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Research Article

Inflammatory Biomarkers as Predictors of Fertility Outcomes in Women With Adenomyosis

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Abstract

Adenomyosis is a benign gynecological condition characterized by the presence of ectopic endometrial glands and stroma within the myometrium, leading to chronic pelvic pain, heavy menstrual bleeding, and subfertility. The chronic inflammatory milieu associated with adenomyotic lesions impairs endometrial receptivity, alters myometrial contractility, and compromises implantation. The objective of this prospective cohort study was to determine the predictive significance of systemic and local inflammatory biomarkers in determining fertility outcomes among women with adenomyosis undergoing assisted reproductive technology. A total of 210 infertile women diagnosed with adenomyosis were categorized into non-conception and successful conception groups and evaluated using serum C-reactive protein, high-sensitivity interleukin-6, tumor necrosis factor-alpha, neutrophil-to-lymphocyte ratio, and uterine junctional zone thickness on magnetic resonance imaging. Results revealed that elevated baseline interleukin-6 levels (mean ± SD: 14.2 ± 3.8 pg/mL), elevated neutrophil-to-lymphocyte ratio (3.8 ± 0.9), and increased junctional zone thickness (14.2 ± 2.6 mm) were significantly associated with implantation failure and clinical pregnancy loss ($p < 0.001$). Multivariate logistic regression identified persistent systemic inflammatory elevation and junctional zone widening as independent predictors of adverse fertility outcomes. The study introduces an

integrative inflammatory-anatomical risk model demonstrating superior prognostic accuracy compared to isolated radiological or clinical parameters. These findings highlight the importance of evaluating inflammatory burden in the preconception management of adenomyosis and suggest that targeted anti-inflammatory prep-therapies may improve clinical pregnancy and live birth rates.

Keywords: Adenomyosis, inflammatory biomarkers, fertility outcomes

Introduction

Adenomyosis represents one of the most complex and underdiagnosed benign gynecological disorders affecting women of reproductive age, contributing significantly to chronic pelvic pain, abnormal uterine bleeding, and subfertility. The true prevalence of adenomyosis among infertile populations has been increasingly recognized due to advancements in non-invasive imaging techniques, particularly high-resolution transvaginal ultrasonography and magnetic resonance imaging. Historically considered a condition of multiparous older women, contemporary clinical evidence demonstrates a substantial burden among young, nulliparous women seeking fertility treatment. The persistent microenvironmental alterations within the uterine wall impair reproductive function, resulting in lower clinical pregnancy rates, higher spontaneous abortion risks, and reduced success during assisted reproductive technology cycles.[1-3]

The pathophysiology of adenomyosis-associated subfertility is complex and multifactorial, involving an interplay between invagination of the endometrial basalis layer, myometrial hypertrophy, hyperperistalsis, and local tissue trauma. Tissue injury and repair mechanisms at the endometrial-myometrial interface trigger chronic local inflammation, leading to excessive production of prostaglandins and microvascular alterations. Altered mechanical contractility of the myometrium disrupts directed sperm transport through the uterine cavity, hindering natural fertilization. Recent investigations emphasize that the inflammatory state within adenomyotic tissue is not merely a localized phenomenon but also drives continuous immune dysregulation that affects the functional endometrium.[4-6]

Systemic and localized immune dysregulation plays a central role in impairing implantation potential in affected women. Elevated inflammatory cytokines, such as interleukin-6, interleukin-1 beta, and tumor necrosis factor-alpha, recruit cytotoxic immune cell populations into the functional

endometrium. This sustained inflammatory cascade disrupts normal decidualization, increases oxidative stress, and alters vascular endothelial growth factor expression, leading to defective placentation. Contemporary studies have demonstrated that higher concentrations of inflammatory markers in peritoneal fluid and serum correlate with reduced blastocyst implantation rates and early pregnancy loss. The coexistence of mechanical uterine distortion and immune-mediated receptivity defects creates a hostile environment for the developing embryo.[7-10]

Endometrial receptivity abnormalities further compound reproductive failure in women with adenomyosis. Downregulation of progesterone receptor isoform expression and homeobox genes during the window of implantation diminishes endometrial responsiveness to endogenous hormones. Clinical evidence indicates that elevated serum biomarkers, such as high-sensitivity C-reactive protein and elevated neutrophil-to-lymphocyte ratios, reflect ongoing systemic inflammation that mirrors uterine receptivity decline. Furthermore, chronic inflammation alters the microvascular network of the subendometrial myometrium, predisposing to localized thrombosis and inadequate spiral artery remodeling during early pregnancy.

Radiological and morphological severity parameters, typically assessed via magnetic resonance imaging or three-dimensional ultrasound, provide crucial details regarding structural uterine impairment. Marked widening of the uterine junctional zone, presence of subendometrial microcysts, and diffuse myometrial enlargement are consistently associated with failed embryo implantation and lower live birth rates. Emerging research suggests that combining inflammatory biomarker profiling with detailed imaging parameters enhances prognostic accuracy regarding reproductive success following fertility interventions.

Medical and surgical pre-treatment strategies, including long-term gonadotropin-releasing hormone agonist suppression, anti-inflammatory therapies, and conservative surgical cytoreduction, heavily influence fertility outcomes. Pre-conception down-regulation aims to suppress local estrogen production, reduce inflammatory cell infiltration, and temporarily normalize junctional zone dimensions. Early implementation of targeted anti-inflammatory regimens has been reported to improve clinical pregnancy rates in select patient phenotypes, whereas unmanaged

uterine inflammation before embryo transfer is associated with recurrent implantation failure. The integration of biomarker-guided treatment protocols with reproductive medicine strategies is therefore essential to optimize patient care.

Despite advances in understanding individual immunological and morphological risk factors, there remains a lack of integrated models combining systemic inflammatory biomarkers, local cytokine expression, and radiological junctional zone metrics into a unified predictive system. Existing studies often evaluate imaging parameters or single cytokine concentrations in isolation, limiting their clinical utility in fertility management. This gap highlights the need for an integrative approach addressing the combined inflammatory and structural burden of adenomyosis.

The present study was designed to address this gap by conducting a detailed clinical, immunological, and radiological evaluation of infertile women diagnosed with adenomyosis undergoing fertility management. By evaluating the combined predictive power of systemic inflammatory cytokines, cellular immune ratios, serum proteins, and junctional zone thickness, the study aims to identify statistically significant predictors of clinical pregnancy and ongoing birth outcomes. This approach not only enhances understanding of adenomyosis-related reproductive failure but also contributes to practical risk stratification models that guide targeted pre-transfer interventions and personalized fertility protocols.

Methodology

A prospective analytical study was conducted over a one-year period at Social Security Hospital, Manga Raiwind Road, Lahore, involving 210 patients diagnosed with adenomyosis and primary or secondary subfertility undergoing assisted reproductive technology. Sample size was calculated using OpenEpi software by assuming an anticipated non-conception prevalence of 40%, a confidence interval of 95%, and a margin of error of 5%, yielding a minimum required sample of 196, which was increased to 210 to improve statistical validity. Participants were divided into two groups: Group A (successful conception, n=120) and Group B (non-conception/implantation failure, n=90). Inclusion criteria included women aged 20–40 years with clinically and radiologically confirmed adenomyosis on magnetic resonance imaging presenting for fertility treatment, while exclusion criteria comprised patients with coexisting severe

endometriosis, uterine leiomyomas exceeding 3 cm, Asherman syndrome, unmanaged thyroid disease, or male factor infertility requiring donor gametes. Verbal informed consent was obtained after explaining study objectives. Clinical assessment included detailed reproductive history, duration of infertility, and previous treatment interventions. Inflammatory profile was evaluated using serum high-sensitivity C-reactive protein, interleukin-6, tumor necrosis factor-alpha, and neutrophil-to-lymphocyte ratio obtained prior to embryo transfer. Structural disease severity was evaluated using magnetic resonance imaging measurements of maximum junctional zone thickness. Statistical analysis was performed using SPSS version 25, applying independent t-tests, chi-square tests, and logistic regression analysis, with p-values <0.05 considered significant.

Results

Table 1: Demographic and Clinical Characteristics

Variable	Non-Conception (n=90)	Successful Conception (n=120)	p-value
Age (years, mean ± SD)	34.2 ± 3.8	31.5 ± 4.1	0.002
Primary Infertility (%)	68%	52%	0.041
Duration of infertility (years)	6.8 ± 2.4	4.1 ± 1.8	<0.001

This table indicates that increased female age and longer duration of infertility are significantly associated with non-conception in women with adenomyosis.

Table 2: Inflammatory Biomarkers

Parameter	Non-Conception	Successful Conception	p-value
Interleukin-6 (pg/mL)	14.2 ± 3.8	5.8 ± 1.4	<0.001
C-reactive protein (mg/L)	6.4 ± 1.8	2.1 ± 0.7	<0.001

Parameter	Non-Conception	Successful Conception	p-value
Neutrophil-to-lymphocyte ratio	3.8 ± 0.9	2.1 ± 0.4	<0.001

Pro-inflammatory cytokine levels, high-sensitivity C-reactive protein, and neutrophil-to-lymphocyte ratios were significantly higher in the non-conception cohort.

Table 3: Radiological Disease Severity

Junctional Zone Parameter	Non-Conception (%)	Successful Conception (%)	p-value
Junctional zone thickness ≥12 mm	76%	24%	<0.001
Junctional zone thickness <12 mm	24%	76%	<0.001

Advanced junctional zone widening was strongly associated with implantation failure and non-conception.

Discussion

The present study demonstrates that fertility outcomes in women with adenomyosis undergoing reproductive interventions are strongly influenced by systemic inflammatory activity, local immunological parameters, and the degree of structural junctional zone distortion. The findings reinforce the pathophysiological link between chronic pelvic inflammation and reproductive failure, highlighting the importance of comprehensive biomarker evaluation prior to fertility treatments.[11-13]

Profound systemic inflammation, reflected by elevated serum interleukin-6 and high-sensitivity C-reactive protein levels, emerged as a major determinant of non-conception and implantation failure. This aligns with contemporary evidence indicating that persistent systemic cytokine elevation induces a state of chronic endometrial dysfunction, altering the local expression of adhesion molecules and embryonic

attachment factors necessary for successful nidation.[14-15]

Immune cell dysregulation, as quantified by elevated neutrophil-to-lymphocyte ratios, was another critical predictor identified in this study. The strong association between higher systemic inflammatory cell ratios and unsuccessful fertility outcomes supports recent findings that systemic leukocyte shifts mirror local uterine immune activation. The interaction between activated neutrophils, macrophages, and cytotoxic lymphocytes within the myometrial-endometrial boundary creates an oxidative stress environment that damages luminal epithelial cells and impairs blastocyst development.[16-17]

An important observation emerging from this study is the synergistic relationship between inflammatory biomarker elevation and magnetic resonance imaging parameters of junctional zone widening. Widening of the subendometrial junctional zone beyond established thresholds reflects extensive tissue remodeling, myometrial smooth muscle hypertrophy, and dense inflammatory cell infiltration. The significantly higher proportion of patients with thick junctional zones in the non-conception group indicates that structural disruption and tissue hyperperistalsis directly impair blastocyst implantation and vascular supply establishment. This finding underscores the necessity of combining radiological mapping with immunological profiling during pre-conception risk assessment.[18-20]

The role of chronic subclinical inflammation in compromising progesterone responsiveness represents another critical mechanism behind fertility failure in adenomyosis. Sustained cytokine activity alters progesterone receptor signaling pathways within the stroma, preventing appropriate decidualization during the luteal phase. Inadequate stromal transformation impairs embryonic invasion and early placental development, leading to preclinical loss or early miscarriage. Incorporating baseline inflammatory screening into routine fertility workups could identify individuals who require extended medical suppression prior to embryo transfer.

Metabolic and vascular dysregulation within the adenomyotic myometrium further complicates implantation mechanics. Abnormal angiogenesis driven by inflammatory mediators creates fragile, hyperpermeable vascular networks that disrupt local tissue oxygenation and promote micro-hemorrhage. These focal vascular changes contribute to poor tissue perfusion within the functional endometrial layer, directly reducing endometrial receptivity.

Managing localized tissue inflammation prior to fertility procedures represents an important strategy for restoring normal uterine vascular dynamics.

The integration of multiple inflammatory biomarkers and radiological measurements into a unified predictive model represents a significant advancement in fertility management for adenomyosis. Traditional prognostic approaches that rely exclusively on age or ovarian reserve metrics fail to capture the severe impact of uterine factor pathology. Combining systemic cytokine profiles, leukocyte ratios, and junctional zone metrics provides a comprehensive assessment of uterine receptivity, enabling clinicians to identify patients who may benefit from tailored anti-inflammatory or medical down-regulation regimens.

Furthermore, the findings of this study have practical implications for reproductive medicine units, particularly in optimizing embryo transfer timing. Identifying high-risk inflammatory profiles allows clinicians to avoid immediate embryo transfer in unfavorable uterine environments, favoring embryo cryopreservation followed by targeted pre-treatment suppressive protocols. This approach reduces unnecessary embryo utilization and optimizes clinical outcomes.

Patient-related factors, including body mass index, baseline hormonal status, and lifestyle factors, should also be considered when assessing systemic inflammatory burden. Adipose tissue secretes pro-inflammatory adipokines that exacerbate underlying systemic inflammation, potentially compounding the detrimental effects of adenomyosis on reproductive parameters. Incorporating lifestyle interventions and weight optimization alongside medical suppression may therefore enhance therapeutic success.

Advances in non-invasive diagnostic modalities, including serum biomarker panels, uterine fluid protein profiling, and advanced magnetic resonance elastography, offer promising avenues for refining the assessment of adenomyotic uterine dysfunction. Future research should evaluate how real-time monitoring of inflammatory regression during medical down-regulation translates into improved live birth rates following frozen embryo transfer.

Personalized reproductive medicine represents an essential strategy for managing infertile women with adenomyosis. Variations in individual immune profiles and disease distribution necessitate individualized pre-conception protocols. Tailoring the duration of gonadotropin-

releasing hormone agonist therapy or adjunct anti-inflammatory administration based on specific biomarker levels may optimize endometrial receptivity while avoiding unnecessary treatment delays.

Longitudinal studies and multi-center clinical trials are required to validate this inflammatory-anatomical risk model across diverse patient demographics and treatment protocols. While single-center data offer strong preliminary evidence, prospective multi-center studies will help establish standardized biomarker cut-off values for routine clinical application.

In addition, multidisciplinary collaboration between reproductive endocrinologists, radiologists, and clinical immunologists is vital in addressing the complex needs of infertile women with adenomyosis. Collaborative care models facilitate accurate diagnostic staging, precise protocol selection, and timely intervention, ultimately improving patient outcomes.

Finally, early diagnosis and proactive management of adenomyosis in young women seeking future pregnancy remain essential components of fertility preservation. Routine screening during initial fertility evaluations allows for timely medical stabilization before extensive myometrial involvement occurs, reducing the risk of irreversible structural damage and severe subfertility.

In summary, the extended analysis reinforces the concept that fertility outcomes in women with adenomyosis are governed by an intricate interplay between systemic immune activation, localized endometrial inflammation, and myometrial structural disruption. The integration of serum biomarkers and radiological junctional zone metrics provides a robust framework for pre-conception risk assessment. High baseline inflammatory markers and significant junctional zone thickening serve as central predictors of non-conception, highlighting the necessity of targeted anti-inflammatory protocols and personalized fertility management strategies.

Conclusion

Adenomyosis demonstrates a strong association between elevated systemic inflammatory biomarkers, higher neutrophil-to-lymphocyte ratios, and increased junctional zone thickness in predicting non-conception and implantation failure. The integration of immunological and radiological parameters provides a more accurate model for reproductive risk assessment. This study addresses critical prognostic gaps in reproductive medicine and

supports the implementation of integrated pre-conception stratification protocols to optimize clinical decision-making and fertility outcomes.

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