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1 Operative hysteroscopy for retained products of conception: Efficacy and subsequent fertility.

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30 Running headline: Operative hysteroscopy for RPOC

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32 Conflict of interest: None

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34

35 ABSTRACT

36

37 Retained product of conception complicates nearly 1% of pregnancies and can lead to
38 synechiae and compromise uterine fertility. The aim of this study is to evaluate efficiency of
39 operative hysteroscopy in management of retained products of conception (RPOC).
40 Secondary objectives are assessments of intra-uterine adhesions rate and later fertility.

41 This unicentric retrospective study includes women who undertook an operative hysteroscopy
42 for retained products of conception between January 2012 and March 2014. Assessment of
43 the efficiency of operative hysteroscopy is defined by a complete resection of retained
44 products of conception confirmed by office hysteroscopy.

45 One hundred fourteen women were included in the study. Efficiency of operative
46 hysteroscopy for retained products of conception is 91 % for women with a postoperative
47 office hysteroscopy. The authors observed a 7.5% rate of postoperative intra-uterine
48 adhesions. Fertility rate was 83 % (30 women out of 36 with a desired pregnancy).

49 Hysteroscopic resection of retained products of conception is an efficient procedure and
50 seems to be a real alternative.

51

52 Key Words:

53 Hysteroscopy; Retained product of conception; intra-uterine adhesions; Fertility; Placental
54 retention; Trophoblastic retention

55

56

57 Key Message:

58 Hysteroscopic resection of retained products of conception is an efficient procedure and
59 should be proposed as an alternative to dilatation and evacuation.

60 Introduction

61 Retained product of conception (RPOC) is defined by abnormal trophoblastic
62 persistence or retained placenta inside the uterus cavity after a pregnancy independently of the
63 outcome. It complicates around 6% of pregnancy (1) whether it is a miscarriage, a late fetal
64 loss, a medical pregnancy termination, a voluntary pregnancy interruption, a normal delivery
65 or a caesarean section (2).

66 RPOC is mostly symptomatic (menstrual disorders, pain, fever, amenorrhea) but can
67 also be fortuitously discovered throughout exploration of late fetal loss or repeated
68 miscarriage. Untreated RPOC can compromise future fertility (3).

69 Surgical management is the treatment of reference by uterine curettage which removes
70 residual trophoblastic tissue inside the uterine cavity after cervical dilatation (4). However,
71 this treatment leads to a high level of intra-uterine adhesions (10 to 40% depending on
72 studies(5-8)risk of incomplete resection (6) and uterine perforation. In case of incomplete
73 removal of RPOC, a second procedure is needed, increasing the risk of complexe intra-uterine
74 adhesions, such as Asherman's syndrome (9). A postoperative office hysteroscopy is
75 therefore recommended by French guidelines (10)

76

77 Operative hysteroscopy is therefore an alternative to uterine curettage which display
78 the advantage of a "visual control", leading to higher level of complete treatment, a reduction
79 of second procedure rate and a decrease of postoperative intra-uterine adhesions by limitation
80 of the operative field (5, 11).

81 Aim of this study is to evaluate efficiency of operative hysteroscopy in RPOC.
82 Secondary objectives include rate of intra-uterine adhesions, rate of subsequent pregnancy
83 and time delay to pregnancy.

84

85 Methods

86 This retrospective unicentric study was performed in the gynaecologic unit of a
87 teaching hospital. Women who underwent operative hysteroscopy for RPOC between January
88 2012 and March 2014 were included. Excluding criteria stand in performing both curettage
89 and operative hysteroscopy during the same procedure.

90 Primary objective was assessment of efficiency of operative hysteroscopy defined by
91 diagnosis hysteroscopy confirming complete treatment and secondary objective was intra-
92 uterine adhesion rate and pregnancy rate after surgical procedure.

93 Diagnosis of RPOC was assessed by clinical examination, pelvic sonography and
94 office hysteroscopy after a minimum period of 45 days (1, 3). Operative hysteroscopies were
95 performed in operative rooms under locoregional or general anaesthesia. Women were in
96 gynaecologic position and procedure was carried out after cervical dilatation using Hegar's
97 candle, two Pozzi tenaculum and a speculum. A 9 mm resectoscope was employed and
98 resection was realized as often as possible without energy in order to preserve endometrium
99 and limit intrauterine adhesions. When energy was necessary, bipolar energy was used.
100 Preferential distending medium used was physiological serum with a pressure between 70 and
101 150 mmHg. Pathological examination of resected tissue was fulfilled.

102 Postoperative office hysteroscopy was systematically prescribed 4 to 8 weeks
103 following surgical procedure, which confirmed complete treatment and absence of intra-
104 uterine adhesions. When office hysteroscopy concludes to abnormality (persistent
105 trophoblastic retention or intra-uterine adhesions), a second operative procedure was
106 performed. In these cases, March criteria were applied.

107 A distant phone survey was then performed to obtain information about subsequent
108 pregnancy. Women were informed about the study by both a postal letter and a phone call in
109 which patient's consent was accounted for. An ethical committee approbation was obtained:
110 CEROG 2014-GYN-0208. Statistical analysis was performed using STATA software

111 (STATA/SE 10.0, Stata Press, 204 Zachry Engineering center College Station, TX, 77843,
112 USA). Results are reported as percentage and mean with 95% confidence interval [IC95%].
113

114 Results

115 One hundred fourteen (114) women undertook operative hysteroscopy for RPOC
116 during the study period and were therefore included in the study. Mean age was 33.5 [31.7-
117 35.2] years old with a rate of previous pregnancy of 2.82 [2.50-3.16] and previous deliveries
118 of 1.41 [1.14-1.68]. Preoperative sonography and office hysteroscopy identified mean size of
119 RPOC of 22 [19-25] mm. Mean times from end of the pregnancy to operative hysteroscopy
120 was 109 [70-149] days. These results are presented in Table 1.

121 RPOC were revealed in most of cases by abnormal bleeding (76% of cases); others
122 symptoms included amenorrhea, pain, infectious (endometritis) or others. These results are
123 presented in Figure 1. Diagnosis was confirmed by pathological exam in 100 women out of
124 103 (97%). Myoma was differential diagnosis for the 3 other women. For 11 women, there
125 was no pathological exam (9.7%).

126 RPOC occurred mostly after medical therapy for first trimester miscarriage (23%) and
127 vaginal birth delivery (17%), as they are the most frequent providers. These results are
128 reported in Figure 2.

129 Twenty-nine women (25.4%) were excluded: 3 because of a misdiagnosis (myoma
130 instead of RPOC) and 26 were lost to follow-up and did not honour their appointment for
131 postoperative office hysteroscopy. Thirty-two women out of the 85 others did not have office
132 hysteroscopy. There was no significant difference for age, size of the retention, time until
133 diagnosis of retention and achieving of pregnancy between women who honor their
134 appointment for diagnosis hysteroscopy and the ones who didn't. Fifty-three (46.5%) women
135 had a postoperative office hysteroscopy and 5 of them showed persistent RPOC (9%).
136 Operative hysteroscopy then totally removed RPOC in 91% of cases of women with a
137 diagnosis hysteroscopy. These results are presented in the flow chart in Figure 3.

138 Out of the 53 women who had office hysteroscopy, 4 (7.5%) women presented
139 synechiae. Three of them were type 1 synechiae according to March's criteria described as
140 velamentous and one of them had complex isthmic synechiae (type 2 of March criteria).

141 For subsequent fertility, 36 women out of 84 (42.9%) desired another pregnancy.
142 Thirty of them obtained a pregnancy (83%) in a mean time of 224 [121-322] days. Pregnancy
143 outcomes are 17 vaginal birth deliveries (57%), 8 caesarean section (27%) and 5 miscarriages
144 (17%). For the 6 women with a pregnancy desire who did not achieve pregnancy, the follow-
145 up time was shorter than a year.

146 There was no significant difference in the issue or pregnancy between the women who
147 had the office hysteroscopy control and the ones who did not have it. The rate of miscarriage
148 was 12.5% (2/16) in women who didn't attempt the postoperative hysteroscopy. There was no
149 placentation abnormality in the reported pregnancy.

150

151

152 Discussion

153

154 Operative hysteroscopy seems like a valid alternative for the management of RPOC.
155 Efficiency in this study is 91% in women with a diagnosis hysteroscopy and led to few
156 complications such as intra-uterine adhesions (7,5%). Subsequent pregnancy rate is 83% of
157 women with a pregnancy desire in a short mean time (around 8 months).

158 Published studies about operative hysteroscopy for RPOC show similar results with a
159 success rate around 95% (4, 12-14). Golan et al. reported 159 women with a 100% rate of
160 normal menses after hysteroscopy procedure but in this study only 21 women (13%) had a
161 postoperative office hysteroscopy (normal in 100% of cases)(13). Goldenberg et al. also
162 published a 100% success rate of office hysteroscopy for RPOC in 18 women(14). On the

163 opposite, Hrazdirova et al. found that a second operative procedure was necessary for 64,4%
164 of the 45 women included (15).

165 For subsequent fertility, published studies also found that operative hysteroscopy led higher
166 rate of spontaneous pregnancy (69 to 92%) within a short mean time of conception (6) .
167 Golan et al. reported a 82% rate of pregnancy in 28 women with a 75% rate of “take home
168 baby”(13). Cohen et al. also reported a 82% rate of pregnancy (5). These results are reported
169 in Table 2.

170 As previously mention, gold standard for RPOC is currently uterine curettage
171 nevermind higher risk of complications such as intra-uterine adhesions and endometritis
172 mainly. Two studies compared operative hysteroscopy to uterine curettage and reported a
173 longer mean time for pregnancy after uterine curettage; 12.9 versus 7.4 months for Ben-Ami
174 et al. and 11 months versus 7.3 months for Cohen et al.(5, 16). The present study reported the
175 same mean time for subsequent pregnancy after operative hysteroscopy.

176 Rate of intra-uterine adhesions after uterine curettage has been evaluated from 17 to 30% (6).
177 It increases with the number of previous curettage. Friedler and al. found a 16.3% synechiae
178 rate after a single curettage. This rate increases up to 32% after three procedures (including
179 more than 50% of complex synechiae) (9). Romer et al. also reported a high rate of intra-
180 uterine adhesions after multiple procedures (47.6%) (17). In a literature review, a rate of
181 22.4% of intra-uterine synechiae was reported significantly different after dilatation –curetage
182 (30%) compared to operative hysteroscopy (13%) (6). The rate of intra-uterine adhesions is
183 lower in the presented study. However, the risk of intra-uterine adhesions is real and probably
184 justifies indication of office hysteroscopy 4 to 6 weeks after operative hysteroscopy to
185 diagnosed and managed these intra-uterine adhesions. However, when an office hysteroscopy
186 is proposed, like in the presented study, the rate of 38% of women who did not honour their
187 appointment out of the lost to follow-up women. This rate is high even if it is lower than the

188 49.7% rate reported in another study (18) and might be the result of an apprehension of
189 women about office hysteroscopy.

190

191 Rein et al. compared dilatation curettage to hysteroscopic resection for residual
192 trophoblastic tissue in two centres, which evaluated intrauterine adhesions rate. Hysteroscopic
193 led to significantly less intrauterine adhesions (4.2%) compared to curettage (30.8%). Rate of
194 conception was also improved after hysteroscopic resection (68.8% versus 59.9%) and lower
195 mean time to obtain pregnancy (11.5 months versus 14.5 months)(11). Operative
196 hysteroscopy seems to reduce rate of intra-uterine adhesions. However there is no prospective
197 comparative study between office hysteroscopy and uterine curettage. Published synechiae
198 rate after office hysteroscopy for RPOC are from 0 to 9.1%. Faivre et al. reported a 9%
199 synechiae rate (2 women out of the 22 with office hysteroscopy)(12). This rate is similar to
200 the one reported in this study.

201 Another important argument in favour of operative hysteroscopy to treat RPOC is
202 peroperative finding of uterine malformation. In this study, no uterine malformation was
203 reported but Faivre et al. reported a 10% uterine malformation rate discovered during
204 procedure in their series (12). A uterine septum should even be treated during the same
205 procedure.

206 Strength of this study is its size with only one other study with a higher number of
207 women with a postoperative office hysteroscopy and a systematic review that includes more
208 women but with more heterogeneity compared to a unique center study (6, 18)
209 (REF). There is however limits to this study; first of all, the retrospective character of the
210 study but also the absence of comparative group with uterine curettage. A prospective
211 randomized trial is performed and should allow definitive conclusions about the interest of
212 operative hysteroscopy for RPOC (19) .

213

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Figure 1 : Warning symptoms

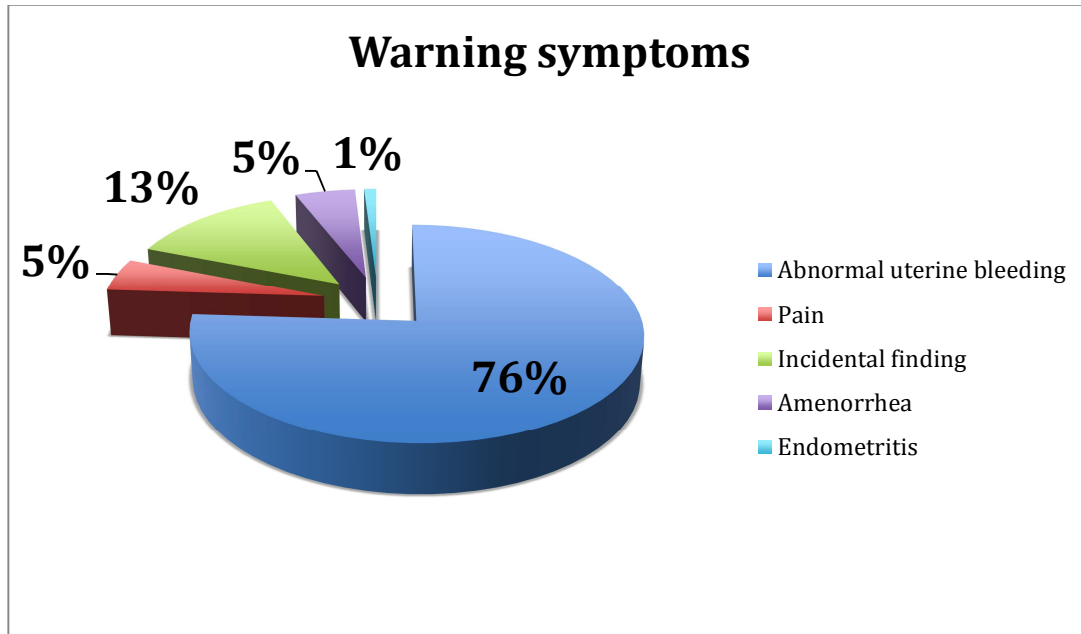


Figure 2: Etiology of retained product of conception

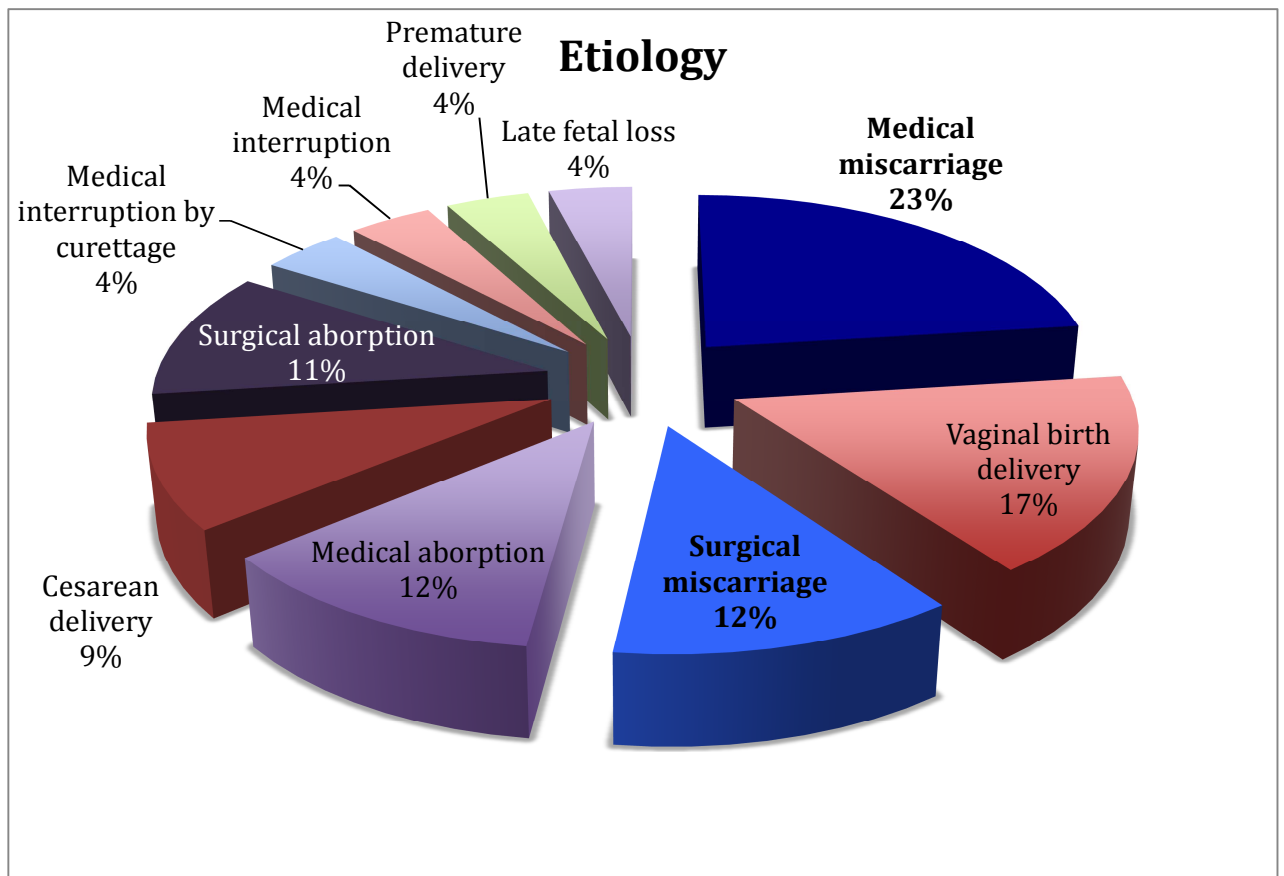


Figure 3 : Flow chart

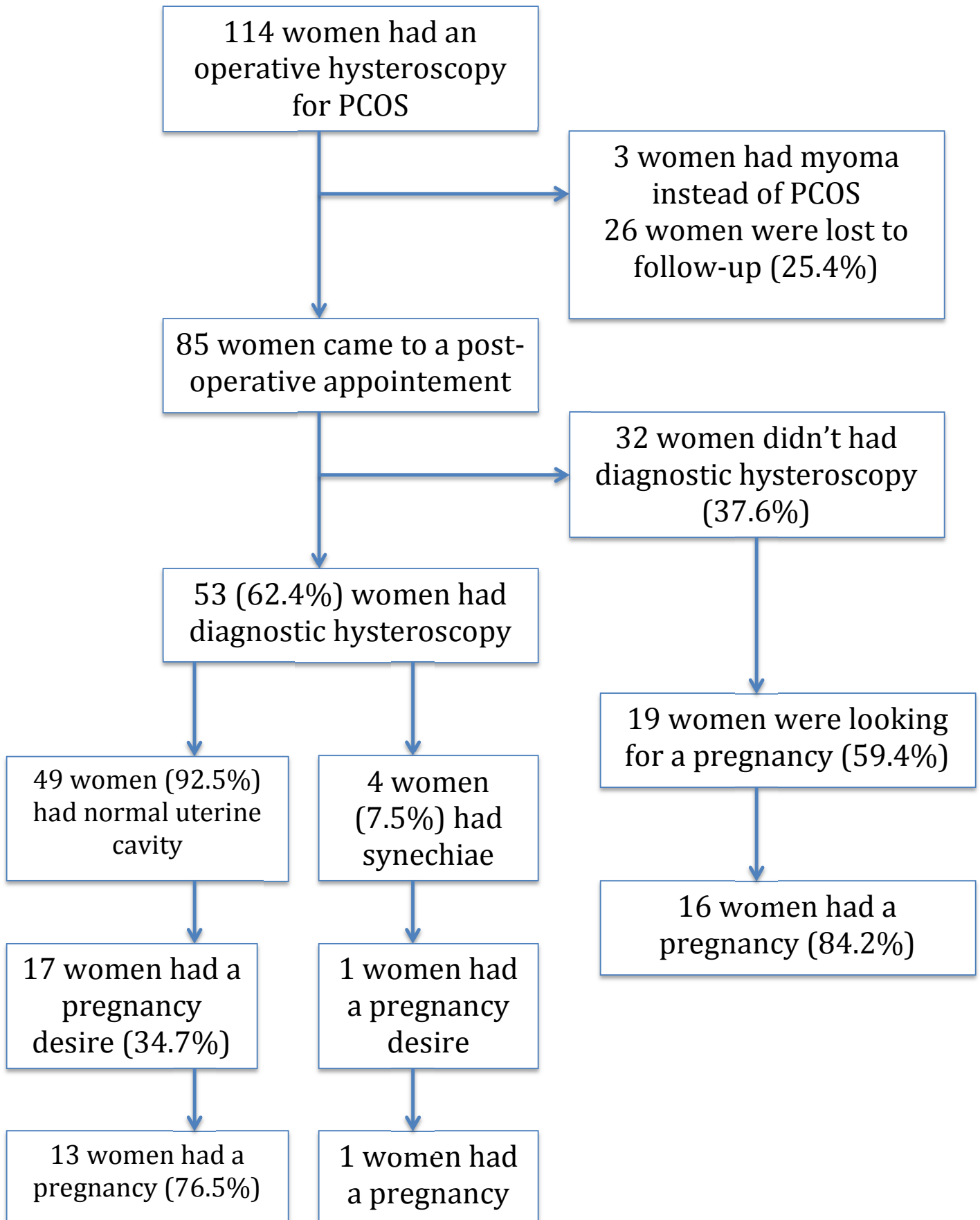


Table 1: Pre and post-operative characteristics

Preoperative characteristics (n=114)	Mean	IC 95%
Age(years)	33.5	31.7-35.2
Number of previous pregnancy	2.82	2.50-3.16
Number of previous delivery	1.41	1.14-1.68
Time between end of the pregnancy and operative hysteroscopy (days)	109	70-149
Size of the retained product of conception (RPOC) (mm)	22	19-25

Post-operative characteristics (n=85)	N	Rate
Complete removal of RPOC	80	94.1%
Postoperative office hysteroscopy	53	46.5%

Table 2 : Comparison with published results

	n	Efficacy	Pregnancy deisre	Pregnancy rate	Mean time	Office hysteroscopy	Synechia
Goldenberg <i>et al.</i> 1997	18	100%	-	-	-	5 (27.8%)	0 (0%)
Cohen <i>et al.</i> 2001	46	100%	17	14 (82%)	7.3 +/- 6.7		
Faivre <i>et al.</i> 2009	50	98%	30	23 (77%)	-	22 (44%)	2 (9.1%)
Golan <i>et al.</i> 2011	159	100%	28	23 (82%)		21 (13,2%)	0 (0%)
Rein <i>et al.</i> 2011	53	100%	45	31 (69%)	27 months [7-39]	48 (90.6%)	2 (4.2%)
Presented study	114	94,1%	36	30 (83%)	7.3 months [4.0-10.6]	53 (46.5%)	4 (7.5%)