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The Sexually Dimorphic Nature of the Human Placenta: A Literature Review

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Abstract

Introduction: Neonatal growth is dependent on the ability of the mother's placenta to deliver nutrients. As such, placental health is an important aspect of obstetric care. Existing literature has suggested an association between fetal sex and placental growth and development; however, no centralized study has been conducted. This paper aims to conduct a narrative review that summarizes findings from published literature on the effects of fetal sex on the growth and development of the placenta through three facets: placental function, structure, and outcome.

Methods: Databases including Medline, Embase, and EMCare in Ovid, CINAHL, Web of Science, and Scopus were searched using keywords for the concepts of fetal sex and placenta. These were searched in combination with keywords relevant to placental function, placental structure, and pregnancy outcomes, using Boolean operators "OR/AND/NOT" as necessary. Studies written in English and published in peer reviewed journals were considered, with an emphasis on those published between 2017-2021.

Results: Sexual dimorphism is evident in the fetal responses to stressful maternal environmental conditions, onset by conditions such as asthma and obesity. Sex-specific differences have also been observed in complications of pregnancy, including gestational diabetes mellitus (GDM), preeclampsia, preterm delivery, stillbirth, and insufficient uteroplacental circulation.

Discussion: Despite the placentas from male and female births being categorized together in previous literature, this review highlights the sexually dimorphic nature of the ephemeral organ. Knowledge of fetal sex as early as possible during the pregnancy will help clinicians take proactive measures to optimize the health of the mother and the fetus.

Conclusion: This study provides a holistic review of the effects of placental development among the fetal sexes, a critical aspect to monitor for effective obstetric care. Hence, further research into the sexually dimorphic nature is warranted.

Keywords: fetal sex; sexually dimorphic; sex-specific differences; stressful maternal environment; pregnancy complications; placental function; pregnancy outcomes

Introduction

Fundamental differences exist between the human sexes which are a result of natural and sexual selection. Such dimorphic nature is prevalent in courtship, copulatory and parenting behaviour and can be observed on both the phenotypical and hormonal levels. Recent literature sheds light on the possibility of fetal sex playing a major role in pregnancy outcomes and complications including neonatal morbidity and mortality [1,2]. Male fetuses are 20% more likely to experience a poorer outcome in pregnancies complicated by preeclampsia, preterm delivery, and intrauterine growth restriction [3]. Studies have also observed gender specific differences in fetal growth and development [4]. Preeclampsia and gestational diabetes mellitus (GDM) have been more greatly associated with the male fetal sex, while other pregnancy complications such as gestational hypertension, placental abruption, preeclampsia, post-partum hemorrhage, and have been more associated with the female fetal sex [5]. Despite these differences, the placenta fails to be regarded as sexually dimorphic [6].

The placenta has been implicated in differing fetal outcomes due to its essential role and function throughout pregnancy. Acting as the interface between the mother and the fetus, the placenta is designed for the exchange of oxygen and nutrients essential for fetal growth and development [4]. The placenta also has major endocrine contributions as it is involved in the synthesis of cytokines and hormones, as well as the modulation of maternal physiology to provide a protective environment for the fetus [4,7]. As a result, placental health is a critical consideration of obstetric care.

Most relevant studies fail to differentiate between the male and female placenta, with several collating data retrieved from both male and female births into one group [6]. However, growing evidence suggests that the placenta has sex-specific adaptations which may be central to differences in fetal growth, development, and outcomes [6].

For instance, the growth trajectory of the placenta in females is generally slower compared to males and shows altered adaptive responses to stressful environments. These placental adaptations are likely to depend on the type of stressor, duration, severity, and the window of exposure during development [8]. Di Renzo *et al.* reported that male and female placentas adopt different strategies to optimize health outcomes [4]. The male placenta responds to adverse maternal environments through a minimalist approach with few genes, proteins, and functional changes while the female placenta makes multiple placental gene and protein changes. As such, placental adaptations and functions are suggested to be influenced by the sex of the fetus.

Despite increased research into the relationship between the sex of the placenta and pregnancy outcomes, there is a lack of published evidence that implicates differences in placental structure, growth and function based on fetal sex [6,8]. More so, the specific biochemical mechanisms by which sex-specific adaptations occur in the placenta also remain poorly understood [8]. The growth and development of the placenta is determined by its function and the structure which influence maternal and fetal outcomes. As such, this paper aims to conduct a narrative review to synthesize associations between fetal sex and the placenta through three key facets: function, structure, and outcome.

Methods

A literature search was conducted on databases Medline, Embase, and EMCare in Ovid, CINAHL, Web of Science, and Scopus on May 27, 2021. Keywords were utilized for the concepts of fetal sex and placenta, which were searched in combination with keywords relevant to placental function, placental structure, and pregnancy outcomes. Boolean operators "OR/AND/NOT" were utilized where appropriate, and searches were optimized for each database. Only studies written in the English language and published in peer-reviewed journals were considered. Both human studies and those with animal models were considered in the review. Forward and backward citation tracing was utilized to identify additional relevant studies in the reviews considered. An emphasis was placed on studies published between 2017-2021 to ensure recent data and information in this field was reported.

Results

The growth and development of the placenta as well as pregnancy outcomes are vastly dependent on the fetal environment. When the fetus is in a stressful environment, often preceded by conditions like asthma and obesity, it can induce sex-specific differences in the placenta resulting in different male and female fetal outcomes. Due to the different mechanisms male and female fetuses utilize under adverse environments, it alters the placental growth and development and can lead to complications during pregnancy and at parturition. This includes preeclampsia, stillbirth, sex-specific differences in placental delivery and gestational diabetes mellitus (GDM).

Stress/Environmental Conditions

Asthma

Previous studies on maternal asthma have identified sex-specific differences in placental function impacting fetal outcomes [9]. Asthma is a respiratory disease that occurs as a result of altered immune response to environmental antigens [9]. This is one of the most common conditions that affect pregnant women, with 3-12% affected worldwide [10,11]. The effect of asthma on placental growth and development, fetal outcome and maternal health is dependent on the asthma severity and intensity of treatment throughout pregnancy. A third of patients with maternal asthma report worsening disease severity as pregnancy progresses with 50% reporting having uncontrolled symptoms [10].

The loss of asthma control during pregnancy can contribute to an increase in maternal and fetal cortisol levels, systemic inflammation, and oxidative stress. It can also reduce maternal oxygen levels, inducing hypoxia and respiratory alkalosis, which decreases placental blood flow and fetal blood oxygen [10]. This predisposes asthmatic pregnant women to a greater risk of intrauterine growth restriction, preterm birth, stillbirth, neonatal sepsis, preeclampsia, GDM and hemorrhage [9,12]. Placenta previa, placental abruption, and premature rupture of the amniotic membranes is also associated with asthma. In pregnancies complicated with maternal asthma, female fetuses often had reduced birth weight while male fetuses continued to grow normally [13]. When exposed to acute asthma exacerbation, female fetuses adapted by reducing their growth trajectory to increase their survival [13]. This adaptation reduces oxygen and nutrient supply to the female fetuses, resulting in reduced birth weight. In 2017, Majewska *et al.* studied the transcriptomic profile of human placental tissue and identified gene expression changes correlating with fetal growth/birth weight and susceptibility to preeclampsia. Increased *PHLDA2* expression is correlated with lower birth weight while mutations in EPAS1 is considered as a potential biomarker for susceptibility of preeclampsia [14]. The transcripts associated with these gene expression changes were responsible for cell proliferation, integrins and antigen presentation. This suggests that a pregnancy complicated with maternal asthma can induce adaptations that negatively impact the support of normal growth for the fetus, affecting fetal growth.

For years, the mechanism by which these adverse outcomes are reported in asthmatic pregnancies was unknown, but recently, a promising explanation has been proposed. During pregnancy, glucocorticoids, a class of steroid hormones derived from the maternal system, play a fundamental role in both placental and fetal brain development. Excess or irregular fetal-placental exposure to

glucocorticoids may potentially lead to abnormalities in the fetal and placental growth [15]. To protect the fetus from excess glucocorticoid exposure, the placenta has a glucocorticoid barrier. However, the efficiency of this barrier is compromised in pregnancies complicated by maternal asthma which leads to elevated intracellular concentrations of cortisol in both male and female fetuses, increasing the risk of fetal growth restriction [16]. Research by Saif *et al.* suggests that the sex-specific differences in fetal growth during asthmatic pregnancies are a result of sex-specific differences in glucocorticoid regulated growth and inflammatory pathways that are mediated by placental glucocorticoid receptors (GR) [16]. There are 13 different GR protein isoforms that have been identified in the human placenta. The varied expression of these GR isoforms are regulated by complex mechanisms with the first layer of regulation carried out by the GR gene promoter region. In male placentas, the expression of GRα D1 and D3 proteins increases, but greater concentrations of GRα D3 do not enhance GRα A induced-glucocorticoid sensitivity. Male placentas are therefore able to maintain a reduced sensitivity to glucocorticoids through GRα D isoforms [13,16]. Further, GRα D isoforms do not mediate glucocorticoid-induced apoptosis and, as such, act as a protective mechanism ensuring continued growth of the male fetus despite maternal asthma and excess glucocorticoid exposure. In addition, male placentas have increased GRβ, which assists in inducing a state of glucocorticoid resistance and thus allowing the growth pathway to function normally. When comparing the female placental GR isoform profiles, significant differences between healthy and asthmatic pregnancies are observed. In the presence of maternal asthma, female placentas upregulated nuclear expression of GRα A and GRα D3 and increased cytoplasmic GRα C expression [10,12]. GRα C is known to enhance GRα A sensitivity to glucocorticoids and mediate glucocorticoid-induced apoptosis.

A 2019 study by Saif *et al.* was the first to provide evidence of multiple GR exon 1 promoter expression in the placenta that change together under the influence of different pregnancy conditions like asthma [16]. The expression of GR exon 1 is regulated in a sex-specific manner. In males they cause the upregulation of GRα D isoforms and drive a state of glucocorticoid resistance. In female placentas there are no changes in the preferential expression of GR exon 1 promoters. Instead, a promoter variant is upregulated that has limited effect in altering GR transcription and translation and thus increasing sensitivity [11]. To test placental sensitivity to glucocorticoids, a study by Meakin *et al.* used placental explant models and observed that female placentas from asthmatic pregnancies were sensitive to an inflammatory stimulus and more responsive to glucocorticoid induced cytokine inhibition [13]. In contrast, the cytokines produced by male placentas with asthmatic pregnancies were not inhibited by glucocorticoids supporting their state of glucocorticoid resistance. There were also sex-specific differences in placental genes involved in immune function and inflammation between asthmatic and non-asthmatic groups. Baseline placental expression of Tumour necrosis factor alpha, interleukin-1β, interleukin-6, interleukin-5 and interleukin-8 mRNA were increased in female placentas of asthmatic pregnancies [17]. However, no changes to immune pathways or cytokines were noted for male placentas which work to support the notion that male placentas induce a state of glucocorticoid resistance in response to maternal asthma during pregnancy. Due to the aforementioned differences, the sex of the fetus influences the growth and development of the placenta in a sexually dimorphic manner in asthmatic pregnancies.

Obesity

The sexually dimorphic nature of the placenta is apparent in cases of maternal obesity where placental adaptations differ vastly based on fetal sex. Maternal obesity results in the dysregulation of placental metabolism as indicated by changes in proteins involved in fatty acid oxidation, mitochondrial function, and placental lipid uptake [18]. Ultimately, this leads to epigenetic modifications, increased production of reactive oxygen species and higher expression of inflammatory markers in a sexually dimorphic manner. Greater inflammation is often observed in overweight and obese women with thicker and less efficient placentas [18,19]. More specifically, male fetuses were longer, heavier and had larger head circumferences than females. The placentas of male fetuses were also more efficient than those of female fetuses [19].

In order to sustain the metabolic activity of the placenta, oxidative phosphorylation and placental mitochondrial biogenesis are key processes. As such, altering the mitochondrial structure and its function, via conditions like maternal obesity, negatively impacts the placental growth. In cases of obesity, a suppression of placental β-oxidation, a metabolic process used to break down fatty acids to produce energy and molecules used in metabolism, is observed. Bucher *et al.* implicates the suppression of β-oxidation in male placentas to deficiency of carnitine, a critical metabolite for mitochondrial β-oxidation [18]. In females, there is a reduction in Carnitine palmitoyltransferase I (CPT1) and Carnitine palmitoyltransferase I (CPT2) transporters [18,20]. CPT1 aids with the transport of long chain fatty acids into the mitochondria and CPT2 codes for the carnitine palmitoyltransferase 2 enzyme used in β-oxidation [20,21]. In contrast, a 2020 study by Powell *et al.* only found low placental carnitine levels in female placentas, suggesting down-regulation of placental mitochondrial function due to impaired lipid metabolism [22]. In addition, they suggest a decreased placental DHA transfer in male fetuses resulting in reduced delivery of critical fatty acids. Ultimately, this can negatively affect fetal neurodevelopment outcomes in obese mothers. Further research is warranted to confirm these trends.

Complications of Pregnancy

Recently, there has been a 16% increase in the prevalence of pregnancy complications [23]. GDM, preeclampsia, preterm delivery, stillbirth and insufficient uteroplacental circulation are among the most common complications experienced by mothers worldwide, which come alongside negative repercussions on both the mother and the fetus. Previous literature has studied and found sexual dimorphism in relation to all these complications.

Gestational Diabetes Mellitus (GDM)

GDM is one of the most prevalent metabolic disorders that can occur during pregnancies, affecting between 7-10% of pregnancies worldwide [24]. Maternal pancreatic β-cell dysfunction is the main pathophysiological basis of GDM. The maternal β-cells are unable to produce a sufficient amount of insulin to recoup the insulin resistance that is characteristic of GDM. The resulting hyperglycemia is used to diagnose a mother with GDM. Retnakaran *et al.* showed that GDM incidence rates are higher for mothers with a male fetus due to decreased maternal β-cell function after adjustment for GDM risk factors [25]. Prolactin and placental lactogens intricately operate in a pathway alongside downstream mediators to increase β-cell mass and ultimately insulin secretion as well. Male fetuses have particular characteristics that impair placental secretion of proteins and hormones involved in increasing β-cell mass and hence insulin production, that may be attributed to the presence of a Y chromosome.

A major concern of GDM on the fetus is fetal macrosomia, a condition where the fetus weighs over 4000 grams at birth. It has been hypothesized that sexual dimorphism exists between the transport and metabolism of fatty acids across the placenta, especially in women with GDM. In 2020, Yang *et al.* followed a cohort of Hispanic/Latinx women to study this proposed sexual dimorphism [26]. They found that the expression of the gene fatty acid-binding protein 4, one of the primary genes involved in the process of fatty acid transport across the placenta, was increased in obese women with GDM with a documented history of fetal macrosomia. This increased expression was observed in male fetuses relative to females, resulting in a higher incidence rate of fetal macrosomia for males due to enhanced lipid transportation. Sexual dimorphism was further noted in the placental lipoprotein lipase (LPL) levels. LPL is a gene that codes for the lipoprotein lipase enzyme which is involved in the uptake of LDL from maternal blood circulation into the placenta via the trophoblast cells. The expression of LPL further increased the rate of lipid uptake into the placenta from maternal blood circulation, resulting in the higher incidence rate of fetal macrosomia in male fetuses.

The placenta is an organ that mediates maternal and fetal metabolism by facilitating exchanges in a bi-directional manner. Placental efficiency is an important indicator of placental function in humans and is calculated as fetal weight divided by placental weight. Low placental efficiency values are due to decreased transportation of nutrients or failure to adapt and are associated with fetal growth restriction whereas high placental efficiency values are indicative of greater nutrient transport and hence average sized fetuses [27]. In 2021, Diceglie *et al.* found that obese women, whether having the comorbidity of GDM or not, often had lower placental efficiencies than women who were considered to have normal weight with no GDM [27]. When comparing the three groups under investigation (normal weight, obese and no GDM, obese with GDM), placental efficiency gradually decreased as the number of comorbidities increased. Fetal sex was determined to impact "placental biometrical and functional features," namely placental efficiency [27]. Female fetuses whose mothers were both obese and suffered from GDM had decreased placental efficiency compared to their male counterparts. Ultimately, maternal obesity impacts the fetus in a sexually dimorphic manner, yet the mechanism behind this needs further investigation.

Preeclampsia

Preeclampsia is one of four hypertensive disorders of pregnancy characterized by the development of hypertension as well as proteinuria after 20 weeks of gestation. It has an unknown etiology, although the most popular theory posits preeclampsia as a disease with placental origins due to defects in the spiral artery remodelling process [28]. Preeclampsia is a maternal disorder; however, it puts both the mother and fetus at risk. It is one of many pregnancy complications that highlight the different mechanisms male and female fetuses utilize to cope with an adverse environment [6]. Many studies have highlighted the association between fetal sex and preeclampsia. Male fetuses are 20% more likely to experience poorer outcomes, such as increased rates of death in early gestation [3,29]. For women with preeclampsia, maternal inflammatory responses are more exaggerated in male fetuses [30]. Such obstetric outcomes are the result of complex interactions between the mother, fetus, and the placenta in a sex-dependent fashion. However, the exact mechanisms are unknown [1].

With preeclampsia posited as a disease with placental origins, the placenta plays a critical role in the sex-specific adaptations of the fetus that occur in women with preeclampsia. It was found that male and female fetuses utilize different strategies to cope with mild preeclampsia in order to ensure normal growth, as observed in the maternal microvascular circulation [31]. This was demonstrated in a study where peripheral microvascular responses were examined between healthy pregnant women and those with preeclampsia in response to the vasodilator, corticotropin-releasing hormone [31]. Male fetuses were associated with a more vasoconstricted state in the maternal microvascular circulation, in an attempt to have normal growth. This may be due to the fetus redirected blood flow to the uteroplacental circulation. Contrastingly, female fetuses did not institute

any new strategies and likewise their growth was reduced in preeclamptic pregnancies [31]. Moreover, sexual dimorphism in placental function is reflected by how placental immune function reacts to the preeclamptic inflammatory state. This is demonstrated by male placentas in preeclamptic pregnancies having a higher expression of inflammatory, apoptotic, and hypoxia molecules than female placentas in severe preeclampsia [32]. The exact mechanism behind this sexual dimorphism is unknown, but it has been linked to gonadal steroids. Compared to healthy pregnancies, women with preeclamptic pregnancies have higher levels of plasma testosterone levels, with male-bearing pregnancies having substantially higher levels than female ones [32]. Higher levels of testosterone during gestation are known to induce hypertension, as demonstrated in a study with rats [10].

Overall, incidence of preeclampsia been found to be more common in pregnant women carrying female fetuses as compared to male fetuses. This was demonstrated by a 2011 paper which further elaborated that the incidence rate for twin pregnancies with male-female fetuses had intermediate values [33]. A 2018 study concluded similar results, with the female fetal sex being associated with higher rates of early preterm preeclampsia [34]. However, the exact physiological reasons behind these differences, and whether the placenta's sexually dimorphic immune response is implicated in these changes, is not yet known.

Preterm Delivery

Further evidence towards sex-specific survival strategies being employed by the placenta in harsh maternal environments include a 2015 paper by Gray et al [35]. They demonstrate that in preterm female deliveries, the placental bed can maximally relax in response to magnesium sulfate. This vascular tone difference between female and male placentas is what facilitates better fetal nutrient delivery and gas exchange for female fetuses. In addition, a 2012 retrospective study examined whether there was a placental origin for sex-specific differences in high-risk pregnancies leading to pre-term delivery [36]. They referred to high-risk pregnancies caused by diseases attributed to placental dysfunction, such as preeclampsia and intrauterine growth restriction. They found a sex-dependent pattern of placental pathology, as defined in preterm deliveries that occurred before 33 weeks of gestation. Specifically, they found that females had higher rates of villous infarctions and males had more chronic deciduitis and velamentous umbilical cord insertions. Holistically, the study further supported how fetal sex can affect the growth and development of the placenta, as shown in the complication of preterm delivery.

Still Birth

Stillbirth is one of the most common pregnancy complications, affecting roughly 1 in 160 pregnancies in the United States [36]. Uterine artery pulsatility index (UtA-PI) is a critical indicator of placental health as it is reflective of uteroplacental perfusion and is an indicator for stillbirth. Higher PI values increase the risk of pregnancy conditions such as placental perfusion insufficiency (PPI) and preeclampsia resulting in stillbirth [18]. Female fetuses are reported to have an increased risk of stillbirth than male. Upon examining the risk factor for stillbirth, a 2021 study by Wu *et al.* attributed 58.0% of the risk to PPI. While in male fetuses, PPI was the only factor, accounting for 94.5% of the risk of stillbirth [19]. PPI is a complication in pregnancy when the placenta is no longer able to deliver an adequate supply of blood flow and is often accompanied by impaired placental function. PPI impairs oxygen transport, reducing oxygen supply to the fetus vasculature and as a result can lead to placental apoptosis and accelerated placental aging, which ultimately compromises viability of the fetus [19]. An additional factor involved in stillbirth of female fetuses is preeclampsia. Wu *et al.* reported different sexually dimorphic pathways toward stillbirths: a PPI mediated pathway in male fetuses without preeclampsia involvement, while female fetuses had an additional preeclampsia mediated pathway as well as PPI. Knowledge of the sexual dimorphism in relation to fetal sex will ensure clinicians are able to take proactive measures to prioritize the health of the fetus.

Insufficient Uteroplacental Circulation

The placenta receives blood supplies from two unique circulatory systems: the uteroplacental circulation and fetoplacental circulation. The exchange of oxygen and nutrients is dependent on the adequate uteroplacental circulation and is critical for placental growth and development. Spiral arteries play a crucial role in providing both the placenta and fetus with an adequate supply of nutrients. The production of maternal fibrinolytic and angiogenic factors is impacted by sex differences and further influences both spiral artery remodeling and angiogenesis of the placenta in a sexually dimorphic manner [37]. Maternal blood flow into the intervillous space also requires lower resistance of uteroplacental vessels, efficient and effective perfusion of blood flow with normal uteroplacental vasculature following a "high flow and low resistance" model [38]. The resistance in the uteroplacental circulation is assessed via the UtA-PI where a higher value is indicative of stiff and narrow spiral arteries. A high UtA-PI is often associated with adverse perinatal outcomes and high-risk pregnancies [39]. The impact of fetal sex on uteroplacental circulation resistance is consistent throughout the gestation term in obese women. A study by Teulings *et al.* consistently reported women pregnant with male fetuses have a higher UtA-PI compared to those with female fetuses at all times throughout the pregnancy [37]. Resistance in uteroplacental circulation, measured via the umbilical artery pulsatility index (UA-PI), is also indicative of placental development. Normal pregnancies begin with a higher UA-PI and decline towards the end of term reflecting normal placental

development. However, in obese women with female fetuses, the UA-PI levels remain higher and constant throughout gestation than obese women with male fetuses. Teulings *et al.* attributes this difference to abnormal placental development or fetal cardiac function [37].

Discussion

Despite being under researched, sexual dimorphism has been observed in relation to placental function, structure, and outcome. The growth and development of the placenta is impacted in a sexually dimorphic manner, especially if the fetus is exposed to long term stressful environments induced by conditions like maternal asthma and obesity. In asthmatic pregnancies, male fetuses can develop glucocorticoids resistance and continue normal growth trajectories while females reduce their growth trajectory to increase survival rates. Pregnancies where the mother is obese also report sexually dimorphic fetal outcomes where the male fetuses were heavier at birth and had thicker placentas.

The prevalence of GDM is higher for pregnancies with male fetuses due to decreased maternal β-cell function. Furthermore, male fetuses have increased expression of the gene fatty acid-binding protein 4, which enhances lipid transportation and results in a greater risk of fetal macrosomia for them compared to female fetuses. Placental efficiency is also lower for male fetuses compared to female fetuses resulting from pregnancies where the mother suffers from GDM.

Moreover, pregnancies complicated by preeclampsia highlight different sex-specific adaptions in placental structure and function. Most prominently, this is emphasized by male placentas having higher expression of inflammatory, apoptotic, and hypoxia molecules than female placentas. The sexual dimorphism exhibited by the placenta may contribute to the differences in pregnancy outcomes for male and female fetuses. However, further research is warranted to understand the complex interactions between mother, fetus, and placenta in a sex-dependent nature.

Furthermore, pregnancy complications of preterm delivery, still birth, and insufficient uteroplacental circulation further highlight the sexual dimorphic nature of the placenta, as these high-stress environments emphasize fetal sex-specific adaptions. These stressful environments can induce sexually dimorphic responses on the mitochondrial, genetic, and hormonal levels. Together, these structural and functional changes impact the outcomes of both the fetus and the pregnancy at large in a sex-specific manner.

In 2017, Al-Quaraghouli *et al.* conducted a review to summarize literature surrounding sexual dimorphism in relation to pathologic and physiologic changes of the placenta, as well as the impact on both maternal and fetal outcomes [40]. The authors documented sexual dimorphism in relation to end of term complications, such as stillbirth. O'Tierney-Ginn *et al.* carried out a similar review in 2020 revolving around sex differences in the growth and development of the placenta in both healthy pregnancies and pregnancies impacted by comorbidities. Sexual dimorphism was observed for in utero nutritional requirements as well as long term outcomes for the fetus [41]. These previous literature reviews investigating the effect of fetal sex on the growth and development of the human placenta during pregnancy have drawn conclusions that strongly align with those mentioned in this review, increasing its validity.

One of the major limitations of this paper is the lack of research that has been conducted in this field. The placenta is one of the lesser studied organs despite the integral role it plays during pregnancy. Oftentimes, researchers use the term placenta to collectively refer to the placentas of both male and female fetuses. Recently, a greater focus is being placed on the distinction between fetal sex in relation to the placenta, resulting in a majority of the literature used in this review to be from 2019-2021. However, even within this cohort of papers, many studies were conducted on animal models, impairing the generalizability of the conclusions made to the human placenta as well.

Fetal sex is most often determined 18 weeks into the gestation period using ultrasound technology. Recent technological developments allow fetal sex to be discovered as early as 7 weeks into gestation using blood testing [42]. For parents, knowing the sex of the fetus provide a sense of control over the pregnancy and peace of mind [43]. Given the sexually dimorphic nature of the human placenta, knowing the sex of the fetus is extremely important from a clinical perspective. Knowing whether the fetus is biologically male or female, clinicians will be able to proactively diagnose any fetal illnesses, treat such conditions appropriately and prevent gestational and end of term complications.

While the placentas of male and female fetuses already differ morphologically, both respond uniquely when exposed to the same intrauterine environment due to variations at the cellular and molecular levels [44]. Studies supporting the different sex-specific strategies employed by male and female fetuses in response to adverse maternal environments warrant the question of whether fetal sex is a factor that should influence treatment plans. In the event that the mother suffers from conditions such as asthma, obesity or GDM, knowledge of the fetal sex can help clinicians adapt to improve treatment outcomes. This is highlighted by the disproportionate sex-specific difference in outcomes previously discussed, where male fetuses are 20% more likely to experience a poorer outcome [3].

Conclusion

Despite placental research often failing to distinguish between fetal sex, there is a significant amount literature supporting the notion that fetal sex impacts the growth and development of the human placenta during pregnancy, especially when the maternal environment is stressful. Conditions such as asthma, GDM and obesity further increase the sexual dimorphism between the sexes,

particularly in relation to how the fetus reacts in the environment. Knowledge of the sexual dimorphism between the placentas of male and female fetuses in relation to different maternal stress environments can improve the diagnosis, treatment, and outcome of the fetus through a proactive approach. Before any clinical changes can be introduced, further research is needed to better understand the sexually dimorphic nature of the placenta and sex-specific differences.

List of Abbreviations Used
CPT1: carnitine palmitoyltransferase 1
CPT2 : carnitine palmitoyltransferase 2
GDM : gestational diabetes mellitus
GR: placental glucocorticoid receptors
LPL: lipoprotein lipase
PI: pulsatility index
PPI: placental perfusion insufficiency
UA-PI: umbilical artery pulsatility index
UtA-PI: uterine artery pulsatility index

Conflicts of Interest
The authors declare no conflicts of interest.

Ethics Approval and/or Participant Consent
As this paper is a review, no ethics approval was required.

Authors' Contributions
VB: made equal contributions to the entirety of this manuscript as well as the conception and design of the work and is to be held equally accountable for all aspects. This includes drafting the manuscript, critically examining it for its content and collectively approving the final version to be submitted.
MB: made equal contributions to the entirety of this manuscript as well as the conception and design of the work and is to be held equally accountable for all aspects. This includes drafting the manuscript, critically examining it for its content and collectively approving the final version to be submitted.
JC: made equal contributions to the entirety of this manuscript as well as the conception and design of the work and is to be held equally accountable for all aspects. This includes drafting the manuscript, critically examining it for its content and collectively approving the final version to be submitted.

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