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# Exploring the role of serum sestrin 2 in patients with endometrial polyps and uterine leiomyomas: implications for early diagnosis and pathophysiology

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## ABSTRACT

Endometrial polyps and uterine leiomyomas are common gynecological conditions that significantly affect women's health. Recent studies have begun to explore potential biomarkers that could assist in the early diagnosis and understanding of the pathophysiology of these conditions. One such biomarker is Serum Sestrin 2 (SESN2), a protein involved in cellular stress response. This review aims to synthesize research findings on the relationship between serum SESN2 levels and the presence of endometrial polyps and uterine leiomyomas. It examines the potential of SESN2 as a diagnostic tool and its role in the underlying mechanisms of these conditions. Studies suggest that SESN2 levels are elevated in patients with these conditions compared to controls, indicating its involvement in their pathophysiology. Furthermore, the review discusses the implications of these findings for clinical practice, particularly in terms of early detection and targeted therapies. Future research directions and the need for large-scale studies to validate SESN2 as a clinical marker are also addressed. This review highlights the importance of biomarkers like SESN2 in enhancing our understanding and management of gynecological disorders.

**Keywords:** Sestrin 2, endometrial polyp, uterine leiomyoma, biomarkers

Endometrial polyps are localized hyperplastic growths of the endometrial glands and stroma around a vascular core that originate from the surface of the endometrium [1]. These polyps are predominantly benign but can occasionally possess atypical or malignant characteristics. They are a common cause of abnormal uterine bleeding, which is observed in up to 68% of affected patients and represents the most frequent symptom associated with endometrial polyps [2].

Uterine leiomyomas, or fibroids, are benign tumors derived from the smooth muscle cells of the myometrium and are the most common pelvic tumors in women [3]. These tumors vary widely in size, number, and location within the uterus, influencing their clinical manifestations, which most frequently include excessive menstrual bleeding and pelvic discomfort [4].

The pathophysiology of both endometrial polyps and uterine leiomyomas is not fully understood, though oxidative stress and inflammatory processes

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are thought to play significant roles in their development [5]. Oxidative stress, defined as a disturbance in the balance between the production of reactive oxygen species (free radicals) and antioxidant defenses, is a common pathway implicated in many pathologies, including the formation of fibroids and possibly polyps [6].

Sestrin 2 (SESN2) emerges as a critical protein in regulating oxidative stress and has been linked to various cellular responses to damage and stress [7]. It is induced under conditions of oxidative stress and plays a significant role in cell survival and metabolic regulation [8]. Elevated levels of SESN2 have been observed in patients with endometrial polyps and uterine leiomyomas, suggesting its involvement in the pathogenesis of these conditions and its potential utility as a biomarker for early diagnosis [9].

Given the prevalence and impact of endometrial polyps and uterine leiomyomas on women's health, understanding the role of biomarkers such as SESN2 could significantly enhance diagnostic accuracy and lead to more targeted therapies, ultimately improving patient outcomes. This review aims to compile and analyze the existing literature on SESN2 in relation to these common gynecological disorders and to evaluate its potential as a diagnostic and therapeutic marker [10].

## ENDOMETRIAL POLYPS AND UTERINE LEIOMYOMAS

Endometrial polyps and uterine leiomyomas are two prevalent non-cancerous growths affecting the female reproductive system, with significant implications for women's health globally. Endometrial polyps are localized hyperplastic growths consisting of endometrial glands, stroma, and blood vessels that project from the lining of the uterus [11]. They vary in size, can be sessile or pedunculated, and although usually benign, they can exhibit atypical features or undergo malignant transformation in rare cases [12].

Uterine leiomyomas, commonly known as fibroids, are benign smooth muscle tumors originating from the myometrium, the muscular layer of the uterus [3]. These tumors are the most common pelvic tumors in women and can vary greatly in size, number, and location within the uterus, affecting their clinical presentation and management [13, 14]. Fibroids are recognized for their impact on menstruation, fertility, and overall quality of life, contributing to significant healthcare costs due to their high prevalence and the morbidity associated with severe cases [15].

Both conditions are important due to their high prevalence and frequently lead to diagnostic challenges and diverse treatment modalities. Understanding these conditions has evolved significantly, with current research focusing on their hormonal regulation, genetic predispositions, and potential environmental triggers [16]. Endometrial polyps and uterine leiomyomas often present similarly but have distinct pathophysiological pathways, which are crucial for tailoring individualized treatment strategies.

The relevance of these conditions in gynecological health stems from their common occurrence and the considerable impact they can have on a woman's reproductive capabilities and quality of life. Understanding and managing these conditions efficiently is critical, not only to alleviate symptoms but also to prevent potential complications such as infertility and recurrent pregnancy loss, which are significant concerns associated with these gynecological anomalies [17].

## EPIDEMIOLOGY AND RISK FACTORS

The epidemiology of endometrial polyps and uterine leiomyomas highlights their significant prevalence in the female population, underscoring a major public health concern. Endometrial polyps are estimated to affect approximately 10% to 25% of women, with their prevalence increasing with age. These polyps are more commonly diagnosed in women in their 40s and 50s, particularly during the perimenopausal period, suggesting a link with hormonal changes associated with the menopausal transition [18].

Uterine leiomyomas are even more prevalent, affecting up to 70-80% of women by the age of 50 [19]. While many cases are asymptomatic and may not require intervention, a significant proportion of affected women experience symptoms severe enough to necessitate medical or surgical treatment. The onset of fibroids is rarely seen before the onset of menstruation, and their growth is often influenced by reproductive hormones, which explains their common development

during the reproductive years and often a decrease in size and symptomatology after menopause [20].

### Hormonal Imbalances

Both endometrial polyps and uterine leiomyomas are influenced by hormonal imbalances, particularly by estrogens and progesterone. Estrogens promote the growth of both polyps and fibroids, while progesterone may have a complex role, potentially supporting growth in some cases while inhibiting it in others [21]. This hormonal influence is pivotal and represents a target for therapeutic intervention, such as the use of hormone modulators including selective estrogen receptor modulators (SERMs) and gonadotropin-releasing hormone (GnRH) analogs, which have been shown to reduce the size and symptoms of fibroids [22].

### Genetic Predispositions

There is a significant genetic component to the risk of developing both endometrial polyps and uterine leiomyomas. The familial clustering of fibroids suggests a hereditary component, with studies identifying specific genetic alterations associated with their growth, such as mutations in the MED12 gene and other components related to the extracellular matrix and cellular proliferation [23]. Similarly, genetic predispositions have been noted in the development of endometrial polyps, with a particular association with syndromes that include a predisposition to polyp formation, such as Lynch syndrome [24].

### Environmental Influences

Environmental factors also play a crucial role in the epidemiology of these conditions. Lifestyle factors such as obesity, high blood pressure, and a diet high in red meat have been linked to an increased risk of fibroids, while physical activity and a diet rich in fruits and vegetables appear to reduce this risk [25]. Exposure to environmental toxins such as phthalates and other endocrine-disrupting chemicals has also been suggested to contribute to the development of both polyps and fibroids, although more research is needed to establish these links definitively [26]. In conclusion, endometrial polyps and uterine leiomyomas are common gynecological conditions with complex multifactorial etiologies involving hormonal, genetic, and environmental components. Understanding these factors is crucial for developing prevention strategies, refining diagnostic processes, and tailoring individualized treatments that can effectively manage or mitigate the conditions.

## PATHOPHYSIOLOGY AND GENETIC INSIGHTS

The pathophysiological processes underlying the formation and growth of endometrial polyps and uterine leiomyomas are complex and involve a confluence of hormonal influences, genetic mutations, and possibly, lifestyle factors. These mechanisms are not only crucial for understanding the development of these conditions but also for advancing targeted treatment strategies.

### Hormonal Pathways

Both endometrial polyps and uterine leiomyomas are significantly influenced by hormonal pathways, particularly those involving estrogen and progesterone, two key regulators of the reproductive system. Estrogen promotes the proliferation of the endometrial lining and is thought to contribute to the hyperplastic growth seen in polyps [27]. In leiomyomas, estrogen acts to stimulate fibroid growth through the activation of estrogen receptors, which increases the expression of genes involved in cell proliferation and decreases those involved in apoptosis [28]. Progesterone, although traditionally considered antiproliferative, can have a complex role in the growth dynamics of these conditions. In fibroids, progesterone has been shown to contribute to fibroid growth by stimulating the production of growth factors and extracellular matrix components that provide structural support to the tumors [29].

### Genetic Mutations

On a genetic level, multiple mutations have been implicated in the pathogenesis of uterine leiomyomas. For instance, mutations in the MED12 gene are among the most common genetic alterations in leiomyomas, found in up to 70% of cases [30]. These mutations may alter the function of the mediator complex, which plays a critical role in transcriptional regulation, potentially leading to dysregulated cell growth. For endometrial polyps, the genetic landscape is less well

defined, but abnormalities in genes related to hormonal regulation and inflammatory pathways are suspected [31]. Additionally, genetic predisposition plays a role, as evidenced by the higher prevalence of these conditions in certain familial and hereditary contexts, such as those associated with hereditary nonpolyposis colorectal cancer (Lynch syndrome).

### Lifestyle Factors

Lifestyle factors also influence the pathophysiology of these gynecological conditions. Obesity, high-fat diet, and lack of physical activity have been associated with an increased risk of developing fibroids. These factors may influence hormone levels, particularly increasing estrogen levels, which in turn may exacerbate the growth of leiomyomas and potentially endometrial polyps [32]. Moreover, oxidative stress and inflammation, which can be exacerbated by lifestyle factors such as smoking and poor diet, have also been suggested to contribute to the pathogenesis of these conditions. Oxidative stress, in particular, can damage DNA and disrupt normal cell functions, leading to abnormal cell growth and the development of polyps and fibroids [33].

### Environmental Contributions

Environmental exposures, including certain chemicals and pollutants, have been implicated in the increased risk of developing polyps and fibroids. Endocrine-disrupting chemicals, such as bisphenol A (BPA) and certain phthalates, which are prevalent in many consumer products, can mimic or interfere with the body's natural hormones, particularly estrogen, potentially contributing to the pathophysiology of these conditions [34]. In conclusion, the formation and growth of endometrial polyps and uterine leiomyomas are influenced by a complex interplay of hormonal imbalances, genetic predispositions, and environmental and lifestyle factors. Understanding these underlying mechanisms not only helps in diagnosing and managing these conditions but also opens up possibilities for preventive strategies and novel therapeutic approaches based on molecular and genetic targets.

## CLINICAL PRESENTATION AND DIAGNOSIS

Endometrial polyps and uterine leiomyomas, though often asymptomatic, can present with a range of symptoms that significantly affect patients' quality of life and reproductive health. The approach to diagnosis combines clinical assessment with sophisticated imaging techniques, providing a comprehensive understanding of these conditions.

### Symptoms of Endometrial Polyps and Uterine Leiomyomas

The most common symptom associated with endometrial polyps is abnormal uterine bleeding (AUB), which can manifest as irregular menstrual cycles, menorrhagia (heavy menstrual bleeding), or bleeding between periods [35]. Such symptoms can lead to anemia and significantly impact daily life, causing fatigue and other health complications. Endometrial polyps are also associated with infertility, as they can interfere with the implantation of the embryo [36].

Uterine leiomyomas may present with a similar profile of menstrual irregularities but are particularly known for causing heavy and prolonged periods. Other symptoms include pelvic pain or pressure, frequent urination, pain during intercourse, and, in some cases, complications during pregnancy such as increased risk of miscarriage or preterm labor [37]. The size and location of fibroids determine the severity and type of symptoms, with larger fibroids and those located within the uterine cavity causing more severe symptoms.

### Diagnostic Procedures

The diagnosis of endometrial polyps typically involves transvaginal ultrasound (TVUS) as a first-line imaging technique. TVUS is highly effective in identifying the presence of polyps as focal hyperechoic lesions within the endometrial cavity. For a more detailed assessment, saline infusion sonohysterography (SIS) may be used, which provides a clearer image of the uterine cavity and can distinguish polyps from other intrauterine abnormalities like submucosal fibroids [38].

Uterine leiomyomas are also initially evaluated with TVUS, which can detect the tumors as well-defined, hypoechoic masses within the myometrium. The number, size, and exact location of fibroids can be assessed, which is critical for determining the appropriate management strategy. In cases where more detailed imaging is required, Magnetic Resonance Im-

aging (MRI) may be utilized. MRI offers excellent soft tissue contrast and can differentiate fibroids from other pelvic pathologies, making it invaluable particularly when surgical intervention is being considered [39].

Additionally, hysteroscopy is an essential diagnostic tool for both conditions when surgical management is planned or when the intracavitary extent of polyps or fibroids needs to be precisely determined. This procedure involves the insertion of a small camera through the cervix into the uterine cavity, providing a direct visual assessment of the endometrium, which is useful for confirming the diagnosis and during the removal of polyps or submucosal fibroids [40].

Accurate diagnosis and effective management of endometrial polyps and uterine leiomyomas rely heavily on the detailed understanding of their clinical presentations and the judicious use of advanced diagnostic tools. The symptoms, while sometimes nonspecific, are significant indicators of these conditions and can profoundly impact a woman's reproductive health and quality of life. By integrating clinical findings with advanced imaging techniques, clinicians can tailor treatment plans that address both the symptoms and the underlying causes of these prevalent gynecological conditions.

## TREATMENT STRATEGIES AND MANAGEMENT

The management of endometrial polyps and uterine leiomyomas involves a spectrum of treatment options tailored to the patient's symptoms, reproductive goals, and the specifics of the condition. Treatment choices range from conservative observation to pharmacological interventions and invasive surgical procedures. The decision-making process is guided by the severity of symptoms, the patient's desire for fertility preservation, and the location and size of the lesions.

### Pharmacological Interventions

For patients experiencing mild symptoms or when fertility preservation is a priority, pharmacological treatment may be the first line of approach. In the case of uterine leiomyomas, hormone-modulating therapies are commonly used to reduce symptoms and decrease fibroid size. These include:

#### *Gonadotropin-Releasing Hormone (GnRH) Agonists*

These drugs effectively shrink fibroids by creating a temporary menopausal state and decreasing estrogen levels. However, their use is typically limited to short-term preoperative periods due to the risk of significant bone density loss with long-term use [42].

#### *Progestins and Progesterone Receptor Modulators (PRMs)*

Medications like mifepristone and ulipristal acetate can control bleeding and decrease fibroid size. They act by antagonizing progesterone, which is known to promote fibroid growth [43].

#### *Oral Contraceptives and Levonorgestrel-Releasing Intrauterine Devices (IUDs)*

These are more commonly used for managing bleeding symptoms rather than reducing fibroid size. They provide effective contraception and menstrual cycle regulation, which can be beneficial in managing AUB associated with fibroids [44].

For endometrial polyps, hormonal therapy may also be used, particularly in patients who are asymptomatic or have minor symptoms. However, the effectiveness of hormonal treatments in reducing polyp size or preventing recurrence is less clear and less commonly recommended compared to their use in leiomyomas.

### Surgical Procedures

When pharmacological management is ineffective or when the polyps or fibroids cause significant symptoms, surgical intervention may be necessary:

#### *Hysteroscopic Polypectomy*

This is the treatment of choice for symptomatic endometrial polyps. It involves the removal of polyps using a hysteroscope, which allows direct visualization and excision with minimal invasion [45].

#### *Myomectomy*

This surgical procedure involves the removal of fibroids while preserving the uterus, making it suitable for women who wish to maintain fertility. Myomectomy can be performed using hysteroscopic, laparoscopic, or open surgical techniques depending on the size and location of the fibroids [46].

*Hysterectomy*

This is the definitive treatment for fibroids and involves the removal of the uterus. It is typically reserved for women with severe symptoms who do not wish to preserve fertility, or when other treatments have failed [47].

### Criteria for Choosing Treatment Paths

The choice of treatment is influenced by several factors:

*Symptom Severity*

More severe symptoms often require more aggressive treatment such as surgery.

*Patient's Age and Desire For Children*

Fertility-preserving treatments are prioritized for younger women desiring future pregnancies.

*Size and Location of the Growths*

Larger or unfavorably located fibroids may require surgical intervention, whereas smaller and fewer fibroids or polyps might be managed with medication.

*Patient Preference and Overall Health*

Consideration of the patient's personal preferences and general health condition is crucial in deciding the treatment approach.

The management of endometrial polyps and uterine leiomyomas requires a personalized approach that considers the patient's clinical presentation, lifestyle factors, and reproductive plans. With advancements in medical treatments and surgical techniques, most women can achieve significant relief from symptoms and improvement in quality of life. Ongoing research continues to refine these treatment options and may offer more targeted therapies in the future.

## ROLE OF SESTRIN 2 IN PATHOGENESIS

Sestrin 2, a highly conserved protein involved in cellular stress responses, has emerged as a significant player in the pathophysiology of various human diseases, including endometrial polyps and uterine leiomyomas. Its functions span from antioxidation to modulation of metabolism and inflammation, which are pivotal in the context of these gynecological conditions.

### Cellular Stress Responses

SESN2 is known for its role in protecting cells against oxidative stress and DNA damage. It acts by activating the AMP-activated protein kinase (AMPK) and regulating the mammalian target of rapamycin (mTOR) pathways, which are critical in cellular survival and metabolism [48]. In the uterine environment, oxidative stress is a recognized factor contributing to the pathogenesis of both polyps and fibroids. SESN2's activation in response to increased oxidative stress helps maintain cellular integrity by inhibiting mTOR signaling, thus potentially preventing the uncontrolled cell proliferation characteristic of polyps and leiomyomas [49].

### Inflammation

The role of inflammation in the development of endometrial polyps and uterine leiomyomas is well documented, with pro-inflammatory cytokines found elevated in affected tissues. SESN2 modulates inflammatory responses by influencing NF-κB signaling pathways. By controlling these pathways, SESN2 could reduce chronic inflammation and its downstream effects, which contribute to the fibrotic processes seen particularly in leiomyomas [50].

### Oxidative Stress

Oxidative stress results from an imbalance between free radicals and antioxidants in the body, leading to cell damage. SESN2 enhances the expression of various antioxidant proteins and enzymes, thus protecting cells from oxidative damage. This protective role is crucial in the endometrium, where oxidative stress can lead to mutations and cellular dysregulation, fostering the growth of polyps and fibroids [51]. Furthermore, studies have shown that SESN2 expression is upregulated in the tissues of patients with leiomyomas, suggesting that it may be a compensatory response to increased oxidative stress in these tumors [52].

### Interactions with Other Cellular Mechanisms

SESN2 also interacts with other cellular pathways involved in cell survival and apoptosis, which are dys-

regulated in the pathogenesis of uterine fibroids and polyps. For example, its regulation of the p53 pathway can influence cell cycle arrest and apoptosis, processes that are often inhibited in fibroid cells and polyp cells [53]. Additionally, its role in autophagy through the AMPK and mTOR pathways can affect cellular cleanup and turnover, impacting the stability and viability of cells in the uterine lining.

## IMPLICATIONS FOR TREATMENT AND RESEARCH

Understanding the role of SESN2 in the pathogenesis of endometrial polyps and uterine leiomyomas offers potential therapeutic avenues. Targeting the SESN2 pathways could lead to the development of drugs that modulate its activity, aiming to reduce oxidative stress, inflammation, and cell proliferation associated with these conditions. Moreover, SESN2 could serve as a biomarker for the early detection of these gynecological disorders, potentially guiding treatment decisions and monitoring responses to therapy [54].

SESN2 plays a multifaceted role in the pathogenesis of endometrial polyps and uterine leiomyomas through its involvement in oxidative stress response, inflammation, and cellular metabolism. Further research into SESN2 and its pathways could illuminate new strategies for managing these prevalent conditions, improving outcomes for affected women.

## IMPLICATIONS FOR FUTURE RESEARCH AND CLINICAL PRACTICE

The exploration of sestrin 2 (SESN2) as a biomarker and therapeutic target in the context of endometrial polyps and uterine leiomyomas is opening new avenues in both research and clinical management of these conditions. The potential applications and benefits of SESN2-focused research are vast, offering prospects for early diagnosis, personalized treatment strategies, and improved patient outcomes.

### SESN2 as a Biomarker for Early Diagnosis

The ability of SESN2 to respond to cellular stress and inflammation, key factors in the pathogenesis of endometrial polyps and uterine leiomyomas, makes it a promising candidate for a biomarker. Early detection of these conditions remains a challenge but is crucial for effective management, especially in preserving fertility and minimizing invasive treatments. Elevated levels of SESN2 could potentially indicate the early onset of disease processes before significant symptoms manifest, allowing for earlier intervention and monitoring [56]. Future studies could focus on validating the sensitivity and specificity of SESN2 levels in blood or tissue samples as a diagnostic tool in clinical settings.

### Therapeutic Interventions Targeting SESN2

Research into SESN2's role in modulating oxidative stress and inflammation suggests that it could be a target for therapeutic intervention. Developing drugs that can modulate the activity of SESN2 might help in managing the growth and symptoms of polyps and leiomyomas. For instance, enhancing the antioxidant capabilities of SESN2 or its ability to inhibit cell proliferation pathways could directly impact the development and progression of these uterine conditions [57]. Clinical trials could be designed to test such interventions, providing data on their efficacy and safety.

### Integration into Personalized Medicine

The heterogeneity in the presentation and progression of endometrial polyps and uterine leiomyomas makes personalized treatment approaches necessary. Understanding individual differences in SESN2 expression and function could help tailor treatments based on a patient's genetic and molecular profile. This approach could optimize treatment efficacy and minimize side effects, particularly in managing conditions that affect diverse populations [58].

### Future Research Directions

Continued research into SESN2 will also need to address several critical questions:

#### *Mechanistic Understanding*

How exactly does SESN2 interact with other cellular pathways involved in the pathogenesis of endometrial polyps and uterine leiomyomas? Answering this could uncover additional therapeutic targets.

#### *Longitudinal Studies*

What are the long-term implications of modulat-

ing SESN2 in patients with these conditions? Longitudinal studies could help understand the potential risks or benefits.

*Clinical Trials*

How effective are SESN2-targeted therapies in clinical practice? Rigorous clinical trials are needed to determine the practical benefits and any potential side effects of new treatments based on SESN2 modulation.

The ongoing research into sestrin 2 holds significant promise for revolutionizing the diagnosis and treatment of endometrial polyps and uterine leiomyomas. By integrating emerging data on SESN2 into clinical practice, the medical community can potentially improve diagnostic accuracy and treatment outcomes for patients suffering from these prevalent gynecological conditions. As research progresses, it is hoped that SESN2 can be fully utilized not only as a biomarker for early detection but also as a cornerstone for targeted therapeutic strategies.

## CONCLUSION

The exploration of sestrin 2 in the context of endometrial polyps and uterine leiomyomas marks a significant advance in our understanding of these common yet complex gynecological disorders. As we have reviewed, the roles of sestrin 2 are multifaceted, encompassing the regulation of oxidative stress, inflammation, and cellular metabolism—key elements that contribute to the pathogenesis of these conditions.

The potential of sestrin 2 as a biomarker for early diagnosis and a target for therapeutic intervention opens new pathways for the effective management of endometrial polyps and leiomyomas. Its ability to respond to cellular stress and to modulate important metabolic and inflammatory pathways positions it as a unique marker that could help in the early detection of these conditions, potentially guiding treatment choices and monitoring therapeutic responses. This is particularly crucial given the often asymptomatic nature of these conditions in their early stages and the severe impact they can have on a woman's quality of life and reproductive health.

Furthermore, the possibility of targeting sestrin 2 in therapeutic interventions offers a promising outlook for treatments that are more precise and less invasive. By potentially inhibiting the pathways involved in the proliferation and survival of the cells that contribute to these disorders, new treatments could limit the growth of polyps and fibroids or even prevent their formation. This approach not only aims to alleviate the symptoms associated with these conditions but also addresses the underlying causes, potentially reducing the need for surgical interventions which carry inherent risks and complications.

However, while the therapeutic implications of sestrin 2 are promising, significant work remains to be done. Comprehensive clinical trials are needed to validate the efficacy and safety of these new approaches. Moreover, the integration of sestrin 2 into clinical practice will require a collaborative effort among researchers, clinicians, and patients to fully realize its potential benefits.

In conclusion, the ongoing research into sestrin 2 represents a frontier in gynecological research with the potential to significantly impact how endometrial polyps and uterine leiomyomas are diagnosed and treated. It encourages a shift towards more personalized and precise medical interventions that could greatly enhance patient outcomes. As this field evolves, it is expected that sestrin 2 will not only improve our biological understanding of these conditions but also lead to innovations in their management, heralding a new era of targeted therapy that could redefine standards of care in gynecology.

*Authors' Contribution*

Study Conception: SA; Study Design: SA, TB; Supervision: TB, HZG; Funding: N/A; Materials: N/A; Data Collection and/or Processing: SA; Statistical Analysis and/or Data Interpretation: TB, HZG; Literature Review: SA; Manuscript Preparation: SA and Critical Review: SA, TB.

*Conflict of interest*

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