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Pregnancy Complications in Women with Uterine Fibroids and the Role of Stem Cells

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Abstract

Introduction: Uterine fibroids are a prevalent and benign tumor in the uterine wall that commonly affects women of reproductive age. These growths can lead to adverse pregnancy outcomes. This study aims to investigate the crucial role of myometrial stem cells in the development of fibroids and their impact on pregnancy complications.

Methods: The following terms were used in the PubMed, Embase, Scopus, ScienceDirect and MEDLINE databases to search for articles in English: Uterine Fibroids, Myometrial stem cells, Pregnancy complications, and Hormones. The articles selected were systematic reviews, meta-analyses, randomized controlled trials, and reviews. These data were searched from 2016 to May 2023.

Results: The study found that myometrial stem cells differentiated into smooth muscle cells, contributing to fibroid development. These fibroid stem cells had distinct hormone receptor characteristics. Hormonal imbalances and genetic predisposition led to the uncontrolled growth of myocytes, which played a central role in the formation of fibroids. Estrogen and progesterone, which support
uterine tissue growth, were identified as key factors in this process. In addition, ECM remodeling, angiogenesis, inflammation, and dysregulated signaling pathways were shown to be implicated in fibroid development.

Conclusion: Uterine fibroids have a significant impact on pregnancy outcomes, leading to various complications such as preterm birth, cesarean delivery, placental abnormalities, and heavy bleeding. The severity of these complications depends on factors like fibroid size, location, and individual factors. Therefore, understanding the complex interplay of factors, including the involvement of myometrial stem cells, hormonal influence, inflammation, and ECM changes, is crucial for improving patient care.

The knowledge gained from this study has the potential to inform targeted therapies and interventions for women with fibroids during pregnancy, ultimately improving the health of both mother and baby. However, further research is needed to elucidate precise mechanisms and develop more effective treatments for managing pregnancies complicated by fibroids.

Keywords: Uterine fibroids, Pathophysiology, stem cells, hormones, genetics

Introduction

Uterine fibroids, or leiomyomas or myomas, are the most common benign tumors of the female reproductive tract, affecting a substantial proportion of women during their reproductive years (Stewart et al. 2016). While most of these growths are asymptomatic and often go unnoticed, uterine fibroids can present various clinical challenges, particularly concerning pregnancy. The association between uterine fibroids and adverse pregnancy outcomes has been the focus of

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extensive research and clinical inquiry in recent years. Increasing community awareness and education on uterine fibroids can lead to a better understanding of the risk factors linked with this illness. It is important to note that there is a lack of data from research on uterine fibroids within underrepresented groups (Marsh et al. 2018). This review article offers a complete assessment of the existing research, focusing on the complicated relationship between uterine fibroids and pregnancy problems.

Uterine fibroids, characterized by the abnormal growth of smooth muscle cells within the uterine wall, can manifest in various sizes and locations within the uterine cavity. These non-malignant growths often give rise to bothersome symptoms, comprising heavy menstrual bleeding, pelvic pain, and reproductive issues (Stewart et al. 2017). Beyond their impact on gynaecological health, uterine fibroids have emerged as a significant concern in pregnancy, with growing evidence suggesting their association with adverse maternal and fetal outcomes (Jayes et al. 2019).

Given the occurrence of uterine fibroids among women of reproductive age and the potential implications for maternal and fetal health, careful consideration of the impact of uterine fibroids on pregnancy complications is of paramount importance (Ezzedine and Norwitz 2016). The most frequent mode of delivery was cesarean section (61.82%). Threatened preterm labor was a significant issue in 21.82% of pregnancies, and blood transfusion was necessary in 20.00% of cases. Postpartum hemorrhage (PPH) was experienced in 9.09% of pregnancies, while 47 patients (42.72%) remained symptom-free throughout their pregnancies (Choudhary, Inamdar and Sharma 2023). While some investigations have reported an amplified risk of undesirable results such as preterm birth, cesarean delivery, and placental abnormalities in pregnant women with uterine fibroids, the exact mechanisms underlying these associations remain a subject of ongoing investigation (Dasgupta et al. 2017).

This review aims to synthesize the current body of knowledge, shedding light on the intricate relationships between uterine fibroids and pregnancy complications. In pursuit of this goal, we will systematically examine the available literature, explore potential pathophysiological mechanisms, and critically assess the clinical implications of these findings. By consolidating the existing evidence, we hope to provide clinicians, researchers, and healthcare providers with a comprehensive resource for informed decision-making and improved patient care from the perspective of pregnancy complicated by uterine fibroids.

The origin of uterine fibroids is believed to stem from the unchecked growth of smooth muscle cells within the uterine wall. Mesenchymal stem cells (MSCs) are thought by some researchers to have a part in the formation of uterine fibroids. These MSCs can differentiate into numerous cell types, such as smooth muscle cells, and may be involved in developing fibroid tumors (Shen et al. 2013). Due to their regenerative potential, stem cells could potentially be involved in the formation and sustenance of uterine fibroids. A possible explanation for the growth of fibroids is that stem cells found in the uterine tissue may develop into smooth muscle cells (Mas et al. 2020). Scientists are exploring potential therapies for uterine fibroids using stem cells. Mesenchymal stem cells (MSCs) could be used to target the development of fibroids and alleviate the symptoms associated with them. These treatments aim to control the disease using stem cells' regenerative and anti-inflammatory properties (Nishino et al. 2019).

Nonetheless, it's crucial to underscore that further research is required to comprehensively grasp the precise function of stem cells in uterine fibroids and to formulate efficient stem cell-driven treatments. Despite these ideas and potential therapeutic approaches, precise references may be scarce. Therefore, it is recommended to refer to recent scientific publications or ongoing clinical trials (Donnez and Dolmans 2016). It is estimated that 0.1% to 3.9% of women experience this condition during pregnancy, but it affects approximately 20% to 40% of women (Cavaliere et al. 2021). In specific research findings, the documented occurrence of uterine fibroids during pregnancy ranges from 1.6% to 16.7%, with variations noted from trimester to trimester (Tîrnovanu et al. 2022).

Methods

To find relevant papers for our literature review, we conducted a thorough search of several electronic databases, including PubMed, MEDLINE, Scopus, EMBASE, and ScienceDirect, from January 2016 to May 2023. We used the following text words as search terms: "uterine leiomyomas," "hormonal imbalance," "pregnancy complications," and "uterine fibroids." We only considered papers written in English and did not apply any geographic restrictions. Additionally, we examined the reference lists of all identified articles to find studies not captured by electronic searches. Two authors (JM and RV) independently assessed the electronic search and the eligibility of the studies. The final inclusion of the studies was decided after a detailed examination, and we included all randomized clinical trials, retrospective studies, literature reviews, case reports, and series that dealt with patients having evidence of uterine leiomyomas. Nearly 89 studies were reviewed and only 57 have passed the inclusion criteria of the current study. Any differences were discussed, and a consensus was reached.

Stem cells in the uterus and fibroid development

Recent research has shed light on the connection between uterine fibroid development and the association of stem cells in the uterine tissue. One key aspect of this relationship is the role of myometrial stem cells, which are indispensable for the typical growth of the myometrium and the expansion of the uterus during pregnancy (El Sabeh et al. 2021). These myometrial stem cells undergo division, ultimately generating progenitor cells that undergo differentiation into smooth muscle cells, constituting the primary structural component of the myometrium (Ono et al. 2015). Uterine fibroids develop from the myometrial cells, which are the smooth muscle cells of the uterus.

The growth of these fibroids is predominantly influenced by the concentrations of estrogen circulating in the bloodstream (Longo and Bulun 2013). Figure 1 illustrates the proliferation of smooth muscles in the uterine fibroid. A solitary mutation in a stem cell can potentially initiate the formation of fibroid tumors (Moravek and Bulun 2015). Stem cells within fibroids, capable of self-renewing and differentiating, play a pivotal role in maintaining the equilibrium of myometrial tissue. These specialized cells are essential for preserving the regular functioning and structure of the myometrium (Ono et al. 2012). Maintaining myometrial tissue homeostasis is contingent upon the crucial attributes of self-renewal and differentiation found in fibroid stem cells (Salas et al. 2022). Fibroid stem cells exhibit minimal expression of estrogen and progesterone receptors, specifically ERα and PGR, respectively (Serna et al. 2018).

Researchers isolated normal myometrial and fibroid cells, demonstrating essential stem/progenitor cell characteristics using distinct surface markers to enrich a subset of myometrial or fibroid cells. These samples were obtained from women undergoing surgery for symptomatic uterine fibroids, including hysterectomy or myomectomy (Mas et al. 2015). Estrogen and progesterone, hormones that prepare the uterine lining for pregnancy each menstrual cycle, seem to encourage fibroid growth. Fibroids possess more estrogen and progesterone receptors than regular uterine muscle cells (Kim, Kurita and Bulun 2013).

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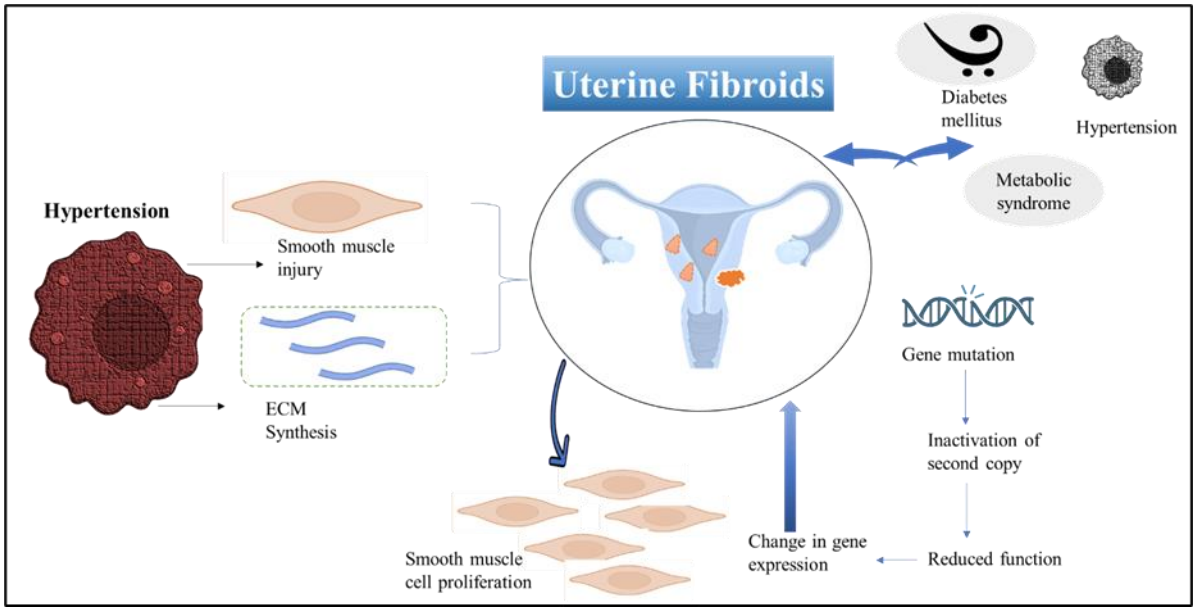

Figure 1. Smooth muscle proliferation in uterine fibroids

Impact of uterine fibroids during pregnancy

Among some women with uterine fibroids, they experience pain, heavy bleeding, and concerns about being able to get pregnant. Women's experience of uterine fibroids during pregnancy can vary considerably based on several factors, such as the size and location of the fibroids and their overall health (Coutinho et al. 2022). Compared to women who do not have fibroids, women with fibroids face an increased relative risk of experiencing pregnancy loss regardless of the fibroid's location. In such cases, a pre-conception saline infusion sonogram is extremely helpful for identifying submucosal fibroids (Guo and Segars 2012). If fibroids cause incomplete cervical dilation, the birth canal may be blocked, requiring a cesarean. As a result of fibroids, there is a possibility of placenta previa (implantation of the placenta over the cervix) and placental abruption, which may cause heavy bleeding and negatively affect the oxygen supply to the baby (Kwas et al. 2021). Fibroids can interfere with fertility by blocking the fallopian tubes or preventing embryo implantation in the uterus (McWilliams and Chennathukuzhi 2017). There is a possibility that fibroids may grow during pregnancy due to increased levels of hormones and blood flow. As a result of this growth, the patient may experience increased discomfort and complications (Wong et al. 2016). It is essential to highlight that not all women with uterine fibroids may have these pregnancy difficulties, and many have normal, healthy pregnancies. The effect of fibroids on pregnancy varies greatly depending on the person (Grube et al. 2019).

Stem cell research and uterine fibroids

Stem cell research has been conducted to gain a deeper understanding of how stem cells contribute to the formation of uterine fibroids and to pioneer innovative treatment strategies for addressing these fibroids (Carneiro 2016). Researchers created organoids from human myometrial and uterine fibroid stem cells to explore uterine fibroids' pathophysiology and uncover new treatment targets (Santamaria et al. 2018) Figure 2. Based on current research findings, uterine stem cells have been observed to transform stem cells that initiate tumors in the context of leiomyomas, endometriosis, and adenomyosis (Wilczynski et al. 2022). Research has used stem cell-derived organoids to study uterine fibroids' pathophysiology and develop new therapies (Elkafas et al. 2020). Other studies have focused on identifying uterine fibroids' risk factors, developmental origins, and pathogenetic pathways to create novel targeted therapeutics (Yang et al. 2022).

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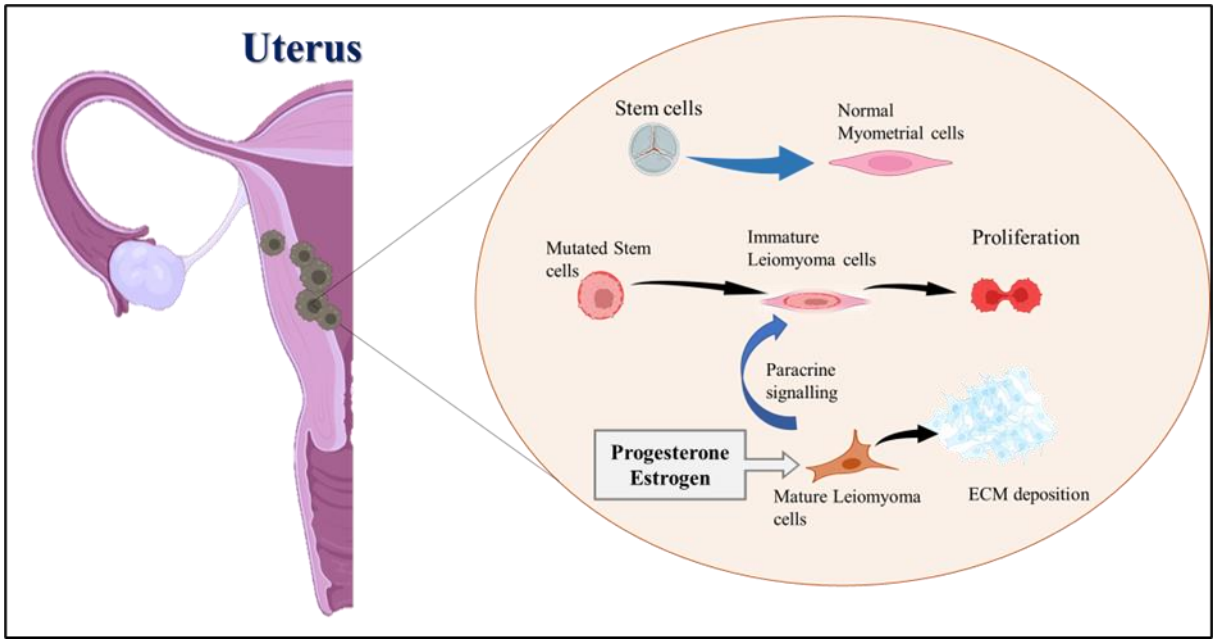

Figure 2. Proliferation of stem cells in Uterine fibroids

Pathophysiology

The precise mechanisms and pathophysiology of stem cells linked to uterine fibroids in pregnant women remain incompletely understood. However, recent research has begun to provide some insights into this area. In contrast, the myometrium usually remains moderately quiescent throughout the reproductive cycle; it undergoes substantial expansion during pregnancy and then regresses after childbirth (El Sabeh et al. 2021). Uterine stem cells have been associated with various gynecological conditions, including endometrial cancer, fibroids, endometriosis, and pregnancy loss. Researchers have isolated myometrial and fibroid stem cells using specific surface markers, enriching a subset of these cells that display essential progenitor and stem cell features. Fibroid stem cells possess self-renewal and differentiation capabilities and are crucial in maintaining myometrial tissue balance (Banerjee et al. 2022).

Biomechanical forces play a role in determining the transformation of fibroid stem cells and the receptivity status of the endometrium. Most myometrial cells are expanded during pregnancy from stem cells in the human myometrium (Celik et al. 2022). Models of OCT4-GFP transgenic mice have been used to study myometrial stem cell ontogeny (Brakta, Mas, and Al-Hendy 2018). Nevertheless, further research is required to understand the mechanisms and pathophysiology of stem cells associated with uterine fibroids in pregnant women, as illustrated in Figure 3.

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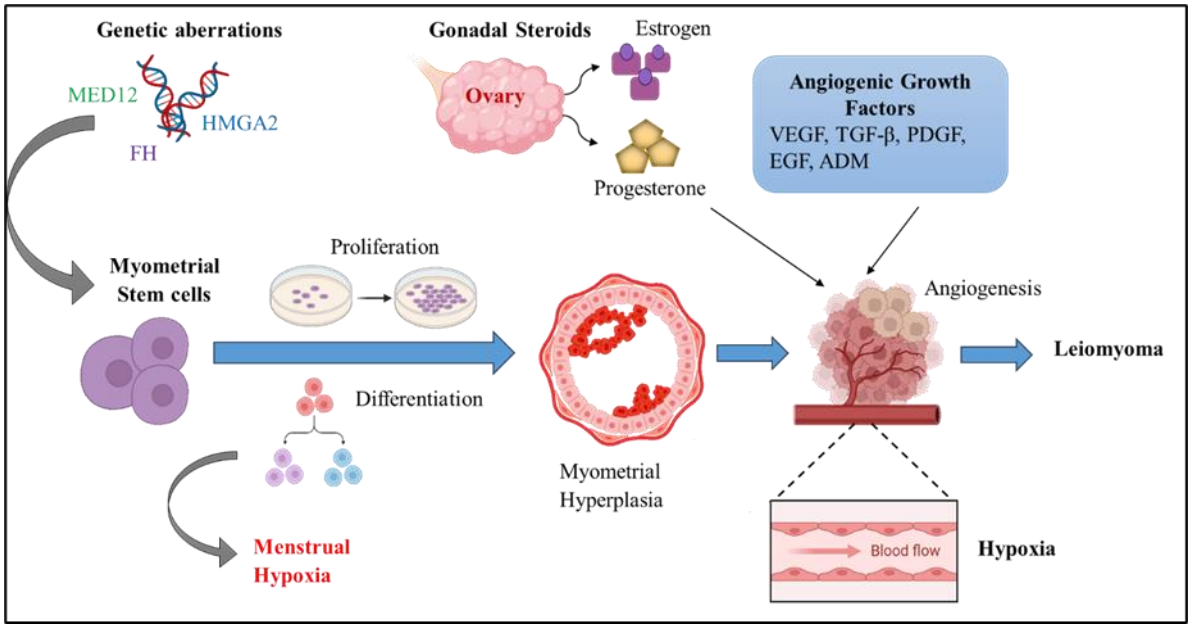

Figure 3. Pathophysiology of uterine fibroid stem cells

Predisposition

There is an aspect to the development of fibroids. Women with a family history of fibroids are more likely to develop them. Fibroids may develop when specific gene mutations involve cell growth and extracellular matrix regulation (ECM) (Girigoswami et al. 2021). Stem cell mutations have been allied with the formation of uterine fibroids. Most fibroid tumors have alterations in the MED12 gene, and mutations in HMGA2 expression in myometrial cells also result in abnormal proliferation (Gallagher and Morton 2016). A biallelic germline mutation in the fumarate hydratase gene (FH) has been associated with fumarate hydratase deficiency, resulting in uterine fibroids (Prusinski, Al-Hendy, and Yang 2019). These mutations may cause abnormal stem cell growth, leading to fibroids forming in the uterus (Giuliani, As-Sanie, and Marsh 2020).

While the exact cause of leiomyomas remains unclear, genetic factors have been identified as playing a part in the development of uterine fibroids. Here are several genes that have been linked to the development of these growths. RAD51L1 gene partners with HMGIC in translocations, causing structural disruptions in genes and contributing to the onset of uterine fibroids (Mediakare et al. 2011); Mutations in the Fumarate hydratase (FH) gene have been correlated with the progress of uterine fibroids (Kubinova et al. 2012); TERT, TERC, OBFC1 genes are involved in regulating telomere length, which is linked to genetic susceptibility to uterine leiomyoma (Valimaki et al. 2018).

ATM and TP53 genes play a role in safeguarding genome stability and are also associated with a genetic predisposition to uterine leiomyoma (Guleria and Chandna 2016). Recent research has revealed that the transcription factor protein known as AP-1 is inhibited in leiomyomas, potentially influencing gene transcription and contributing to the formation of uterine fibroids. While additional molecular investigations are needed to comprehend the origins and development of uterine fibroids fully, genetic studies have offered valuable insights into the genetic underpinnings of this condition (Edwards et al. 2019).

Hormonal Influences

Estrogen and progesterone, two hormones for females, play a part in the growth of fibroids. These hormones support the growth and maintenance of the lining of the uterus (endometrium) during the cycle. Fibroids often have levels of receptors for estrogen and progesterone, making them responsive to changes (Chakrabarti 2023). Estrogen plays a role in the growth of fibroids during the reproductive years. It stimulates cell proliferation and activates blood vessel growth

within fibroids (Borahay et al. 2017). Similarly, progesterone contributes to fibroid growth by supporting the maintenance of the lining. Fibroid cells contain receptors for progesterone (Ilicic, Zakar, and Paul 2017).

Other influences

Fibroids are muscle cells (myocytes) in the wall that grow abnormally due to factors like imbalances or genetic influences. The development of a cluster of cells eventually leads to the formation of a fibroid (Islam et al. 2018).

Restructuring of Extracellular Matrix (ECM)

A build-up of ECM components, including collagen and fibronectin, characterizes fibroids. This restructuring of the ECM supports the fibroid and aids in its enlargement (Leppert, Jayes, and Segars 2014).

Formation of New Blood Vessels

A blood supply is necessary for fibroids to continue to grow. They can stimulate the formation of blood vessels, known as angiogenesis, ensuring an oxygen and nutrient supply (Tal and Segars 2014). As fibroids increase, their oxygen requirements may surpass the available supply, resulting in localized hypoxia or low oxygen levels. In this manner, further stimulation of angiogenesis and factors that promote fibroid growth can be achieved (Kirschen et al. 2021).

Inflammation

Persistent uterine inflammation can cause fibroid proliferation. Cytokines and inflammatory signals released during chronic inflammation can increase cell proliferation, gene expression alterations, angiogenesis, and ECM formation, promoting fibroid growth. The effects of this can have a significant impact on an individual's health and quality of life (Van den Bosch et al. 2015). Cellular signaling pathways involving growth factors like TGF-beta, IGF, VEGF, and cytokines may become dysregulated in fibroid tissue. These signaling molecules can influence cell proliferation, the deposition of ECM components, and inflammation (Borahay et al. 2015). Angiogenic factors involved in Figure 4 illustrate uterine fibroids. Enlarging fibroids can exert physical pressure on adjacent organs and structures, causing pelvic pain, increased urination frequency, and constipation (Rezk, Kahn, and Singh 2023). The condition affects primarily middle-aged women with painful lesions on their extremities (Subbrayan et al. 2021).

The interplay of these factors collectively contributes to uterine fibroids' initiation, enlargement, and persistence. The pathophysiology of fibroids can differ among individuals, and not all fibroids follow the same course. Moreover, the specific triggers for fibroid development may vary from person to person, making it a complex and multifactorial condition. Ongoing research aims to uncover more insights into the underlying mechanisms of fibroid pathophysiology, which could lead to improved diagnostic and treatment approaches in the future.

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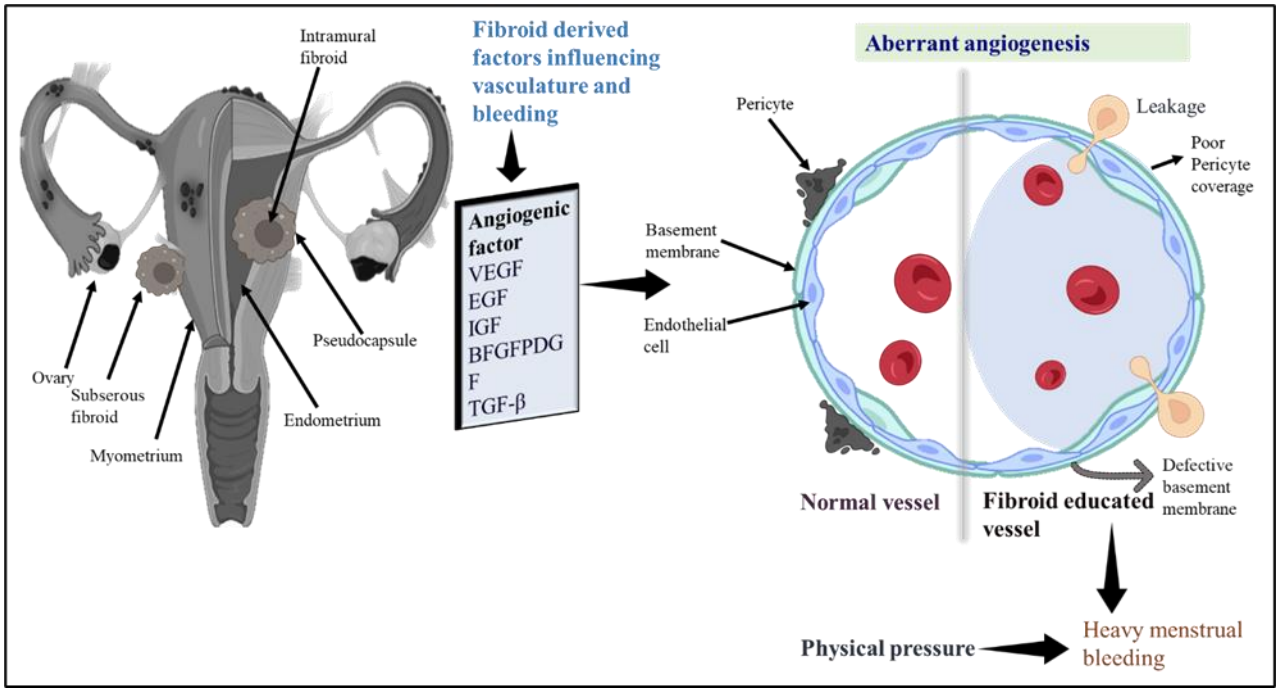

Figure 4. Development of angiogenic factor in uterine fibroids

Results and Discussion

The purpose of this review is to explore the complex mechanisms that contribute to fibroids development. During pregnancy, myometrial stem cells are essential for the growth of the uterus. These stem cells differentiate into smooth muscle cells, which are the primary structural component of the uterus. However, a single mutation in a stem cell can trigger fibroid formation. Stem cells within fibroids maintain myometrial tissue balance through self-renewal and differentiation.

Fibroids can cause complications during pregnancy, leading to pregnancy loss, cesarean sections, placenta-related issues, and fertility problems. Although not all women experience these issues, the impact of fibroids varies among individuals. Stem cell research offers valuable insights into fibroid pathophysiology. Organoids created from myometrial and uterine fibroid stem cells help with understanding and potential treatments. Uterine stem cells can transform into tumor-initiating stem cells in various gynecological conditions.

Ongoing research into the pathophysiology of stem cells in uterine fibroids during pregnancy focuses on biomechanical forces and myometrial cell expansion during pregnancy. Family history and gene mutations play a role in fibroid development, with specific gene mutations linked to abnormal stem cell growth and fibroid formation. Estrogen and progesterone promote fibroid growth by stimulating cell proliferation, blood vessel growth, and uterine lining maintenance.

Fibroid development is influenced by genetic imbalances, extracellular matrix restructuring, angiogenesis, and inflammation. Uterine fibroids are a complex condition influenced by stem cells, genetic factors, hormonal influences, and other contributors. Understanding these interactions can lead to improved diagnostic and treatment approaches in the future, benefiting women's health and well-being.

Conclusions and future perspectives

Uterine fibroids, the most common benign tumors affecting women, have garnered increasing attention for their potential adverse impact on pregnancy outcomes. These growths, characterized by the abnormal proliferation of smooth muscle cells within the uterine wall, can

manifest with various symptoms, including pelvic pain and heavy menstrual bleeding. However, their association with pregnancy complications, such as preterm birth and cesarean delivery, has raised concerns and sparked extensive research.

Understanding the intricate relationship between uterine fibroids and pregnancy complications is paramount due to their prevalence among women of reproductive age. While some studies have reported increased risks associated with uterine fibroids during pregnancy, including placental abnormalities and heavy bleeding, the precise mechanisms underlying these associations remain subject to ongoing investigation.

Recent research has shed light on the potential involvement of stem cells, and uterine fibroids are often caused by myometrial stem cells. Moreover, hormonal influences, genetic predisposition, extracellular matrix restructuring, angiogenesis, and inflammation have all been implicated in the pathophysiology of fibroids. Despite the complexity of uterine fibroids and their impact on pregnancy, it is crucial to emphasize that not all women with fibroids experience pregnancy complications, and many have normal, healthy pregnancies.

Therefore, personalized care and understanding the unique factors influencing each individual's experience are essential. Stem cell research offers promising avenues for comprehending the underlying mechanisms of uterine fibroids and developing novel treatment approaches. Mesenchymal stem cells, with their regenerative and anti-inflammatory properties, have emerged as potential targets for therapeutic interventions.

In conclusion, uterine fibroids represent a multifaceted condition with diverse implications for pregnancy. While research has made significant strides in unravelling their pathophysiology and potential treatments, ongoing investigations are necessary to provide more precise insights and improve diagnostic and therapeutic options. This comprehensive understanding will empower healthcare providers to deliver informed care and support women facing pregnancy complicated by uterine fibroids, ultimately enhancing maternal and fetal health.

Competing interests: The authors declare no conflict of interest to report

Authors' contributions

JM wrote the contents, edited the figures and tables of this manuscript
RV designed the study, edited the contents of this manuscript, and approved the manuscript for submission. “All authors read and approved the final manuscript”

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