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REPRODUCTIVE AND OBSTETRIC OUTCOME AFTER HYSTEROSCOPIC REMOVAL OF RETAINED PRODUCTS OF CONCEPTION

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Masterproef voorgedragen in de master in de specialistische geneeskunde gynaecologie-verloskunde

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List of abbreviations

AFS	American Fertility Society
ART	assisted reproductive technology
BMI	body mass index
CI	confidence interval
CMV	cytomegalovirus
D&C	dilation and curettage
ESH	European Society for Hysteroscopy
HM	hysteroscopic morcellation
ICSI	intracytoplasmic sperm injection
IUA	intrauterine adhesions
IUGR	intrauterine growth restriction
IUI	intrauterine insemination
IVF	in vitro fertilization
IQR	interquartile range
LR	loop resection
MPR	manual placenta removal
PPROM	preterm premature rupture of membranes
RCT	randomized controlled trial
RPOC	retained products of conception
SD	standard deviation
US	ultrasonography

1. Abstract

Objective

To conduct a follow-up study considering the reproductive and obstetric outcome in a cohort treated for retained products of conception (RPOC) by hysteroscopy (loop resection (LR) versus hysteroscopic morcellation (HM)).

Methods

The patients included in a previous randomized controlled trial (RCT), comparing LR (n = 40) with HM (n = 46) for the removal of RPOC, were reviewed for reproductive and obstetric outcome. The primary outcome measures were live birth and pregnancy complications, subdivided into uterine rupture, abnormal placentation (including placenta accreta/increta/percreta, placenta previa, vasa previa, retained placenta after delivery or incomplete expulsion with the need for manual removal or curettage, and RPOC six weeks after the delivery or expulsion) and other complications (blood loss in the first, second and/or third trimester, preterm labor, preterm premature rupture of membranes (PPROM), hypertensive disorder of pregnancy or intrauterine growth restriction (IUGR)). The secondary outcome measure was time to pregnancy.

Results

The response rate was 75% (30/40) for the LR group and 84.8% (39/46) for the HM group (p = 0.07). The median follow-up was four years (interquartile range (IQR) 4 – 6) in the HM group and five years (IQR 4 -5) in the LR group (p = 0.90). 71% (49/69) wished to conceive. In the intention-to-treat analysis, live birth for morcellation, 88.9% (24/27), and for LR, 68.2% (15/22), was not statistically different (p = 0.09). Uterine rupture occurred only in the morcellation group in 4.2% (1/24). This was a patient with a hemi-uterus in whom perforation occurred during dilation (p = 1.00). Placental complications were found in 20.8% (5/24) and 22.2% (4/18) (p = 0.33), and other pregnancy complications in 33.3% (8/24) and 16.6% (3/18) (p = 0.33) for respectively HM and LR. The median time to pregnancy was 14 weeks (IQR 5 – 33) in the morcellation group and 15 weeks (IQR 6 – 37) in the LR group (p = 0.96).

Conclusions

Hysteroscopic resection of RPOC, using LR or morcellation, seems to have no detrimental effect on reproductive outcome. The pregnancy rates are comparable but a trend towards more live births is seen in the morcellation group.

2. Introduction

2.1 Retained products of conception

Retained products of conception (RPOC) consist of intrauterine tissue that develops after conception and persists after miscarriage, termination of pregnancy, delivery or caesarean section (1). Histologic examination of the tissue shows non-villous trophoblast, chorionic villi and/or fetal membranes. The presence of decidua alone is not considered sufficient evidence of RPOC (2). Nevertheless, there is no general consensus on the histologic definition.

RPOC is a common problem after pregnancy. Depending on pregnancy duration, pregnancy outcome, and management thereafter the prevalence ranges from 0.5% to much as 19% (3).

The existence of RPOC may be suspected based on clinical **symptoms** such as abnormal bleeding, abdominal pain and/or fever. RPOC is one of the most common causes of both primary or secondary postpartum hemorrhage (1). However, RPOC may also be present in asymptomatic patients (4).

Diagnosis of RPOC relies on a combination of clinical symptoms and signs, physical examination, sonographic assessment and/or diagnostic hysteroscopy (5). Transvaginal Doppler ultrasonography (US) is more sensitive in identifying women suspected to have RPOC as compared with clinical estimation (table 1). On the other hand, the clinical estimation demonstrates a higher specificity and positive predictive value for sonographic evaluation. Furthermore, women in whom there is combined sonographic and clinical suspicion of RPOC are more likely to having such tissue as compared to those who only have clinical or sonographic suspicion. With combined sonographic and clinical suspicion of RPOC there was 87.5% confirmation by histological examination, a significantly higher rate compared to ultrasonographic (45.5%, $p < 0.002$) or clinical suspicion only (62.5%, $p = 0.07$) (6).

	Sonographic evaluation	Clinical estimation	*P*
Sensitivity	34/39 (87.2)	19/39 (48.7)	<0.05
Specifity	3/29 (10.3)	24/29 (82.8)	<0.01
Positive predictive value	34/60 (56.7)	19/24 (79.2)	<0.05
Negative predictive value	3/8 (37.5)	24/44 (54.5)	NS
Diagnostic accuracy	37/68 (54.4)	43/68 (63.2)	NS

Values in parentheses are percentages.
NS = non-significant.

Table 1: Comparison between sonographic and clinical evaluation regarding RPOC as confirmed by histological examination *(6)*

An ultrasonographic finding suggestive for RPOC is a thickened endometrium or intrauterine mass. Cut off values of the endometrium thickness ranges between eight and 13mm (1,2,7). The occurrence of a thickened endometrium together with an echogenic mass predicts the presence of RPOC with higher probability (2). However, there is no consensus on US criteria for RPOC. Addition of color or power Doppler to detect vascularity may contribute to the diagnosis. Both the sensitivity and positive predictive value increase with addition of Doppler US (1,8–10).

The **management** of women suspected of RPOC is challenging because there are no clearly defined diagnostic criteria, evidence-based guidelines, or treatment protocols. Hence, there is no gold standard for treatment of RPOC. Options for treatment are expectant management, medical or surgical treatment. Surgical treatment options are dilation and curettage (D&C) and hysteroscopic resection. Traditionally D&C using vacuum aspiration and/or a metal curette is used for removal of RPOC. Hence, this blind removal of tissue can cause destruction or damage to healthy surrounding tissue (11). Long-term complications of this damage include formation of intrauterine adhesions (IUA) (12–14). Many classifications of IUAs are suggested. A classification is essential in order to describe severity and extend of the IUAs. The European Society for Hysteroscopy made a classification based on hysteroscopic findings (figure 1). The American Fertility Society (AFS) classification correlates the menstrual history with hysteroscopic and hysterosalpingography findings (figure 2)(15).

Grade	Extent of intrauterine adhesions
I	Thin or filmy adhesions Easily ruptured by hysteroscope sheath alone Cornual areas normal
II	Singular firm adhesions Connecting separate parts of the uterine cavity Visualization of both tubal ostia possible Cannot be ruptured by hysteroscope sheat alone
IIa	Occluding adhesions only in the region of the internal cervical os Upper uterine cavity normal
III	Multiple firm adhesions Connecting separate parts of the uterine cavity Unilateral obliteration of ostial areas of the tubes
IIIa	Extensive scarring of the uterine cavity with amenorrhea or hypomenorrhea
IIIb	Combination of III and IIIA
IV	Extensive firm adhesions with agglutination of uterine walls at least both tubal ostial areas occluded

Figure 1: Classification of IUA according to the European Society for Hysteroscopy (15)

	Characteristics		
Extent of cavity involved	<1/3	<1/3–2/3	>2/3
	1	2	4
Type of adhesions	Filmy	Filmy and dense	Dense
	1	2	4
Menstrual pattern	Normal	Hypomenorrhoea	Amenorrhoea
	0	2	4
Prognostic classification		HSG score[a]	Hysteroscopy score
Stage I (mild)	1–4	–[b]	–[b]
Stage II (Moderate)	5–8	–[b]	–[b]
Stage III (severe)	9–12	–[b]	–[b]

[a] All adhesion should be considered dense.
[b] Additional findings

Figure 2: American Fertility Society classification of IUA (15)

IUAs may significantly affect future reproductive outcomes due to subfertility, repeated pregnancy loss and pregnancy complications such as placenta accreta (16). Operative

hysteroscopy is a suitable alternative for the treatment of RPOC (17). Operative hysteroscopy is considered to be safe, with low complication rates ranging from 0.76 to 0.95%, depending on the uterine pathology treated, the procedure performed and the patient characteristics. In retrospective studies hysteroscopic removal of RPOC is favored over D&C (3).

The major advantage of hysteroscopic removal is the possibility to selectively resect RPOC under direct visualization without affecting the adjacent endometrium and so reducing the risk of IUA formation. Additionally, rates of complete removal and histologic confirmation are high. Both hysteroscopic resection and morcellation have been described for hysteroscopic removal of RPOC (3). With hysteroscopic resection the cold loop technique can be used. The loop electrode of the resectoscope is used as a curette without applying electrical current (figure 3). The hysteroscopic morcellator (figure 4) on the other hand consists of a set of two hollow tubes with each a window-opening lateral at the end with cutting edges The two tubes fit into each other and rotates within each other. By means of a vacuum source connected to the inner tube, the tissue can be sucked into the window opening and cut and shaved as the inner tube is rotated. When the rotation is not activated, the window opening is closed to prevent suction of the distension fluid and uterine cavity collapse and perforation (18).


Figure 3: resectoscope


Figure 4: hysteroscopic morcellator (18)

A recent randomized controlled trial from our study group comparing HM with hysteroscopic LR for RPOC shows that both techniques are safe, show high rates of complete removal and tissue availability and low rates of de novo IUAs. According to this study, HM is a faster alternative compared to LR (11).

Both the presence and the treatment of RPOC may influence fertility and obstetric outcome. However, the evidence is limited and is mainly based on observational studies.

2.2 Influence of RPOC on reproductive and obstetric outcome

Only one study reports the influence of RPOC itself on reproductive and obstetrical outcome. In a retrospective study of **Ben Ami** et al. 368 women were admitted due to suspected RPOC (19) (Appendix 1). All of them underwent surgical management, either with D&C or hysteroscopic resection. In 244 patients (66.3%) the diagnosis of RPOC was confirmed by histological examination. After exclusion of four patients because of lost to follow up or refusing for further participation, reproductive outcomes were analyzed in 240 patients (65.2%). 162 of them (67.5%) had positive pathologic findings. The conception rate after the procedure was significantly higher among women with negative pathologic findings compared with pathologically confirmed RPOC (71.8% versus 55.6%, respectively, $p = 0.017$). Moreover, the mean time to conception was significantly shorter among women with negative pathologic findings compared with pathologically confirmed RPOC (3.3 months SD 5.5 versus 10.6 months SD 13.7 months, respectively, $p < 0.001$). Furthermore, the rate of a new subfertility problem was significantly higher in women with pathologically confirmed RPOC compared to those with negative findings (26.7% versus 11.9%, $p = 0.029$). The definition of 'new subfertility problem' is not given. The main conclusion of this study was that RPOC associated subfertility is primarily related to the presence of trophoblastic tissue rather than the surgical intervention per se in the gravid uterus. In that context, hypomenorrhea was more prevalent in women with pathologically confirmed RPOC compared to those with negative findings. It is suggested that the presence of residual trophoblastic tissue may contribute to the formation of IUA, which are clinically manifested both by subfertility and hypomenorrhea.

2.3 Influence of (operative) hysteroscopy on reproductive and obstetric outcome

Hysteroscopy, with or without surgical removal of intrauterine structures, is increasingly used during subfertility workup (20). A Cochrane review concluded that a large benefit with the hysteroscopic removal of submucous fibroids for improving the chance of clinical pregnancy in women with otherwise unexplained subfertility cannot be excluded. Endometrial polyps suspected on US treated with hysteroscopic resection in women prior to intrauterine insemination (IUI) may increase the clinical pregnancy rate. However, more randomized studies are needed to substantiate the effectiveness of the hysteroscopic removal of suspected intrauterine pathology such as endometrial polyps, submucous fibroids, uterine septum or IUAs in women with unexplained subfertility or prior to IUI, in vitro fertilization (IVF) or

intracytoplasmic sperm injection (ICSI) (21). As noted before, operative hysteroscopy is considered to be safe, with low complication rates (22). Diagnostic hysteroscopic procedures have a significantly lower complication rate (0.13%) than operative procedures (rate 0.95%, $p < 0.01$). Uterine perforation is the most frequent complication in hysteroscopy (0.76%), and approximately half of the perforations are entry related.

However, most studies about operative hysteroscopy in relation to reproductive and pregnancy outcome are dated and focus on the reproductive and obstetrical outcome after metroplasty for uterine septum or operative hysteroscopy for other intrauterine structures than RPOC. Observational studies found a major benefit for removing a uterine septum by hysteroscopic metroplasty in subfertile women with a uterine septum (23–25).

2.4 Influence of the treatment of RPOC on reproductive and obstetric outcome

2.4.1 Influence on reproductive outcomes

2.4.1.1 Expectant management versus surgical treatment

Only one study compared reproductive outcome after expectant management versus surgical treatment for RPOC (26) (Appendix 2). In this study, RPOC after spontaneous first trimester miscarriage were analysed. Nine of twelve women (75%) with a future desire for pregnancy from the expectant group conceived within 6 months. Six of nine (66%) from the surgical group who attempted to conceive succeed (no significant difference, p-value was not reported). For both groups the median time for return to normal periods was 28 days.

2.4.1.2 Medical treatment

No studies were found reporting on the effect of medical treatment for RPOC on future reproductive outcome.

2.4.1.3 Curettage versus hysteroscopic resection of RPOC

Five studies compare reproductive outcomes after treatment of RPOC by D&C versus hysteroscopic removal (appendix 2)

The retrospective study of ***Cohen*** et al. compared 24 women who underwent D&C with 46 women who underwent hysteroscopic resection of RPOC (27). Both groups had similar reproductive outcome, with a trend to conceive earlier in the hysteroscopy group (a mean time to conception of 7.3 months after hysteroscopy versus 11.0 months after D&C ($p < 0.03$)).

However no difference in overall pregnancy rates was found. Spontaneous miscarriage was seen 30% versus 7.1% in the D&C group versus hysteroscopy group, live birth occurred in 70% and 71.4% respectively for both groups. Both results were not significant different.

In the observational study of ***Rein*** et al. 42 patients were treated with US-guided D&C with metal curette were compared to 53 patients treated with hysteroscopic resection using the cold loop technique (28). The follow up was at least 24 months (range 8-38 months). 82 patients wanted to become pregnant after the initial procedure. Conception rates were 68.8% in the hysteroscopy group and 59.9% in the D&C group ($p = 0.035$). In patients younger than 35 years of age who underwent hysteroscopic resection, the pregnancy rate was also significantly increased compared with patients who underwent D&C (78.1% vs 66.6%, $p = 0.028$). In addition, patients from the hysteroscopy group demonstrated a significantly shorter time to conception (27 months vs 34 months, $p=0.036$). First and second trimester spontaneous miscarriage occurred in respectively 6.9% and 3.4% in the hysteroscopy group versus 15% and 0% in the D&C group (respectively $p = 0.227$ and $p = 0.382$). The live birth was 57.8% in the hysteroscopy group, 45.9% in de D&C group (p-value not available).

A retrospective study of ***Ben Ami*** et al. compared 94 patients who underwent D&C with metal curette with 83 who underwent hysteroscopic resection (cold loop technique) of RPOC (29). The time for follow up is not reported. A significantly shorter time to subsequent conception was seen after hysteroscopic resection compared with D&C (mean time 7.4 ± 7 versus 12.9 ± 16.8 months, $p = 0.037$). Furthermore, the rate of occurrence of a new subfertility problem was significantly higher following D&C compared to hysteroscopic resection for RPOC (24.5% vs 12.0%, $p = 0.034$). Miscarriage occurred in 19.3% in the hysteroscopy group versus 11.7% in the D&C group (p-value is not reported). 80.7% of the hysteroscopy group delivered in future follow up versus 88.3% in the D&C group (p-value is also not reported).

Hooker et al. also compared reproductive outcome for both techniques (13). The technique for D&C was not described, for hysteroscopy the cold loop technique was used. 105 patients were included in the D&C group, 22 patients were treated with hysteroscopy. 56 patients were available for further follow up after at least one year. Of them 26 women tried to conceive. Five of these did not succeed, the other 21 women conceived spontaneously. The pregnancy rate in the curettage group was 80% (4 of 5) and the hysteroscopic group 75% (12 of 16), the

difference was not statistically significant (p = 0.62). Five (23.8%) had a spontaneous miscarriage in the first trimester. Term delivery occurred in 76.2% (16 of 21).

Reproductive outcomes of women treated for RPOC by hysteroscopy versus suction curettage were also retrospectively analyzes by ***Smorgick*** et al. (30). Information on subsequent pregnancies was available for 161 out of 441 patients (36.4%) . In 150 of them, one or more live births were reported (93.2%). Out of 27 women treated with suction curettage, 25 (92.6%) had 1 or more deliveries in subsequent pregnancies versus 125 out of 134 patients (93.3%) treated with operative hysteroscopy (p = 1.0). For spontaneous abortion the percentage was 19.4% in the suction curettage group versus 18.7% in the operative hysteroscopy group (p = 0.7).

Based on these five studies comparing hysteroscopic removal with D&C for treatment of RPOC, the mean time to conception appears shorter after hysteroscopic resection. Also, there is a lower rate of newly diagnosed subfertility problems with the hysteroscopic resection of RPOC compared to D&C. The odds for miscarriage and live birth are not significantly different between both techniques.

2.4.1.4 Hysteroscopic resection of RPOC

The influence of hysteroscopic resection of RPOC on reproductive outcome is reported in six studies (appendix 3).

In the retrospective study of ***Golan*** et al. the conception rate was 82% (23 of 28), with a live-birth rate of 75% (21 of 28) during follow up for at least three years after the operative hysteroscopy (cold loop technique) because of suspected RPOC (31).

The prospective study of ***Faivre*** et al. reports on the feasibility, efficiency, and reproductive outcomes of hysteroscopic resection of late residual trophoblastic tissue in 50 patients in an observational study (32). The hysteroscopic removal was performed with cold loop technique. When complete resection was difficult to obtain, electrical energy was secondarily applied. Fertility and pregnancy outcome was recorded among 39 patients who underwent hysteroscopy at least 12 months before the study. Three were lost to follow up. For the remaining 36 patients the median follow up was 43 (23-69) months. Thirty of them described a desire for pregnancy, and 23 became pregnant (pregnancy rate 76%). The live birth rate was 21/30 (70%). The conception rate was 88% (15/17) in patients aged ≤ 35 years compared with 66% (8/13) in patients > 35 years old.

In the study of ***Fuchs*** et al. women who underwent hysteroscopic treatment (with cold loop technique) because of RPOC were randomized to either have their uterine cavity filled with Oxiplex/AP gel (study group, n = 26) or not (control group, n = 26) in order to reduce IUA formation (33). Three patients were lost to follow up during a period of 20 months (range 3-41 months) and eight discontinued intervention in this time period. Finally, seven out of 21 patients in the study group compared to three out of 20 patients in the control group achieved pregnancy (p = 0.50).

In descriptive retrospective study of ***Jimenez*** et al., 84 women with suspected RPOC or placental polyp after pregnancy underwent hysteroscopic examination (34). Suspected tissue was removed with hysteroscopic biopsy forceps in the office under direct visualization of the uterine cavity, without anesthesia or cervical dilatation. The time for follow up was not reported. After the procedure, 30 women sought to conceive, and 24 (78.6%) of them were successful. Fifteen women had a full-term delivery (63.6%), four had an abortion (18.2%), and four are continuing pregnancy (18.2%). The average time to conception was 8.4 months (SD 7.1). Live birth rates were not reported.

A retrospective cohort study of ***Ikhena*** et al. included 111 patients who underwent hysteroscopic management for RPOC (35). Hysteroscopic resection was done by either hysteroscopic scissors and forceps (n = 43) or with bipolar resectoscope (n = 68). At time of surgery, the individual provider decided whether to use electrosurgery or not. Patients were followed for a minimum of 18 months (range not reported) after hysteroscopic removal of RPOC. Of these 111 patients, 55 conceived. The live birth rate was 69% (38/55).

Sonnier et al.'s retrospective cohort included 115 treated for RPOC by cold loop hysteroscopy (36). Among the 53 patients who were exposed to pregnancy, the conception rate was 71.1% (95% confidence intervals (CI) 58.1-82.9) at six months and 83.5% (95% CI 71.8-92.2) at one year. 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.

Overall the conception rate varies widely based on these six studies (24% to 82%). The chance for live birth vary between 63.3 to 75%.

2.4.2 IUAs after treatment of RPOC

Trauma to the basal layer of the gravid endometrium by curettage, local infection, or both may result in Asherman syndrome, which applies to partial or complete obliterations of the uterine cavity by IUA. IUAs can cause menstrual abnormalities, subfertility, repeated pregnancy loss and other pregnancy complications including miscarriage, abnormal placentation, fetal growth restriction, premature labor and delivery and postpartum hemorrhage (5).

As the endometrium depends on estrogen for regeneration, in the puerperal period (hypoestrogenic state) the uterus is more vulnerable for trauma which may engender adhesions of the myometrium at opposing walls of the uterus (5,15). Also trauma to a non-gravid uterus may result in occurrence of IUA (31). Ben Ami suggests that the presence of RPOC has an independent role in the contribution to the formation of IUA. RPOC may play a role in the pathogenesis in subfertility since hypomenorrhea was more prevalent in women with pathologically confirmed RPOC compared to those with negative findings (29).

Second-look hysteroscopy to assess for IUAs after treatment for RPOC was performed in eight studies. Hooker and Rein et al. compared curettage vs hysteroscopic removal of RPOC (appendix *) (13,37). The studies of Fuchs, Faivre, Golan, Barel, Dankert and Hamerlynck et al. were on hysteroscopic removal (appendix 3) (11,17,31,33,38,39).

Hooker et al. performed second-look hysteroscopy in 33% of their study population after initial removal of RPOC. They reported a non-significant difference ($p = 0.55$) with a lower percentage of IUAs in the curettage group, namely 19.6% versus 25.0% in the hysteroscopy group (13). ***Rein*** et al. found a significantly lower IUA rate three months after hysteroscopic removal compared to D&C (30.8% in the D&C group versus 4.2% in the hysteroscopy group, $p < 0.001$) (28).

Fuchs et al. performed a second-look hysteroscopy in all patients to assess for IUAs (33). Findings were graded according to the AFS. Three patients (14%) in the control group had moderate to severe IUAs compared to 1 woman (4%) in the group treated with Oxiplex gel ($p = 0.30$). Half (50.3%) of the patients treated for RPOC with operative hysteroscopy in the study of ***Barel*** et al. underwent follow-up hysteroscopy to assess for IUAs (39). Sixteen of 84 women (19.0%) had evidence of IUAs. Of those, using the modification described of the AFS classification for IUAs, ten (11.9%) were considered mild, three (3.6%) were moderate, and

three (3.6%) were severe. Age of the patient, gravidity, parity, time period from termination of pregnancy to surgery, use of electro-surgery, and positive pathology were not found to have statistical significance on the development of IUAs. RPOC occurring after cesarean delivery were significantly associated with IUA (p=0.028, 95% CI 0.003-0.713). In ***Faivres*** et al.'s study 44% underwent a second-look hysteroscopy after initial hysteroscopic removal of RPOC (32). Mild IUAs were found in two patients (9%), and adhesiolysis was immediately and easily performed with blunt hysteroscopic dissection. In the retrospective study of ***Dankert*** et al. Ten women underwent hysteroscopic visualization and resection of RPOC because of secondary postpartum hemorrhage (17). Nine of the ten patients underwent a second hysteroscopy. In all cases, the uterine cavity was without adhesions. In ***Golan*** et al.'s study all patients had hysteroscopic removal of RPOC (40). Second-look hysteroscopy was not performed routinely, nevertheless, 21 patients underwent second look hysteroscopy and no IUAs were demonstrated.

In the RCT of our study group, office second-look hysteroscopy was performed in 82% (68/83) of patients (11). Moderate de novo IUAs were seen in one of 35 patients (3%) in the HM group and de novo mild IUAs were observed in one patient out of 30 patients in the hysteroscopic resection group. In the resection group, three patients had pre-existing IUAs preoperatively (mild: n=2, moderate: n=1).

Based on these studies, there is a wide variation in prevalence of IUAs. However, in most studies IUAs were found to be relatively rare after hysteroscopy for treatment of RPOC compared to D&C.

2.4.3 Influence of treatment of RPOC on obstetric outcome

2.4.3.1 Abnormal placentation

Abnormal placentation is defined as placenta accreta, increta, percreta, vasa previa, or placenta previa. Retained placenta is defined as a placenta that fails to be expelled after birth of the fetus. A placenta is retained when the uterus fails to contract after the delivery of its content, or when the placenta is abnormally attached to the myometrium (mesh). Patients with a history RPOC are more likely to have abnormal placentation. To our knowledge, it is unknown if this is the result of the RPOC itself and/or the treatment of the RPOC.

A retrospective study of ***Ben Ami*** et al. comparing pregnancy outcomes in function of histopathological examination of RPOC after either D&C or hysteroscopy revealed a significantly increased placental complication rate (including placenta accreta and placenta previa) among women with negative pathologic findings compared with pathologically confirmed RPOC (22.5% versus 8.1%, respectively, p = 0.042) (appendix *) (19). The authors suggest that damage to the endometrial basalis layer predisposes to abnormal placental implantation.

Another study of ***Ben Ami*** et al. showed no significant difference in placental complications following hysteroscopy vs D&C (respectively 13.3% versus 4.3%, p = 0.177) (appendix 2) (29). However, in this study placental complications were not explicitly defined.

Ikhena et al.'s retrospective cohort study characterizes the pregnancy outcomes after hysteroscopic resection of RPOC (35). Of the 111 patients 55 conceived. Ten of them had abnormal placentation in their subsequent pregnancy (18%). These consisted of three with placenta previa, two with placenta accreta, and five with retained placenta. Histories of D&C and of abnormal placentation in a prior pregnancy were associated with higher odds of abnormal placentation (odds ratio, 15.72 [95% CI, 0.84–295.3], p = 0.066, and odds ratio, 6.26 [95% CI, 0.89–43.63], p = 0.064), respectively. The group concluded that women who undergo hysteroscopic resection of RPOCs have a higher rate of abnormal placentation in subsequent pregnancies when compared with the general population. Although the etiology is likely multifactorial, the underlying pathology leading to the initial diagnosis of RPOCs is believed to play a major role according to Ikhena.

Smorgick et al.'s retrospective analysis of 161 women surgically treated for RPOC by D&C or hysteroscopy showed in 44 (27.3%) cases third stage of labor placental problems (including retained placenta or cotyledons, need for manual placental removal (MPR) immediately after birth and placenta accreta) (41). Especially women who had been managed by suction curettage were at greater risk. In the suction curettage group 12 out of 27 (44.4%) showed third stage of labor placental problems in subsequent pregnancies versus 32 out of 143 (23.0%) in the hysteroscopy group (p = 0.03).

2.4.3.2 Recurrence of RPOC

Only one study reported on the recurrence of RPOC in a subsequent pregnancy. It is a retrospective analysis done by ***Smorgick*** of 161 women surgically treated for RPOC by

suction curettage or hysteroscopy (41). Recurrent RPOC was diagnosed in 25 cases (15.5%). Treatment of the initial RPOC by D&C in comparison with hysteroscopy was significantly associated with an increased risk of recurrent RPOC (33.3% versus 11.9%, OR = 3.6, 96% CI 1.3-10.5, p = 0.015).

2.4.3.3 Uterine rupture

Complete uterine rupture is defined as the disruption of the full-thickness of the uterine wall during pregnancy or delivery. This includes the myometrium and uterine serosa (42). The reported incidence of spontaneous uterine rupture of the unscarred uterus is in one in 8000 to one in 15000 deliveries (43). It is known that defects in the integrity of the myometrium may leave the uterus susceptible to rupture in a subsequent pregnancy (44). Uterine perforation during operative hysteroscopy has been associated with the possibility of uterine rupture during subsequent pregnancies (43). Despite that uterine perforation is the most important complication of D&C, no incidence of uterine rupture during pregnancy after a repaired or spontaneously healed uterine perforation of previous D&C is reported (45). Only one case report is found about prelabor uterine rupture at 20 weeks of gestation two years after D&C for removal of RPOC after a spontaneous abortion at three months of gestation (45).

Few case reports are found about uterine rupture following operative hysteroscopy. **Uccella** et al.'s review on 24 cases with prelabor uterine rupture in primigravid women showed that in almost half the cases a partial wall defect was the principal recognizable risk factor (46). In the review of **Ducarmes** et al. 16 case reports of uterine rupture in women with a history of operative hysteroscopy, there had been a uterine perforation during the intervention in eight cases (47). ***Sentilhes*** et al. reviewed 14 cases of uterine rupture following operative hysteroscopy (43). In nine cases (64%) uterine septa were involved. In nine of the 13 cases (69%) where the operative technique was known, monopolar energy was used. Eight uterine ruptures (57%) occurred when previous operative hysteroscopy was complicated by uterine perforation. In nine of the 14 case reports (64%) the uterine rupture occurred spontaneously before 37 weeks, without labor.

Only one case report was found about uterine rupture in pregnancy following hysteroscopic removal of RPOC (43). The resection of the RPOC was done by monopolar energy and the procedure was complicated by perforation. Uterine rupture in the subsequent pregnancy five years later occurred during labor.

It has to be noticed that literature is dated and that there was no use of bipolar current during operative hysteroscopy. They reported monopolar section, rigid scissors or potassium-titanyl-phosphate laser. Also, the indication for hysteroscopy was mostly metroplasty (43).

2.4.3.4 Other pregnancy complications

2.4.3.4.1 Intrauterine growth restriction

Theoretically, although defective placentation may predispose to IUGR, there have been only a few cases of IUGR described in pregnant women with Asherman's syndrome following endometrial ablations (5).

Only two studies on reproductive outcome after surgical treatment for RPOC reported the birth weight in subsequent pregnancy. ***Ben Ami*** et al. could not find a significant difference in mean birthweight after D&C or hysteroscopic resection of RPOC (3055 ± 528.4 grams versus 2984 ± 485.7 grams, p = 0.551) (29). ***Ikhena*** et al. reported a mean birth weight of 3.8 ± 0.4 kg in subsequent pregnancy after hysteroscopic resection of RPOC (35).

2.4.3.4.2 Preterm birth

Little information is found on preterm birth after treatment of RPOC. ***Ben Ami*** et al.'s study showed no significant difference in gestational age at delivery following hysteroscopy versus D&C, respectively 38.1 ± 4.2 versus 38.2 ± 2.5 weeks (p = 0.811) (29). ***Ikhena*** et al. reported a mean gestational age at delivery of 37 ± 5.6 weeks in subsequent pregnancy after hysteroscopic resection of RPOC (35).

2.5 The aim of this study

To our knowledge there is to date no publication comparing reproductive and obstetric outcome after HM with LR for removal of RPOC. Since little is known regarding the correlation between HM or LR for removal of RPOC and reproductive and obstetric outcomes, we aimed to evaluate the results of these two different techniques of hysteroscopic removal of RPOC.

3. Material and methods

3.1 Study parameters

We conducted a follow-up study of all women included in the randomized trial comparing HM with LR for removal of placental remnants (11). Reproductive and pregnancy outcomes after operative hysteroscopy were evaluated.

The study was approved by ethics committees of Ghent University (Belgium) and Catharina Hospital, Eindhoven (The Netherlands). The trial was registered at ClinicalTrials.gov (NCT01537822). After informed consent, medical records of all included cases were reviewed to obtain data regarding reproductive and pregnancy outcomes following the hysteroscopic treatment of placental remnants. When data were lacking in the medical records, patients were queried by contacting them via phone. Data and responses were recorded in a preset form.

3.2 Outcomes

Reproductive and pregnancy outcomes after operative hysteroscopy were evaluated for all patients in the 2 centers between May 2011 and April 2018. Definitions for medical assisted reproduction technology and their outcomes were according to the terminology of the International Committee for Monitoring Assisted Reproductive Technology ICMART and WHO, published in 2009 (48).

3.2.1 Primary outcomes

- **Live birth rate** was defined as the complete expulsion or extraction from its mother of a product of fertilization, irrespective of the duration of the pregnancy, which, after such separation, breathes or shows any other evidence of life, such as heart beat, umbilical cord pulsation, or definite movement of voluntary muscles, irrespective of whether the umbilical cord has been cut or the placenta is attached. We count the delivery of singleton, twin or multiple pregnancies as one live birth.

- **Pregnancy complications**

1) Placental complications

- Abnormal placentation was defined as placenta accreta, placenta increta, placenta percreta, vasa previa, or placenta previa.

- Retained placenta after delivery with the need for manual removal or curettage.
- Persistence of RPOC after delivery.

2) Uterine rupture during pregnancy was defined as a complete separation or tear in the wall of the uterus with or without expulsion of the fetus (mesh).

3) any other pregnancy complication defined as blood loss during first, second or third trimester of the pregnancy, gestational hypertension, pre-eclampsia, eclampsia, preterm contractions, PPROM, IUGR (small for gestational age defined as birth weight less than 2 standard deviations below the mean of less than the 10^{th} percentile according to local intrauterine growth charts)

3.2.2 Secondary outcomes

If there was desire to future pregnancy, **the time to pregnancy**, was calculated.

3.2.3 Other study parameters

Baseline characteristics (age, general history, ASA score, race and body mass index (BMI)), and characteristics about subsequent pregnancy were asked. Mode of conception (spontaneous or assisted reproductive technology (ART)) was reported. ART was defined as all treatments or procedures that include the in vitro handling of both human oocytes and sperm or of embryos for the purpose of establishing a pregnancy. This includes, but is not limited to, in vitro fertilization (IVF) and embryo transfer, gamete intrafallopian transfer, zygote intrafallopian transfer, tubal embryo transfer, gamete and embryo cryopreservation, oocyte and embryo donation, and gestational surrogacy. ART does not include assisted insemination (artificial insemination) using sperm from either a woman's partner or a sperm donor.

Other pregnancy outcomes such as birth weight, start of delivery (spontaneous, induction or primary cesarean section), delivery mode (spontaneous, vaginal assisted delivery by vacuum or forceps extraction or secondary section) and gestational age at delivery were reported for the live births. In case of postpartum hemorrhage, defined as a blood loss of 500 ml or more within 24 hours after delivery, the need for treatment by uterotonics, manual removal of the placenta, curettage, embolization, placing of a Bakri balloon or hysterectomy were noted. Also the need for blood transfusion after delivery were recorded.

3.3 Statistical analysis

Data were collected and analyzed in the statistical program SPSS version 25 (IBM SPSS Statistics 25.0, IBM Corp., Armonk, NY, USA). For symmetric distributed continuous variables, means, standard deviations, and 95% CI were reported and the mean differences were analyzed using Student t test. For non-symmetric continuous variables median, interquartile range, minimum and maximum were computed, analyses was performed using Mann-Whitney U test. Categorical data were presented as frequency and percentage and analysed using chi-squared test or Fisher's Exact test. FIRTH log regression was used for the analysis of the primary outcome measures if the univariate analysis was significantly different. Time to pregnancy was analyzed using time-to-event analysis. A p value of $< .05$ was considered to be statistically significant. Statistical analysis was done for both intention-to-treat analysis and per-protocol analysis.

4. Results

The total response rate was 69/86 (80.2%). Patient's response is shown in figure 5. Three out of 86 (3.5%) of the women refused to participate and 14/86 (16.3%) were lost to follow up.

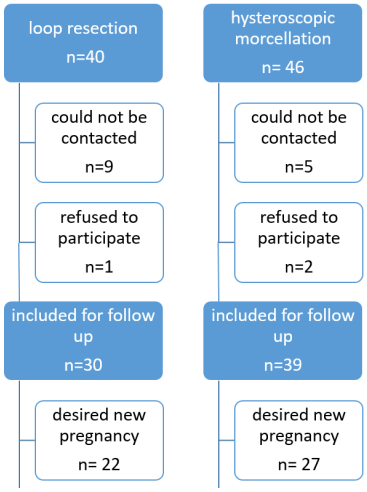

Figure 5: response rate of the current study

After hysteroscopic removal of RPOC, 49/69 (71.0%) wished to conceive (27/39 (69.2%) in the HM group and 22/30 (73.3%) in the LR group (p = 0.71). Patient demographics of the intention to treat groups are presented in table 4.

There were no statistically significant differences. The median follow-up was four years (IQR 4 – 6) in the HM group and five years (IQR 4 -5) in the LR group (p = 0.90).

		Morcellation						Loop resection						
		Total N	Median	P 25	P 75	N	%	Total N	Median	P 25	P 75	N	%	p
Age (years)		27	32	28	38			22	34	27	37			.90
BMI* (kg/m²)		26	22	20	24			21	23	21	26			.90
Race		26						22						.25
	White					25	92.6%					20	90.9%	
	Asian					0	0					1	4.5%	
	Black					0	0					1	4.5%	
	Other					2	7.7%					0	0	
ASA score		27						22						
	1					24	88.9%					20	90.9%	.82
	2					3	11.1%					2	9.1%	
Smoker		27						22						.83
	Yes					2	7.4%					2	9.1%	
Obstetric history*		27						22						
	Gravity		1	1	2				2	1	3			.68
	Parity		1	0	1				1	1	2			.47
	Abortions		1	0	1				1	0	1			.26

*at start trying to conceive

Table 4: Patient demographics

Descriptive data regarding the reproductive outcome are shown in table 5. Women tried to conceive by assisted reproduction in 4/27 (14.8%) and in 2/20 (10%) for HM and LR respectively (p = 1.00). In the HM group, ovulation induction was performed in one case (25%), IUI in a stimulated cycle in two out of four (50%) and IVF/ICSI in one patient (25%), in the LR group, ovulation induction and IUI in a stimulated cycle were both performed in ½ (50%). The primary outcome measure live birth rate was 24/27 (88.9%) after HM and 15/22 (68.2%) after LR, this was not statistically different (p = 0.09).

		Morcellation			Loop resection			
		Total N	N	%	Total N	N	%	p
Pregnancy		27			22			1.00
	Yes		24	88.9%		19	86.4	
Conception mode		27			20			1.00
	Spontaneously		23	85.2%		18	90%	
Pregnancy outcome		27			22			
	Miscarriage		0	0.0%		3	13.6%	.08
	Abortus provocatus		0	0.0%		1*	4.5%	.45
	Live birth		24	88.9%		15	68.2%	.09
Singleton		24			19			
	Yes		24	100%		19	100%	á

á Fisher's-Exact test is not measured because of constant value

* Pregnancy termination was performed at 13 weeks 4 days because of intrauterine CMV infection

Table 5: Descriptive data regarding the reproductive outcome

The other primary outcome measure, namely pregnancy complications subdivided into uterine rupture, placental complications and other pregnancy complications are presented in table 6. There were no significant differences between the groups of RPOC removal by HM or LR.

There was one case of uterine rupture in a patient with a known congenital anomaly of the uterus (hemi-uterus) in the HM group (4.2%). The initial procedure for removal of RPOC was complicated by a perforation at the time of dilation of the cervix. The procedure was completed by blunt dissection with a miniature hysteroscope. In the following pregnancy, the patient was admitted on 36 weeks 5 days because of sudden onset of severe abdominal pain. Maternal hypotension (81/53mm Hg) and foetal distress were noted. US revealed intra-abdominal fluid. An urgent caesarean section was performed with diagnosing of hemoperitoneum with uterine rupture on the posterior side of the uterus (site where the perforation had occured). A boy was born with birthweight 2388 gram, apgar 1-4-9. Neonatal assessment with MRI for peripartal asphyxia was negative.

Abnormal placentation occurred in the HM group as an accrete placenta in one out of 24 (4.2%), in the LR group placenta accreta and placenta previa were seen in two out of 14 (14.3%) (p = 0.54). In the HM group, RPOC occurred after manual removal of the placenta after vaginal delivery in one out of 24 (4.2%), in the LR group, RPOC occurred in two out of

17 (11.8%) after placenta accrete and after pregnancy termination at gestational age of 13weeks 4 days because of a cytomegalovirus (CMV) infection.

The one pregnancy complicated by first trimester blood loss resulted in a miscarriage (1/18, 5.5%), in the HM group all cases (3/24, 12.5%) of first trimester blood loss resulted in a live birth. In the HM group, one out of 24 (4.2%) of the pregnancies were complicated by preterm contractions which, nevertheless all led up to term delivery. IUGR occurred in three out of 24 (12.5%) of the pregnancies in the HM group, and were not related to pregnancy induced hypertension. One case of third trimester blood loss in the LR group was related to placenta previa and ended in a live birth. The other cases of blood loss in the third trimester were not related to placental complications and resulted in two live births.

		Morcellation			Loop resection			
		Total N	N	%	Total N	N	%	p
Uterine rupture		24			19			1.00
	Yes		1	4.2%		0	0.0%	
Placental complications		24			18			1.00
	Yes		5	20.8%		4	22.2%	
Abnormal placentation		24			14			.54
	Yes		1	4.2%		2	14.3%	
Third stage of labor		19			11			.63
	Manual removal of placenta		4	21.1%		1	9.1%	
RPOC after vaginal delivery or expulsion		24			17			.63
	Yes		1	4.2%		2	11.8%	
Other pregnancy complications		24			18			.33
	Yes		8	33.3%		3	16.6%	
Vaginal blood loss GA ≤ 12 weeks		24			18			.62
	Yes		3	12.5%		1	5.5%	
Vaginal blood loss GA > 12 - ≤ 28 weeks		24			15			a
	Yes		0	0.0%		0	0.0%	
Vaginal blood loss GA > 28 weeks		24			15			1.00
	Yes		2	8.3%		1	6.7%	
Preterm labor		24			15			1.00
	Yes		1	4.2%		0	0.0%	
Preterm premature rupture of membranes		24			15			1.00
	Yes		1	4.2%		0	0.0%	
Pregnancy induced hypertension		24			15			1.00
	Yes		2	8.3%		1	6.7%	
Preeclampsia		24			15			a
	Yes		0	0.0%		0	0.0%	
Eclampsia		24			15			a
	Yes		0	0.0%		0	0.0%	
Intrauterine growth restriction		24			14			.28
	Yes		3	12,5%		0	0,0%	

a Fisher's-Exact test is not measured because of constant value
GA = gestational age

Table 6: Other primary outcome measures (uterine rupture, placental complications and other pregnancy complications)

The secondary outcome measure, time to conception, was 14 weeks (IQR 5 – 33) in the HM group and 15 weeks (IQR 6 – 37) in the LR group (p = 0.96).The descriptive data considering live birth are shown in table 7 and there are no significant differences.

		Morcellation						Loop resection						
		Total N	Median	P 25	P 75	N	%	Total N	Median	P 25	P 75	N	%	p
Start of delivery		24						15						.07
	Spontaneous labor					13	54.2%					11	73.3%	
	Induction of labor					9	37.5%					1	6.7%	
	Primary C-section					2	8.3%					3	20.0%	
Delivery mode		22						12						.99
	Vacuum extraction					2	9.1%					1	8.3%	
	Secondary C-section					2	9.1%					1	8.3%	
Gestational age at delivery (weeks + days)		24	40+3	38+0	40+5			15	38+1	36+0	40+1			.58
Birth weight (gram)		24	3 130	2 830	3 738			14	3 470	3 170	3 850			.73
Postpartum haemorrhage		24						15						1.00
	Yes					5	20.8%					3	20.0%	

Table 7: Descriptive data considering live birth

The results of the per-protocol analysis are comparable with the intention-to-treat analysis. There were no statistically significant differences.

5. Discussion

5.1 Main findings

The overall live birth rate after hysteroscopic treatment of RPOC was 79.5% in our study. This is comparable with live birth rates in previous reports on pregnancy rates after hysteroscopic removal of RPOC, namely 57.3 to 80.7% (36) (13,27–29,38,40). Although the percentage after HM was higher (88.9%) compared to LR (68.2%) this difference did not reach statistical significance. Also the miscarriage rate after LR was higher compared to the HM group, but this did also not reach statistical significance.

Apart from the technique used and successful removal of RPOC is the effect of maternal **age** on the average rate of pregnancy. Maternal age is the single most important determinant of spontaneous as well as treatment-related conception with a gradual decline in fertility after the age of 35 years (49). In our study, there was no significant difference between the median maternal age in both groups (32 years in HM group, 34 years in LR group). Ikhena et al. reported a median maternal age of 35 years, live birth rate was 69.5% (35). In the study of Ben Ami et al. a mean age of 30.5 years was seen with a live birth rate of 80.7% after hysteroscopic resection of RPOC(29).The maternal age in the study of Sonnier et al. was average 32 years, however, they did not analysed live birth rate (36). One could conclude that maternal age is indeed an important determining factor for live birth rate.

In the present study, there were no significant differences in overall **placental complications** (20.8% vs 22.2%). More specifically, no significant differences were observed between the two study groups for abnormal placentation (4.2% in HM group versus 14.3% in LR group), retained placenta after delivery with need for MPR (21.1% in HM group versus 9.1% in LR group) or persistence of RPOC (4.2% in HM group versus 11.8% in LR group). Comparison with other studies is not straight forward since there is a difference in definitions of placental complications. The study of Ikhena et al. describing reproductive outcomes after hysteroscopic resection of RPOC showed a rate of 18% of abnormal placentation defined as placenta accreta increta and percreta, vasa or placenta previa and retained placenta (35). Ben Ami et al. reported placental complications in 11% of patients who had hysteroscopic removal of RPOC. However, they did not describe what subtypes of abnormal placentation were analysed.

In the HM group four cases needed **manual removal of the placenta after delivery** versus one case in the resection group, which was not significant different. One could have expected

less MPRs in the HM group since with use of the hysteroscopic morcellator, theoretically less damage is done to the surrounding tissue, especially when comparing to curettage or using LR with energy. It has been postulated that injury to the endometrium, even in non-gravid uteri, due to intrauterine procedures may have implications on placental implantation. This injury may restrict the detachment of the placenta during labor resulting in retained placenta after delivery (50).

In this study, **recurrent RPOC in the subsequent pregnancy** occurred in each group only in one patient. A recent study of Smorgick concluded that women treated for RPOC are at risk for recurrent RPOC, especially those who had been managed by D&C in comparison with operative hysteroscopy (41). The small numbers presented in our study may be explained by the selective removal of RPOC with both hysteroscopic techniques with minimal endometrial injury.

There was one major adverse pregnancy outcome, namely a prelabor **uterine rupture** in a patient with a known congenital anomaly of the uterus (hemi-uterus) in the HM group where the initial procedure for removal of RPOC was complicated by a perforation at the time of dilation of the cervix. According to the Belgian Obstetric Surveillance System, the prevalence of uterine rupture in Belgium is estimated at 3.6 (95% CI 2.9 to 4.4) per 10 000 deliveries, which is comparable with the data of the WHO (0.03% in developed countries). Known risk factors for uterine rupture are scarring by a previous caesarean section, gestational age beyond 37 weeks, labor and induction or augmention of labor (42). Evidence on the risk of uterine rupture following complicated operative hysteroscopy remains inconclusive as only case reports are found in literature. In the other seven patients were perforation occurred in the initial RCT, five became pregnant. In none of these cases, adverse obstetric events occurred. In the review of Sentilhes et al. on uterine rupture after operative hysteroscopy, metroplasty for uterine septa or synechiae are a primary condition at risk for obstetrical morbidity (12 of the 14 cases retrieved in this review). Uterine perforation and monopolar electrosurgery are associated risk factors for uterine rupture (43). When perforation occurs, notification in the patient's file needs to be done. It is important to inform the patient to bear in mind the operation-conception interval, however no data exist on this object.

In the current study, there were no significant differences in **other pregnancy complications**. Limited literature was found about obstetric outcome for subsequent pregnancy following hysteroscopic removal of RPOC. For IUGR and preterm birth in subsequent pregnancy

following surgical removal of RPOC data was found in the studies of Ben Ami and Ikhena (29,35). Both compared these outcomes for D&C with hysteroscopic resection and no significant differences were found. Although not statistically significant, other pregnancy complications in our study were more prevalent in the morcellation group (33.3%) compared to the resection group (16.6%). This is probably because of the long list of variables included in our definition of 'other pregnancy complications' and the small numbers of cases. These variables could have a lot of confounders, besides a possible influence of the resection technique of RPOC.

In our study, the **time to conception** was not significantly different between LR and morcellation. Ben Ami et al. found a significantly reduced interval tot conception in the group who underwent hysteroscopic resection of RPOC compared to the group treated with D&C (7.4 months vs 12.9 months) (29). Ikhena et al. reported a mean time to pregnancy of 29 weeks after hysteroscopic removal of RPOC (35). Sonnier et al. examined the time to conception after RPOC removal by LR, they found an average interval of 22 weeks (36). Our intervals were slightly shorter (14 weeks and 15 weeks for HM group and LR group respectively).

5.2 Strengths and limitations

To our knowledge, the present study is the first to report on reproductive and obstetric outcome of women who underwent HM compared to LR for the removal of RPOC. According to the initial RCT, both an intention-to-treat and per-protocol analysis were done to correct for initial protocol deviations.

A limitation of the present study is its retrospective nature. Part was done by telephone interview which may be associated with recall bias. Due to the relative little sample size in our follow up study, some outcomes may not be significant. Also the initial RCT was not powered for our primary and secondary outcome measures.

5.3 Interpretation

Previous RCT concluded that HM is a faster, effective, and safe alternative to LR for removal of RPOC. The conception rate after RPOC removal using HM or LR are similar. There was a tendency towards more live birth in the HM group but more well conducted research is necessary group. The time to pregnancy was comparable between HM and LR, there seems to be no detrimental effect on fertility.

References

1. Sellmyer M a, Desser TS, Maturen KE, Jeffrey RB, Kamaya A. Physiologic, histologic, and imaging features of retained products of conception. Radiographics. 2013; 33(3):781-796.

2. Pather S, Ford M, Reid R, Sykes P. Postpartum curettage: An audit of 200 cases. Australian and New Zealand Journal of Obstetrics and Gynaecology 2005;45:368-371.

3. Hamerlynck TWO, Blikkendaal MD, Schoot BC, Hanstede MMF, Jansen FW. An alternative approach for removal of placental remnants: Hysteroscopic morcellation. Journal of Minimally Invasive Gynecology. 2013;20(6):796–802.

4. Van Den Bosch T, Daemen A, Van Schoubroeck D, Pochet N, De Moor B, Timmerman D. Occurrence and outcome of residual trophoblastic tissue: A prospective study. Journal of Ultrasound in Medicine. 2008;27:357-361.

5. Yu D, Wong YM, Cheong Y, Xia E, Li TC. Asherman syndrome-one century later. Fertility and Sterility. 2008;89(4):759-779.

6. Ben-Ami I, Schneider D, Maymon R, Vaknin Z, Herman A, Halperin R. Sonographic versus clinical evaluation as predictors of residual trophoblastic tissue. Human Reproduction. 2005;20(4):1107–1111.

7. Ustunyurt E, Kaymak O, Iskender C, Ustunyurt OB, Celik C, Danisman N. Role of transvaginal sonography in the diagnosis of retained products of conception. Archives of Gynecology and Obstetrics. 2008;277:151-154.

8. Matijevic R, Knezevic M, Grgic O, Zlodi-Hrsak L. Diagnostic accuracy of sonographic and clinical parameters in the prediction of retained products of conception. Journal of Ultrasound in Medicine. 2009;28:295-299.

9. Van den Bosch T, Van Schoubroeck D, Lu C, De Brabanter J, Van Huffel S, Timmerman D. Color Doppler and gray-scale ultrasound evaluation of the postpartum uterus. Ultrasound in Obstetrics and Gynecology. 2002;20:586-591.

10. Atri M, Rao A, Boylan C, Rasty G, Gerber D. Best predictors of grayscale ultrasound combined with color doppler in the diagnosis of retained products of conception. Journal of Clinical Ultrasound. 2011;39:122-127.

11. Hamerlynck TWO, van Vliet HAAM, Beerens AS, Weyers S, Schoot BC. Hysteroscopic Morcellation Versus Loop Resection for Removal of Placental Remnants: A Randomized Trial. In: Journal of Minimally Invasive Gynecology. 2016; 23(7):1172-1180.

12. Westendorp ICD, Ankum WM, Mol BWJ, Vonk J. Prevalence of Asherman's syndrome after secondary

removal of placental remnants or a repeat curettage for incomplete abortion. Human Reproduction. 1998;13(12):3347-3350.

13. Hooker AB, Muller LT, Paternotte E, Thurkow AL. Immediate and long-term complications of delayed surgical management in the postpartum period: a retrospective analysis. Journal of Maternal-Fetal & Neonatal Medicine. 2015;28(16):1884–1889.

14. Hooker A, Fraenk D, Brölmann H, Huirne J. Prevalence of intrauterine adhesions after termination of pregnancy: a systematic review. The European Journal of Contraception & Reproductive Health Care. 2016;21(4):329–335.

15. Al-Inany H. Intrauterine adhesions: An update. Acta Obstetricia et Gynecologica Scandinavica. 2001;80:986-993.

16. Inal MM, Yildirim Y, Ertopcu K, Ozelmas I. The predictors of retained products of conception following first-trimester pregnancy termination with manual vacuum aspiration. The European Journal of Contraception & Reproductive Health Care. 2006; 11(2):98-10

17. Dankert T, Vleugels M. Hysteroscopic resection of retained placental tissue: A feasibility study. Gynecological Surgery. 2008;5(2):121–124.

18. Emanuel MH, Wamsteker K. The Intra Uterine Morcellator: A new hysteroscopic operating technique to remove intrauterine polyps and myomas. The Journal of Minimally Invasive Gynecology. 2005;12(1):62–66.

19. Ben-Ami I, Ofir T, Melcer Y, Smorgick N, Schneider D, Pansky M, et al. Infertility following retained products of conception: Is it the surgical procedure or the presence of trophoblastic tissue? European Journal of Obstetrics, Gynecology and Reproductive Biology. 2014;182:132–135.

20. Indraccolo U, Greco P, Scutiero G, Marrocchella S, Sorrentino F, Mastricci L, et al. The role of hysteroscopy in the diagnostic work-up of infertile asymptomatic patients. Clinical and Experimental Obstetrics & Gynecology. 2014;41(2):124-7.

21. Bosteels J, Kasius J, Weyers S, Broekmans FJ, Mol BWJ, D'Hooghe TM. Hysteroscopy for treating subfertility associated with suspected major uterine cavity abnormalities. The Cochrane Database of Systematics Reviews. 2015 Feb 21;(2):CD009461

22. Jansen FW, Vredevoogd CB, Van Ulzen K, Hermans J, Trimbos JB, Trimbos-Kemper TCM. Complications of hysteroscopy: a prospective, multicenter study. Obstetrics and Gynecology. 2000;96(2):266–270.

23. Mollo A, De Franciscis P, Colacurci N, Cobellis L, Perino A, Venezia R, et al. Hysteroscopic resection of the septum improves the pregnancy rate of women with unexplained infertility: a prospective controlled trial. Fertility and Sterility. 2009; ;91(6):2628-2631.

24. Shokeir T, Abdelshaheed M, El-Shafie M, Sherif L, Badawy A. Determinants of fertility and reproductive success after hysteroscopic septoplasty for women with unexplained primary infertility: A prospective analysis of 88 cases. European Journal of Obstetrics, Gynecology and Reproductive Biology. 2011; 155(1):54-57.

25. Nouri K, Ott J, Huber JC, Fischer E-M, Stögbauer L, Tempfer CB. Reproductive outcome after hysteroscopic septoplasty in patients with septate uterus--a retrospective cohort study and systematic review of the literature. Reproductive Biology, Endocrinology. 2010; 21;8:52.

26. Chipchase J, James D. Randomised trial of expectant versus surgical management of spontaneous miscarriage. British Journal of Obstetrics and Gynaecology.1997;104(7):840–841.

27. Cohen SB, Kalter-Ferber A, Weisz BS, Zalel Y, Seidman DS, Mashiach S, et al. Hysteroscopy may be the method of choice for management of residual trophoblastic tissue. The Journal of the American Association of Gynecologic Laparoscopists. 2001;8(2):199-202.

28. Rein DT, Schmidt T, Hess AP, Volkmer A, Schöndorf T, Breidenbach M. Hysteroscopic Management of Residual Trophoblastic Tissue Is Superior to Ultrasound-Guided Curettage. Journal of Minimally Invasive Gynecology. 2011;18(6):774–778.

29. Ben-Ami I, Melcer Y, Smorgick N, Schneider D, Pansky M, Halperin R. A comparison of reproductive outcomes following hysteroscopic management versus dilatation and curettage of retained products of conception. Internation Journal of Gynecology and Obstetrics. 2014;127:86-89.

30. Smorgick N, Mittler A, Ben-Ami I, Maymon R, Vaknin Z, Pansky M. Retained products of conception: What is the risk for recurrence on subsequent pregnancies? European Journal of Obstetrics, Gynecology and Reproductive Biology. 2018;224:1–5.

31. Golan A, Dishi M, Shalev A, Keidar R, Ginath S, Sagiv R. Operative Hysteroscopy to Remove Retained Products of Conception: Novel Treatment of an Old Problem. Journal of Minimally Invasive Gynecology. 2011;18(1):100–103.

32. Faivre E, Deffieux X, Mrazguia C, Gervaise A, Chauveaud-Lambling A, Frydman R, et al. Hysteroscopic Management of Residual Trophoblastic Tissue and Reproductive Outcome: A Pilot Study. Journal of Minimally Invasive Gynecology. 2009;16(4):487–490.

33. Fuchs N, Smorgick N, Ben Ami I, Vaknin Z, Tovbin Y, Halperin R, et al. Intercoat (Oxiplex/AP Gel) for Preventing Intrauterine Adhesions After Operative Hysteroscopy for Suspected Retained Products of Conception: Double-Blind, Prospective, Randomized Pilot Study. Jounral of Minimally Invasive Gynecology. 2014;21(1):126–30.

34. Jiménez JS, Gonzalez C, Alvarez C, Muñoz L, Pérez C, Muñoz JL. Conservative management of retained trophoblastic tissue and placental polyp with diagnostic ambulatory hysteroscopy. The European Journal of Obstetrics, Gynecology and Reproductive Biology. 2009;145(1):89–92.

35. Ikhena DE, Bortoletto P, Lawson AK, Confino R, Marsh EE, Milad MP, et al. Reproductive Outcomes After Hysteroscopic Resection of Retained Products of Conception. Journal of Minimally Invasive Gynecology. 2016; ;23(7):1070-1074.

36. Sonnier L, Torre A, Broux P, Fauconnier A, Huchon C. Evaluation of fertility after operative hysteroscopy to remove retained products of conception. European Journal Obstetrics, Gynecology and Reproductive Biology. 2017;211:98–102.

37. Rein DT, Schmidt T, Hess AP, Volkmer A, Schöndorf T, Breidenbach M. Hysteroscopic Management of Residual Trophoblastic Tissue Is Superior to Ultrasound-Guided Curettage. Journal of Minimally Invasive Gynecology. 2011; 2011;18(6):774–778

38. Faivre E, Deffieux X, Mrazguia C, Gervaise A, Chauveaud-Lambling A, Frydman R, et al. Hysteroscopic Management of Residual Trophoblastic Tissue and Reproductive Outcome: A Pilot Study. Journal of Minimally Invasive Gynecology. 2009;16(4):487-490.

39. Barel O, Krakov A, Pansky M, Vaknin Z, Halperin R, Smorgick N. Intrauterine adhesions after hysteroscopic treatment for retained products of conception: What are the risk factors? Fertility and Sterility. 2015; 103(3):775-779.

40. Golan A, Dishi M, Shalev A, Keidar R, Ginath S, Sagiv R. Operative Hysteroscopy to Remove Retained Products of Conception: Novel Treatment of an Old Problem. Journal of Minimally Invasive Gynecology. 2011;18(1):100-103.

41. Smorgick N, Mittler A, Ben-Ami I, Maymon R, Vaknin Z, Pansky M. Retained products of conception: What is the risk for recurrence on subsequent pregnancies? European Journal of Obstetrics, Gynecology and Reproductive Biology. 2018; 224:1-5.

42. Vandenberghe G, De Blaere M, Van Leeuw V, Roelens K, Englert Y, Hanssens M, et al. Nationwide population-based cohort study of uterine rupture in Belgium: Results from the Belgian obstetric surveillance system. BMJ Open. 2016; 17;6(5):e010415.

43. Sentilhes L, Sergent F, Roman H, Verspyck E, Marpeau L. Late complications of operative hysteroscopy: Predicting patients at risk of uterine rupture during subsequent pregnancy. European Journal of Obstetrics, Gynecology and Reproductive Biology. 2005; 120(2):134-138.

44. Munro MG, Christianson LA. Complications of hysteroscopic and uterine resectoscopic surgery. Clinical Obstetrics and Gynecology. 2015; 58(4):765-97.

45. Ghahramani L, Moslemi S, Tahamtan M, Hasan Hashemizadeh M, Keshavarzi A. Antepartum Uterine Rupture Occurring at the Site of a Peviously Repaired Dilatation and Curettage-Induced Perforation: A Case Report Case Report. Bulletin of Emergency and Trauma. 2013; ;1(2):96-98.

46. Uccella S, Cromi A, Bogani G, Zaffaroni E, Ghezzi F. Spontaneous prelabor uterine rupture in a primigravida: A case report and review of the literature. American Journal of Obstetrics and

Gynecology. 2011; 205(5):e6-8.

47. Ducarme G, Maitrot F, Robinet G, Gabriel R. Rupture utérine après hystéroscopie opératoire. À propos d'un cas. Gynecologie Obstetrique et Fertilite. 2004;32(2):140-2.

48. Zegers-Hochschild F, Adamson GD, de Mouzon J, Ishihara O, Mansour R, Nygren K, et al. International Committee for Monitoring Assisted Reproductive Technology (ICMART) and the World Health Organization (WHO) revised glossary of ART terminology, 2009*. Fertility and Sterility. 2009; ;92(5):1520-1524.

49. Heffner LJ. Advanced maternal age--how old is too old? The New England Journal of Medicine. 2004; 351(19):1927-1929.

50. Greenbaum S, Wainstock T, Dukler D, Leron E, Erez O. Underlying mechanisms of retained placenta: Evidence from a population based cohort study. Europena Journal of Obstetrics, Gynecology and Reproductive Biology. 2017; 216:12-17.

Nederlandse samenvatting

Doelstelling

In deze masterproef wordt aan de hand van een retrospectieve analyse de follow up studie gedaan betreffende reproductieve en zwangerschapsuitkomsten na hysteroscopische placentarestverwijdering (loop resectie versus morcellatie).

Methodologie

Van alle patiënten die geïncludeerd zijn in voorgaande RCT, waarbij hysteroscopische placentarestverwijdering door middel van loop resectie (n=40) vergeleken werd met morcellatie (n=46), werden fertiliteit en zwangerschapsuitkomsten nagegaan. De primaire uitkomst waren levendgeboorte en zwangerschapscomplicaties, verdeeld in uterusruptuur, abnormale placentatie (placenta accreta/increta/percreta, placenta previa, vasa previa, retentio placentae na de bevalling of expulsie met noodzaak tot manuele verwijdering of curettage en placentarest 6 weken na de bevalling of expulsie) en andere zwangerschapscomplicaties (bloedverlies tijdens het eerste, tweede en/of derde trimester, premature contracties, preterme prematuur gebroken vliezen, hypertensieve aandoeningen gerelateerd aan de zwangerschap of intrauteriene groei restrictie. De secondaire uitkomst was de tijd tot zwangerschap.

Resultaten

Het antwoord percentage bedroeg 75% (30/40) voor de loop resectie groep en 84.8% (39/46) voor de morcellatie groep. The mediane follow-up was 4 jaar (IQR 4 – 6) in de morcellatie groep en 5 jaar (IQR 4 -5) in de loop resectie groep (p = 0.90). 71% (49/69) hadden een zwangerschapswens na de hysteroscopische placentarestverwijdering. In de intention-to-treat analyse, de levendgeboorte in de morcellatiegroep bedroeg 88.9% (24/27), 68.2% (15/22) in de loop resectie groep. Dit niet significant verschillend (p = 0.09). Een uterusruptuur werd alleen in de morcellatie groep gezien in 4.2% (1/24) van de patiënten (p = 1.00). De casus betrof een patiënte met gekende hemi-uterus waarbij een perforatie was opgetreden tijdens de dilatatie. Complicaties betreffende de placenta werden in 20.8% (5/24) en 22.2% (4/18) (p = 0.33) gezien en andere zwangerschapscomplicaties in 33.3% (8/24) en 16.6% (3/18) (p = 0.33) voor respectievelijk de morcellatie en loop resectiegroep. De mediane tijd tot

zwangerschap was 14 weken (IQR 5 – 33) in de morcellatie groep en 15 weken (IQR 6 – 37) in de loop resectie groep (p = 0.96).

Conclusie

Hysteroscopische placentarestverwijdering door middel van zowel loop resectie als morcellatie lijken geen schadelijk effect te hebben op reproductieve en zwangerschapsuitkomsten in een volgende zwangerschap. De zwangerschapspercentages zijn voor beide groepen vergelijkbaar, met een trend tot naar meer levendgeboorte in de morcellatie groep.

Appendix 1: overview of the literature

	Study design	Study period	Number of patients	Selection of patients		Diagnosis of RPOC	Pregnancy preceding RPOC	Time interval from end of pregnancy and treatment for RPOC	Treatment	
				Inclusion criteria	Exclusion criteria				Intervention group	Control group
Ben ami et al., 2014 (19)	retrospective	January 2000 – December 2010	240	Suspicion RPOC	NA	NA	- Delivery - Missed abortion - Induced abortion	- Group positive pathologic findings: 3.7 ± 3 weeks - Group negative pathologic findings: 4 ± 3.8 ➔not significant	D&C or hysteroscopic resection (type NA) and positive pathologic findings (n=162)	D&C or hysteroscopic resection (type NA) and negative pathologic findings (n=78)
Ben Ami et al., 2014 (29)	Retrospective	January 2000-December 2010	177	Pathologic confirmed RPOC	NA	NA	- Delivery - Abortion	- Hysteroscopic resection group: 5.3 ± 3.3 weeks - D&C group: 2.6 ± 2.3 weeks ➔ p<0.001	Hysteroscopic resection cold loop technique (n=83)	Blind D&C with metal curette (n=94)
Chipchase et al., 1997 (26)	RCT	NA	35	Patients with good health with a normal haemoglobin, haemodynamically stable, an estimated gestational age of < 13 weeks and with anterior-posterior diameter of RPOC of < 50 mm	Complete miscarriage Recurrent miscarriage	TVl US	First trimester spontaneous miscarriage	NA	expectant management (n=19)	surgical management (n=16) (type NA)

Cohen et al., 2001 (27)	Retrospective	January 1997-january 2000	70	Persistent vaginal bleeding	NA	TV US	-Abortion curettage -Caesarean section -Vaginal delivery	Days	HR %	D&C %	Hysteroscopic resection cold loop technique (n=46)	Conventional blind D&C (n=24)
								≤ 10	19.6	37.5		
								10-30	34.8	20.8		
								>30	45.6	41.7		
Faivre et al., 2009 (38)	Observational study	October 1999 - September 2006	50	-Metrorrhagia -Secondary amenorrhea -Repeated spontaneous miscarriages	NA	TV Doppler US hysteroscopy	-spontaneous miscarriage -D&C for termination of pregnancy -Medical termination of pregnancy first or second trimester -Term delivery	Median : 60 days (interquartile range 30-90 days)			Hysteroscopic resection with cold loop technique (78%) or secondarily applied electrical energy (22%)	
Fuchs et al., 2014 (33)	Double-blind prospective RCT	September 2009-june 2012	52	Age 18-50 years	-Signs/symptoms of infection -Active bleeding at admission	TVl US Diagnostic office hysteroscopy -	-vaginal delivery -Cesarean section	7 weeks in both groups			Hysteroscopic resection cold loop technique + Oxiplex gel, postoperative hormone treatment and antibiotic therapy (n=21)	Hysteroscopic resection cold loop technique without Oxiplex gel, postoperative hormone treatment and antibiotic therapy (n=20)
Golan et al., 2011	Retrospective	July 2001-August 2007	159	Symptoms and transvaginal US	NA	TV US Symptoms (Continu	-D&C after spontaneous abortion -D&C for	≤ 10 days: 21.3%			Hysteroscopic resection cold loop technique (n=159)	

(40)						ous vaginal bleeding, lower abdominal pain, fever)	termination of pregnancy -Medical abortion -Vaginal delivery -Caesarean section	11-20: 17.6% 21-30: 18.2% 31-180: 42.7%		
Hamerlynck et al., 2016 (11)	RCT	May 2011-July 2015	87	Adult women diagnosed with RPOC	-Evidence of malignancy -Untreated cervical stenosis -General contraindication for operative hysteroscopy	US and/or diagnostic hysteroscopy	-Vaginal delivery -Caesarean section -Incomplete miscarriage -Delayed miscarriage -Termination of pregnancy	-Hysteroscopic morcellation group: 10 weeks (range 8)12) -Hysteroscopic resection group: 10 weeks (range 9-16)	Hysteroscopic morcellation (n=46)	Hysteroscopic cold loop technique (n=40)
Hooker et al., 2015 (13)	Retrospective	January 2004-December 2011	127	Delivery > 32 weeks	-Late termination of pregnancy -Stillbirths -Surgical intervention within 24h after delivery	US Symptoms: excessive or abnormal blood loss, fever, abdominal pain	-Vaginal delivery -Cesarean section	42 days (range 4-171 days)	Hysteroscopic resection cold loop technique (n=22)	Blind D&C (n=105)
Ikhena et al., 2016 (35)	Retrospective	January 2004-december 2014	111	Symptoms (abnormal uterine bleeding, fever, and/or abdominal pain in the presence of persistently elevated serum human chorionic gonadotropin levels (>5.0mIU/ml) and/or US findings	NA	Symptoms and/or US findings	-Vaginal delivery -Cesarean delivery -Early pregnancy loss	NA	Hysteroscopic scissors and forceps (n=43) Bipolar resectoscope (n=68), application of electrosurgery determined by provider at the time of surgery	

Jiménez et al., 2009 (34)	retrospective	January 2001 - March 2008	84	-Vaginal bleeding and/or fever -Persistence of US imaging in asymptomatic patients after expectant management	NA	Diagnostic hysteroscopy	-Vaginal delivery -Abortion -Caesarean section	35 days (range 2-105)			Hysteroscopic biopsy forceps	
Smorgick et al., 2018 (30)	Retrospective	January 2008 – December 2015	442	Women treated for RPOC	NA	TV US, hysteroscopic findings and pathology results	-Vaginal delivery -Caesarean section -Medical abortion -Surgical abortion					
Sonnier et al., 2017 (36)	retrospective	January 2008 - December 2011	115	Persistent bleeding or pelvic pain and US images	NA	TV US	-Abortion (spontaneous or induced) -Delivery	-≤ 10 days: 2 (2%) -11-20 days: 21 (18%) -21-30 days: 15 (13%) -≥ 31 days: 75 (65%)			Hysteroscopic cold loop technique	
Rein et al., 2011 (28)	Cohort study	-D&C: February 2004-January 2007 -Hysteroscopic resection: February 2007-NA	95	Diagnosis RPOC by TV Doppler US	NA	TV Doppler US	Spontaneous first or second trimester miscarriage treated with D&C or term caesarean section	Days	HR %	D&C %	Hysteroscopic resection with cold loop technique (n=53)	D&C: metal curette size no. 4 under guidance of transabdominal US (n=42)
								≤ 10	11.3	11.9		
								10-29	45.3	50		
								≥ 30	43.4	38.1		

Appendix 2: Reproductive and obstetric outcome after curettage versus hysteroscopic resection of RPOC

		Complete resection	IUA	Reproductive outcome				Obstetric outcome			Follow up period
				Time to conception (months)	Pregnancy	Miscarriage	Live birth	Mean pregnancy time	Birth weight	Placental complication	
Ben-Ami et al., 2014 (29)	D&C	/	/	12.9 (SD 16,8)	92.6% (87/94)	11.7% (11)	88.3% (83/94)	38.2 (SD 2.5)	3055 (SD 528.4)	4.3% (4.94)	NA
	HR	/	/	7.4 (SD 7)	92.8% (77/83)	19.3% (16)	80.7% (67/83)	38.1 (SD 4.2)	2984 (SD 485.7)	13.3% (11/83)	
	p-value		/	0.037	0.340	0.276	0.267	0.811	0.551	0.177	
Cohen et al., 2001 (27)	D&C	79.2% (19/42)	/	11.0	62.5% (10/16)	30% (3/10)	70% (7/10)	NA	NA	NA	≥ 6 months (range 6-42 months)
	HR	100% (46/46)	/	7.3	82.3% (14/17)	7.1% (1/14)	71.4% (10/14)				
	p-value	/	/	<0.03	NS	NS	NS				
Hooker et al., 2015 (13)	D&C	84.8% (89/105)	19.6% (18/92)	NA	80% (4/5)	23.8% (5/21)	76.2% (16/21)	NA	NA	NA	At least one-year follow up
	HR	77.3% (17/22)	25.0 (5/20)		75% (12/16)						
	p-value	0.36	0.55		0.62						
Rein et al., 2011 (28)	D&C	97.4% (38/39)	30.8% (12/39)	14.5	-59.5% (22/37) -<35years 66.6% (20/30)	-1st trimester 15% (3) -2nd trimester 0% (0%)	45.9% (17/37)	/	/		At least 24 months (range 8-38 months)
	HR	100% (48/48)	4.2% (2/48)	11.5	-68.8% (31/45) -<35years 78.1%(25/32)	-1st trimester: 6,9% (2) -2nd trimester: 3.4% (1)	57.8% (26/45)	/	/		
	p-value	NA	<0.001	0.036	-0.035 -<35 years 0.028	-1st trimester: 0.227 -2nd trimester: 0.382	/	/	/		

Appendix 3: Reproductive and obstetric outcome after hysteroscopic resection of RPOC

	IUA	Reproductive outcome					Obstetric outcome	Follow up
		Mode of conception	Time to conception	Pregnancy	Miscarriage	Live birth		
Faivre et al., 2009	9% (2/22) mild IUAs	- spontaneous (n=2) - ovulation induction (n=1)		- Overall: 76% (23/30) - 35y: 88% (15/17) - >35y: 66% (8/13)	7	70% (21/30)		39/50 ≥ 12 months follow up (3 lost to follow up, median 43 months (range 23-69) 11/50 NA
Fuchs et al., 2014	- Intervention group: 5% (1/21) IUA AFS stage 3 - Control group: 15% (3/20) IUA AFS stage 2 or 3 - Total: 10% (4/41) IUA AFS stage 2 or 3	NA	NA	- Intervention group: 33% (7/21) - Control group: 15% (10/41) - Total: 24% (10/41)	NA	NA	NA	- Intervention group: median 22 months (range 3-41) - Control group: median 24 months (range 5-31)
Golan et al., 2011	NA	- Spontaneous (n=22) - IVF (n=1)	57% (16/23) conceived within 1 year 14% (4/23) conceived within 2 years 7% (2/23) conceived within 3 years	82% (23/28)	1	75% (21/28)		43/159 ≥ 3 years (reproductive outcome) 116/159: NA
Jimenez et al., 2009	NA	NA	8.4 months (SD 7,1)	78,6% (24/30)	18.2 % (4/24)	63.6% (15/24)	NA	NA
Ikhena et al., 2016	NA	NA	Median time 29 weeks (range 2-295)	49.5% (55/111)	7.3% (4)	69% (38/55)	Abnormal placentation: 18% (10/55) -3 placenta previa	18 months

							-2 placenta accreta -5 retained placenta	
							Postpartum hemorrhage: 1.8% (1/55)	
							Gestational age: 37 weeks ± 5.6	
							Birth weight: 3.8 kg ± 0.4	
Sonnier et al., 2017	6/22	71.1 % at 6 months 83.5% at 1 year	160 (SD ± 139) days	71.1% at 6 months 83.5% at 1 year	4/44	NA	NA	22+-18 months