U.PORTO

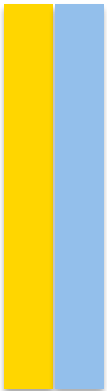
MESTRADO INTEGRADO EM MEDICINA

Maternal Obesity and Risk of Congenital Heart Defects

Helena Vieira Meneses

M

2025



Agradecimentos

Com a tão esperada conclusão desta etapa quero, antes de mais, agradecer aos meus pais: à minha mãe, que me ensinou a ser determinada, corajosa e assertiva, e ao meu pai que me transmitiu o seu empenho, a sensação de missão, a ser "visionária e pragmática". Estou grata pela vossa resiliência e por sempre terem apostado na minha formação, sem mãos a medir. Agradeço aos meus irmãos, que me mostraram (e mostram) como levar a vida com sentido de humor, com companheirismo e confiança. A toda a minha família, que está sempre presente nos momentos fundamentais, obrigada pela fé, carinho, orgulho e motivação.

Quero ainda reconhecer o meu namorado, que sempre me impulsiona, me inspira, me transmite segurança e partilha a minha felicidade; e os meus amigos: os que o ICBAS me apresentou, que foram a minha força motriz destes seis árduos anos e que orgulhosamente levo para vida e os que Espinho me deu, amizades genuínas e duradouras, com quem sempre pude e poderei contar.

Finalmente, um agradecimento especial ao meu orientador, Professor Doutor Luís Guedes-Martins, cuja ética profissional e proatividade faz transparecer a paixão pelo seu trabalho. É, sem dúvida, um exemplo de sucesso e ambição, que admiro, bem como um exemplo enquanto pessoa, médico e docente. Dito isto, agradeço a sua disponibilidade, o seu entusiasmo, incentivo, apoio e confiança ao longo da realização deste artigo.

Obesidade Materna e o Risco de Malformações Cardíacas Congénitas

Artigo de Revisão Bibliográfica

Dissertação de candidatura ao grau de Mestre em Medicina, submetida ao Instituto de Ciências Biomédicas Abel Salazar da Universidade do Porto

Helena Vieira Meneses

Aluna do 6º ano, ano profissionalizante do MIM

Endereço de Correio Eletrónico: helena.v.meneses@hotmail.com

Contacto Telefónico: +351 913901006

Afiliação: Instituto de Ciências Biomédicas Abel Salazar (ICBAS), Universidade do Porto; Centro de Medicina Fetal, Medicina Fetal Porto - Centro Materno Infantil do Norte.

Endereço: ICBAS – Rua de Jorge Viterbo Ferreira nº 228, 4050-313, Porto

Orientador: Professor Doutor Luís Guedes-Martins

Unidade Local de Saúde de Santo António EPE, Centro Materno Infantil do Norte, Serviço de Obstetrícia, Departamento da Mulher e da Medicina Reprodutiva;

Centro de Medicina Fetal, Medicina Fetal Porto – CMIN;

Unidade de Investigação e Formação – CMIN;

Instituto de Ciências Biomédicas Abel Salazar, Universidade do Porto;

Instituto de Investigação e Inovação em Saúde, Universidade do Porto.

Endereço de Correio Eletrónico: luis.guedes.martins@gmail.com

Jornal | Journal: Current Cardiology Reviews, Bentham Science Publishers B.V.

Junho de 2025, Porto

Title: Maternal Obesity and Risk of Congenital Heart Defects.

Authors:

Helena Meneses 1,2*, L. Guedes-Martins1,2,3,4,5

Affiliations:

1Instituto de Ciências Biomédicas Abel Salazar, University of Porto, 4050-313 Porto, Portugal

2Centro de Medicina Fetal, Medicina Fetal Porto - Centro Materno Infantil do Norte, 4099-001 Porto, Portugal

3Unidade Local de Saúde de Santo António EPE, Centro Materno Infantil do Norte, Serviço de Obstetrícia, Departamento da Mulher e da Medicina Reprodutiva, Largo Prof. Abel Salazar, 4099-001 Porto, Portugal

4Unidade de Investigação e Formação – Centro Materno Infantil do Norte, 4099-001 Porto, Portugal

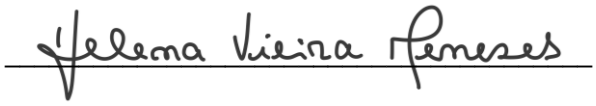
5Instituto de Investigação e Inovação em Saúde, Universidade do Porto, 4200-319 Portugal

*** Corresponding author's e-mail:** helena.v.meneses@hotmail.com (Tel: +351913901006)

Running head: Obesity and congenital heart defects.

Conflicts of interest: None declared.

Manuscript word, table and figure count: 13700 Words of body text (including abstract) and 5 Figures.



(Helena Vieira Meneses)

(Prof. Dr. Luís Guedes-Martins)

Índice | Index

Lista de Figuras | Figure List

List of Abbreviations

APM1 – Adipose Most Abundant Gene Transcript 1
ASD – Atrial Septal Defect
AVSD – Atrioventricular Septal Defects
BMI – Body Mass Index
BMP – Bone Morphogenetic Protein
CHD – Congenital Heart Defects
CoA – Coarctation of the Aorta
CRP – C-Reactive Protein
CV – Cardiovascular
DC – Dendritic Cells
DM – Diabetes Mellitus
EUROCAT – European Surveillance of Congenital Anomalies and Twins
FFA – Free Fatty Acids
GWG – Gestational Weight Gain
HLA – Human Leukocyte Antigen
HLHS – Hypoplastic Left Heart Syndrome
HMW – High Molecular Weight Adiponectin
HRHS – Hypoplastic Right Heart Syndrome
IFN-γ – Interferon Gamma
IGF-1 – Insulin-like Growth Factor 1
IL – Interleukin
IL-1Rα – Interleukin-1 Receptor Antagonist
IUGR – Intrauterine Growth Restriction
Kg – Kilograms
LGA – Large for Gestational Age
LVOTO – Left Ventricular Outflow Tract Obstruction
MCP-1 – Monocyte Chemoattractant Protein 1
M-CSF – Macrophage Colony-Stimulating Factor
MDA – Malondialdehyde
MIP-1α - Macrophage Inflammatory Protein 1α
mtDNA – Mitochondrial DNA
NICU – Neonatal Intensive Care Unit
NK cells – Natural Killer Cells
NO – Nitric Oxide
PDA – Patent *Ductus Arteriosus*
ROS – Reactive Oxygen Species
SGA – Small for Gestational Age
SNRI – Serotonin-Norepinephrine Reuptake Inhibitor
SRF – Serum Response Factor
SSRI – Selective Serotonin Reuptake Inhibitor
TGA – Transposition of the Great Arteries
TGF-β – Transforming Growth Factor β
Th – CD4+ T helper cells
TNF-α – Tumor Necrosis Factor α
ToF – Tetralogy of Fallot
TRAIL – TNF-related Apoptosis-Inducing Ligand
Treg – Regulatory T Cells
uNK – Uterine Natural Killer cells
US – Ultrasound
USA – United States of America
UVH – Univentricular Heart
VEGF – Vascular Endothelial Growth Factor
VSD – Ventricular Septal Defect
βhCG – β Human Chorionic Gonadotropin

Abstract

Congenital heart defects are the most common malformations in newborns and the leading cause of morbimortality due to congenital abnormalities. Being a result of genetic susceptibility and environmental exposure, a portion of these anomalies could be preventable by managing modifiable risk factors. Given that maternal obesity is a predisposing factor for obstetric and fetal complications, this review aims to explore its association with congenital heart disease, while addressing mechanisms underlying its pathophysiology at cellular and molecular levels. For this purpose, a series of searches were carried out on the PubMed database and additional articles were identified via citation search. This review highlights the role of placental dysfunction, pro-inflammatory state, systemic oxidative stress and adiponectin decrease, brought on by maternal obesity, in the disruption of fetal cardiac development and consequent occurrence of congenital heart disease. Overall, obesity seems to impair essential cellular processes involved in cardiogenesis, inflicting long-lasting damage to fetal cells. Literature remains inconsistent regarding the role of confounding factors such as gestational weight gain, gestational diabetes and maternal diet. Further investigation is needed concerning pre-conceptional and gestational prevention and management strategies suited for these mothers.

Keywords: Congenital heart defects, fetal cardiac development, maternal obesity, placental dysfunction, inflammation, oxidative stress, adiponectin, diagnosis, prevention.

Resumo

As malformações cardíacas congénitas são as anomalias mais comuns nos recém-nascidos e representam a principal causa de morbimortalidade associada a doenças congénitas. Uma vez que resultam da interação entre suscetibilidade genética e exposição ambiental, uma parte destas anomalias poderá ser prevenida pelo controlo de fatores de risco modificáveis. Tendo em conta que a obesidade materna é um fator predisponente para complicações obstétricas e fetais, esta revisão tem como objetivo explorar a sua associação com as malformações cardíacas congénitas, abordando os mecanismos subjacentes à sua fisiopatologia a nível celular e molecular. Para tal, foram realizadas múltiplas pesquisas na base de dados PubMed e identificados artigos adicionais através de pesquisa por citações. Esta revisão destaca o papel da disfunção placentária, do estado pró-inflamatório, do stress oxidativo e da redução da adiponectina, induzidos pela obesidade materna, na disrupção do desenvolvimento cardíaco fetal e consequente ocorrência de malformações cardíacas. De forma geral, a obesidade parece comprometer processos celulares essenciais na cardiogénese e causar insultos duradouros nas células fetais. A literatura permanece inconsistente quanto ao papel de fatores confundidores, como o ganho ponderal gestacional, a diabetes gestacional e a dieta materna. É crucial apostar na investigação de estratégias de prevenção e acompanhamento, tanto no período pré-concecional como durante a gravidez, adequadas a estas mulheres.

Palavras-chave: Malformações cardíacas congénitas, desenvolvimento cardíaco fetal, obesidade materna, disfunção placentária, inflamação, stress oxidativo, adiponectina, diagnóstico, prevenção.

Introduction

Currently, congenital heart defects (CHD) constitute the leading group of malformations in newborns worldwide with an estimated prevalence of 6-10 in 1.000 live births (with a geographical variance) [1, 2]. Likewise, in Portugal the prevalence is 8,3 in 1.000 live births [3].

These CHD are the main cause of infant mortality due to congenital abnormalities as well as overall perinatal mortality [2, 4], also causing high morbidity and need of surgical procedures early in life, with a high burden of medical expenses [5]. Nowadays, due to the evolution in identification and treatment of these conditions, most of these patients reach older stages in life, yet with a remarkably high cost in terms of quality of life [2]. In addition, some studies state that these cases are increasing, however in others they appear to be decreasing, and this disparity may be due to innovation of therapeutics or to diagnostic techniques and subsequent termination of pregnancies [2, 6].

In fact, CHD are defined by a functional or structural malformation of the heart or great blood vessels, developed during gestation [2]. They have various levels of severity and can appear by themselves or combined, noting that the most common are atrioventricular septal defects (AVSD), coarctation of the aorta (CoA), transposition of the great arteries (TGA), tetralogy of Fallot (ToF) and univentricular heart (UVH) [7]. In Portugal the more frequently seen are ventricular septal defects (VSD), followed by atrial septal defects (ASD), CoA, ToF and pulmonary stenosis [3]. Furthermore, they can be diagnosed from the prenatal or neonatal period until later in childhood [8]. Besides, in the last 20 years, there has been an increase in CHD discovered prenatally, which adds even more weight to this problem once the numbers of terminated pregnancies are also taken into account [7].

Despite being unclear, the pathophysiology of these anomalies is believed to result from an interplay of genetic and environmental agents [8]. Even with an incomplete comprehension of the etiology of these diseases, there are some maternal risk factors with well-established associations with CHD, for example: maternal age (over 35 years), chronic diseases (such as diabetes mellitus), teratogenic medications or drugs, multiparous mothers (over three births), multi-fetal pregnancies, infections (such as rubella) and smoking while pregnant [1, 5, 7]. The difference in prevalence in certain regions of the globe may also point to the influence of pollution or to the limited access to medical services and to antenatal ultrasounds [5].

Additionally, the frequence of CHD is higher in children of overweight or obese mothers, compared to other recognized maternal factors, yet the relation between these heart defects and maternal body mass index (BMI) is not fully understood [8].

On the other hand, obesity (BMI $\geq$ 30 kg/m^2) is a very prevalent disease that keeps increasing in our society, affecting more and more women of reproductive age with an estimate of about 40% of obese women in the 20 - 39 age bracket [7]. In Portugal, a study conducted in 2016 determined that approximately 21% of women above 18 years old were obese. This condition's etiology is intricate and multifactorial, involving the disruption of hormonal balance and causing many changes in the normal physiology of the organism [9].

When it comes to gestational obesity, it affects significantly both generations by posing risks for short-term and long-term complications: exemplifying, the mother has a higher risk of pregnancy and peripartum complications (like gestational diabetes, preeclampsia, sepsis) and of maintaining cardiovascular (CV) diseases for life (like hypertension), as well as the offspring may suffer from difficulties at birth and has higher chances of

numerous developmental abnormalities [4,10]. In fact, some studies suggest that there is a dose-effect association between changes in interpregnancy BMI and fetal malformations and adverse perinatal outcomes [7]. It must also be noted that the large adipose panicle will limit the visibility of the transabdominal ultrasound, making it more difficult to detect fine abnormalities simply by this method; however, this can be compensated by combining a transvaginal approach [11].

Therefore, since maternal obesity may be a potentially modifiable factor, preventing it can enable the reduction of these malformations. Hence, it is relevant to seek a better understanding of the link between maternal high BMI and CHD [4]. Having that in mind, this review will focus on the teratogenic effect caused by this maternal condition, looking for a pathophysiological connection or a molecular explanation.

Methods

For this review to be constructed it was used the PubMed database, optimizing the search by using the most relevant keywords, such as “gestational obesity” and “congenital malformations”, and MeSH terms, namely “Obesity, Maternal" and "Heart Defects, Congenital", by themselves and in combination. This search was assisted by PubMed’s Advanced Search Builder and was limited to English-language articles published since 1995. Additionally, some articles were identified via citation search. The first search took place in September 2024 and the last was in May 2025. After obtaining the literature needed, it was submitted to thorough selection. Firstly, by examining the title and abstracts of the publications, excluding the ones that did not reflect the theme of this review. Then the full text was read, and the articles were finally included based on their quality and relevance regarding the objective being studied. This process is documented according to the PRISMA 2020 guidelines (Fig.1).

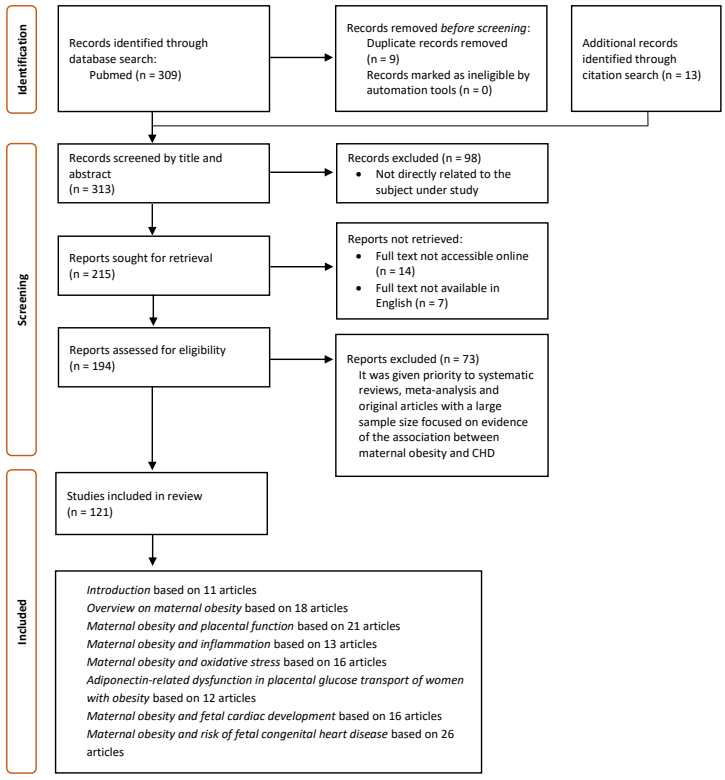


Figure 1. **Search results flowchart according to PRISMA 2020 guidelines**

Maternal obesity – an overview

Maternal obesity is a term used to describe pregnancies in women with a BMI of 30 kg/m^2 or more. In fact, BMI (weight in kg divided by the square of height in meters) is a measure to objectively assess how body weight will affect health [12], being the gold standard to define obesity. In this situation, it is usually calculated using the pre-pregnancy weight and height, if these are unknown, they can be measured at the first prenatal consultation [13], usually and ideally in the first trimester [14].

The percentage of obesity in women of child-bearing age continues to increase, representing a worldwide concern, especially in developed and industrialized countries [15]. Studies point that in the USA more than half of pregnancies have a BMI above the considered normal weight [16](overweight: 25 to 29,9 kg/m^2; obese: 30 to 39,9 kg/m^2; morbid obesity or class III: 40 to 49,9 kg/m^2; superobese: ≥ 50 kg/m^2 [17]) and about 8% of women in reproductive age are morbidly obese. In fact, many women who are obese or overweight do not perceive themselves as such, which can be a contributing factor to the high number of obese pregnancies, since no effort is made to lose weight before conception [16]. Moreover, approximately 60% of obese gravidas gain more gestational weight (GWG) than what is considered healthy. To clarify, there is pre-pregnancy obesity, which is the most common and the main focus of this review, and/or a woman can become excessively heavy during gestation due to exaggerated GWG [18], however both of these conditions have similar or overlapping outcomes and their biological consequences and pathways have been difficult to differentiate [16].

Notably, it has been proven that maternal obesity poses a high risk of complications for the mother such as hypertensive disorders (eclampsia, preeclampsia, gestational hypertension), gestational diabetes mellitus (DM) (risk about three times higher), cardiovascular events (for example infarction, stroke, arrhythmias), thromboembolic events, difficulties in labor and delivery (like the need for cesarean section, amniotomy, augmentation, anesthesia complications, hemorrhage, impaired wound healing, infections and longer hospitalization) [13,16], overall increased maternal morbimortality [14], breastfeeding issues [16], among others. Furthermore, there is a strong likelihood of future or long-time conditions such as coronary heart disease, cerebrovascular disease, metabolic syndrome (about two times more risk to develop type 2 DM later in life), chronic hypertension and more years of life potentially lost [19].

When it comes to offspring, it is shown in numerous studies that maternal obesity has both a negative impact at birth as well as teratogenic effects [15]. In fact, it increases the chances of miscarriages [16], stillbirths, hydramnios, intrauterine growth restriction (IUGR), macrosomia, large for gestational age (LGA) as well as SGA, excessive neonatal adiposity, dystocia, lower APGAR scores, required resuscitation measures at delivery, birth trauma and so forth. Likewise, there is a strong association to congenital malformations, the most frequent being neural tube defects and cardiovascular defects, followed by orofacial clefts, hydrocephaly, rectal or anorectal atresia, hypospadias, anomalies of the ventral wall, and such others [10, 20, 21, 22]. Understandably, there is a greater need for neonatal intensive care (NICU) for infants of obese mothers when compared to normal weight pregnancies [23] (approximately 3,5 times more NICU admissions [12]). In a long-term point of view, maternal obesity increases the chances of infantile disrupted cardiometabolic status [19] with effects such as early obesity and metabolic syndrome, type 2 DM, CV diseases as well as neoplasms, osteoporosis, neurodevelopmental delay [10], and asthma [18]. According to the “Barker’s hypothesis”, the adverse environment in utero and the mother’s

nutritional status will influence embryogenesis and organogenesis, leaving an indelible mark on the offspring's organ structure and systems [24].

As can be seen, the consequences are vast and affect both mother and child, as well as in a short- and long-term manner [10]. Therefore, and because of the markedly high prevalence of this condition, many studies have taken place to explore these associations and understand the pathophysiology behind maternal obesity.

Firstly, it is crucial to understand that pregnancy is a tremendously dynamic period in which the female body goes through extreme changes in hormonal, physical and humoral levels that aim to provide the best environment for the fetus to grow [15]. The pregnant body adapts its composition (proliferation and hypertrophy of uterus and breast tissues, increase of cardiac output, volemia expands, reduction of blood pressure, respiratory work increases, etc.) and metabolic basal rate [24, 25]. It is also relevant to note that gestation on its own provokes a complex rearrangement of the endocrine homeostasis, promoting a diabetogenic status and an increase in circulating free fatty acids (FFA) [24].

Diving into obesity, it is mostly an excess in adiposity, which leads to anatomical and metabolic constraints [15]. Expressed simply, the pathophysiological mechanism that explains the onset of obesity is a disturbance in the equilibrium between food intake and its output as energy according to a certain metabolic rate and influenced by an interplay between genetic predisposition, epigenetic changes and environment – for this reason there can be weight changes due to the slightest imbalance –, hence obesity's etiology may range from eating disorders to grave hormonal issues [9, 12, 15].

The adipose tissue can be distributed subcutaneously or can be confined in the abdomen, which configures the visceral deposit. The latter is the most concerning, causing higher insulin resistance (higher postprandial insulin in about 50 to 60% compared to normal physiological levels [26]) and consequently overproduction of FFA, lipoproteins and higher levels of leptin. Thus, this disorder is associated with hyperglycemia (independently of the presence of DM), dyslipidemia, a pro-thromboembolic state [20, 18, 27], disturbances of the immune system, microbiome and other hormonal axis [16]. Adipocytes are responsible for these phenomena since they secrete inflammatory mediators, proteins and cytokines (like TNFα and IL-1) and inhibit the adiponectin production [18, 19], generating a chronic systemic inflammatory state that is characterized by the rising of acute-phase proteins and oxidative stress, eventually damaging cells and several tissues [23].

Henceforth, these alterations are equally present in pregnant obese women. This means that they exhibit, when compared to a normal pregnancy, higher serum glucose and concentrations of insulin, molecules that can go through the placenta. Additionally, obese women's levels of adiponectin are lower and this has a direct effect on the placenta: even more insulin resistance as well as higher transport of nutrients to the fetus [20]. Similarly, on a molecular scale there is a display of pro-inflammatory cytokines in the placental tissue [16] and reactive oxygen species (ROS) caused by the chronic state of inflammation, resulting in endothelial damage and even greater compromise of placental activity. This way, the effect of the superimposed insulin resistance, that obesity causes on pregnancy, will jeopardize the growth of the fetoplacental unit and its gene expression – which is a major cause of its display of inflammatory mediators along with the systemic pro-inflammatory state. Likewise, obese pregnancy is linked to lipotoxicity as another possible pathway to influence offspring's development in utero.

Also worth highlighting that the first two months of gestation is probably the most important time window of the interaction with maternal metabolism. In fact, the first trimester fetus does not secrete insulin autonomously, being fully exposed to hyperglycemia.

Notably, some possible pathways that explain this causality are disruptions on cell migration and differentiation, a boost of apoptosis, impairment of autophagy and ultimately disruption of organogenesis due to this excessive exposure and transport of nutrients through the placenta – mainly glucose [27]. When it comes to lipotoxicity, it results from the reaction between FFA and ROS that produces oxidized lipids, which are cytotoxic and capable of influencing gene expression. This way, lipotoxicity can affect placental and fetal development [28]. Additionally, insulin and leptin are elevated and can act as growth factors, this way increasing progesterone levels, which can imperil oocyte's maturation and quality. This means that maternal obesity may have an impact on placentation and on embryogenesis since the periconception period [18]. Under these circumstances, it is clear that the fetus in utero will be affected by the mother's metabolic and biochemical derangement [23], and given that obesity is an increasingly common reality, there are many hypotheses and studies taking place to unravel these molecular pathways [16].

Finally, another aspect to take into consideration when discussing obesity's impact on pregnancy is the decreasing quality of ultrasound (US) imaging with the rising of the BMI, knowing that this technique is the cornerstone of prenatal surveillance and screening. Numerous studies show that there is an unsatisfactory sonographic visualization of structural anomalies in the presence of adipose tissue, that is an echogenic structure, therefore the US beam must go through a greater depth of tissue that is going to attenuate it and diminish the resolution of the resulting image. Besides, the inability of the patient to lie in an adequate position also interferes with the quality of this exam.

Naturally, the outcomes of these constraints are improper diagnosis, longer duration of the US, repeated examinations and the need for more refined imaging techniques. In fact, the measurement of nuchal translucency and assessment of the nasal bone is also impaired and the most difficult structures to evaluate are the heart and spine [17] (about 37,3% of suboptimal US visualization in obese women [21]). In order to compensate for this obstacle, it can be performed a fetal MRI – especially when there is a need to better describe an apparent anomaly –, transvaginal ultrasound – depending on the fetus' position – or 3D or 4D imaging techniques. Some studies point that monitoring should be more rigorous in these cases, with an early echocardiography [29] and more frequent US imaging [17]. In this regard, some authors argue that these pregnancies should be classified as high-risk, highlighting the importance of a frequent cardiac ultrasound monitoring in order to detect impactful malfunctions as soon as possible [20].

Similarly, obesity poses a technical difficulty to perform invasive procedures (amniocentesis and sampling of chorionic villus) needed when suspecting a fetal malformation or aneuploidy. In the same note, laboratory studies (like βhCG and maternal serum α-protein) can be inaccurate given the mother's altered metabolic status [17].

Maternal obesity and placental function

The placenta is a crucial organ for a successful pregnancy that establishes the functional connection between the maternal and fetal circulation. Thus, to enable a fruitful fetal development, the placenta takes on a plethora of functions, posing as a gut, liver, kidneys, lungs and even glands to the evolving fetus. This means, in a nutshell, that it is responsible for the flow of nutrients and gases from the mother's circulation to the fetus and eliminates waste and toxins, expressing enzymes of the P450 complex. It also secretes various hormones (growth hormones, activins, relaxin, steroidal hormones) that stimulate fetus growth, maternal adaptation to the pregnancy and acts as a shield against microorganisms, with its own innate immune defenses and passive humoral immunity via maternal immunoglobulins [30, 31]. Similarly, the placenta secretes inflammatory cytokines, justifying their increased serum levels in a normal pregnancy [26]. In general, the placenta conveys the maternal metabolic scenario and general environment to the fetus, being the central regulator of its development and maturation [32].

Briefly, from an anatomical and histological point of view, the placenta is comprised of trophoblasts, endothelial cells, stromal cells and immune cells [33]. Its functional unit or uteroplacental unit is the tree of chorionic villi. These structures consist of fetal blood vessels wrapped in syncytiotrophoblast that has direct contact with maternal blood coming from the spiral arteries, being the epithelium responsible for the production of the placental hormones [26]. On a molecular level, it relies on the mitochondria to keep up with its constant massive activity, generating energy in the form of ATP almost exclusively via aerobic respiration [32].

Thus, the placenta is an extremely complex and yet transient structure, which means its timespan is limited, lasting from embryogenesis to term [30, 31]. In fact, the placenta originates from the trophoblast, in other words, it is a heterogeneous tissue derived from the fetus (trophectoderm) – resulting in sexual dimorphism with different responses to, for instance, inflammatory or redox stress [26,32]. To be properly formed, there are several signaling mechanisms and pathways (namely Wnt, Notch, interleukins, growth factors like TGFβ and VEGF) that make the trophoblast proliferate, migrate, invade and adapt. Later there are factors that contribute to an appropriate attachment of the placenta and the development and remodeling of its vasculature, since the metabolic needs of the fetus are constantly increasing. These mechanisms include expression and repression of genes, epigenetic agents and post-transcriptional events. For this reason, the dysregulation of any of these phenomena can cause major issues, for example changes in the vasculosyncytial membrane thickness, alterations in the normal characteristics of villi or a deficient or excessive amount of nutrient carriers will gravely alter the supply of essential elements to the fetus [31]. After all, correct placentation and optimal placental function is crucial to uphold the maternal-placental-fetal triad – an axis with a pivotal role both on embryogenesis and prenatal development as well as on postnatal status of heath and predisposition to disease known as programming [30].

On a side note, when it comes to the role of the placenta in the fetus' heart development, curiously, these organs develop simultaneously, both interacting as they follow a meticulous choreography of processes. Additionally, for proper cardiogenesis, besides the precise expression of genes and signaling pathways, there are indispensable biomechanical forces that affect its anatomy and cell differentiation – a gradient of pressures to which the placenta contributes with its blood flow [34]. In fact, as highly vascular structures with an

interdependent development, it has been proven that placental dysfunction – for one the dysfunction of its endothelium – is linked to impaired fetal cardiovascular developing and abnormal cardiomyocytes [35].

As seen before, obesity features an environment of low-grade chronic inflammation, oxidative stress, of pronounced hyperinsulinemia, dyslipidemia, hormonal imbalance (higher levels of leptin, growth factors like IGF-1 and lower levels of adiponectin), intestinal dysbiosis and, consequently, endothelial dysfunction. Henceforth, these pregnancies' metabolic derangement tampers, right from the beginning, with the normal placental function on several interacting fronts [26, 36, 37]:

Firstly, it is believed that the obesogenic status promotes an excessive nutrient supply to the fetus. To this end, insulin – it is relevant to note that the placenta maintains most of its insulin sensitivity, contrary to the resistance of the peripheral tissues – contributes by activating placental glucose and amino acid transporters. Similarly, leptin increases placental lipolysis [26] – hydrolyzing triglycerides into FFA that go into placental circulation, later being esterified and causing accumulation of triglycerides both in placental and fetal tissues [38] – and promotes activation of amino acid carriers through the villi. In the opposite way, the deficit of adiponectin equally allows the excessive nutrient exchange, mostly aberrant glucose transport [20,26]. And finally, when it comes to IGF-1, this growth factor that is also increased, activates glucose transport in particular through GLUT1. These altered levels of circulating insulin, leptin, adiponectin and growth factors will activate mTOR signaling, further boosting the transport of nutrients as well as protein synthesis and placental mitochondrial activity. This overload of nutrients is the main cause of overgrowth of obese mothers' offspring – hyperglycemic fetuses with greater adipocyte reserve that are more propense to cardiovascular diseases and obesity later in life – and many mechanisms and pathways are yet to be uncovered that link this overflow of nutrients leaking from the placenta to fetal development errors [26].

As previously stated, adipocytes have endocrine functions, one of them being the secretion of pro-inflammatory cytokines like adipokines [39, 33]. Hence, maternal obesity leads to higher levels of IL-6, IL-8, IL-1β, TNFα (mainly in female fetuses), MCP-1 and C-reactive protein in the bloodstream and enrichment of immune signaling pathways. Understandably, a greater quantity of receptors for those cytokines, like CXCR2, was found in placental cells that were subjected to these conditions. Meanwhile, studies point to hyperactive intracellular signaling pathways such as STAT3 and p38 MAPK [26]. When it comes to immune cell distribution, some articles point to a higher infiltration of macrophages, while others found more neutrophils in placental tissue [26,32]. Likewise, neutrophils were found in the umbilical cord and its blood vessels, indicating fetal inflammation [40]. These cellular agents contribute to the secretion of the aforementioned cytokines and TLR4, consequently attracting more inflammatory cells and enhancing tissue damage and metabolic deregulation [26,32]. Additionally, there can be seen more CD4+ lymphocytes T helper type 1 (Th1), when it would be expected anti-inflammatory Th2 [33]. This way, studies show a mild and persistent placental inflammation as a usual finding in the pregnancies of obese mothers [26]. This uncontrolled inflammation modifies the global placental function as well as contributes to the flow of FFA into the fetal circulation [32]. It is believed that the inter and intracellular inflammation impairs DNA repair systems, henceforth enhancing placental cells' DNA damage, and may as well induce apoptosis and premature deterioration of this temporary organ [41]. Besides, obesity makes the pregnant

woman more susceptible to the occurrence of inflammatory events such as vasculitis, chronic villitis, chorioamnionitis or funisitis [39].

Furthermore, in obese mothers' placentas there is a significantly heightened oxidative and nitrative stress, proven to be another factor contributing to its cellular damage and dysfunction [32]. In fact, evidence has demonstrated the presence of elevated levels of pro-oxidant biomarkers and reduced antioxidant molecules in maternal circulation and umbilical cord blood [38]. Indeed, physiologically in pregnancy the levels of ROS and nitric oxide (NO) are boosted, as a consequence of an overall elevated metabolic activity and high partial pressure of oxygen in the blood. These molecules are mainly originated by the large number of mitochondria in placental cells – knowing that the primary source of endogenous reactive species is mitochondrial [42]. Despite this inevitable production of superoxide and NO in the placenta, the redox balance is maintained by its own system of antioxidant defense. However, in obese pregnancies there is an even more increased metabolic activity and production of free radicals without increased scavenging capacity of these reactive species. On the contrary, the placental oxidative control mechanisms are lost [32,38]. Additionally, in the proliferating endothelium there is an increase of VEGF expression that stimulates more production of NO [43]. This way, an immense oxidative and nitrative stress state rapidly sets in, with ROS and NO produced by various cell types, including immune cells and trophoblast. Additionally, it has been shown that this decreased antioxidant capability of the trophoblast coupled with the increased placental lipid content, placental lipase activity, circulating FFA and placental accumulation of triglycerides promotes a local state of uncounteracted lipotoxicity [32,38,44]. Broadly speaking, oxidative damage of the placenta is responsible for its early senescence [45]. Indeed, this redox imbalance compromises the maternal-placental-fetal unit, affecting embryogenesis and fetal development since the fetus lacks antioxidant defenses [38,46].

When it comes to mitochondrial efficiency it has been proven to be inversely proportional to body adiposity, meaning it decreases with the increase in adipose tissue. This decline in ATP generation is not counterbalanced by alternative mechanisms [32]. Indeed, it is apparent that obesity is associated with mitochondrial dysfunction in various tissues, such as adipose, heart, skeletal muscle and liver. The primary rationale underlying this phenomenon concerns the pro-oxidant environment – which in turn is caused by exacerbated metabolic activity – that impairs nucleic acids as well as proteins and lipids, altering the mtDNA (downregulating about 50% of genes) and mitochondrial structure [42]. In particular, the placenta consumes a massive amount of energy and mitochondrial activity is even more increased in placentas of obese mothers due to the hormonal environment and surplus of nutrients in the bloodstream [32]. When adding to this hyperactivity the long-lasting oxidative and nitrative stress, as previously discussed, mitochondrial function can be gravely jeopardized, culminating in the inhibition of aerobic respiration, that becomes unable to provide for the energetic needs. This phenomenon establishes a vicious cycle that constitutes the core mechanism of placental dysfunction in maternal obesity [42]. Similarly, the inflammatory state of the tissue filled with cytokines exacerbates this damage, further decreasing oxidative phosphorylation [32].

To reiterate, the placenta has a relatively short lifespan, thus macroscopic and microscopic changes, like epigenetic abnormalities, are anticipated to manifest upon its senescence. One of these findings has to do with its methylome, which gradually increases as gestation progresses [32]. In fact, in pregnancies of obese mothers, the DNA methylation of placental cells at any stage of gestation is significantly higher than in pregnancies of lean mothers and even compared to those complicated by preeclampsia or gestational diabetes. It can be seen that maternal obesity also influences the patterns of this methylation [26, 33]. Certainly, this DNA hypermethylation, namely of promotor regions, leads to a repression of the transcription of the genes affected. Subsequently, authors defend that the mother's nutritional status will modify the epigenetic structure of the offspring's genome – particularly during the zygote stage – and, therefore, its genetic expression. The discovery of altered patterns of CpG islands and DNA methylation in cord blood samples provides corroborating data to this hypothesis of fetal epigenetic modifications [33]. As a result, It is possible to conclude that these methylation profiles of placental cells are related to the outcome of the pregnancy, affecting embryogenesis and development [32].

Finally, it is fitting to consider another important front of placental dysfunction: endothelial dysregulation, which is as a consequence of these aggressions. It is known that obesity leads to a chronic activation of endothelial cells and to an impairment of its function due to this upregulation, coupled with the oxidative stress, inflammation, mitochondrial insufficiency and epigenetic events [33,47]. Equally, studies conducted in animals detected that the overload of nutrients can cause aberrant expression of genes associated with placental angiogenesis and cellular growth in mice, reduced vascularity of the placenta in ovine species and placental ischemia in nonhuman primates [48]. This endothelial dysfunction may extend to the circulation of the fetus, the same way the malformations in placental blood vessels will impact the fetus' vascular development [47]. This way, an insufficient vascular perfusion can be seen, that will affect both the mother and the fetus, noting that maternal obesity can be highly associated with placental vascular lesions [33].

Summing up, obesity promotes placental dysfunction through the dysregulation of nutrient carriers, accumulation of nutrients – namely lipids – in its tissue, oxidative and nitrative stress, mitochondrial dysfunction and decreased aerobic respiration, stimulation of inflammatory pathways and infiltration of immune cells, epigenetic factors – namely the hypermethylation of DNA – and, lastly, endothelial dysfunction and abnormalities in vasculature and blood supply [26,32,33]. Nevertheless, it is relevant to highlight that, in the literature reviewed, there is a great difficulty in isolating the changes of placentas complicated only by obesity. Likewise, there are many studies performed in animal models; however, the reliability of these findings when transposing to human pathophysiology is debatable. Significant gaps remain in this area of research [32].

Maternal obesity and inflammation

Inflammation is commonly recognized as a response to cell injury, mediated by cytokine storms and chemokines that trigger various cellular events. However, it also plays a central role in other physiological processes [49]. During a normal pregnancy, the maternal immune system undergoes significant adaptations, just as the entire body does. This immune modulation occurs in three main stages: first, implantation and placentation, which are predominantly pro-inflammatory phases; second, a prolonged state of immunosuppression that extends throughout most of the gestation and is maintained until the peripartum period; and finally, the peripartum stage itself, which is again marked by inflammation – essential for parturition [49,50, 51]. Additionally, the immune system plays a fundamental role in protecting the fetus from microorganisms and other harmful factors. One major challenge is the maternal cellular immune response, which could potentially reject the fetus as an allograft due to the presence of paternal antigens and genetic material that is distinct from the maternal self [50,52]. The crucial role of the immune system in pregnancy is further underscored by the fact that leukocytes constitute approximately 40% of decidual cells [49].

Understandably, it is now known that immunosuppression is not the sole feature essential for a healthy gestation. Rather, there must be an interplay between systemic and local inflammation [53]. With that in mind, it is after nidation that a tolerant landscape must be established, and this is settled by the suppression of Th1 cells and upregulation of Th2, shifting to a predominantly anti-inflammatory response as the pregnancy progresses. In particular, Th1 cells promote a pro-inflammatory environment by polarizing macrophages to the M1 phenotype and secreting cytokines like IFN-γ, IL-2 and IL-17; nonetheless, as previously stated, these lymphocytes are important in early stages of gestation by facilitating the implantation of the embryo and placentation by boosting uterine NK cells. To rephrase, an abnormally prolonged Th1 response hinders proper fetal development causing malformations and infant disorders, and can also lead to miscarriage, intra-uterine infection, preeclampsia and preterm delivery. Therefore, as already mentioned, normal pregnancy is inherently a systemic pro-inflammatory state with a crescent importance of Th2 immunity in its course promoting immunotolerance for the fetus which allows it to develop and grow properly. These Th2 cells induce M2 phenotype macrophages that secrete IL-10 (especially in the last trimester) and IL-1Rα and are present in decidual tissue, greatly contributing to the environment of tolerance [51, 52]. Equally, other stromal decidual cells and trophoblasts favor the M2 phenotype macrophages by secreting M-CSF and IL-10 [49].

Nevertheless, recently it has been demonstrated that this interplay between Th1 and Th2 cells is an oversimplification of the entire process that protects the fetus from being a target of the maternal immune system [49]. The delicate harmony of uterine NK cells – which are the most numerous cells in decidual tissue and undergo a long period of inhibition [51] –, macrophages, dendritic cells and other types of lymphocytes (like regulatory T cells), all present in the uterine lining, is crucial to make sure that the pregnancy develops correctly. It is also relevant to note that the various inflammatory components are indispensable even for the differentiation of the gravid uterus or decidualization process, influencing the microenvironment from the very first moment after conception. Finally, animal and human models show that these uterine immune cells behave in a slightly different manner than the corresponding cells in the periphery – due to factors secreted by decidual stroma cells around them like prolactin, VEGF or TGFβ. These cells (uNK, macrophages, DC, T cells) maintain reactive ability, yet the tolerant environment is predominant due to their respective ligands (HLA-C, G, E) [49].

Cytokines play a crucial role in immune cell differentiation and communication, being produced both systemically and at the maternal-fetal interface. They influence the pregnancy's outcomes through multiple pathways, including their effects on the placenta, as discussed in the previous section, and their ability to cross the placental barrier and directly impact the fetus. The balance between pro- and anti-inflammatory cytokines is essential, as the regulation of cytokine gradients contributes to the three main stages of immunomodulation in an uncomplicated pregnancy, as previously mentioned [49,51,52]. For instance, pro-inflammatory cytokines (such as IL-1, IL-6, and TNFα) can induce systemic insulin resistance, whereas anti-inflammatory cytokines (such as IL-10) help preserve insulin sensitivity, exerting a protective effect [54]. Additionally, cytokines can influence the embryo even before implantation, while it travels through the oviduct. Some cytokines have embryotoxic effects, such as IFN-γ, members of the TNF family, and TRAIL, which can lead to developmental errors or even embryo loss from the earliest stages. Conversely, others have embryotrophic properties, such as IGF-1 and GM-CSF, promoting implantation and adaptation to the uterine environment [55].

To summarize, this modulated system is comprised by a complex interaction among lymphocytes (Treg cells, Th1 cells, Th2, Th17, Th22, uterine NK cells), neutrophils, macrophages and dendritic cells, which will rearrange along the pregnancy and accordingly to the environment required, being coordinated via intracellular communication – with their secreted cytokines that point to a more or less inflammatory response [50, 51]. In a normal pregnancy, this coordination of elements contributes greatly to the precise transformation of the uterus, nidation, placentation, development and growth of the fetus and parturition (Fig. 2).

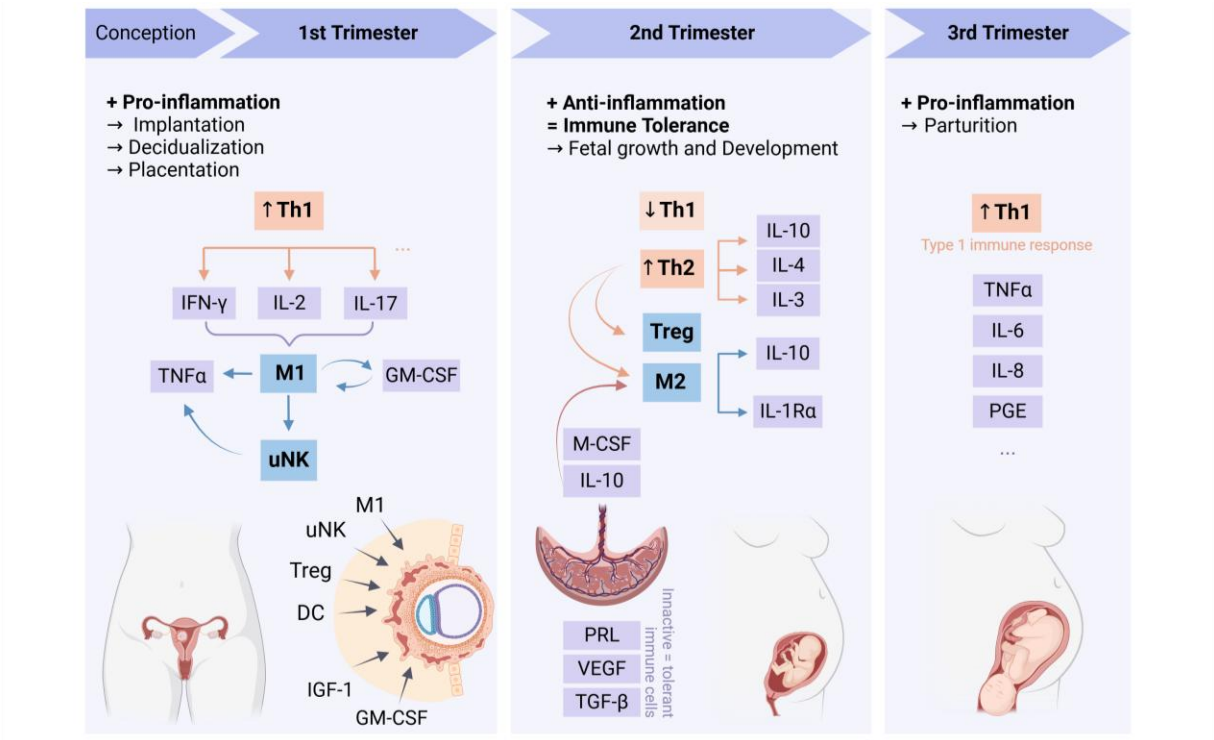


Figure 2. The role of inflammation in pregnancy. Inflammation is of constant importance throughout pregnancy; starting from conception there is a pro-inflammatory environment marked by type 1 inflammation that enables the transformation of uterine tissue (decidualization) to accommodate the product of conception (implantation). Here there is an interplay of cytokines produced by the zygote, fallopian tissue, endometrial and other maternal tissues that allows adjustments from all the agents with the ultimate goal being the survival and

viability of the zygote. Secondly, the implantation of the blastocyst is a process greatly aided by immune cells like uNK cells. Afterwards the trophoblast starts invading the maternal decidua. This phenomenon is the beginning of the formation of the placenta and throughout the whole process (placentation) the immune system plays a key role in promoting proper angiogenesis and expansion. In the second trimester, that is the main period for development, maturation and rapid growth, there is a shift to type 2 immunity, creating a tolerogenic status that inhibits rejection of the fetus. This shift (greater importance of Th2 cells, Treg, M2) is promoted and maintained by decidual and placental signals. Here immune cells become non-reactive to fetal antigens while still communicating among each other. Finally, there is another shift to pro-inflammation that boosts labor along with other stimuli from mother and offspring. M1 – type 1 phenotype macrophages; M2 – type 1 phenotype macrophages. Created in BioRender. Meneses, H. https://BioRender.com/sbhrthy (accessed on 25 March 2025).

Meanwhile, obesity, complementing previous topics, is marked by a significant dysregulation of immune function [52]. This metabolic state, being a consequence of an overload of nutrients and metabolites, leads to a prolonged low-grade inflammation on a systemic level – with an excessive production and release of deleterious cytokines (mainly IL-8, IL-6, TNFα, IFN-γ, adipokines) as well as with an impaired function and coordination of the immune cells [50, 54].

As seen before, this adipose tissue, apart from being comprised by a larger and higher number of adipocytes, differs from lean individuals due to an infiltration of immune cells, like monocytes that differentiate into macrophages with the pro-inflammatory phenotype M1, which contributes to the aforementioned potentiation of endocrine function, releasing adipokines (namely leptin) and cytokines into systemic circulation [54]. This aberrant inflow of immune cells is a result of increased death of adipocytes caused by the high lipotoxicity in this tissue which also explains the excessive and perpetuated release of cytokines with pro-inflammatory action into the circulation – many with chemotaxic effect, culminating in a loop of positive feedback, along with the accumulation of cells with a shift to type 1 phenotype [49]. Among these increased pro-inflammatory cytokines there are some that will exacerbate the metabolic anomalies by interfering in insulin signaling, contributing to the vicious cycle of obesity, inflammation and metabolic dysfunction [56].

Furthermore, obesity can also cause dysbiosis of the maternal gut which can be another predisposing factor for the aberrant inflammation, since microbiota is able to modulate immunity and is vital in sustaining the competence of maternal-fetal immune function [57, 58]. On the other hand, it is unclear if the dysbiosis present in obesity is the cause or a consequence of the state of low-grade chronic inflammation, since the inflammatory response inflicts a metabolic change in the gut allowing other bacteria to thrive [59].

In respect of the impact of maternal obesity in pregnancy, bearing in mind that these conditions have similar characteristics, for example when it comes to the presence of a low-grade maintained inflammatory state or to the insulin resistance, they can have a synergistic effect on each other, perpetuating and increasing the proportions of these alterations [49, 54]. In other words, inflammation plays a key role in both obesity and gestation, thus it is reasonable to believe that there is an upregulation of several mediators which is responsible for many complications [53].

Consequently, it is believed that each pregnancy can be differently affected by inflammatory dysfunction according to its duration, magnitude and content of signals. This way, the direct impact of obesity-

induced inflammation on the fetus must be thoroughly studied [49]. Throughout the literature reviewed, it was noted that this inflammation is a possible insult to pregnancy since the formation of the zygote until the moment of birth [50, 55], with evidence of elevated systemic biomarkers (predominantly in the third trimester) [60].

As seen before, the maternal aberrant inflammation expands to the placenta and intrauterine milieu, reaching the fetus. Namely cytokines, which can easily get to the fetus' circulation through the placenta, will disrupt the epigenome, shape genetic expression, cause erroneous apoptosis, inflict cellular stress and compromise the response to it and, ultimately, impair overall development [53, 55]. Subsequently, some studies have found pro-inflammatory cytokines present in fetal plasma, brain and liver [53]; however, in most studies these results are controversial – these inconsistencies can be attributed to the different timings of the pregnancies, the types of samples collected, diet consumed, sex of the fetus, biological particularities of different populations, among many confounding factors that are challenging to comprehend [51, 53]. With this said, MCP-1 (a chemokine that recruits monocytes, DC, and T cells) and IL-6 appear to be the cytokines most consistently found in obese mother's pregnancies as well as the serum protein CRP [61].

In the same line of thought, the excessive nutrient traffic into fetal cells, which is frankly potentiated by these various pro-inflammatory cytokines, also contributes to the upregulation of inflammatory pathways in its own tissues [53, 55].

Similarly, immune cell imbalances, both systemically and within decidual tissues and the placenta, can have significant consequences. For instance, leukocyte dysfunction in uterine tissue—such as abnormally activated NK cells observed in some animal models—may contribute to fetal development disorders. Obesity further disrupts the presence and activity of these uterine immune cells, ultimately disturbing the delicate balance required for the different stages of gestation. This includes impairing the tolerogenic environment necessary for pregnancy maintenance, altering the decidualization process, and affecting the function and structure of the spiral arteries [49]. Some researchers suggest that certain maternal immune cells, including T cells (Th1, Th17), B cells, and monocytes, may cross the placenta and infiltrate fetal tissues. In fact, studies in mouse models indicate that the predominant type 1 inflammatory response can promote this phenomenon [53, 61].

Moreover, paradoxically, an excess of pro-inflammatory elements can predispose individuals to both viral and bacterial infections by impairing the innate and adaptive immune responses. This immune dysfunction increases the risk of developing conditions such as chorioamnionitis, sepsis, abdominal wall infections, and wound infections, among others. Additionally, microorganisms may reach the fetus either by crossing the placenta directly or by using immune cells, such as neutrophils, as carriers. Consequently, the risk of fetal infections is heightened.

Furthermore, it has been hypothesized that infections during pregnancy may contribute to congenital fetal anomalies, in addition to other complications such as preterm delivery [50].

Hence, with all of this in mind, some studies show that the wrongful activation of the fetus' immunologic functions can affect its own health and be an important risk factor for malformations and disease programming later in life [50] (Fig. 3).

In the same frame, an original study developed to compare the immune function in pregnancies with a diagnosed fetal CHD with the one of mothers carrying not affected fetus concluded that there were outstandingly higher levels of chemokine MIP-1α in plasma samples from cases other than controls. This molecule is responsible for monocyte chemotaxis, is produced by macrophages and has been reported to be increased in decidual tissue in patients with recurrent miscarriages. Other cytokines like INF-γ were detected, however, not with the same significance. It was shown an apparent correlation between CHD in pregnancies with increased MIP-1α and overall higher M1 response in vitro. This strengthens the hypothesis that cardiac developmental abnormalities can be brought on by the dysregulation of maternal inflammatory elements with a prominent role played by cytokines [52].

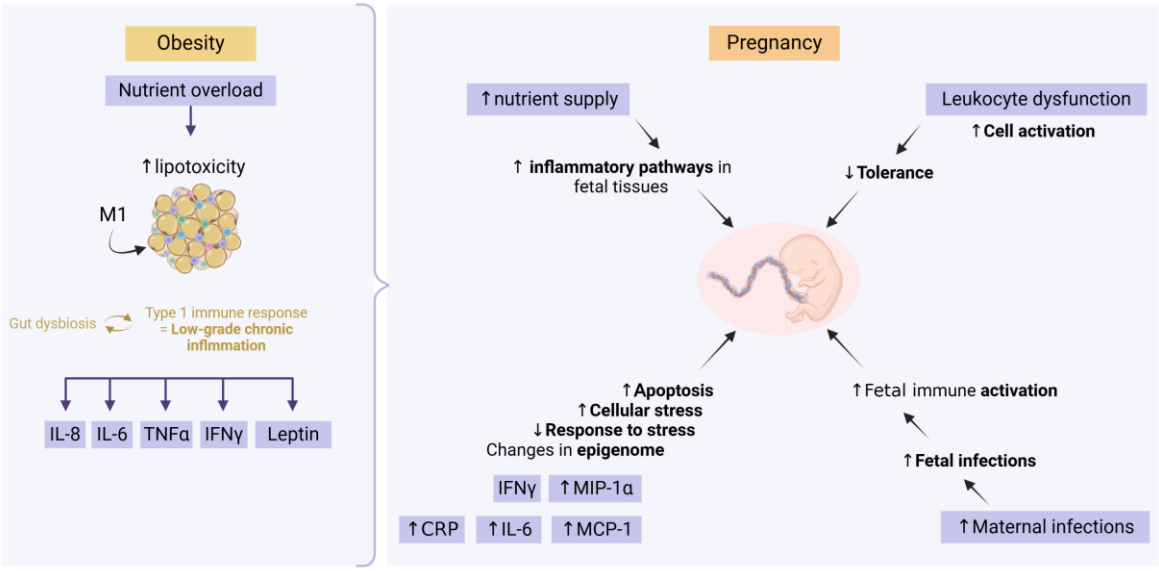


Figure 3. The impact of maternal obesity's inflammation in pregnancy. Obesity is characterized by an overabundance of adipose tissue, particularly visceral, caused by an imbalance between nutrient intake and energy output, usually with excessive food apport compared to the basal metabolism. This leads to an overload of nutrients that disrupts the metabolic environment. Namely excessive lipid content induces lipotoxicity that harms adipocytes, ultimately generating an infiltration of immune cells like M1 macrophages. In this scenario this tissue becomes an important source of inflammatory mediators like chemokines, cytokines and adipokines, culminating in a systemic state of low-grade inflammation. Among many consequences, this can cause dysbiosis or, on the other hand, the inflammation can be potentiated by gut microbiota alterations also induced by obesity. When an obese woman becomes pregnant, there will be a disruption of normal inflammatory modulation. This will have a direct impact on the fetus: nutrient overload on fetal tissues can cause inflammation; pro-inflammatory cytokines will go through the placenta reaching fetal cells causing activation of wrongful pathways with alterations of gene expression, cell stress and apoptosis; there is also a dysfunction on local uterine leukocytes, hampering their state of tolerance; finally, this inflammatory disarrangement increases susceptibility to microorganisms that can escalate to fetal infections and activation of immune pathways. M1 – type 1 phenotype macrophages. Created in BioRender. Meneses, H. https://BioRender.com/aagy3d0 (accessed on 26 March 2025).

Maternal obesity and oxidative stress

Oxidative stress is characterized by an imbalance between pro-oxidant molecules – such as ROS, NO, and malondialdehyde (MDA) – and antioxidant substances, including glutathione, enzymes, and vitamins, which help restore the redox balance through their scavenging activity [62,63]. Reactive oxygen species, like the superoxide radical, are the main pro-oxidant elements, having unpaired electrons that make these substances strongly reactive to lipids, proteins and DNA, interacting and changing these molecules – namely by peroxidation of lipids, protein inactivation, catabolism of nucleotides, among other processes [62, 64] –, ultimately jeopardizing the structure of membranes and the integrity of the cell and its organelles [65]. Accordingly, oxidative stress can be a significant source of genotoxicity [66] and, notably, this noxious environment can lead to mutations and major teratogenicity [62,63].

The mitochondria is the main source of cellular energy, produced as ATP, and is a key agent in the metabolism of nutrients, yet the process of aerobic respiration is the main generator of ROS. In fact, its genetic information is particularly sensitive to oxidative damage [62,67]. The mtDNA responds to this harm by repairing and copying itself, leading to mitochondrial hyperactivity and consequently more oxidant molecules are synthesized due to an impaired consumption of oxygen. In other words, when ROS accumulate and cause dysfunction, an inability to meet cellular needs arises and this reduced energy supply can trigger uncontrolled apoptosis [62, 65, 67]. Notwithstanding, ROS and other pro-oxidant agents also have important physiological roles in intercellular signaling [65], and, lately, the importance of this redox homeostasis is more and more studied in terms of its essential function for normal organic development and function [64]. Therefore, it is the disproportion between pro and antioxidant elements that leads to tissue oxidation, which in turn causes cellular damage and subsequently triggers pathological phenomena. [62].

Oxidative stress' implication in pregnancy is an important factor to be considered. Nevertheless, as with inflammation, moderate levels of pro-oxidant species contribute to a successful pregnancy, stimulating placentation and participating in the initial phase of the embryo's development and organogenesis [63, 64] – since it influences the pathways that lead to cell proliferation, apoptosis and differentiation [68]. Similarly, it is vital to maintain a physiological balance between pro and antioxidant elements, promoted mainly by the placenta – its increased mitochondrial activity induces oxidative stress along with ROS in the mother's circulation, but there is a placental antioxidant defense system –, this way mitigating cell damage, as mentioned in the corresponding section [63, 64]. In fact, along gestation there is a well calculated increase of oxygen levels that is essential to cover for the basal needs of the mother and offspring; however, from these high concentrations of O_2, inevitably, a small portion is reduced incompletely, originating more ROS [65].

In contrast, when there is an exacerbated level of pro-oxidant elements without a parallel increase in scavenging capacity, oxidative stress sets in and can impair the embryo from its earliest stage, throughout its maturation and growth along the trimesters until birth. Many studies have associated oxidative attack with complications such as miscarriage, preeclampsia, IUGR, chromosomal anomalies and fetal malformations, with a prominent focus on the direct teratogenic effect [62, 63, 64]. Similarly, oxidative stress has a potential role in the disruption of cardiogenesis [69], since it can hamper gene expression of progenitor cardiac cells and suppress the differentiation and maturation of cardiomyocytes, all while increasing cell death and decreasing proliferation

[70] – lower predicted oxidative stress based on lifestyle and diet was correlated to less risk of CHD, proving the importance of redox balance in the development of the fetal heart [68].

Consistently, reproductive cells are especially vulnerable to oxidative damage, which can lead to difficulties in conceiving and to sub-optimal zygotes, as demonstrated in animal models with a preexisting chronic condition such as obesity [62]. Additionally, it has been validated that the lack of antioxidants promotes cell injury and developmental disorders [64].

With the impact of oxidative damage in pregnancy in mind, some authors suggest the implementation of an oxidative balance score that is inversely proportional to oxidative stress, meaning that a higher score indicates a heathier lifestyle and better redox equilibrium. This score enables to take into account the cumulative factors of oxidation and lifestyle, helping to understand the influence of oxidative stress in adverse pregnancy outcomes [68].

Furthermore, it is believed that obesity is a major metabolic disruptor that leads to an environment of chronic systemic oxidative stress [63]. Knowing that oxidative stress is tightly linked to the metabolism of lipids [71], obesity, along with causing tissular hypoxia, leads to a high concentration of circulating FFA that can contribute to the disruption of the mitochondrial membrane and its loss of integrity, releasing ROS and potentiating the metabolic dysfunction – in turn more lipids accumulate in various tissues and inflammation is amplified [67, 72]. Additionally, there is an increase in the peroxidation of lipids and a substantial decrease of enzymes with antioxidant properties crucial to counteracting pro-oxidant species [73]. Studies show that oxidative stress biomarkers in obese women are systemically heightened, as are also increased in the circulation of obese expectant mothers – demonstrated by detecting NO and MDA [62, 63]. Moreover, the inflammatory environment detailed in the previous topic contributes, through various pathways, to the generation of more pro-oxidant molecules, that in return fuel more inflammation and mitochondrial malfunction, all in a continuous loop [67].

Pregnant and obese women display higher pro-oxidant molecules, dysregulated defenses and lesser antioxidant elements compared to lean gravidas [74]. Adding obesity to pregnancy, the nutrient overload and its excessive apport to the intrauterine milieu will lead to an even more exaggerated mitochondrial activity resulting in abnormal ROS production both locally – mostly by the impaired placenta and endometrial lining – and systemically, exerting epigenetic changes and direct DNA damage, ultimately compromising the embryo's development and growth [62, 72, 75, 76] (Fig. 4).

Supporting these concepts, it has been demonstrated in obese animal models a hyperactivity of oocyte's and zygote's mitochondria with evidence of a higher level of ROS and oxidation, as opposed to a decrease in glutathione levels [62]. Embryos of obese mares also display modified expression of genes involved in lipid metabolism, oxidative, mitochondrial and endoplasmic reticulum stress [77]. Indeed, it is believed that this disequilibrium reaches and affects the fetus, leaving a lasting mark on its mitochondria. Research conducted in animal models shows altered mitochondrial function in newborn's cardiac and hepatic tissues, as well as in skeletal muscle cells and the hypothalamus. Likewise, there is more data showing reduced scavenging capacity and antioxidant agents in the offspring's heart and liver [65].

This way, a high fat maternal diet (associated with excessive BMI) is proven to result in a state of increased lipid peroxidation and oxidative stress in the offsprings tissues, followed by a poor response to this pro-oxidative environment – with evidence of reduced activity of superoxide dismutase 2 and catalase. These alterations can be found at critical points in the development of the fetus [71]. On top of that, research indicates that the higher the magnitude of oxidative stress, the greater the risk of congenital abnormalities [64].

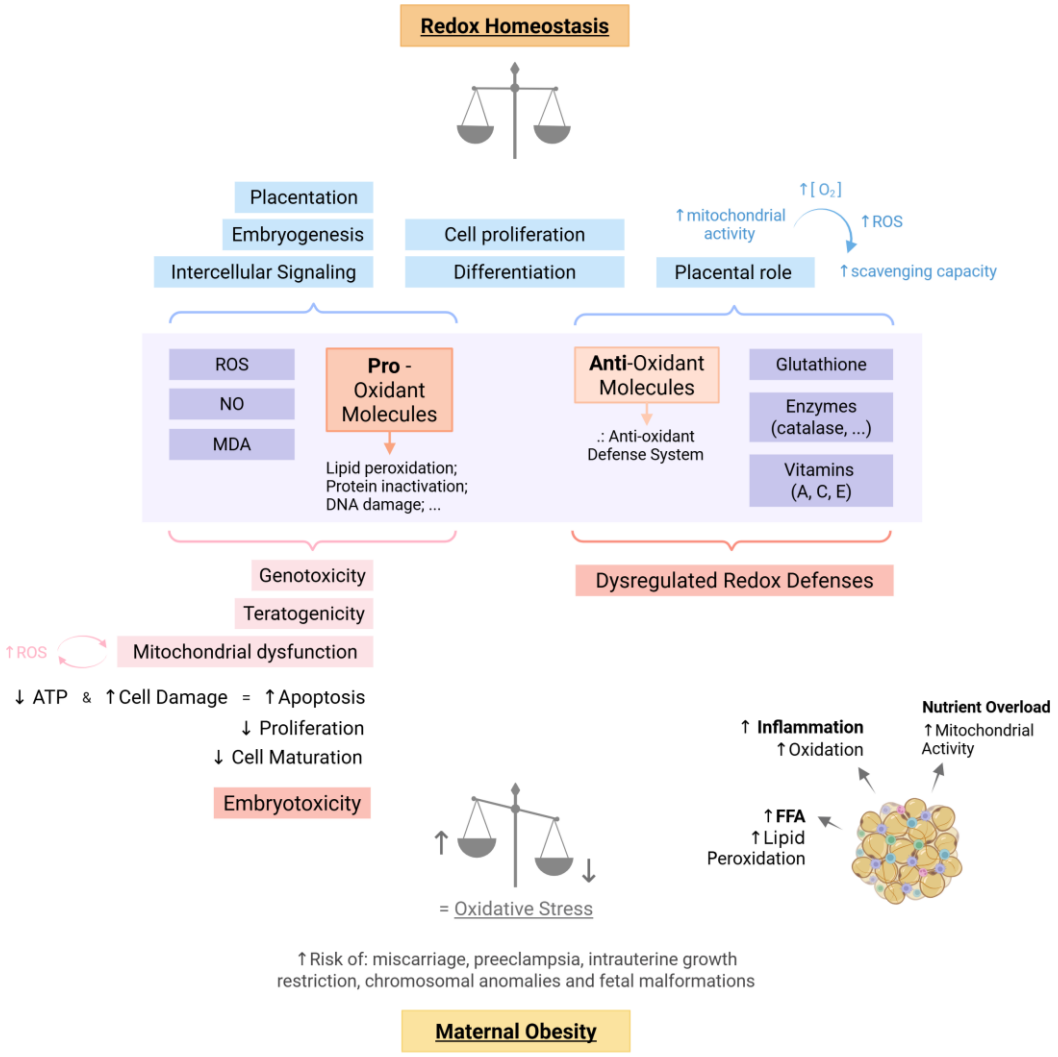


Figure 4. The redox balance in lean *versus* obese pregnancy. When the levels of pro-oxidant molecules are counterbalanced by antioxidants there is an environment favorable to the proper development of pregnancy. Oxygen and nitritive species are important for intercellular communication as well as for coordination of physiological processes by stimulating cell proliferation and correct differentiation. They play a role in early development of the embryo, placentation and contribute to the proper growth of the fetus. It is mostly the placenta that generates locally the pro-oxidant molecules, having a parallel ability to counteract oxidative stress by increasing antioxidant elements. Obesity disrupts homeostasis, by promoting oxidation and depleting the scavenging capacity. Oxidative stress sets in due to this imbalance. This oxidative damage is genotoxic and decreases aerobic respiration, leading to rampant cell death. Finally, there is a high teratogenic and embryotoxic potential that can lead to miscarriage, fetal malformations as well as other pregnancy complications. Created in BioRender. Meneses, H. https://BioRender.com/uoeozsc (accessed on 24 April 2025).

Adiponectin-related dysfunction in placental glucose transport of women with obesity

Adiponectin is a protein synthesized by adipocytes [78] encoded in the APM1 or ADIPOQ gene located in the long arm of chromosome 3 [79,80]. Its most active and abundant form is the high molecular weight adiponectin (HMW). This adipokine has several roles, such as anti-inflammatory and anti-proliferative [79], however its main function is endocrine – increasing sensitivity to insulin in several tissues, mostly in skeletal muscle and hepatic tissue and improving pancreatic β cells performance. Therefore, adiponectin promotes β-oxidation of fatty acids and is a key factor for the cellular uptake of glucose, playing a consequential role in its homeostasis [80, 81]. In fact, there are receptors for this adipokine in several tissues such as the brain, the endometrium, the ovaries and the placenta [79]. This way, adiponectin will have an important influence on the placental nutrient transporters, especially of glucose [78, 81].

The placenta has a plethora of nutrient carriers located on its basal membrane and microvilli, with the dominant category being of glucose transporters – since it is the major nutrient transported, reflecting the great needs for it. This handover of glucose is directly proportional to maternal glycemia, being regulated by the GLUTs family of membrane proteins (which name the corresponding carrier) – it can be noted that among the existing glucose transporters these are the most widely agreed to be present in the human placenta. With this being said, it is crucial to point out that maternal glucose is the main source of energy for both the placenta and offspring, assuming a key role in the growth and proper development of the fetus [82]. When it comes to adiponectin's function in pregnancy, it contributes to placentation with a pro-invasive and pro cell migration effect on the trophoblast, besides its important role in the fine adjustment of glycemia – by promoting glucose uptake by skeletal muscle and liver, this way regulating its availability – and placental nutrient transport [79].

Obesity leads to a decrease in adiponectin production and its circulating levels [78], whilst being known that low concentrations of this adipokine are associated with increased insulin resistance and type 2 DM, dyslipidemia, hypertension, among other complications [81]. Nonetheless, this inhibition of adiponectin production in obesity is not yet fully understood and can be due to gene polymorphisms (as occurs in maternal DM), to the state of hypoxia that the adipose tissue is in, or can be due to the effect of pro-inflammatory cytokines – derived also from adipose tissue like IL-6, IL-8 or TNF-α – that lessen adiponectin mRNA, among other factors not yet investigated [80, 83, 84]. Curiously, when it comes to the APM1 gene polymorphisms, these can be a factor predisposing to obesity, meaning that the lower adiponectin concentrations compared to lean individuals can be potentiated by the excess BMI or can be a contributing factor that makes the individual susceptible to weight gain and insulin resistance [85, 86]. Likewise, it is proven that obese pregnant women have lower total adiponectin and HMW levels when compared to lean gravidas [81, 87], although in the umbilical cord higher concentrations can be found [79]. Moreover, adiponectin is able to convey the effects of obesity into the placenta, affecting placental carrier function, in a sense that its deficiency will lead to an uncontrolled increase in nutrient influx to the fetus. Accordingly, adiponectin levels have notorious effects in fetal development, namely inversely proportionally on fetal growth, being hypothesized its correlation with glucose transport [78,81].

In animal models, obesity seems to contribute to the overexpression and hyperactivity [88] of GLUT1, GLUT3 and GLUT4, with an increase in glucose transport that might lead to changes in fetal growth, namely overgrowth. Indeed, it can be seen that in obese rodent models there is an upregulation of the expression of GLUT1

and GLUT3 proteins and, consistently, in humans an association of adiponectin and altered expression of placental GLUT1 has been observed. Similarly, studies show that adiponectin supplementation of obese mice leads to a decrease in GLUT3 proteins. However, a study mentions that these changes brought by maternal obesity in placental transport of glucose only affect the later trimesters, having minor influence in early pregnancy [82].

Nevertheless, the effect of increased glycemia from the earliest stages of pregnancy due to the reduced uptake by other tissues, related to insulin resistance in the absence of adiponectin, cannot be underestimated. Subsequently, the most vulnerable period of the development of the zygote and embryo is surrounding conception and early gestation, bearing in mind that the heart's formation starts in this early phase and is completed around the embryo's middle stage. Hence, an environment of high glucose and insulin resistance from early stages is associated with a disturbance of fetal heart development [80]. Many studies establish a correlation between adiponectin gene polymorphisms and congenital heart malformations in mothers with gestational DM; however, the literature does not explore this association in the specific context of maternal obesity [80 ,89].

Additionally, the offspring of obese mothers tend to display an elevated concentration of glucose in cord blood due to the increased transport of glucose through the placenta. In fact, glucose is significantly increased in fetal blood [78]. In this line of thought, studies show that this mechanism of increased glucose transport in maternal obesity seems to be a key element associated with LGA newborns as well as the programming of metabolic diseases, in other words, the predisposition to develop obesity, metabolic syndrome, diabetes and cardiovascular complications [88].

Maternal obesity and fetal cardiac development

To further comprehend this review, the normal process of cardiogenesis must be addressed. The heart is formed over a series of four major overlapping stages, with the contribution of cells from different populations, primarily derived from the mesoderm. These are mostly cardiac precursor cells – named the first and second heart fields, adjacent to each other –, and also non-cardiac pools such as the neural crest cells and pre-epicardial progenitors [90, 91].

In fact, the neural crest cells are indispensable for the emergence of the septa in the outflow tract – later major vessels –, for the constitution of the conduction system and of the cardiac ganglia, beyond their role in the genesis of several other organs – namely of the nervous peripheral system and craniofacial tissues [90, 92].

Furthermore, the unfolding of the cardiac formation is dynamic and sequential, with the need for genetic and epigenetic regulation to ensure a harmonious progress. Some of the signaling molecules essential for this rhythmic coordination are nodal, sonic hedgehog and bone morphogenetic proteins, NOTCH signaling pathway, Wnt, retinoic acid, fibroblast growth factors, among others that control multiple cardiac transcription factors (like GATA4 and 5, SRF and Nkx2.5) encoded by several genes. In fact, for the initial promotion of cardiogenesis there is the contribution of the TGF-β superfamily – namely BMP 2 and 4, TGF-β and activin –, along with FGF 2, 4 and 8. This way, organogenesis, in this case the making of the heart, is dependent of genetic factors and influenced by environmental exposures for its proper completion [90, 91].

This process commences around day 8 to 18 after conception, after gastrulation, starting by the organization of the cardiac areas and, subsequently, of a crescent-shaped structure – derived from the first field – that ultimately forms two tubes lined internally by endotheliocytes and covered by cells from myocardial lineage. At around 4 to 8 weeks of gestation comes the morphogenetic stage, where a linear single heart tube with bifurcated terminations is formed in the midline and, after loops, rotation and widening of this structure, appear the primordial structures that constitute the four chambers of the heart – also originating from the second heart field. Meanwhile, from day 30 starts the septation, growth and remodeling of the primordial chambers. It is during this stage that the auricles and ventricles take form. Finally, during the fetal stage, from the 16th week until birth, the heart goes through histodifferentiation and maturation of its tissues, developing the valve's architecture, with its papillary muscles and tendinous cords, as well as the separation of the outflow tracts, coronary vessels and electric impulse conduction system [90].

Accordingly, each stage is marked by the proper genetic expression that enables the changes to happen. In fact, the heart is among the first organs to initiate its development in the embryonic phase [93], and its function is the first identifiable sign of independent activity of the fetus, objectified by ultrasound [94]; however, only around the 35th week after conception, is the heart's morphogenesis finally complete [90].

Moreover, the looping of the initial heart tube is a very complex mechanism and the key to obtaining the outline of the heart's final anatomy, which requires differentiation and proliferation cycles for the tube's widening and for the formation of the chambers. With this said, disturbances at this phase of cardiogenesis can be the cause of heart malformations such as defects of the outflow tract derived from abnormal rotation – leading, for instance, to a TGA. Many studies suggest that these mechanisms are regulated by interactions of TGF-β and Smad proteins, Wnt and β-catenin, among other signaling pathways that induce or inhibit epithelial-mesenchymal transformations [90].

After the completion of the looping, it can be seen the image of a formed heart, where an atrial *septum primum* starts to form – generating the *ostium primum* – along with a ventricular *septum*, followed by the opening of the atrial *ostium secundum* and formation of the *septum secundum*, giving rise to the *foramen ovale*, which persists until a few days or weeks after birth [90].

When it comes to hemodynamics, the embryo's and later fetal cardiovascular system goes through alterations in circulating velocities in order to achieve its anatomical and functional maturity, all while ensuring the required blood supply for the development of the various other organs. In fact, around the sixth week of gestation appears a particular pattern for the first heart contractions and between the 2nd and 3rd trimesters there is adequate compliance – these correspond to the two main cardiac cycle periods identifiable in its development [94].

Thus, besides the aforementioned factors crucial for this process, mechanistic comes into play, being essential for the proper development of the chambers and valves, and these biomechanical forces – like intracardiac pressure, strain and wall shear stress – are mediated by the placenta [34, 95]. Therefore, the state of placental vessels, for example increased vascular resistance, has a direct impact on the developing circulation of the fetus and consequently on its growing heart, which will suffer from an increased afterload. Similarly, studies

show that an abnormal insertion of the umbilical cord can be correlated to cardiac malformations, just as twin-to-twin placental transfusion is associated to cardiac dysfunction and erroneous remodeling in both fetuses [95].

In brief, proper morphogenesis requires the calculated contribution of mechanisms such as cell division, apoptosis, differentiation, maturation, migration and mechanical forces. In reality, genetic expression acts as the orchestrator of these phenomena, enabled by epigenetic processes and factors external to the fetus. Overall, errors in any of these steps will disrupt the process and lead to more or less drastic consequences in the offspring's heart and circulatory system.

Nevertheless, as shown above, the beginning of the development of the embryonic elements that will constitute the heart takes place very early in gestation, when many women may be unaware of the pregnancy. For this reason, they may not act cautiously enough regarding possible teratogenic agents, being exposed to substances or situations that can easily hamper cardiac development [90].

Furthermore, important factors that can impact the upcoming heart are the maternal age and maternal comorbidities, like asthma and metabolic homeostasis disruption (such as the opposite extremes of BMI or gestational diabetes), the father's sperm quality, maternal infections such as rubella, deficiency of folic acid, smoking and alcohol consumption, among others, that can for example interfere with the quality of gametes, cause genetic disturbances or epigenetic changes. These aspects, according to the particular pregnancy stage that is most significantly affected by them, may be the cause of either subtle changes in cardiac structure and/or function or of major heart malformations [90,96].

To elaborate further, it is believed that the maternal metabolic state can impact the fetal heart's morphogenesis through a series of several intertwined mechanisms. In line with previous sections, there can be an important detrimental impact on the mitochondria of the fetus' cardiomyocytes, which can be correlated to hyperglycemia, leading to an impaired function, structural abnormalities and overall decreased aerobic respiration and increased cell death. Likewise, glucose can interact directly with proteins that bind to RNA, modulating the expression of genes. Other mechanisms involve ROS as the agent of both immediate and long-term cardiac cell damage. Finally, nutritional abnormalities are known to exert severe damage on cardiac tissue through methylation of DNA, histone proteins modification and expression of non-coding and microRNA [93].

When it comes to maternal obesity, studies support the hypothesis that it disrupts the embryonic development of the heart through alterations on the transcriptome and proteome with consequent changes on cellular level [97]. Specifying its impact, there is evidence of altered histone codification, related to metabolic phenomena like the overload of nutrients and consequent increased susceptibility to cardiac pathology. Similarly, studies point to an upregulation of a specific microRNA that can mimic MAPK signaling pathways and promote myocardial hypertrophy [93]. These changes appear to be similar to those present in a hyperglycemic environment, however murine models with normal serum glucose also developed them, which can be explained by the lipotoxicity inherent to obesity along with the gradually increasing insulin resistance [20,97]. Consequenly, signaling pathways, like the semaphorin proteins, crucial for the migration of neural crest cells, seem particularly

altered in a recent study, just as the Wnt/planar cell polarity signaling, responsible for cardiac cell movement, polarization and shape [97].

Besides, oxidative stress has been confirmed as a main teratogenic agent derived from maternal obesity, disrupting several organelles such as the endoplasmic reticulum, the mitochondria, the cytoskeleton, among others, and ultimately triggering apoptosis in developing heart structures. Furthermore, as discussed in the respective section, ROS hampers the maturation, proliferation and potential for differentiation of cardiomyocytes mostly via DNA impairment [97].

Another factor to acknowledge is the disruption of the normal structure and function of the placenta, due to a complex interaction of factors that ultimately leads to an impaired angiogenesis and an increase in vasoconstriction. This has a direct effect on the developing heart, since it leads to pathological hemodynamic alterations, as well as limiting blood supply to the growing fetus – resulting in an aberrant heart development while attempting to maintain its output [20, 98]. Another aspect that can potentiate myocardial hypertrophy, besides the increased afterload, is the nutrient overload, that results in hyperglycemia and insulin resistance [99], as well as chronic low-grade inflammation, which leads to high levels of pro-inflammatory molecules such as TGF-β and CRP. These induce a wrongful accumulation of collagen between fetal cardiomyocytes, with this promoting fibrosis that increases the thickness of the walls and weakens both the relaxation and contractile functions [100] – this mechanism has been found in ovine animal models, with evidence of impaired cardiomyocyte contractile capacity at term [101].

Finally, another intriguing factor possibly associated with fetal heart formation is the disruption of the maternal microbiota – previously demonstrated in this review to be another imbalance caused by obesity. Altered maternal gut microbiota can have a teratogenic action via the activation of signaling pathways that disrupt insulin sensitivity, by potentiating systemic inflammation, by contributing to a folate deficiency and by increasing the metabolic imbalance and altered lipid metabolism [58].

To conclude, obesity during gestation exerts a detrimental impact on fetal heart development by disrupting the intrauterine homeostasis, placental function, inflammatory system and redox balance (Fig. 5). Additionally, there is a disruption of key factors responsible for the transcription of proteins and signaling molecules that regulate the cardiac progenitors' differentiation, for the coordination of development and for a long-term gene maintenance. This way maternal obesity can be the cause of heart malformations, cardiac dysfunction – that can last from the first trimester, throughout the pregnancy and even after birth – and higher susceptibility to the development of CV diseases later in life when compared to lean mother's offspring – fetal programming [102].

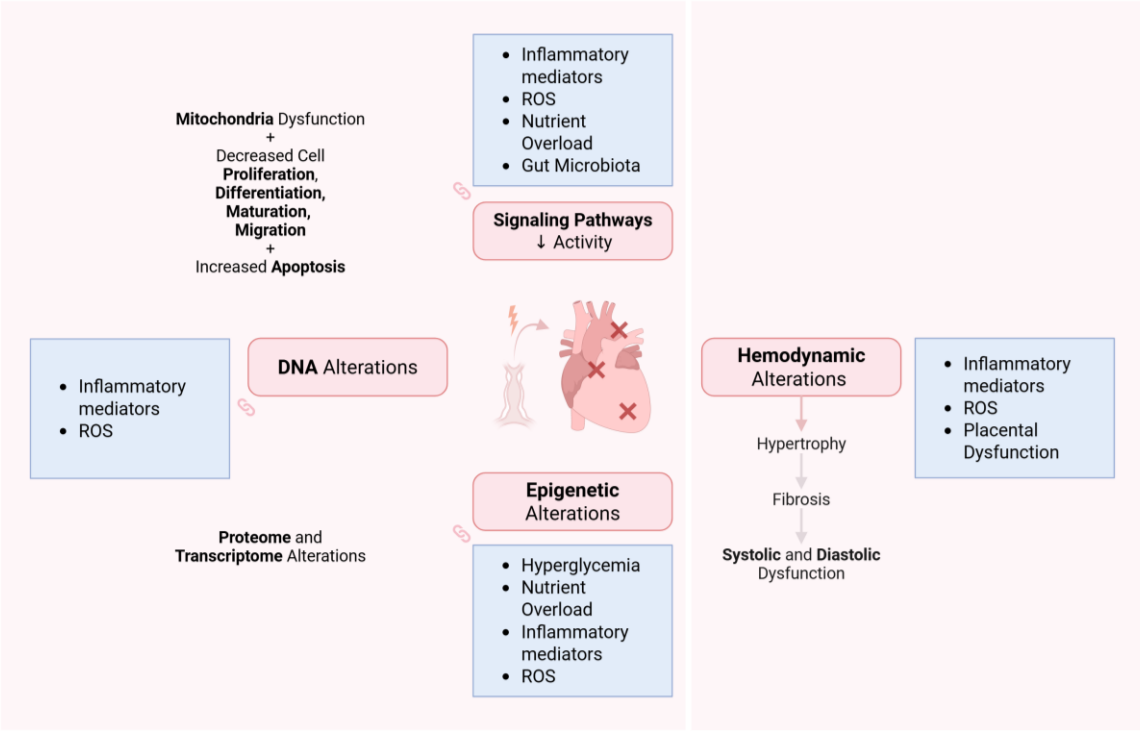


Figure 5. **The impact of maternal obesity on fetal cardiac development**. Maternal obesity is a disruptive metabolic status with an overload of circulating nutrients, such as glucose and lipids, being associated to phenomena like insulin resistance and lipotoxicity. This condition is known to induce a chronic low-grade inflammatory state, increasing several pro-inflammatory mediators systemically, provoking oxidative stress, with increased ROS and decreased antioxidant defenses, disrupting the homeostasis of gut microbiota and, finally, culminating in an alteration of the intrauterine milieu and placental function. Cardiogenesis starts very early in gestation, being comprised of various phases coordinated by genetic expression and signaling pathways– for this process to be successful there must be present proper cell division, controlled cell death, differentiation, maturation, timely migration and polarization, in addition to mechanical forces. Through complex mechanisms, the pro-inflammatory molecules and ROS will inflict DNA damage, which can impact crucial genes responsible for heart development. Similarly, hyperglycemia and lipotoxicity, along with inflammation and oxidative stress, will cause epigenetic alterations that lead to errors in the process of DNA expression and RNA transcription and transduction. In fact, these alterations cause proteome and transcriptome abnormalities, leading to the deficit of important components for the functioning of signaling pathways. Likewise, gut dysbiosis contributes to exacerbating the metabolic imbalance, while also producing metabolites that hinder these intracellular pathways. Lastly, obesity leads to placental malfunction and, along with the pro-inflammatory and oxidative state, there is poorer angiogenesis and an increase in vascular resistance that leads to inadequate blood flow to the fetus and increased afterload for the forming heart, culminating in hemodynamic changes – this can impair the development of the chambers and the proper organization of tissues. This combination of pathological processes can result in improper embryogenesis and cardiogenesis, leading to malformations on a molecular, cellular and/or anatomical level. Created in BioRender. Meneses, H. https://BioRender.com/jzur61u (accessed on 25 May 2025).

Maternal obesity and risk of fetal congenital heart disease

Congenital heart disease or congenital heart defects are, by definition, anatomical or functional malformations of the heart or great vessels that are present at the moment of birth, occurring at some point during the embryological and fetal development [103, 104, 105]. More precisely, these malformations can be characterized as a failure to complete the formation of the cardiac outline from the 1st to the 6th weeks of gestation [106].

It is estimated that there is an incidence of 4 or 6-10 in 1.000 live births, varying between countries and literature, and it is estimated that about 10% of the affected die within the first year of life [1, 2, 90, 103]. Consequently, these conditions have a high morbidity and mortality both at perinatal period and long-term [107]. In fact, these are the most common congenital defects diagnosed globally in newborns and the most frequent cause of death among infants diagnosed with any birth defect [105, 106].

Besides, nearly 50 years ago the vast majority of children with these cardiac congenital malformations would die between the first days of life and the first 6 months after birth. However, nowadays, owing to the advances of overall knowledge and investigation, diagnostic technology, intensive pediatric care, medical approaches and cardiac surgery techniques, about 85% of offspring born with these conditions have a much longer life expectancy, reaching adulthood [103, 108].

These malformations can be classified according to their overall impact – in mild (or minor), moderate (or significative) and severe (or complex) –, which can be based on the structural abnormality, quality of life, mortality (meaning if the defect is life threatening), in the need for immediate measures and even on its expected psychological influence [103]. To be specific, mild defects include the ASD, VSD, patent *ductus arteriosus* (PDA), aortic valve stenosis, pulmonary stenosis, mitral regurgitation and CoA. For instance, the significative defects comprise ToF, hypoplastic right heart (HRHS), Ebstein anomaly, TGA, pulmonary atresia and cardiomyopathy. The complex defects correspond to a combination of the above, such as ASD and VSD, ASD and PDA, ASD plus VSD and PDA, ASD and aortic stenosis, ASD and tricuspid regurgitation [109].

On the other hand, based on a more recent classification of the European Surveillance of Congenital Anomalies (EUROCAT), the malformations can be divided into two subgroups of severity. The minor or nonsevere comprise VSD, ASD, PDA, patent *foramen ovale*, persistent left superior vena cava, persistent right aortic arch, among others. The severe subgroup classified by EUROCAT are the ones that lead to a heart that functions as univentricular: UVH, HRHS, HLHS, Ebstein anomaly, *truncus arteriosus*, double outlet right or left ventricle, TGA, AVSD, ToF, pentalogy of Fallot, CoA, aortic stenosis/atresia, pulmonary atresia, mitral stenosis/atresia, tricuspid valve atresia, malformations of the coronaries, among others [7, 110].

With this said, the most prevalent, with a tendency to increase, are milder defects such as ASD, followed by VSD and PDA. In contrast, the left ventricular outflow tract obstruction (LVOTO) has been decreasing. The temporal evolution of the prevalence of these pathologies can be explained by earlier detection via prenatal diagnostic methods and consequent termination of pregnancies afflicted by major defects [111].

Despite their presence since the beginning of life, there are cases only identified at infancy or adolescence; however, at present, their diagnosis is usually perinatal [103]. Briefly, in a normal pregnancy, the screening of the heart's condition first takes place in the morphological sonography of the second trimester

following the systematic steps suggested by the International Society of Ultrasound in Obstetrics and Gynecology [107]. Moreover, there is a subsequent indication for fetal echocardiogram – which is the gold standard for antenatal diagnosis [112] – if any risk factors for CHD are present or if the detailed ultrasound had any suspicious findings [107]. Alternatively, the American College of Cardiology recommends a fetal echocardiogram assessment when any morphological anomalies are detected, when there is family history of CHD, fetal arrythmias or maternal risk factors [112].

Furthermore, the rate of antenatal detection ranges from 30 to 60%, according to the country, based on EUROCAT data. Later on, these CHD can be identified through newborn screening or further on if there are clinical manifestations [107].

When it comes to the etiology of these conditions, studies point to a multifactorial cause, with an interaction between genetic factors and environmental exposures. These risk factors can either be maternal, paternal, fetal or external, also being either modifiable or non-modifiable.

It seems consensual in the literature reviewed that the following maternal factors are associated to a higher risk of CHD: age of 35 years or higher – which can be related to chromosomal anomalies –, obesity, DM (pre-gestational or gestational), hypertension, autoimmune disorders, exposure to drugs (such as SNRIs or SSRI antidepressants like fluoxetine and paroxetine), exposure to lithium and chemicals (like solvents), and infections (such as rubella and measles). In addition, other studies point that smoking, alcohol ingestion, pollution, coffee intake and exposure to radiation may also be related to the development of CHD [104, 105, 106, 107, 113]. Likewise, family history is also presumably a risk factor for CHD – heredity was found especially in HLHS and bicuspid aortic valve [114]. Finally, there are also paternal factors that increase the risk of these anomalies, specifically the ones with the potential to decrease sperm quality – namely causing mutations and aneuploidies – like the father's age $\geq$ 40 years, smoking and alcohol intake [105,106]. Notwithstanding, authors defend distinct levels of evidence strength for the causal association of many of these factors, which can be explained by the different populations evaluated, the different methodologies of studies, multiple confounding factors, among other unexpected and uncontrolled variables [115].

At last, diving into the main subject of this review, maternal obesity appears to have a strong correlation with the development of several congenital malformations, such as neural tube defects, CHD, orofacial clefts, anal atresia, omphalocele, hypospadias, limb defects, among others [116].

When it comes to congenital heart disease, it seems to be, in fact, promoted by obesity, since an increased number of cases in mothers with higher BMI has been shown when compared to lean gravidas. With this said, the exact dose-effect relationship is not yet clear, nor is the pathophysiology of this association [117]. Thereafter, it has been suggested that obese mother's offspring have about a 17 - 32% increase in risk of having CHD when compared to normal weight mothers. Likewise, meta-analysis indicates that each increase in BMI of 5 kg/m2 can lead to a 7% increase in the risk of CHD, yet this relationship is not linear. Nevertheless, observational research articles still show inconsistent results to prove this association [115, 117].

Throughout this review several possible factors have been explored to approach the molecular basis of this causal relation. Hence, it was shown that the teratogenic effect of obesity is attributable to a conjuncture of factors, not only due to the abnormal metabolism of glucose or by direct damage of surplus nutrients [118].

In a nutshell, the exaggerated nutrient intake that surpasses metabolic needs will potentiate the accumulation of visceral adiposity. This increased adipose mass, that participates in endocrine functions, will be the cause of subclinical chronic inflammation – with increased levels of cytokines (MCP-1, IL-6, IL-8, TMFα, IFN-γ, among others), leptin, pro-coagulant factors and endocrine molecules such as estrogen –, of systemic oxidative stress, dysfunction of the endothelium, increased insulin resistance and hyperinsulinemia, and overall glucotoxicity and lipotoxicity. Additionally, obesity is linked to intestinal dysbiosis, which in turn can exacerbate the inflammation, oxidative stress and overall metabolic imbalance [37, 58]. Moreover, obese mothers have a higher susceptibility to developing diabetes – a well-known teratogenic condition – and hypertensive disorders – which themselves also constitute risk factors for cardiac developmental errors [105, 106, 118]. Besides, it is relevant to note that a less healthy diet with less intake of glutathione and folate, very common in these obese cases, can lead to a suboptimal uterine environment and errors in embryogenesis [114, 117]. This phenomenon occurs even when subjected to standard supplementation, given that these patients have a higher demand for folic acid than normal weight pregnant women [119, 120].

All of these metabolic, vascular, inflammatory and redox alterations will contribute to a disruptive intrauterine milieu, disfunction of the placenta and, importantly, to impair signaling paths, alter gene expression and manipulate epigenetic mechanisms of the embryo. Ultimately, these insults lead to the inhibition of cellular processes like proliferation, differentiation, maturation and migration, of both cardiac and non-cardiac cells (like neural crest cells) indispensable for cardiogenesis, as mentioned in the previous section [97]. Analogously, there is also an impairment of the embryo's stem cells, impaired cardiomyocyte function, possible accumulation of connective tissue, infiltration of inflammatory cells on fetal tissues and overall impairment of the heart's morphogenesis [105, 117].

In addition to the systemic consequences of this metabolic disarrangement, the maternal adipose layer can be a limiting factor for the proper early diagnosis of malformations in the antenatal period, by hindering the echographic window. This way, the increased independent risk for teratogenicity and fetal malformations is coupled with poor sonographic visibility, culminating in the termination of fewer pregnancies bearing severe fetal anomalies and a consequent higher prevalence of these disorders at birth [116, 118].

As a concluding remark, maternal obesity is believed to increase the risk for all cardiac defects, but it is more associated with certain subtypes of CHD like ASD and conotruncal or outflow tract defects. Moreover, reports also state increased incidence of complex defects, HLHS, CoA, AVSD and, arguably, VSD and ToF. It is also important to acknowledge the discrepancy in the results of several studies that may be due to different sample sizes, confounding factors and the prevalence of different subtypes of CHD in different populations [105, 116, 118, 121].

Discussion

Congenital heart defects are anatomical or functional malformations of the heart or great vessels, present at birth, developed somewhere between embryological and fetal development [2, 103, 104, 105]. They constitute the main cause of infant morbimortality due to congenital abnormalities [2, 4, 5]. It is believed that the etiology of CHD is based on a complex interplay of genetic and environmental agents, with several modifiable and non-modifiable risk factors identified [1, 5, 7, 8]. This way, maternal obesity may be a condition worth investigating as a modifiable factor for CHD [4].

Maternal obesity (BMI ≥ 30 kg/m2 pre-pregnancy or at the first consultation) seems to be a disruptive condition for pregnancy and fetal development in many ways, constituting a modifiable risk factor for adverse outcomes [4, 12]. In fact, obesity is a current epidemic, increasing among fertile women, being a disease with a high morbimortality [9, 15]. Therefore, this metabolic and anatomic disarrangement leads to complications, both for the mother – such as hypertensive disorders, gestational DM, cardiovascular and thromboembolic events, need for c-section and amniotomy, hemorrhage, infections, among others [13, 16] – and the fetus – macrosomia, IUGR, dystocia, birth trauma and lower APGAR scores, NICU admission, several malformations, higher susceptibility to cardiometabolic diseases later in life, and more [4, 12, 20, 21, 22] – with either immediate or long-term consequences [10].

Broadly speaking, obesity induces in the pregnant woman a higher insulin resistance, a systemic inflammatory state [24] – with alterations of cytokines [50,54] and adipokine concentrations [20, 27, 78] – oxidative stress [62], increased circulating FFA and glucose – resulting in lipotoxicity and glucotoxicity [24, 27] – and intestinal microbiota dysbiosis [37,58]. Overall, obesity impacts the oocyte's quality and all of the embryo's and later fetal development [18].

It is worth highlighting the influence of obesity on the fetoplacental unit. The nutrient overload coupled with hormonal imbalances (hyperinsulinemia, increased leptin and IGF-1, and decreased adiponectin) stimulate placental transporters – of glucose, amino acids and FFA –, delivering this surplus of nutrients to the fetus [20,26,38]. The placenta is also invaded by immune cells and cytokines [26,32], inducing early senescence due to DNA damage [41], as well as increasing the susceptibility to inflammatory events like vasculitis or even chorioamnionitis [39]. Likewise, heightened oxidative and nitritive stress in placental tissues contribute to its dysfunction and deterioration, while the antioxidant defenses are weakened [38,45,46]. These prior mechanisms also contribute to placental mitochondrial dysfunction, culminating in the inability to meet energy requirements through aerobic respiration [32,42]. Finally, obesity, through this interplay of processes, causes endothelial dysregulation, impairing placental angiogenesis and leading to an insufficient blood flow to the fetus [33,47,48]. In addition, the placenta plays a distinct role in cardiogenesis, being the source of biomechanical forces that influence the fetal heart's anatomy and its cardiomyocytes [34,35].

As discussed above, obesity leads to a pro-inflammatory environment, that will negatively impact the fetus, with an increase in IL-8, IL-6, TNFα, IFN-γ, MCP-1, MIP-1α CRP, among other molecules that are characteristic of a type 1 inflammatory response [50, 52, 54]. Similarly, the immune cell population in the uterine landscape changes, with a disruption of the tolerant environment and abnormal activation of uNK cells [49]. These cytokines and immune cells will damage the decidua and placenta and, consequently, can be found in fetal tissues, disrupting genetic expression and inflicting cellular stress [52, 53,55]. Lastly, the imbalance of the immune system can even increase the susceptibility to maternal infection, which can reach the fetus [50].

Likewise, anti-inflammatory molecules like adiponectin are decreased [79]. This specific adipokine, when reduced, will increase glycemia, due to the reduced uptake by muscle and liver [79,80], and will potentiate the nutrient influx, namely glucose, through the placental carriers to the fetus [78,81]. This will lead to developmental errors similar to the ones associated with DM, even when this condition's diagnostic criteria are not present [78,88,118].

About the redox imbalance: obesity leads to an increase in pro-oxidant molecules, like ROS, NO and MDA, that is not counteracted by antioxidant species, which in turn are decreased, culminating in oxidative stress [63,74] – this is linked both to the excessive lipid peroxidation [73], tissular hypoxia [62,72] and the chronic low-grade inflammatory state [67]. These abnormally increased pro-oxidant species have a well-known capacity of being reactive towards lipids, proteins and DNA, damaging the genetic information and impairing embryological and fetal development – genotoxicity and teratogenicity [62,64,65,71].

Additionally, due to the large adipose panicle and anatomical restraints, maternal obesity limits the sonographic visibility of the fetus – crucial for monitoring the pregnancy and screening for potential malformations [17, 116, 118].

Thereafter, maternal obesity can hamper fetal cardiac development, that begins very early in gestation [90], on a molecular scale via the impairment of mitochondrial function, direct and indirect DNA damage – with genetic or epigenetic changes –, causing the alteration of the transcriptome and proteome, and consequent inhibition of the normal signaling pathways and involved molecules (NOTCH, Wnt, TGF-β, FGF, BMP, GATA transcription factors, SRF, and others) [93, 97]. Having embryogenesis in mind, the cellular processes needed for the heart's formation will be hampered – proliferation, differentiation, maturation, migration and polarization [97]. For instance, the embryo's stem cells pluripotent capacity can be limited, cardiac precursor cells may not differentiate or migrate properly, cardiomyocyte function can be abnormal and there can be fibrosis of heart tissue [101,105,117]. Similarly, the placental abnormalities will induce deleterious hemodynamic forces [98].

These metabolic, inflammatory, oxidative and vascular changes have the potential to manifest at any time during pregnancy; however, congenital heart disease will occur if the earliest stages of embryogenesis are disrupted, noting that the defect will be more severe the earlier the cardiogenesis error occurs [90,96, 102].

In light of the evidence reviewed, maternal obesity does increase the theoretical risk of all CHD, though studies show a stronger association to ASD and outflow conotruncal defects and, debatably, HLHS, CoA, AVSD, VSD and ToF [105, 116, 118, 121].

Upon examining the existing literature, some limitations were identified, that created a certain inability to objectively analyze all studies from the same point of view. Firstly, multiple articles use different epidemiological data concerning CHD, while not always identifying whether only live births were accounted or whether terminations and cases of CHD diagnosed after birth (for instance in nursery or childhood) were included as well. For this scenario we suggest including all cases in order to obtain a more reliable depiction of the actual reality. Likewise, questions remain about the impact of different classes of obesity as well as the differentiation of the impact of excessive GWG. Similarly, there remains the uncertainty of whether the impact of the aforementioned molecular mechanisms is different according to offspring's sex. We suggest, as well, that special attention should be paid to other confounding factors, namely gestational DM, to clarify their different mechanisms of teratogenicity. Additionally, there should be a particular focus on recording active or passive

maternal exposures or paternal factors, which are often overlooked and can hamper results. Finally, another crucial factor that ought to be controlled and explored for a better understanding of the association here reviewed is the maternal diet, both before and during gestation.

In order to address these limitations in current literature, we recommend perhaps carrying out a large-scale cohort study with detailed data gathering. Another interesting possibility is a stratified analysis in population-based registries, in hopes to better elucidate the prevalence, the timing and biological pathways underlying the association between maternal obesity and congenital malformations, especially CHD. Lastly, investing in studies with animal or cellular models can continue to improve the knowledge of these molecular mechanisms. Randomized trials with pre-conceptional interventions can also be considered, with due regard for ethical concerns.

All things considered, this review highlights key issues worth investigating in further studies, focusing on these pathological mechanisms, to better understand the causality of birth defects linked to maternal obesity. This way, improvements can be made in the prevention and early detection of these cardiac malformations, focusing on obesity's management and ensuring optimum pre-conceptional care, proper supplementation and obstetric surveillance.

Conclusion

To summarize, obesity is an endocrine disease that leads to metabolic, inflammatory, oxidative and vascular changes. Hence, in the situation of maternal obesity, the intrauterine milieu reflects these changes, manifested by placental dysfunction, embryological and fetal consequences, as well as obstetrical difficulties. In this review it was shown that obese mothers are, indeed, more likely to have a child with CHD, and the pathophysiology of this association, at a cellular and molecular level, is becoming clearer. These biological pathways seem to be related to the nutrient overload, chronic low-grade inflammatory status, systemic oxidative stress and placental alterations, such as unrestrained nutrient transport and mitochondrial dysfunction. Finaly, as obesity seems to be a modifiable risk factor, there should be a greater investment in determining how and when to intervene in order to prevent the development of CHD, as well as to define the optimal techniques for early diagnosis in obese women.

Ethics Committee Approval

N/A

Peer-review

Externally peer-reviewed.

Author Contributions

Concept – H.M., L.G-M.; Design – H.M., L.G-M.; Supervision – L.G-M.; Literature Review – H.M., L.G-M.; Writer – H.M., L.G-M.; Critical Review- L.G-M.

Consent for Publication

Not applicable.

Conflicts of Interest

We have no conflicts of interest in this review.

Financial Disclosure

The authors declared that this study received no financial support.

References

[1] Mamasoula, C.; Addor, M. C.; Carbonell, C. C.; Dias, C. M.; Echevarría-González-de-Garibay, L. J.; Gatt, M.; Khoshnood, B.; Klungsoyr, K.; Randall, K.; Stoianova, S.; Haeusler, M.; Nelen, V.; Neville, A. J.; Perthus, I.; Pierini, A.; Bertaut-Nativel, B.; Rissmann, A.; Rouget, F.; Schaub, B.; Tucker, D.; Wellesley, D.; Zymak-Zakutnia, N.; Barisic, I.; de Walle, H. E. K.; Lanzoni, M.; Mullaney, C.; Pennington, L.; Rankin, J. Prevalence of Congenital Heart Defects in Europe, 2008–2015: A Registry-Based Study. *Birth Defects Research* **2022**, *114* (20), 1404–1416. https://doi.org/10.1002/bdr2.2117.

[2] Faim, D.; Tiago, J.; Castelo, R.; Francisco, A.; Alves, R.; Pires, A. Congenital Heart Disesase: A Retrospective Analysis from a Tertiary Referral Centre in Portugal. *International Journal of Cardiovascular Sciences* **2021**, *34* (5), 105–113. https://doi.org/10.36660/ijcs.20200238.

[3] de Melo, I. S.; Braz, P.; Roquette, R.; Sousa, P.; Nunes, C.; Dias, C. Congenital Heart Disease Prevalence in Portugal in 2015: Data from the National Register of Congenital Anomalies. *Acta Medica Portuguesa* **2020**, *33* (7–8), 491–499. https://doi.org/10.20344/amp.12111.

[4] Correa, A. Maternal Body Mass Index and Congenital Heart Defects ∗. *Journal of the American College of Cardiology* **2019**, *73* (1), 54–57. https://doi.org/10.1016/j.jacc.2018.10.047.

[5] Pei, L.; Kang, Y.; Zhao, Y.; Yan, H. Prevalence and Risk Factors of Congenital Heart Defects among Live Births: A Population-Based Cross-Sectional Survey in Shaanxi Province, Northwestern China. *BMC Pediatrics* **2017**, *17* (1), 1–8. https://doi.org/10.1186/s12887-017-0784-1.

[6] Morris, J. K.; Springett, A. L.; Greenlees, R.; Loane, M.; Addor, M.-C.; Arriola, L.; Barisic, I.; Bergman, J. E. H.; Csaky-Szunyogh, M.; Dias, C.; Draper, E. S.; Garne, E.; Gatt, M.; Khoshnood, B.; Klungsoyr, K.;

Lynch, C.; McDonnell, R.; Nelen, V.; Neville, A. J.; O'Mahony, M.; Pierini, A.; Queisser-Luft, A.; Randrianaivo, H.; Rankin, J.; Rissmann, A.; Kurinczuk, J.; Tucker, D.; Verellen-Dumoulin, C.; Wellesley, D.; Dolk, H. Trends in Congenital Anomalies in Europe from 1980 to 2012. *PloS one* **2018**, *13* (4), e0194986. https://doi.org/10.1371/journal.pone.0194986.

[7] Hedermann, G.; Hedley, P. L.; Gadsbøll, K.; Thagaard, I. N.; Krebs, L.; Hagen, C. M.; Sørensen, T. I. A.; Christiansen, M.; Ekelund, C. K. Maternal Obesity, Interpregnancy Weight Changes and Congenital Heart Defects in the Offspring: A Nationwide Cohort Study. *International journal of obesity (2005)* **2024**, *48* (8), 1126–1132. https://doi.org/10.1038/s41366-024-01531-5.

[8] Persson, M.; Razaz, N.; Edstedt Bonamy, A.-K.; Villamor, E.; Cnattingius, S. Maternal Overweight and Obesity and Risk of Congenital Heart Defects. *Journal of the American College of Cardiology* **2019**, *73* (1), 44–53. https://doi.org/10.1016/j.jacc.2018.10.050.

[9] Alves, P.; Malheiro, M. F.; Gomes, J. C.; Ferraz, T.; Montenegro, N. Risks of Maternal Obesity in Pregnancy: A Case-Control Study in a Portuguese Obstetrical Population. *Revista Brasileira de Ginecologia e Obstetricia* **2019**, *41* (12), 682–687. https://doi.org/10.1055/s-0039-3400455.

[10] Korkmaz, L.; Baştuğ, O.; Kurtoğlu, S. Maternal Obesity and Its Short- and Long-Term Maternal and Infantile Effects. *Journal of clinical research in pediatric endocrinology* **2016**, *8* (2), 114–124. https://doi.org/10.4274/jcrpe.2127.

[11] Rayburn, W. F.; Jolley, J. A.; Simpson, L. L. Advances in Ultrasound Imaging for Congenital Malformations during Early Gestation. *Birth defects research. Part A, Clinical and molecular teratology* **2015**, *103* (4), 260–268. https://doi.org/10.1002/bdra.23353.

[12] Scialli, A. R. Teratology Public Affairs Committee Position Paper: Maternal Obesity and Pregnancy. *Birth defects research. Part A, Clinical and molecular teratology* **2006**, *76* (2), 73–77. https://doi.org/10.1002/bdra.20236.

[13] Andreasen, K. R.; Andersen, M. L.; Schantz, A. L. Obesity and Pregnancy. *Acta obstetricia et gynecologica Scandinavica* **2004**, *83* (11), 1022–1029. https://doi.org/10.1111/j.0001-6349.2004.00624.x.

[14] Liu, W.; Ren, L.; Fang, F.; Chen, R. Maternal Pre-Pregnancy Overweight or Obesity and Risk of Birth Defects in Offspring: Population-Based Cohort Study. *Acta obstetricia et gynecologica Scandinavica* **2024**, *103* (5), 862–872. https://doi.org/10.1111/aogs.14786.

[15] Guglielmi, V.; Dalle Grave, R.; Leonetti, F.; Solini, A. Female Obesity: Clinical and Psychological Assessment toward the Best Treatment. *Frontiers in Endocrinology* **2024**, *15* (May), 1–21. https://doi.org/10.3389/fendo.2024.1349794.

[16] Davis, A. M. Collateral Damage: Maternal Obesity During Pregnancy Continues to Rise. *Obstetrical & gynecological survey* **2020**, *75* (1), 39–49. https://doi.org/10.1097/OGX.0000000000000734.

[17] Siddiqui, F.; Kalache, K.; Ahmed, B.; Konje, J. C. Challenges of Prenatal Diagnosis in Obese Pregnant Women. *Best Practice and Research: Clinical Obstetrics and Gynaecology* **2024**, *95* (February), 102470. https://doi.org/10.1016/j.bpobgyn.2024.102470.

[18] Iessa, N.; Bérard, A. Update on Prepregnancy Maternal Obesity: Birth Defects and Childhood Outcomes. *Journal of pediatric genetics* **2015**, *4* (2), 71–83. https://doi.org/10.1055/s-0035-1556739.

[19] Purohit, A.; Oyeka, C. P.; Khan, S. S.; Toscano, M.; Nayak, S.; Lawson, S. M.; Blumenthal, R. S.; Sharma, G. Preventing Adverse Cardiovascular Outcomes in Pregnancy Complicated by Obesity. *Current*

obstetrics and gynecology reports **2023**, *12* (2), 129–137. https://doi.org/10.1007/s13669-023-00356-9.

[20] Salmeri, N.; Seidenari, A.; Cavoretto, P. I.; Papale, M.; Candiani, M.; Farina, A. Maternal Prepregnancy Weight as an Independent Risk Factor for Congenital Heart Defect: Systematic Review and Meta-Analysis Stratified by Subtype and Severity of Defect. *Ultrasound in Obstetrics and Gynecology* **2024**, *64* (3), 294–307. https://doi.org/10.1002/uog.27659.

[21] Blomberg, M. I.; Källén, B. Maternal Obesity and Morbid Obesity: The Risk for Birth Defects in the Offspring. *Birth defects research. Part A, Clinical and molecular teratology* **2010**, *88* (1), 35–40. https://doi.org/10.1002/bdra.20620.

[22] Lewandowska, M. Maternal Obesity and Risk of Low Birth Weight, Fetal Growth Restriction, and Macrosomia: Multiple Analyses. *Nutrients* **2021**, *13*, 1213.

[23] Tsang, R.; Hilvers, P.; Lupo, P. J.; Bronicki, R.; McKenzie, D.; Checchia, P. A. Maternal Obesity and Excessive Maternal Weight Gain during Pregnancy: Effects on Outcomes after Neonatal Cardiac Surgical Procedures. *Cardiology in the young* **2018**, *28* (3), 391–396. https://doi.org/10.1017/S1047951117001597.

[24] Parrettini, S.; Caroli, A.; Torlone, E. Nutrition and Metabolic Adaptations in Physiological and Complicated Pregnancy: Focus on Obesity and Gestational Diabetes. *Frontiers in Endocrinology* **2020**, *11* (November), 1–19. https://doi.org/10.3389/fendo.2020.611929.

[25] (25) Guedes-Martins, L.; Carvalho, M.; Silva, C.; Cunha, A.; Saraiva, J.; Macedo, F.; Almeida, H.; Rita Gaio, A. Relationship between Body Mass Index and Mean Arterial Pressure in Normotensive and Chronic Hypertensive Pregnant Women: A Prospective, Longitudinal Study. *BMC Pregnancy and Childbirth* **2015**, *15* (1). https://doi.org/10.1186/s12884-015-0711-0.

[26] Kelly, A. C.; Powell, T. L.; Jansson, T. Placental Function in Maternal Obesity. *Clinical Science* **2020**, *134* (8), 961–984. https://doi.org/10.1042/CS20190266.

[27] Hedermann, G.; Hedley, P. L.; Thagaard, I. N.; Krebs, L.; Ekelund, C. K.; Sørensen, T. I. A.; Christiansen, M. Maternal Obesity and Metabolic Disorders Associate with Congenital Heart Defects in the Offspring: A Systematic Review. *PloS one* **2021**, *16* (5), e0252343. https://doi.org/10.1371/journal.pone.0252343.

[28] Jarvie, E.; Hauguel-de-Mouzon, S.; Nelson, S. M.; Sattar, N.; Catalano, P. M.; Freeman, D. J. Lipotoxicity in Obese Pregnancy and Its Potential Role in Adverse Pregnancy Outcome and Obesity in the Offspring. *Clinical Science* **2010**, *119* (3), 123–129. https://doi.org/10.1042/CS20090640.

[29] Bak, G. S.; Shaffer, B. L.; Madriago, E.; Allen, A.; Kelly, B.; Caughey, A. B.; Pereira, L. Impact of Maternal Obesity on Fetal Cardiac Screening: Which Follow-up Strategy Is Cost-Effective? *Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology* **2020**, *56* (5), 705–716. https://doi.org/10.1002/uog.21895.

[30] Fox, A.; Hayes, B.; Doyle, E. Advancing Our Knowledge of Placental Function and How It Relates to the Developing Fetal Brain. *Seminars in Fetal and Neonatal Medicine* **2024**, *29* (2–3), 101549. https://doi.org/10.1016/j.siny.2024.101549.

[31] Liu, L.; Tang, L.; Chen, S.; Zheng, L.; Ma, X. Decoding the Molecular Pathways Governing Trophoblast Migration and Placental Development; a Literature Review. *Frontiers in Endocrinology* **2024**, *15* (November), 1–16. https://doi.org/10.3389/fendo.2024.1486608.

[32] Myatt, L.; Maloyan, A. Obesity and Placental Function. *Seminars in reproductive medicine* **2016**, *34* (1), 42–49. https://doi.org/10.1055/s-0035-1570027.

[33] Louwen, F.; Kreis, N. N.; Ritter, A.; Yuan, J. Maternal Obesity and Placental Function: Impaired Maternal–Fetal Axis. *Archives of Gynecology and Obstetrics* **2024**, *309* (6), 2279–2288. https://doi.org/10.1007/s00404-024-07462-w.

[34] Leon, R. L.; Bitar, L.; Rajagopalan, V.; Spong, C. Y. Interdependence of Placenta and Fetal Cardiac Development. *Prenatal Diagnosis* **2024**, *44* (6–7), 846–855. https://doi.org/10.1002/pd.6572.

[35] Ferreira, B. D.; Barros, T.; Moleiro, M. L.; Guedes-Martins, L. Preeclampsia and Fetal Congenital Heart Defects. *Current Cardiology Reviews* **2022**, *18* (5). https://doi.org/10.2174/1573403x18666220415150943.

[36] Justesen, S.; Bilde, K.; Olesen, R. H.; Pedersen, L. H.; Ernst, E.; Larsen, A. ABCB1 Expression Is Increased in Human First Trimester Placenta from Pregnant Women Classified as Overweight or Obese. *Scientific reports* **2023**, *13* (1), 5175. https://doi.org/10.1038/s41598-023-31598-5.

[37] Hu, C.; Yan, Y.; Ji, F.; Zhou, H. Maternal Obesity Increases Oxidative Stress in Placenta and It Is Associated With Intestinal Microbiota. *Frontiers in Cellular and Infection Microbiology* **2021**, *11* (August), 1–11. https://doi.org/10.3389/fcimb.2021.671347.

[38] Malti, N.; Merzouk, H.; Merzouk, S. A.; Loukidi, B.; Karaouzene, N.; Malti, A.; Narce, M. Oxidative Stress and Maternal Obesity: Feto-Placental Unit Interaction. *Placenta* **2014**, *35* (6), 411–416. https://doi.org/10.1016/j.placenta.2014.03.010.

[39] Åmark, H.; Säker, L.; Papadogianakis, N. Placental Inflammation and Overweight or Obesity in Term Singleton Stillbirths in Stockholm County 2002–2018; a Case Control Study. *PLoS ONE* **2023**, *18* (4 April), 1–11. https://doi.org/10.1371/journal.pone.0284525.

[40] Zhang, C. X. W. W.; Candia, A. A.; Sferruzzi-Perri, A. N. Placental Inflammation, Oxidative Stress, and Fetal Outcomes in Maternal Obesity. *Trends in Endocrinology and Metabolism* **2024**, *35* (7), 638–647. https://doi.org/10.1016/j.tem.2024.02.002.

[41] Hoch, D.; Majali-Martinez, A.; Bandres-Meriz, J.; Bachbauer, M.; Pochlauer, C.; Kaudela, T.; Tokic, S. Obesity-Associated Non-Oxidative Genotoxic Stress Alters Trophoblast Turnover in Human First-Trimester Placentas. **2024**, *30* (8).

[42] Mele, J.; Muralimanoharan, S.; Maloyan, A.; Myatt, L. Impaired Mitochondrial Function in Human Placenta with Increased Maternal Adiposity. *American journal of physiology. Endocrinology and metabolism* **2014**, *307* (5), E419-25. https://doi.org/10.1152/ajpendo.00025.2014.

[43] Salvolini, E.; Vignini, A.; Sabbatinelli, J.; Lucarini, G.; Pompei, V.; Sartini, D.; Cester, A. M.; Ciavattini, A.; Mazzanti, L.; Emanuelli, M. Nitric Oxide Synthase and VEGF Expression in Full-Term Placentas of Obese Women. *Histochemistry and cell biology* **2019**, *152* (6), 415–422. https://doi.org/10.1007/s00418-019-01819-y.

[44] Mueller, A.; Koebnick, C.; Binder, H.; Hoffmann, I.; Schild, R. L.; Beckmann, M. W.; Dittrich, R. Placental Defence Is Considered Sufficient to Control Lipid Peroxidation in Pregnancy. *Medical Hypotheses*. **2005**, pp 553–557. https://doi.org/10.1016/j.mehy.2004.08.008.

[45] Tao, Y.; Chen, W.; Xu, H.; Xu, J.; Yang, H.; Luo, X.; Chen, M.; He, J.; Bai, Y.; Qi, H. Adipocyte-Derived Exosomal NOX4-Mediated Oxidative Damage Induces Premature Placental Senescence in Obese Pregnancy. *International Journal of Nanomedicine* **2023**, *18* (August 2023), 4705–4726. https://doi.org/10.2147/IJN.S419081.

[46] Perrone, S.; Laschi, E.; Buonocore, G. Biomarkers of Oxidative Stress in the Fetus and in the Newborn. *Free Radical Biology and Medicine*. **2019**, pp 23–31. https://doi.org/10.1016/j.freeradbiomed.2019.03.034.

[47] Helle, E.; Priest, J. R. Maternal Obesity and Diabetes Mellitus as Risk Factors for Congenital Heart Disease in the Offspring. *Journal of the American Heart Association* **2020**, *9* (8), e011541. https://doi.org/10.1161/JAHA.119.011541.

[48] Zhao, H.; Wong, R. J.; Stevenson, D. K. The Placental Vasculature Is Affected by Changes in Gene Expression and Glycogen-Rich Cells in a Diet-Induced Obesity Mouse Model. *PLoS ONE* **2023**, *18* (11 November), 1–20. https://doi.org/10.1371/journal.pone.0294185.

[49] St-Germain, L. E.; Castellana, B.; Baltayeva, J.; Beristain, A. G. Maternal Obesity and the Uterine Immune Cell Landscape: The Shaping Role of Inflammation. *International Journal of Molecular Sciences* **2020**, *21* (11). https://doi.org/10.3390/ijms21113776.

[50] Rizzo, G. S.; Sen, S. Maternal Obesity and Immune Dysregulation in Mother and Infant: A Review of the Evidence. *Paediatric Respiratory Reviews* **2015**, *16* (4), 251–257. https://doi.org/10.1016/j.prrv.2014.10.005.

[51] Denizli, M.; Capitano, M. L.; Kua, K. L. Maternal Obesity and the Impact of Associated Early-Life Inflammation on Long-Term Health of Offspring. *Frontiers in Cellular and Infection Microbiology* **2022**, *12* (September), 1–17. https://doi.org/10.3389/fcimb.2022.940937.

[52] Blossom, S. J.; Rau, J. L.; Best, T. H.; Bornemeier, R. A.; Hobbs, C. A. Increased Maternal Cytokine Production and Congenital Heart Defects. *Journal of reproductive immunology* **2013**, *97* (2), 204–210. https://doi.org/10.1016/j.jri.2012.12.004.

[53] Parisi, F.; Milazzo, R.; Savasi, V. M.; Cetin, I. Maternal Low-Grade Chronic Inflammation and Intrauterine Programming of Health and Disease. *International Journal of Molecular Sciences* **2021**, *22* (4), 1–16. https://doi.org/10.3390/ijms22041732.

[54] Pendeloski, K. P. T.; Ono, E.; Torloni, M. R.; Mattar, R.; Daher, S. Maternal Obesity and Inflammatory Mediators: A Controversial Association. *American Journal of Reproductive Immunology* **2017**, *77* (5), 1–8. https://doi.org/10.1111/aji.12674.

[55] Robertson, S. A.; Chin, P. Y.; Femia, J. G.; Brown, H. M. Embryotoxic Cytokines—Potential Roles in Embryo Loss and Fetal Programming. *Journal of Reproductive Immunology* **2018**, *125* (October 2017), 80–88. https://doi.org/10.1016/j.jri.2017.12.003.

[56] Pomar, C. A.; Trepiana, J.; Besné-Eseverri, I.; Castillo, P.; Palou, A.; Palou, M.; Portillo, M. P.; Picó, C. Maternal Dietary Improvement or Leptin Supplementation During Suckling Mitigates the Long-Term Impact of Maternal Obesogenic Conditions on Inflammatory and Oxidative Stress Biomarkers in the Offspring of Diet-Induced Obese Rats. *International journal of molecular sciences* **2024**, *25* (22), 1–17. https://doi.org/10.3390/ijms252211876.

[57] Basak, S.; Das, R. K.; Banerjee, A.; Paul, S.; Pathak, S.; Duttaroy, A. K. Maternal Obesity and Gut Microbiota Are Associated with Fetal Brain Development. *Nutrients* **2022**, *14* (21). https://doi.org/10.3390/nu14214515.

[58] Wang, T.; Chen, L.; Huang, P.; Yang, T.; Zhang, S.; Zhao, L.; Chen, L.; Ye, Z.; Luo, L.; Qin, J. Association of Maternal Gut Microbiota and Plasma Metabolism with Congenital Heart Disease in Offspring: A Multi-

Omic Analysis. *Scientific reports* **2021**, *11* (1), 5339. https://doi.org/10.1038/s41598-021-84901-7.

[59] Gohir, W.; Ratcliffe, E. M.; Sloboda, D. M. Of the Bugs That Shape Us: Maternal Obesity, the Gut Microbiome, and Long-Term Disease Risk. *Pediatric Research* **2015**, *77* (1), 196–204. https://doi.org/10.1038/pr.2014.169.

[60] Vaghef-Mehrabani, E.; Bell, R. C.; Field, C. J.; Jarman, M.; Evanchuk, J. L.; Letourneau, N.; Dewey, D.; Giesbrecht, G. F. Maternal Pre-Pregnancy Weight Status and Gestational Weight Gain in Association with Child Behavior: The Mediating Role of Prenatal Systemic Inflammation. *Clinical Nutrition ESPEN* **2024**, *59*, 249–256. https://doi.org/10.1016/j.clnesp.2023.12.006.

[61] Ingvorsen, C.; Brix, S.; Ozanne, S. E.; Hellgren, L. I. The Effect of Maternal Inflammation on Foetal Programming of Metabolic Disease. *Acta Physiologica* **2015**, *214* (4), 440–449. https://doi.org/10.1111/apha.12533.

[62] Poston, L.; Igosheva, N.; Mistry, H. D.; Seed, P. T.; Shennan, A. H.; Rana, S.; Karumanchi, S. A.; Chappell, L. C. Role of Oxidative Stress and Antioxidant Supplementation in Pregnancy Disorders. *The American journal of clinical nutrition* **2011**, *94* (6 Suppl), 1980S-1985S. https://doi.org/10.3945/ajcn.110.001156.

[63] Blanco, A. L. Y.; Díaz-López, K. M.; Vilchis-Gil, J.; Diaz-Garcia, H.; Gomez-Lopez, J.; Medina-Bravo, P.; Granados-Riveron, J. T.; Gallardo, J. M.; Klünder-Klünder, M.; Sánchez-Urbina, R. Diet and Maternal Obesity Are Associated with Increased Oxidative Stress in Newborns: A Cross-Sectional Study. *Nutrients* **2022**, *14* (4), 1–11. https://doi.org/10.3390/nu14040746.

[64] Pietryga, M.; Tobola-Wrobel, K.; Dydowicz, P.; Ziolkowska, K.; Napierala, M.; Florek, E.; Brazert, J. Can Redox Imbalance Predict Abnormal Foetal Development? *Ginekologia Polska* **2022**, *93* (3), 209–216. https://doi.org/10.5603/GP.a2021.0122.

[65] Diniz, M. S.; Magalhães, C. C.; Tocantins, C.; Grilo, L. F.; Teixeira, J.; Pereira, S. P. Nurturing through Nutrition: Exploring the Role of Antioxidants in Maternal Diet during Pregnancy to Mitigate Developmental Programming of Chronic Diseases. *Nutrients* **2023**, *15* (21). https://doi.org/10.3390/nu15214623.

[66] Bláhová, L.; Janoš, T.; Mustieles, V.; Rodríguez-Carrillo, A.; Fernández, M. F.; Bláha, L. Rapid Extraction and Analysis of Oxidative Stress and DNA Damage Biomarker 8-Hydroxy-2′-Deoxyguanosine (8-OHdG) in Urine: Application to a Study with Pregnant Women. *International Journal of Hygiene and Environmental Health* **2023**, *250* (April). https://doi.org/10.1016/j.ijheh.2023.114175.

[67] de Oliveira, M. P.; da Silva, L. E.; Fernandes, B. B.; Steiner, M. R.; Pistóia, D. G.; Santos Cichella, T. dos; Jacinto, L. B.; Spuldaro, K. M.; Pinto Moehlecke Iser, B.; Rezin, G. T. The Impact of Obesity on Mitochondrial Dysfunction during Pregnancy. *Molecular and Cellular Endocrinology* **2025**, *598* (December 2024). https://doi.org/10.1016/j.mce.2025.112463.

[68] Yang, J.; Du, Q.; Xiao, Z.; Guo, R.; Chang, Q.; Li, Y. H. Maternal Oxidative Balance Score during Pregnancy and Congenital Heart Defects. *Nutrients* **2024**, *16* (12), 2–11. https://doi.org/10.3390/nu16121825.

[69] Choudhury, T. Z.; Greskovich, S. C.; Girard, H. B.; Rao, A. S.; Budhathoki, Y.; Cameron, E. M.; Conroy, S.; Li, D.; Zhao, M. T.; Garg, V. Impact of Genetic Factors on Antioxidant Rescue of Maternal Diabetes–Associated Congenital Heart Disease. *JCI Insight* **2024**, *9* (23), 1–15.

https://doi.org/10.1172/jci.insight.183516.

[70] Maduro, C.; Castro, L. F. De; Moleiro, M. L.; Guedes-Martins, L. Pregestational Diabetes and Congenital Heart Defects. *Revista Brasileira de Ginecologia e Obstetricia* **2022**, *44* (10), 953–961. https://doi.org/10.1055/s-0042-1755458.

[71] Stegmann, S. K.; Vohlen, C.; Im, N. G.; Niehues, J.; Selle, J.; Janoschek, R.; Kuiper-Makris, C.; Lang, S.; Demir, M.; Steffen, H. M.; Quaas, A.; Lackmann, J. W.; Nierhoff, D.; Neumann-Haefelin, C.; Dötsch, J.; Alejandre Alcazar, M. A.; Kasper, P. Perinatal Obesity Primes the Hepatic Metabolic Stress Response in the Offspring across Life Span. *Scientific Reports* **2025**, *15* (1), 1–13. https://doi.org/10.1038/s41598-025-90082-4.

[72] Mandò, C.; Abati, S.; Anelli, G. M.; Favero, C.; Serati, A.; Dioni, L.; Zambon, M.; Albetti, B.; Bollati, V.; Cetin, I. Epigenetic Profiling in the Saliva of Obese Pregnant Women. *Nutrients* **2022**, *14* (10), 1–18. https://doi.org/10.3390/nu14102122.

[73] Bautista, C. J.; Reyes-Castro, L. A.; Lomas-Soria, C.; Ibáñez, C. A.; Zambrano, E. Late-in-Life Exercise Ameliorates the Aging Trajectory Metabolism Programmed by Maternal Obesity in Rats: It Is Never Too Late. *Archives of Medical Research* **2024**, *55* (4). https://doi.org/10.1016/j.arcmed.2024.103002.

[74] Chen, W.; Qiu, C.; Hao, J.; Liao, J.; Lurmann, F.; Pavlovic, N.; Habre, R.; Jones, D. P.; Bastain, T. M.; Breton, C. V; Chen, Z. Maternal Metabolomics Linking Prenatal Exposure to Fine Particulate Matter and Birth Weight. *ISEE Conference Abstracts* **2023**, *2023* (1). https://doi.org/10.1289/isee.2023.op-141.

[75] Fernandez-Jimenez, N.; Fore, R.; Cilleros-Portet, A.; Lepeule, J.; Perron, P.; Kvist, T.; Tian, F. Y.; Lesseur, C.; Binder, A. M.; Lozano, M.; Martorell-Marugán, J.; Loke, Y. J.; Bakulski, K. M.; Zhu, Y.; Forhan, A.; Sammallahti, S.; Everson, T. M.; Chen, J.; Michels, K. B.; Belmonte, T.; Carmona-Sáez, P.; Halliday, J.; Daniele Fallin, M.; LaSalle, J. M.; Tost, J.; Czamara, D.; Fernández, M. F.; Gómez-Martín, A.; Craig, J. M.; Gonzalez-Alzaga, B.; Schmidt, R. J.; Dou, J. F.; Muggli, E.; Lacasaña, M.; Vrijheid, M.; Marsit, C. J.; Karagas, M. R.; Räikkönen, K.; Bouchard, L.; Heude, B.; Santa-Marina, L.; Bustamante, M.; Hivert, M. F.; Bilbao, J. R. A Meta-Analysis of Pre-Pregnancy Maternal Body Mass Index and Placental DNA Methylation Identifies 27 CpG Sites with Implications for Mother-Child Health. *Communications Biology* **2022**, *5* (1). https://doi.org/10.1038/s42003-022-04267-y.

[76] Diceglie, C.; Anelli, G. M.; Martelli, C.; Serati, A.; Dico, A. Lo; Lisso, F.; Parisi, F.; Novielli, C.; Paleari, R.; Cetin, I.; Ottobrini, L.; Mandò, C. Placental Antioxidant Defenses and Autophagy-Related Genes in Maternal Obesity and Gestational Diabetes Mellitus. *Nutrients* **2021**, *13* (4). https://doi.org/10.3390/nu13041303.

[77] Gonnella, F.; Konstantinidou, F.; Donato, M.; Gatta, D. M. P.; Peserico, A.; Barboni, B.; Stuppia, L.; Nothnick, W. B.; Gatta, V. The Molecular Link between Obesity and the Endometrial Environment: A Starting Point for Female Infertility. *International journal of molecular sciences* **2024**, *25* (13). https://doi.org/10.3390/ijms25136855.

[78] Aye, I. L. M. H.; Rosario, F. J.; Powell, T. L.; Jansson, T. Adiponectin Supplementation in Pregnant Mice Prevents the Adverse Effects of Maternal Obesity on Placental Function and Fetal Growth. *Proceedings of the National Academy of Sciences of the United States of America* **2015**, *112* (41), 12858–12863. https://doi.org/10.1073/pnas.1515484112.

[79] Arroyo-Jousse, V.; Jaramillo, A.; Castaño-Moreno, E.; Lépez, M.; Carrasco-Negüe, K.; Casanello, P.

Adipokines Underlie the Early Origins of Obesity and Associated Metabolic Comorbidities in the Offspring of Women with Pregestational Obesity. *Biochimica et Biophysica Acta - Molecular Basis of Disease* **2020**, *1866* (2). https://doi.org/10.1016/j.bbadis.2019.165558.

[80] Luo, L.; Zhang, S.; Wang, T.; Diao, J.; Li, J.; Li, Y.; Zhao, L.; Chen, L.; Ye, Z.; Huang, P.; Qin, J.; Maugeri, A. G. Associations of Maternal Diabetes Mellitus and Adiponectin Gene Polymorphisms with Congenital Heart Disease in Offspring: A Case-Control Study. *Medicine* **2021**, *100* (9), e24672. https://doi.org/10.1097/MD.0000000000024672.

[81] Dumolt, J.; Powell, T. L.; Jansson, T. Normalization of Maternal Adiponectin in Obese Pregnant Mice Prevents Programming of Impaired Glucose Metabolism in Adult Offspring. **2023**, *36* (7), 1–24. https://doi.org/10.1096/fj.202200326R.Normalization.

[82] Joshi, N. P.; Mane, A. R.; Sahay, A. S.; Sundrani, D. P.; Joshi, S. R.; Yajnik, C. S. Role of Placental Glucose Transporters in Determining Fetal Growth. *Reproductive sciences (Thousand Oaks, Calif.)* **2022**, *29* (10), 2744–2759. https://doi.org/10.1007/s43032-021-00699-9.

[83] Geiger, K.; Muendlein, A.; Stark, N.; Saely, C. H.; Wabitsch, M.; Fraunberger, P.; Drexel, H. Hypoxia Induces Apelin Expression in Human Adipocytes. *Hormone and Metabolic Research* **2011**, *43* (6), 380–385. https://doi.org/10.1055/s-0031-1273767.

[84] Bruun, J. M.; Lihn, A. S.; Verdich, C.; Pedersen, S. B.; Toubro, S.; Astrup, A.; Richelsen, B. Regulation of Adiponectin by Adipose Tissue-Derived Cytokines: In Vivo and in Vitro Investigations in Humans. *American Journal of Physiology - Endocrinology and Metabolism* **2003**, *285* (3 48-3), 527–533. https://doi.org/10.1152/ajpendo.00110.2003.

[85] Wu, J.; Liu, Z.; Meng, K.; Zhang, L. Association of Adiponectin Gene (ADIPOQ) Rs2241766 Polymorphism with Obesity in Adults: A Meta-Analysis. *PLoS ONE* **2014**, *9* (4). https://doi.org/10.1371/journal.pone.0095270.

[86] Payab, M.; Amoli, M. M.; Qorbani, M.; Hasani-Ranjbar, S. Adiponectin Gene Variants and Abdominal Obesity in an Iranian Population. *Eating and Weight Disorders* **2017**, *22* (1), 85–90. https://doi.org/10.1007/s40519-016-0252-1.

[87] Dumolt, J. H.; Rosario, F. J.; Barentsen, K.; Urschitz, J.; Powell, T. L.; Jansson, T. Trophoblast-Specific Overexpression of Adiponectin Receptor 2 Causes Fetal Growth Restriction in Pregnant Mice. *FASEB journal : official publication of the Federation of American Societies for Experimental Biology* **2024**, *38* (19), e70100. https://doi.org/10.1096/fj.202302143R.

[88] Rosario F J , Kanai Y , Powell T L, and J. T. Increased Placental Nutrient Transport in a Novel Mouse Model of Maternal Obesity with Fetal Overgrowth. *Obesity (Silver Spring)* **2015**, *23(8):1663*.

[89] Chen, Z. Y.; Mao, S. F.; Guo, L. H.; Qin, J.; Yang, L. X.; Liu, Y. Effect of Maternal Pregestational Diabetes Mellitus on Congenital Heart Diseases. *World Journal of Pediatrics* **2023**, *19* (4), 303–314. https://doi.org/10.1007/s12519-022-00582-w.

[90] Zubrzycki, M.; Schramm, R.; Costard-jäckle, A.; Grohmann, J.; Gummert, J. F.; Zubrzycka, M. Cardiac Development and Factors Influencing the Development of Congenital Heart Defects (CHDs): Part I. *International Journal of Molecular Sciences* **2024**, *25* (13). https://doi.org/10.3390/ijms25137117.

[91] Muñoz-chápuli, R.; Pérez-pomares, J. M. Cardiogenesis : An Embryological Perspective. **2010**, No. October 2009, 37–48. https://doi.org/10.1007/s12265-009-9146-1.

[92] Dees, E.; Baldwin, H. S. New Frontiers in Molecular Pediatric Cardiology. **2002**, 627–633.

[93] Ren, Z.; Luo, S.; Cui, J.; Tang, Y.; Huang, H.; Ding, G. Research Progress of Maternal Metabolism on Cardiac Development and Function in Offspring. *Nutrients* **2023**, *15* (15). https://doi.org/10.3390/nu15153388.

[94] Leiva, M. C.; Tolosa, J. E.; Binotto, C. N.; Weiner, S.; Huppert, L.; Denis, A. L.; Huhta, J. C. Fetal Cardiac Development and Hemodynamics in the First Trimester. **1999**, 169–174. https://doi.org/10.1046/j.1469-0705.1999.14030169.x.

[95] Camm, E. J.; Botting, K. J.; Sferruzzi-perri, A. N. Near to One ' s Heart : The Intimate Relationship Between the Placenta and Fetal Heart. **2018**, *9* (June). https://doi.org/10.3389/fphys.2018.00629.

[96] Nørregaard, M. M. O.; Basit, S.; Sillesen, A.-S.; Raja, A. A.; Jørgensen, F. S.; Iversen, K. K.; Bundgaard, H.; Boyd, H. A.; Vøgg, R. O. B. Impact of Maternal Age and Body Mass Index on the Structure and Function of the Heart in Newborns: A Copenhagen Baby Heart Study. *BMC medicine* **2023**, *21* (1), 499. https://doi.org/10.1186/s12916-023-03207-9.

[97] McMullan, A.; Zwierzynski, J. B.; Jain, N.; Haneline, L. S.; Shou, W.; Kua, K. L.; Hota, S. K.; Durbin, M. D. Role of Maternal Obesity in Offspring Cardiovascular Development and Congenital Heart Defects. **2025**, 1–20. https://doi.org/10.1161/JAHA.124.039684.

[98] Harink, T. Den; Roelofs, M. J. M.; Id, J. L.; Painter, C.; Roseboom, T. J.; Deutekom, A. W. Van. Maternal Obesity in Pregnancy and Children's Cardiac Function and Structure : A Systematic Review and Meta-Analysis of Evidence from Human Studies. **2022**, 1–20.

[99] Wang, J.; Ma, H.; Tong, C.; Zhang, H.; Lawlis, G. B.; Li, Y.; Zang, M.; Ren, J.; Nijland, M. J.; Ford, S. P.; Nathanielsz, P. W.; Li, J. Overnutrition and Maternal Obesity in Sheep Pregnancy Alter the JNK-IRS-1 Signaling Cascades and Cardiac Function in the Fetal Heart. **2010**. https://doi.org/10.1096/fj.09-142315.

[100] Bayoumy, S.; Habib, M.; Abdelmageed, R. Impact of Maternal Diabetes and Obesity on Fetal Cardiac Functions. **2020**, 10–16.

[101] Wang, Q.; Zhu, C.; Sun, M.; Maimaiti, R.; Ford, S. P.; Nathanielsz, P. W.; Ren, J.; Guo, W. Maternal Obesity Impairs Fetal Cardiomyocyte Contractile Function in Sheep. **2018**, 1–12. https://doi.org/10.1096/fj.201800988R.

[102] Ahmed, A.; Liang, M.; Chi, L.; Zhou, Y.; Sled, J. G.; Wilson, M. D. Maternal Obesity Persistently Alters Cardiac Progenitor Gene Expression and Programs Adult- Onset Heart Disease Susceptibility. **2021**, *43* (November 2020), 1–16.

[103] Miranović, V. The Incidence of Congenital Heart Defects in the World Regarding the Severity of the Defect. *Vojnosanitetski pregled* **2016**, *73* (2), 159–164. https://doi.org/10.2298/vsp140917033m.

[104] Sun, R. R.; Liu, M.; Lu, L.; Zheng, Y.; Zhang, P. Congenital Heart Disease: Causes, Diagnosis, Symptoms, and Treatments. *Cell Biochemistry and Biophysics* **2015**, *72* (3), 857–860. https://doi.org/10.1007/s12013-015-0551-6.

[105] Zhang, T.-N.; Wu, Q.-J.; Liu, Y.-S.; Lv, J.-L.; Sun, H.; Chang, Q.; Liu, C.-F.; Zhao, Y.-H. Environmental Risk Factors and Congenital Heart Disease: An Umbrella Review of 165 Systematic Reviews and Meta-Analyses With More Than 120 Million Participants. *Frontiers in cardiovascular medicine*. Switzerland **2021**, p 640729. https://doi.org/10.3389/fcvm.2021.640729.

[106] Wu, L.; Li, N.; Liu, Y. Association Between Maternal Factors and Risk of Congenital Heart Disease in

Offspring: A Systematic Review and Meta-Analysis. *Maternal and child health journal* **2023**, *27* (1), 29–48. https://doi.org/10.1007/s10995-022-03538-8.

[107] Meller, C. H.; Grinenco, S.; Aiello, H.; Córdoba, A.; Sáenz-Tejeira, M. M.; Marantz, P.; Otaño, L. Congenital Heart Disease, Prenatal Diagnosis and Management. *Archivos Argentinos de Pediatria* **2020**, *118* (2), E149–E161. https://doi.org/10.5546/aap.2020.eng.e149.

[108] MacGillivray, T. E.; Lin, C. H. The Growing Number of Adults Surviving with Congenital Heart Disease. *Methodist DeBakey cardiovascular journal* **2019**, *15* (2), 97–98. https://doi.org/10.14797/mdcj-15-2-97.

[109] Khalil, H. S.; Saleh, A. M.; Subhani, S. N. Maternal Obesity and Neonatal Congenital Cardiovascular Defects. *International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics* **2008**, *102* (3), 232–236. https://doi.org/10.1016/j.ijgo.2008.05.005.

[110] Bergman, J. E. H.; Perraud, A.; Barišić, I.; Kinsner-Ovaskainen, A.; Morris, J. K.; Tucker, D.; Wellesley, D.; Garne, E. Updated EUROCAT Guidelines for Classification of Cases with Congenital Anomalies. *Birth Defects Research* **2024**, *116* (2), 1–20. https://doi.org/10.1002/bdr2.2314.

[111] Liu, Y.; Chen, S.; Zühlke, L.; Black, G. C.; Choy, M. K.; Li, N.; Keavney, B. D. Global Birth Prevalence of Congenital Heart Defects 1970-2017: Updated Systematic Review and Meta-Analysis of 260 Studies. *International Journal of Epidemiology* **2019**, *48* (2), 455–463. https://doi.org/10.1093/ije/dyz009.

[112] Batalha, S.; Rebelo, M.; Freitas, I.; Borges, A.; Pinto, F. Validação Da Importância Dos Ecocardiografia Fetal. **2011**, *24*, 339–346.

[113] Nie, X.; Liu, X.; Wang, C.; Wu, Z.; Sun, Z.; Su, J.; Yan, R.; Peng, Y.; Yang, Y.; Wang, C.; Cai, S.; Liu, Y.; Yu, H.; Wu, Q.; Peng, X.; Yin, C. Assessment of Evidence on Reported Non-Genetic Risk Factors of Congenital Heart Defects: The Updated Umbrella Review. *BMC pregnancy and childbirth* **2022**, *22* (1), 371. https://doi.org/10.1186/s12884-022-04600-7.

[114] Alvarado-Terrones, E. G.; Perea-Cabrera, M.; Klünder-Klünder, M.; Segura-Stanford, B.; Erdmenger-Orellana, J. R.; Lopez-Yañez Blanco, A.; Hernández-Carbajal, E.; Granados Riverón, J. T.; Mejía-Marín, L. J.; Balderrabano-Saucedo, N. A.; Contreras-Ramos, A.; Díaz-Rosas, G.; Sánchez-Urbina, R. Maternal Obesity as a Risk Factor for the Development of Total Anomalous Pulmonary Venous Connection in Their Offspring. *Archives of medical research* **2018**, *49* (2), 109–113. https://doi.org/10.1016/j.arcmed.2018.06.001.

[115] Gomersall, J. C.; Moore, V. M.; Fernandez, R. C.; Giles, L. C.; Grzeskowiak, L. E.; Davies, M. J.; Rumbold, A. R. Maternal Modifiable Factors and Risk of Congenital Heart Defects: Systematic Review and Causality Assessment. *BMJ open* **2024**, *14* (8), e082961. https://doi.org/10.1136/bmjopen-2023-082961.

[116] Racusin, D.; Stevens, B.; Campbell, G.; Aagaard, K. M. Obesity and the Risk and Detection of Fetal Malformations. *Seminars in perinatology* **2012**, *36* (3), 213–221. https://doi.org/10.1053/j.semperi.2012.05.001.

[117] Liu, X.; Ding, G.; Yang, W.; Feng, X.; Li, Y.; Liu, H.; Zhang, Q.; Ji, L.; Li, D. Maternal Body Mass Index and Risk of Congenital Heart Defects in Infants: A Dose-Response Meta-Analysis. *BioMed research international* **2019**, *2019*, 1315796. https://doi.org/10.1155/2019/1315796.

[118] Brite, J.; Laughon, S. K.; Troendle, J.; Mills, J. Maternal Overweight and Obesity and Risk of Congenital

Heart Defects in Offspring. *International journal of obesity (2005)* **2014**, *38* (6), 878–882. https://doi.org/10.1038/ijo.2013.244.

[119] Tang, X.; Cleves, M. A.; Nick, T. G.; Li, M.; MacLeod, S. L.; Erickson, S. W.; Li, J.; Shaw, G. M.; Mosley, B. S.; Hobbs, C. A. Obstructive Heart Defects Associated with Candidate Genes, Maternal Obesity, and Folic Acid Supplementation. *American journal of medical genetics. Part A* **2015**, *167* (6), 1231–1242. https://doi.org/10.1002/ajmg.a.36867.

[120] Hobbs, C. A.; Cleves, M. A.; Karim, M. A.; Zhao, W.; MacLeod, S. L. Maternal Folate-Related Gene Environment Interactions and Congenital Heart Defects. *Obstetrics and gynecology* **2010**, *116* (2 Pt 1), 316–322. https://doi.org/10.1097/AOG.0b013e3181e80979.

[121] Turunen, R.; Pulakka, A.; Metsälä, J.; Vahlberg, T.; Ojala, T.; Gissler, M.; Kajantie, E.; Helle, E. Maternal Diabetes and Overweight and Congenital Heart Defects in Offspring. *JAMA Network Open* **2024**, *7* (1), E2350579. https://doi.org/10.1001/jamanetworkopen.2023.50579.

INSTITUTO DE **CIÊNCIAS BIOMÉDICAS ABEL SALAZAR**