Impact of antibiotic treatment for chronic endometritis on unexplained recurrent pregnancy loss

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Short Title: Treatment of Chronic Endometritis and Recurrent Miscarriages

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Key Words: Recurrent Miscarriage ; Chronic Endometritis ; Early Pregnancy Loss ; Late Pregnancy Loss ; Antibiotic treatment ; Implantation Failure

Trial Registration: 2019-17-10-006 (Aix Marseille University Ethics Committee)

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ABSTRACT

Introduction

Recurrent Pregnancy Loss (RPL) affects about 1% of all couples and is likely to cause therapeutic vagrancy and psychological distress. Multiple origins can explain RPL, and recent studies suggest the influence of chronic endometritis. The aim of our study is to evaluate the impact of antibiotic treatment on obstetrical prognosis among patients consulting for RPL with isolated chronic endometritis.

Material and methods

We conducted a monocentric retrospective comparative study. Patients consulting for RPL, with normal etiologic examinations (except for chronic endometritis), were included.

In the case of chronic endometritis, patients could receive antibiotic treatment (14 days of doxycycline and metronidazole). Pregnancy outcomes, collected one year after inclusion, were compared between 3 groups: patients without chronic endometritis, patients with treated chronic endometritis, patients with untreated chronic endometritis. Univariate and multivariate analyses were performed.

Results

42 patients were included. 22 patients had chronic endometritis. Groups were comparable in terms of age, BMI, the number of miscarriages, tobacco consumption, AMH, and FSH levels on day 2. In multivariate analysis, a significant improvement of live birth rate was observed among patients treated for chronic endometritis, compared to the no endometritis group (OR 21.4 [1.93-236.70] p=0.013) and the untreated endometritis group (OR 24.90 [1.64-376.93] p=0.020).

Conclusion

In our patients examined for RPL, the live birth rate was improved after treatment of chronic endometritis with 14-day antibiotic treatment in comparison to patients with untreated chronic endometritis.

Introduction

Miscarriage is defined as a pregnancy loss before the gestational age of 24 weeks of gestation (1). It includes early pregnancy losses (early miscarriages EM), before 12 weeks of gestation, and late pregnancy losses (late miscarriage LM), 12 to 24 weeks. It excludes ectopic pregnancy and molar pregnancy. Unrepeated miscarriages affect 15 to 25% of pregnancies, getting more frequent with advanced maternal age and number of previous episodes (2).

Recurrent Pregnancy Loss (RPL) affects about 1% of all couples and is likely to cause therapeutic vagrancy and psychological distress. It is defined by a history of at least 2 consecutive early pregnancy losses (1).

Multiple origins can explain RPL (3), among which are: genetic abnormalities (boosted by maternal age, so as balanced or Robertsonian translocation (4)), uterine defect (malformation, intracavitary process…(5), thrombophilia (antiphospholipid antibody syndrome, S or C protein deficit, factor II or V Leiden mutation, essential thrombocythemia (6)), auto-immune disease (lupus, inflammatory bowel disease, celiac disease, autoimmune thyroiditis (7–9)), endocrinal diseases (hypo or hyperthyroidism, hyperprolactinemia, polycystic ovary syndrome, unbalanced diabetes,…), environmental factors (pollutants, endocrine disruptor, coffee, alcohol, tobacco, cocaine, psychological stress,…(7,10)), ovarian insufficiency, vaginal infection. According to Collège National des Gynécologues et Obstétriciens de France (CNGOF), the current recommended etiologic examinations are parental karyotypes (possibly completed by other genetic analyses), biological examinations (hormonal analyses, ovarian reserve, hyperandrogenism, thyroid, prolactin, blood sugar), hereditary thrombophilia and immunological examinations (anticardiolipin antibody, antiphospholipid, lupus anticoagulant, thyroid antibodies, antithrombin III mutation, factor II and V Leiden, S and C protein), uterine examinations (pelvic ultrasound or diagnostic hysteroscopy), infectious examinations (vaginal sample), male examinations (sperm analysis), and environmental examinations (11).

Jaslow et al. proved that abnormalities in etiological examinations for miscarriage are as frequent in couples who underwent 2 miscarriages as those who experienced more (12). In another study, Cardinale et al. brought to light that the prevalence of abnormalities in etiologic examinations were the same between couples undergoing consecutive and non-consecutive miscarriages (13). Thus, examinations of RPL can be reasonably considered after the occurrence of 2 early miscarriages.

However, despite these examinations, 50% of RPL cases remain unexplained (14).

Recent studies suggest the influence of chronic endometritis on implantation troubles (15-17). Bouet et al. found that this chronic endometrial inflammation is frequent among patients suffering from repeated implantation failure (prevalence of 14%) or RPL (27%) (18).

Chronic endometritis is suspected during hysteroscopy facing (19) endometrial stromal edema, strawberry aspect of mucosa (congested and red endometrium, with white spots), endometrial micro-polyps (<1 mm), and endometrial irregularities. Hysteroscopy can suggest the diagnosis of chronic endometritis, although with limited sensibility and sensitivity, and anatomopathological analysis of endometrial biopsy is necessary to confirm the diagnosis (20). Chronic endometritis is defined by the existence of plasma cells in endometrial stroma. Immunostaining (antiCD138/Syndecan-1) improves diagnosis sensitivity (21). Bouet et al. (18) showed that endometrial biopsy with immunohistochemistry is more specific and sensitive than office hysteroscopy, and should be realized systematically for the diagnosis of chronic endometritis.

The aim of our study is to evaluate the interest of antibiotic treatment on obstetrical prognosis among patients consulting for RPL, for whom etiologic examinations were negative, except for chronic endometritis.

Materials and Methods

We conducted a monocentric retrospective comparative study in the Gynecology-Obstetrics service of Hospital Nord, Marseille, France, between January 1st, 2013, and January 1st, 2018. All patients aged between 18 and 42 years consulting for repeated pregnancy losses (including early or late miscarriages) were included. Early spontaneous pregnancy loss was defined as loss of a embryo before 12 weeks of gestation. Late pregnancy loss was defined as loss of a fetus between 12 and 24 weeks of gestation. Recurrent pregnancy loss was defined as the loss of two or more pregnancies, consecutive or not, according to ESHRE guidelines(1). Patients refusing to participate in the study and those with abnormalities in their miscarriage etiologic examinations were excluded.

The etiologic examinations were parental karyotypes, hormonal tests (FSH, AMH, TSH, prolactin on the 3rd day of the menstrual cycle), immunologic tests (antib2GP1, anticardiolipin, lupus anticoagulant, antinuclear antibodies, thyroid antibodies), thrombophilia examinations (ATIII, PS, PC, Factor II, and V Leiden mutation, homocysteinemia), blood sugar, sperm analyses (spermiogram, culture), uterine morphological examinations (pelvic sonography and/or hysteroscopy), and infectious examinations (vaginal sample with culture and PCR tests for STI).

Moreover, endometrial biopsy was done during diagnostic hysteroscopy or with Pipelle de Cornier to evaluate the presence of chronic endometritis. The diagnosis criterion was the existence of at least one plasma cell per field on endometrial biopsy, which is the often used threshold in the literature (22, 23). Plasma cells were identified by means of traditional hematoxylin and eosin staining and by immunohistochemistry for Syndecan-1 (CD138). In case of chronic endometritis, according to French recommendations about pelvic inflammatory diseases (24), patients received antibiotic treatment, after excluding any related allergy: with an antibiotic adapted to antibiogram if germ was isolated, or with doxycycline (100mgx2/day) and metronidazole (500mgX2/day) by mouth for 14 days in other cases.

Data regarding the clinical parameters and etiologic examinations of the patients were extracted. Data concerning BMI, age, and tobacco consumption were analyzed as well. Finally, obstetrical outcomes were collected one year after the inclusion as pregnancy wish, pregnancy occurrence, and pregnancy outcome. Pregnancy outcome was compared between 3 groups: patients without chronic endometritis, patients with treated chronic endometritis, and patients with untreated chronic endometritis (corresponding to patients who got pregnant before antibiotic treatment or those refusing to undergo the treatment). LBR was defined by the delivery of viable children (according to the WHO).

Qualitative variables are evaluated as number and percentage, and continuous variables are evaluated as median and interquartile range. The characteristics of each groups were compared according to conditions required, with Fisher's exact test for qualitative values, and Kruskal Wallis-H test for quantitative values. Post hoc analyses were performed when overall p value was less than 0.05. Also, a multiple logistic regression analysis was done with a backward elimination strategy. Variables significant at p-value <0.20 in univariate analysis were introduced into the multivariate model and step by step eliminated until the model conserve variables with a p value <0.05. Results are presented with Odds Ratios (OR) and their 95% Confidence Interval (95%CI). The significance level was chosen as 5%. Statistical analyses were performed using the SPSS software.

Our study received a favorable opinion from the Aix-Marseille University Ethics Committee (2019-17-10-006).

Results

364 patients consulted our service for examination for RPL or late miscarriage during the specified period. Among them, 208 had abnormal etiologic examinations and were thus excluded from the study. Some examinations were missing for 92 patients (notably no endometrial biopsy when the patient got pregnant or the hysteroscopy was done outside of the

service), and these patients were excluded as well. 64 patients were included and corresponded to those with negative etiologic examinations, among whom 37 patients had chronic endometritis (60%). 6 patients were excluded because they no longer had wishes to get pregnant (new partner, life project, abortion). 5 patients did not get pregnant during the 12-month follow-up. 14 patients dropped out of the study. Finally, 42 patients were analyzed; 22 of whom had chronic endometritis (figure 1).

Among untreated patients, 7 got pregnant before the prescription, and 2 did not receive the prescription (because it was forgotten to be sent).

Groups were comparable in terms of age, BMI, the number of miscarriages, AMH, and FSH levels on day 2 (Table 1). The delay before pregnancy was lower in the untreated endometritis group in comparison to the no endometritis and treated endometritis groups (3.0, 7.8, and 5.8 months, respectively, p=0.02).

A germ was identified among 5 out of 13 (38.5%) patients with treated chronic endometritis (Streptococcus agalactiae and Gardnerella vaginalis), and among 3 out of 9 (33.3%) patients with untreated chronic endometritis (Streptococcus agalactiae, Gardnerella vaginalis, and Escherichia coli).

A significant improvement of live birth rate (LBR) was observed among patients with treated chronic endometritis compared to the untreated and no endometritis groups (85%, 44%, and 40%, respectively, p=0.032). There was a significant reduction of miscarriages in the treated group in comparison to the untreated and no endometritis groups (15%, 56%, and 60%, respectively, p=0.032; Table 2).

In multivariate analysis, a significant improvement of LBR was observed among patients treated for chronic endometritis compared to the no endometritis group (OR 21.4 [1.93-236.70] p=0.013), and the untreated endometritis group (OR 24.90 [1.64-376.93] p=0.020).

Discussion

In our study, there was an improvement of LBR among patients treated by antibiotics for chronic endometritis in comparison to those with untreated chronic endometritis.

So far, only a small number of studies have evaluated the impact of antibiotic treatment for chronic endometritis on pregnancy outcomes among patients consulting for RPL. Cicinelli et al. (25) showed that LBR was higher after treatment and hysteroscopic endometritis recovery than after treatment with persistent hysteroscopic signs of endometritis. McQueen et al. (26) observed improved LBR after antibiotic treatment among patients consulting for RPL in comparison to LBR before treatment. These findings support the effects of antibiotic treatment (adapted to antibiogram, if available, or empirical). Three other studies are available concerning antibiotic treatment, but these have evaluated implantion failure (27, 28) or unexplained infertility (29). Kitaya et al. (27) observed improved LBR after antibiotic treatment among patients with cured endometritis in comparison to those with no endometritis in a population of patients suffering from repeated implantation failure. Cicinelli et al. (29) showed that antibiotic treatment for chronic endometritis among patients suffering from unexplained infertility improved LBR. Despite our small number of patients, our study is the first one to compare outcomes between treated and untreated patients among unexplained RPL cases.

Various germs were found in our population, including commensal germs of the vaginal flora; these results are close to those of Cicinelli (25). Concerning antibiotic treatment, doxycycline (100mg orally twice a day) and metronidazole (500 mg orally twice a day) for 14 days was the proposed antibiotic protocol in most available studies, according to CDC guidelines (30). In addition to its action against germs, antibiotic use for treating chronic endometritis could be effective in modulating the immune response, thanks to doxycycline immunomodulating action (31, 32).

Of course, our study presents several limits. The number of included patients was low, and 21 patients were excluded (33%). Indeed, the statistical power of our results was also limited. Correct medication intake could not be checked and the treatment was not compared to placebo. Stress is a factor favoring miscarriage, and the placebo effect could play a role in the next pregnancy outcome (33). However, Kitaya et al. (27) explained the impossibility to perform a randomized controlled trial, because 95% of infertile couples desired antibiotic treatment and refused to take a placebo.

Patients who did not have pregnancy during the 12-month follow-up represented 11% of our patients, which is close to the general population (18% according to INSERM data (34)). These patients were excluded since they presented infertility as well, and the aim of our study was to evaluate the impact of chronic endometritis on miscarriage. We also chose to exclude any other pathology that could be a confounding factor.

In the current study, we did not analyze the result of control endometrial biopsy or hysteroscopy due to the small percentage of realization. The time necessary to perform the examinations and wait for conception was demotivating for several patients. However, the comparison of pregnancy outcomes would be interesting to investigate between patients with persistent endometritis and those with normal endometrial biopsy. Cicinelli et al. (25, 29) showed that pregnancy outcomes were improved after antibiotic treatment and chronic endometritis recovery (normal hysteroscopy and endometrial biopsy).

The definition of anatomopathological chronic endometritis is unclear, and the plasma cell level by fields differs from one study to another. Most studies define endometritis as a level of 1 plasma cell per field in the endometrial stroma. The presence of pathogenicity in a few plasma cells is not established and would not necessarily be associated with an inflammatory process. The biopsy sampling site could change the diagnosis (deep or superficial sample, sample site, associated hysteroscopy…). Likewise, the day of the cycle during biopsy could

also play a role but is rarely studied (35). A consensual pathological definition would be necessary to correctly analyze chronic endometritis. In 2019, the International Working Group for the Standardization of Chronic Endometritis Diagnosis published a unified diagnostic criterion for chronic endometritis at fluid hysteroscopy (36). This could lead to a consensus on anatomopathological diagnosis in the future.

Conclusion

In our patients examined for RPL, LBR could be improved after antibiotic treatment of chronic endometritis in comparison to patients with untreated chronic endometritis.

A randomized controlled trial with a wider population of patients, an analysis of control endometrial biopsy after treatment, and a strict anatomopathological definition for chronic endometritis would be necessary to precisely determine the action of antibiotic treatment in chronic endometritis and clinical outcomes.

However, in case of a history of fetal losses and diagnosis of chronic endometritis, in the context of therapeutic dead-ends induced by repeated miscarriages and the low medical risk associated with short antibiotic treatment, the benefit-risk ratio seems to be in favor of systematic treatment (except for contraindications), which awaits stronger findings.

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Conflicts of Interest: None

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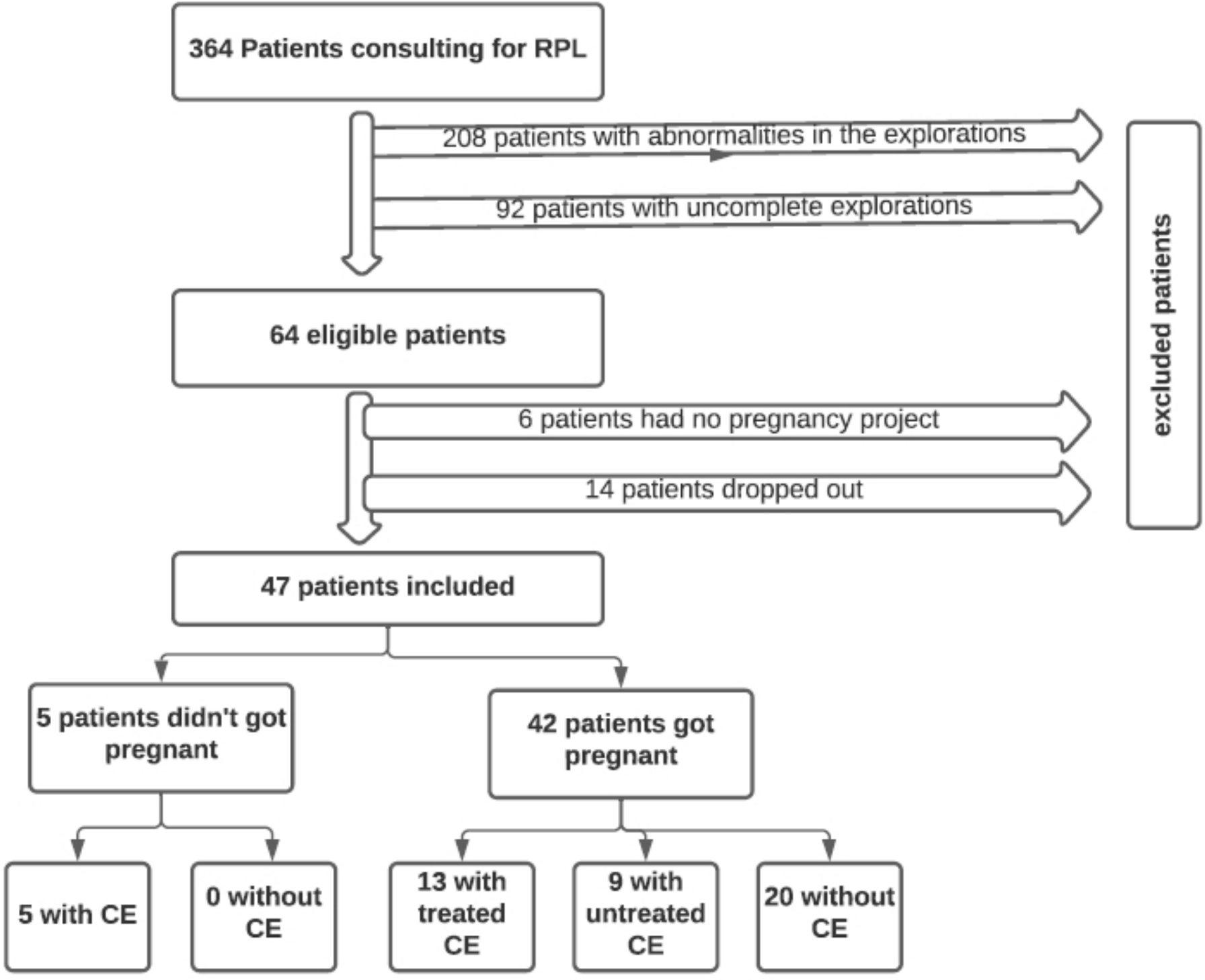
364 Patients consulting for RPL
208 patients with abnormalities in the explorations
92 patients with uncomplete explorations
excluded patients
64 eligible patients
6 patients had no pregnancy project
14 patients dropped out
47 patients included
5 patients didn't got pregnant
42 patients got pregnant
5 with CE
0 without CE
13 with treated CE
9 with untreated CE
20 without CE

	No endometritis (n=20)	Treated endometritis (n=13)	Untreated endometritis (n=9)	Total (n=42)	Median (IQR)	
Age (year)	33,9	30,5	31,2	32,3	33 (9)	p=0.211
BMI (kg/m²)	24,3	23,4	26,3	24,5	24 (3)	p=0.867
Tobacco (patients)	6 (30%)	6 (46%)	1 (11%)	13 (31%)		p=0.236
Number of EM (number among concerned patients)	4,2 (/19 patients)	3,4 (/11 patients)	4,2 (/6 patients)	3,9 (/36 patients)		p=0.210
Number of LM (number among concerned patients)	1 (/1 patient)	1,5 (/2 patients)	1 (/3 patients)	1,2 (/6 patients)		p=0.11
AMH (ng/mL)	2,37	3,47	3,17	2,95	2 (2)	p=0.908
FSH (UI/L)	7,0	7,7	5,2	6,7	7 (4)	p=0.521
Delay before pregnancy (month)	7,8	5.8	3	6.2	5 (3)	P=0.02

Table 1: Main included patient's characteristics:

(BMI Body Mass Index ; EM Early Miscarriage ; LM Late Miscarriage, IQR Interquartile Range)

	No endometritis (n=20)	Treated endometritis (n=13)	Untreated endometritis (n=9)	Total (n=42)	
Live birth (n)	8 (40%)	11 (85%)	4 (44%)	23 (55%)	p=0.032
Miscarriage (n)	12 (60%)	2 (15%)	5 (56%)	19 (45%)	p=0.032

Table 2 : Pregnancy outcome in multiple analysis