Study protocol and statistical analysis plan

The Efficacy of A New Crosslinked Hyaluronan Gel in the Prevention of Postoperative Intrauterine Adhesion After Dilatation and Curettage in Women With Delayed Miscarriage: A Prospective, Randomized, Controlled Trial

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Introduction

Intrauterine adhesions (IUAs) are defined as fibrous strings opposing walls of the uterus and/or cervix leading to partial or complete obliteration of the cavity. IUAs are frequently encountered in one out of five women after miscarriage. Trauma to a gravid uterine cavity is known to be the main cause of IUAs. Such trauma could be induced by uterine curettage in the postpartum period, after spontaneous miscarriage or during termination of pregnancy, or by cesarean section. After pregnancy, the uterus could be in a vulnerable state that making the basal layer of endometrium more easily damaged by any trauma, especially dilatation and curettage (D&C).

Study Objective

To evaluate the efficacy of a new crosslinked hyaluronan gel (Materegen®) in reducing intrauterine adhesions formation after D&C.

Study Design

Randomized controlled trial.

Study Site:

Six hospitals for maternal and child health care in China.

- Department of Obstetrics, Hunan Province Meternal and Child Health Care Hospital, Changsha, Hunan, China
- The Women's Health Center, Changsha Hospital for Maternal & Child Health Care, Changsha, Hunan, China
- Department of Obstetrics, The Maternal and Child Health Care Hospital of Hengyang City, Hengyang, Hunan, China
- Department of Obstetrics, The Maternal and Child Health Care Hospital of Changde City, Changde, Hunan, China
- Department of Obstetrics, Huaihua City Meternal And Child Health Care Hospital, Huaihua, Hunan, China
- Department of Obstetrics, Yueyang Maternal and Child Health-Care Hospital, Yueyang, Hunan, China

Statistical Analysis Site:

School of Medicine, The Third Xiangya Hospital of Central South University,

Changsha, Hunan, China.

Study Device:

A new crosslinked hyaluronan gel (MateRegen®), manufactured and supplied by BioRegen Biomedical (Changzhou, China), is a sterile, transparent, viscoelastic and non-pyrogenic gel composed of highly purified crosslinked hyaluronan molecules.

Participants:

Women undergoing dilatation and curettage for delayed miscarriage without previous dilatation and curettage. All participants were required to give their written, signed informed consent before participating.

The inclusion criteria:

- Patients to be female, aged 18-45 years
- Without previous dilatation and curettage
- Undergoing dilatation and curettage for the current delayed miscarriage
- All participants should be with normal liver/rental function and without systemic disease
- Agree to use adequate forms of contraception throughout the study
- Be in good compliance with the follow-up examination according to the study protocol

The exclusion criteria:

- Known/suspected intolerance or hypersensitivity to hyaluronan or its derivatives
- Genital tract malformation
- Inflammation of genital tract or pelvic cavity, clinical evidence of cancer in genital tract
- Suspected genital tuberculosis
- Abnormal blood coagulation
- Medical histories of peripheral vascular disease, alcohol/drug abuse, and mental illness
- Acute or severe infection
- Autoimmune diseases.

Trial Process Flow

Trail processes	Recruitment and Treatment		Follow-up
Time points	Two weeks before surgery	Surgery	Three months after surgery（±7 day）
Window period	X		
Informed consent form	X		
Inclusion/exclusion criteria	X		
Dropout criteria			X
General data	X		
Physical exam on vital signs	X		
Medical history	X		
Surgical history	X		
Diagnosis	X		
Surgery evaluation		X	
Medication		X	
AFS adhesion evaluation	X		X
Clinical symptoms and vital signs	X	X	X
AE		X	X
Randomization		X	
Device application		X	

Randomization and Interventions:

The participants were randomly assigned into group of either D&C alone (control group) or D&C plus intrauterine MateRegen® gel application (treatment group) in a 1:1 ratio; and the random sequences were generated by SAS® 9.13 (center stratified blocked randomization, block=10) (SAS Institute, Cary NC).

Surgical Procedure and Gel Application

All D&C procedures were performed by suction curettage under general anesthesia in accordance with procedural standards. At the end of the D&C procedure a syringe of MateRegen® gel (3ml) was applied to the uterine cavity for patients assigned to the treatment group through a 15-cm sterile delivery cannula, whereas nothing was applied to the uterine cavity for patients in the control group.

Follow-up and Measurement:

A follow-up hysteroscopic examination was scheduled 3 months (±7 days) after the D&C procedure at about one week after the clean of menstrual bleeding. A pregnancy test was performed and before hysteroscopic examination. For patients with positive pregnancy test, the hysteroscopic examination was canceled.

Findings at follow-up hysteroscopy were evaluated and recorded according to the American Fertility Society (AFS) classification.

Table. The American Fertility Society (AFS) classification of intrauterine adhesion (1988)#

Extent of cavity involved	<1/3	1/3-2/3	>2/3
Score	1	2	4
Type of adhesions	Filmy	Filmy & dense	Dense
Score	1	2	4
Menstrual pattern	Normal	Hypomenorrhea	Amenorrhea
Score	0	2	4
Prognostic classification			
Disease severity	Cumulative score		
Stage I (mild)	1-4		
Stage II (moderate)	5-8		
Stage III (severe)	9-12		

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Endpoints:

The primary endpoint was the number of women with formation of IUAs. The secondary endpoints included the adhesion scores of extent of uterine cavity involved, type of adhesion and menstrual pattern, the cumulative adhesion score and the severity of IUAs graded according to AFS classification. The safety was monitored based on the complications and adverse events recorded that was possibly related to the MateRegen® gel application.

Participant number

The primary hypothesis of this trial was to demonstrate the superiority of D&C plus MateRegen® gel over the D&C alone, with respect to the incidence of IUAs. The primary assumption was that the estimated incidence was 30% in control group and would be reduced to 15% by application of MateRegen® gel. With a 2-tailed 0.05 significance level and 20% loss rate during follow-up, 300 patients with 1:1 allocation would yield 80% power to detect the superiority.

Statistical analysis Plan

All randomized women who started treatment were included in analysis according to the intent-to-treat (ITT) principle. Continuous variables were expressed as mean ± standard deviation (SD) or median ± quartile range (QR). Categorical variables were described by counts and percentages. The student's t-test/Wilcoxon rank-sum non-parametric test and chi-square test/Fisher's exact test were used to check the homogeneity of baseline characteristics. The Wilcoxon rank-sum non-parametric test was used if variables do not follow the normal distribution and the results were expressed as median (Quartile Range) (QR). The Cochran-Mantel-Haenszel (CMH) Chi-Square test with center effect adjustment was performed to estimate the incidence difference between groups. The analysis of covariance with center effect adjustment was performed to estimate the difference of intrauterine adhesion scores between groups. All analyses were performed by using SAS® 9.13 (SAS Institute, Cary NC), and a $p \leq 0.05$ (two-tailed, $\alpha=0.05$) was considered to be statistically significant.

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