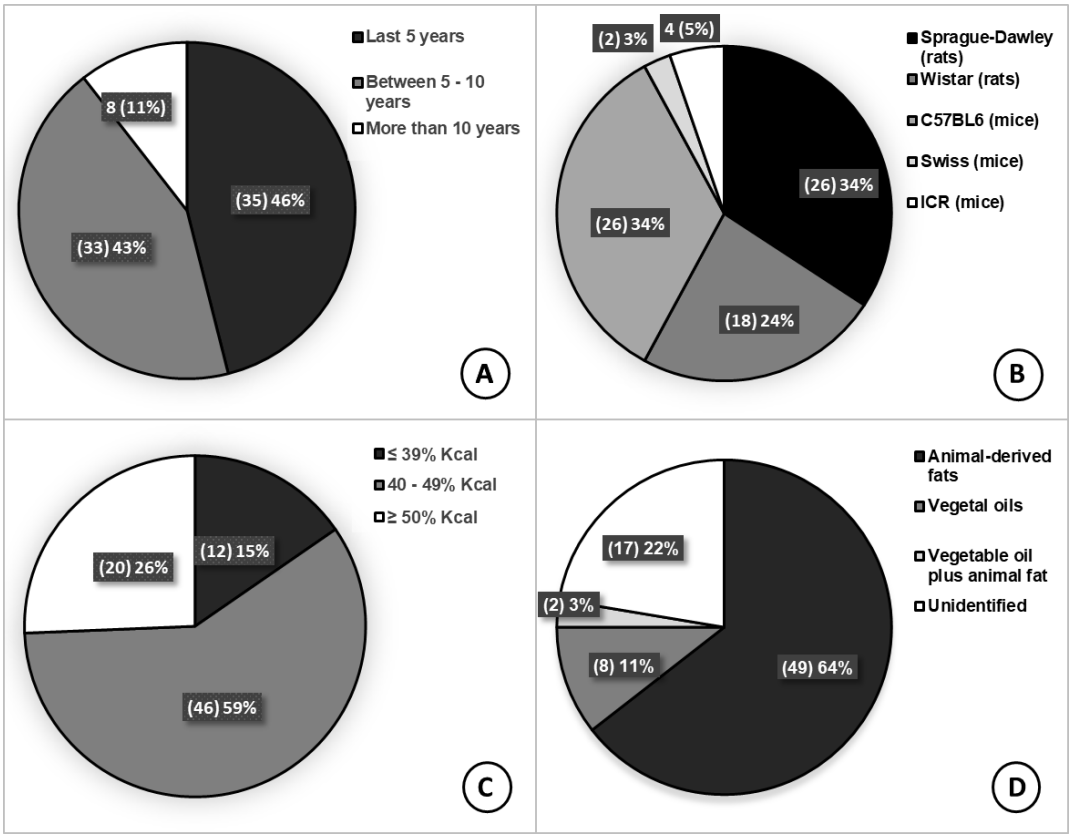

Figure 2. Characteristics of the studies. A: Publication dates; B: Strain of rodents; C: Energy value in% kilocalories; D: Main Source of fat.

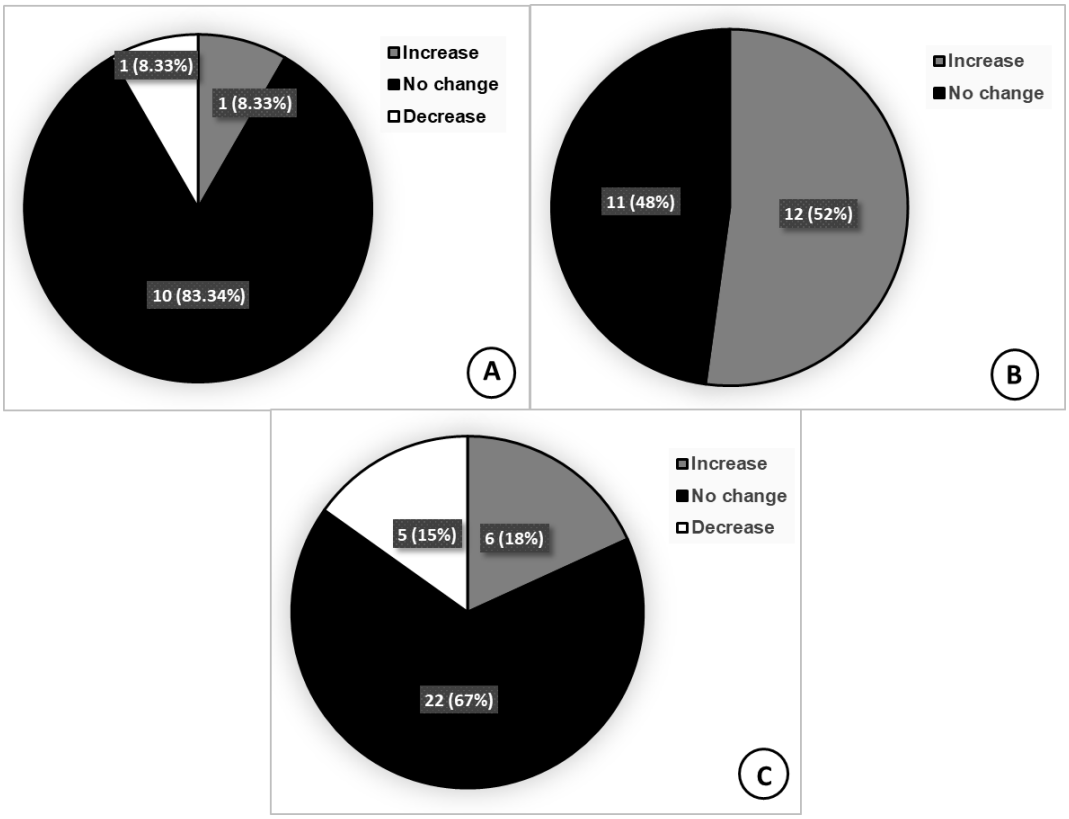

Figure 3. Reproductive repercussions. A: Litter size; B: Maternal body weight; C: Offspring body weight.

Table1. Biochemical repercussions of dams.

References	Animal	Kcal of fat	Maternal HFD consumption (days)	Outcomes of dams									
				TG	TC	HDL	LDL	ALT	MDA	ROS	SOD	GPX	Scavenging capacity of reactive oxygen species
Lin *et al.,* 2011[a]	Rats	40%	19	↑	NM	↔	NM	NM	↑	NM	NM	NM	↓
Lin *et al.,* 2011[b]	Rats	40%	19	NM	NM	NM	NM	NM	↑	NM	NM	NM	↓
Rahman *et al.,* 2017	Rats	57,50%	35	↑	NM	NM	NM	NM	NM	NM	NM	NM	NM
Nasu *et al.,* 2007	Rats	56.7 %	42	↔	NM	NM	NM	NM	NM	NM	NM	NM	NM
Guo *&* Jen., 1995[a]	Rats	64%	49	↓	NM	NM	NM	NM	NM	NM	NM	NM	NM
Mdaki *et al*., 2016[a]	Rats	40%/	49	↑	NM	NM	NM	NM	NM	NM	NM	NM	NM
Albert *et al.,* 2017	Rats	45%	52	↑	NM	NM	NM	NM	NM	NM	NM	NM	NM
Yamaguchi *et al*., 2010[a]	Rats	33%	84	↑	NM	NM	NM	NM	NM	NM	NM	NM	NM
Franco *et al.,* 2012[a]	Rats	29%	98	↑	↓	NM	NM	NM	NM	NM	NM	NM	NM
Franco *et al.,* 2012[b]	Rats	29%	98	↑	↑	NM	NM	NM	NM	NM	NM	NM	NM
Desai *et al.,* 2014[a]	Rats	60%	98	↔	↑	NM	NM	NM	NM	NM	NM	NM	NM
Seet *et al.,* 2015[a]	Rats	60%	98	↔	NM	NM	NM	NM	NM	NM	NM	NM	NM
MacPherson *et al*., 2015	Rats	41%	110	↑	NM	NM	NM	NM	NM	NM	NM	NM	NM
Kim *et al.,* 2016 [a]	Mice	45%	63	↑	↑	↔	NM	↔	↑	NM	NM	NM	NM
Kim *et al.,* 2016[b]	Mice	45%	63	↑	NM	NM	NM	NM	NM	NM	NM	NM	NM
Umekawa *et al.,* 2015[a]	Mice	45%	63	↔	↔	NM	NM	NM	NM	NM	NM	NM	NM
Yu *et al.,* 2013[a]	Mice	32%	63	NM	↑	↑	↑	NM	NM	NM	NM	NM	NM
Yu *et al.,* 2013[b]	Mice	32%	63	NM	↑	↑	↑	NM	NM	NM	NM	NM	NM
Masuyama & Hiramatsu, 2012[a]	Mice	62%	70	↑	NM	NM	NM	NM	NM	NM	NM	NM	NM

Masuyama & Hiramatsu, 2014[a]	Mice	62%	70	↑	NM	NM	NM	NM	NM	NM	NM	NM	NM
Masuyama *et al*., 2015[a]	Mice	62%	70	↑		NM	NM	NM	NM	NM	NM	NM	NM
Tokuza *et al*., 2009[a]	Mice	57.50%	79	↑	↑	NM	NM	NM	NM	NM	NM	NM	NM
Ornellas *et al*., 2013[a]	Mice	49%	105	↑	↑	NM	NM	NM	NM	NM	NM	NM	NM
Vega *et al*., 2015[a]	Mice	46%	141	NM	NM	NM	NM	NM	↑	↑	↑	↑	NM
Vega *et al*., 2015[b]	Mice	46%	141	↑	↑	NM	NM	NM	NM	NM	NM	NM	NM

Abbreviations: TG – Triglycerides; TC – Total cholesterol; HDL – High density lipoprotein cholesterol; LDL – Low density lipoprotein cholesterol; ALT – Alanine transaminase; AST – Aspartate transaminase; MDA – Malondialdehyde; ROS – Reactive oxygen species; SOD – Superoxide dismutase; CAT – Catalase; GPx – Glutathione peroxidase; ROS - Scavenging capacity of reactive oxygen species; NM - not measured.

Table2. Biochemical repercussions of offspring.

References	Animal	Kcal of fat	Maternal HFD consumption (days)	Sex offspring	Death age (days)	Outcomes of offspring												
						TG	TC	HDL	LDL	ALT	AST	MDA	8-OHdG	ROS	SOD	CAT	GPX	Thiols
Lin *et al.,* 2011[c]	rats	40%	19	M/F	1	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Cerf *et al.,* 2011[a]	rats	20%	21	M/F	1	↔	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Cerf *et al.,* 2011[b]	rats	30%	21	M/F	1	↔	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Cerf *et al.,* 2011[c]	rats	40%	21	M/F	1	↔	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Dong *et al.*, 2011	rats	35%	21	M	98	↑	NM	↓	↑	NM	NM	NM	NM	NM	NM	NM	NM	NM
Emiliano *et al.,* 2011[a]	rats	47%	21	F	90	↑	↔	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Emiliano *et al.,* 2011[b]	rats	47%	21	F	180	↑	↔	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Emiliano *et al.,* 2011[c]	rats	47%	21	F	90	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Emiliano *et al.,* 2011[d]	rats	47%	21	F	180	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Kunle-Alabi *et al.*, 2018[a]	rats	30%	21	M	120	↔	↓	↑	↓	↑	↔	NM	NM	NM	NM	NM	NM	NM
Kunle-Alabi *et al.*, 2018[b]	rats	30%	21	F	120	↔	↓	↔	↔	↑	↔	NM	NM	NM	NM	NM	NM	NM
Resende *et al.*, 2013[a]	rats	47.40%	21	M	90	↑	↔	NM	NM	NM	NM	↑	NM	NM	NM	NM	NM	NM
Resende *et al.*, 2013[b]	rats	47.40%	21	M	90	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Resende *et al.*, 2013[c]	rats	47.40%	21	M	180	↑	↔	NM	NM	NM	NM	↑	NM	NM	NM	NM	NM	NM
Resende *et al.*, 2013[d]	rats	47.40%	21	M	180	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
khan *et al.,* 2005[a]	rats	48%	31	M	180	↔	↔	↔	NM	NM	NM	NM	NM	NM	↓	↓	↓	NM
khan *et al.,* 2005[b]	rats	48%	31	F	180	↔	↔	↔		NM	NM	NM	NM	NM	↓	↓	↓	NM
Rahman *et al.,* 2017	rats	57.50%	35	M	28	NM	↔	↔	↔	NM	NM	NM	NM	NM	↓	↓	↓	NM

Moussa *et al.,* 2017[a]	rats	44%	42	M	70	↔	↔	↔	↔	NM	NM	NM	NM	NM	↓	↓	↔	NM
Moussa *et al.,* 2017[b]	rats	44%	42	F	70	↔	↔	↔	↔	NM	NM	NM	NM	NM	NM	NM	NM	NM
Moussa *et al.,* 2017[c]	rats	44%	42	M	140	↑	↔	↔	↔	NM	NM	NM	NM	NM	NM	NM	NM	NM
Moussa *et al.,* 2017[d]	rats	44%	42	F	140	↔	↔	↔	↔	NM	NM	NM	NM	NM	NM	NM	NM	NM
Moussa *et al.,* 2017[e]	rats	44%	42	M	210	↑	↔	↔	↔	NM	NM	NM	NM	↔	NM	NM	NM	NM
Moussa *et al.,* 2017[f]	rats	44%	42	F	210	↔	↑	↓	↔	NM	NM	NM	NM	NM	NM	NM	NM	NM
Yang *et al*., 2012[a]	rats	45%	42	F	84	↑		NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Yang *et al*., 2012[b]	rats	45%	42	F	84	↔	↔	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Zhang *et al*., 2011[a]	rats	45%	42	M	84	↑	NM	NM	NM	NM	NM	↔	NM	NM	NM	NM	NM	NM
Zhang *et al*., 2011[b]	rats	45%	42	M	84	↔	NM	NM	NM	NM	NM	↑	NM	NM	NM	NM	NM	NM
Zhou *et al.,* 2015	rats	45%	42	M/F	84	↑	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Kokkou *et al.,* 1998	rats	54%	47	?	15	↔	↓	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Guo *&* Jen*.,* 1995[a]	rats	64%	49	M/F	1	↔	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Guo *&* Jen*.,* 1995[b]	rats	64%	49	M/F	22	↑	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Mdaki *et al*., 2016[a]	rats	40%/	49	M/F	1	↔	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Mdaki *et al*., 2016[b]	rats	40%	49	M/F	1	NM	NM	NM	NM	NM	NM	↑	NM	NM	NM	NM	NM	NM
Albert *et al.,* 2017	rats	45%	52	M	110	↑	↔	↔	↔	↔	↔	NM	NM	NM	NM	NM	NM	NM
Ashino *et al.,* 2012[a]	rats	45%	52	M	28	↑	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Ashino *et al.,* 2012[b]	rats	45%	52	M	82	↑	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Ghosh *et al.,* 2001	rats	43%	52	F	160	↑	↔	↓	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Gray *et al.,* 2015[a]	rats	45%	52	M	140	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
khan *et al.,* 2003[a]	rats	48%	52	M	80	↔	↔	↔	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
khan *et al.,* 2003[b]	rats	48%	52	M	180	↔	↔	↔	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
khan *et al.,* 2003[c]	rats	48%	52	M	360	↔	↓	↓	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM

khan *et al.,* 2003[d]	rats	48%	52	F	80	↔	↔	↔	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
khan *et al.,* 2003[e]	rats	48%	52	F	180	↔	↔	↔	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
khan *et al.,* 2003[f]	rats	48%	52	F	360	↑	↑	↓	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
khan *et al.,* 2004[a]	rats	48%	52	M	180	↔	↔	↔	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
khan *et al.,* 2004[b]	rats	48%	52	F	180	↔	↔	↔	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
khan *et al.,* 2005[c]	rats	48%	52	M	180	↔	↔	↔	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
khan *et al.,* 2005[d]	rats	48%	52	F	180	↔	↔	↔	NM	NM	NM	NM	NM	NM	↓	NM	NM	NM
Reynold *et al*., 2015[a]	rats	45%	52	F	24		↑		↑	NM	NM	NM	NM	NM	NM	NM	NM	NM
Reynold *et al*., 2015[b]	rats	45%	52	F	150	↑	↑	↔	↑	NM	NM	NM	NM	NM	NM	NM	NM	NM
Hou *et al*., 2015[a]	rats	31%	56	M	1	↔	↔			NM	NM	NM	NM	NM	NM	NM	NM	NM
Hou *et al*., 2015[b]	rats	31%	56	M	56	↔	↔			NM	NM	NM	NM	NM	NM	NM	NM	NM
Gray *et al.,* 2015[*b*]	rats	45%	63	M	150	↔		↑	↔	NM	NM	NM	NM	NM	NM	NM	NM	NM
Chen *et al.,* 2012[a]	rats	43%	76	M	91	↑		NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Chen *et al.,* 2012[b]	rats	43%	76	M	91	↔		NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Rajja *et al*., 2013	rats	43%	76	F	98	↔		NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Sheen *et al.,* 2018	rats	58%	77	M	120	↔	↔	NM	NM	↔	↔	NM	NM	NM	NM	NM	NM	NM
Chen *et al.,* 2014	rats	43%	83	M	63	↔		NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Chen *et al.,* 2014[a]	rats	43%	83	M	63	↔		NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Chen *et al.,* 2014[b]	rats	43%	83	M	63	↑	NM	NM	NM	NM	NM		NM	NM	NM	NM	NM	NM
Nguyen *et al.,* 2017	rats	43.5%	84	F	20	↑	NM	NM	NM	NM	NM	NM	NM	NM	↓	↓	↓	↓
Yamaguchi *et al*., 2010[a]	rats	33%	84	M	1	↔	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Yamaguchi *et al*., 2010[b]	rats	33%	84	M	28	↑		NM	NM	NM	NM	NM	NM	NM	↓	↓	↔	↔
Férézou-Viala *et al.,* 2007[a]	rats	64.50%	91	M	70	↔	↓	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM

Férézou-Viala *et al.,* 2007[b]	rats	64.50%	91	F	70	↔	↔	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Desai *et al.,* 2014[a]	rats	60%	98	M/F	1	↓	↓	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Desai *et al.,* 2014[b]	rats	60%	98	M/F	21	↔	↔	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Desai *et al.,* 2014c	rats	60%	98	M	168	↑	↔	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Desai *et al.,* 2014[d]	rats	60%	98	F	168	↑	↔	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Huang *et al*., 2017[a]	rats	45%	98	M/F	7	↑		NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Huang *et al*., 2017[b]	rats	45%	98	M/F	21	↑	↑	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Mazzucco *et al.,* 2016[a]	rats	45%	98	M	21	↑	↔	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Mazzucco *et al.,* 2016[b]	rats	45%	98	F	21	↑	↔	NM	NM	NM	NM	NM	NM	NM	↓	↓	↓	NM
Mazzucco *et al.,* 2016[c]	rats	45%	98	M	140	↔	↔	NM	NM	NM	NM	NM	NM	NM	↓	↓	↓	NM
Mazzucco *et al.,* 2016[d]	rats	45%	98	F	140	↔	↔	NM	NM	NM	NM	NM	NM	NM	↓	↓	↓	NM
Miranda *et al*., 2018[a]	rats	29%	98	M	180	↑	NM	NM	NM	↔	↔	NM	NM	NM	↓	↓	↓	NM
Miranda *et al*., 2018[b]	rats	29%	98	M	180	↑	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Miranda *et al*., 2018[c]	rats	29%	98	F	180	↔	NM	NM	NM	↔	↔	NM	NM	NM	NM	NM	NM	NM
Miranda *et al*., 2018[d]	rats	29%	98	F	180	↔	NM	NM	NM	NM	NM	NM	NM	NM	↑		↑	NM
Seet *et al.,* 2015[a]	rats	60%	98	M	1	↓	NM	NM	NM	NM	NM	NM	NM	NM	↔		↔	NM
Seet *et al.,* 2015[b]	rats	60%	98	M	180	↑	NM	NM	NM	NM	NM	NM	NM	NM	↑		↑	NM
MacPherson *et al*., 2015	rats	41%	110	M/F	90	↑	NM	NM	NM	NM	NM	NM	NM	NM	↓	NM	↓	NM
Zambrano *et al*., 2016	rats	46%	121	M	36	↑	NM	NM	NM	NM	NM	NM	NM	NM	↑	NM	↑	NM
Zambrano *et al*., 2016	rats	46%	121	F	36	↔	NM	NM	NM	NM	NM	NM	NM	NM	↓	NM	↓	NM
Zambrano *et al*., 2016	rats	46%	121	M	110	↑	NM	NM	NM	NM	NM		NM	NM	NM	NM	NM	NM

Zambrano *et al.*, 2016	rats	46%	121	F	110	↑	NM	NM	NM	NM	NM		NM	NM	NM	NM	NM	NM
Rodriguez-Gonzalez *et al.,* 2015[a]	rats	46%	141	M	110	NM	NM	NM	NM	NM	NM	↑	NM	NM	NM	NM	NM	NM
Rodriguez-Gonzalez *et al.,* 2015[b]	rats	46%	141	M	110	NM	NM	NM	NM	NM	NM	↔	NM	NM	NM	NM	NM	NM
Rodriguez-Gonzalez *et al.,* 2015[c]	rats	46%	141	M	450	NM	NM	NM	NM	NM	NM	↑	NM	NM	NM	NM	NM	NM
Rodriguez-Gonzalez *et al.,* 2015[d]	rats	46%	141	M	450	NM	NM	NM	NM	NM	NM	↑	NM	NM	NM	NM	NM	NM
Rodriguez-Gonzalez *et al.,* 2015[e]	rats	46%	141	M	650	NM	NM	NM	NM	NM	NM	↑	NM	NM	NM	NM	NM	NM
Rodriguez-Gonzalez *et al.,* 2015[f]	rats	46%	141	M	650	NM	NM	NM	NM	NM	NM	↑	NM	NM	NM	NM	NM	NM
Zambrano *et al.*, 2010	rats	46%	141	M	21	↑	NM	NM	NM	NM	NM		NM	NM	NM	NM	NM	NM
Lomas-Soria *et al.*, 2018[a]	rats	46%	142	M	110	↑	NM	NM	NM	NM	NM		NM	NM	NM	NM	NM	NM
Lomas-Soria *et al.*, 2018[b]	rats	46%	142	F	110	↑	NM	NM	NM	NM	NM		NM	NM	NM	NM	NM	NM
Lomas-Soria *et al.*, 2018[c]	rats	46%	142	M	110	↑	NM	NM	NM	NM	NM		NM	NM	NM	NM	NM	NM
Lomas-Soria *et al.*, 2018[d]	rats	46%	142	F	110	↑	NM	NM	NM	NM	NM		NM	NM	NM	NM	NM	NM
Lecoutre *et al.,* 2016[a]	rats	60%	154	M	272	↔	↔	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Lecoutre *et al.,* 2016[b]	rats	60%	154	F	272	↔	↔	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Tsuduki *et al.*, 2016[a]	mice	16%	21	F	21	↔	↑	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Tsuduki *et al.*, 2016[b]	mice	16%	21	F	21	↓	↔	NM		↔	↔	NM	NM	NM	NM	NM	NM	NM
Tsuduki *et al.*, 2016[c]	mice	16%	21	F	77	↑	↑	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Tsuduki *et al.*, 2016[d]	mice	16%	21	F	77	↓	↓	NM	NM	↑	↑	NM	NM	NM	NM	NM	NM	NM
Ito *et al.,* 2016[a]	mice	31%	42	M/F	21	↑	↑	NM	NM	NM	NM	↑	NM	NM	NM	NM	NM	NM
Ito *et al.,* 2016[b]	mice	31%	42	M/F	21	↑		NM	NM	NM	NM		NM	NM	NM	NM	NM	NM
Ito *et al.,* 2016[c]	mice	31%	42	M/F	77	↔	↔	NM	NM	NM	NM		NM	NM	NM	NM	NM	NM

Ito *et al.,* 2016[d]	mice	31%	42	M/F	77	↔	↔	NM	NM	NM	NM	↔	NM	NM	NM	NM	NM	NM
Mousavi *et al*., 2017	mice	45%	42	F	42	↓	↓	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Yokomizo *et al*., 2014[a]	mice	62.20%	42	M	140	↑	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Yokomizo *et al*., 2014[b]	mice	62.20%	42	F	140	↔	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Yokomizo *et al*., 2014[c]	mice	62.20%	42	M	140		NM	NM	NM	NM	NM	NM	↑	NM	NM	NM	NM	NM
Yokomizo *et al*., 2014[d]	mice	62.20%	42	F	140		NM	NM	NM	NM	NM	NM	↔	NM	NM	NM	NM	NM
Zhao *et al.,* 2018[a]	mice	45%	42	M/F	1	↔	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Zhao *et al.,* 2018[b]	mice	45%	42	M	21	↔	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Zhao *et al.,* 2018[c]	mice	45%	42	M	21	↔	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Zhao *et al.,* 2018[d]	mice	45%	42	F	21	↔	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Zhao *et al.,* 2018[e]	mice	45%	42	F	21	↔	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Zheng *et al.,* 2014[a]	mice	58%	42	F	21	↔	↔	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Zheng *et al.,* 2014[b]	mice	58%	42	M	21	↔	↑	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Ashino *et al.,* 2012[c]	mice	45%	49	M	82	↔		NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Chechi *et al.,* 2009[a]	mice	41%	56	M	77	↑	↔	↔	↔	NM	NM	NM	NM	NM	NM	NM	NM	NM
Chechi *et al.,* 2009[b]	mice	41%	56	F	77	↔	↑	↔	↑	NM	NM	NM	NM	NM	NM	NM	NM	NM
Melo *et al*., 2014	mice	46%	63	M	28	↑		NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Kim *et al.,* 2016 [a]	mice	45%	63	M	21	↔	↑	NM	NM	↔	NM	↑	NM	NM	NM	NM	NM	NM
Kim *et al.,* 2016[b]	mice	45%	63	M	21	NM	NM	NM	NM	NM	NM	↑	NM	NM	NM	NM	NM	NM
Umekawa *et al.,* 2015[a]	mice	45%	63	M	1	↔	↔	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Umekawa *et al.,* 201[5b]	mice	45%	63	M	245	↔	↔	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Umekawa *et al.,* 2015[c]	mice	45%	63	M	245	↑	↔	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM

Yu *et al.,* 2013[a]	mice	32%	63	M	98	NM	↑	↑	↑	NM	NM	NM	NM	NM	NM	NM	NM	NM
Yu *et al.,* 2013[b]	mice	32%	63	M	70	NM	↑	↑	↑	NM	NM	NM	NM	NM	NM	NM	NM	NM
Masuyama & Hiramatsu, 2012[a]	mice	62%	70	M/F	84	↑	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Masuyama & Hiramatsu, 2012[b]	mice	62%	70	M/F	168	↑	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Masuyama & Hiramatsu, 2014[a]	mice	62%	70	M	84	↑	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Masuyama & Hiramatsu, 2014[b]	mice	62%	70	F	84	↑	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Masuyama & Hiramatsu, 2014[c]	mice	62%	70	M	168	↑	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Masuyama & Hiramatsu, 2014[d]	mice	62%	70	F	168	↑	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Masuyama *et al.*, 2015[a]	mice	62%	70	F	84	↑	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Masuyama *et al.*, 2015[b]	mice	62%	70	F	168	↑	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Tanaka *et al.*, 2018[a]	mice	62%	70	F	105	↔	↔	NM	NM	NM	NM	↔	NM	NM	NM	NM	NM	NM
Tanaka *et al.*, 2018[b]	mice	62%	70	M	105	↔	↔	NM	NM	NM	NM	↔	NM	NM	NM	NM	NM	NM
Tanaka *et al.*, 2018[c]	mice	62%	70	F	105	↔	↔	NM	NM	↔	NM	NM	NM	NM	NM	NM	NM	NM
Tanaka *et al.*, 2018[d]	mice	62%	70	M	105	↔	↔	NM	NM	↑	NM	NM	NM	NM	NM	NM	NM	NM
Torrens *et al.*, 2012[a]	mice	45%	70	M	105	NM	NM	NM	NM	NM	NM	NM	NM	↑	NM	NM	NM	NM
Torrens *et al.*, 2012[b]	mice	45%	70	M	210	NM	NM	NM	NM	NM	NM	NM	NM	↑	NM	NM	NM	NM
Brenseke *et al.*, 2015	mice	60%	77	F	126	↔	↔	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Tokuza *et al.*, 2009[a]	mice	57.50%	79	M	1	↔	↔	NM	NM	NM	NM	↔	NM	NM	NM	NM	NM	NM
Tokuza *et al.*, 2009[b]	mice	57.50%	79	M	10	↑	↑	NM	NM	NM	NM	↑	NM	NM	NM	NM	NM	NM
Tokuza *et al.*, 2009[c]	mice	57.50%	79	M	21	↑	↑	NM	NM	NM	NM	↑	NM	NM	NM	NM	NM	NM
Tokuza *et al.*, 2009[d]	mice	57.50%	79	M	70	↑	↔	NM	NM	NM	NM	↔	NM	NM	NM	NM	NM	NM
Elahi & Matata, 2017	mice	45%	84	F	168	NM	↑	NM	↑	NM	NM	NM	NM	NM	NM	NM	NM	NM

Elahi *et al.,* 2009[a]	mice	45%	84	M	252	NM	↑	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Elahi *et al.,* 2009[b]	mice	45%	84	F	252	NM	↔	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Glastras *et al*., 2016	mice	43%	84	M	224	NM	NM	NM	NM	NM	NM	NM	↑	NM	NM	NM	NM	NM
Glastras *et al*., 2017[a]	mice	43%	84	M	224	↔	↔	NM	↔	NM	NM	NM	NM	NM	NM	NM	NM	NM
Glastras *et al*., 2017[b]	mice	43%	84	M	224	NM	NM	NM	NM	NM	NM	NM	↑	NM	NM	NM	NM	NM
Bringhenti *et al.,* 2015[a]	mice	49%	98	M	1	↑	NM	NM	NM	NM	NM	NM	NM	NM	↓	↔	↔	NM
Bringhenti *et al.,* 2015[b]	mice	49%	98	M	10	↑	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Bringhenti *et al.,* 2016	mice	49%	102	M	180	↑	↑	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Ornellas *et al*., 2013[a]	mice	49%	105	M	84	↑	↑	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Ornellas *et al*., 2013[b]	mice	49%	105	F	84	↑	↑	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Ornellas *et al*., 2013[c]	mice	49%	105	M	84	↑	↑	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Ornellas *et al*., 2013[d]	mice	49%	105	F	84	↔	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Li *et al*., 2012	mice	60%	132	M	?	↑	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Jungheim *et al.,* 2010[a]	mice	59%	133	M	70	NM	↑	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Jungheim *et al.,* 2010[b]	mice	59%	133	F	70	NM	↔	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Vega *et al*., 2015[a]	mice	46%	141			NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Vega *et al*., 2015[b]	mice	46%	141	M	36	↑	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Vega *et al*., 2015[c]	mice	46%	141	F	36	↔	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM

Abbreviations: TG – Triglycerides; TC – Total cholesterol; HDL – High density lipoprotein cholesterol; LDL – Low density lipoprotein cholesterol; ALT – Alanine transaminase; AST – Aspartate transaminase; MDA – Malondialdehyde ; 8-OHdG – 8-hydroxy-2' -deoxyguanosine; ROS – Reactive oxygen species; SOD – Superoxide dismutase; CAT – Catalase; GPx – Glutathione peroxidase; NM - not measured.

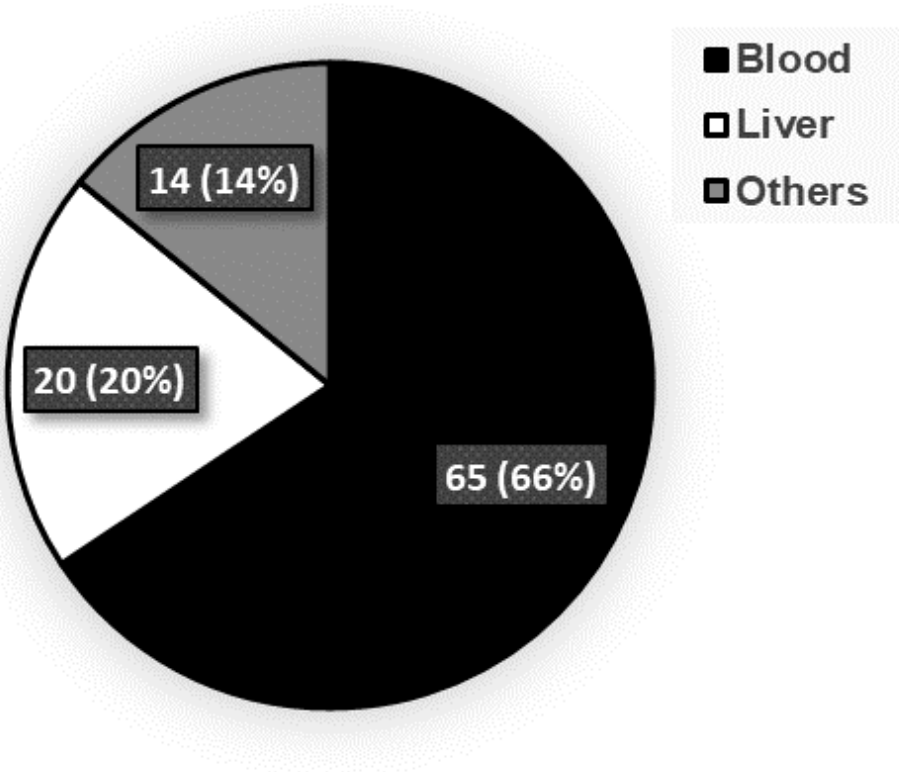

Figure 4. Type of sample used in the studies.

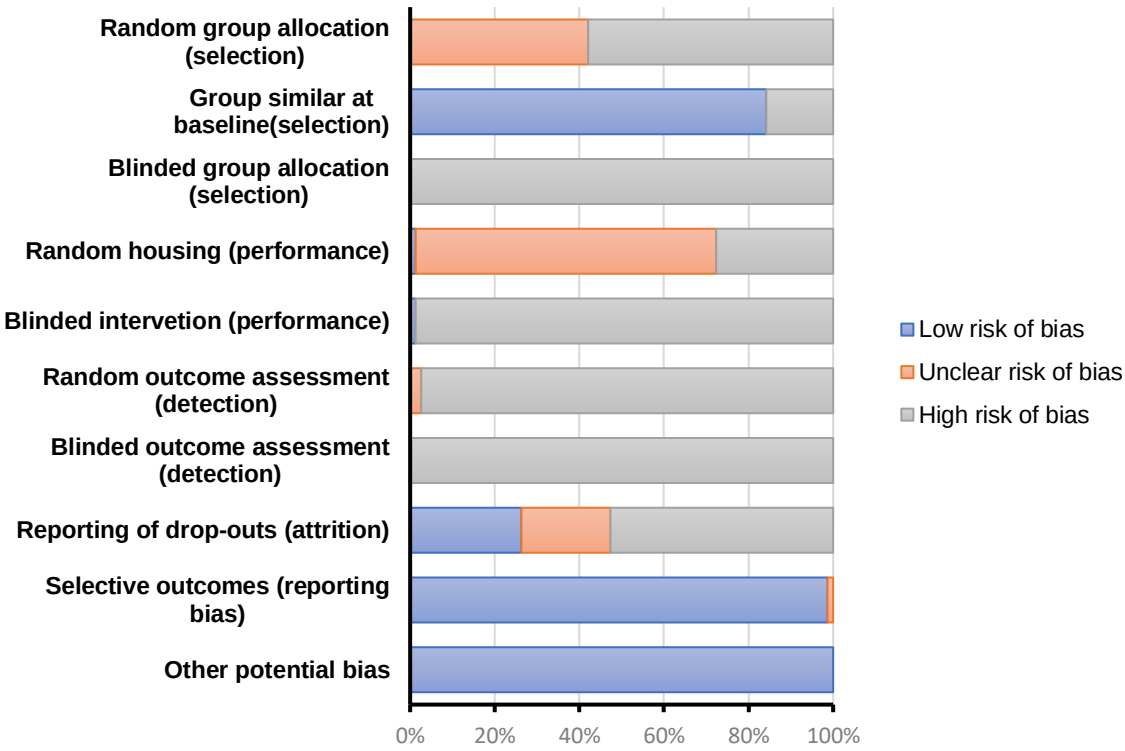

Figure 5. Risk of bias score for each risk item in animal studies, as assessed using the SYRCLE tools.

VII. Appendix S1. Supplementary methods

Database: PubMed (December/13/2018)

_____

(overnutri*[All Fields] OR obes*[All Fields] OR overweight[All Fields] OR overfeed*[All Fields] OR overfed[All Fields] OR high fat[All Fields] OR high-fat[All Fields] OR high-fat diet*[All Fields] OR high fat diet*[All Fields] OR dietary fat[All Fields] OR high fat fed[All Fields]) AND (matern*[All Fields] OR parent*[All Fields] OR perinatal[All Fields] OR prenatal[All Fields] OR gestat*[All Fields] OR fetal*[All Fields] OR fetus[All Fields] OR pregnan*[All Fields] OR offspring*[All Fields] OR progeny[All Fields] OR lactation[All Fields]) AND (offspring*[All Fields] OR litter*[All Fields]) AND (“oxidative stress” [All Fields] OR “lipid peroxidation” [All Fields] OR glutathione[All Fields] OR “glutathione peroxidase” [All Fields] OR catalase[All Fields] OR “superoxide dismutase” [All Fields] OR “superoxide dismutase” [All Fields] OR malondialdehyde[All Fields] OR thiobarbituric[All Fields] OR triglyceride[All Fields] OR triacylglycerol[All Fields] OR cholesterol[All Fields] OR “low density lipoprotein”[All Fields] OR “high density lipoprotein” [All Fields] OR “alanine transaminase” [All Fields] OR “alanine aminotransferase” [All Fields]) AND (rat*[All Fields] OR mice*[All Fields] OR mouse[All Fields] OR rodent*[All Fields])

****

Database: Ovid EMBASE (December/13/2018)

_____

1 (overnutri$ OR obes$ OR overweight OR overfeed$ OR overfed OR high?fat OR high?fat diet$ OR dietary fat OR high?fat fed)
2 (matern$ OR parente$ OR perinatal OR prenatal OR gestat$ OR fetal$ OR fetus OR pregnan$ OR offspring$ OR progeny OR lactation)
3 (offspring$ OR litter$)
4 (oxidative stress OR lipid peroxidation OR glutathione OR glutathione peroxidase OR catalase OR superoxide dismutase OR superoxide dismutase OR malondialdehyde OR thiobarbituric OR triglyceride OR triacylglycerol OR cholesterol OR low density lipoprotein OR high density lipoprotein OR alanine transaminase OR alanine aminotransferase)
5 (rat$ OR mice OR mouse OR rodent$)

****

Database: Web of science (13/12/2018)

_____

TS=(overnutri* OR obes* OR overweight OR overfeed* OR overfed OR high?fat OR high?fat diet* OR dietary fat OR high?fat fed)
TS=(matern* OR parente* OR perinatal OR prenatal OR gestat* OR fetal* OR fetus OR pregnan* OR offspring* OR progeny OR lactation)

TS=(offspring* OR litter*)
TS=(oxidative stress OR lipid peroxidation OR glutathione OR glutathione peroxidase OR catalase OR superoxide dismutase OR superoxide dismutase OR malondialdehyde OR thiobarbituric OR triglyceride OR triacylglycerol OR cholesterol OR low density lipoprotein OR high density lipoprotein OR alanine transaminase OR alanine aminotransferase)
TS=(rat* OR mice OR mouse OR rodent*)

ANEXO 1

unesp
Universidade Estadual Paulista
Faculdade de Medicina de Botucatu

Fone: (14) 3880-1608/3880-1609
E-mail Secretaria:
ceua@fmb.unesp.br/graziela@fmb.unesp.br/sara.sampaio@fmb.unesp.br
Rua: João Buttignoli, s/nº - Distrito Rubião Junior – Botucatu/SP
CEP: 18.618-970

Instituída na Faculdade de Medicina através da Portaria do Diretor nº 30 de 26/04/99

Comissão de Ética no Uso de Animais

Ofício nº 008/2019-CEUA-FMB/UNESP

Botucatu, 07 de janeiro de 2019.

Prezada Senhora,

Conforme apresentado à **Comissão de Ética no Uso de Animais** da Faculdade de Medicina de Botucatu, o Projeto de Pesquisa intitulado: "**Avaliação do perfil lipídico e do estresse oxidativo decorrente do ambiente intrauterino diabético associado à dieta hiperlipídica em roedores: Revisão sistemática**", que será conduzido pela pesquisadora **Rafaianne Queiroz de Moraes Souza**, informo que não há necessidade de parecer Ético por esta Comissão, por trata-se de uma revisão sistemática.

Título: "Avaliação do perfil lipídico e do estresse oxidativo decorrente do ambiente intrauterino diabético associado à dieta hiperlipídica em roedores: Revisão sistemática."
Pesquisador: Rafaianne Queiroz de Moraes Souza
Orientador: Profa. Dra. Débora Cristina Damasceno M. dos Santos
Coorientador: Prof. Ass. Gustavo Tadeu Volpato
Colaborador: Giovana Vesentini

Atenciosamente,

Prof. Ass. Guilherme Antônio Moreira de Barros
Presidente da Comissão de Ética no Uso de Animais
Faculdade de Medicina de Botucatu-UNESP

Ilustríssima Senhora
Profa. Dra. Débora Cristina Damasceno M. dos Santos
Faculdade de Medicina de Botucatu - UNESP

ANEXO 2

unesp UNIVERSIDADE ESTADUAL PAULISTA "JÚLIO DE MESQUITA FILHO" Campus de Botucatu

FMB FACULDADE DE MEDICINA BOTUCATU

Botucatu, 22 de abril de 2019.

Ilmo. Sr.
Prof. Associado Guilherme Antônio Moreira de Barros
DD. Presidente da Comissão de Experimentação no Uso de Animais (CEUA)
Faculdade de Medicina de Botucatu - Unesp

Prezado Presidente,

Gostaria de solicitar de V. Sa. e dos demais membros desta CEUA alteração do título do projeto "Avaliação do perfil lipídico e do estresse oxidativo decorrente do ambiente intrauterino diabético associado à dieta hiperlipídica em roedores: Revisão sistemática", sob responsabilidade de minha aluna de pós-graduação Rafaianne Queiroz de Moraes Souza (Nível: Doutorado), para **"Repercussões bioquímicas e reprodutivas de mães e descendentes após o consumo materno de dieta hiperlipídica em roedores: Revisão Sistemática".** Esta solicitação se deve ao fato de que os membros da banca sugeriram adequação do título frente aos resultados obtidos e a tese corrigida final deverá ser encaminhada à Seção de Pós-graduação com carta de aprovação de alteração do título emitida pela CEUA.

Este projeto teve isenção de análise da referida CEUA (Ofício 008/2019) por se tratar de um trabalho de revisão sistemática. Conta com a minha participação como Orientadora, do Prof. Associado Gustavo Tadeu Volpato (Universidade Federal do Mato Grosso) como Coorientador e Giovana Vesentini como colaboradora.

Certa de contar com sua colaboração, agradeço desde já a atenção dispensada.

Damasceno

Profa. Dra. Débora Cristina Damasceno M Santos
Orientadora

23/04/2019 12:58 0000000 COMITE DE ETICA EM PESQUISA FMB - UNESP

ANEXO 3

Thank you for your submission

Submitted to
Biological Reviews

Manuscript ID
BRV-05-2019-0136

Title
Biochemical and reproductive repercussions of mothers and their offspring after maternal consumption of high-fat diet in rodents: a systematic review

Authors
Souza, Rafaianne
Vesentini, Giovana
Paula , Verônyca
Sinzato, Yuri
Soares, Thaigra
Gelaleti , Rafael
Volpato, Gustavo
Damasceno, Débora

Date Submitted
16-May-2019

Capítulo 3

Submission in International prospective register of systematic reviews - PROSPERO

Animal review

1. * Review title.

Give the working title of the review. This must be in English. The title should have the interventions or exposures being reviewed and the associated health or social problems.

Evaluation of lipid profile and oxidative stress arising from a diabetic intrauterine environment associated with the high fat diet in rodents: Systematic review

2. Original language title.

For reviews in languages other than English, this field should be used to enter the title in the language of the review. This will be displayed together with the English language title.

English

3. * Anticipated or actual start date.

Give the date when the systematic review commenced or is expected to commence.

01/08/2018

4. * Anticipated completion date.

Give the date by which the review is expected to be completed.

01/05/2019

5. * Stage of review at time of this submission.

Indicate the stage of progress of the review by ticking the relevant Started and Completed boxes. Additional information may be added in the free text box provided.

Please note: Reviews that have progressed beyond the point of completing data extraction at the time of initial registration are not eligible for inclusion in PROSPERO. Should evidence of incorrect status and/or completion date being supplied at the time of submission come to light, the content of the PROSPERO record will be removed leaving only the title and named contact details and a statement that inaccuracies in the stage of the review date had been identified.

This field should be updated when any amendments are made to a published record and on completion and publication of the review.

The review has not yet started: No

Review stage	Started	Completed
Preliminary searches	Yes	No
Piloting of the study selection process	Yes	No

Formal screening of search results against eligibility criteria	Yes	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

6. * Named contact.
The named contact acts as the guarantor for the accuracy of the information presented in the register record.
Rafaianne Queiroz de Moraes Souza
Email salutation (e.g. "Dr Smith" or "Joanne") for correspondence:
Ms Queiroz de Moraes Souza

7. * Named contact email.
Enter the electronic mail address of the named contact.
rafaiannequeiroz@hotmail.com

8. * Named contact address.
PLEASE NOTE this information will be published in the PROSPERO record so please do not enter private information
Enter the full postal address for the named contact.
AVENIDA XQD B LT 07- Monte Sinai - Barra do Garças/MT

9. Named contact phone number
Enter the telephone number for the named contact, including international dialling code.
+5566992165629

10. * Organizational affiliation of the review.
Full title of the organizational affiliations for this review and website address if available. This field may be completed as ‘none’ if the review is not affiliated to any organization.
Universidade Estadual Paulista
Organization web address:
http://www.unesp.br/

11. * Review team members and their organizational affiliations.
Give the title, first name and last name of all members of the team working directly on the review. Give the organizational affiliations of each member of the review team.
Ms Rafaianne Queiroz de Moraes Souza. Universidade Estadual Paulista, Botucatu, SP, Brazil
Miss Giovana Vesentini. Universidade Estadual Paulista, Botucatu, SP, Brazil
Miss Verônyca Gonçalves Paula. Universidade Estadual Paulista, Botucatu,

SP, Brazil
Dr Yuri Karen Sinzato. Universidade Estadual Paulista, Botucatu, SP, Brazil
Ms Thaigra de Sousa Soares. Universidade Estadual Paulista, Botucatu, SP, Brazil
Dr Rafael Bottaro Gelaleti. Universidade Estadual Paulista, Botucatu, SP, Brazil
Dr Gustavo Tadeu Volpato. Universidade Federal de Mato Grosso, Barra do Garças, MT, Brasil
Dr Débora Damasceno. Universidade Estadual Paulista, Botucatu, SP, Brazil

12. * Funding sources/sponsors.
Give details of the individuals, organizations, groups or other legal entities who take responsibility for initiating, managing, sponsoring and/or financing the review. Any unique identification numbers assigned to the review by the individuals or bodies listed should be included.
FAPESP / Brasil (Process Number 2016/25207-5)

13. * Conflicts of interest.
List any conditions that could lead to actual or perceived undue influence on judgements concerning the main topic investigated in the review.
None

14. Collaborators.
Give the name, affiliation and role of any individuals or organizations who are working on the review but who are not listed as review team members.

15. * Review question.
Give details of the question to be addressed by the review, clearly and precisely.
• Does the type of high fat diet can predict impaired outcomes of lipidic profile and oxidative stress for pregnant rodents?
• Which outcomes of oxidative stress can be expected of the offspring from these dams?
• What type of HFD is similar to the human obesity model in pregnant rodents
• What are the markers (lipid profile and oxidative stress) that can identify this model?

Context and rationale
Research involving appropriate experimental models is necessary because of limitations in the human species, not only for
ethical reasons, but also because of uncontrollable variables. In addition,

they allow the differentiation between genetic and
environmental factors and the interaction between the two factors. Therefore, we performed a systematic review of animal
models (rodents) that were exposed to the high fat diet during pregnancy, to investigate the diet models used in the
research and the effects for offspring. This review reports the maternal and offspring outcomes in an effort to identify
possible relationships to facilitate and focus on future research.

16. * Searches.
Give details of the sources to be searched, and any restrictions (e.g. language or publication period). The full search strategy is not required but may be supplied as a link or attachment.
The searched will be carried out in the following databases: PubMed, EMBASE, Web of Science. PubMed search terms and keywords will be adapted for all other databases. The searches will be restricted to studies on rodents that were published in English-language

17. URL to search strategy.
Give a link to the search strategy or an example of a search strategy for a specific database if available (including the keywords that will be used in the search strategies).
Do not make this file publicly available until the review is complete.

18. * Human disease modelled.
Give a short description of the disease, condition or healthcare domain being modelled.
Obesity

19. * Animals/population.
Give summary criteria for the animals being studied by the review, e.g. species, sex, details of disease model. Please include details of both inclusion and exclusion criteria.
Inclusion criteria: All rodent models
Exclusion criteria: Non-rodents, animals spontaneously obese, genetically modified, *ex vivo*, *in vitro* and studies involving human subjects.

20. * Intervention(s), exposure(s).
Give full and clear descriptions of the nature of the interventions or the exposures to be reviewed (e.g. dosage, timing, frequency). Please include details of both inclusion and exclusion criteria.
Inclusion criteria: Studies on rodents where dams were subjected to a HFD around gestation (before and/or during whole or any part of

pregnancy), lactation or postweaning period. HFD will be considered chow-based HFD from any fat type.
Exclusion criteria: Custom-made diet (i.e. cafeteria) high-fibre diet, high-calorie diet, high-glucose diet, low-fat diet. in short, any other diet
than non-high-fat diet.

21. * Comparator(s)/control.
Where relevant, give details of the type(s) of control interventions against which the experimental condition(s) will be compared (e.g. another intervention or a non-exposed control group). Please include details of both inclusion and exclusion criteria.
Inclusion criteria: Dams that were fed standard diet
Exclusion criteria: Dams and offspring that were subjected to nutritional manipulation (surgery, drugs, stress and exercise)

22. * Study designs to be included.
Give details of the study designs eligible for inclusion in the review. If there are no restrictions on the types of study design eligible for inclusion, or certain study types are excluded, this should be stated. Please include details of both inclusion and exclusion criteria.
Inclusion criteria: Controlled animal studies with a control group
Exclusion criteria: Reviews, meta-analysis, poster presentations, conference abstracts, human studies

23. Other selection criteria or limitations applied.
Give details of any other inclusion and exclusion criteria, e.g. publication types (reviews, conference abstracts), publication date, or language restrictions.
Studies that are not published in English language

24. * Outcome measure(s).
Give detail of the outcome measures to be considered for inclusion in the review. Please include details of both inclusion and exclusion criteria.
Inclusion criteria:
Primary outcomes:
The primary outcomes will be lipid profile and oxidative stress of the dams.
Lipidic profile
• Triglyceride concentrations
• Cholesterol concentrations
• High-density lipoprotein (HDL) concentrations
• Low-density lipoprotein (LDL) concentrations
• ALT activity
• AST activity

Secondary outcomes will be oxidative stress and offspring and reproductive outcomes.
Oxidative stress
•MDA/TBARS (lipid oxidation)
•SOD activity
•CAT
•GPx
•8-OHdG (DNA oxidation)
• Eliminação de oxidantes
• ERO
• Reproductive outcomes
•Litter size
•Maternal weight
• Offspring weight
Exclusion criteria: Any other outcome that is not as quoted in the inclusion criterion item above.

25. N/A
This question does not apply to systematic reviews of animal studies for human health submissions.

26. * Study selection and data extraction.
Procedure for study selection
Two authors will independently screen titles and abstracts followed by full-text analysis that meet inclusion criteria. The same two authors will then use standardized data extraction form and the relevant study information will be extract into a database. Conflicts in screening or data extraction process will be resolved by discussion or third party

Prioritize the exclusion criteria
Title, abstract screening and full-text analysis- 1) Not an animal study; 2) Not appropriate intervention; 3) Not appropriate control/placebo; 4) Not appropriate outcome; 5) Not appropriate study: Not an original full research paper (e.g. review, editorial, conference abstract) Not appropriate intervention.

Methods for data extraction
Two reviewers will independently extract data from each article, study eligibility, study design, animal characteristics, intervention and control details, and outcomes. A data extraction form will be developed in a Microsoft Excel database before data collection to enable two authors to independently extract information from tables and text. Conflicts in the data extraction process will be resolved by discussion or referral to a third-party decision.

Data to be extracted: animal model
Rodent strain, age, weight, offspring sex and diet type and length of exposure.

Data to be extracted: intervention of interest
Diet composition of the diet, fat type, period of supplementation and intervention used in the control group.

Data to be extracted: primary outcome(s)
Lipidic profile (continuous data)
• Triglyceride concentrations expressed in: mmol/L, µg/mg, µmol⁄g, mg/dL, g/dL, g/g, nmol/g, mg/g, mg/ml, mM and g/l.
• Cholesterol concentrations expressed in: mmol/L, g/l, mg/dL, g/dL, mM, mg/ml, µmol⁄g and µg/uL.
• High-density lipoprotein (HDL) concentrations expressed in: mmol/L and mM.
• Low-density lipoprotein (LDL) concentrations expressed in: mmol/L and mM.
• ALT activity expressed in: IU/L and µ/L.
• AST activity expressed in: IU/L and µ/L.

Data to be extracted: secondary outcome(s)
NA

Data to be extracted: other
Author, year, biological material analyzed.

27. * Risk of bias and/or quality assessment.
State whether and how risk of bias and/or study quality will be assessed. Assessment tools specific for pre-clinical animal studies include SYRCLE's risk of bias tool and the CAMARADES checklist for study quality
By use of SYRCLE's risk of bias tool adapted as follows: Yes
Method for risk of bias and/or quality assessment
Included studies will be assessed using SYRCLE's risk of bias tool independently by two reviewers and any discrepancies will be solved by discussion. We will not exclude studies based on high risk of bias.

28. * Strategy for data synthesis.
Planned approach
We will provide a qualitative analysis in the form of a critical interpretive synthesis of the available evidence on animal/subgroups, type of interventions and content, type comparators and outcomes.
Effect measure

NA
Effect models
NA
Heterogeneity
NA
Other
NA

29. * Analysis of subgroups or subsets.
Subgroup analyses
If the necessary data are available, subgroup analyses will be done for the following categories:
- High fat Diet composition
- Fetal development according to maternal nutrition

Sensitivity
no sensitivity analyses are planned at this time

Publication bias
no publication assessment are planned at this time

30. * Review type.
Type of review: Experimental animal exposure review

31. Language.
Select each country individually to add it to the list below, use the bin icon to remove any added in error. There is an English language summary.
English

32. Country.
Select the country in which the review is being carried out from the drop down list. For multi-national collaborations select all the countries involved.
Brazil

33. Other registration details.
List other places where the systematic review protocol is registered. The name of the organization and any unique
identification number assigned to the review by that organization should be included.

34. Reference and/or URL for published protocol.
Give the citation and link for the published protocol, if there is one.
No, I do not make this file publicly available until the review is complete

35. Dissemination plans.
Give brief details of plans for communicating essential messages from the review to the appropriate audiences. Do you intend to publish the review on completion?
Yes

36. * Keywords.
Animals, high fat diet, gestation, weight, biochemical parameters (Biomarkers)

37. Details of any existing review of the same topic by the same authors.
Give details of earlier versions of the systematic review if an update of an existing review is being registered, including full bibliographic reference if possible.

38. * Current review status.
Review status should be updated when the review is completed and when it is published.
Review_Ongoing

39. Any additional information.
Provide any further information the review team consider relevant to the registration of the review.

40. Details of final report/publication(s).
This field should be left empty until details of the completed review are available. Give the full citation for the final report or
publication of the systematic review.

PROSPERO registration mensagem

Dear Ms Queiroz de Moraes Souza,

Thank you for submitting details of your systematic review protocol "Evaluation of lipid profile and oxidative stress arising from a diabetic intrauterine environment associated with the high fat diet in rodents: Systematic review" to PROSPERO. We are pleased to confirm that your protocol will be published in the register within the next hour.

Your registration number is: CRD42019120418

You are free to update the record at any time, all submitted changes will be displayed as the latest version, with previous versions available to public view. Please also give brief details of the key changes in the Revision notes facility. You can log in to PROSPERO and access your records at https://nam04.safelinks.protection.outlook.com/?url=https%3A%2F%2Fwww.crd.york.ac.uk%2FPROSPERO&data=02%7C01%7C%7C4b9b473b3be745e7ee2c08d6a3cdd0eb%7C84df9e7fe9f640afb435aaaaaaaaaaaa%7C1%7C0%7C636876501700537039&sdata=Hrkj%2FvtccOEDpXJXGMPhokIiXtVSigUg0XFktHNLoa0%3D&reserved=0

Comments and feedback on your experience of registering with PROSPERO are welcome at: crd-register@york.ac.uk

Best wishes for the successful completion of your review.

Yours sincerely,
Carlijn hooijmans
PROSPERO Administrator
e: CRD-register-2@york.ac.uk

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