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Evaluation of fertility after operative hysteroscopy to remove retained products of conception

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ABSTRACT

Evaluation of fertility after operative hysteroscopy to remove retained products of conception.
Objective: To study fertility after operative hysteroscopy for the management of prolonged trophoblastic retention, and the complications of this procedure.
Study design: Retrospective cohort in a university hospital.
Results: 115 patients underwent operative hysteroscopy for the treatment of prolonged post-partum and post-abortum retention between January 2008 and December 2011. Of the 115 patients included in this study, 53 desired a postoperative pregnancy. Using the survival model, the conception rate was 71.1% (95%CI; 58.1–82.9) at 6 months and 83.5% (95%CI; 71.8–92.2) at 1 year. The overall rate of intraoperative complications was 15%. The rate of complications ≥ grade 3 was 5%. Logistic regression analysis showed that only retentions of greater than 25 mm were associated with complications generally (aOR = 7.4; 95% CI; 2.3–24.5) and with Clavien-Dindo complications ≥ grade 3 (OR = 27.2; 95%CI; 2.8–263).
Conclusion: The management of prolonged retention by operative hysteroscopy allows the preservation of future fertility. There are more complications when the retentions are >25 mm.

1 Introduction

Post-partum and post-abortum retention of trophoblastic tissue can lead to endometritis and menstruation disturbances in the short term and, in the long run, fertility problems due to synechiae [1–4].

Prolonged retention of trophoblastic tissue is defined as retained product of conception persisting after menstruation. This prolonged retention can be recognized by the association of clinical signs (amenorrhea, bleeding, pain) with endo-uterine ultrasound images that show interruptions of the endometrial stripe or visible areas of mixed echogenic material [5,6].

The reference treatment for prolonged retention is currently endo-uterine aspiration. However, this technique blindly removes the retention while possibly damaging the healthy mucosa and creating synechiae [7]. The risk of synechiae correlates with the number of intra-uterine surgeries: 19% on average after one aspiration for a miscarriage in the first trimester to up to 30% after multiple aspirations [2–4].

Operative hysteroscopy may permit the selective resection of intra-uterine retentions under direct vision. It seems that this procedure is less traumatic for the healthy mucosa than blind aspiration, and less likely to generate synechiae [5,8,9]. In descriptive studies with few subjects, the lead-time to a new pregnancy was shorter for patients treated by operative hysteroscopy compared to endo-uterine aspiration [9,10]. Although the reported complications seem infrequent, their rate is not well known because of the small numbers of patients studied.

The objective of our study was to evaluate the repercussion on fertility and the complications of operative hysteroscopy in the management of prolonged post-partum and post-abortum retention.

2 Material and methods

We performed a descriptive single-center retrospective study in the Obstetrics and Gynecology department of the Poissy Saint Germain en Laye Medical Center. This study received ethical

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We included all hospitalized patients treated for trophoblastic or placental retention by operative hysteroscopy between January 2008 and December 2011. This retention followed an initial obstetrical event: abortion (spontaneous or induced) or birth. The diagnosis of retention was made when women were coming to emergency room with symptoms: persistent bleeding or pelvic pain, and ultrasound images showing areas of mixed echogenic material.

2.1 Operative hysteroscopy

Operative hysteroscopy was performed under general anesthesia, following 48 h of prophylactic antibiotic treatment with amoxicillin + clavulanic acid with or without fluoroquinolone. Clindamycin was used instead of amoxicillin for patients with an established allergy to penicillin.

After cervical dilation of up to 9 mm using a Hegar dilator, a 9.3 mm resectoscope was introduced into the uterine cavity using physiological saline as distension medium. After complete examination of the uterine cavity and localization of the tubal ostia, products of conception were removed under visual guidance using the mechanical action of the resectoscope loop without electrical energy in the first instance. Any intraoperative complications were recorded according to the Clavien-Dindo classification [11].

The patient was seen one month after the operative hysteroscopy. Depending on the patient interview and clinical examination, the operator performed a diagnostic hysteroscopy in consultation. The presence of adhesions or residual retention detected during this hysteroscopy was recorded.

2.2 Fertility

We collected monitoring data from the patient files and supplemented this with a telephone survey in February 2013. We determined exposure to pregnancy based on the desire to become pregnant and regular sexual intercourse without contraception. We noted the subsequent obstetric events to evaluate post-operative fertility related to exposure to pregnancy.

2.3 Statistical analysis

The data were analyzed using SigmaPlot® version 12.5 (San Jose, CA), GraphPad Prism® version 6.02 (San Diego, CA) and Stata 13.0 (Stata Corp., College Station, TX, USA) software.

We analyzed the fertility data of patients desiring a pregnancy as a function of the time between the date at the beginning of wanting to be pregnant and the date of conception using Kaplan-Meier curves; we also analyzed the fertility data as a function of the time between the initial event and the date of delivery. Factors associated with fertility were assessed using the log-rank test.

We analyzed the risk factors for intraoperative complications using the Chi2 test or the Fisher's exact test, when the expected sample size was too small, for qualitative variables. For quantitative variables, a Student test was performed. We then performed multivariate analysis by logistic regression to search for the

Table 1
General and obstetric characteristics of the population (n = 115).

	Total population N = 115	Women who expressed the desire to become pregnant n = 53	Women who didn't express the desire to become pregnant n = 62
Age (years), mean ± SD	32 ± 7	32 ± 5	31 ± 8
Gravidity, median (min-max)	2 (1–10)	2 (1–6)	2 (1–10)
Parity, median (min-max)	1 (0–6)	1 (0–3)	1 (0–6)
Previous aspiration, n (%)	27 (23%)	10 (19%)	16 (26%)
1	16 (14%)	6 (11%)	10 (16%)
2	9 (8%)	4 (8%)	5 (8%)
3	1 (1%)	0	1 (2%)
Previous caesarean section, n (%)	20 (17%)	15 (28%)	6 (10%)
1	10 (9%)	7 (13%)	3 (5%)
2	6 (5%)	3 (6%)	3 (5%)
3	4 (3%)	4 (8%)	0
Initial obstetrical event, n (%)			
Vaginal delivery	10 (9%)	2 (4%)	8 (13%)
Placental delivery			
Complete (managed)	7	2	5
UE	1		1
MEUE	2		2
Caesarean section	2 (2%)	0	2 (3%)
Aspiration (SAB/VTP)	27 (23%)	17 (32%)	10 (16%)
Misoprostol to stop pregnancy/VTP	76 (66%)	34 (64%)	42 (68%)
Gestational age (WG), mean ± SD	12 ± 10	9 ± 6	16 ± 13
Symptomatic patients, n (%)	97 (84%)	39 (74%)	58 (94%)
Bleeding	89 (77%)	36 (68%)	54 (87%)
Abdominal pain	28 (24%)	11 (21%)	18 (29%)
Asymptomatic patients, n (%) (retention detected by US only)	18 (16%)	14 (26%)	4 (6%)
Antero-posterior size by US, mean ± SD	19 ± 9	19 ± 10	19 ± 7
Interval initial event/op HSC (d), mean ± SD	49 ± 47	50 ± 33	50 ± 59
≤10d	2 (2%)	0	2 (3%)
11-20d	21 (18%)	11 (21%)	10 (16%)
21-30d	15 (13%)	6 (11%)	9 (15%)
≥ 31d	75 (65%)	36 (68%)	41 (66%)
Complications,n (%)	17 (15%)	8 (15%)	9 (15%)

n (%) or mean ± standard deviation.
UE: uterine exploration, US: ultrasound, MEUE: manual extraction and uterine exploration, SAB: spontaneous abortion, VTP: voluntary termination of pregnancy, WG: weeks of gestation, op HSC: operative hysteroscopy, d: days.

independent variables associated with complications, including variables associated with complications by univariate analysis with a limit of $p < 0.05$.

3 Results

This study included 115 patients hospitalized for operative hysteroscopy to treat retention. Their clinical characteristics are presented in Table 1. The initial obstetrical event was a full-term delivery for 10% of the patients. For 90% of the patients, the retention was diagnosed following an abortion occurring between four and 19 weeks of gestation (WG) (spontaneous miscarriage, medical termination of pregnancy (MTP), or voluntary termination of pregnancy): 74% were treated with misoprostol and 26% by aspiration. In 65% of the cases, the time between the initial obstetric event and operative hysteroscopy was more than 30 days. The average anteroposterior size of the retention, as measured by ultrasound in emergency room, was 19 (SD ± 9) mm. The operation had a median duration of 27.5 (95%CI; 20–40) minutes, and bipolar electro-surgery was only used four times (3.5%) to aid in the resection of the retention. The diagnosis of trophoblastic retention was histologically confirmed in 90% of cases.

3.1 Fertility

We evaluated fertility, on average, 22 (SD ± 18) months after the procedure. We received information for 96 patients of which 53 expressed a desire to be pregnant. Among these 96 patients, 78 patients have been reassessed at least one year after hysteroscopy; 27 had an immediate desire to become pregnant following the procedure and 46 within the following 6 months. Of the 18 patients who could not be reassessed after one year, 14 did not express a desire to become pregnant during their postoperative consultation.

Among the 53 patients who were exposed to pregnancy, the conception rate was 71.1% (95%CI; 58.1–82.9) at 6 months and 83.5% (95%CI; 71.8–92.2) at 1 year using the survival model. The median follow-up length for these 53 patients was 33 months (Min–Max: 1–56).

Of the 44 patients who became pregnant, four had a miscarriage in the 1st trimester, one had a MTP at 14 weeks of gestation (WG) for trisomy 21, one had an ectopic pregnancy, and one patient was less than 22 weeks pregnant at her reassessment.

Fig. 1 shows the Kaplan-Meier plot of pregnancies that evolved beyond 22WG as a function of the time between wanting to become pregnant and the date of conception. For the 37 pregnancies in the 53 patients exposed to pregnancy, the average time between their wanting to become pregnant and the date at the beginning of the pregnancy was 160 (SD ± 139) days.

Univariate analysis showed that fertility was inversely proportional to the initial size of the retention as measured by ultrasound, with a decrease of 6.8% fertility per mm in the size of the retention (OR 0.93; 95%IC; 0.87–0.99, p = 0.03) with no threshold effect.

We found an intrauterine synechiae in 6 of the 22 patients who had secondarily a diagnostic hysteroscopy, with no effect on their future fertility (three of four patients who wanted to become pregnant became pregnant). One synechia was lysed during diagnosis hysteroscopy, 4 during secondary operative hysteroscopy and one patient without desire of pregnancy was lost of follow. On the other hand, a persistent retention was found in two patients, treated by a second operative hysteroscopy.

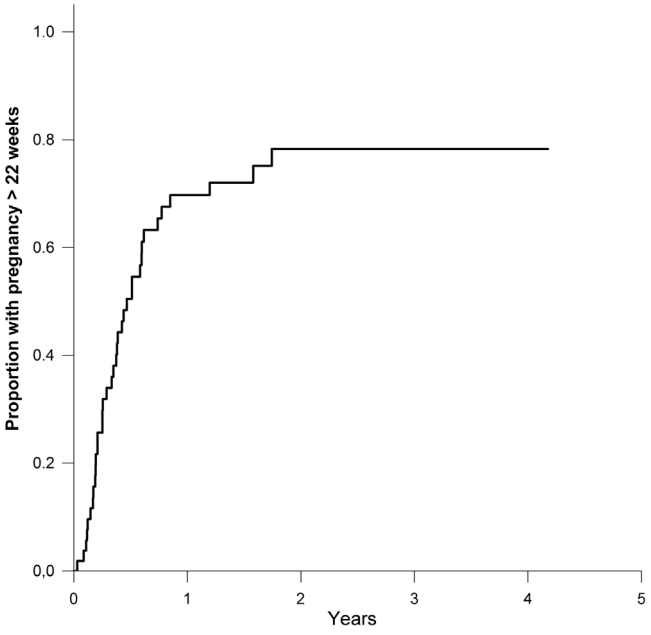

Fig. 1. Time (months) between wanting to become pregnant and the beginning of pregnancy (ongoing pregnancy ≥ 22WG) after operative hysteroscopy for prolonged retention.

3.2 Complications

Table 2 presents the intraoperative complications. Among the 115 patients who underwent operative hysteroscopy, adverse events occurred in 17 patients (15%). Heavy bleeding was present in 10 patients during surgery, of which five had severe anemia (hemoglobin (Hb) ≤8 g/dl or a fall >2 points of Hb), one required embolization for placenta accreta, and one patient was hospitalized in the ICU for 24 h for disseminated intravascular coagulation (DIC) requiring transfusion of packed red blood cells.

Eight surgeries were complicated by a uterine perforation, of which four required immediate laparoscopy to assess the damage. No secondary surgeries were performed.

In univariate analysis, complications were significantly positively correlated with postpartum (relative to post-abortum), with gestationnal age of initial obstetrical event, with aspiration of post-abortum retentions compared to treatment with misoprostol, with size of the retention, and with hCG level (Table 3). The 6 severe complications (Clavien-Dindo classification >3) were correlated with initial event, with size of the retention, and with hCG level.

Logistic regression analysis showed that only a retention larger than 25 mm was associated with complications (Adjusted Odds Ratio (aOR) = 7.4; 95%CI; 2.3–24.5) and with Clavien-Dindo complications ≥ 3 (aOR = 27.2; 95%CI; 2.8–263).

4 Comment

We studied 115 patients with post-partum or post-abortum prolonged retention who were treated by operative hysteroscopy. Our population was particularly representative of patients at risk of synechiae because of the high rate of very prolonged retentions (65% with the time between the initial obstetrical event and the operative hysteroscopy ≥ 31days).

We analyzed the post-operative fertility for the 53 patients who wanted to become pregnant. The conception rate was 83.5% according to the survival model at 1 year after operative hysteroscopy. The conception rate was higher if the initial size of the retention as determined by ultrasound was small. We followed up 78 patients (68% of our initial cohort) for more than one year, which is more patients than in previously published studies [5,9,10,12,13]. The intraoperative complication rate was

Table 2
Intraoperative complications.

	Complications of Hysteroscopy
All causes	17 (15)
Heavy bleeding of which	10 (9)
Anemia < 8.5 g/dL	5 (4)
Embolization	1 (0.1)
Hospitalization in ICU, transfusion PBRC, FFP, PF	1 (0.1)
Perforation, of which 4 laparoscopies	8 (7)
Complications by initial event	
Aspiration (SAB/VTP)	8 (47)
Miscarriage/VTP by misoprostol	4 (24)
Postpartum	5 (29)
Time between initial event and hysteroscopy (d)	49 ± 47
11-20d	2 (12)
21-30d	5 (29)
≥ 31d	10 (59)
Size measured by ultrasound S(mm)	19 ± 9
n (%) complication if S = 11–20 mm	6 (35)
n (%) complication if S = 21–30 mm	7 (41)
n (%) complication if S ≥ 31 mm	4 (24)
Previous events,n (%)	
Aspiration	5 (29)
Caesarean	4 (24)

n (%) or mean ± standard deviation.
ICU: intensive care unit, PRBC: packed red blood cells, FFP: fresh frozen plasma, PF: plasma fibrinogen, SAB: spontaneous abortion, VTP: voluntary termination of pregnancy, d: day, mm: millimeter.

Table 3
Complication risk factors.

	No complications (n = 98)	Complication (n = 17)	p	Odds Ratio (95% CI)
Gravidity	2.5 ± 1.7	3.1 ± 2.4	0.24	
Parity	1.1 ± 1.3	1.4 ± 1.3	0.49	
Previous aspiration	21/98 (21)	5/17 (29)	0.53	1.5 (0.5–4.9)
Previous caesarean	16/98 (16)	4/17 (24)	0.49	1.6 (0.5–5.5)
Gestational age of initial event,WG	10.7 ± 8.8	19.2 ± 13.4	**0.01**	
Initial event,n/N (%):			<**0.001**	4.8 (2.3–10.3)
Miscarriage/VTP by misoprostol	72/98 (73)	4/17 (24)		
Aspiration	19/98 (19)	8/17 (47)		
Delivery	7/98 (7)	5/17 (29)		
Postpartum, n/N (%)	7/98 (7)	5/17 (29)	**0.02**	5.4 (1.4–20.8)
U/S Size of retention, mm (+/−DS)	18 ± 8	27 ± 11	<**0.0001**	
US retention > 25 mm, n/N (%)	12/98 (12)	9/17 (53)	<**0.001**	8.1 (2.4–27.3)
WBC, G/L	8264 ± 2657	9261 ± 2267	0.17	
CRP, mg/L	20 ± 42	4 ± 7	0.32	
hCG, mUI/mL	187 ± 327	1950 ± 4121	**0.03**	
Time to HSC, d	50 ± 49	45 ± 26	0.68	
Experienced operator, n/N (%)	17/98 (17)	3/17 (18)	1	1.0 (0.3–4.0)
Second HSC	14/98 (14)	8/17 (47)	**0.004**	5.3 (1.7–17.1)
Duration op HSC, min	28.9 ± 15.3	71.5 ± 37.5	<**0.0001**	
Fertility (op >22 SA)	33/45 (73)	4/8 (50)	0.22	

For quantitative variables: mean ± standard deviation.
For qualitative variables: n/N (%).
US: ultrasound, WBC: white blood cell, Hb: hemoglobin, CRP: C reactive protein, WG: weeks of gestation, HSC: hysteroscopy, d: days, mm: millimeter, op HSC: operative hysteroscopy.
Experienced operator: operator with over two years of experience after residency.

15%. Logistic regression analysis showed that only a retention of greater than 25 mm was associated with complications.

In our study, as in published studies, we analyzed both postpartum and post-abortum patients together. However, the pathology of the retention and uterine fragility may differ between these two obstetrical periods and may require separate analyses. We found that there were more complications and a lower desire to become pregnant (17% vs 46%) among the 20 postpartum patients than for the cohort overall.

The reported conception rate after operational hysteroscopy varies between 68 and 93% [5,9,10,12–14], with an average time to conception of seven to 27 months, which appears to be shorter than that after aspiration [9,10,13,15]. However, these fertility studies concern either small groups (between 14 and 45 patients) [5,9,10,12], or they are biased by a high rate of patients of whom they lost track during the evaluation: 73% in the study of Golan et al., [12], or not reported [10,15]. It is probable that patients who did not become pregnant were less likely to respond to the questionnaires.

Times to conception should be compared with care as the calculation method may differ between studies: the beginning of the period may be defined as the initial obstetrical event [16], operative hysteroscopy [9,12] or the desire to become pregnant [17], and sometimes it is not defined at all thus complicating the

analysis of the results [10,15]. The end of the period is in some studies defined as conception [9,10,12] and other delivery [16]. Some studies report a conception rate that includes spontaneous miscarriage [9,10,12] whereas others only include information for pregnancies that arrive at term [12,16].

We found a high conception rate, 83%, with a short average time, nine months, between the initial obstetrical event and the beginning of pregnancies that progressed beyond 22 WG. Our study is retrospective and does not permit direct comparison of hysteroscopy with aspiration. Nonetheless, this weakness is compensated by the size of the cohort and the low rate of lost patients. Because we did not have a control group treated by aspiration, we compared our data with that of the MIST trial that studies conception among women who had a miscarriage (fertility assessed for 762 of 1199 patients) [16,18]: the pregnancy rate after treatment by aspiration for an incomplete miscarriage or an interrupted pregnancy was 82%, indistinguishable from that of our study (with superimposable Kaplan-Meier plots). However, our study focused on a subgroup of patients presenting a retention, which is normally associated with a lower fertility rate [3]. Thus, the management of these patients by operative hysteroscopy probably resulted in a better fertility rate than that associated with aspiration.

Reported rates of intraoperative complications are 1% [5,8,9,12,13], and thus lower than our 15%. However, published rates may be artificially low because of the small number of subjects and more importantly, the heterogeneous definition of complications or the lack of any definition at all. Many studies only report the rate of confirmed uterine perforation [5,8,9]. Golan et al. only reported severe complications such as pulmonary edema, persistent hemorrhage after surgery, severe sepsis and DIC [12]. Based on these criteria, the complications rate of this present study would be 5% (Clavien-Dindo complications $\geq$3).

We found a higher rate of complications in postpartum patients than in other patients, as did Golan et al.; two thirds of all complications occurred in postpartum patients [12]. Similarly, Cohen et al. reports that hysteroscopy was more difficult to perform in their 12 postpartum patients [10]. The high risk of intraoperative complications among postpartum patients may be because hysteroscopy is more difficult in such patients; the cervix is still open and the cavity is expandable, the physiological serum disperses and the uterine cavity does not sufficiently distend. The operator may thus have poor intrauterine visibility. In addition, it is likely that the post-partum retention of trophoblastic tissue results in placenta accreta, making the procedure more complicated.

From the physiopathological point of view, our procedure permits the elective resection of the retention which avoids abrasion of the healthy endometrium, contrary to aspiration which is done blindly. Also, the formation of synechiae, secondary to inflammation of the uterine mucus, is theoretically reduced; consequently, these patients are expected to have a conception rate close to that of the population without any history of trophoblastic retention.

5 Conclusions

The conception rate and time to conception for patients treated by operative hysteroscopy for trophoblastic retention are comparable to those following any miscarriage. Nonetheless, this surgical procedure, that protects the future fertility of the patients, can have complications. There is a risk of hemorrhage and uterine perforation even though it is carried out under direct vision. These complications correlate with the size of the retention by ultrasound and are most often encountered when the retention occurs postpartum or after aspiration.

A randomized controlled study comparing aspiration and operative hysteroscopy will be necessary for the objective determination of which procedure presents the best benefit to risk ratio for the treatment of these retentions, and the identification of appropriate precautions.

5.1 Condensation

The management of prolonged retention by operative hysteroscopy allows the preservation of future fertility. There are more complications when the retentions are >25 mm.

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