

Clinical and Sonographic Findings in Suspected Retained Trophoblast: Correlation with Histological Findings

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ABSTRACT: **Background:** Different clinical and sonographic parameters have been suggested to identify patients with retained products of conception. In suspected cases, the main treatment is hysteroscopic removal.

Objectives: To compare clinical, sonographic, and intraoperative findings in cases of hysteroscopy for retained products of conception, according to histology.

Methods: The results of operative hysteroscopies that were conducted between 2011 and 2016 for suspected retained products of conception were evaluated. Material was obtained and evaluated histologically. The positive histology group (n=178) included cases with confirmed trophoblastic material. The negative histology group (n=26) included cases with non-trophoblastic material.

Results: Patient demographics were similar in the groups, and both underwent operative hysteroscopy an average of 7 to 8 weeks after delivery/abortion. A history of vaginal delivery was more common among the positive histology group. The main presenting symptom in all study patients was vaginal bleeding, and the majority of cases were diagnosed at their routine postpartum/abortion follow-up visit. Sonographic parameters were similar in the groups. Intraoperatively, the performing surgeon was significantly more likely to identify true trophoblastic tissue as such than to correctly identify non-trophoblastic tissue ($P < 0.001$).

Conclusions: Suspected retained trophoblastic material cannot be accurately differentiated from non-trophoblastic material according to clinical, sonographic, and intraprocedural criteria. Thus, hysteroscopy seems warranted in suspected cases.

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KEY WORDS: abortion, hysteroscopy, retained products of conception (RPOC), trophoblast

follow-up examination. RPOC may lead to intrauterine adhesions, with resultant hypomenorrhea or amenorrhea, and infertility [3]. Although numerous studies have evaluated different sonographic parameters to accurately identify RPOC [4-6], none have proven as ideal predictive tools.

Although past treatment regimens included curettage, the main treatment now is removal of the suspected material via operative hysteroscopy [7]. This approach entails a lower risk for intrauterine adhesions and incomplete evacuation, with similar reproductive outcomes, as compared to dilatation and curettage [8]. Successful pregnancies following treatment have been described but they entail a higher rate of pathological placenta-tion and cesarean delivery [9]. More recently, reports of office see-and-treat vacuum aspiration procedures have emerged [10]. This small series shows promising results, with a similar safety profile and reproductive outcomes.

Most earlier studies regarding the correlation between clinical and sonographic variables to eventual histology in cases of suspected RPOC were relatively small [11], and hysteroscopy was not the mode of treatment in any of the cases [5,12-14]. Therefore, we aimed to identify clinical, sonographic, and intraoperative variables associated with positive trophoblastic histology obtained during hysteroscopy. We examined whether certain variables have a higher predictive value than others that may aid in the decision to proceed to operative hysteroscopy and minimize the number of unnecessary procedures performed.

PATIENTS AND METHODS

This retrospective cohort study included patients treated at the Wolfson Medical Center between January 2011 and December 2016. The study was approved by our institutional review board in accordance with the Helsinki Declaration. Informed consent was not required due to the retrospective and anonymous nature of the study.

Charts of patients who underwent an operative hysteroscopy due to suspected RPOC were retrieved from hospital records according to ICD-9 coding and reviewed for patient demographics, gynecological history, clinical presentation, sonographic evaluation, and surgical findings. Our study included

Retained products of conception (RPOC) following a miscarriage or delivery have been reported to complicate up to 6% of pregnancies in prospective studies [1]. The most common presenting symptoms are vaginal bleeding and pain [2]. Patients are often diagnosed due to persistent bleeding and signs of infection or as part of a routine sonographic

cases in which suspected RPOC were obtained following both elective medical and surgical termination of pregnancy, as well as spontaneous pregnancy loss. In all cases the gestational age was recorded. Also included were cases of RPOC removal following delivery, in which we noted gestational age, delivery type (vaginal or cesarean), multiple pregnancy, manual removal of the placenta or revision of uterine cavity during delivery and postpartum hemorrhage, as coded during hospitalization. For study purposes, deliveries were considered as such at 22 weeks gestation or greater. Surgical reports were reviewed, and the surgeon's description of the materials that were removed indicated the compatible or incompatible appearance of RPOC. The positive histology group consisted of patients with microscopic demonstration of gestational tissue, whereas the negative histology group consisted of patients with no gestational tissue on histological examination.

All operative hysteroscopies were performed in our ambulatory surgery unit under general anesthesia. Misoprostol 400 mcg was administered intravaginally by a physician 1–4 hours prior to the procedure, with cervical dilatation with Hegar dilators used as needed. The uterine cavity was distended with normal saline and a fluid management system was used. Material that was suspected to be RPOC was removed with a 4 millimeter loop resectoscope, which was used as a gentle curettage. Electrical current was not used. All material removed was placed in formalin and sent to the laboratory for histological examination.

Data were analyzed with Epi Info™, version 7.0 (Centers for Disease Control and Prevention, Atlanta, GA, USA). Continuous variables were calculated as mean \pm standard deviation and compared using Student's *t*-test or the non-parametric Mann–Whitney test as appropriate. Categorical variables were calculated as rate (percentage), and compared with chi-square or Fisher's exact test as appropriate. All tests were two tailed, and the threshold for statistical significance was defined as $P < 0.05$.

RESULTS

During the study period, 204 operative hysteroscopies, which met the inclusion criteria, were performed at our medical center. Of these, 178 pathological reports confirmed the presence of gestational tissue (positive histology group) and 26 did not (negative histology group).

Patient demographics are presented in Table 1. The average patient age was 30.5 ± 5.6 and 31.2 ± 7.1 years in the positive and negative histology groups, respectively, $P = 0.98$. No differences were observed in patient gravidity, parity, or history of past cesarean delivery. A history of previous RPOC was noted in 3.3% and 4.0% of patients in the positive and negative histology groups, respectively, $P > 0.99$. Both groups had undergone the operative hysteroscopy an average 7–8 weeks following delivery or abortion.

Delivery and abortion characteristics are presented in Table 2. In the positive histology group, 85 procedures were performed following delivery and 93 following abortion. In the negative histology group, 10 procedures were performed following delivery and 16 following abortion. The average gestational age at delivery was similar in the groups, with a higher non-significant rate of patients in the positive histology group who underwent a vaginal delivery (86.9% vs. 60.0%, respectively, $P = 0.05$). A similar rate of multiple gestation deliveries was noted among the groups, as was the rate of manual removal of the placenta at delivery or revision of uterine cavity. A diagnosis of postpartum hemorrhage following delivery was noted in 27.0% and 20.0% of positive and negative histology patients, respectively, $P > 0.99$. For patients who underwent the hysteroscopy following an abortion, gestational age was similar in both groups (10–11 weeks). The most common type of abortion and treatment was missed abortion treated medically, followed by surgical termination of pregnancy, medical termination of pregnancy, surgical treatment for missed abortion, and complete spontaneous abortion for both groups.

The main presenting symptom in both the positive and negative histology groups was vaginal bleeding (72.3% and 71.4%, respectively, $P > 0.99$) [Table 3], followed by signs of infection (fever, abdominal tenderness). Interestingly, more than 80% of patients in both groups did not refer to their physician despite these symptoms, and were diagnosed at their routine postpartum/abortion follow-up visit, which was performed 4–6 weeks following abortion/delivery. On ultrasound examination, suspected findings were of similar size. Irregularly shaped echogenic material was noted in 75.9% and 66.6% of examinations in the positive and negative histology groups, respectively, $P = 0.43$, while hypervascularity was noted in 47.6% and 50.0%, respectively, $P = 0.86$. Finally, during operative hysteroscopy, surgeon's impression of the material was the only significant variable in the groups; 98.8% of true histological RPOC were identified as such, as compared to 7.6% of material negative for trophoblastic tissue, $P < 0.001$.

Table 1. Demographic characteristics of study participants

	Positive histology group N=178	Negative histology group n=26	P value
Age, years, mean \pm SD	30.5 \pm 5.6	31.2 \pm 7.1	0.98
Gravidity, median (range)	3 (1–10)	2 (1–8)	0.25
Parity, median (range)	2 (0–7)	1 (0–5)	0.09
Previous cesarean delivery, n (%)	21/175 (12.0%)	2/25 (8.0%)	0.74
Previous history of RPOC, n (%)	6 (3.3%)	1 (4.0%)	> 0.99
Time from abortion/delivery, weeks, mean \pm SD	7.5 \pm 3.4	7.8 \pm 3.2	0.65

Data are presented as mean \pm standard deviation, median (range), or number (rate) as appropriate

RPOC = retained products of conception, SD = standard deviation

Table 2. Delivery/abortion characteristics of study participants

	Positive histology group N=178	Negative histology group n=26	P value
Deliveries	N=85	N=10	
Gestational age at delivery, weeks, mean ± SD	38.8 ± 2.8	37.1 ± 4.5	0.19
Multiple gestation, n (%)	7 (8.2%)	1 (10.0%)	> 0.99
Vaginal delivery, n (%)	73/84 (86.9%)	6 (60.0%)	0.05
Cesarean delivery, n (%)	11/84 (13.0%)	4 (40.0%)	0.05
Manual removal of the placenta/revision of uterine cavity at vaginal delivery, n (%)	30 (41.1%)	3 (50.0%)	0.69
Postpartum hemorrhage, n (%)	23 (27.0%)	2 (20.0%)	> 0.99
Abortions	N=93	N=16	
Gestational age at abortion, weeks, mean ± SD	10.0 ± 4.3	11.2 ± 5.0	0.46
Termination pregnancy: medical, n (%)	17/91 (18.6%)	4 (25.0%)	0.51
Termination of pregnancy: surgical, n (%)	25/91 (27.4%)	4 (25.0%)	> 0.99
Missed abortion: medical treatment, n (%)	35/91 (38.4%)	5 (31.2%)	0.78
Missed abortion: surgical treatment, n (%)	14/91 (15.3%)	2 (12.5%)	> 0.99
Spontaneous abortion: complete, n (%)	1/91 (6.2%)	0 (0%)	0.14

Data are presented as mean ± standard deviation, median (range), or number (rate) as appropriate

SD = standard deviation

Table 3. Clinical presentation, sonographic findings and surgical course of study participants

	Positive histology group n=178	Negative histology group n=26	P value
Symptoms and diagnosis			
Vaginal bleeding, n (%)	115/159 (72.3%)	15/21 (71.4%)	> 0.99
Signs of infection: fever/uterine tenderness, n (%)	3/160 (1.8%)	1/21 (4.7%)	0.39
Diagnosis at routine postpartum visit, n (%)	128/150 (85.3%)	18/22 (81.8%)	0.74
Sonographic findings			
Maximal endometrial thickness on ultrasound (mm), mean ± SD	20.8 ± 10.3	20.0 ± 15.4	0.80
Irregular shape on ultrasound, n (%)	82/108 (75.9%)	10/15 (66.6%)	0.43
Increased flow (hypervascularity) on ultrasound, n (%)	50/105 (47.6%)	7/14 (50.0%)	0.86
Surgical course			
*Surgeon correct identification, n (%)	176 (98.8%)	2 (7.6%)	< 0.001
Size of suspected RPOC (mm), mean ± SD	17.5 ± 7.5	14.0 ± 5.5	0.07

Data are presented as mean ± standard deviation, median (range), or number (rate) as appropriate

*In cases of positive histology: surgeons described material as compatible with RPOC. In cases of negative histology: surgeons described material as non-compatible with RPOC

RPOC = retained products of conception, SD = standard deviation

DISCUSSION

The aim of our study was to examine the correlation between different clinical, sonographic, and intra-procedural parameters of suspected RPOC, as well as the histological presence of trophoblastic material obtained during operative hysteroscopy. Our findings demonstrate that no clinical, sonographic, or intra-procedural variables accurately predicted the presence of true RPOC.

A number of past studies have attempted to correlate clinical and sonographic parameters with a positive histology of trophoblastic tissue. In the studies of these samples obtained during curettage for suspected RPOC, 41% were verified as true trophoblastic tissue [12]. Variables that correlated with a positive histology included advanced gestational age at initial curettage, experience of sonographic examiner, sonographic suspicion of RPOC, and symptoms of continuous vaginal bleeding. Ben-Ami and colleagues [13] compared the positive predictive value of a clinical, sonographic, or combined (clinical and sonographic) diagnosis of suspected RPOC. In cases of a combined diagnosis, 87.5% were verified as trophoblastic material on histological examination, compared to 45% of cases diagnosed solely by ultrasound. This improved sensitivity realized by combining clinical and sonographic parameters was later reaffirmed in additional research [5,14]. Finally, Levin and co-authors [11] examined the correlation between histologic results of material removed during hysteroscopy for suspected RPOC and clinical, sonographic, and intraoperative parameters. The only parameter proven to correlate to true trophoblastic material was the surgeon's impression of the material during the procedure.

The natural history for a substantial number of cases suspected as RPOC on ultrasound is resolution with no need for treatment. Hence, an approach of watchful waiting is often warranted in non-symptomatic cases [15], as dependent on time passed from delivery or abortion and patient symptoms. In addition, some cases respond favorably to medical treatment with subsequent sonographic follow-up [16]. Accordingly, patients in our study represented the final step in a process of selection of patients who necessitated surgical intervention, which may confer a form of selection bias. This finding is evident because the majority of our patients are symptomatic. It is possible that in a prospective design, in which more asymptomatic patients would undergo hysteroscopy, clinical symptoms and even sonographic findings would better correlate with histopathology.

An additional limitation of our study is the lack of a uniform assessment process. Different sonographic parameters have been studied as predictive tools for RPOC, including endometrial thickness, endometrial irregularity, endometrial mass, and vascularity [17,18]. The positive predictive values of these different screening parameters vary among studies, and may also relate to the experience of the examiner.

The patients in our study did not necessarily undergo a sonographic examination at our institution, and data regarding all aforementioned sonographic variables was not available for all patients. Finally, the study is limited by its retrospective nature. For example, data regarding previous medical treatment for suspected RPOC prior to referral for hysteroscopy is missing. This omission may affect the interpretation of our results. Nevertheless, most of our findings are in agreement with previous studies [11].

Our study is notable for several strengths. It is one of the few large series to report the correlation between clinical and sonographic parameters and histopathological findings. In addition, our series includes solely cases treated with hysteroscopy, now the mainstay of treatment for RPOC in many centers. The correlation between intraoperative findings (surgeon's impression of material and size) and histopathology may serve to show the necessity of diagnostic hysteroscopies. In our study, surgeons described most material visualized as retained trophoblastic tissue, both in cases with an eventual positive and with negative histology, thus possibly suggesting that an initial non-interventional procedure may not contribute to patient selection.

CONCLUSIONS

This retrospective study suggests that no clinical, sonographic, or intraoperative variable correlates well with the presence of true trophoblastic tissue in cases of suspected RPOC. It would thus seem warranted to proceed with hysteroscopy in suspected cases after an initial period of evaluation, which most probably does affect fertility outcomes [19]. Further research is needed to reaffirm our findings, preferably in a well-controlled prospective study design, to allow for a management algorithm.

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"A person who won't read has no advantage over one who can't read"

Mark Twain, (1835–1910), American humorist, writer

"Anyone who has lost track of time when using a computer knows the propensity to dream, the urge to make dreams come true and the tendency to miss lunch"

Tim Berners-Lee, (born 1955), also known as TimBL, English engineer and computer scientist, best known as the inventor of the World Wide Web.