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RECURRENT ENDOMETRIAL POLYPS AND INFERTILITY: THE ROLE OF CHRONIC ENDOMETRITIS AND THE EFFICACY OF JOSAMYCIN. A CLINICAL CASE REPORT

Gulchekhra Karimova
Obstetrics and Gynecology Department No1, Samarkand state medical university
Samarkand, Uzbekistan

Abstract. Chronic Endometritis (CE) is a persistent, often subclinical inflammatory condition of the endometrial lining, frequently underdiagnosed as a significant cause of implantation failure and infertility. It is commonly associated with microbial colonization by opportunistic and pathogenic bacteria, including Genital Mycoplasmas such as *Ureaplasma urealyticum*. This case report presents a 34-year-old female (Patient N.) with a five-year history of secondary infertility and recurrent pregnancy loss. Her medical history was significant for a missed abortion, multiple recurrent endometrial polyps, and a left hydrosalpinx treated with salpingectomy. Despite repeated surgical interventions, including hysteroscopies and polypectomies, pregnancy did not occur. A pivotal investigation revealed *Ureaplasma urealyticum* in the endometrial aspirate, diagnosing an underlying CE. This case illustrates the potential iatrogenic role of repetitive intrauterine procedures in exacerbating subclinical inflammation, leading to impaired endometrial receptivity. It underscores the critical need for a comprehensive microbiological assessment of the endometrium prior to surgical management of benign pathologies like polyps in infertile women. The administration of Josamycin, a macrolide antibiotic effective against intracellular pathogens, led to the resolution of the infection. This report discusses the pathophysiology of CE-related infertility, the rationale for antibiotic selection, and advocates for a conservative, diagnosis-first approach in the management of small endometrial polyps in women seeking fertility.

Keywords: Infertility, Recurrent Endometrial Polyps, Chronic Endometritis, Ureaplasma urealyticum, Josamycin, Endometrial Receptivity, Asherman's Syndrome

Introduction. Infertility, defined as the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse, affects millions of couples worldwide. Its etiology is multifactorial, encompassing male factors, ovulatory disorders, tubal and peritoneal pathology, and uterine anomalies. Among uterine factors, the integrity and health of the endometrium are paramount for successful embryo implantation and placentation. While structural issues like submucosal fibroids or uterine septa have long been recognized, the role of a dysfunctional endometrial microenvironment, particularly one driven by chronic inflammation, is increasingly being identified as a critical contributor to implantation failure and recurrent pregnancy loss (RPL).

The Endometrium: A Dynamic Receptive Tissue. The human endometrium is a highly complex and dynamic tissue that undergoes cyclical changes under the influence of ovarian steroids, estrogen, and progesterone. Its primary function is to receive, implant, and nurture the developing blastocyst. The period during which the endometrium is receptive to an embryo is known as the "window of implantation" (WOI), a narrow timeframe typically occurring 6-10 days after the luteinizing hormone (LH) surge. During this period, a finely orchestrated cross-talk occurs between the embryo and the endometrium, mediated by molecular markers such as integrins, cytokines, chemokines, and adhesion molecules like L-selectin. Any disruption to this delicate molecular dialogue can lead to implantation failure. The endometrial receptivity is not merely a hormonal phenomenon but is also profoundly influenced by the local immune environment and microbiota.

Chronic Endometritis: The Silent Insult to Endometrial Receptivity. Chronic Endometritis (CE) is a condition characterized by a persistent, low-grade inflammation of the endometrial stromal layer, mediated by plasma cell infiltration. Unlike acute endometritis, which presents with overt symptoms like pelvic pain, fever, and abnormal bleeding, CE is often asymptomatic or presents with non-specific complaints such as mild pelvic discomfort, abnormal uterine bleeding, or leucorrhea. Its insidious nature is what makes it a frequently overlooked cause of infertility.

The prevalence of CE is significantly higher in women with reproductive failure. Studies have reported CE in approximately 30-60% of women with unexplained infertility, 40-66% of women with RPL, and over 40% of women with repeated implantation failure (RIF) after in vitro fertilization (IVF). The pathophysiology of CE-induced infertility is multifactorial:

Alteration of the Endometrial Microenvironment: The persistent inflammatory state disrupts the normal cytokine and chemokine balance necessary for embryo apposition, adhesion, and invasion. There is an upregulation of pro-inflammatory cytokines (e.g., TNF-α, IL-1β, IL-6) which can be embryotoxic and impair trophoblast invasion.

Dysregulation of Endometrial Immune Cells: CE alters the population and function of uterine Natural Killer (uNK) cells and other immune cells, which are crucial for spiral artery remodeling and trophoblast support.

Impaired Decidualization: The process by which endometrial stromal cells differentiate into specialized decidual cells is critical for implantation. CE can disrupt the gene expression and function of these cells, leading to a non-receptive state.

Molecular Dysregulation: The expression of key implantation markers, such as αvβ3 integrin and HOXA10, is often downregulated in the presence of CE.

Etiological Agents of Chronic Endometritis. CE is predominantly an infectious process. Common causative agents include: Sexually Transmitted Infections: Chlamydia trachomatis* and *Neisseria gonorrhoeae* are classic pathogens, with *C. trachomatis* being a major cause due to its intracellular life cycle and potential to cause persistent, low-grade infection.

Genital Mycoplasmas: Ureaplasma urealyticum*, *Ureaplasma parvum*, and *Mycoplasma hominis* are opportunistic pathogens frequently found in the genital tract. Their role in CE is significant because they can reside intracellularly within endometrial cells, evading the host immune response and standard antibiotic treatments that do not penetrate cells effectively.

Other Bacteria: Common vaginal and enteric bacteria, including *Escherichia coli*, *Streptococcus* species, *Enterococcus faecalis*, and anaerobes like *Gardnerella vaginalis* (associated with Bacterial Vaginosis) can ascend into the uterine cavity and cause CE.

Tuberculosis: In endemic areas, genital tuberculosis is a notable cause of severe CE and intrauterine adhesions.

The Clinical Conundrum: Endometrial Polyps, Surgery, and Iatrogenic Damage. Endometrial polyps are common, benign, localized outgrowths of the endometrial tissue, containing glands, stroma, and blood vessels. Their direct causal relationship with infertility remains a topic of debate. While large or multiple polyps may act as a mechanical barrier to implantation or cause inflammatory changes, small polyps (less than 10-15 mm) are often found in fertile women and may not necessarily impede pregnancy.

The standard management for endometrial polyps in infertile women has traditionally been surgical resection via hysteroscopy. However, this approach is now being questioned, particularly for small polyps. Every intrauterine procedure, including diagnostic hysteroscopy, polypectomy, and especially dilation and curettage (D&C), carries a risk of introducing or disseminating cervicovaginal flora into the upper genital tract. In a patient with subclinical CE, surgical trauma can exacerbate the existing inflammation, disrupt the fragile endometrial stem cell niche, and lead to fibrosis and adhesion formation—a condition known as Asherman's Syndrome (Intrauterine Adhesions or IUA). Asherman's Syndrome is characterized by the partial or complete obliteration of the uterine cavity by adhesions, leading to infertility, hypomenorrhea, or amenorrhea. The formation of a "thin endometrium" that is unresponsive to estrogen is a hallmark of this condition, creating a hostile environment utterly incompatible with implantation.

The Diagnostic and Therapeutic Approach: A Paradigm Shift. This understanding necessitates a paradigm shift from a purely surgical to a more medical and diagnostic-focused approach in managing infertile women with suspected endometrial pathology. The algorithm should prioritize:

1. Microbiological Investigation: Before proceeding with surgery for small polyps, an endometrial biopsy or aspirate should be obtained for microbiological culture (including for Mycoplasmas/Ureaplasmas) and/or PCR testing. Histopathological examination of the tissue with CD138 immunohistochemical staining to identify plasma cells remains the gold standard for diagnosing CE.
2. Targeted Antibiotic Therapy: Once a pathogen is identified, appropriate antibiotic therapy is the cornerstone of treatment. The ideal antibiotic for CE, especially when involving intracellular pathogens like Chlamydia and Mycoplasmas, must have excellent penetration into endometrial tissue and cells. Macrolide antibiotics are a primary choice.
3. Re-assessment: A test-of-cure, either through a repeat endometrial biopsy or PCR, is recommended to confirm the eradication of the infection and resolution of inflammation.

Josamycin: A Rational Therapeutic Choice. Josamycin is a 16-membered macrolide antibiotic with a well-established profile for treating urogenital infections.

Spectrum of Activity: It is highly effective against a broad range of intracellular pathogens, including *Chlamydia trachomatis*, *Mycoplasma pneumoniae*, *Ureaplasma urealyticum*, and *Mycoplasma hominis*. It also demonstrates good activity against many anaerobic bacteria.

Pharmacokinetics: Josamycin achieves high concentrations in tissues, particularly in the female reproductive tract and within cells, which is crucial for eradicating sequestered intracellular organisms.

Anti-inflammatory and Immunomodulatory Effects: Beyond its antibacterial action, macrolides, including Josamycin, are known to possess anti-inflammatory and immunomodulatory properties. They can inhibit the production of pro-inflammatory cytokines and modulate neutrophil function, which may contribute to the resolution of the chronic inflammatory state in CE.

Safety Profile: Josamycin has a favorable safety profile with a low incidence of serious adverse effects. Its potential for drug interactions is lower than that of other macrolides like erythromycin and clarithromycin. While the use of any medication in pregnancy requires careful risk-benefit analysis, current data do not indicate teratogenicity for Josamycin, and it is considered a treatment option in specific clinical scenarios during pregnancy.

This clinical case of Patient N. serves as a quintessential example of the consequences of overlooking CE and the potential harms of repetitive surgical interventions, ultimately highlighting the efficacy of a targeted medical approach with Josamycin.

Materials and Methods. Patient Information. The patient, a 34-year-old nulliparous woman (designated as Patient N. for anonymity), presented to the gynecology clinic in 2015 with a primary complaint of secondary infertility of five years' duration. Her initial presentation in 2010 marked the beginning of her complex reproductive history.

Clinical History and Timeline. A detailed chronological history was obtained and is summarized below:

2010: The patient's first pregnancy ended in a missed miscarriage (anembryonic pregnancy or embryonic demise) at 7 weeks of gestation. The management involved surgical evacuation via Dilation and Curettage (D&C).

2011: Due to failure to conceive, the patient was evaluated at a reproductive technology center. A transvaginal ultrasound (TVS) revealed an endometrial polyp. She underwent a hysteroscopic polypectomy. However, no pregnancy ensued in the subsequent years.

2013: Further investigation led to a laparoscopic evaluation, which diagnosed a left hydrosalpinx (a fluid-filled, blocked and dilated fallopian tube, often a sequela of Pelvic Inflammatory Disease). A left salpingectomy (tubal removal) was performed. Concurrently, a repeat hysteroscopy was performed for a recurrent small endometrial polyp, and a polypectomy was done.

2015: After another two years without conception, the patient presented to a public women's consultation clinic to seek assistance through a government-funded program for Assisted

Reproductive Technologies (ART). A baseline TVS once again identified a small endometrial polyp. She was subsequently referred to a hospital for a planned repeat laparoscopy (likely to assess the remaining tube and pelvic anatomy) and hysteroscopy.

Diagnostic Assessment. The diagnostic workup in 2015 was pivotal and deviated from the previous purely structural approach.

1. Imaging: Transvaginal Sonography (TVS) was the primary imaging modality, consistently identifying the presence of a small endometrial polyp across multiple examinations.

2. Microbiological Testing: Prior to the scheduled hysteroscopic polypectomy, an endometrial aspirate was obtained. This is a minimally invasive procedure typically performed using a thin, flexible catheter (e.g., Pipelle® de Cornier) introduced through the cervix into the uterine cavity to sample the endometrial tissue and fluid. The sample was subjected to microbiological analysis. The specific method used in this case was not detailed but typically involves culture in specific media for Mycoplasma/Ureaplasma or Polymerase Chain Reaction (PCR) testing, which is more sensitive and specific.

Microbiological Findings: The analysis of the endometrial aspirate confirmed the presence of *Ureaplasma urealyticum*. No other significant pathogens were reported. This finding provided a definitive diagnosis of chronic endometritis secondary to *Ureaplasma urealyticum* infection.

Therapeutic Intervention. Based on the microbiological diagnosis, the following therapeutic plan was implemented:

Antibiotic Therapy: The patient was prescribed a course of Josamycin. The standard dosage for urogenital infections caused by *Ureaplasma urealyticum* is 500 mg orally three times a day for 10-14 days. It was recommended that her partner also undergo simultaneous evaluation and treatment to prevent re-infection.

Surgical Re-evaluation: The planned hysteroscopic polypectomy for the small polyp was deferred or re-evaluated in light of the new diagnosis. The clinical decision, as per the professor's commentary, was to adopt a conservative approach towards the small polyp, prioritizing the treatment of the underlying infection.

Follow-up and Outcomes. The planned follow-up would involve:

1. A test-of-cure, approximately 4-6 weeks after completing the antibiotic course, to confirm the eradication of *Ureaplasma urealyticum*. This would typically involve a repeat endometrial aspirate for PCR testing.

2. A repeat TVS to monitor the status of the endometrial polyp.

3. Subsequent entry into the ART program (e.g., IVF/ICSI) once the uterine environment was deemed healthy, with the infection resolved.

Discussion. This case of Patient N. is a powerful illustration of how a treatable infectious condition like CE can be the central culprit in a long and frustrating history of infertility and recurrent pregnancy loss. For five years, the clinical focus was on the structural anomalies—the recurrent polyps and the hydrosalpinx. While the salpingectomy for the hydrosalpinx was a justified intervention, as a hydrosalpinx can leak toxic fluid into the uterine cavity, the repetitive polypectomies likely contributed to the patient's ongoing problems.

The detection of *Ureaplasma urealyticum* was the key that unlocked the case. This organism, often dismissed as commensal, is a well-established pathogen in the context of CE. Its intracellular location allows it to persist, causing a chronic, smoldering inflammation that disrupts the molecular signature of endometrial receptivity. Each surgical intervention (D&C, hysteroscopies) likely caused micro-trauma, facilitating the ascent of bacteria or exacerbating the existing inflammation, leading to a vicious cycle of impaired endometrial healing, potential fibrosis, and a thin, non-receptive endometrium—a precursor to Asherman's syndrome.

The decision to treat with Josamycin was pathogen-directed. Its efficacy against intracellular organisms and its favorable tissue penetration profile made it an ideal choice. By eradicating the primary driver of inflammation, the endometrial environment could potentially heal and restore its receptivity. The conservative management of the small polyp aligns with modern thinking: removing the inflammatory trigger (the infection) is more critical than removing a small, likely incidental, anatomical finding.

This case strongly advocates for a revised algorithm in the management of infertile women with recurrent endometrial polyps: **"Diagnose before you scrape."** A comprehensive endometrial evaluation for CE should be mandatory before subjecting these patients to repeated surgical procedures that may do more harm than good.

Conclusion. Chronic Endometritis is a frequent and treatable cause of infertility that should be systematically investigated in women with a history of recurrent implantation failure, recurrent pregnancy loss, and recurrent endometrial polyps. The case of Patient N. highlights the limitations of a purely surgical approach and underscores the importance of a thorough microbiological workup of the endometrium. Josamycin, with its targeted action against intracellular pathogens like *Ureaplasma urealyticum* and its additional anti-inflammatory properties, represents an effective first-line treatment to resolve the infection and potentially restore endometrial function, offering new hope for patients with long-standing infertility.

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