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Hysteroscopy

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..... this book is dedicated to all those who have a dream in the drawer, who are constantly trying to improve, who do not want to stop at current scientific knowledge. Because only those who are tenacious, who are stubborn and those who seek to improve the future can realize their dreams .....

We have tried to realize a scientific dream and we probably have succeeded with the help of so many colleagues who believed in our initiative.

Thanks to all our colleagues and friends who have been valuable adventure companions and have been walking our way.

Preface

Hysteroscopy for years has been part of the cultural baggage and main diagnostic instrumentation of each gynecologist. Hysteroscopy allows performing any intravaginal and intrauterine diagnoses and surgical treatments, in "office" or in operating room, even in the most complex cases.

From the knowledge of the technique, it is possible to carry out a diagnosis and to perform, at the same time, the treatment in the outpatient, by a "see and treat" modality. And it is in the hysteroscopy that we have devoted some of our scientific and life experiences.

After a few scientific meetings, where we, the three Editors, have met, we have come to life with a deep friendship and idea: to have on hysteroscopy topic a whole world congress and a manual, the most up-to-date and detailed possible, consisting of the most big world experts, some of whom were invited as speaker and chairmen.

Thus, a great project was born: the Global Congress on Hysteroscopy, which was held in Barcelona from 3 to 5 May 2017, with over 750 colleagues from more than 60 nations and from all continents. The Book has been presented to the congress, consisting of more than 60 chapters, illustrated by over 700 images, of which over 600 are in color. Each chapter was made up to the maximum that the topic chosen for the author could offer, devoting a lot of space to graphic illustrations, photographs, and images. In fact, the manual is a kind of Hysteroscopic Atlas Book, which aims to help most gynecologists improve their hysteroscopic know-how and clarify some of the possible doubts that normally arise during their common practice.

The Hysteroscopy Book intends to be a valuable daily work companion, for all the curious gynecologists in their work and eager for a continuous improvement. And this is the purpose for which our idea has grown and realized. We do not know where we can get it, but we know we have made a big leap to offer a strictly scientific and didactic approach to hystoscopy to all colleagues and gynecology students.

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Contents

The Role of Hysteroembryoscopy in the Management of Spontaneous and Repeated Pregnancy Loss

Vasilios Tanos, Demetra Georgiou, Marios Neofytou, Eleftherios Meridis, and Minas Paschopoulos

16.1 Introduction

Three major patient populations are affected by spontaneous and repeated pregnancy loss (RPL).

(a) Older nulliparous women, with or without infertility problem. The miscarriage occurs during 5–10 weeks of gestational age and most often aneuploidy (trisomy) and less frequently deletions and insertions are diagnosed. The RPL is attributed to the aged oocytes and IVF combined with an ovum donation program proved to be very efficient treatment. (b) Patients presenting high blood pressure or antiphospholipid antigen syndrome or anticardiolipin syndrome and usually treated with LMH, aspirin and cortisone. The RPL in this category occurs at progressively earlier gestational age and severe utero—placental vascular insufficiency leading to miscarriage. (c) Younger multiparous women, prone to intermittent fetal loss around the tenth weeks of gestational age. In 3% of the cases, parental unbalanced chromosomal translocation is present. However, the great majority of these patients have no firm diagnosis and are treated empirically [1, 2].

Early sporadic or repeated pregnancy losses might present other and/or more genetic causes. Repeated pregnancy loss (RPL) mainly concerns pregnancies around 8 weeks' gestation and aneuploidies account for less than half of recurrent spontaneous abortions. Information about early aborted embryos remains very limited [3]. Cytogenetic analysis of abortion specimens from couples with recurrent miscarriage has shown that the percentage of chromosomally normal abortions is significantly higher in women (<36 years old) with recurrent miscarriage than in women (<36 years old) in the general population [4, 5]. Detection of a chromosomally normal miscarriage conveys an increased risk for a subsequent chromosomally normal miscarriage [6]. However, the detection of a previous aneuploid abortion has not been proven to increase the chance of a subsequent aneuploid miscarriage [6, 7].

Technological advances provide today small diameter telescopes with excellent viewing ability. Easily a 2.9 mm hysteroscope can be progressed into the cervical canal reaching the endometrial cavity and search for the implantation of the pregnancy sac, its content (embryo, umbilical cord, and yolk sac) and the surrounding decidua in so called hystero-embryoscopy procedure. Dr. Bjorn Westin in 1954 performed hystero-embryoscopy in three embryos, before termination of pregnancy (TOP) during early second trimester. He used the McCarthy's 10 mm telescope. Two cases were performed under GA and one with local anesthesia. He reported active embryo extremities movements and he counted over 30 swallowing movements per minute. Hystero-embryoscopy can be used for an in situ autopsy of an embryo in sporadic as well as in repeated pregnancies loss. Such an autopsy of a miscarriage embryo can provide useful information regarding the morphology of the embryo ruling out anatomical defects and by collecting the embryo and sending it to cytogenetic analysis anticipating an accurate embryo karyotyping. It is well known that the karyotype after collection of products of conception by D&C is unreliable because the risk maternal tissue contamination of female embryos is up to 22% [8].

Many RPL cases that have been diagnosed and treated may experience a consequent miscarriage during next

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pregnancy. The cause of spontaneous miscarriages and RPL cases after diagnosis and treatment facing an additional first trimester loss has been investigated by embryo in situ autopsy and karyotyping. Embryo autopsy was performed using the hystero-embryoscopy technique. The embryo morphology results were correlated with the genetic results and compared with the patients' diagnosis, ultrasound findings and treatment during the last miscarriage. The results of causes leading to miscarriage after treatment could also help to identify the diagnosis accuracy and effectiveness of therapy. Additionally, it was investigated whether information about the cause of the miscarriage would alleviate women pain about their loss, relieve their stress from future uncertainty, encourage and accelerate effort for another pregnancy.

16.2 Patients and Methods

16.2.1 Patients

This is a cooperative, prospective, ongoing study, started in January 2008, run by the departments of Obstetrics and Gynecology at Aretaeio Hospital, St. George's Medical School, in Nicosia University in Cyprus and Ioannina University Hospital, at Ioannina, Greece. Overall, 187 women with first trimester pregnancy loss, 111 patients with a spontaneous miscarriage and 76 with a past history of at least two consecutive repeated pregnancy loss participated in this study.

All patients underwent history, general body and gynecological examinations and laboratory investigations, hystero-embryoscopy and D&C after they signed a consent form.

Patients Inclusion criteria: (1) Women with first trimester miscarriage interested to know about the cause of the pregnancy loss (2) Any miscarriage below 12 weeks of gestational age, according to trans vaginal sonography scan estimation (3) TVU verification of pregnancy sac and absent embryo heart beat (4) no active vaginal bleeding (5) All patients performed FBC, coagulation tests, VDRL, Toxoplasmosis IgG, IgM, Rubella IgG, VZV IgG, IgM HIV I + II, Hepatitis A and Hepatitis C (6) Miscarriages with indication to uterine products of conception evacuation and endometrial curettage (7) Consented patient to undergo hystero-embryoscopy prior to cervical dilatation and uterine suction curettage.

16.2.2 RPL Patients Past Clinical Treatments

All RPL patients were examined and treated when necessary, prior to the study for the following pathologies: (a) congenital uterine anomalies (Septum, T-shaped uterus, etc.); (b) acquired myometrial, endometrial, cervical pathol-

ogies pathologies (fibroids, polyps, cervical insufficiency); (c) microbiological factors (bacterial vaginosis), endocrine factors (LPD, thyroid dysfunctions, obesity, PCOS, androgenism, insulin resistance), nutritional status, alloimune and autoimmune factors, and congenital thrombophilic factors; and (d) during their last repeated miscarriage the one under study did not have vaginal bleeding, transvaginal ultrasound confirmation for absence of embryo heart pulse, and sonographic details like CRL.

16.2.3 Method and Technique

The patients were placed at the lithotomy position and no analgesia or anesthesia was used for the stage of embryoscopy. Embryoscopy of the dead embryos was performed. Once the embryo/s was evacuated from the endometrial cavity, general anesthesia using propofol and oxygen facial or laryngeal mask, cervical dilation up to Hegar, 9 mm and a suction curettage followed. Sharp curettage reassured clearing of the uterine wall.

Hysteroscopes of 2.9 mm and/or 5 mm and/or 8 mm telescope with 30° optic connected to cold light were used. Normal saline was used as a distending medium in order to expand the uterine cavity and visualize the pregnancy sac and the decidua. No analgesia or anesthesia was routinely used for the stage of embryoscopy. Only 30% of the cases requested sedation by propofol after initiation of embryoscopy and mainly was due to psychological reasons and not due to pain.

The decidua, the pregnancy sac and their contents were investigated and embryo sent to genetic analysis. General anesthesia was then applied, cervical dilatation up to Hegar 9 mm was performed and POC suction evacuation followed by an endometrial curettage verifying the clearance of the endometrial cavity.

16.2.4 Hystero-Embryoscopy

Hystero-embryoscopy was used to examine in situ the pregnancy sac, embryo, umbilical cord, yolk sac and decidua. Hystero-embryoscopy without anaesthesia was performed in 38% of the patients. The cervical canal is soft and progression of a 5 mm diameter telescope is smooth and atraumatic. Once entering the endometrial cavity the fluid distention preset pressure to 100 mmHg increased slowly until good viewing conditions are managed.

The cervical canal, endometrium, decidua, cornua and ostia when visible were noted, the pregnancy sac and its implantation site were studied and any abnormalities were registered. Using the 5Fr scissors the pregnancy sac and chorion was open allowing the telescope to enter and visualize

the embryo via the amniotic see through membrane. Most of the cases the final diagnosis about the embryo, umbilical cord and yolk sac condition managed transamniotically. In cases that the embryo should manipulated further in order to be able to establish the final diagnosis the amniotic membrane was incised, the hysteroscope approached and using a 5Fr grasper the embryo was turned to the position best visible. Using 5Fr scissors the umbilical cord was incised to the endometrium site, grasped, and pulled outwards by a hysteroscopic grasper. Small and/or macerated embryos are collected and engaged within the grasper space. The bigger embryos (1–2 cm) were pulled by the umbilical cord or from the head and evacuated using 5 mm or 8 mm diameter scopes, enabling the passing of the embryo through the cervical lumen. The evacuation was completed under vision until the embryo was placed in the culture medium and send to cytogenetic laboratory.

The Carnegie human embryo staging was used to evaluate the embryo development and classify the morphologically normal and abnormal embryos [9]. The genetic analysis performed until 2014 by embryo tissue cultures, extraction of DNA, and cytogenetic analysis and by 2015 using CGH [10].

16.3   Results

Women with spontaneous miscarriage had mean age 32.5 years (27–38), while in RPL mean age was 36 years (25–42). Secondary RPL was noted in 3% of our cases, i.e., they managed to deliver a baby after treatment but during their next attempt to pregnancy faced another miscarriage.

In the spontaneous miscarriage group in eight cases hystero-embryoscopy was unsuccessful and complete evaluation of the embryo and pregnancy sac could not be performed and was excluded from the study. In 87/94 women (70%) miscarriage was diagnosed for the first time at a variable number of pregnancies while 24% (23/94) already delivered at least one child. The cytogenetic results were contaminated in nine cases (8.7%). The 69/94 (73.4%) embryos of women with spontaneous miscarriage were diagnosed with chromosomal abnormalities and 79 (84%) with morphological defects. The types of genetic abnormalities is demonstrated in Table 16.1 and compared with the abortion rate and karyotype in ART cases [11]. Embryos with normal karyotype but morphological abnormalities were diagnosed in (7/94) 7.5% of the cases. Twenty-two embryos (23.4%) found to have normal karyotype and morphology. The embryo in situ morphology and genetic analysis in both SM and RPL cases is presented in Table 16.2. Umbilical cord problem was diagnosed in five embryos, in seven cases defective implantation was noted, four cases presented disputed findings and in six cases no cause of the miscarriage was detected (Table 16.3).

Table 16.1 Embryo genetic analysis in SM, RPL, and SM after ART

Embryo karyotype	Spontaneous miscarriages (94) (%)	RPL (51) (%)	3278 ART abortion cases Qin et al. (2013) (%)
Normal	30	29	51.1
Abnormal	70	72	48.9
Trisomies	62	58.3	71.3
Turner syndrome	21	19.4	Not reported
Tetrasomies	10	15.4	0.9
Monosomy	4	2.8	7.3
Mosaic	3	4	2.4

Table 16.2 Embryo in situ morphology and genetic analysis

Embryo status	Spontaneous miscarriages (94) (%)	RPL (51) (%)
Normal morphology and karyotype	13	15.7
Normal morphology and abnormal karyotype	7	4
Abnormal morphology and normal karyotype	17	13.7
Abnormal morphology and abnormal karyotype	62	66.7

Table 16.3 Non-embryonal factors contributing to miscarriage—umbilical cord and decidua characteristics

Defect/Abnormality	Spontaneous miscarriages (94)	RPL (51)
Umbilical cord defect	5	3
Decidua hematoma/implantation defect	7	2
Disputed reason	4	1
Unknown reason	6	2
Overall	22 (23.4%)	8 (15.7%)

All RPL couples had normal karyotype and women before recruitment were checked per speculum vaginal examination and high vaginal swabs for microscopy and microbiological cultures. Patients underwent ultrasound examination for abdominal and uterine pathologies and hysteroscopy to rule out congenital uterine anomalies. In addition they were examined for alloimmune and autoimmune factors, for thrombophilia, for endocrine factors (thyroid function, insulin resistance, HbA1c, and fasting glucose). The BMI was below 30 for (33/51) 65% of the participants. All patients had normal nutrition and nobody was vegetarian.

Twenty-four of the patients had unexplained RPL. In 12 women congenital uterine anomalies were diagnosed, nine with septum and three with a T-shape uterus, all operated, had second look hysteroscopy reported with normal endometrial cavity. Nine were diagnosed with thrombophilia and treated with low molecular heparin, four diagnosed with

hypothyroidism and received thyroxine with normal TSH FT3 FT4 serum levels and three with luteal phase insufficiency treated with vaginal and/or subcutaneous progesterone. Two women with anticardiolipin syndrome were administrated steroids and two with alloimmunization were treated with their husband WBC. All patients upon admission were examined with TVS to verify the pregnancy loss, to measure the pregnancy sac diameter and embryo CRL, to look for the yolk sac, to check the endometrial cavity and cervical canal for blood collection.

The 55 out of 56 embryos were evaluated. In 55 cases hystero-embryoscopy was successful and complete evaluation of the embryo and pregnancy sac was performed. The cytogenetic results were contaminated in five cases (9%). In 15 out of 51 cases 29.4%, normal karyotype was reported. In 36 cases (71.7%) an abnormal karyotype was found, whereas 21/36 cases were trisomies 58.3% (14—Trisomy 22, 4—Trisomy 16, and 4—Trisomy 18), 7 (19.4%) were Turner syndrome, 7 (19.4%) tetrasomies, and one (2.8%) was monosomy (Fig. 16.1). Correlation of the embryo morphology and embryo karyotype revealed 66.7% (34/51) embryos with abnormal karyotype and morphology, 4% (2/51) with abnormal karyotype and normal morphology, 13.7% (7/51) with abnormal morphology and normal karyotype and 15.7%
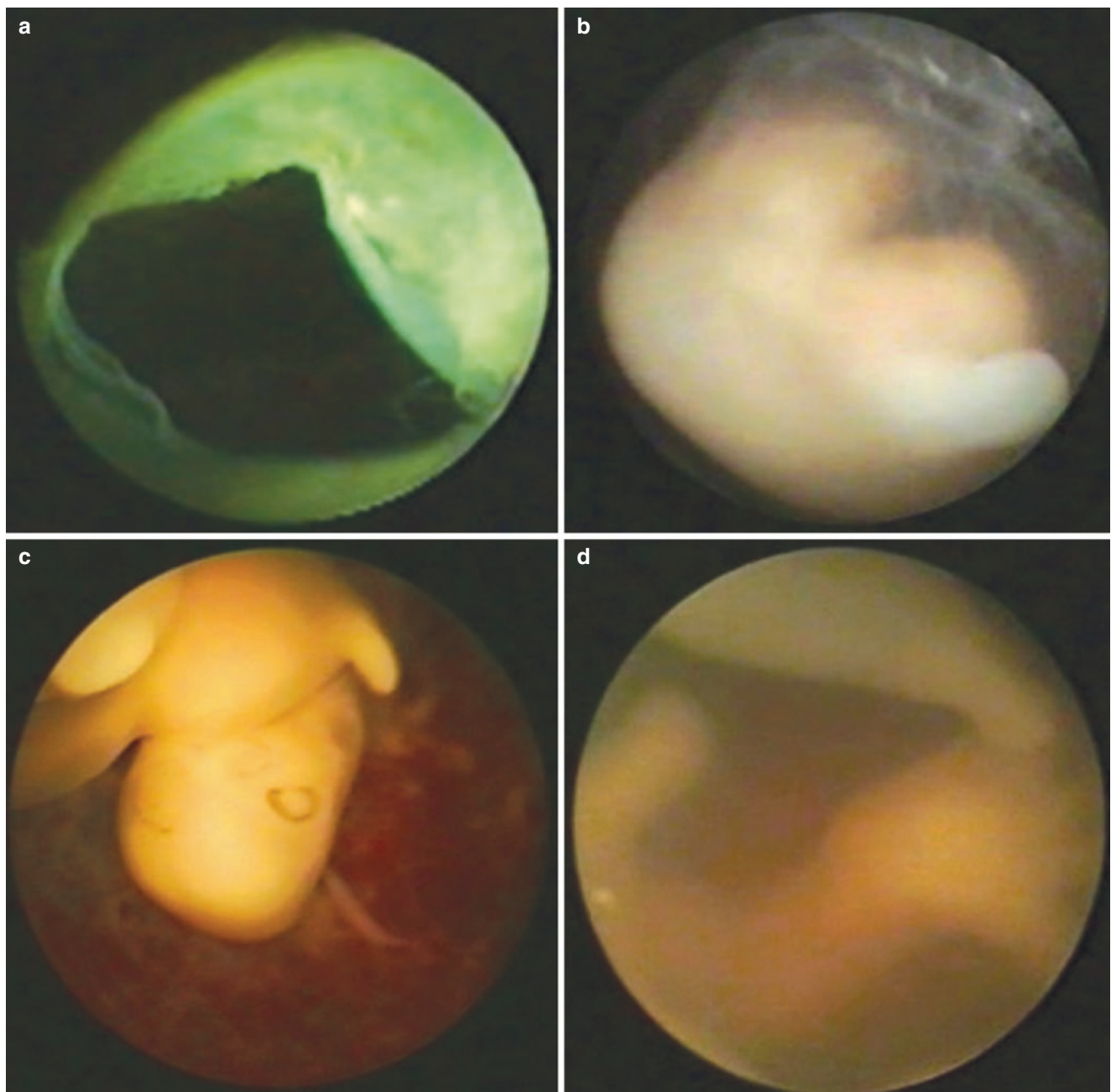
Fig. 16.1 (**a**) Incision of the pregnancy sac (**b**) Embryo 8w with anencephaly normal female karyotype (**c**) Embryo 9w with maldevelopment of the left eye, normal male karyotype (**d**) Male phallus observed at 11 weeks
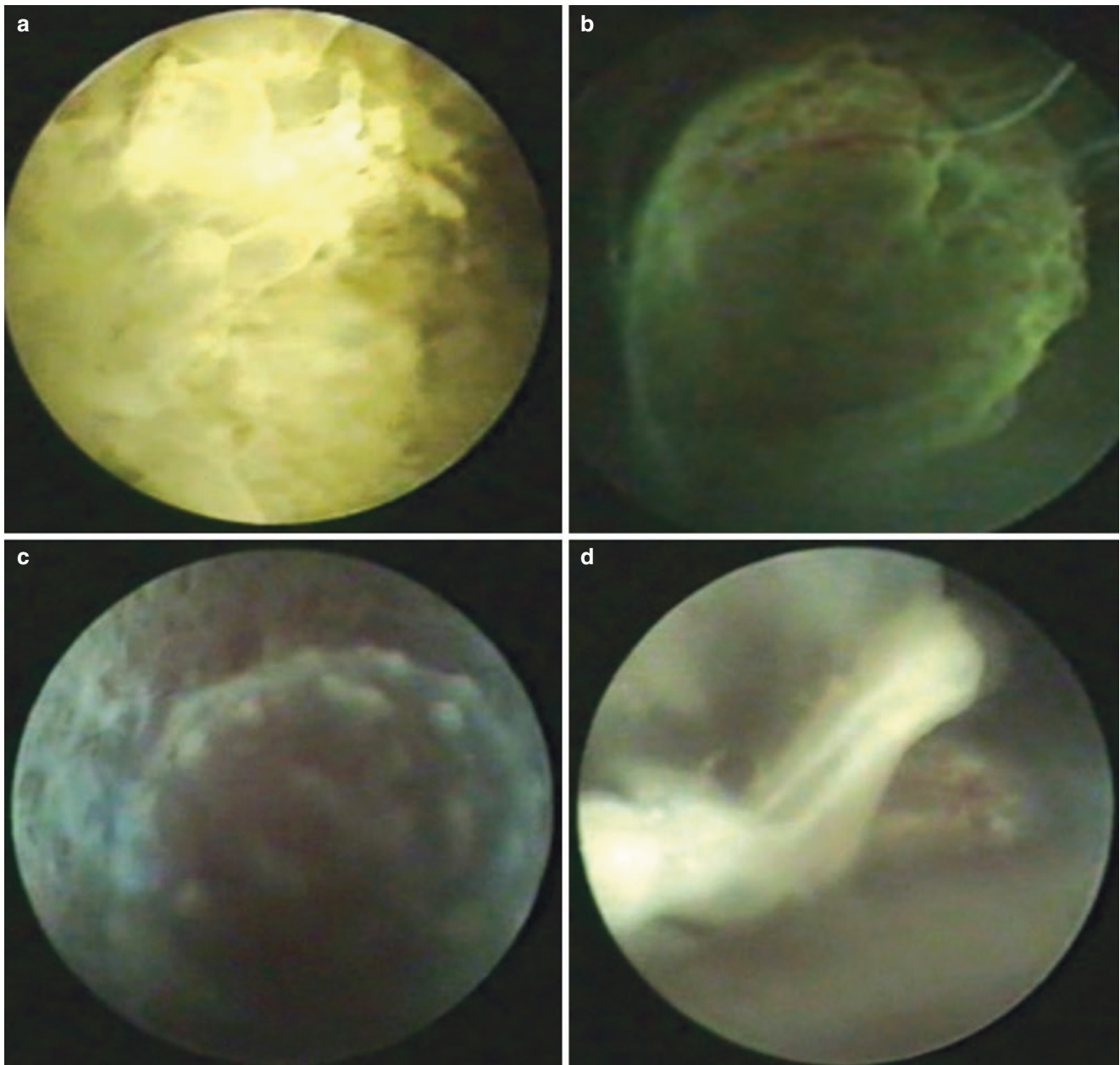
Fig. 16.2 (**a**) Anembryonic pregnancy—trophopblast [92,XXYY] tetrasomy at 6 weeks (**b**) Macerated embryo 7w tertiary monosomy [46XY, +der(11;22)(q23;q11.2),-22] (**c**) Malformed (prickly) yolk sac at 6 weeks [47, XX+8] (**d**) Deformed embryo (stick) [47, XX+8]

(8/51) with normal morphology and karyotype (Fig. 16.2). Eight embryos found to have normal karyotype and morphology. Three embryos had umbilical cord suspected problem two cases with clot in the cord and one case cord disruption. In another three embryos with normal phenotype the cord was also within normal limits; however, in two cases decidua blood clots (old and fresh) were prominent. In two cases we were unable to detect the cause of the miscarriage.

The embryo morphology and genetic analysis for both spontaneous and repeated miscarriages are presented in Tables 16.1 and 16.2. Other factors such as decidua hematoma, and implantation and umbilical cord defects are shown in Table 16.3.

16.4   Discussion

According to the literature first trimester miscarriage is the most common complication of pregnancies conceived either spontaneously or through assisted reproductive treatment (ART), with embryonic chromosome anomalies accounting for approximately 50% of these losses [12]. In our study, the major cause of the pregnancy loss in both SM and RPL groups, were chromosomal abnormalities accounting up to 70%, followed by embryo morphological defects in 17% and 15.7% respectively. To less extend the reason of the miscarriage was attributed to no embryonal cause such as decidua

hematoma, implantation and umbilical cord defects 17% in SM and 12% in RPL. In 10.6% of the SM cases and in 5.9% of the RPL the cause of the miscarriage remained undiagnosed even after HEpy. First-trimester miscarriage occurs in 10–15% of all clinical recognized pregnancies, with embryonic chromosomal abnormalities being the most common cause of spontaneous miscarriage, which accounting for approximately 60% of these pregnancy losses [13, 14]. Our study aligns with several studies demonstrating that the major reason of miscarriages is aneuploidy and one of the determining factors is increasing maternal age [15–17]. The main cause is chromosomal disarrangements arising due to the prolonged time arrested oocytes in meiosis I before ovulation [18, 19]. The incidence of meiotic error in oocytes is elevated in women with advancing maternal age and usually IVF by ovum donation offer the best treatment option. The rate of early spontaneous abortion in patients after ART is ranging from 22%–63%. The failure of ART treatment is associated with many factors, genetic defects especially embryonic chromosomal abnormalities, are one of the major causes of spontaneous miscarriage during the first trimester [17, 20, 21]. The techniques employed for ART may also have an increased risk of chromosomally abnormal products of conceptions compared to natural conception, and result in early pregnancy loss. Furthermore, it has been assumed that the risk of embryonic chromosomal abnormalities may be associated with different type of assisted reproductive technologies utilized [11, 22].

Following pregnancies in young and healthy women after SM usually lead to a take home baby. In SM using HEpy and embryo genetic analysis we diagnose the cause of the miscarriage in more than 90% of the cases. In a study with combined SM and RPL cases, HEpy also demonstrated high accuracy competence in diagnosing the cause of the pregnancy loss at 86–91% [3, 23, 24]. HEpy can answer in most of the cases, patients' questions, especially about the reasons leading to pregnancy loss, alleviating the psychological stress. Occasionally as in CNS embryo defects high doses of folic acid are recommended before initiation of the next pregnancy.

RPL occurs in 1–3% of couples aiming pregnancy, mainly involves pregnancies 6–11 weeks' gestation and embryo aneuploidy is found in over 50% of the cases. Our selected group of RPL patients, were all examined for the reason of RPL in their previous miscarriages hence the study miscarriage presented a quiz regarding the cause of the loss. All couples had normal karyotype examinations ruling out parental balanced translocation; however, in women over the age of 35 the risk of chromosomal abnormalities was high, explaining probably the loss. In our series chromosomal aberrations consisted 70% of the cases being the most prevalent reason of pregnancy loss. Information about early aborted embryos remains limited and aneuploidies account for less than half of recurrent spontaneous abortions in many literature reports. Our study demonstrated that RPL have more genetic causes up to 70% of the cases and similar results reported by others [3, 25].

In our study the abnormal karyotype correlated with the early gestational age. The earlier the miscarriage occurs, the greater the likelihood that an embryonic/fetal chromosome aberration present. First trimester RPL chromosomal abnormalities are around 50% of cases and second trimester RPL chromosomal anomalies are about 20% [26, 27]. Chromosomal abnormalities, is the most common cause of RPL [3, 28]. The rate of chromosomally abnormal embryos decreases as the number of miscarriages increases. Higher maternal age increases the risk of embryonic/fetal trisomy from incorrect distribution of chromosomes. A study by Philipp T et al. in 2003 [29] in SM detected Trisomy 16 in 30%, Trisomy 22 in 14%, Triploidy in 15% and Turner syndrome in 20%. No association with maternal age has been found for Turner syndrome, polyploidy or structural chromosomal disorders.

Robertsonian translocation affects the (a) acrocentric chromosomes 13, 14, 15, 21, 22 and (b) reciprocal translocations [30, 31]. Women are carriers in 2/3 of cases, while men are carriers in 1/3 of cases. Structural aberrations (paracentric or pericentric inversion) are much rarer [28]. Parental chromosomal anomalies account for about 3% of cases when more than 3 miscarriages. The risk increases to 5% if the couple has a previous history of stillbirth or already has a previous child with major congenital impairments or mental retardation [31, 32].

The youngest and morphologically normal embryo detected by hysteron-embryoscopy (HEpy) in our series according to Carnegie human embryo staging was 28 days (Fig. 16.1).

The HEpy assisted to in situ evaluation of early embryo development and its surrounding environment. In 51/56 cases the following were clearly visualized: cervical canal, intrauterine cavity, pregnancy sac, chorion and amnion, umbilical cord, embryo, and yolk sac. Both yolk sac and chorion seem to be also affected from the genetic abnormality expressed in the embryo. In 14% off the SM and in 10% of the RPL cases the miscarriage cause was due to implantation or umbilical cord defects. The clear cause of the loss could not be diagnosed in 6% of the RPL and 10.6% of the SM cases. Other etiological factors such as myometrial pathologies (fibroids, adenomyosis) or abnormal endometrial contractility or endometritis or immunological and epigenetic factors of unknown yet origin during the very early gestational age negatively affect embryo normal development [33].

The patients recruited for Hystero-embryoscopy were women wanted to know the cause of their SM, and RPL cases under treatments with aspirin, heparin, cortisone, etc.,

patients after repair of congenital uterine anomalies (septectomy, T shape uterus) and excision of acquired pathologies (myoma and adenomyosis). Also, women after IVF–ET repeated implantation failure and IVF failure after ovum donation. Although the aging factor is the major reason for the RPL the high rate of chromosomal abnormalities even after treatment of these patients, probably indicates other unknown yet, sub-clinical conditions contributing to genetic abnormalities during fertilization. More than 50% of the RPL cases remain undiagnosed even after extensive immunological and coagulation testing, parental karyotyping and products of conception genetic analysis [30–32, 34].

The RPL specialized clinics assisted to approach patients in a systematic way, providing standardized investigation protocols. RPL clinics provide organized and protocol based examinations by rheumatologists, endocrinologists, hematologists, ultrasound experts, and nurses, aiming that this multidisciplinary approach will substantially diminish RPL. The immunological factors seem to be more complex than previously appreciated and coagulopathies including thrombophilia are diagnosed in less cases than before due to improved technologies and disease understanding. Most of the RPL cases are still treated arbitrarily using steroids and/or low molecular heparin. Many colleagues continue to prescribe low dose aspirin in RPL patients and repeated implantation failures after ET by IVF cycles, although this treatment is not supported by the literature. The positive effect of prolonged and/or short treatments of low dose aspirin in RPL is disputed. Among our RPL cases 18% were receiving low molecular heparin postulating that their past cause of RPL was hypercoagulability state after borderline laboratory results or MTHFR heterozygous suspicious high titers. HEpy revealed that in all cases embryos had chromosomal abnormalities ensuring patients that the problem of their loss was not the followed treatment. The clinical diagnosis of RPL varies, but future directions are to investigate biomolecular risk factors for RPL due to multifactorial etiology, SNPs, copy number of variations, gene/protein expression, epigenetic regulation in studies of single genes, and whole-genome analysis [35–37].

HEpy can diminish the number of undiagnosed and misdiagnosed cases, the number of empiric and unnecessary treatments, the discomfort and psychological stress of the patients. Many RPL cases are treated arbitrarily due to lack of evidence regarding the causation of the past miscarriages. Unfortunately, the vast majority of the existing literature reports RPL cases together with spontaneous miscarriages include both first and second trimester abortions and some studies use as the RPL cutoff count the second and others the third miscarriage as definition and inclusion criteria. Inevitably, these results cannot lead to conclusive remarks, neither reviews, or meta-analysis can guide or indicate any specific actions.

Table 16.4 RPL and SM clinical characteristics and patients' inclusion criteria as reported by many studies

	Clinical symptoms and treatment code
A	Definition of RPL after 2 or 3 pregnancy loss. No convincing reasoning as to which definition should be used
B	RPL after consecutive or non-consecutive miscarriages
C	Treatment of RPL initiates after 2 or 3 and more miscarriages
D	Should separate primary from secondary RPL
E	Mixing up results with spontaneous miscarriages and RPL
F	Mixing up results between RPL and repeated implantation failure
G	Endometritis and isolation of pathogens impossible to isolate microbes even during hysteroscopic endometritis
K	Congenital uterine anomalies insufficiently diagnosed (arcuate uterus etc)

The variability of unsettled and/or miss defines biases leading to contradictive and confusing results

Table 16.4 shows the clinical symptoms and treatment code variability as reported in the literature. All studies show about 50% of the early first trimester recurrent abortions are due to embryo chromosomal aberrations. Recent studies demonstrated 60–77% of embryo abnormal karyotype in 1st trimester of RPL although female embryo karyotypes on products of conception after D&C carry up to 22% risk of maternal contamination [8].

Maternal blood may be used to verify questionable female embryo karyotype results however this is costly and not reported in most of the studies. The majority of studies that correlate embryo karyotype to RPL are mixing spontaneous miscarriages with early repeated pregnancy loss, consecutive with nonconsecutive losses and primary with secondary RPL. A substantial percentage of early pregnancy loss report anembryonic pregnancies and karyotype of POC endanger contamination with the maternal tissue. Technically the most difficult part of the hystero-embryoscopy is the evacuation of the embryo as a complete structure and intact as possible. The most efficient way is to cut the umbilical cord from the endometrial side and then use the grasping forceps to pull it all the way out of the endometrial cavity and through the cervical canal under vision and directly place it in the culture medium. Occasionally the whole hysteroscope is removed together with the grasping forceps and the embryo since its bigger diameter prevents the cervical canal to collapse and destroy the tissue or disable the evacuation process. In cases of macerated embryo, and/or very soft is important to grasp and secure part of the embryo within the grasper and pull it through the 5Fr working channel. Recent technological advances in sonography will probably open new ways to explore the etiology of miscarriages. The silhouette sono-embryoscopy technology will probably allow diagnosing embryo morphological abnormalities as early as HEpy, encouraging further embryo genetic analysis by direct in situ

autopsy. Pathologies of junctional zone endometrium, subendometrial adenomyosis and endometrial contractility frequency might present an additional reason of SM and RPL or might be the sole cause, especially in those cases without embryo genetic or morphologic abnormalities.

Conclusion

Chromosomal abnormalities diagnosed in 70% of both SM and RPL cases while morphological defects observed in 51% and 15.7%, respectively. Embryoscopy seems to be a valuable method for accurate diagnosis of the cause during first trimester SM and RPL and can be especially useful for future treatment purposes. In 10.6% of the SM and 5.9% of the RPL cases HEpy failed to diagnose a clear cause of the miscarriage indicating other etiological factors such as myometrial anatomical and functional abnormalities. The diagnosis about the cause of the miscarriage alleviates women pain about their loss, relieve their stress from future uncertainty, encourage and accelerate effort for another pregnancy. Standardization of RPL patients' clinical characteristics criteria and treatment protocols are imperative to perform clinical studies with reliable results. HEpy might have an added value in the armamentarium of modern RPL specialized clinics. The combination of 4D sonography, in situ embryo autopsy together with embryo genetic analysis can probably enlighten our knowledge about the cause of SM and RPL.

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Hysteroscopy During Pregnancy

José Alanís Fuentes and Ana Laura Gutíerrez Aguayo

The development of hysteroscopy has provided a minimally invasive method for common gynecological problems such as abnormal uterine bleeding (Price and Harris [1]).

The increase in the training of doctors, smaller diameter hysteroscopes, a greater emphasis on performed procedures in the medical office, and innovation of procedures during pregnancy have led to widespread use of this important technology.

A *hysteroscope* is a telescope that is inserted through the vagina and cervix all the way into the uterus to visualize the endometrial cavity and both ostia of the fallopian tubes, cervical canal, cervix, and vagina. Hysteroscopy may be performed for diagnostic or therapeutic indications.

The use of hysteroscopy for initial evaluation offers the potential benefit of combining the evaluation with the treatment. It also avoids the risk of losing the focal pathology, as can occur with the random taking of endometrial samples.

As an alternative, hysteroscopy can be used to evaluate deeply or treat lesions identified on imaging studies such as abnormal endometrial transvaginal ultrasound (Hatfield et al. [2]), or to confirm the absence of disease when symptoms persist and initial diagnostic tests are normal (Hinckley et al. 2004 [3]).

The use of hysteroscopy for monitoring abnormal image findings helps to rule out ovarian or tubal pathology that may contribute to abnormal uterine bleeding (Shalev et al. 2014 [4]).

Most women are able to undergo diagnostic hysteroscopy without anesthesia. The benefits of not using it is the prevention of adverse drug reactions, procedure time, and reduced costs (De Iaco et al. 2000 [5]).

Avoiding the use of anesthesia seems particularly suitable for diagnostic procedures utilizing a hysteroscope <4 mm in diameter. For women undergoing simple surgical hysteroscopy such as IUD removal or hysteroscopy with a hysteroscope 4 mm or more, a paracervical blockade is preferred in some countries because it is inexpensive, well tolerated, and reduces pain (Kremer et al. 1998 [6]).

Hysteroscopy during pregnancy by Agüero (1966) has gained more impact, since the first 118 cases of hysteroscopy and pregnancy were gathered in a preliminary statement to the *American Journal of Obstetrics and Gynecology*. In this paper, Professor Howard C. Taylor, Jr. accepted the manuscript changing the title to "Amnioscopy to Hysteroscopy" and adding as a subtitle, "A New Diagnostic Tool;" the rehearsal was continued and modifications were made.

Among them, it was the change of the McCarthy cystoscope for the cold light of Richard Wolf from Germany and in 1967 he unveiled a series of 504 hysteroscopic examinations in which the indications were: premature rupture of membranes, prolonged pregnancy, third-trimester bleeding, fetal death, hypertension induced by pregnancy, Rh incompatibility, suspected hydatidiform mole, and hydramnios.

As of the 1960s hysteroscopy began its work in the field of the pregnant patient with Agüero's 1966 report of 106 pregnant patients who underwent hysteroscopic study with the diagnoses of prolonged pregnancy, premature rupture of membranes, bleeding in the second half of pregnancy, stillbirth, fetal maternal isoimmunization, polyhydramnios, and trophoblastic gestational disease [7].

Our indications in 2016 are described in Table 17.1.

With the birth of access from vaginoscopy, the principle of seeing and treating, and technological development achieved reduction of the diameter of the hysteroscopes. With the knowledge of uterine anatomy, sources of cold light, and the presence of hysteroscopic pumps, from constant pressure and variable volume, with the incorporation of energy applied to bipolar hysteroscopy, the concept of

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hysteroscopic surgery has changed. Many hysteroscopic procedures leave the operating room and are performed in the doctor's office (Fig. 17.1).

Carrera (1998), holds that the field of hysteroscopy during pregnancy has been limited by the hysteroscopists themselves having the Spanish Association of Hysteroscopy as first evidence, which limits the use of the hysteroscope in the first trimester of pregnancy only to removal of an intrauterine device [8] (Fig. 17.2).

Biopsies of embryos by hysteroscopy can be up to 97% of gestational sacs directly from the embryo showing significant differences compared to conventional curettage due to contamination with maternal tissue in 22%, whereas direct biopsies allow a true mosaic diagnosis (Fig. 17.3).

The reduction of embryos (banned in some countries) is feasible via hysteroscopy. It is feasible under direct vision realization without the potential risk compared with that performed with ultrasound guidance (Fig. 17.4).

The study of anembryonic pregnancy clearly shows the presence of fetal material (embryoscopy) in the amniotic sac with possible later genetic study (Fig. 17.5).

Fig. 17.2 Hysteroscopy in pregnancy

Table 17.1 Indications of hysteroscopy during pregnancy

• Polyp of the implantation site
• Ovuloplacental remnants
• Placental acretism
• Embryoscopy
• Fetoscopy
• Embryonic reduction
• Chorionic villus biopsy
• Removal of foreign bodies
• Metroplasty (partial septum)
• Pathology of the isthmus (polyps)
• Pathology of the cervix (polyps)
• Ectopic pregnancy
– Cervical pregnancy (including in isthmocele)
– Cornual pregnancy
– Heterotopic pregnancy (in utero/cervix)

Fig. 17.3 Biopsy

Fig. 17.1 Hysteroscopy in office vaginoscopic approach without anesthesia

Fig. 17.4 Embryonic reduction
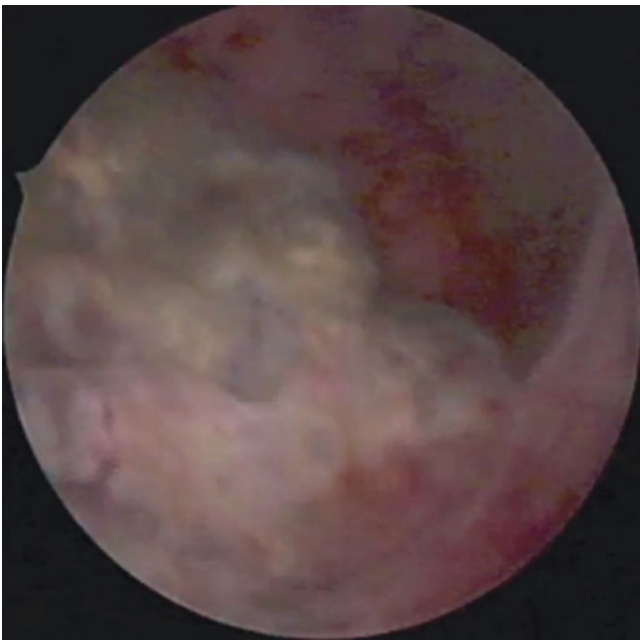
Fig. 17.5 Anembryonic pregnancy

The chorionic villus sampling is feasible by hysteroscopy even from week 6, reducing complications such as caudal regression, which favors the opportunity for genetic diagnosis long before amniocentesis [9].

One of the main fields of hysteroscopy is IUD removal during pregnancy. Timothy and Hardy commented that the pathology of the isthmus and neck are like polyps and momas during pregnancy and is a sparsely researched field. It can be treated by hysteroscopy as long as cervical dilation is provoked, and to avoid the risk of abortion or childbirth, special attention must be paid to prevent the development of uterine activity [10] (Fig. 17.6).

Embryoscopy and fetoscopy can be performed in justified cases such as the infancy of amniotic bands (Figs. 17.7 and 17.8).
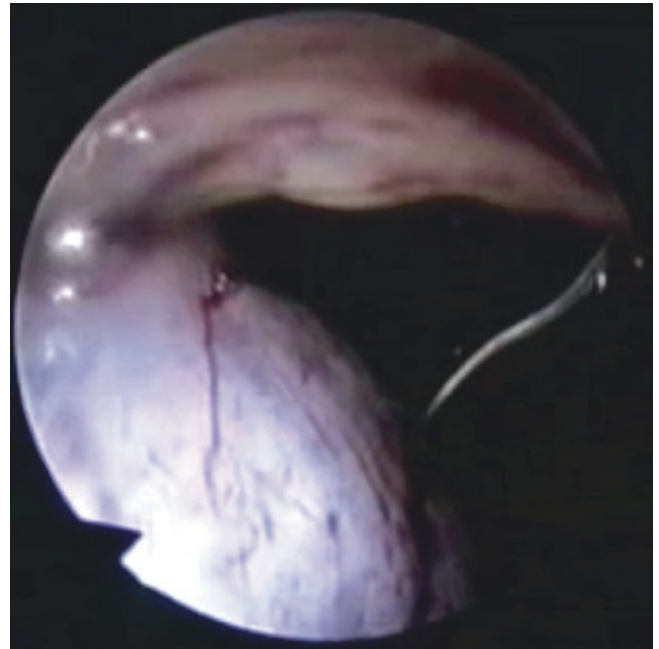
Fig. 17.6 IUD and pregnancy
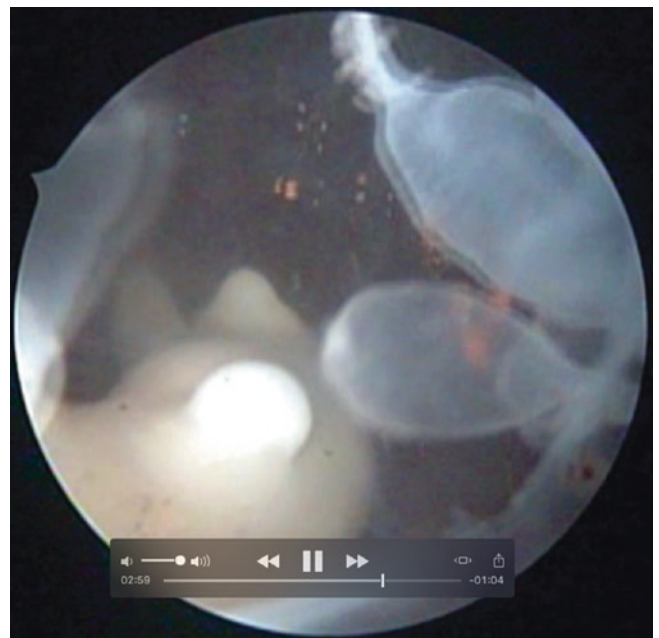
Fig. 17.7 Embryoscopy HMR
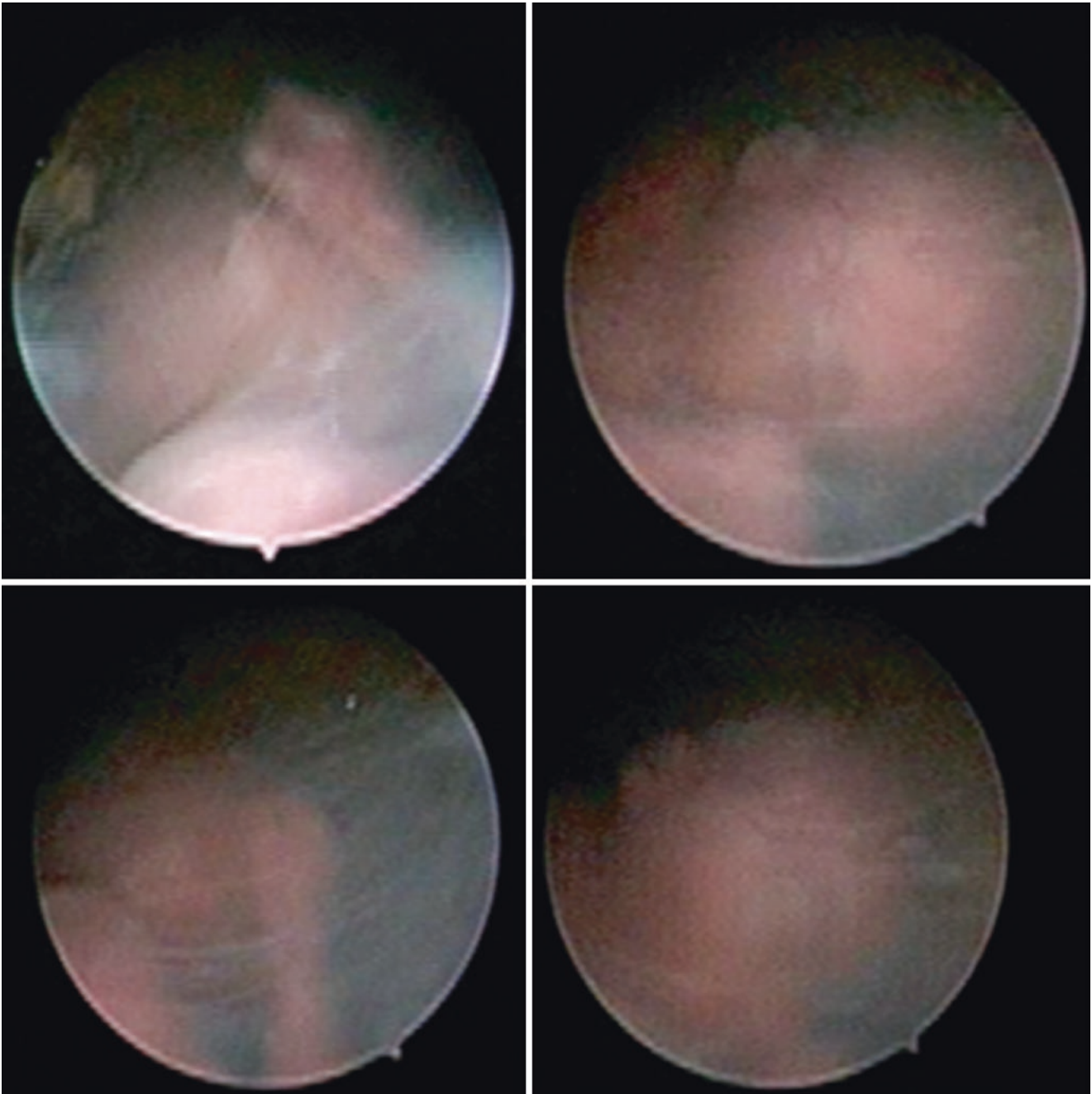
Fig. 17.8 Fetoscopy

Cervical and isthmic polyps during gestation are reserved only if they cause cervical bleeding or dilation that compromise the pregnancy (Fig. 17.9)

Sanz and Verosko (2002) [11]. Cervical pregnancy (Fig. 17.10) offers a real challenge because a large percentage of the patients previously underwent hysterectomy whereas hysteroscopy provides a conservative surgery [12].

There are few reported cases of cornual pregnancies treated by hysteroscopy and sometimes using the laparo-scopic control and the consequent emptying of the uterine cavity by endouterine suction (Fig. 17.11).

In some cases the intrauterine heterotopic cervical pregnancy is also treated in the same way as cervical pregnancy only with the resolution of intrauterine pregnancy to term. In women with pregnancy and with an intrauterine device, it should be removed to prevent pregnancy loss.

Pasic (2002) [13] posits one of the techniques for removal of the IUD is hysteroscopy, inasmuch as a camera and light source allow you to look inside the uterine cavity, and locate
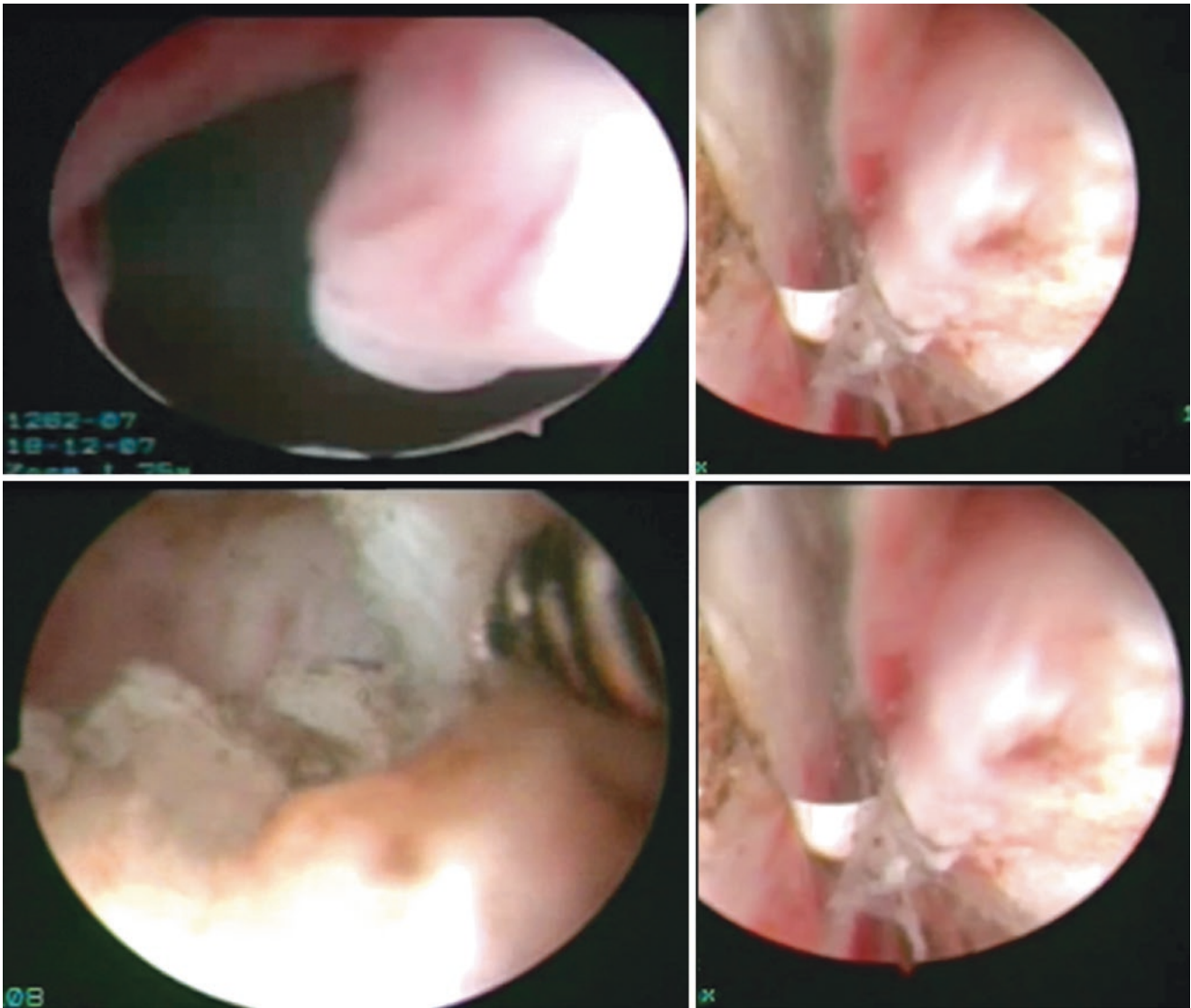
Fig. 17.9 Polypectomy during pregnancy

the gestational vesicle and its relationship with the intrauterine device

Lin et al. (1993) [14]. The hysteroscopy in pregnancy assumes the probable theoretical risk of inducing abortion by membrane rupture and possible harmful effects to the embryo. Assaf et al. (1992) [15] recount the possibility of injury to the optic nerve of the fetus when subjected to the light beam from the light sources commonly used. The optic nerve is a set of fibers born in the retina that uses the optic stalk covered by the meninges. The first draft in embryology of the eye appears at the fourth week as outgrowth pairs of the diencephalon wall.

Hysteroscopy during pregnancy is a topic with little scientific literature (Van der Pas [16]) but it is known that CO_2 flow has been used as a means of carrying out these cases of hysteroscopy such as the use of flexible hysteroscopes or in particular cases rigid hysteroscopes.

The myelination of optical fibers is not complete at birth. After exposure of the eyes to light for about 10 weeks, the myelination is completed, but the process usually ends near the optic disc, the place where the optic nerve enters the eyeball. Alanís recently found that normal newborns can see, although not too well; they respond to changes in light and are capable of fixing contrast points [17].

In Mexico in the Manuel GEA González Hospital 13 withdrawals of intrauterine devices were made during pregnancy by hysteroscopy during the period of 2000–2008. The
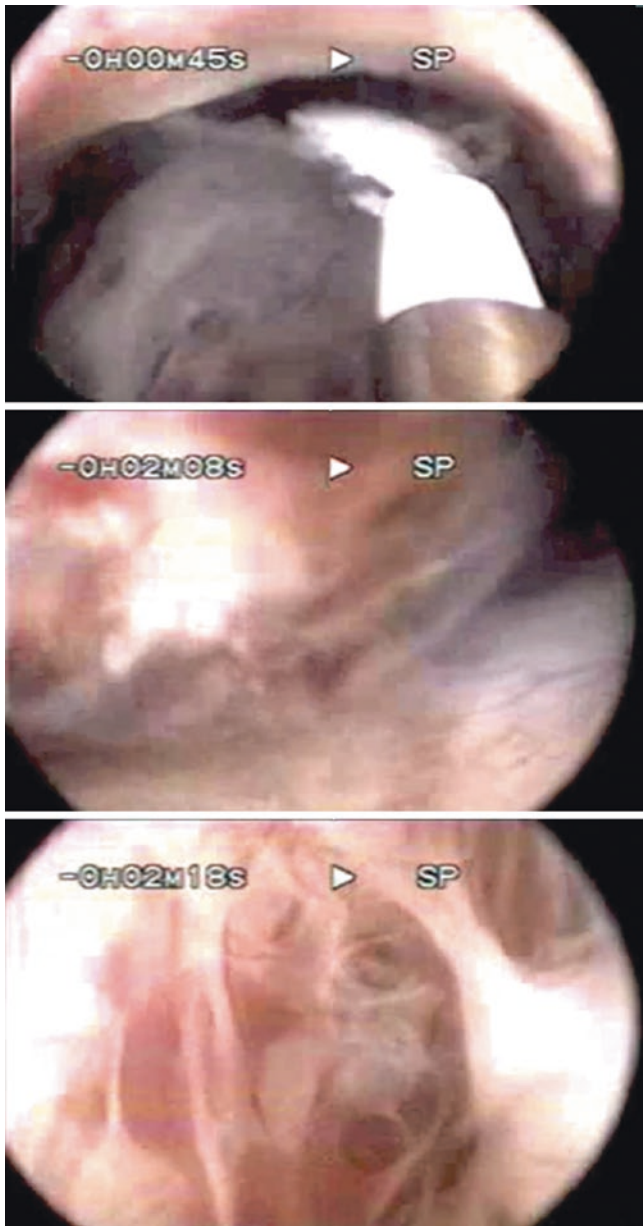
Fig. 17.10 Ectopic pregnancy cervical

Table 17.2 Visual acuity results refraction $n = 13$

Myopia	0
Hyperopia	4
Presbyopia	0
Emmetropia	1
Astigmatism	8

IUD removals took place during the first trimester in 10 patients (76.9%), in the second trimester 3 patients (23.1%) and none in the third trimester. No patient had congenital anomalies and all visual reflexes were normal Alanís (2014) [18]. The evaluation of 13 children born after the removal of the IUD comprised females equal to 38.5%, and eight males corresponding to 61.5% (Table 17.2).

The application of hysteroscopy in pregnancy currently is repressed by the theoretical risk of inducing abortion and possible harmful effects to the embryo. Injury to the optic nerve of the fetus should be assessed in all possible cases when subjected to the light beam from the light sources commonly used, That is why the European Society of Hysteroscopy does not recommend performing this technique in pregnant women over 10 weeks; in our experience removal of IUDs was carried out during the first quarter from 6.5 weeks to 17 weeks; all underwent ophthalmologic examination of integrity of the optic nerve and retina although prevalent refractive errors such as farsightedness and astigmatism in their simple or mixed component but not results of altered optic nerve disorders [18] were considered.

We recently (Menocal 2016 [19]) ventured into the partial septum metroplasty in a patient with five previous pregnancy losses at the request of the patient achieving a successful procedure with a favorable perinatal outcome Fig. 17.12.

We conclude that the medical office hysteroscopy is a safe and minimally invasive procedure during pregnancy with good clinical and functional results, even missing lines of research and scientific input on the subject, but in pioneering jobs its use has been a major benefit during pregnancy.
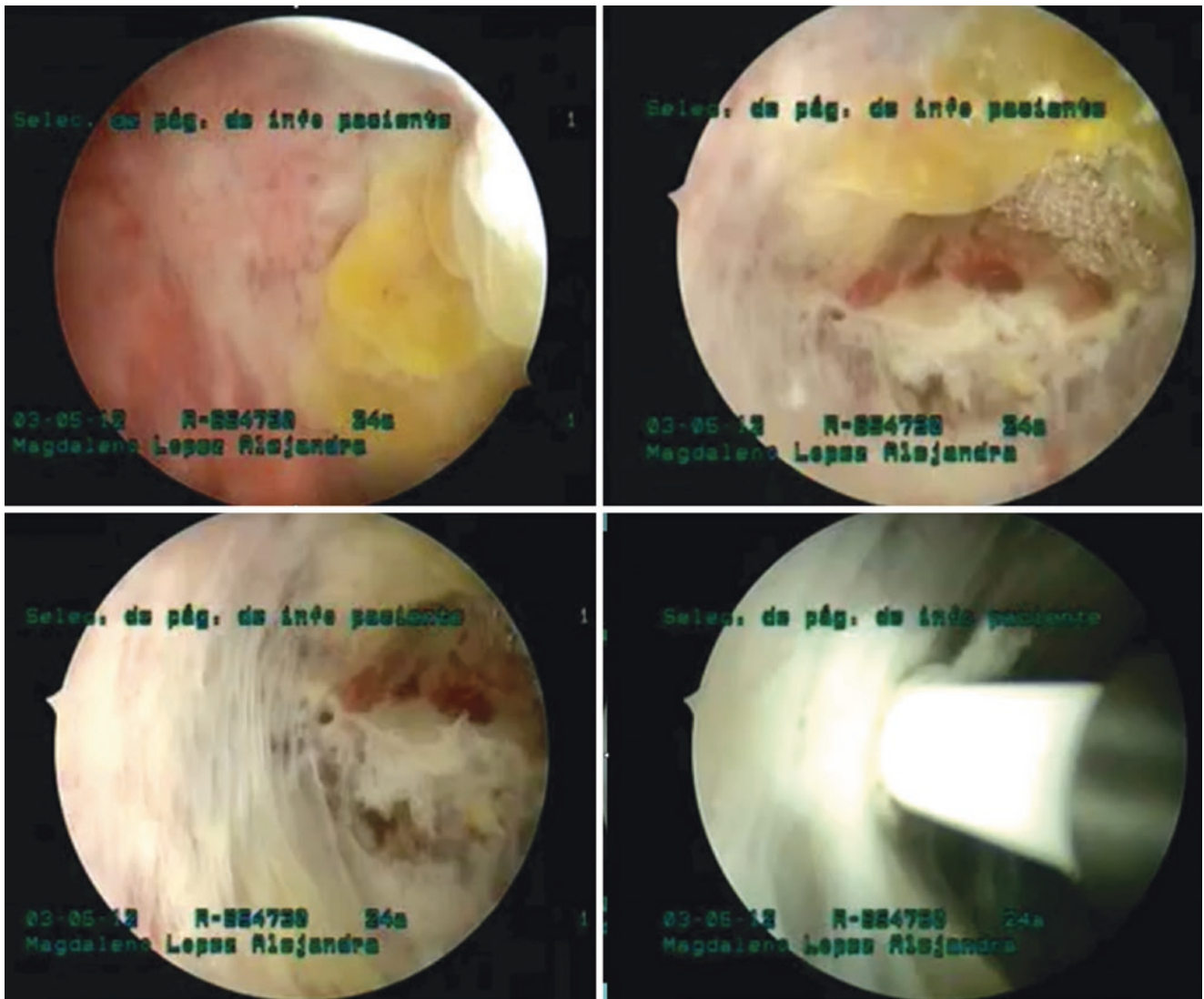
Fig. 17.11 Ectopic pregnancy cornual
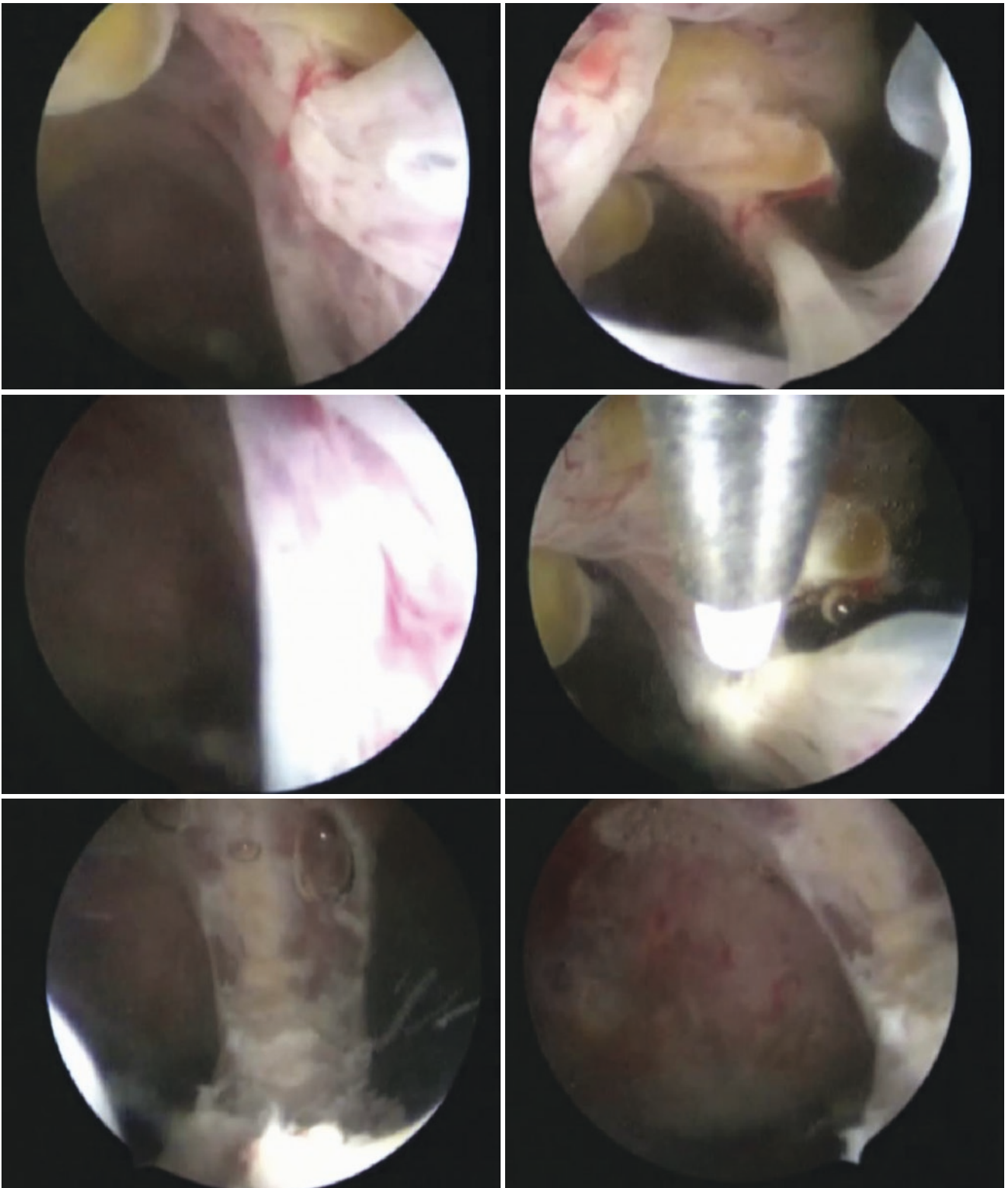
Fig. 17.12 Metroplasty during gestation

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Cervical Ectopic Pregnancy: The Role of Hysteroscopy

18

Salvatore Giovanni Vitale,
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18.1 Introduction

The implantation and development of a fertilized ovum outside the uterine cavity is defined as an ectopic pregnancy. Ectopic pregnancy can occur as an acute emergency and a life-threatening event, accounting for up to about 10% of all maternal mortality [1, 2].

The incidence rate of ectopic pregnancy is approximately 2% of all pregnancies. Over 95% of ectopic pregnancies are implanted in the fallopian tube (tubal pregnancy), usually at the level of the ampullary tract. In other cases, they may be located at various levels of the fallopian tube: isthmic, infundibular, and interstitial. Non-tubal ectopic pregnancies include ovarian, abdominal, cervical, and caesarean scar pregnancy. Occasionally, pregnancy can be located in both intrauterine and extrauterine sites; in this case, it is defined as a heterotopic pregnancy [3].

Cervical pregnancy (CP) is a rare form of ectopic pregnancy accounting for approximately less than 1% of all pregnancies; it is defined as the implantation of the blastocyst in the endocervix below the internal os [4–7] (Fig. 18.1).

The first report of cervical pregnancy in the literature was in 1817 by Home, but only later, in 1860, did Rokitansky introduce the current term "cervical pregnancy" [8]. In 1911, Rubin [4] outlined the anatomic criteria for the definition of cervical pregnancy: placental tissue in the immediate vicinity of the cervical mucosa. In 1959, Paalman and McElin [9] proposed some clinically practical criteria, which included

profuse but painless vaginal bleeding and amenorrhea; a soft distended cervix that is usually larger than the corpus; palpable placenta in the endocervix; and a closed internal cervical os. CP is a potentially life-threatening condition as the trophoblast can erode the endocervix as a result of its invasive capacity, causing serious and heavy bleeding [10] (Fig. 18.2). In the past, to save the patient's life, treatment often required a hysterectomy, particularly in those patients with a large and unrecognized cervical ectopic mass. The improvement in ultrasound resolution and thus an earlier detection of these pregnancies has led to the development of more conservative treatments, with the attempt to limit morbidity and preserve fertility. Recently, there has been a
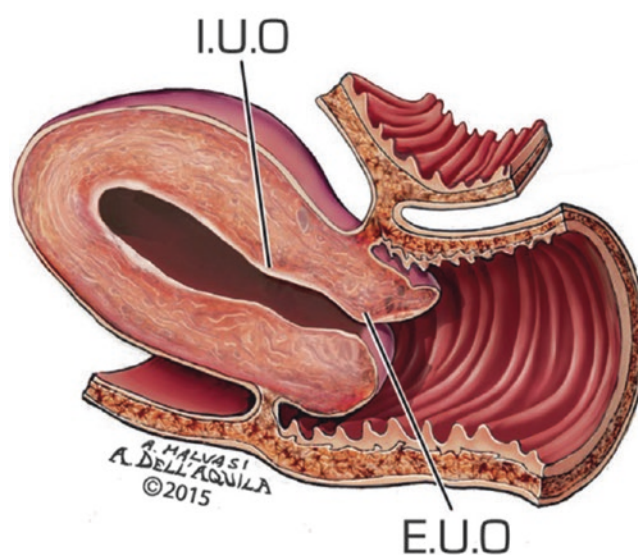
Fig. 18.1 Cervical ectopic pregnancy is defined as implantation of a fertilized ovum in the endocervical canal, located between the external uterine orifice (EUO) and internal uterine orifice (IUO). Figure is taken *from: Malvasi A, Tinelli A, Di Renzo GC. MANAGEMENT AND THERAPY OF EARLY PREGNANCY COMPLICATIONS – First and Second Trimester. SPRINGER UK-USA Publisher, 2016; Hardcover, ISBN 978-3-319-31375-7*

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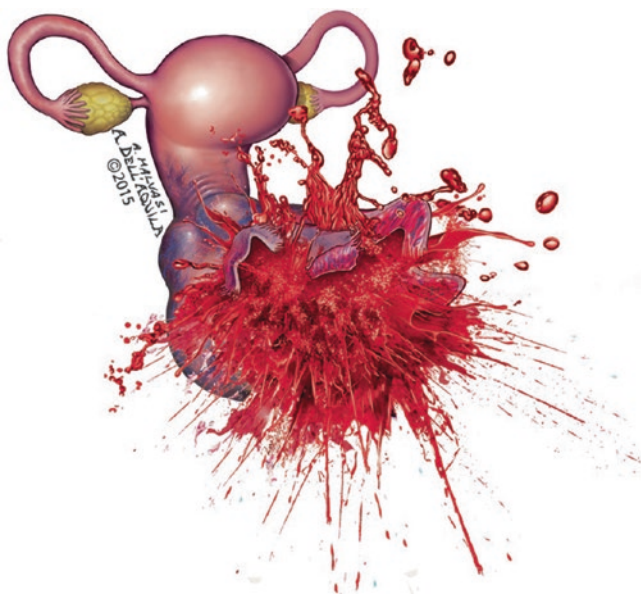
Fig. 18.2 The cervical pregnancy could lead to life-threatening situations for massive hemorrhage by uterine cervix explosion, usually without pain. Figure is taken *from: Malvasi A, Tinelli A, Di Renzo GC. MANAGEMENT AND THERAPY OF EARLY PREGNANCY COMPLICATIONS – First and Second Trimester. SPRINGER UK-USA Publisher, 2016; Hardcover, ISBN 978-3-319-31375-7*

greater spread in the use of the hysteroscopic technique, offering the advantage of enabling a diagnostic and therapeutic approach at the same time [11–13].

However, even today, given the rarity of this condition, the most effective management is under investigation. In the chapter we discuss the current knowledge regarding CP, the importance of a early diagnosis in order to provide a conservative treatment, and available therapeutic options, highlighting the role of hysteroscopy and its advantages in the conservative management of CP.

18.2 Epidemiology

The overall incidence of ectopic pregnancies is approximately 2%, yet it remains the leading cause of death during the early trimester of pregnancy, accounting for 4–6% of all pregnancy-related deaths [14, 15]. Cervical ectopic pregnancy is a rare variant of ectopic pregnancy. It comprises less than 1% of all ectopic pregnancies with an estimated incidence varying between one in 1000 to one in 18,000 [5]. However, it carries the potential risk of large-scale blood loss and, when unrecognized, a mortality rate of between 40% and 45% has been reported [16].

In recent years, the incidence of CP has increased. This may be a result of the increase in assisted reproductive technology and cervical surgery as well as better diagnostic modalities [17].

18.3 Pathogenesis and Etiology

The etiology of cervical ectopic pregnancy still remains unknown. Varying hypotheses regarding its occurrence have been postulated: on the one hand, it has been hypothesized as an overly rapid transport of the blastocyst through an immature endometrium, thus incapable of accepting a fertilized ovum for nidation; on the other, it has been considered as a condition in which fertilization occurs in the cervix with subsequent implantation in the cervical canal [18]. Thus, all those factors that may cause a deterioration in the structure of the endometrium, compromising the nidation of the ovum in the uterine cavity, or those that promote the nidation of the ovum in the endocervical portion of the uterus, can be considered as risk factors that could lead to cervical pregnancy [19]. Most of the cervical pregnancies are iatrogenic in origin, and others may depend on a combination of several factors (Table 18.1). Manipulation of the endocervical canal, uterine curettage as a result of miscarriage, presence of an IUD, endometriosis in the cervical portion of the uterus, endomyometritis and pelvic inflammatory disease (PID), anatomic abnormalities, Asherman's syndrome, fibroids, intrauterine adhesions, previous caesarean section and uterine surgery in general, as well as assisted reproduction techniques and a history of diethylstilbestrol exposure are all factors associated with cervical pregnancy. Among these, a history of uterine curettage is considered to be the main risk factor and can be found in up to 70% of cervical pregnancies. Cervical pregnancy may also be more prevalent in pregnancies resulting from assisted reproductive technology, occurring in an estimated 0.1% of in vitro fertilization pregnancies. Cigarette smoking has been discovered to be a moderate risk factor of ectopic pregnancy in general. All described risk factors may lead to a disturbed materno-embryonal dialogue with a subsequent alteration in the implantation process of the blastocyst [20–25].

Table 18.1 Risk factors for cervical ectopic pregnancy

Induced abortion with sharp curettage
Manipulation of the endocervical canal
History of caesarean section
Uterine surgery
Structural uterine and cervical anomalies
Uterine fibroids
Endometrial atrophy
Asherman's syndrome
Intrauterine devices
Previous sexually transmitted disease
Endometritis
Pelvic inflammatory disease
Endocervical endometriosis
Cigarette smoking
Diethylstilboestrol exposure
In vitro fertilization

Cervical implantation can occur in different ways. The gestational sac could grow up to the external os. It also could reach the uterine cavity, in a normal evolution of the pregnancy, even if the implantation of the placenta would be on the internal uterine os. Alternatively, it could also completely develop in the cervical channel. The cervix is a highly vascularized area, potentially suitable for implantation of a fertilized ovum but also extremely vulnerable to heavy bleeding. Microscopically, only 20% of cervixes contain smooth muscle. The majority of non-contractile fibrous tissue has a suboptimal hemostatic mechanical capacity and is insusceptible in terms of responding to uterotonic agents [18].

18.4   Diagnosis

Diagnosis and treatment of CP have changed enormously in the last 20 years. In previous decades, a diagnosis was made when dilation and curettage, performed in the case of a presumably incomplete abortion, resulted in sudden and uncontrollable hemorrhage. Hysterectomy was used in order to save the woman's life. The fast improvement of ultrasound techniques already changed the scenario of pregnancy management [26].

Today, cervical pregnancy can be diagnosed by ultrasound (US) during the first trimester of pregnancy, so that the patient's fertility can be preserved trough a praecox recognition of the condition [27]. A diagnosis of cervical pregnancy can be given on the basis of symptoms, a physical examination, and laboratory investigations. The most common symptom is vaginal bleeding, which is often profuse and painless. Lower abdominal pain or cramps occur in fewer than one-third of patients; pain without bleeding is rare [24, 28]. Urinary symptoms due to physical irritation or compression of the urethra can be present in more advanced cases. Severe intra-abdominal hemorrhage following a rupture may be present initially with nausea, vomiting, and diarrhea. This may erroneously suggest a gastrointestinal disorder, delaying diagnosis. Bimanual examination usually reveals an enlarged, soft, globular, extended cervix with an open and enlarged external os and a closed internal os. Cervical assessment may be accompanied by severe bleeding [29–31]. Diagnosis of cervical pregnancy requires the visualization of an intracervical ectopic gestational sac or trophoblastic mass. Transvaginal ultrasound (TVS) has improved visualization in cases of early cervical pregnancy, allowing assessment of the gestational sac and, additionally, the endometrium and adnexa [29].

The main ultrasound criteria for diagnosis of cervical pregnancies were primarily given by Hofmann et al. (1987) [8], they are as follows:

– An echo-free uterine cavity, or a false gestational sac without fetal structures in the cavity.

– A decidual transformation of the endometrium.
– An hourglass uterine shape.
– A ballooned cervical canal.
– Presence of a gestational sac in the endocervix, with or without fetal structures.
– Presence of placental tissue in the cervical canal.
– A closed internal os.

Differentiation of a true cervical pregnancy from an isthmic-cervical pregnancy or a miscarriage is important and depends on the stage of gestation. Early cervical pregnancy may be mistaken for the cervical stage of miscarriage, defined as "spontaneous abortion" of an intrauterine pregnancy into the cervical canal where the abort is retained by a resistant external os, thereby ballooning out the cervical canal. Various findings may help to differentiate the latter from a cervical pregnancy. Differences in the shape of the uteri are particularly helpful. A larger or globular uterus is observed in a intrauterine pregnancy, the hourglass configuration of the uterus is peculiar to cervical pregnancy [29, 32]. The "sliding sign" described on transvaginal scanning, which occurs when the gestational sac of an abort slides against the endocervical canal following gentle pressure by the sonographer and which will not be seen in an implanted cervical pregnancy may also assist in the differentiation [33]. A criterion for differential diagnosis of a true cervical pregnancy from an isthmic-cervical pregnancy or a miscarriage is the demonstration of a closed internal os [34]. The internal os (on a coronal view) is located at the level of the uterine artery insertion. Thus, the ectopic sac in CP should be below the uterine artery insertion, which should be identifiable [35] (Fig. 18.3). Another important feature of cervical pregnancy is trophoblastic invasion of the endocervical tissue. Cervical mucosa has no protection against trophoblastic invasion and allows a deep penetration of chorionic villi into the fibromuscular layer. On TVS, this may be seen as a hyperechoic trophoblastic ring in the area of invasion [36]. TVS also affords the ability to assess the blood supply of the pelvic organs using color and a spectral Doppler. In cases of cervical pregnancy, an extensive vascular supply with the characteristics of peritrophoblastic blood flow can be seen originating from the maternal arteries at the implantation site within the cervix (Fig. 18.4). The product of conception, transiting through the cervix after detaching from the normal intrauterine implantation site, will not display any peritrophoblastic blood flow. Therefore, an ectopic implantation in the cervical channel can be distinguished from an incomplete miscarriage using Doppler studies [37, 38]. Ultrasonographic diagnostic criteria for CP are summarized in Table 18.2. In some cases, magnetic resonance imaging might be required to improve diagnostic accuracy; it is reserved for those cases where diagnosis is difficult [39].

Fig. 18.3 A ultrasonographic sagittal scan showing location of the products of conception below the internal orifice. Figure is taken *from: Malvasi A, Tinelli A, Di Renzo GC. MANAGEMENT AND THERAPY OF EARLY PREGNANCY COMPLICATIONS – First and Second Trimester. SPRINGER UK-USA Publisher, 2016; Hardcover, ISBN 978-3-319-31375-7*
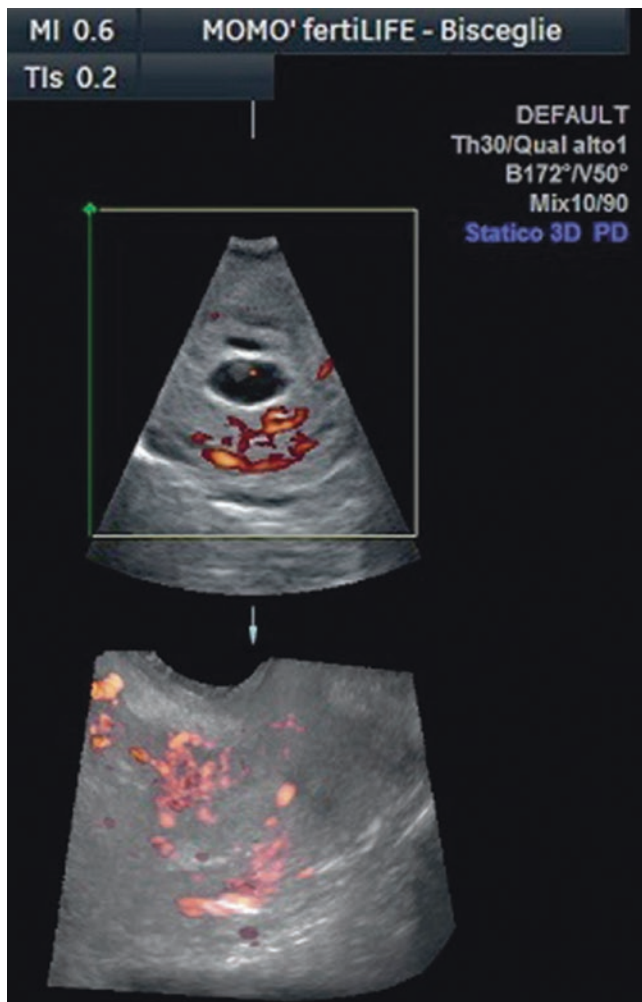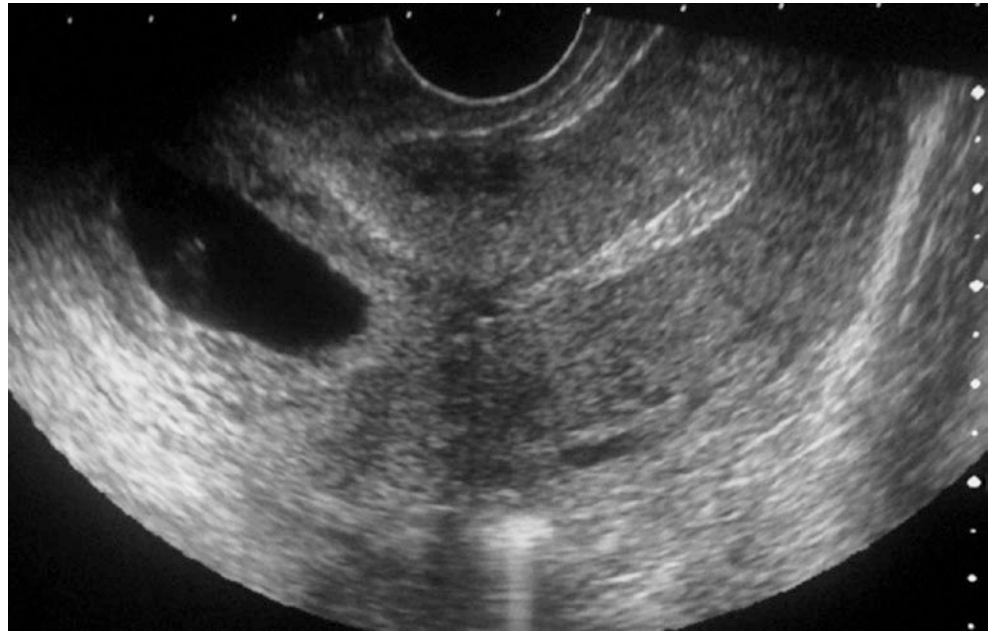
Fig. 18.4 The ultrasonographic image shows the peritrophoblastic blood flow with the use of color Doppler. Figure is taken *from: Malvasi A, Tinelli A, Di Renzo GC. MANAGEMENT AND THERAPY OF EARLY PREGNANCY COMPLICATIONS – First and Second Trimester. SPRINGER UK-USA Publisher, 2016; Hardcover, ISBN 978-3-319-31375-7*

Table 18.2 Ultrasound criteria for cervical ectopic pregnancy

Anatomic structure	Ultrasound Features
Uterus	Empty Decidual transformation of the endometrium Hourglass shape
Cervix	Gestational sac in the endocervix Ballooned or dilated barrel-shaped cervix
Gestational Sac	Below internal os Below the uterine arteries
Internal ostium	Closed
External ostium	Open
Doppler blood flow	Increased around gestational sac
Sliding sign	Absent

18.5 Treatment

A strategy in the treatment of cervical pregnancy can be considered as optimal and successful if no additional interventions are required, hysterectomy is avoided, and maternal fertility is preserved. Different approaches have been used, however due to the rarity of this condition, there has been no consensus on the preferred treatment and standard recommendations have not yet been elucidated. Management options range from conservative drug therapies to radical surgical procedures [22]. They include the use of local [35, 40] or systemic [41] chemotherapy with methotrexate (MTX); an ultrasound-guided injection of KCl [25]; curettage associated with procedures to block the bleeding such as a balloon tamponade [42–44]; prostaglandin administrations [45] or cervical cerclage [46]; or hysteroscopic endocervical resection combined with MTX [47] or associated with procedures to reduce blood supply, such as laparoscopy-assisted uterine artery ligation [48] or angiographic uterine artery embolization [49].

18.5.1 Systemic or Local Chemotherapy

The anti-metabolite cytotoxic drug MTX is the most commonly used agent in the conservative management of cervical ectopic pregnancy. Methotrexate (MTX) treatment can be administered either systemically or locally, in a single [50] or in multiple [41] doses. Various MTX protocols have been described for use in women with ectopic pregnancies but, unlike tubal ectopic pregnancy, cervical pregnancy has no established criteria for methotrexate treatment. The choice between single-dose and multidose protocols should depend on patient factors [22]. Some parameters have been linked to an unsatisfactory result in primary MTX treatment, including: a gestational age of ≥9 weeks, serum β-HCG concentration of ≥10,000 mIU/ml, a crown–rump length ≥ 10 mm and embryonic cardiac activity. However, methotrexate may be associated with bone marrow suppression, gastrointestinal disturbances and an elevation of hepatic transaminases [51, 52]. Among the various routes for methotrexate administration, the intramuscular route is usually preferred. The patient should be hemodynamically stable and must comply with post-treatment monitoring. In cases of cervical pregnancy, usually the multidose methotrexate regimen, i.e., 1.0 mg/kg body weight on days 1, 3, 5, and 7 interspaced by leucoverin 0.1 mg/kg body weight is preferred. Possible systemic adverse effects for MTX are thrombocytopenia, leucopenia, elevated serum liver enzymes, fever, and gastrointestinal symptoms [27, 41, 53]. The post-treatment decline in weekly serum beta hCG level is demonstrative of a successful therapeutic intervention. In the presence of fetal cardiac activity, ultrasound-guided intra-amniotic instillation of potassium chloride and/or methotrexate has been recommended as a concomitant treatment, as it has been found that concomitant feticide can enhance the therapeutic effect of systemic MTX treatment [27, 54]. In some cases a complete resolution after a single, ultrasound-guided, local MTX injection has been reported. Therefore, this strategy can be effective in the treatment of CP without the need for concomitant procedures or surgical interventions. However, chemotherapy with MTX can have disadvantages: the possibility of a slow resolution of trophoblasts, the probable need for adjuvant procedures to remove the ectopic pregnancy or cease the bleeding, and a time-consuming follow-up [55].

18.5.2 Reduction of Blood Supply

The uterine artery is one of the major branches of the hypogastric artery, it supplies the uterine corpus and cervix, by entering into the uterus at the uterine isthmus level. Sudden heavy bleeding can occur when the detachment of CP from the cervix, due to either surgical manipulation or spontaneous abortion, leads to the breaking of the underlying vessels that supply blood flow around the cervix [48]. Thus, when a treatment for CP is planned, anticipation of significant bleeding and management of procedures to prevent and/or control hemorrhage can help to avoid hysterectomy. All patients should have blood products available and should understand the potential need for hysterectomy. Several blockade methods have been reported, including cervical cerclage, angiographic embolization of hypogastric arteries, vaginal ligation of cervical branches, and laparoscopy-assisted ligation of uterine arteries. Generally, the effect of the lone blood supply blockade is insufficient to eradicate the CP, and thus, additional use of chemotherapy or a surgical evacuation is often required [46, 48, 49].

18.5.3 Bleeding Management with Tamponade

Treating obstetrical hemorrhage by means of tamponing is a well-established strategy. Packing the uterus with a sterile gauze was one of the historical methods (Fig. 18.5). Use of a Foley catheter, placed gently over the external os, followed by inflation of the bulb with saline solution has been mostly used after curettage (Fig. 18.6). Recently, the use of balloon
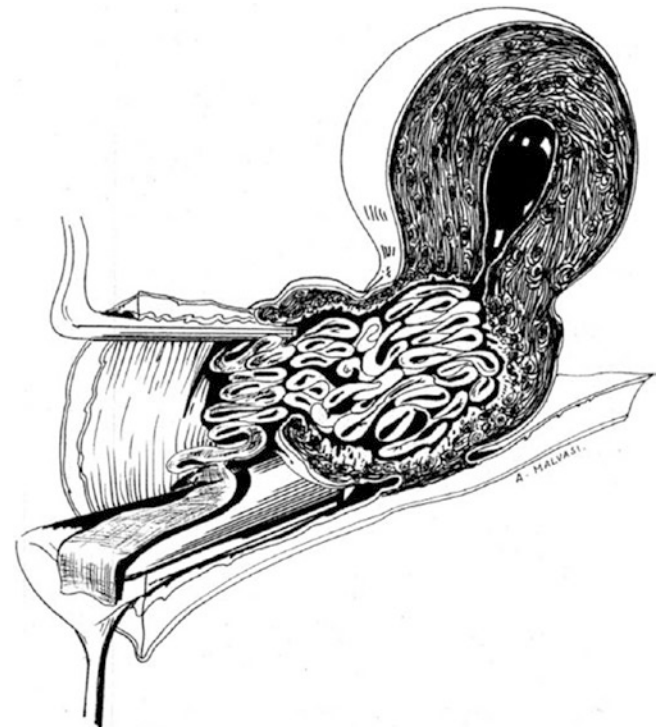
Fig. 18.5 After cervical pregnancy removal, clinicians can use a gauze crammed into the cervix for hemostasis. Figure is taken *from: Malvasi A, Tinelli A, Di Renzo GC. MANAGEMENT AND THERAPY OF EARLY PREGNANCY COMPLICATIONS – First and Second Trimester. SPRINGER UK-USA Publisher, 2016; Hardcover, ISBN 978-3-319-31375-7*
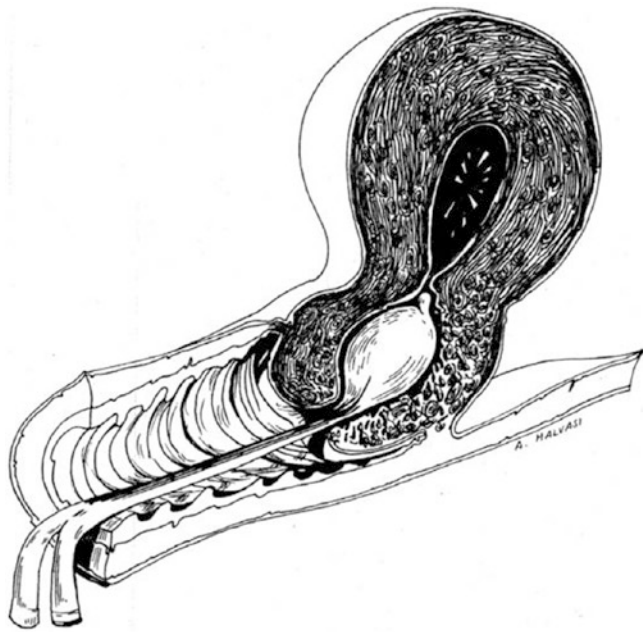
Fig. 18.6 The figure shows a Foley balloon tamponade after curettage for cervical pregnancy. Figure is taken *from: Malvasi A, Tinelli A, Di Renzo GC. MANAGEMENT AND THERAPY OF EARLY PREGNANCY COMPLICATIONS – First and Second Trimester. SPRINGER UK-USA Publisher, 2016; Hardcover, ISBN 978-3-319-31375-7*

technology has been suggested and used to tamponade. This involves the placement of a rubber or silicone balloon into the uterine cavity or cervical canal, which is then inflated with normal saline, exerting pressure upon the bleeding vessel to slow or stop bleeding until the vessels are occluded and full hemostasis takes place [35, 42].

18.5.4 Surgical Excision

Dilation and curettage or suction evacuation are the traditional methods in surgical treatment of CP. Curettage has been widely used as a highly effective and fertility-preserving technique, but it is associated with a high risk of hemorrhage. Therefore, it has been used in conjunction with mechanical methods like cervical artery ligation and tamponade [6]. Primary hysterectomy may still be performed in an intractable hemorrhage and possibly to avoid emergency surgery and blood transfusion in a woman who does not desire to retain her fertility [56, 57]. Recently, hysteroscopic resection of ectopic CP has been described as an effective and fertility-preserving surgical therapy. It has been used alone or in combinations with another complementary therapy [58, 59]. We discuss below in a more detailed manner the advantages and indications of this technique in the management of CP.

18.6 Hysteroscopy in Management of Cervical Pregnancy

To date, hysteroscopy has represented the gold standard in the evaluation of the uterine cavity and for related endocavitary surgical procedures in gynecological pathologies [60, 61]. The effectiveness of this tool, as well as the security and reproducibility of the technique, and the ease of performance when used by experienced operators, have demonstrated its potential for widespread use. Technological progress has continuously increased the field of applications that may be used in operative hysteroscopy [62].

Hysteroscopy has also been used in the field of ectopic pregnancy (Fig. 18.7) despite the fact that, to date, numbers are small and further experience would be helpful in determining the safest and most appropriate technique. Several advantages have been noted with respect to hysteroscopy (Table 18.3), such as its permitting a confirmed diagnosis of cervical pregnancy. Furthermore, unlike other techniques such as curettage, hysteroscopy provides a direct visualization of the ectopic location and its vascularity in the endocervical canal. Conservative treatment with hysteroscopy has the advantage of a 24-h availability of instrumentation. It also offers immediate evidence of success or failure. CP can be completely resected under direct vision and an accurate cauterization of any bleeding points can be performed. Moreover, over systemic and local injection techniques, it has been shown that it leads to a shorter follow-up time and a more rapid return to fertility [58, 59, 63]. However, although being a minimally invasive surgical
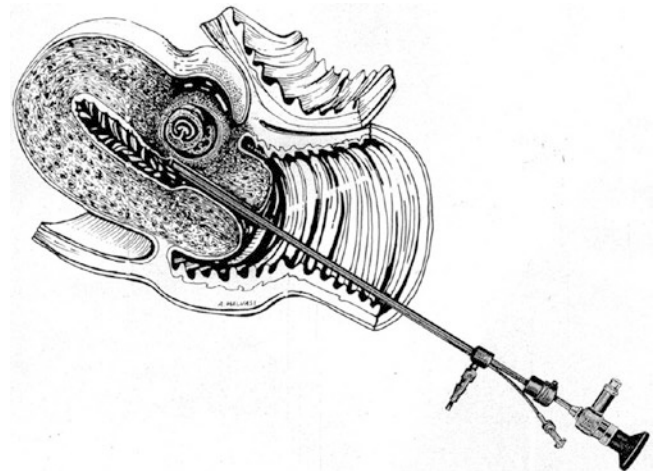
Fig. 18.7 The image shows a hysteroscopic removal of the products of conception in a cervical pregnancy. Figure is taken *from: Malvasi A, Tinelli A, Di Renzo GC. MANAGEMENT AND THERAPY OF EARLY PREGNANCY COMPLICATIONS – First and Second Trimester. SPRINGER UK-USA Publisher, 2016; Hardcover, ISBN 978-3-319-31375-7*

Table 18.3 Advantages of hysteroscopy in cervical ectopic pregnancy

Confirmation of the diagnosis
Direct visualization of the ectopic location
Definition of vascularity in the endocervical canal
24-h availability of instrumentation
Immediate evidence of success or failure
Resection under direct vision
Possibility of accurately cauterizing any bleeding
Shorter follow-up time
Well tolerated procedure
Possibility of avoiding general anaesthesia
Low cost
Rapid return to fertility

method, it still carries the risk of uncontrolled bleeding, and the patient should be aware of the possible need for an emergency hysterectomy [64].

In 1992, Roussis et al. [65] described the first case in which hysteroscopy was used to visualize a CP after sonography revealed the failure of systemic MTX treatment. The hysteroscopy confirmed minimal vascularity in the endocervical canal, permitting the authors to proceed with suction aspiration of the tissue. Four years later, Ash and Farrell [58] published the first case of successful treatment using operative hysteroscopy, without prior chemotherapy, to completely resect a 6-week viable CP, immediately after vaginal ligation of the cervical branch of the uterine artery. Despite the obvious advantages of hysteroscopy, it may not always be the most appropriate treatment. The choice of hysteroscopy as a treatment method in cervical pregnancy should be made based on clinical findings, gestational age, and an ultrasound examination [59].

A more advanced gestation can significantly enlarge and distort the cervix and it can have a better-developed blood supply. Under such circumstances, attempting a hysteroscopic resection may be less efficacious than curettage [58].

To date, it has been difficult to define the exact role of hysteroscopy in the management of CP. Some authors have proposed the use of hysteroscopy as a complementary approach to chemotherapy with systemic MTX [47, 64, 66], or to an injection of MTX into gestational sac [11]. Nevertheless, others believe that it could be used only as a rescue method in cases of MTX failure [13].

Conservative treatment with MTX chemotherapy is considered as initial in most cases. However, although it is able to induce the abortion of a viable CP and halt trophoblast proliferation, it is often not completely resolved and additional therapeutic approaches are required. Moreover, it often involves restrictions and complications in adverse events.

Recently, Kim et al. [67] have proposed the use of hysteroscopy combined with an intrauterine irrigation of H2O2 solution. H_2O_2 solution releases a large amount of free oxygen via catalase, which induces cell death due to oxygen toxicity. When contact with H_2O_2 takes place, cell death is induced, vasoconstriction occurs, and the trophoblastic cells become atrophied. With this method, vascularity around the gestational sac is reduced and throphoblastic tissue is safely removed via hysteroscopy. This method therefore appeared very effective, without concern for systemic adverse effects unlike MTX chemotherapy, due to the fact that no additional treatment was required.

Hysteroscopy can be effective not only due to its advantageous ability to preserve fertility, but it could be even more useful when a medical therapy is contraindicated, or in special circumstances in which the toxic effects of methotrexate must be avoided. A very interesting case, described by Jozwiak et al. [68] reports the successful treatment of a 6-week viable heterotopic CP with hysteroscopic resection alone. Cervical ectopic pregnancy was resected by roller ball electrocautery. During the intervention, the tip of the resectoscope did not go beyond the internal cervical os and the uterine cavity was not touched. At 12 weeks of gestation, a McDonald cerclage suture was placed in the cervix to prevent cervical incompetence. The concomitant intrauterine gestation was carried to term, and a healthy baby was born.

However, the safety and efficacy of single hysteroscopic resection alone without the prerequisite of blood supply reduction remains uncertain and further studies with a large population are needed.

Kung et al. [48] have reported the successful use of laparoscopy-assisted uterine artery ligation in conjunction with hysteroscopic endocervical resection. Although such a technique could eliminate the need for adjuvant chemotherapy prior to hysteroscopy, and it could be effective in bleeding control and uterus preservation, it has been criticized as being too invasive [69]. The main concerns have been related to the subsequent reproductive performance post-uterine artery ligation in women who wish to preserve fertility.

Uterine artery embolization (UAE) with office hysteroscopic resection has been proposed as an effective option in the treatment of cervical ectopic pregnancy and as a useful alternative to curettage [10]. Such a report demonstrated the feasibility and minimal invasiveness of the procedure. However, it requires a specific set of skills and appropriate training.

Further studies comparing this procedure with other treatment modalities are needed to define the exact role of hysteroscopy in the management of CP. So far, studies are promising and it cannot be excluded that in the coming decades hysteroscopy could become a treatment of choice in the management of a condition like CP.

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Hysteroscopy and Retained Products of Conception

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19.1 Introduction

The term retained products of conception refers to the placental and/or fetal tissue that remains inside the uterine cavity after an abortion, miscarriage, or parturition. Other terms used to define this uncommon complication are "placental polyp," "retained placental fragment," and "residual trophoblastic tissue."

The occurrence of residual tissue is observed in about 0.5% of surgical abortions performed in the first trimester [1] and this occurrence is higher in cases of medical abortion. A meta-analysis of the efficacy of medical abortion found that the success rate decreases with increasing gestational age and conclude that medical abortion has high levels of success at ≤49 days gestation but may have lower efficacy at longer gestation [2]. Approximately 1% of term pregnancies are complicated by the persistence of retained trophoblastic tissue [3].

There are some risk factors related to the presence of RPOC. Residual trophoblastic tissue is more frequent after second trimester demise, there is also a relation between RPOC and abnormal uterine cavities and some recent studies suggest that ART-related pregnancies may be a risk factor of RPOC [4].

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Baer published in 1884 a case report of a placental polyp that occurred 12 years after the pregnancy [5]; this was the first report of this condition. Since then, different cases and series have been reported.

Tchabo in 1984 identified the location of RPOC with contact hysteroscopy, and subsequently the tissue was removed easily with the use of a polyp forceps [6]. In 1997, Goldenberg reported the use of hysteroscopy for removal of residual trophoblastic tissue using a cutting loop as a curette for a selective removal [7]. In all cases, the postoperative ultrasound revealed a cavity free of residual tissue.

19.2 Pathogenesis

The retained products of conception are usually of trophoblastic origin. The trophoblast forms numerous branching projections from the external surface of the chorion called chorionic villi; these villi allow for the passage of respiratory, metabolic, and other products between maternal and fetal blood systems (Fig. 19.1).

Two different theories have been proposed to explain the pathogenesis of retained products of conception and to date they remain to be confirmed.

According to the theory proposed by Eastman and Hellman, the retention of trophoblastic tissue represents an unrecognized partial or focal type of placental accreta. It has been suggested that decidua formation is less in the cornual area, the fundal area, and the lower uterine segment; if the implantation occurs in one of these sites, the chorionic villi could be attached directly to the myometrium, leading to increased risk for retention of products of conception [8].

The second theory, proposed by Ranney, sets a direct relationship between the thickness and tone in different areas of the myometrium with the existence of RPOC. As per this theory, fundal and uterotubal areas are relatively atonic after second stage of labor which explains the phenomenon of retained placenta [9].

An important risk factor for the development of RPOC is placental accreta. This is a severe pregnancy complication associated with high maternal morbidity and mortality rates and occurs when all or part of the placenta grows into the myometrium. It is associated with previous uterine scars, multiparity, prior uterine infections, and placenta previa.

In a prospective observational study to evaluate the occurrence of residual trophoblastic tissue after miscarriage or delivery, this residual tissue was seen more frequently after second trimester demise (40%) [10], than after first trimester miscarriage (17.8%) or after third-trimester delivery (2.7%). On the other hand, there is a well-documented relation between RPOC and abnormal uterine cavities, with a prevalence of such anomalies of 10% of the patients with retained products [11]; it could be caused by difficulties during the D&C evacuation or by an abnormal uterine contractility during a spontaneous miscarriage (Fig. 19.2).

19.3 Clinical Manifestation

Symptoms of RPOC can vary in intensity and frequency, and severity depending on the size, vascularization, and the duration of the retained material.

The main clinical symptom of retained products of conception is vaginal bleeding that can range from a light bleeding to life-threatening. There is always some uterine bleeding after a pregnancy termination and no clear criteria have been established to define when that bleeding has to be considered abnormal in quantity. As a rule, any bleeding heavier or longer than usual must be considered abnormal and can be related to RPOC. Other related symptoms are uterine tenderness, pelvic pain, and fever.

Fig. 19.1 Detailed view of chorionic villi
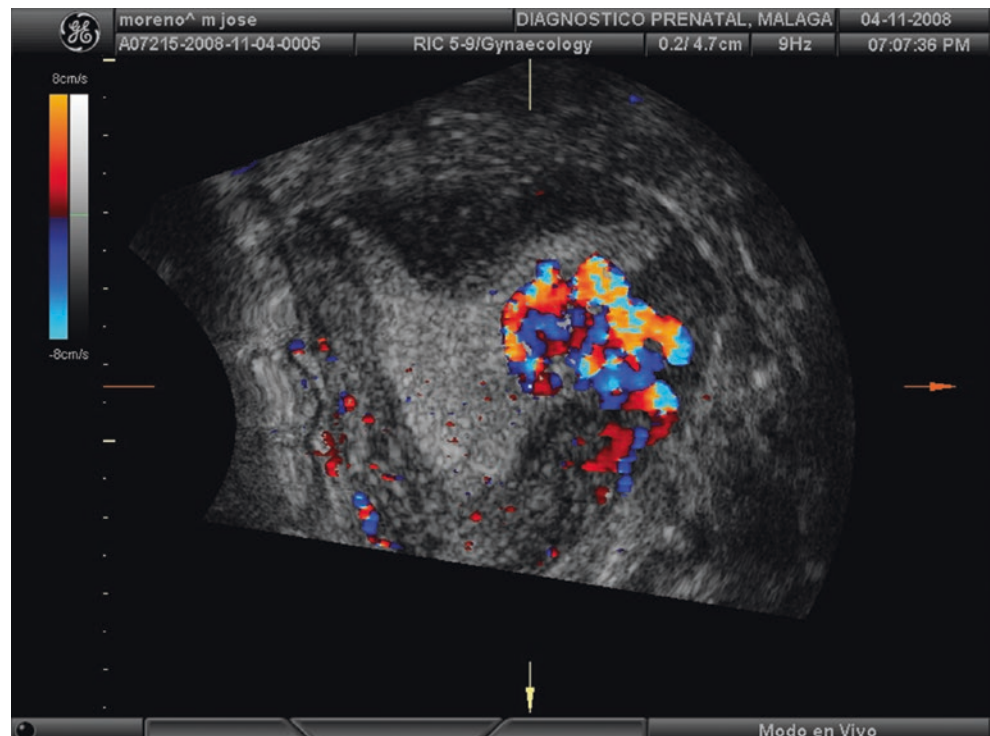
Fig. 19.2 Retained products of conception (RPOC) over a subseptate uterus
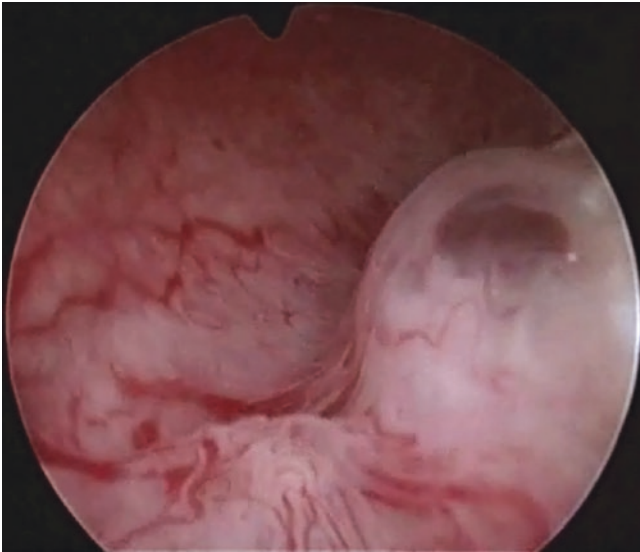
Fig. 19.3 Persistent products of conception more than 1 year after the miscarriage

This variety in clinical manifestation affects also the time of presentation. This took to Dyer and Bradburn to divide placental polyps into acute and chronic types. Acute type often presents with postpartum hemorrhage within a few days to 6 weeks after abortion or delivery and are likely to be remnants of placenta with blood and clots. Chronic type of placental polyps may persist for years with mild or no symptoms [12].

Other frequently used term is late residual trophoblastic tissue, defined by the persistence of trophoblastic tissue after the first menstruation, after termination of pregnancy or in cases of persistent amenorrhea [11]. This amenorrhea for more than 6 weeks after abortion or delivery can be associated with the presence of viable trophoblastic tissue.

There are some reports of retained products persisting for years. It is interesting to highlight the case reported by Swan discovered 21 years after the last documented pregnancy in a patient with normal menses [8] (Fig. 19.3).

19.4 Diagnosis

The diagnosis of retained products of conception is a real challenge as it is normal to have some bleeding and discomfort after a miscarriage, abortion, or delivery. A clinical history of previous pregnancy with persistent abnormal bleeding, or heavier than usual bleeding, should make us suspect retention of products of conception.

In the gynecological examination it shows the presence of vaginal bleeding that could vary from light bleeding to a massive life-threatening. In cases of massive bleeding, some clots can be seen protruding through the cervical canal, and the cervical OS can be dilated. The bimanual exam allows to assess the cervix, and uterine size and tenderness. In few cases, a mass of products of conception is found protruding from the cervix [13].

Laboratory studies are often of limited value, and the quantitative determination of human chorionic gonadotropin (hCG) is not useful as this hormone can remain >5 mIU/ml in the immediate period after labor or abortions and a negative result does not exclude the persistence of RPOC. It is well documented that this retained tissue can maintain some endocrine activity for long time, maintaining some hCG in the blood usually at low levels [14].

Ultrasound is the first-line imaging modality for the diagnosis of RPOC. The identification of an endometrial mass is the most sensitive finding for RPOC and the absence of sonographic findings suggestive of RPOC accurately excludes this pathology with a predictive value of 100% [15]. The aspect of the endometrium changes over time, and on ultrasound the uterine cavity is empty appearing as a thin white line 8 weeks postpartum [16] and within 1 week after a first-trimester abortion [17].

In a retrospective study of patients who underwent uterine re-evacuation for RPOC comparing different measures of the endometrium, an endometrial thickness of 13 mm or more, detected by transvaginal sonography, demonstrated to be the best diagnostic criteria to detect RPOC [18].

Usually, the placental polyp is highly vascularized and with the use of color Doppler there is a high rate of positive blood flow within the placental polyp, and sometimes an increasing trend of neovascularity in the implantation area can be seen (Fig. 19.4). Regarding the use of color Doppler as a definitive diagnosis tool, while some studies conclude that the use of color Doppler is accurate for confirming or excluding residual trophoblastic tissue [10, 19], others have shown that the its use is not helpful in the diagnosis of RPOC. Durfee affirms that the implantation area may remain vascular during the involution period and if there are clots attached to this area, color Doppler may appear to be within the endometrium, leading to misdiagnoses [15].

A special mention must be made of the study published by Kamaya to characterize color Doppler image features of RPOC [19]. This retrospective study presented four types of color Doppler appearances of RPOC, from type 0 (avascular) to type 3 (marked vascularity), which can be mistaken for an AVM, and it was the first attempt to classify RPOF considering the vascularization.

We are working on our own classification that correlates ultrasonographic findings with hysteroscopy view of retained products of conception. We have established four hysteroscopic patterns based in vascularization and echogenicity of RPOC. Type 0 is a hyperechogenic avascular pattern. Type 1 is characterized by different grades of echogenicity but
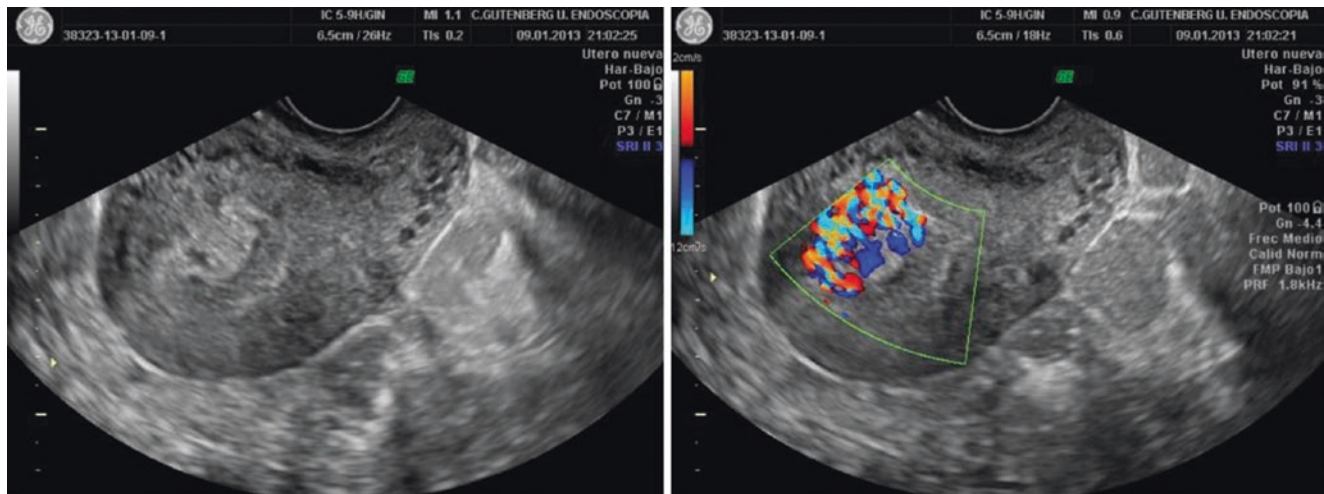
Fig. 19.4 Positive blood flow within the placental polyp

minimally vascularized, while type 2 corresponds to a hyper-vascularized intracavitary mass and, lastly, type 3 is characterized by hypervascularized intracavitary mass with a highly vascularized myometrium (Fig. 19.5).

The MRI classical imaging finding of RPOC is an intra-cavitary uterine soft-tissue mass with variable degrees of myometrial thinning and disruption of the junctional zone with heterogeneous signal intensity on T1 and T2 imaging and variable enhancement on gadolinium-enhanced T1 W images [20].

Hysteroscopy is considered the gold standard for the diagnosis of intrauterine pathology including RPOC. The hysteroscopic appearance of retained trophoblastic tissue have different patterns depending on the involution of the trophoblast and the chorionic villi, the necrosis of the nonviable tissue and the deposit of fibrin. These changes are correlated with different patterns included in our morphological hysteroscopic classification. This appearance varies from a white mass in which is not possible identify any structure (Type 0) to the visualization of well-defined avascular chorionic villi (Type 1) or well-defined and well-vascularized chorionic villi (Type 2 and 3). In the Type 3, some changes in the myometrial vascularization under the implantation area of the RPOC can be found as aneurism, or big vessels or arteriovenous shunts (Fig. 19.6). Usually, there is some blood and clots in the uterine cavity floating free or attached at the residual trophoblastic tissue; for this reason, it is important to perform a gentle washing to achieve a good image.

Definitive diagnosis is histological and the key point is the presence of chorionic villi indicating the existence of placental tissue. Sometimes, chorionic villi with a rim of normal syncytiotrophoblasts are observed, while other findings are necrotic and hyalinized villi, also called "ghost villi." The base usually contains highly vascularized decidualized stroma [21].

19.5 Differential Diagnosis

Occasionally, we may find similar echographic patterns in cases of postpartum clots or during the normal involution of the postpartum endometrium. This is why there is a great variability in the sensitivity and specificity for the diagnosis of PROC according to different studies (S 44–93% and E 74–92%) [15]. There are different factors that play a role in the accuracy of the diagnosis, such as the use of a protocol for examination, observer's experience, and the use of US-Doppler. In contrast, the absence of suggestive echographic findings of RPOC excludes the diagnosis, with a positive predictive value (PPV) close to 100%.

In the differential diagnosis of RPOC three different pathologies, in particular, must be considered such as acquired arteriovenous malformations, placental site trophoblastic tumor and choriocarcinoma.

The acquired uterine arteriovenous malformation (AVM) is a rare condition and presumably over diagnosed, with RPOC or the sub-involution of the placental implantation site as most frequent cause of this pitfall [22]. Most cases of AVM develop over uterine lesions produced after curettage or uterine surgery, calling them acquired arteriovenous malformation to differentiate from the congenital malformations. Although on ultrasound evaluation there can be some confusion with RPOC, in cases of AVM either acquired or
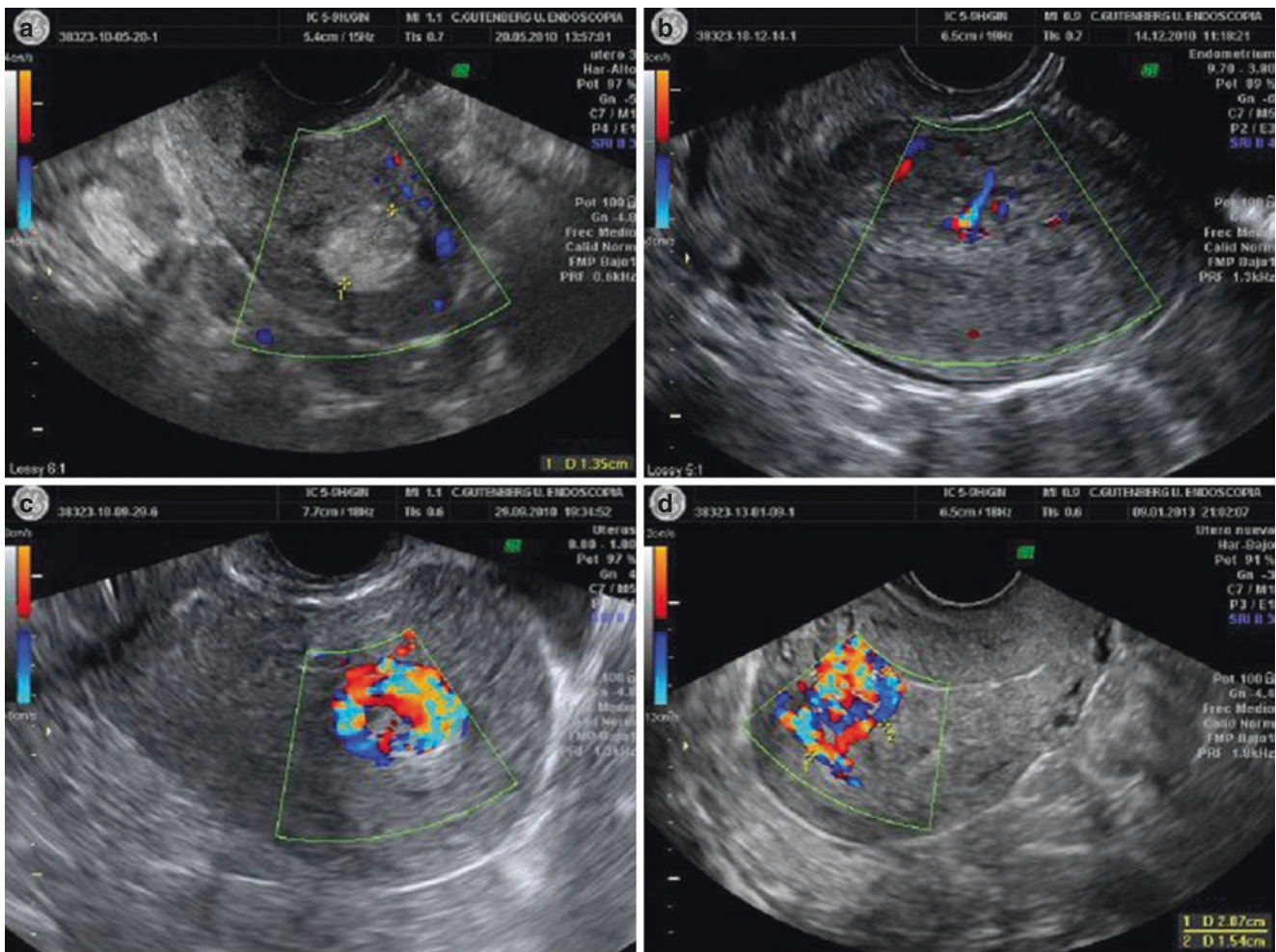
Fig. 19.5 Ultrasonographic patterns of RPOC. Gutenberg Classification. (**a**) Type 0: hyperechogenic avascular mass. (**b**) Type 1: Different echoes with minimally or no vascularization. (**c**) Type 2: Highly vascularized mass confined to the cavity. (**d**) Type 3: Highly vascularized mass with highly vascularized myometrium

congenital, the vascular component is confined to the myometrium with a turbulent pattern of arterial and venous flow with high peak velocities and low resistance [23]. Diagnostic suspicion and identification of AVM is very important, and the treatment of choice is selective arterial embolization (Fig. 19.7).

Placental site trophoblastic tumor is a rare form of gestational trophoblastic disease (GTD) arising from intermediate trophoblast. Typically occurs in women of childbearing age after delivery but can also occur after abortion, ectopic pregnancy or molar pregnancy. In cases with polypoid morphology growing from the myometrium to the endometrial cavity, a differential diagnosis with RPOC should be considered. The placental site trophoblastic tumor is characterized by low levels of BHCG and little production of human placental lactogen (hPL) [24]. The key point in the diagnosis is the proliferation of trophoblastic cells without chorionic villi in the histopathological study.

Choriocarcinoma is a highly invasive neoplasm that affects women of reproductive age with hematogenous metastasis appearing in early stages of the disease. Around 50% of cases develop from molar gestations, and the rest occurs after a spontaneous abortion, normal delivery, or ectopic pregnancy [25]. On ultrasound, there is no typical pattern, but necrosis and hemorrhage are often present. The BHCG levels are usually high and can guide us in the diagnosis. Histopathological examination is required to determine the diagnosis.
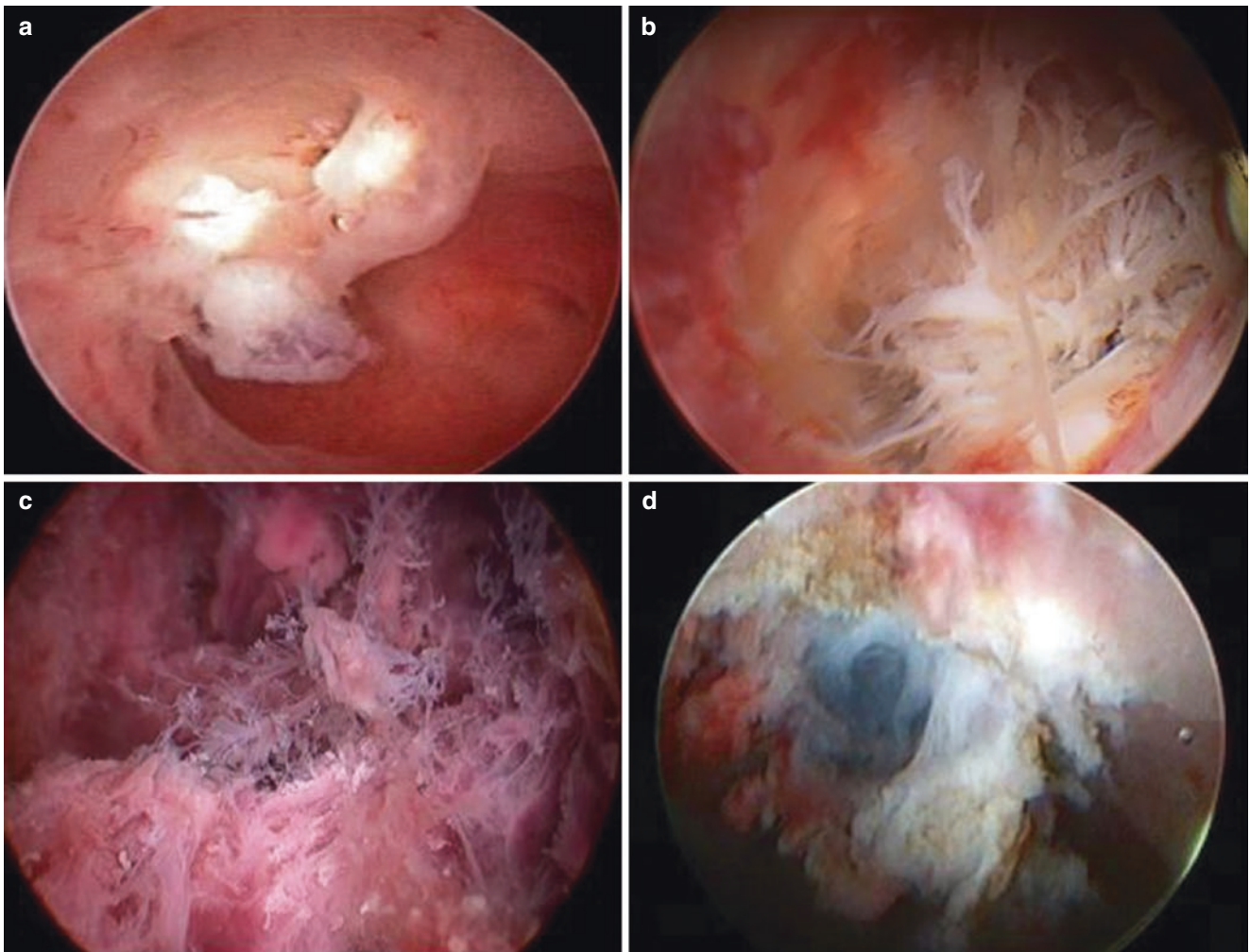
Fig. 19.6 Hysteroscopic patterns of RPOC. Gutenberg classification. (**a**) Type 0: White mass in with no clear structures. (**b**) Type 1: Well-defined avascular chorionic villi. (**c**) Type 2: Well-vascularized chorionic villi. (**d**) Type 3: Aneurysm over myometrium in the implantation area

19.6   Treatment

The treatment depends on factors such as clinical hemodynamic condition, gestational age, available resources, and operator's experience. Traditionally, the management for RPOC has been dilatation and curettage, and it is still the most common treatment. Other alternative treatments as expectant management or hysteroscopic selective resection have recently emerged. The main objective of these alternative treatments is to reduce the risks associates with the classical D&C.

Evacuation of retained products of conception with sharp metal curettage or with suction curettage is a widely used method for the management of this pathology. A recent review evaluating vacuum aspiration versus sharp metal curettage found that the vacuum aspiration was safer, quicker, less pain-ful [26] and with less blood loss [27] than sharp curettage; however, larger studies are needed to confirm these findings.

This procedure can lead to several associated complications as incomplete evacuation of retained products, intrauterine adhesions and uterine perforation due to the blind nature of the procedure.

The retained products of conception are often focal, and the blind nature of curettage carries a risk of incomplete evacuation (Fig. 19.8). There are limited data on the incidence of repeat evacuation for suspected retained products. In a retrospective study on patients who underwent suction curettage for RPOC, the rate of repeat evacuation was 3.1% [28]. Another retrospective analysis comparing selective curettage of RPOC by hysteroscopy with conventional blind curettage reported higher rates after blind evacuation of the uterus with 20.8% of persistence of residual tissue [29].

Fig. 19.7 3D volume view of AV malformation
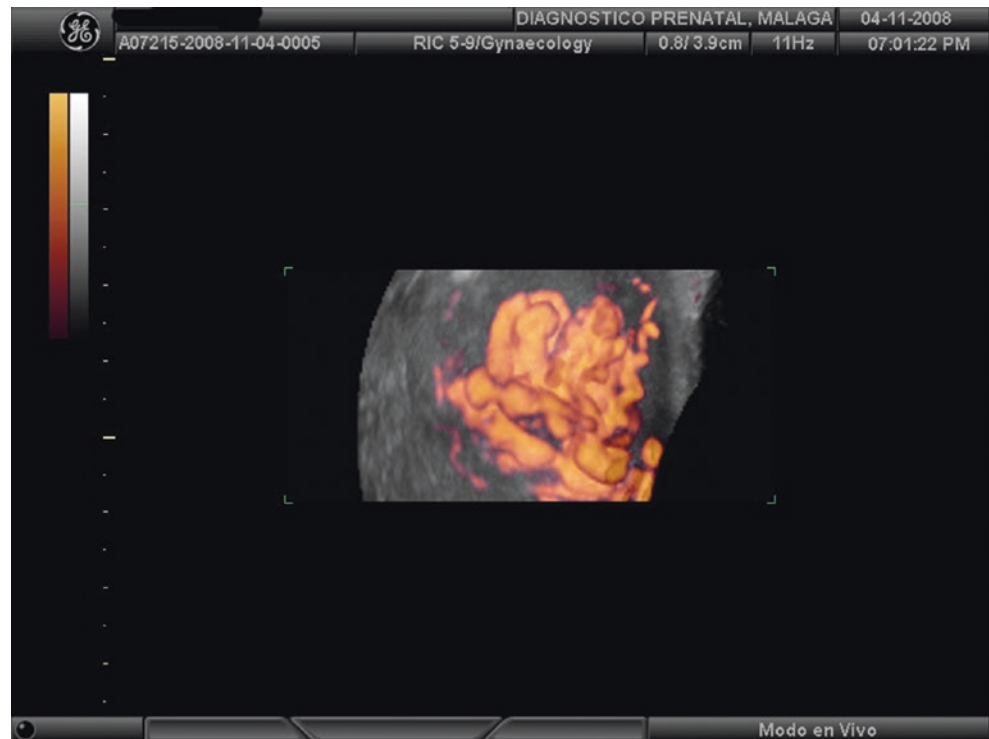
Fig. 19.8 RPOC have a focal implantation

As we set before, the retained products are often focal, and the use of blind curettage causes trauma to the basal layer of endometrium that can lead to development of intrauterine adhesions (IUA) or even Asherman's syndrome (Fig. 19.9). The incidence of IUA following curettage for missed abortion is around 30% diagnosed by hysteroscopy [30]. On the other hand, the incidence of IUA in women undergoing repeated evacuation is 40% of whom 75% of them has grade II–IV diagnosed by hysteroscopy performed 3 months after the procedure [31].
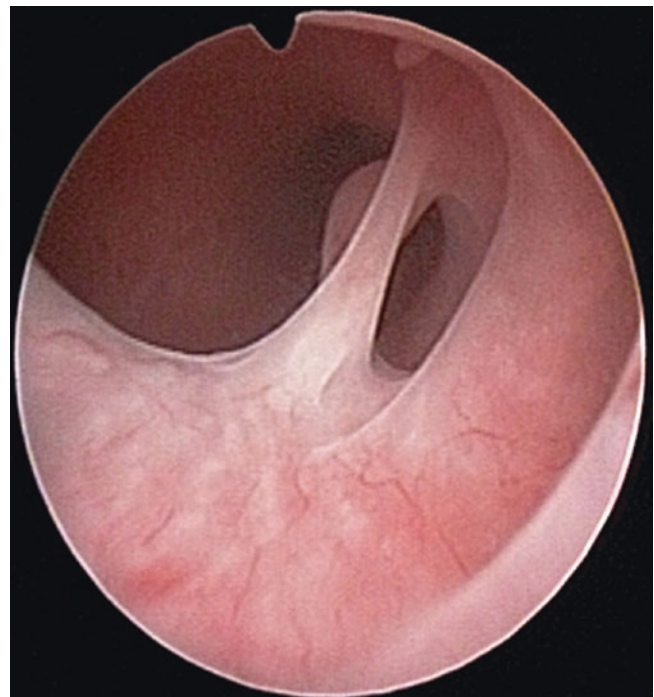
Fig. 19.9 Intrauterine adhesions after repeated curettage

Other related problem associated to the uterine curettage is uterine perforation, it is estimated that this complication affects to 5.70% of patients who underwent to evacuation of retained products of conception in cases of postpartum

hemorrhage [32]. The existence of RPOC makes the curettage a high-risk procedure for uterine perforation due to a decrease in the resistance of the uterine wall. Uterine perforation is the most common complication of curettage and can lead to bleeding, injury of internal organs and peritonitis.

To avoid those complications mentioned above, different strategies have been proposed. Among those we should mention expectant management, medical treatment, ultrasound guided evacuation and above all, hysteroscopic management of retained products of conception.

Expectant management is an option for women with RPOC who have mild or no symptoms. A randomized clinical trial comparing surgical versus expectant management in patients with incomplete miscarriage at a period of amenorrhea of <14 weeks and retained products of conception of <50 mm found a success in the expectant group of 90.1% at 1 week and 94.4% at 2 weeks [33]. Additionally, delaying of surgical timing could be an attractive approach to reduce intra-polyp blood flow and to decrease blood loss during operative procedure [34]. Therefore, expectant management of retained products of conception should be the first choice in patients with mild or no symptoms.

Different medical treatments have been used for the management of RPOC. Different oxytocic agents have been classically used but misoprostol is the most common medication used for the evacuation of RPOC, but there is no agreement about the correct dosage and route of administration. Treatment with misoprostol has shown to be effective in more than 90% of cases of first trimester incomplete miscarriages but some women need multiple doses and usually oral analgesia is needed. A literature review found evidence supporting misoprostol as a safe and effective treatment for uterine evacuation and recommended a dose of 600 μm oral for the treatment of incomplete abortion [35]. Comparing the effectiveness of curettage vs misoprostol, curettage is superior in achieving a complete evacuation of the retained material and severity of pain, bleeding and emergency evacuation was higher with misoprostol [36].

The use of the hysteroscopy in the management of ROPC was first published by Tchabo in a series of 95 patients in which a contact hysteroscope was used for the visualization of the products inside the uterine cavity and cases of postpartum and post-abortion bleeding. Using hysteroscopy in such way was possible to determine the exact location of the problem, the need of uterine evacuation and the diagnosis of associated uterine anomalies [10].

Years later, panoramic hysteroscope was used as an auxiliary method for uterine surgical evacuation. A diagnostic hysteroscopy was performed before the curettage to identify where the RPOC were attached into the uterine cavity, in this way the surgical evacuation was "guided" by this previous visualization of the cavity. In a study over 287 women, Goldfarb concluded that there was significant evidence to support the routine use of hysteroscopy as an adjunct to D&C [37].

Regarding the use of the resectoscope for a selective removal of RPOC, the first report was published by Goldenberg in 1997. Using the resectoscope with a cutting loop, he achieved a successful removal of the retained material in all patients using the cutting loop as a curette avoiding the lesion of the remaining tissue. This excision under direct visualization allowed higher accuracy in the evacuation, complete the procedure in one surgical procedure and reduce the risk of intrauterine adhesions related to the injury of the healthy surrounding tissue. No complications during or after the surgery were reported with this technique [7] (Fig. 19.10).

There are no conclusive studies indicating the optimal time to perform the evacuation of the retained material in those cases in which there is no life-threatening vaginal bleeding. In a study comparing different parameters as conception rate, mean time to conception, and the rate of a new infertility problem in women with early surgical intervention (in the first 3 weeks after the vaginal delivery or pregnancy termination) versus late surgical intervention, no differences were found between the groups [38].

On the other hand, it seems that a delay of surgical timing is associated with a decrease in the vascularization of both the placental polyp and the implantation area. Those changes in the vascularization pattern of the RPOC are correlated with less bleeding during the surgical procedure. This decrease can be explained by two mechanisms, a time-dependent disappearance of AV fistula within polypoid mass and a time-dependent vasospasm caused by the release of prostaglandins [34].

In cases of highly vascularized retained fragments a hysteroscopic resection using only the cool-loop as a curette is not always possible, and the use of electrocoagulation is usu-
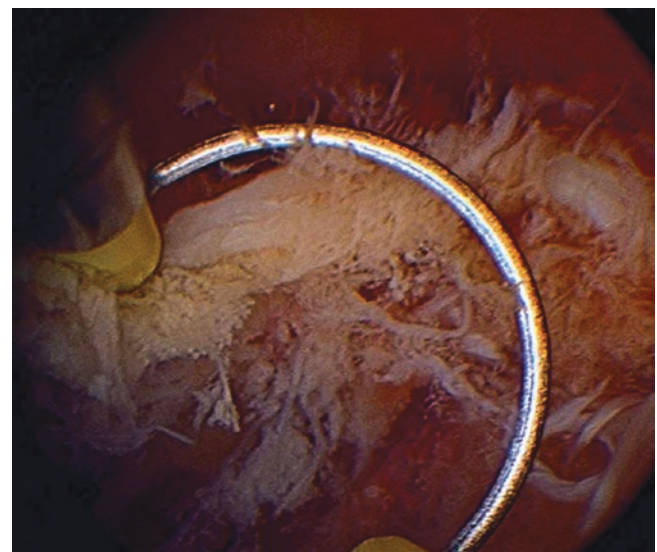
Fig. 19.10 Detailed view of the loop used as curette

ally required. The coagulation of the implantation area implies a damage of the underlying myometrium and the possibility of develop future intrauterine adhesions. Takeda proposed the use of preoperative uterine artery embolization in patients with neovascularization in the placental polyp tissue assessed by computed tomographic angiography before the hysteroscopic resection to decrease the bleeding during the surgical procedure [39].

Our therapeutic protocol is based in the result of the Doppler ultrasound and hysteroscopy. As we mentioned above, the ultrasonographic appearance of RPOC can be different depending on the echogenicity and on the vascularization of the retained tissue and the surrounding endometrium. In cases of a hyperechogenic avascular pattern (type 0) or cases with different echogenicity but minimal vascularization inside the RPOC (type 1) and after failure of medical treatment, we use the resectoscope as a curette, in the same way proposed by Goldenberg. This is usually a safe and quick procedure, with no or minimal bleeding, in which the retained tissue is easily detached from the uterine wall. The use of electrosurgery is not required (Fig. 19.11).

In cases with a pattern of different echogenicity inside the cavity but highly vascularized (type 2), the management is similar to previously described, but in these cases, it is common to use electrosurgery after the excision of the retained tissue to fulgurate the implantation area that is highly vascularized. A selective fulguration is mandatory, for avoiding injury to the healthy surrounding tissue.

The last case is that of a highly vascularized intracavitary mass with highly vascularized myometrium, as result of invasion of the myometrium with destruction of the uterine vasculature by the trophoblast. This situation is very uncommon and potentially dangerous. After the excision of the retained tissue, a concomitant use of superficial resection of the myometrial tissue and a fulguration of the actively bleeding vessels is needed (Fig. 19.12). In some cases, an intrauterine catheter is left in place compressing the myometrial blood vessels (Fig. 19.13).

We also perform systematic second-look hysteroscopy in all patients 1–2 months after the evacuation to evaluate the cavity and the presence of intrauterine adhesions.

19.7 Obstetrics Outcomes

Patients with RPOC usually express concerns about the impact of this pathology on their future fertility and their reproductive health, and this is why we must be aware of the evolution in the treatment of this entity, changing from the uterine curettage to the hysteroscopic management.

As commented above, the uterine curettage can lead to development of intrauterine adhesions (IUA) or even Asherman's syndrome due to the "blind" nature of the tech-
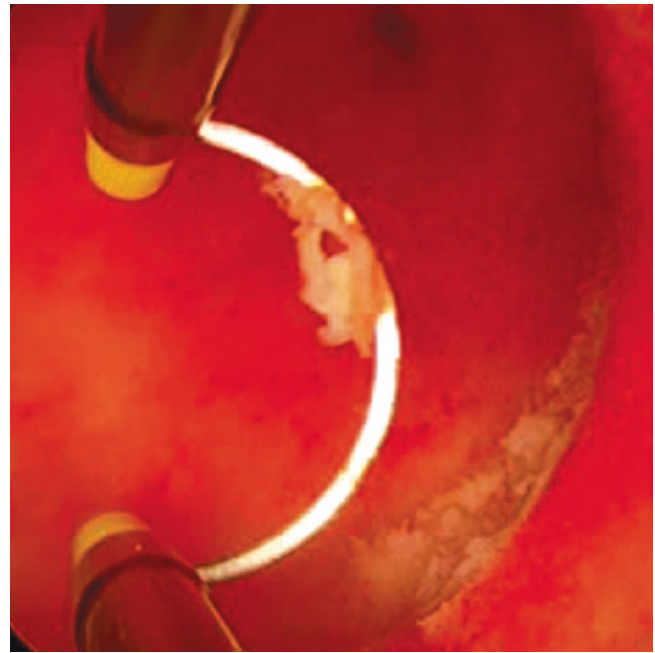
Fig. 19.11 Implantation area after resection
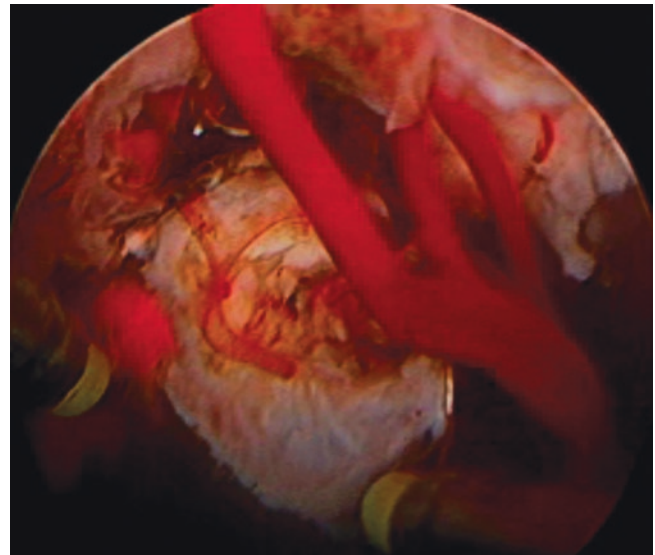
Fig. 19.12 Active bleeding

nique. Hysteroscopy has shown lower rates of intrauterine adhesions after the evacuation of RPOC. Different recently published studies found low rates of IUA with an incidence of <5% [40]. In addition, hysteroscopy has also been associated with a lower number of surgical complications, significantly reducing the risk of uterine perforation and contributing to the diagnosis and treatment of intracavitary abnormalities that can also be associated with recurrent abortions or higher incidence of RPOC.
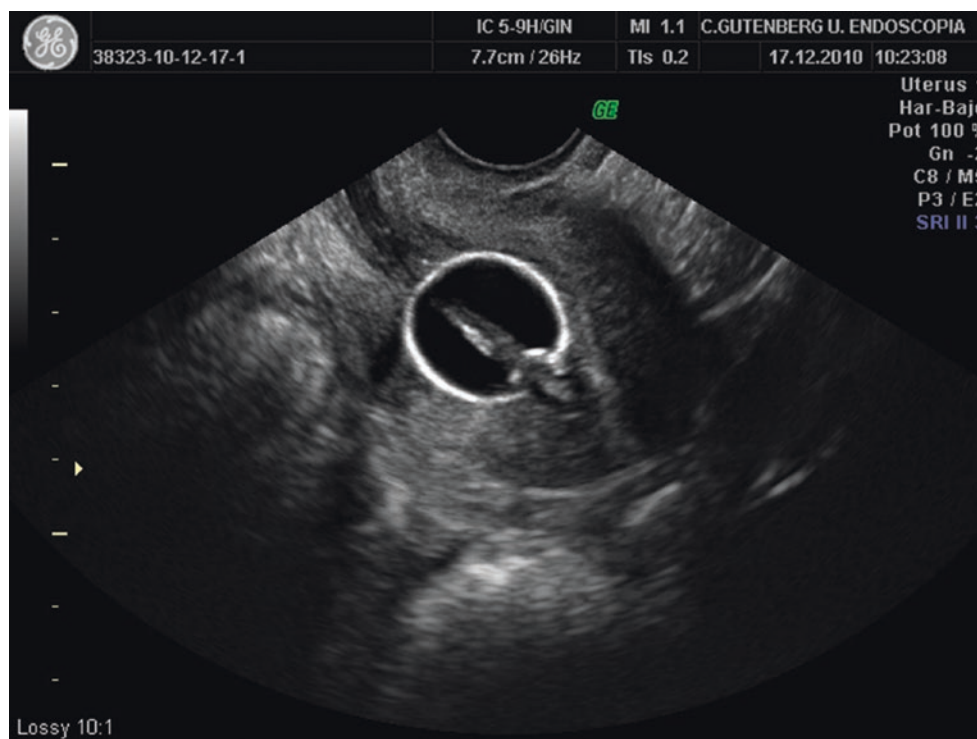
Fig. 19.13 Catheter inside uterine cavity

Although further studies on long-term obstetric outcomes in women following RPOC treatment are still required, data available to date show acceptable post-treatment pregnancy rates [11], varying widely across studies between 50 and 88%, being influenced by the patient age and by the technique used for uterine evacuation, in favor of hysteroscopy in all published studies. The rates of live births range from 70–80%, and the mean time to achieve pregnancy is around 7–8 months, and it has been found in one study that the probability of abnormal placentation in a later pregnancy is 18%, compared to 0.19% of the general population, more frequently in women treated with curettage than with hysteroscopy.

Conclusion

Hysteroscopy is a safe and effective option for the treatment of RPOC, as the latter are often focal and the endoscopic management allows for a selective evacuation under direct vision, thus avoiding any trauma to healthy endometrium. With this technique rates of IUA after the uterine evacuation are lower compared with curettage. A successful removal of the retained material in all patients is achieved in most cases in one surgical session. Hysteroscopy has low rates of intrauterine adhesions and may help in the diagnosis of intrauterine anomalies. Finally, data available to date show acceptable post-treatment pregnancy rates.

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Hysteroscopic Embryo Transfer: HEED and SEED

20

Michael Kamrava

Abbreviations

ET   Embryo transfer
HEED   Hysteroscopic endometrial embryo transfer
ICSI   Intra cytoplasmic sperm injection
IVF   In vitro fertilization
PGS   Preimplantation genetic screening
SEED   Subendometrial embryo delivery

It has been 40 years since the first human pregnancy from IVF, which ended up as an ectopic pregnancy in 1976 [1]. Since then, much progress has been made to improve outcomes and decrease side effects from these procedures. These include: management and control of the menstrual cycle, follicular stimulation, and recruitment, precise timing of ovulation [2–9], oocyte retrieval [10–16], fertilization of the oocyte and embryo culture, and post-ovulatory hormonal supplementation [17–24]. However, there has been little change in embryo transfer technique which uses a "blind" procedure. In spite of the use of various catheters and ultrasound techniques [25–31], a significant risk of major side effects from these techniques persists. These include: lack of identifying uterine contractions with a high degree of precision, endometrial injuries [32], lost or retained embryos, ectopic or heterotopic pregnancies, and placenta previae.

There is a paucity of reports on the use of hysteroscopic embryo transfers, beginning with Spingler et al. [33] in 1989, and then a decade later Kitamura [34] reported on the use of hysteroscopy for intratubal embryo transfer. The intratubal embryo transfers clearly have had an inherent major risk of ectopic pregnancies. As it is pointed out, it is also technically difficult to consistently engage the very small diameter of the tubal ostia without damaging the fallopian endothelial lining,

especially when the endometrium is thickened due to exogenous gonadotropin stimulation. Then, Kilani reported in 2009 on a single patient using a metallic large bore hysteroscope for embryo transfer in a patient under general anesthesia [35]. In both of these reports, carbon dioxide was used for uterine distention, even though exposure to this gas may be potentially detrimental to embryo growth and development [36].

We have previously reported our experience with a flexible mini hysteroscope with an articulating tip since 2001 [37–42], and would like to add a new report on its use for either transferring embryos onto (HEED) or actually implanting the embryo(s) into the endometrium (SEED).

Embryo transfer was done using a flexible mini hysteroscope with an articulating tip. This was accomplished by either placing the embryo gently on the surface of the endometrium (HEED) in 35 patients undergoing IVF, or embedding the embryo just beneath the endometrial surface (SEED) in 24 patients starts using egg donation. Once pregnancy was confirmed with a positive serum hCG, they were followed up with transvaginal ultrasounds and serial serum hCGs in the first trimester. They were then referred to their local obstetricians and final outcomes were recorded after deliveries.

There were a total of 35 patients in the early (days 2 or 3) embryo transfer group (HEED) which resulted in 16 (46%) total pregnancies, which included two biochemical pregnancies, zero ectopic, five spontaneous miscarriages, and three multiple pregnancies (Table 20.1).

Table 20.1 Pregnancy outcomes from HEED

	Day 2 Transfer	Day 3 Transfer	Combined
Patients started	22	13	35
Total pregnancy/started	9	7	16 (46%)
Biochemical pregnancies	2	0	2
Ectopic pregnancies	1	1	2
Spontaneous abortions	3	2	5
Multiple pregnancies	2	1	3
Live/started	3	4	7 (20%)

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Table 20.2 Pregnancy outcomes from SEED

	Day 5 Implantation	Day 6 Implantation	Combined
Patients started	*14*	*10*	*24*
Total pregnancy/started	8 (57%)	8 (80%)	16 (67%)
Biochemical pregnancies	*2*	*2*	*4*
Ectopic pregnancies	*0*	*0*	*0*
Spontaneous abortions	2	3	5
Multiple pregnancies	*4*	0	4
Live/started	4 (29%)	3 (30%)	7 (29%)

Table 20.3 Pregnancy outcomes from combined HEED and SEED

	Combined
Patients started	59
Total pregnancy/started	32
Biochemical pregnancies	6
Ectopic pregnancies	2
Spontaneous abortions	10
Multiple pregnancies	7
Live/started	14 (24%)

There were seven (20%) live births. In the second group of patients with day 5 or 6 embryo implantations (SEED), there were a total of 24 patients starts, with 16 (67%), 4, 0, 5, and 4 total, biochemical, ectopic, and multiple pregnancies respectively. There were seven (29%) live births (Table 20.2).

The combined results are shown in Table 20.3 for a total of 24% live births and no ectopic pregnancies.
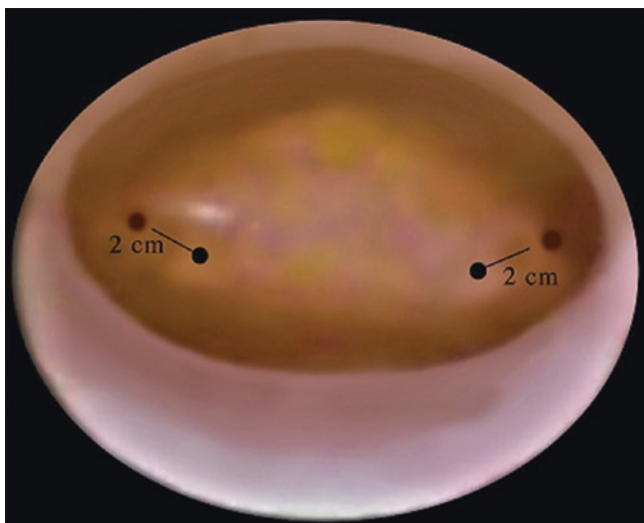
Since the first successful human IVF pregnancy in 1978 [1], there have been over 8,000,000 IVFs done worldwide [43]. At an average total success rate of 22% for live births, there are close to 1.76 million babies born so far and increasing per year. Adverse effects include: lost embryos—at 10% or higher [44–47], ectopic and heterotopic pregnancies, placenta previae [48–51], and multiple pregnancies. Ectopic pregnancies have been reported to occur in as many as 4.8% of patients in some series [52–63]. This translates to a 20% risk in patients with tubal disease or a history thereof. The incidence of multiple pregnancies has been 24% [63–66] in the USA with 7% triplets or more [67], that are associated with increased risks of diabetes, preeclampsia, and prematurity [68, 69]. Furthermore, failed IVF procedures increase maternal anxiety and the cost to achieve a successful pregnancy with a live-born child.

Advances in human embryo culture and growth [70–76] and in embryo freezing at various stages of development [77–81] have allowed for better embryo selection and conservation. Recently, preimplantation genetic screening (PGS) has been introduced as an added procedure to facilitate single embryo selection [82–84]. As a result, reductions in multiple pregnancies can now be focused on selecting the healthiest single embryo by highly trained and skilled embryologists. However, in spite of these efforts and the intensive work done in identifying the exact mechanism of embryo implantation in humans [85, 86], a biologically therapeutic solution remains elusive. In the meantime, clinician's expertise has been cited for varying success rates and the risks and side effects from IVF procedures [87–90].

The endoscopic embryo delivery is an alternative method for embryo delivery whether by direct placement of the embryo onto the endometrial epithelium (HEED) and will standardize embryo transfer procedures. In addition, the hysteroscopic subendometrial embryo transfer (SEED) technique provides for direct embryo implantation into the endometrium and therefore bypasses defects that can prevent the natural process of embryo implantation after embryo transfer onto the endometrium.

Hysteroscopic embryo deliveries (HEED or SEED) provide a visually confirmed technique for precise embryo placement. It allows for a targeted positioning of the embryo(s), which will increase live delivery rate and decrease untoward side effects from embryo transfer (Figs. 20.1, 20.2, 20.3, and 20.4).
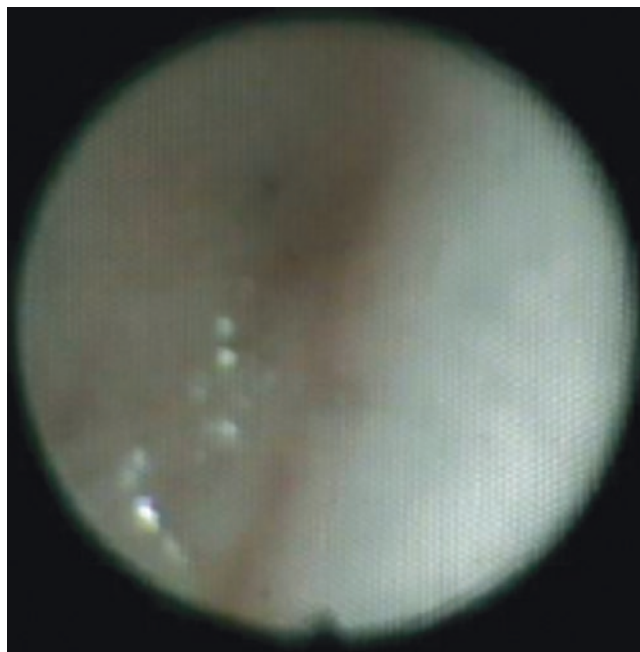
The flexible mini hysteroscope with an articulating tip allows for an atraumatic passage through the cervical canal and the internal os. It is then guided into the already expanded uterine cavity and the site of delivery is then determined (Figs. 20.1. 20.2, and 20.4).

Fig. 20.1 Alternative endometrial locations for embryo delivery HEED or SEED

Fig. 20.2 Placement of embryo(s) under hysteroscopic guidance for HEED; *arrow* points to the tip of the catheter; catheter tip at 8 o'clock position; Tubal ostia at 11 o'clock position

With particular attention to detail in loading the embryo(s) into the catheter by the embryologist [21], the embryo(s) is delivered under direct visual placement of embryo(s) away from both internal the cervical os and the junction of endometrium with endosalpingeal epithelium. This in contrast to blind transfers at a fixed distance from cervical os, as it does not account for variations in cervical length and uterine size [91].

HEED and SEED provide an individualized approach that minimizes ectopic and heterotopic pregnancies and placenta previas. Uterine contractions can be visually confirmed and embryo delivery deferred. SEED technique is especially appealing in patients with prior tubal pregnancies and failed IVF. Additionally, patients will feel more at ease because they can simultaneously see the procedure on a live video monitor while undergoing treatment. A successful pregnancy outcome will also lower the cost to the patient because it will decrease the number of attempts necessary to achieve a successful singleton pregnancy using IVF procedures.

Hysteroscopic embryo delivery, whether by transfer onto the endometrium or implantation into the endometrium, will allow for a reliable and targeted, visually confirmed precision placement of a single embryo delivery onto (HEED) or into (SEED) the endometrium. The procedures are done in an office setting with administration of mild analgesics. These techniques will increase successful pregnancies and decrease major risks and side effects from IVF procedures that pose a major threat to public health, and maternal and infant safety worldwide.
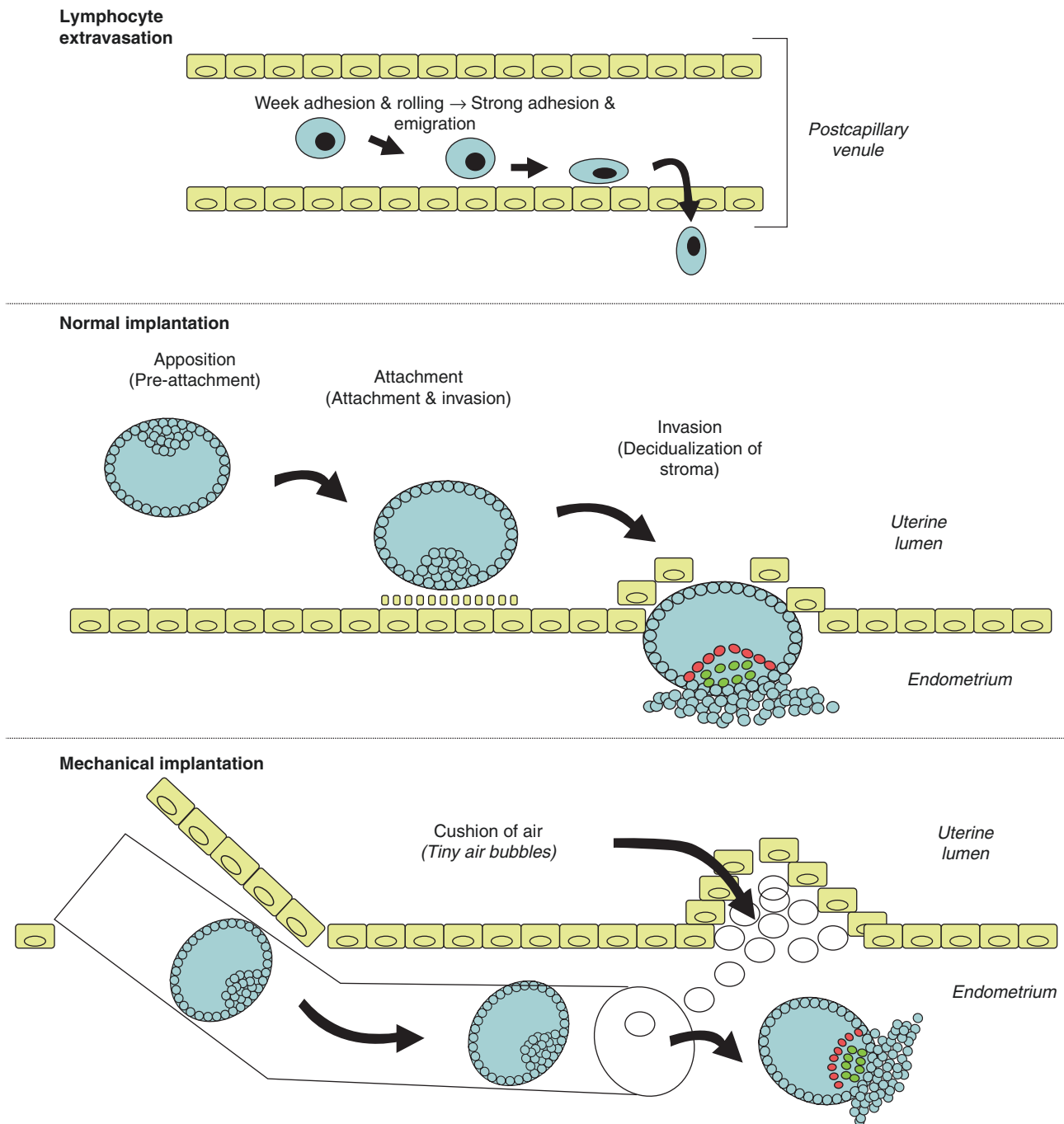
Fig. 20.3 Diagram of implantation concept. There is a strong relationship between how we understand the way lymphocytes are attracted to the site of inflammation and how the embryo implants into receptive endometrium. This relationship includes various cytokines (growth factors), chemokines, and cell adhesion molecule complexes (CAMs) to name a few (*top row*). With SEED the initial steps of implantation, i.e., apposition and attachment are circumvented and biological invasion is voided. Clinically, this is similar to the ICSI procedure where a single sperm is mechanically inserted into the oocyte, bypassing biochemical fertilization. The middle diagram shows the natural stages of apposition, attachment and invasion of embryo into the endometrium. The *bottom row* shows the mechanical subendometrial implantation of the embryo
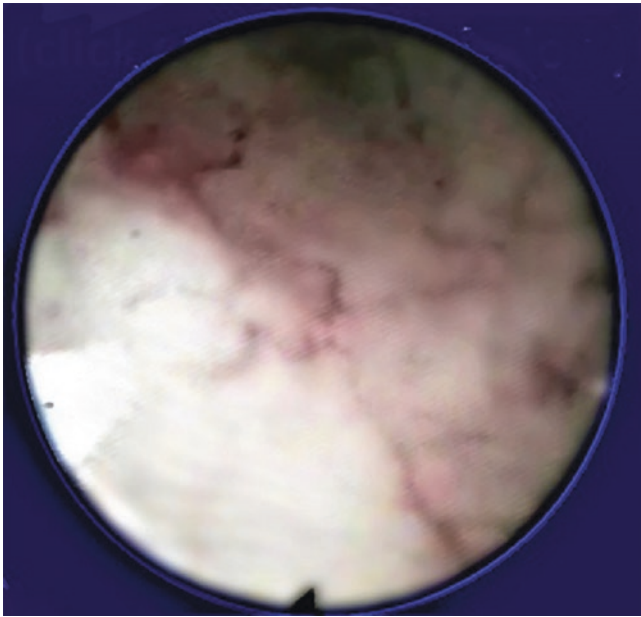
Fig. 20.4 Placement of embryo(s) under hysteroscopic guidance for SEED; catheter tip at 8 o'clock position; Tubal ostia at 12 o'clock position

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Hysteroscopy in Patients with Repeated Implantation Failure

Alka Kumar

21.1 Manuscript

Repeated implantation failure presents a major clinical challenge and is a cause of considerable stress to patients and clinicians in assisted reproductive technology (ART). Besides the psychological and physical burden of each IVF treatment cycle, it also adds to the considerable costs associated with fertility treatment [1]. If progress is to be made in improving implantation rates, a greater understanding of the factors which determine successful implantation is required.

Implantation failure could be due to the embryo, uterine environment, or a combination of both. Even minor uterine cavity abnormalities, such as endometrial polyps, small submucous myomas, adhesions, and septa are considered to have a negative impact on the chance to conceive through IVF [2]. The prevalence of unsuspected intrauterine abnormalities, diagnosed by hysteroscopy prior to IVF, has been reported to be 11–45% [3–13].

Moreover, hysteroscopy enables diagnosis and treatment of intrauterine pathology in the same setting.

The NVOG (Dutch society of Obstetrics and Gynecology) as well as the ESHRE (European Society for Human Reproduction and Embryology) and RCOG (Royal College of Obstetricians and Gynecologists) do not recommend SIS nor hysteroscopy as initial investigation prior to starting IVF [14–16]. It has been argued that the significance of treating unsuspected intrauterine abnormalities has not yet been proven.

Gera et al. compared the pregnancy rate after operative hysteroscopy of patients with intrauterine abnormalities at SIS to the pregnancy rate of patients with a normal uterine cavity. A 31.6% increase in pregnancy rate was observed after treatment of detected abnormalities [17].

Observational studies suggest higher pregnancy rates after the hysteroscopic removal of endometrial polyps, submucous fibroids, uterine septum, or intrauterine adhesions, which are detectable in 10–15% of women seeking treatment for subfertility [18].

Hysteroscopy is considered to be the gold standard prior to IVF [19].

There is accumulated evidence that hysteroscopy is beneficial for women experiencing implantation failures after IVF. Not only the correction of hysteroscopic findings improves the pregnancy rates, at least when compared to controls not having a hysteroscopy, but also the procedure itself may have a positive prognostic value for achieving a subsequent pregnancy [13].

Abnormal findings on hysteroscopy are significantly higher in patients with previous ART failure and hysteroscopy could be seen as a positive prognostic factor for achieving pregnancy in subsequent IVF procedure in women with a history of repetitive replantation failure [20].

Systematic evaluation of the ectocervix, endocervix, endometrium, both the tubal ostia at hysteroscopy is a necessary part of the patient work-up.

21.2 Uterine Septum

A uterine septum is created from a congenital malformation, where the uterine cavity is partitioned by a longitudinal septum; the outside of the uterus has a normal typical shape. The wedge-like partition may involve only the superior part of the uterine cavity resulting in an incomplete septum or a subseptate uterus, or less frequently the total length of the cavity (complete septum) and the cervix resulting in a double cervix. The septation may also continue caudally into the vagina resulting in a "double vagina." The uterus is formed during embryogenesis by the fusion of the two Mullerian ducts, and during this fusion a resorption process eliminates the partition between the two ducts to create a single cavity. This process begins caudally and advances cranially, thus a

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