Title: Incidence of intrauterine adhesions following myomectomies with the use of an intrauterine anti-adhesion gel

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RATIONALE

Intrauterine adhesions, also known as synechiae, refer to the formation of fibrotic tissue within the uterus. This phenomenon is secondary to trauma caused by surgical procedures or infections. Uterine synechiae represent a pathological response of endometrial tissue to injury or inflammation. During the healing process, excessive scar tissue formation may lead to the fusion of uterine walls that should remain separated. These adhesions can compromise normal uterine functionality, negatively impacting fertility and causing menstrual disturbances or pregnancy complications.

Following endometrial injury, a process of coagulation and inflammation begins, followed by the migration of new cells to the damaged site. Normally, the body's fibrinolytic activity plays a crucial role: fibrinogen in blood clots is dissolved, facilitating wound healing. However, during surgical procedures, fibrinolytic capacity may be insufficient, leading to fibrin accumulation. This fibrin acts like glue, sealing the lesion. Consequently, fibrin bands form a temporary structure to stabilize the injury site. These fibrin bands may then stimulate fibroblast proliferation and angiogenesis (neovascularization), two fundamental processes in tissue repair. However, if fibrin accumulation persists, the development of fibrotic adhesions may occur. This pathological phenomenon involves scar tissue uniting surfaces that should remain separated.

Myomectomy is currently considered the surgical procedure most associated with adhesion formation [1]. Despite being the first-choice intervention for patients wishing to preserve fertility, it carries risks, particularly regarding reproductive health [2]. The increased risk of developing postoperative adhesions can significantly impair fertility [3;4].

Recent studies have shown that basal layer trauma of the endometrium is one of the primary events responsible for the formation of intrauterine adhesions (IUAs) [7;8]. Among the factors contributing to adhesion development and postoperative infertility, the location and size of fibroids are of primary importance [9;10].

Although the literature has established a clear link between hysteroscopic myomectomy—especially in cases of multiple fibroids—and the formation of IUAs, few studies analyze the impact of laparoscopic and minimally invasive approaches on such adhesions [11]. Capmas et al. [18] reported that the incidence of intrauterine adhesions reaches 25.51% in patients undergoing laparotomic

myomectomy. Uterine cavity access represents a risk factor for adhesions, but the same study shows that even without cavity access, laparotomic myomectomy increases adhesion incidence. These findings were confirmed by Laganà et al. [19], highlighting increased adhesion incidence three months post-laparotomic approach or uterine cavity access.

The use of minimally invasive surgical techniques, such as traditional or robot-assisted laparoscopy, combined with new operative strategies and anti-adhesion methods, has shown to reduce but not completely eliminate adhesion risk [12;13].

Thus, the pursuit of increasingly effective solutions to prevent adhesion formation remains a crucial priority in the medical field.

The use of an anti-adhesion gel represents a potential strategy. This is a sterile, transparent, and highly viscous medical device. Due to its hydrophilic properties and viscosity, it provides protection against adhesion formation. A prototype of anti-adhesion gel, for instance, consists of a sterile and absorbable combination of sodium carboxymethylcellulose (CMC) and polyethylene oxide (PEO) with calcium chloride and sodium chloride in aqueous solution.

This unique formulation allows the gel to act as a temporary mechanical barrier, separating traumatized tissue surfaces during healing and reducing the formation of intrauterine adhesions. Its safety and efficacy have been tested in both in vitro and in vivo settings.

A 2003 study [14] reported lower rates of postoperative adhesions at 60–90 days of follow-up in the group treated with an intrauterine gel obtained from cross-linked hyaluronic acid compared to the untreated group (27.8% versus 77.8%). Further benefits have been demonstrated with the application of intrauterine gel following operative hysteroscopic procedures, with significant reductions in intrauterine adhesions at follow-up compared to control groups [15;16].

Today, the possibility of using an intrauterine gel represents an option in the ongoing challenge of modern surgery to combat the development of intrauterine adhesions, further exploring its advantages in improving reproductive outcomes for women [17].

The proposed study aims to combine, hoping for a synergistic effect, the benefits of adhesion prevention from both a minimally invasive approach, such as robotic surgery, and the application of anti-adhesion gel.

OBJECTIVES

The primary objective of the study is to evaluate the efficacy of intrauterine gel in reducing the formation of intrauterine adhesions following robotic-assisted laparoscopic myomectomy.

The secondary objective is to assess patients' reproductive outcomes, including clinical pregnancy rate, live birth rate (LBR), miscarriage rate, pregnancy complications, mode of delivery, and neonatal outcomes up to 24 months.

STUDY DESIGN

Materials and Methods
The study will be conducted as a prospective, randomized, non-profit trial.

Population
The study will include 62 patients undergoing surgery for myomectomy.

PATIENTS WILL BE DIVIDED INTO TWO GROUPS:

- **Group 1 (intervention group):** Women will receive the application of an anti-adhesion gel at the end of the myomectomy procedure.
- **Group 2 (control group):** Women will not receive any anti-adhesion methods.

Patients enrolled in the two groups must meet the following criteria:

Inclusion Criteria

- Age between 18 and 45 years;
- BMI 18–35;
- One or more fibroids diagnosed via ultrasound;
- First myomectomy or uterine surgery;
- Incomplete reproductive plans and/or infertility;
- Adequate immune, respiratory, liver, cardiac, bone marrow, and kidney function;
- Compliance and psychological ability to follow study procedures;
- Acceptance and signing of informed consent.

Exclusion Criteria

- Age under 18 years;
- Age over 46 years;
- Pregnancy or breastfeeding;
- History of intrauterine adhesions;
- Diagnosis or suspicion of malignant gynecological pathologies and/or autoimmune diseases;
- Completed reproductive plans;
- Severe respiratory, bone marrow, liver, or kidney dysfunction preventing safe surgical access.

QUALITY CONTROL AND DATA MANAGEMENT

The following clinical data will be collected:

- Age;
- Body mass index;
- Personal and family medical history;

- Obstetric history;
- Pre-, intra-, and postoperative imaging and video;
- Histological examination;
- Data on future pregnancies: implantation rate, B-HCG positivity rate, miscarriage rate, pregnancy complications, delivery mode, and neonatal outcomes.

Data will be stored in an Excel document. Quality control of screening, data management, and protocol adherence verification will be performed regularly by co-investigators.

The principal investigator will have overall responsibility for study conduct, subject recruitment supervision, and ensuring adherence to the protocol and principles of Good Clinical Practice (GCP). Any complications will be recorded by the investigators.

STUDY PROCEDURES

Enrolled patients will undergo the following procedures within 30 days of surgery:

1. **Preoperative evaluations**
   - Transvaginal/transabdominal ultrasound (USG-TV/TA) to assess fibroids and pelvic adhesion syndrome.
   - Outpatient hysteroscopy to evaluate intrauterine adhesions and/or submucosal fibroids.
2. **Surgical procedure**
   - Robotic-assisted myomectomy, with gel application on the uterine suture via endoscopy and intracavitary application via the vaginal route.
3. **Follow-up evaluations**
   - **1 month:** Transvaginal/transabdominal ultrasound (performed by a single experienced operator) to check for pelvic adhesions.
   - **2 months:** Diagnostic hysteroscopy (performed by an expert operator) to assess intrauterine adhesions.
   - **Up to 24 months:** Patients will be contacted by phone to gather information on reproductive outcomes via spontaneous pregnancy or assisted reproductive techniques.

POTENTIAL RISKS AND BENEFITS

No specific risks are expected for this study apart from those related to the surgical procedure itself, for which detailed informed consent will be obtained. Thorough medical history and investigation of allergies or adverse reactions will be conducted to prevent any reaction to gel components.

DATA PRIVACY AND CONFIDENTIALITY

All data will be treated with strict confidentiality. However, national health authorities, the Ethics Committee, and research assistants may access clinical and diagnostic information collected during the study.

COSTS

The device will be provided free of charge for the study by the manufacturer.

DATA COLLECTION AND ANALYSIS

For each enrolled patient, a specific CRF (Case Report Form) will be completed, collecting personal, clinical, and laboratory test data. Privacy will be respected by anonymizing data and focusing solely on pathology-related information.

An electronic database will be generated and housed at the University Hospital Policlinico "Federico II," Building 9, Gynecology and Obstetrics. The data controller will be Prof. Attilio Di Spiezio Sardo.

Statistical Analysis
Assuming a 20% prevalence difference between the two populations and a 10% drop-out rate during recruitment, a total of 62 women (31 per arm) are required, with an alpha error of 0.05 and a beta error of 20% (80% power).

Continuous variables will be described as means, standard deviations, and interquartile ranges. Categorical variables will be presented as percentages or numbers (percentages). Both parametric and non-parametric tests will be performed, with justification for the selected method. Logistic regression will estimate the odds ratio (OR) and 95% confidence interval (CI) comparing the study cohorts. Statistical analysis will be conducted using SPSS version 20.0.

Patients will be randomized 1:1 using dedicated electronic software to ensure balanced and unbiased group allocation. The software will generate unpredictable random sequences, recorded in a secure database to ensure traceability and adherence to GCP principles.

PUBLICATION POLICY AND DATA ARCHIVING

After data analysis, results will be published in scientific journals and presented at conferences, regardless of the study's outcome. Data from samples will comply with Italian Legislative Decree 196/2003 and the Data Protection Authority's regulations on genetic data.

REGULATORY AND ETHICAL ISSUES

The study will be approved by the Ethics Committee of the University of Naples Federico II.

COMPLIANCE

The study will comply with the Declaration of Helsinki (2008).

DATA STORAGE

Investigators will securely store materials and clinical records for at least one year after study completion.

CONFLICT OF INTEREST

Investigators have no financial or competing interests that could affect the study's scientific value or related editorial activities.