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RESEARCH ARTICLE
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# DELAYING MOTHERHOOD: UNRAVELING THE COMPLEX LINK BETWEEN REPRODUCTIVE TIMING AND ENDOMETRIOSIS RISK" A COMPREHENSIVE LITERATURE REVIEW WITH IN-CALL DEPTH HORMONAL AND METHODOLOGICAL ANALYSIS

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****Abstract****

****Background****

Endometriosis remains is an estrogen dependent disorder occurring in approximately 10 % of reproductive age women arises with chronic pelvic pain dysmenorrhea infertility women. There is a recent demographic pattern of delayed childbearing age which increases the likelihood of prolonged unopposed estrogen exposure due to high chances of endometriosis.

****Objective****

Conduct a systematic review analyzing epidemiological and mechanistic factors exploring the association between delayed childbearing and heightened endometriosis risk with special emphasis on hormonal changes and methodological concerns such as reverse causation.

****Methods****

A systematic literature search was done on PubMed, Scopus, and Web of Science using including "endometriosis," "delayed childbearing," "nulliparity", "exposure to estrogen," and "reproductive aging." Included were peer reviewed articles, systematic reviews, meta analyses, and epidemiology of the research published in English.

****Results****

We recorded the systematic study design data including population characteristics, hormonal mechanisms, and possible confounding factors.

Observational studies have shown consistently that women who delay their first pregnancy or remain nulliparous tend to have a higher incidence of endometriosis. In the case of women temporally delaying conception, the definitive hormonal protective milieu of pregnancy featuring cyclic estrogen suppression with high progesterone is absent. Instead, there is likely transient

prolonged estrogen exposure which may facilitate endometrial proliferation, angiogenesis, and inflammation. Nonetheless, considerable methodological issues, for instance, diagnostic heterogeneity and reverse causation where endometriosis literally procures infertility, muddles causal interpretation.

The majority of the connections discussed in the previous sections are obscured by some level of confounding factors, and so are the endometriosis.

**Conclusion**
The defended association between delaying childbearing and increased risk for endometriosis is justified by both epidemiological as well as biological reasoning, though the interaction of reverse causation with confounding factors is highly complicated and requires prospective research with stringent standardized diagnostic protocols coupled with extensive biomarker evaluation. Resolving these matters becomes essential towards effective clinical guidance and favorable preventive methods.

**Keywords: ** Delayed childbearing; Endometriosis; Estrogen exposure; Nulliparity; Hormonal mechanisms; Reverse causation

## Introduction
Endometriosis is an ailment characterized by the abnormal external growth of endometrial tissue, causing chronic pelvic pain, dysmenorrhea, and infertility. It is estimated to affect 10 percent of women during reproductive years posing a significant health and socioeconomic burden.

At the same time, a sociological shift toward postponed childbearing has also heightened exposure to estrogen because of an increased number of menstrual cycles. The pregnancy related protective effect of high progesterone and the subsequent resting of cyclic estrogen surge pruning is well known. On the other hand, women who choose to delay having children for further studies or advanced career options undergo prolonged stimulation of estrogen which can lead to the proliferation of endometrial tissues and lesions formation. This review collects epidemiological evidence, analyzes the supporting hormonal pathways, and addresses the methodology concerns with regards to the impact of childbearing postponement on the risk of endometriosis.

## Methods
### Literature Search Strategy
The following databases were systematically searched for relevant literature:

- **Pubmed**
- **Scopus**
- **Web of Science**

**Search Terms**
“Endometriosis”; “Delayed childbearing”; “Nulliparity”; “Exposure to Estrogen”; “Reproductive aging”

### Inclusion and Exclusion Criteria
**Inclusion: **
- Published in English peer-reviewed articles, systematic reviews, meta-analyses, and original epidemiological articles which assess the association between age at first pregnancy or childbearing and the frequency or severity of endometriosis.

**Exclusion: **
- Non-peer-reviewed publications, opinion articles, case reports without substantial evidence, and mono perspective intervention studies are excluded.

The two independent scholars manually pulled details regarding study design, population, hormonal mechanisms, and even calculated statistical risk estimates (e.g., odds ratios, confidence intervals). Data was classified into the following thematic areas:

1. Epidemiological Evidence
2. Hormonal Mechanisms
3. Methodological Considerations: including confounding or reverse causation.

## **Results**
### **Epidemiological Evidence**
Consistent observational studies indicate that women who have children later and those who are childless tend to have a greater prevalence of endometriosis. Women with a first pregnancy at 30 years of age and above tend to have higher chances of surgical diagnosis of endometriosis in cohort studies.

#### Table 1. Summary of Key Epidemiological Studies
| Endometriosis Epidemiology: A Systematic Review Modena et al.  2020.
| Endometriosis Epidemiology: A Systematic Review Modena et al. 2020.

##Hormonal Mechanisms
## Protective Role of Pregnancy

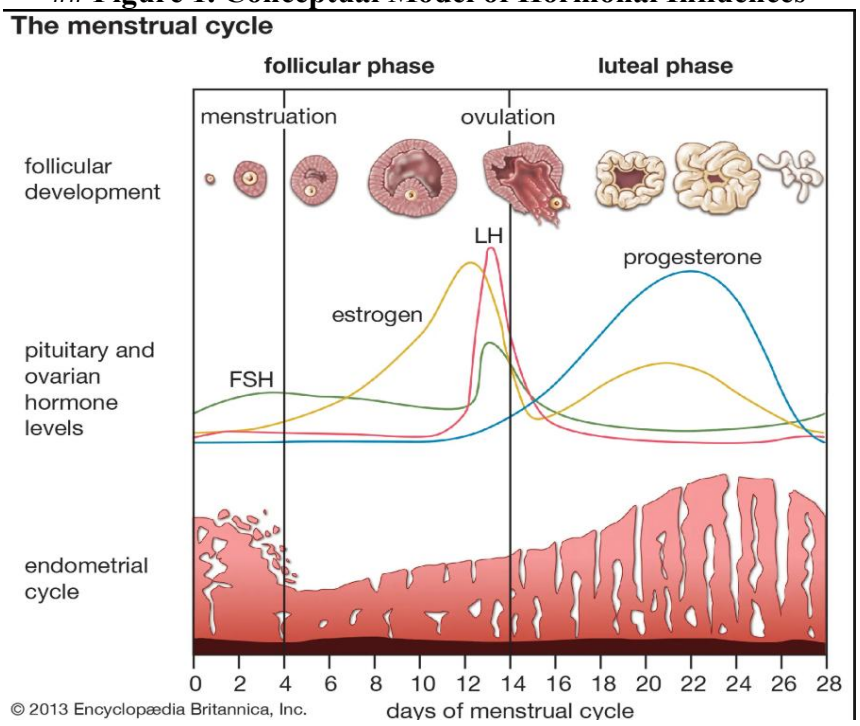
- **Progesterone Surge:**
During pregnancy, elevated progesterone leads to the downregulation of estrogen receptors. Also, cyclic endometrial inflammation and lesion formation is reduced and proliferation is inhibited.

- **Estrogen Suppression:**
Pregnancy-amenorrhea state helps in avoiding recurrent spikes of estrogen resulting in “reset” endometrial stimulation and precondition that is further protective endometriosis.

## Risks of Prolonged Menstrual Exposure

- **Chronic Estrogen Exposure:**
In non-pregnant cycles, single or multiple peaks of estrogen tend to boost proliferation of endometrial cell, angiogenesis and inflammation which assists ectopic endometrial tissue developed in non-pregnant cycles.

**## Figure 1. Conceptual Model of Hormonal Influences**




## **Methodological Considerations**

## **Diagnostic Heterogeneity**

- **Variability in Diagnostic Criteria:**

Diagnosis of endometriosis includes clinical assessment and laparoscopic confirmation, which creates challenges in comparison across studies.

## **Reverse Causation and Confounding**

- **Reverse Causation: **

Infertility outcomes and subsequent childbearing leads to an enduring time span for child-rearing. This relationship has a cyclical nature rather convolutes spaces where cause is derived from influence.

- **Additional Confounders: **

Hereditary and lifestyle attributes such as body mass index and diet, as well as environmental factors, may influence the endometriosis risk as well as the timing precision of reproduction independently.

**Table 2. Key Methodological Challenges and Confounders**

| Challenge | Description | Impact on Findings |
|---|---|---|
| **Diagnostic Variability** | Inconsistent criteria for endometriosis diagnosis | Limits the comparability and generalizability across studies. |
| **Reverse Causation** | Endometriosis-induced infertility may cause delayed pregnancy | Obscures the cause–effect relationship between reproductive timing and disease risk. |
| **Sample Selection Bias** | Recruitment from specialized clinics | Reduces generalizability to the broader population. |
| **Confounding Lifestyle Factors** | Variability in BMI, environmental exposures, and dietary habits | May introduce residual confounding despite multivariate adjustments. |

## Recommendations for Future Research
Further studies need to:
Capture hypothalamic-pituitary-adrenal activity changes in repeated intervals longitudinally.
Confirm unified standards of diagnostic criteria for laparoscopy.
Conduct analysis on genetic markers for disease using multi-omics techniques.
Incorporate advanced lifestyle and environmental factors correlation at the constituency level in explainable multivariate statistical evaluation.

## Discussion
Estrogen dominance phases due to the absence of pregnancy during later childbearing years is heightened. This surge leads to a faster weakening of pregy barriers causing endometrial neoplasm formation—this heightened surges gives rise to increased chances of undergoing excision treatment.

Research has approached this topic concerning the strong probability correlation with endometriosis.

It is still unclear if delaying childbirth is an independent risk factor or, in this context, whether women with subclinical endometriosis are pre-disposed to infertility and hence purposefully delay childbirth. These uncertainties require further longitudinal research with pre-defined diagnostic protocols and objective hormone measurement evaluation.

## Conclusion
This review extends the link of increased risk attributable to delayed childbearing to endometriosis and attempts to explain it via prolonged, unopposed estrogen exposure while emphasizing the absence of pregnancy with its protective hormonal shifts. However, the cyclic nature of endometriosis- infertility creates a paradox that becomes difficult to interpret. There is a need for prospective studies having standardized diagnostic approaches to powerful and comprehensive biomarkers to ascertain causation and refine clinical direction.

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**Conflict of Interest**
The authors declare that there are no conflicts of interest regarding to the publication of this paper.

**Author Contributions**
Dr Amber Shams: Conceptualization, literature search and drafting of the manuscript.
Dr Phou Vitharith: Figure and table design, final editing and correspondence with the journal.
Assistant Professor Zareena Begu: Data extraction, method critique, and substantial revising.

## Figures and Tables
**Figure 1. Endometriosis and Hormonal Relation Modeling**
**Table 1. Summation of Important Epidemiological Researches**
*(Refer to the table in the Results section.)*
**Table 2. Important Methodological Limitations and Confounding Factors**
*(Refer to the table in the Results section.)*

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