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Asherman syndrome: current and future perspectives on treatment and prevention of recurrence

Ana Teresa Baltazar Bação Guerra

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Orientado por:
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Janeiro 2017

ABSTRACT

Background: Asherman syndrome (AS) is characterized by the presence of adhesions in the uterine cavity. Clinical presentation includes amenorrhea/hypomenorrhea and dysmenorrhea. It is associated with a high rate of infertility and pregnancy complications.

Objective: To provide an update on the management of AS, with special regard to the future perspectives on treatment and prevention of recurrence.

Study design: Literature review.

Search methods: A literature search was conducted using MEDLINE, PubMed and The Cochrane Library electronic resources. The searched keywords included the terms "Asherman's syndrome", "Asherman syndrome", "intrauterine synechiae", "uterine synechiae" and "intrauterine adhesions". The search was restricted to studies published in the last 5 years and written in English or French languages.

Discussion: Comprehensive management, consisting in hysteroscopic adhesiolysis followed by postoperative prevention of recurrence, provides the best possible outcomes. New developments in hysteroscopy, such as ultrasound guidance and office hysteroscopy, have contributed to an overall success rate of 95% and a low rate of complications. However, intrauterine adhesions (IUAs) recurrence is a major problem, occurring in 28.7% of patients who had successful adhesiolysis. Several methods to prevent IUAs recurrence have been proposed: (1) mechanical devices, including various types of intrauterine balloons and intrauterine devices; (2) postoperative estrogen therapy; (3) barrier gels (hyaluronic acid and its derivates) and (4) human amniotic membrane grafting.
Stem cells (SCs), specifically bone marrow-derived SCs, have been explored as a new therapeutic strategy in AS, with promising results. However, more randomized controlled studies are needed to confirm these results.

Conclusions: Hysteroscopic adhesiolysis is the established gold standard for IUAs treatment, with proven safety and efficacy. Over the last years, the focus has been on the prevention of IUAs recurrence, with the development of several effective methods. Finally, recent experimental studies highlight SCs therapy as a promising therapeutic option for AS.

KEY WORDS: Asherman syndrome, intrauterine adhesions, infertility, hysteroscopic adhesiolysis, stem cells therapy

RESUMO

Contextualização: O síndrome de Asherman (SA) é caracterizado pela presença de sinéquias na cavidade uterina. O quadro clínico inclui amenorreia/hipomenorreia e dismenorreia. Associa-se a uma elevada taxa de infertilidade e de complicações da gravidez.

Objetivo: Rever a abordagem terapêutica do SA, com especial destaque para as futuras opções terapêuticas e de prevenção das recorrências.

Desenho do estudo: Revisão da literatura.

Métodos de pesquisa: A pesquisa foi efetuada com recurso às bases de dados MEDLINE, PubMed e The Cochrane Library. Foram utilizadas as seguintes palavras-chave: "Asherman's syndrome", "Asherman syndrome", "intrauterine synechiae", "uterine synechiae" e "intrauterine adhesions". A pesquisa restringiu-se a estudos publicados nos últimos 5 anos, escritos em língua inglesa ou francesa.

Discussão: Uma abordagem compreensiva, englobando a lise histeroscópica das sinéquias seguida da prevenção pós-operatória das recorrências, permite otimizar os resultados alcançados. Os novos avanços no âmbito da histeroscopia, nomeadamente a histeroscopia eco-guiada e a histeroscopia de ambulatório, contribuíram para uma taxa de sucesso global de 95%, associada a uma baixa taxa de complicações. No entanto, a recorrência das sinéquias é um problema *major*, ocorrendo em 28.7% das doentes. Vários métodos para a prevenção das recorrências têm sido propostos: (1) dispositivos mecânicos, incluindo vários tipos de balões e dispositivos intrauterinos; (2) terapêutica pós-operatória com estrogéneos; (3) géis de efeito barreira (ácido hialurónico e derivados) e (4) enxertos de membrana amniótica humana.
A terapia com célula estaminais (CEs), nomeadamente com CEs derivadas da medula óssea, tem sido amplamente estudada no âmbito do SA, com resultados promissores. No entanto, é necessário um maior número de estudos aleatorizados e controlados para confirmar estes resultados.

Conclusões: A lise histeroscópica é considerada o *gold standard* no tratamento das sinéquias uterinas, com eficácia e segurança demonstradas. Ao longo dos últimos anos, tem sido dado especial enfoque à prevenção da recorrência das sinéquias, com o desenvolvimento de vários métodos preventivos eficazes. Por fim, estudos experimentais recentes têm destacado a terapia com CEs como uma opção terapêutica promissora.

PALAVRAS-CHAVE: síndrome de Asherman, sinéquias intrauterinas, infertilidade, adesiólise histeroscópica, terapia com células estaminais

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INTRODUCTION

Asherman syndrome (AS), described in 1948 by Joseph Asherman[1], is an acquired condition characterized by the presence of adhesions in the uterine cavity. Women with this disease may present with menstrual irregularities (amenorrhea or hypomenorrhea), dysmenorrhea, infertility, recurrent pregnancy losses and history of abnormal placentation.[2,3] The terms 'Asherman syndrome' and 'intrauterine adhesions' (IUAs) are often used interchangeably. However, some filmy IUAs are clinically inconsequential. Therefore, and according to the original definition of the syndrome, some authors prefer to reserve the term 'Asherman syndrome' to symptomatic patients.[2,4,5]

Although uterine curettage following miscarriage or retained products of conception (RPOC) is the most common predisposing factor, any uterine injury can cause IUAs.[5–7] For example, uterine compression suturing during postpartum hemorrhage has a high rate of IUAs development (16% to 18.5%).[8–11] Also hysteroscopic metroplasty for uterine septum correction and treatment of symptomatic myomas – both open and hysteroscopic myomectomy and uterine artery embolization – are associated to IUAs development.[12–15] The role of infection as a cause of IUAs still remains unclear, regarding the limited number of related studies.[3] However, genital tuberculosis and schistosomiasis have been associated to IUAs development.[6,16,17]

In the general population AS is a rare condition. However, it is reported an incidence of 13% in women undergoing routine infertility investigations and of 7% in women with secondary amenorrhea.[18,19] An increase in the number and complexity of uterine surgical procedures, as well as the increased awareness and more detailed diagnostic approaches, is contributing to a higher number of reported cases.[20]

Taking into account the reproductive impact of this condition, with a high rate of infertility and pregnancy complications, the aim the current review is to provide an update on the management of AS, with special regard to the future perspectives on treatment and prevention of recurrence.

SEARCH METHODS

A literature search was conducted in September/October 2016 using MEDLINE, PubMed and The Cochrane Library electronic resources. The searched keywords included the MeSH (Medical Subject Headings) terms "Asherman's syndrome", "Asherman syndrome", "intrauterine synechiae", "uterine synechiae" and "intrauterine adhesions" combined using the

operator “OR”. The search was restricted to studies published in the last 5 years and written in English or French languages.

SEARCH RESULTS

162 studies were found. Among those, 58 studies were selected according to their clinical relevance and suitability. References of selected studies were examined to identify additional relevant literature not found by the initial searches. Relevant references were also included in this review, without any published date restriction. By the end of the selection process, a total of 87 studies were included, with the following designs: 11 randomized controlled studies; 20 retrospective cohort studies; 13 prospective cohort studies; 1 case-control study; 4 basic research studies; 10 systematic reviews; 22 non-systematic reviews; 3 practice guidelines; 3 case-reports.

DISCUSSION

REPRODUCTIVE PROGNOSIS

The impact of AS on pregnancy is well documented with a high rate of infertility and pregnancy complications such as placental abruption, preterm premature rupture of membranes (PROM), abnormal placentation and recurrent spontaneous abortions. Some etiologies of infertility are easy to explain, such as obstruction of the tubal ostia or endocervix. Other mechanisms include reduced uterine cavity size, poor endometrial receptivity, myometrial fibrosis, and reduced uterine blood flow.[7]

In a retrospective cohort study published in 2012[21], women with IUAs were more than threefold more likely to have placental abruption and more than twofold more likely to have preterm PROM when compared with women without IUAs. They were also nearly twofold more likely to have cesarean delivery for malpresentation. Although a causal relationship between IUAs and these pregnancy complications is not proved yet, it seems to be biologically plausible. Placental implantation near the poorly vascularized adhesions may predispose to placental abruption and the wrapping of fetal membranes around IUAs may lead to premature rupture as the uterus enlarges. Furthermore, the presence of IUAs, especially when large, may distort the uterine cavity, resulting in malpresentation and the need for cesarean delivery.[21,22]

IUAs are also related to abnormal placentation, namely placenta accreta, due to trauma of the endometrium with defects in the basal decidua. Consequently, pregnant patients with IUAs should be thoroughly examined for possible abnormal placentation and, in case of suspicion, the patient should

be scheduled for planned cesarean due to risk of severe postpartum hemorrhage.[23]

A 2012 prospective study[24] including 265 women with recurrent pregnancy loss (RPL), defined as two or more consecutive miscarriages, has found an incidence of IUAs of 7% in this population. There is some evidence that adhesions can cause RPL by mechanisms such as diminished functional intrauterine volume and endometrial fibrosis, which restricts expansion. Therefore, diagnostic hysteroscopy with eventual adhesiolysis is recommended after two miscarriages.

DIAGNOSIS

Hysteroscopy remains the gold standard in the assessment of IUAs. It provides a direct visualization of the uterine cavity, allowing for a meticulous characterization of the adhesions and offering the possibility of an immediate treatment. Before the advent of hysteroscopy, hysterosalpingography (HSG) was the main method for the diagnosis of IUAs. The information provided by HSG is limited and the high rate of false-positive diagnoses, coupled with radiation exposure and invasiveness are the main disadvantages of this diagnostic tool.[3,4]

Imaging methods such as ultrasound and saline infusion sonography (SIS) have gained popularity as less invasive diagnostic tools. 2D-Ultrasound has shown a high sensitivity for IUAs diagnosis, although its specificity is very low (97% and 11%, respectively). 3D-Ultrasound has proved to be superior (with a sensitivity and specificity of 87% and 45%, respectively), as it provides panoramic views of the uterine cavity in the coronal plane, with much clearer views of the endometrial-myometrial junction.[4,25]

SIS is less invasive than hysteroscopy and almost devoid of complications. Furthermore, it allows for identification of eventual extra-uterine or adnexal pathology, it is cheaper, relatively easy to perform and better tolerated than hysteroscopy.[26–28] However, it does not allow for concurrent treatment of IUAs.[29] According to a systematic review and meta-analyses published in 2015,[27] the sensitivity and specificity of SIS in the detection of IUAs were 82% and 99%, respectively. Therefore, they recommend that SIS should become the first-line screening tool in the assessment of subfertile women.

A number of classification systems have been developed to grade the adhesions in terms of severity. The widely used classification of the American Fertility Society (1988)[30] takes into account the hysteroscopic/ hysterosalpingographic aspect of IUA and the menstrual pattern (Table 1). More recently, in 2000, it was

published a clinicohysteroscopic scoring system,[31] which include not only the menstrual symptoms but also the obstetric history of the patient (Table 2). Studies of reproductive outcomes using these classification systems have not been reported yet. Therefore, there is still no clear consensus regarding the optimum classification system.[3,5]

MANAGEMENT

The primary goal of the management of AS is to restore the uterine cavity to its normal size and shape and stimulate regeneration of the destroyed endometrium. Secondary goals include treating associated symptoms (including infertility) and preventing adhesions recurrence.[20,32] Comprehensive management provides the best possible outcomes, especially in poor-prognosis women with severe adhesions. This approach involves operative treatment of IUAs followed by postoperative prevention of recurrence.[33,34]

Centralization of care is also very important, as AS is a rare disease and its operative treatment is a difficult procedure with potential complications. Centralization allows to reach higher volumes of patients per center and therefore to improve success rates and to stimulate the research, especially randomized clinical trials that do not suffer from lack of recruitment.[35]

1. OPERATIVE TREATMENT

Dilatation and curettage (D&C) was widely used before the widespread use of hysteroscopy. Nowadays it is still used at centers with limited resources. A retrospective study published in 2015[36], including 100 cases of AS managed at a center in Nigeria has shown that blind D&C has a relatively poor outcome, with correction of menses seen in just 37.2% of the patients and a pregnancy rate of 32.1%. Also, D&C is associated with a high risk of uterine perforation and should therefore be considered obsolete.[3,20,37]

Hysteroscopic adhesiolysis (HA) is the established gold standard for IUAs treatment because of its minimally invasive nature and because it can be performed under direct visualization.[37]

1.1. Mechanical, electrical and laser techniques

Mechanical instruments or energy sources (monopolar/bipolar energy or laser) can be used in HA. The mechanical approach with scissors is the most accessible method, with a low cost. It allows separation of the adhesions without thermal damage of the surrounding normal endometrium, thus reducing the rate of perforation during the procedure. In case of perforation, the risk of visceral injury is lower when compared to energy sources. Another advantage of

hysteroscopic scissors is the use of a smaller hysteroscope without the need of dilatation. As a disadvantage, scissors may become blunt easily with compromised cutting ability and are not able to stop eventual bleeding. In contrast, the use of energy sources is associated with potential thermal damage to the residual endometrium, although it provides effective and precise cutting as well as good hemostasis. Thermal damage of endometrium may be limited by using the minimal amount of energy.[19,37–39]

Electrosurgical instruments include the bipolar electrode Versapoint® and resectoscopes using monopolar or, more recently, bipolar current. The distending media used with monopolar current has to be a non-electrolyte, non-conductive solution, such as glycine 1.5%, sorbitol 3-5%, or mannitol 5%. Absortion of large volumes of these fluids may result in fluid overload with hypervolemia, hyponatremia, hypo-osmolarity, pulmonary edema and cerebral edema, although these major complications are extremely rare. Bipolar energy has the advantage that isotonic solutions (normal saline and lactated Ringer) can be used as distension medium, decreasing the risks of fluid absorption. Fluid input and output should still be monitored and if excessive intravasation occurs, the fluid overload is generally readily treatable with intravenous diuretics. The main disadvantage of bipolar compared with monopolar electrodes is the higher number of gas-bubbles that are created, disturbing visibility.[19,40]

A 2013 case-control study,[41] including 1842 hysteroscopic procedures, has compared the complication rates of hysteroscopic surgery performed using monopolar and bipolar energy. They concluded that both techniques are safe, with no statistically significant difference in complication rates between the two groups (4.1% and 2.8%, respectively; P-value = 0.08). However, because of the previously mentioned fluid overload complications, the authors recommend that bipolar system should be preferred when available.

Lasers (e.g. neodymium-doped yttrium aluminium garnet [Nd-YAG], potassium-titanyl-phosphate [KPT] and argon) offer no advantages over electrocoagulation. As these lasers have a significant risk of thermal damage, are more expensive and not readily available in all hospitals, their use has almost disappeared.[19,40]

Since no randomized controlled studies have been published specifically on HA techniques, different treatment modalities for IUAs are based on individual experience.[40] Some surgeons use a combination of both mechanical and electrical energy to remove IUAs.[39]

1.2. Ultrasound guidance

As previously mentioned, HA carries a significant risk of uterine perforation, especially during the dilatation of the cervical channel and introduction of the hysteroscope. To avoid this complication and to improve the likelihood of complete resection, laparoscopic and, more recently, ultrasound guidance have been used.[37] According to a 2012 retrospective cohort study[42] including a total of 159 hysteroscopic procedures, transabdominal ultrasound guidance significantly decreases the risk of perforation, with an incidence of 1.9% contrasting to 8.7% with laparoscopic guidance and 5.3% with no guidance. All perforations in the laparoscopic-guidance group occurred after insertion of the laparoscope, while in the ultrasound-guidance group they occurred prior to carrying out ultrasonography; when ultrasound was used properly, no uterine perforation occurred. Also, ultrasound guidance costs less than laparoscopic guidance and adds no cost to conventional hysteroscopy without guidance. Ultrasound is therefore the optimal mean of assisting HA, with high efficacy and safety.

1.3. Efficacy and reproductive outcomes

Hysteroscopic lysis releases the traction exerted by the IUAs and decreases the resistence against subendometrial blood flow, thereby stimulating endometrial healing and increasing endometrial thickness, which is essential for a good endometrial receptivity and successful fertility treatments.[43,44] A prospective study published in 2013[13] has concluded that 67% and 96% of women achieved a complete endometrial recovery 1 month and 2 months after HA, respectively. Therefore, they recommend a waiting period for subsequent fertility treatment of 3 months. However, it should be noted that severe and extensive IUAs take a longer time to complete the endometrial recovery process, as their treatment must sometimes be performed in several separate procedures. Each new procedure results in new wounds and healing process resumes. It could be hypothesized that these repetitive interventions would cause worse reproductive outcomes or a higher rate of complications. However, a retrospective case series study[45] including 23 women with AS who required more than two hysteroscopic adhesiolysis procedures has concluded that it is appropriate to treat women until visualization of both uterine ostia is possible, even if multiple HA procedures are needed. With respect to fertility outcomes, namely pregnancy rate, no significant difference was observed between the groups who underwent three, four and five procedures (45.5%, 37.5% and 50%, respectively; P-value = 1). Thus, the

number of hysteroscopic procedures should not be a limiting factor.

The most recent data regarding the efficacy and reproductive outcomes of HA comes from a large cohort study published in 2015[35], including a total of 638 women with AS operated between 2003 and 2013. According to this study, the overall success rate of HA, which includes restoration of both normal uterine anatomy and menses, achieved 95%. Among patients who had successful HA, 28.7% had spontaneous adhesion recurrence. Also, multivariate analysis has shown that higher grades of adhesions were predictive of a higher chance of IUAs recurrence, when compared to low grades (P-value = 0.013). Besides the grade of IUAs, the success of HA also depends on their etiology. A 2014 retrospective cohort study[39] including 76 patients has shown that IUAs following uterine artery embolization have a significantly poorer prognosis than IUAs caused by trauma, with a higher grading score at second look hysteroscopy, less improvement in menstrual pattern and reduced conception and live birth rates. According to another retrospective cohort study published in 2015[46], including 115 women, there is also an association between the location and extent of IUAs and postoperative adhesion recurrence, with a higher risk when original adhesions are located at the uterine cornua, at the cervico-isthmic region and when a large portion of the uterine cavity is involved.

1.4. Office hysteroscopy (OH)

With the new developments in hysteroscopy, namely the reduction of instruments size, OH in an outpatient setting has begun to replace the conventional hysteroscopy performed in operating-room.[40] A small retrospective series[47] including 20 cases of AS has shown that these patients may be successfully treated by OH without general or regional anesthesia. After the treatment, 84% of the patients had no adhesion or just mild adhesions, all of them achieved normal menses, 6 had a spontaneous pregnancy and 5 went on to have a term delivery to date. In 94.6% of cases oral analgesia was sufficient to pain control (89% nonsteroidal anti-inflammatory drugs; 5.6% oral lorazepam). Consequently, the anesthetic risk is very low, with faster return to work, decreased cost and high patient satisfaction with their procedure experience and analgesia control.[47–49] Furthermore, according to a 2012 retrospective cohort study[50] including 1028 procedures, OH is safe, with a low complication rate during the procedure and an extremely low risk of long-term complications (0.001%), namely infection, in either diagnostic or therapeutic procedures. Therefore, there is no indication

for prophylactic antibiotics or antiseptical measures.

Vaginoscopic approach is the currently used technique in the outpatient setting. Patient is placed in the lithotomy position and the hysteroscope is inserted through the internal cervical orifice under direct endoscopic vision, without the need of a speculum. Ideally, this is carried out with no, or minimal, cervical dilatation.[40] A systematic review with meta-analysis[51] of 4 randomized studies has proved that vaginoscopic approach is less painful than the traditional technique using a vaginal speculum, which is clearly advantageous in outpatient procedures to optimize acceptability to patients. However, traditional approach with a vaginal speculum and possibly cervical instrumentation is still necessary in the minority of cases in which visualization of the cervical canal is difficult or when cervical stenosis is encountered.

2. POST-OPERATIVE ASSESSMENT

Evaluation of uterine cavity after HA is an important step in AS management, as timely recognition of adhesion recurrence is essential to provide the best prognosis.[3] Hysteroscopy, particularly OH, is the most commonly used follow-up method, as it permits immediate treatment of reformed adhesions.[3,13,46] Although there is no clear consensus, follow-up is recommended one-two months after the initial surgery.[3]

3. PREVENTION OF ADHESION RECURRENCE

As mentioned in the last section, adhesion recurrence is one of the major problems following HA. Several methods to prevent IUAs recurrence have been proposed, including (1) mechanical devices, (2) medical therapies, (3) anti-adhesion barrier gels and (4) human amniotic membrane grafting.

According to a Cochrane Database systematic review published in 2015[52] and including 11 randomized studies, anti-adhesion therapy was associated with fewer IUAs at second-look hysteroscopy when compared with no treatment or placebo (P value = 0.0005) (Figure 1), although no differences were found with respect to live birth rates (P value = 0.98) (Figure 2). However, the methodological quality of most of the included studies (9 of 11) was low, which may compromise the results of the systematic review.

3.1. Mechanical devices

Mechanical devices include various types of intrauterine balloons and intrauterine devices (IUDs). They help to keep opposing surfaces of the uterine cavity separate and the subsequent removal of the IUD may also help to remove some

adhesions that may have reformed.[53] Next paragraphs describe the currently available intrauterine balloons (Foley's catheter and heart-shaped balloon) and IUDs (T-shaped, Lippes loop and heart-shaped IUD) and their outcomes.

Foley's catheter balloon was one of the first mechanical devices used for prevention of adhesion recurrence.[3] Due to its spherical shape, it is not likely to fit into the uterine sidewall and corneal region and therefore may not be an effective barrier in these regions.[54] A small retrospective cohort study[55] including 26 women who underwent open myomectomy during which the uterine cavity was breached reported no IUAs formation (0%) in the group treated with Foley's catheter following breach of uterine cavity, compared to a rate of 30% of IUAs formation in controls. However, there are no randomized controlled trials attesting its efficacy and there is risk of uterine perforation and ascending infection.[3] Thus, American Association of Gynecologic Laparoscopists does not recommend Foley's catheter routine use outside of clinical trials.[56]

The heart-shaped uterine balloon (Cook Medical balloon) is a silicone made, triangular shape device. It was specially designed for IUAs prevention and fits the normal shape of the uterine cavity. However, it is more difficult to insert and more expensive than Foley's catheter.[3,54] One potential risk of intrauterine balloon is ascending infection. However, a 2014 prospective, randomized, controlled study[57] including 60 women who underwent hysteroscopic surgery has proved that bacterial colonization did not increase significantly after 30 days, in both intrauterine balloon group and control group. All the identified bacteria represent normal vaginal flora and no woman developed pelvic inflammatory disease. Therefore, intrauterine balloon may be placed in uterus for up 30 days without increased risk of infection. This result is compatible with the American College of Obstetricians and Gynecologists guidelines against routine antibiotic prophylaxis following hysteroscopic surgery.[58]

Lippes loop IUD was favored for prevention of IUAs due to its large area but is no longer available in many countries.[52,59] T-shaped IUD has no contact with the sidewall, and so is not expected to be effective in preventing marginal adhesions.[54] Heart-shaped copper IUD is a semi-flexible, stainless steel device impregnated with copper and anti-inflammatory agent. Due to its shape, it also fits well in the uterine cavity, pressing against the lateral wall.[54]

A systematic review published in 2014[59] and including 28 studies has concluded that IUDs are safe and effective but they need to be combined with other ancillary treatments (hormonal, anti-

adhesions barrier gels or amnion graft) to obtain maximal outcomes, particularly in patients with moderate to severe IUAs. This review also alerts for the lack of evidence about the ideal IUD, the duration course of IUD therapy and the stage of adhesion in which IUD therapy will be most beneficial.

According to a 2015 prospective, randomized, controlled study[54] including 201 women with AS, heart-shaped intrauterine balloon and heart-shaped copper IUD appear to be of similar efficacy in the prevention of IUAs recurrence after HA, with no significant differences in the median adhesion score reduction and in the adhesion reformation rate.

A retrospective cohort study[53] including 107 women has shown that both heart-shaped balloon and copper coil IUD achieved greater results in adhesion recurrence prevention after HA than hyaluronic acid gel (P value < 0.001), which results are similar to the control groups. However, a carefully designed randomized controlled study is needed to confirm the latter results.

3.2. Medical therapy

Hormonal therapy with estrogen stimulate the remodeling and proliferation of endometrium by up-regulating the expression of growth factors, such as vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF) and transforming growth factor (TGF-β1).[32]

Estrogen administration can be performed preoperatively and postoperatively. Preoperative administration stimulates endometrial proliferation so that endometrium would be seen at transabdominal ultrasound guidance when HA is performed, reducing the risk of perforation. However, an overly stimulated endometrium would difficult the visualization of the ostial tube. There is lack of good-quality evidence confirming the efficacy of preoperative estrogen and establishing proper protocols.[32]

Postoperative estrogen therapy stimulates endometrium regeneration with consequent covering of the denuded endometrial layer before new adhesions formation. According to a systemic review published in 2014[32] and including 28 studies, postoperative estrogen therapy improved menstrual and fertility outcomes in patients with IUAs, regardless the stage of adhesions. However, and similar to IUD, it needs to be combined with ancillary treatment to obtain maximal outcomes, particularly in patients with moderate to severe adhesions. Although various protocols have been proposed, there is no shared consensus about the ideal dosage, duration of treatment and combination of hormones.[32,60] The most commonly used regimen consists of estradiol valerate 4mg/day for at least 21 days, with

the addition of medroxyprogesterone acetate 10mg for the last 7 of the 21 days.[32]

Besides hormonal therapy, other medical therapies have been proposed. A small non-randomized study published in 2010[61] has shown that vitamin E (600mg/day orally), l-arginine (6g/day orally) or sildenafil citrate (100mg/day intravaginally) improved uterine vascularization and endometrial thickness in patients with thin endometrium. Perhaps these therapies could inhibit IUAs reformation and improve endometrial growth, however, they have never been tested in a randomized controlled fashion.[60]

3.3. Anti-adhesion barrier gels

Barrier gels prevent direct contact between opposing uterine walls.[62] The ideal barrier should be non-immunogenic, stay in place without sutures, promote the healing of endometrium tissue, remain active in the presence of blood and be completely biodegradable.[63,64]

Hyaluronic acid is a water-soluble polysaccharide composed by glucuronic acid and N-acetylglucosamine. Due to its biocompatibility, viscoelasticity and antiadhesive properties, hyaluronic acid and its derivates have been studied for IUAs prevention.[64,65] Hyaluronic acid is not the ideal substance for all procedures, due to its limited residence time when applied to a surgical site and its fast metabolization.[52,64] To circumvent these disadvantages, derivates of hyaluronic acid have been developed. These substances include auto-crosslinked hyaluronic acid gel and combination of hyaluronic acid with other anti-adhesion components, namely carboxymethylcellulose and alginate.

Auto-crosslinked hyaluronic acid gel is a highly viscous gel obtained through an internal auto-crosslinking reaction of pure hyaluronic gel. A recent systematic review and meta-analysis[66] including 5 randomized controlled studies has shown that auto-crosslinked hyaluronic acid gel is effective in the prevention of both intraperitoneal adhesions after laparoscopic myomectomy and IUAs after hysteroscopic surgery.

Hyaluronic acid with carboxymethylcellulose is a well-known anti-adhesive material with long-lasting action for about 7 days.[65] Alginate has also demonstrated efficacy in the prevention of intra-abdominal adhesions in an animal model.[67] A randomized, single-blind clinical trial[65] including 187 women with a surgically treatable intrauterine lesion (myomas, polyps, septa, IUAs or dysfunctional bleeding) has concluded that alginate carboxymethylcellulose hyaluronic acid (ACH) and carboxymethylcellulose hyaluronic acid (CH) have comparable anti-adhesive effects. In the subgroup of women without baseline IUAs, ACH has actually

shown a lower rate of IUAs than CH. Importantly, there were no severe adverse effects related to both ACH and CH. One patient reported lower back pain in CH group and two patients reported diarrhea and general itching sensation, respectively, in the ACH group. These events were mild and recovered spontaneously.

Intercoat (Oxiplex/AP gel) is a viscoelastic gel commonly used for prevention of pelvic adhesions. It is composed of polyethylene oxide and carboxymethylcellulose stabilized by calcium chloride.[62,68,69] A randomized controlled study published in 2011[70], including 110 women who underwent hysteroscopic surgery demonstrated a significant reduction in the incidence of new IUAs in Intercoat group comparing to control group (6% vs. 22%, P-value < 0.05). Furthermore, the application of Intercoat seemed to reduce the severity of IUAs, with fewer moderate and severe IUAs at follow-up hysteroscopy (33% vs. 92%). More recently, in 2014, another randomized controlled study[62] has shown that intrauterine application of Intercoat after hysteroscopic treatment of RPOC is safe, with a tendency toward reduction of new IUAs development and toward enhanced reproductive outcomes when compared to control group, although not statistically significant.

According to a 2014 systematic review and meta-analysis[64] including 5 studies, the use of any anti-adhesion gel following operative hysteroscopy decreases the incidence of new adhesions formation, comparing to no gel use (Figure 3). If new adhesions formation occurs, there are less moderate or severe adhesions (Figure 4) and more mild adhesions (Figure 5) by using any anti-adhesion gel. However, there is no evidence of efficacy for the outcomes of live birth or clinical pregnancy (Figure 6), and there is no data on the outcome miscarriage. Despite these results, the authors emphasize that the included studies are of very low quality and in a small number, with possible compromise of the veracity of the results. More well-designed and randomized studies are needed to assess the efficacy of anti-adhesion barrier gels in the prevention of IUAs recurrence.

3.4. Human amniotic membrane grafting (HAMG)

Amniotic membrane graft, besides functioning as an anatomical barrier, facilitates epithelialization by acting as a basement membrane substrate and inhibits inflammation and fibrosis. Both fresh and dried (lyophilized) amnion grafts can be used with similar efficacy. However, dried graft holds some advantages as availability, prevention of cross-infection, and easier surgical application.[71]

A prospective randomized controlled trial,[71] including 45 patients with AS, compared HAMG to intrauterine balloon placement. The study has found that adhesions grade was significantly reduced in the HAMG group comparing to intrauterine balloon group (P-value = 0.003), with a non-statistically significant increase in uterine length and menstrual flow.

HAMG is a promising anti-adhesion intervention, however, it has not been very popular in the clinical practice and evidence is not sufficient to recommend its utilization. It is not approved for intrauterine use in the United States of America.[52,60]

4. FUTURE PERSPECTIVES

Adult stem cells (SCs), also referred to as tissue-specific SCs, play important roles in tissue repair and reconstruction. They proliferate by asymmetric cell division, eventually differentiating into specific cell lineages. It had long been speculated that endometrial SCs existed, based on the fact that endometrium is a dynamic tissue regenerating in every menstrual cycle.[72] Finally, in 2004, adult SCs were first isolated from the endometrium.[73] Three kinds of SC exist in the human endometrium: epithelial, mesenchymal and endothelial SCs. Mounting evidence has confirmed that there are SCs in both the functionalis and basalis of the human endometrium.[74–76]

As endometrial SCs have a key role in maintaining tissue homeostasis, it is likely that their function is aberrant in disorders associated with inadequate endometrial proliferation. Specifically in AS, it is hypothesized that there is a loss of endometrial SCs, which may or may not be dysfunctional.[77,78] Therefore, SCs therapy holds great promise for the treatment of this disorder.

Lately, bone marrow-derived stem cells (BMDSCs) have also been explored as a new therapeutic strategy in AS. Next paragraphs summarize the main conclusions of some recent clinical trials, in both murine and human models, regarding BMDSCs therapy.

An experimental study[79] in a rat model, published in 2014 aimed to investigate the possibility that BMDSCs could regenerate the endometrium in AS. A mouse model of AS has been developed using a needle to traumatize the lumen of both uterine horns. Immediately following the damage, BMDSCs or saline were administered. Histological analysis 3 months later showed . reduced fibrosis and a pregnancy rate of 90% in the bone marrow-transplanted animals, compared with 30% of saline-treated mice.

Another randomized controlled trial[80] in a murine model of thin endometrium,

induced by uterine injection of anhydrous ethanol, has shown that BMDSCs intravenous transplantation resulted in increased endometrial thickness when compared to control group (P-value < 0.01). It was also observed an increase in the number of endometrial glands and capillaries.

A prospective case series[81] including 6 women with refractory AS, published in 2014, has evaluated the role of sub-endometrial autologous SCs implantation. Bone-marrow mononuclear SCs were implanted in sub-endometrial zone followed by oral estrogen therapy. Endometrial thickness, assessed at 3, 6, and 9 months, has increased significantly when compared to pretreatment level (P < 0.05). Also, 5 out of 6 patients resumed menstruation.

Taken together, the results of these studies indicate that BMDSCs play a key role in regeneration of thin and damaged endometrium. This regeneration can be due to (1) BMDSCs incorporation in endometrium and trans-differentiation into endometrial epithelium and stroma or (2) BMDSCs immunomodulatory effect with activation of the remaining resident endometrial progenitor cells by providing growth factors.[80,81]

BMDSCs expressing CD133/VEGFR2 represent a subpopulation of BMDSCs with endothelial progenitor capacity that contributes to neoangiogenesis[82,83], with good results in pathologies such as limb ischemia, postmyocardial infarction, refractory angina and atherosclerosis.[84,85] A 2016 prospective, non-controlled study[82] including 16 women with AS or endometrial atrophy, tried to elucidate if CD133+ BMDSC therapy is a safe and efficient approach in these patients. CD133+ cells were isolated from the peripheral blood and instilled into the spiral arteries to repopulate the SC niche and promote endometrial reconstruction. As a result, endometrial thickness increased significantly two months after therapy (from an average of 4.3mm to 6.7mm, in AS patients). Also, there was an increase in the mature vessel density and in the duration/ intensity of menses in the first 3 months, with a return to the initial levels 6 months after the treatment. These results are compatible with an effective, although transitory, reconstruction of the endometrium.

CD133+ BMDSCs therapy appears to be a promising therapeutic option for patients with IUAs. However, randomized controlled studies with a larger sample size are needed to confirm these results.

PRIMARY PREVENTION

To prevent AS it is essential to avoid any trauma to the uterus, especially in the pregnant or postpartum state. Prevention should be based in 3 main principles:

(1) Expectant or medical management of miscarriages/RPOC should be preferred instead of surgical options.[37,86]

(2) If surgery is needed, D&C should be avoided as far as possible. A systematic review published in 2016[87] reports a significantly higher rate of IUAs after D&C compared to hysteroscopic resection (30% vs. 13%) in the management of RPOC. Hysteroscopy should therefore be considered a safer method for diagnosis and treatment of RPOC.

(3) If D&C is indeed required it should be performed gently, with the use of either suction or a blunt (not sharp) curette to avoid unnecessary trauma.[37]

CONCLUSIONS

IUAs have a high negative impact on female fertility and pregnancy. The introduction of hysteroscopy, the current gold standard for IUAs treatment, has significantly improved the treatment success rate and the reproductive outcomes, comparing to the old, conventional D&C technique. New developments in hysteroscopy, namely ultrasound guidance and office hysteroscopy, have contributed to increase the safety and efficacy of the procedure. Due to the high rate of post-operative adhesions re-formation, various methods for prevention of recurrence have been developed with proven efficacy, although more studies are needed. Finally, recent experimental studies highlight SCs therapy as a promising therapeutic option for AS.

Despite the good outcomes achieved nowadays with the comprehensive treatment, primary prevention of AS should not be forgotten. Greater effort should be made in order to avoid uterine curettages, giving preference to less traumatic interventions.

REFERENCES

1. Asherman JG. Amenorrhoea traumatica (atretica). *J Obstet Gynaecol Br Emp*. 1948;55:23-30.
2. March CM. Management of Asherman's syndrome. *Reprod Biomed Online*. 2011;23(1):63-76. doi:10.1016/j.rbmo.2010.11.018.
3. Conforti A, Alviggi C, Mollo A, De Placido G, Magos A. The management of Asherman syndrome: a review of literature. *Reprod Biol Endocrinol*. 2013;11:118. doi:10.1186/1477-7827-11-118.
4. Amin TN, Saridogan E, Jurkovic D. Ultrasound and intrauterine adhesions: a novel structured approach to diagnosis and management. *Ultrasound Obstet Gynecol*. 2015;46(2):131-139. doi:10.1002/uog.14927.
5. Hatasaka H. Clinical Management of the Uterine Factor in Infertility. *Clin Obstet Gynecol*. 2011;54(4):696-709. doi:10.1097/GRF.0b013e3182353d68.
6. Schenker JG, Margalioth EJ. Intrauterine adhesions: an updated appraisal. *Fertil Steril*. 1982;37(5):593-610. doi:10.1016/S0015-0282(16)46268-0.
7. March CM. Asherman's Syndrome. *Semin Reprod Med*. 2011;29(2):83-94. doi:10.1016/j.rbmo.2010.11.018.
8. Jamard A, Turck M, Chéret-Benoist A, Dreyfus M, Benoist G. Risque de synéchie utérine après capitonnage utérin pour hémorragie du post-partum. *Gynécologie Obs Fertil*. 2014;42(10):681-685. doi:10.1016/j.gyobfe.2014.04.013.
9. Ibrahim MI, Raafat TA, Ellaithy MI, Aly RT. Risk of postpartum uterine synechiae following uterine compression suturing during postpartum haemorrhage. *Aust New Zeal J Obstet Gynaecol*. 2013;53(1):37-45. doi:10.1111/ajo.12017.
10. Alouini S, Coly S, Mégier P, Lemaire B, Mesnard L, Desroches A. Multiple square sutures for postpartum hemorrhage: Results and hysteroscopic assessment. *Am J Obstet Gynecol*. 2011;205(4):335.e1-335.e6. doi:10.1016/j.ajog.2011.05.006.
11. Rasheed SM, Amin MM, Abd Ellah AH, Abo Elhassan AM, El Zahry MA, Wahab HA. Reproductive performance after conservative surgical treatment of postpartum hemorrhage. *Int J Gynaecol Obstet*. 2014;124(3):248-252. doi:10.1016/j.ijgo.2013.08.018.
12. Mazzon I, Favilli A, Cocco P, et al. Does cold loop hysteroscopic myomectomy reduce intrauterine adhesions? A retrospective study. *Fertil Steril*. 2014;101(1):294-298.e3. doi:10.1016/j.fertnstert.2013.09.032.
13. Yang JH, Chen MJ, Chen C Der, Chen SU, Ho HN, Yang YS. Optimal waiting period for subsequent fertility treatment after various hysteroscopic surgeries. *Fertil Steril*. 2013;99(7):2092-2096.e3. doi:10.1016/j.fertnstert.2013.01.137.
14. Mara M, Horak P, Kubinova K, Dundr P, Belsan T, Kuzel D. Hysteroscopy after uterine fibroid embolization: Evaluation of intrauterine findings in 127 patients. *J Obstet Gynaecol Res*. 2012;38(5):823-831. doi:10.1111/j.1447-0756.2011.01782.x.
15. Conforti A, Krishnamurthy GB, Dragamestianos C, et al. Intrauterine adhesions after open myomectomy: an audit. *Eur J Obstet Gynecol Reprod Biol*. 2014;179:42-45. doi:10.1016/j.ejogrb.2014.04.034.
16. Bukulmez O, Yarali H, Gurgan T. Total corporal synechiae due to tuberculosis carry a very poor prognosis following hysteroscopic synechialysis. *Hum Reprod*. 1999;14(8):1960-1961. doi:10.1093/humrep/14.8.1960.
17. Krolikowski A, Janowski K, Larsen J V. Asherman syndrome caused by schistosomiasis. *Obstet Gynecol*. 1995;85(5, Part 2):898-899. doi:http://dx.doi.org/10.1016/0029-7844(94)00371-J.
18. The Practice Committee of the American Society for Reproductive Medicine. Current evaluation of amenorrhea. *Fertil Steril*. 2006;86(4):148–155. doi:10.1016/j.fertnstert.2004.02.098.
19. Panayotidis C, Weyers S, Bosteels J, Van Herendael B. Intrauterine adhesions (IUA): Has there been progress in understanding and treatment over the last 20 years? *Gynecol Surg*. 2009;6(3):197-211. doi:10.1007/s10397-008-0421-y.
20. Deans R, Abbott J, Hons BMED. Review of Intrauterine Adhesions. *J Minim Invasive Gynecol*. 2010;17(5):555-569. doi:10.1016/j.jmig.2010.04.016.
21. Tuuli MG, Shanks A, Bernhard L, Odibo AO, Macones G a., Cahill A. Uterine Synechiae and Pregnancy Complications. *Obstet Gynecol*. 2012;119(4):810-814. doi:10.1097/AOG.0b013e31824be28a.

22. Finberg H. Uterine Synechiae in Pregnancy: Expanded Criteria for Recognition and Clinical Significance in 28 Cases.pdf. *J Ultrasound Med*. 1991.

23. Engelbrechtsen L, Langhoff-Roos J, Kjer JJ, Istre O. Placenta accreta: adherent placenta due to Asherman syndrome. *Clin case reports*. 2015;3(3):175-178. doi:10.1002/ccr3.194.

24. Seckin B, Sarikaya E, Oruc AS, Celen S, Cicek N. Office hysteroscopic findings in patients with two, three, and four or more, consecutive miscarriages. *Eur J Contracept Reprod Heal Care´*. 2012;17(5):393-398. doi:10.3109/13625187.2012.698767.

25. Sylvestre C, Child TJ, Tulandi T, Tan SL. A prospective study to evaluate the efficacy of two- and three-dimensional sonohysterography in women with intrauterine lesions. *Fertil Steril*. 2003;79(5):1222-1225. doi:10.1016/S0015-0282(03)00154-7.

26. Seshadri S, Khalil M, Osman A, Clough A, Jayaprakasan K, Khalaf Y. The evolving role of saline infusion sonography (SIS) in infertility. *Eur J Obstet Gynecol Reprod Biol*. 2015;185:66-73. doi:10.1016/j.ejogrb.2014.11.037.

27. Seshadri S, El-Toukhy T, Douiri A, Jayaprakasan K, Khalaf Y. Diagnostic accuracy of saline infusion sonography in the evaluation of uterine cavity abnormalities prior to assisted reproductive techniques: a systematic review and meta-analyses. *Hum Reprod Update*. 2015;21(2):262-274. doi:10.1093/humupd/dmu057.

28. Van Dongen H, De Kroon CD, Van Den Tillaart SAHM, Louwé LA, Trimbos-Kemper GCM, Jansen FW. A randomised comparison of vaginoscopic office hysteroscopy and saline infusion sonography: a patient compliance study. *BJOG An Int J Obstet Gynaecol*. 2008;115(10):1232-1237. doi:10.1111/j.1471-0528.2008.01858.x.

29. Pundir J, Pundir V, Omanwa K, Khalaf Y, El-Toukhy T. Hysteroscopy prior to the first IVF cycle: A systematic review and meta-analysis. *Reprod Biomed Online*. 2014;28(2):151-161. doi:10.1016/j.rbmo.2013.09.025.

30. Buttram Jr VC Siegler A, DeCherney A, Gibbons W, March C. G V, American Fertility Society. The American Fertility Society classifications of adnexal adhesions, distal tubal occlusion, tubal occlusion secondary to tubal ligation, tubal pregnancies, mullerian anomalies and intrauterine adhesions. *Fertil Steril*. 1988;49(6):944-955. doi:10.1016/S0015-0282(16)59942-7.

31. Nasr AL, Al-Inany HG, Thabet SM, Aboulghar M. A clinicohysteroscopic scoring system of intrauterine adhesions. *Gynecol Obs Invest*. 2000;50(3):178-181. doi:goi50178 [pii].

32. Johary J, Xue M, Zhu X, Xu D, Velu PP. Efficacy of Estrogen Therapy in Patients With Intrauterine Adhesions: Systematic Review. *J Minim Invasive Gynecol*. 2014;21(1):44-54. doi:10.1016/j.jmig.2013.07.018.

33. Myers EM, Hurst BS. Comprehensive management of severe Asherman syndrome and amenorrhea. *Fertil Steril*. 2012;97(1):160-164. doi:10.1016/j.fertnstert.2011.10.036.

34. Xiao S, Wan Y, Xue M, et al. Etiology, treatment, and reproductive prognosis of women with moderate-to-severe intrauterine adhesions. *Int J Gynecol Obstet*. 2014;125(2):121-124. doi:10.1016/j.ijgo.2013.10.026.

35. Hanstede MMF, van der Meij E, Goedemans L, Emanuel MH. Results of centralized Asherman surgery, 2003–2013. *Fertil Steril*. 2015;104(6):1561-1568.e1. doi:10.1016/j.fertnstert.2015.08.039.

36. Takai IU, Kwayabura AS, Ugwa EA, Idrissa A, Obed JY, Bukar M. A 10-year Review of the Clinical Presentation and Treatment Outcome of Asherman's Syndrome at a Center with Limited Resources. *Ann Med Heal Sci Res*. 2015;5(6):442-446. doi:10.4103/2141-9248.177984.

37. Yu D, Med M, Wong Y, Cheong Y, Xia E. Asherman syndrome — one century later. *Fertil Steril*. 2008;89(4):759-779. doi:10.1016/j.fertnstert.2008.02.096.

38. Deans R, Abbott J. Review of Intrauterine Adhesions. *J Minim Invasive Gynecol*. 2010;17(5):555-569. doi:10.1016/j.jmig.2010.04.016.

39. Song D, Liu Y, Xiao Y, Li TC, Zhou F, Xia E. A matched cohort study comparing the outcome of intrauterine adhesiolysis for Asherman's syndrome after uterine artery embolization or surgical trauma. *J Minim Invasive Gynecol*. 2014;21(6):1022-1028. doi:10.1016/j.jmig.2014.04.015.

40. Emanuel MH. New developments in hysteroscopy. *Best Pract Res Clin Obstet Gynaecol*. 2013;27(3):421-429. doi:10.1016/j.bpobgyn.2012.11.005.

41. Bahar R, Shimonovitz M, Benshushan A, Shushan A. Case-Control Study of Complications Associated With Bipolar and Monopolar Hysteroscopic Operations. *J Minim Invasive Gynecol*. 2013;20(3):376-380. doi:10.1016/j.jmig.2012.12.012.

42. Kresowik JD, Syrop CH, Van Voorhis BJ, Ryan GL. Ultrasound is the optimal choice for guidance in difficult hysteroscopy. *Ultrasound Obstet Gynecol*. 2012;39(6):715-718. doi:10.1002/uog.11072.

43. Amer MIM, Omar OH, El Sherbiny Hamed M, Dahroug EG. Subendometrial Blood Flow Changes by 3-Dimensional Power Doppler Ultrasound After Hysteroscopic Lysis of Severe Intrauterine Adhesions: Preliminary Study. *J Minim Invasive Gynecol*. 2015;22(3):495-500. doi:10.1016/j.jmig.2014.12.165.

44. Malhotra N, Bahadur A, Kalaivani M, Mittal S. Changes in endometrial receptivity in women with Asherman's syndrome undergoing hysteroscopic adhesiolysis. *Arch Gynecol Obstet*. 2012;286(2):525-530. doi:10.1007/s00404-012-2336-0.

45. Fernandez H, Peyrelevade S, Legendre G, Faivre E, Deffieux X, Nazac A. Total adhesions treated by hysteroscopy: must we stop at two procedures? *Fertil Steril*. 2012;98(4):980-985. doi:10.1016/j.fertnstert.2012.06.032.

46. Yang J, Chen C, Chen S, Yang Y, Chen M. The influence of the location and extent of intrauterine adhesions on recurrence after hysteroscopic adhesiolysis. *BJOG An Int J Obstet Gynaecol*. 2015;123:618-623. doi:10.1111/1471-0528.13353.

47. Bougie O, Lortie K, Shenassa H, Chen I, Singh SS. Treatment of Asherman's Syndrome in an Outpatient Hysteroscopy Setting. *J Minim Invasive Gynecol*. 2015;22(3):446-450. doi:10.1016/j.jmig.2014.12.006.

48. Marsh F, Kremer C, Duffy S. Delivering an effective outpatient service in gynaecology. A randomised controlled trial analysing the cost of outpatient versus daycase hysteroscopy. *BJOG An Int J Obstet Gynaecol*. 2004;111(3):243-248. doi:10.1111/j.1471-0528.2004.00064.x.

49. Bougie O, Wang V, Lortie K, Shenassa H, Singh SS. High Patient Satisfaction with Office Hysteroscopy Using Tailored Analgesia Protocols. *J Gynecol Surg*. 2014;30(2):100-104. doi:10.1089/gyn.2013.0067.

50. Van Kerkvoorde TC, Veersema S, Timmermans A. Long-Term Complications of Office Hysteroscopy: Analysis of 1028 Cases. *J Minim Invasive Gynecol*. 2012;19(4):494-497. doi:10.1016/j.jmig.2012.03.003.

51. Cooper NAM, Smith P, Khan KS, Clark TJ. Vaginoscopic approach to outpatient hysteroscopy: a systematic review of the effect on pain. *BJOG An Int J Obstet Gynaecol*. 2010;117(5):532-539. doi:10.1111/j.1471-0528.2010.02503.x.

52. Bosteels J, Weyers S, Kasius J, Broekmans FJ, Mol BW illem J, D'Hooghe TM. Anti-adhesion therapy following operative hysteroscopy for treatment of female subfertility. *Cochrane Database Syst Rev*. 2015;11(11). doi:10.1002/14651858.CD011110.pub2.

53. Lin X, Wei M, Li TC, et al. A comparison of intrauterine balloon, intrauterine contraceptive device and hyaluronic acid gel in the prevention of adhesion reformation following hysteroscopic surgery for Asherman syndrome: a cohort study. *Eur J Obstet Gynecol Reprod Biol*. 2013;170(2):512-516. doi:10.1016/j.ejogrb.2013.07.018.

54. Lin XN, Zhou F, Wei ML, et al. Prospective, randomized, controlled trial comparing the efficacy of intrauterine balloon and intrauterine contraceptive device in the prevention of adhesion reformation after hysteroscopic adhesiolysis. *Fertil Steril*. 2015;104(1):235-240. doi:10.1016/j.fertnstert.2015.04.008.

55. Gupta S, Talaulikar VS, Onwude J, Manyonda I. A pilot study of Foley's catheter balloon for prevention of intrauterine adhesions following breach of uterine cavity in complex myoma surgery. *Arch Gynecol Obstet*. 2013;288(4):829-832. doi:10.1007/s00404-013-2838-4.

56. AAGL. AAGL Practice Report: Practice Guidelines for Management of Intrauterine Synechiae. *J Minim Invasive Gynecol*. 2010;17(1):1-7. doi:10.1016/j.jmig.2009.10.009.

57. Lin YH, Jang TN, Hwang JL, et al. Bacterial colonization with balloon uterine stent placement in the uterus for 30 days: A randomized controlled clinical trial. *Fertil Steril*. 2014;103(2):513-518.e2. doi:10.1016/j.fertnstert.2014.10.032.

58. ACOG. ACOG Practice Bulletin No. 104: Antibiotic Prophylaxis for Gynecologic

Procedures. *Obstet Gynecol*. 2009;113(5):1180-1189. doi:10.1097/AOG.0b013e3181a6d011.

59. Salma U, Xue M, Md Sayed AS, Xu D. Efficacy of Intrauterine Device in the Treatment of Intrauterine Adhesions. *Biomed Res Int*. 2014;2014. doi:10.1155/2014/589296.

60. Evans-Hoeker EA, Young SL. Endometrial Receptivity and Intrauterine Adhesive Disease. *Semin Reprod Med*. 2014;32(5):392-401. doi:10.1055/s-0034-1376358.

61. Takasaki A, Tamura H, Miwa I, Taketani T, Shimamura K, Sugino N. Endometrial growth and uterine blood flow: a pilot study for improving endometrial thickness in the patients with a thin endometrium. *Fertil Steril*. 2010;93(6):1851-1858. doi:10.1016/j.fertnstert.2008.12.062.

62. Fuchs N, Smorgick N, Ben Ami I, et al. Intercoat (Oxiplex/AP Gel) for Preventing Intrauterine Adhesions After Operative Hysteroscopy for Suspected Retained Products of Conception: Double-Blind, Prospective, Randomized Pilot Study. *J Minim Invasive Gynecol*. 2014;21(1):126-130. doi:10.1016/j.jmig.2013.07.019.

63. Nappi C, Di Spiezio Sardo A, Greco E, Guida M, Bettocchi S, Bifulco G. Prevention of adhesions in gynaecological endoscopy. *Hum Reprod Update*. 2007;13(4):379-394. doi:10.1093/humupd/dml061.

64. Bosteels J, Weyers S, Mol BWJ, D'Hooghe T. Anti-adhesion barrier gels following operative hysteroscopy for treating female infertility: a systematic review and meta-analysis. *Gynecol Surg*. 2014;11(2):113-127. doi:10.1007/s10397-014-0832-x.

65. Kim T, Ahn KH, Choi DS, et al. A Randomized, Multi-Center, Clinical Trial to Assess the Efficacy and Safety of Alginate Carboxymethylcellulose Hyaluronic Acid Compared to Carboxymethylcellulose Hyaluronic Acid to Prevent Postoperative Intrauterine Adhesion. *J Minim Invasive Gynecol*. 2012;19(6):731-736. doi:10.1016/j.jmig.2012.08.003.

66. Mais V, Cirronis MG, Peiretti M, Ferrucci G, Cossu E, Melis GB. Efficacy of auto-crosslinked hyaluronan gel for adhesion prevention in laparoscopy and hysteroscopy: a systematic review and meta-analysis of randomized controlled trials. *Eur J Obstet Gynecol Reprod Biol*. 2012;160(1):1-5. doi:10.1016/j.ejogrb.2011.08.002.

67. Hirasaki Y, Fukunaga M, Kidokoro A, et al. Development of a novel antiadhesive material, alginate flakes, ex vivo and in vivo. *Surg Today*. 2011;41(7):970-977. doi:10.1007/s00595-010-4410-1.

68. Lundorff P, Donnez J, Korell M, Audebert AJM, Block K, diZerega GS. Clinical evaluation of a viscoelastic gel for reduction of adhesions following gynaecological surgery by laparoscopy in Europe. *Hum Reprod*. 2005;20(2):514-520. doi:10.1093/humrep/deh651.

69. Schonman R, Corona R, Bastidas A, De Cicco C, Mailova K, Koninckx PR. Intercoat Gel (Oxiplex): Efficacy, Safety, and Tissue Response in a Laparoscopic Mouse Model. *J Minim Invasive Gynecol*. 2009;16(2):188-194. doi:10.1016/j.jmig.2008.12.014.

70. Di Spiezio Sardo A, Spinelli M, Bramante S, et al. Efficacy of a Polyethylene Oxide-Sodium Carboxymethylcellulose Gel in Prevention of Intrauterine Adhesions After Hysteroscopic Surgery. *J Minim Invasive Gynecol*. 2011;18(4):462-469. doi:10.1016/j.jmig.2011.04.007.

71. Amer MI, Abd-El-Maeboud KHI, Abdelfatah I, Salama FA, Abdallah AS. Human Amnion as a Temporary Biologic Barrier after Hysteroscopic Lysis of Severe Intrauterine Adhesions: Pilot Study. *J Minim Invasive Gynecol*. 2010;17(5):605-611. doi:10.1016/j.jmig.2010.03.019.

72. Xu Y, Zhu H, Zhao D, Tan J. Endometrial stem cells: Clinical application and pathological roles. *Int J Clin Exp Med*. 2015;8(12):22039-22044.

73. Chan RWS, Schwab KE, Gargett CE. Clonogenicity of Human Endometrial Epithelial and Stromal Cells. *Biol Reprod*. 2004;70(6):1738-1750. doi:10.1095/biolreprod.103.024109.

74. Gargett CE, Nguyen HPT, Ye L. Endometrial regeneration and endometrial stem/progenitor cells. *Rev Endocr Metab Disord*. 2012;13(4):235-251. doi:10.1007/s11154-012-9221-9.

75. Gargett CE, Masuda H. Adult stem cells in the endometrium. *Mol Hum Reprod*. 2010;16(11):818-834. doi:10.1093/molehr/gaq061.

76. Masuda H, Matsuzaki Y, Hiratsu E, et al. Stem cell-like properties of the endometrial side population: Implication in endometrial regeneration. *PLoS One*. 2010;5(4). doi:10.1371/journal.pone.0010387.

77. Gargett CE, Schwab KE, Deane JA.

Endometrial stem/progenitor cells: The first 10 years. *Hum Reprod Update*. 2016;22(2):137-163. doi:10.1093/humupd/dmv051.

78. Gargett CE, Ye L. Endometrial reconstruction from stem cells. *Fertil Steril*. 2012;98(1):11-20. doi:10.1016/j.fertnstert.2012.05.004.

79. Alawadhi F, Du H, Cakmak H, Taylor HS. Bone Marrow-Derived Stem Cell (BMDSC) Transplantation Improves Fertility in a Murine Model of Asherman's Syndrome. *PLoS One*. 2014;9(5):e96662. doi:10.1371/journal.pone.0096662.

80. Jing Z, Qiong Z, Yonggang W, Yanping L. Rat bone marrow mesenchymal stem cells improve regeneration of thin endometrium in rat. *Fertil Steril*. 2014;101(2):587-594.e3. doi:10.1016/j.fertnstert.2013.10.053.

81. Singh N, Mohanty S, Seth T, Shankar M, Bhaskaran S, Dharmendra S. Autologous stem cell transplantation in refractory Asherman's syndrome: A novel cell based therapy. *J Hum Reprod Sci*. 2014;7(2):93-98. doi:10.4103/0974-1208.138864.

82. Santamaria X, Cabanillas S, Cervelló I, et al. Autologous cell therapy with CD133+ bone marrow-derived stem cells for refractory Asherman's syndrome and endometrial atrophy: a pilot cohort study. *Hum Reprod*. 2016;31(5):1087-1096. doi:10.1093/humrep/dew042.

83. Cervelló I, Gil-Sanchis C, Santamaría X, et al. Human CD133+ bone marrow-derived stem cells promote endometrial proliferation in a murine model of Asherman syndrome. *Fertil Steril*. 2015;104(6):1552-60-3. doi:10.1016/j.fertnstert.2015.08.032.

84. Rafii S, Lyden D. Therapeutic stem and progenitor cell transplantation for organ vascularization and regeneration. *Nat Med*. 2003;9(6):702-712. doi:10.1038/nm0603-702.

85. Jimenez-Quevedo P, Gonzalez-Ferrer JJ, Sabate M, et al. Selected CD133+ Progenitor Cells to Promote Angiogenesis in Patients With Refractory Angina - Final Results of the PROGENITOR Randomized Trial. *Circ Res*. 2014;115(11):950-960. doi:10.1161/CIRCRESAHA.115.303463.

86. Hooker AB, Lemmers M, Thurkow AL, et al. Systematic review and meta-analysis of intrauterine adhesions after miscarriage: prevalence, risk factors and long-term reproductive outcome. *Hum Reprod Update*. 2014;20(2):262-278. doi:10.1093/humupd/dmt045.

87. Hooker AB, Aydin H, Brölmann HAM, Huirne JAF. Long-term complications and reproductive outcome after the management of retained products of conception: A systematic review. *Fertil Steril*. 2016;105(1):156-164e2. doi:10.1016/j.fertnstert.2015.09.021.

APPENDIX – FIGURES AND TABLES

TABLE 1

Classification	**Condition**		
Cavity involved	<1/3 1	1/3 - 2/3 2	>2/3 3
Type of adhesions	Filmy 1	Filmy and dense 2	Dense 3
Menstrual pattern	Normal 0	Hypomenorrhea 2	Amenorrhea 4
Prognostic classification			
Stage I (Mild)	1-4		
Stage II (Moderate)	5-8		
Stage III (Severe)	9-12		

TABLE 2

		Score
Hysteroscopic findings		
Isthmic fibrosis		2
Filmy adhesions	Few	1
	Excessive (i.e., >50% of the cavity)	2
Dense adhesions	Single band	2
	Multiple bands (i.e., >50% of the cavity)	4
Tubal ostium	Both visualized	0
	Only one visualized	2
	Both not visualized	4
Tubular cavity (sound less than 6)		10
Menstrual pattern		
Normal		0
Hypomenorrhea		4
Amenorrhea		8
Reproductive performance		
Good obstetric history		0
Recurrent pregnancy loss		2
Infertility		4
0-4 = mild (good prognosis); 5-10 = moderate (fair prognosis); 11-22 = severe (poor prognosis)		

FIGURE 1

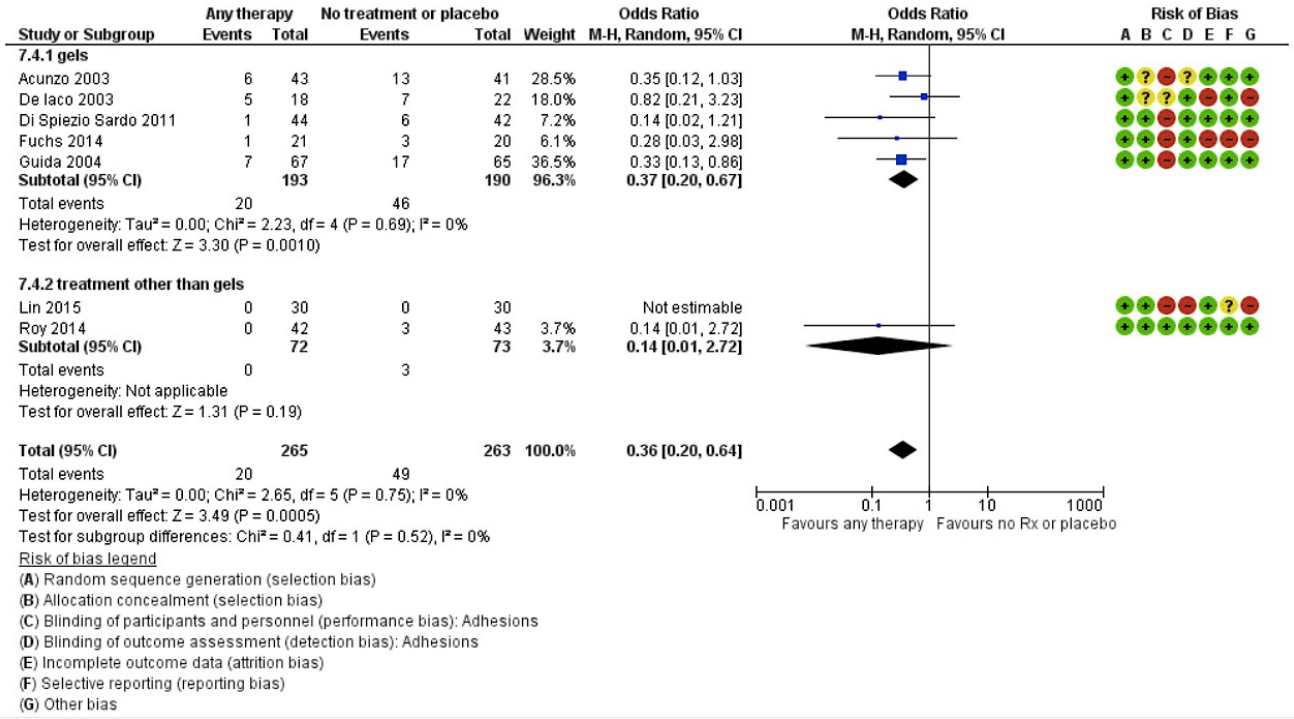
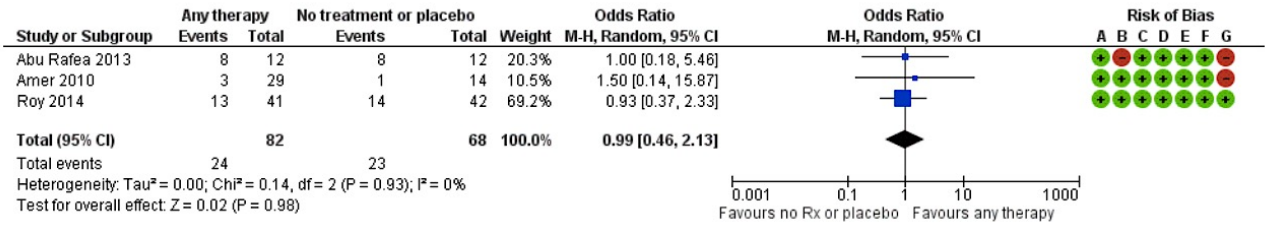

Any therapy
No treatment or placebo
Odds Ratio
Odds Ratio
Risk of Bias
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
A B C D E F G
7.4.1 gels
Acunzo 2003 6 43 13 41 28.5% 0.35 [0.12, 1.03]
De Iaco 2003 5 18 7 22 18.0% 0.82 [0.21, 3.23]
Di Spiezio Sardo 2011 1 44 6 42 7.2% 0.14 [0.02, 1.21]
Fuchs 2014 1 21 3 20 6.1% 0.28 [0.03, 2.98]
Guida 2004 7 67 17 65 36.5% 0.33 [0.13, 0.86]
Subtotal (95% CI) 193 190 96.3% 0.37 [0.20, 0.67]
Total events 20 46
Heterogeneity: Tau² = 0.00; Chi² = 2.23, df = 4 (P = 0.69); I² = 0%
Test for overall effect: Z = 3.30 (P = 0.0010)
7.4.2 treatment other than gels
Lin 2015 0 30 0 30 Not estimable
Roy 2014 0 42 3 43 3.7% 0.14 [0.01, 2.72]
Subtotal (95% CI) 72 73 3.7% 0.14 [0.01, 2.72]
Total events 0 3
Heterogeneity: Not applicable
Test for overall effect: Z = 1.31 (P = 0.19)
Total (95% CI) 265 263 100.0% 0.36 [0.20, 0.64]
Total events 20 49
Heterogeneity: Tau² = 0.00; Chi² = 2.65, df = 5 (P = 0.75); I² = 0%
Test for overall effect: Z = 3.49 (P = 0.0005)
Test for subgroup differences: Chi² = 0.41, df = 1 (P = 0.52), I² = 0%
0.001 0.1 1 10 1000
Favours any therapy Favours no Rx or placebo
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): Adhesions
(D) Blinding of outcome assessment (detection bias): Adhesions
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

FIGURE 2



Risk of bias legend

(**A**) Random sequence generation (selection bias)

(**B**) Allocation concealment (selection bias)

(**C**) Blinding of participants and personnel (performance bias): Live birth, pregnancy or miscarriage

(**D**) Blinding of outcome assessment (detection bias): Live birth, pregnancy or miscarriage

(**E**) Incomplete outcome data (attrition bias)

(**F**) Selective reporting (reporting bias)

(**G**) Other bias

FIGURE 3

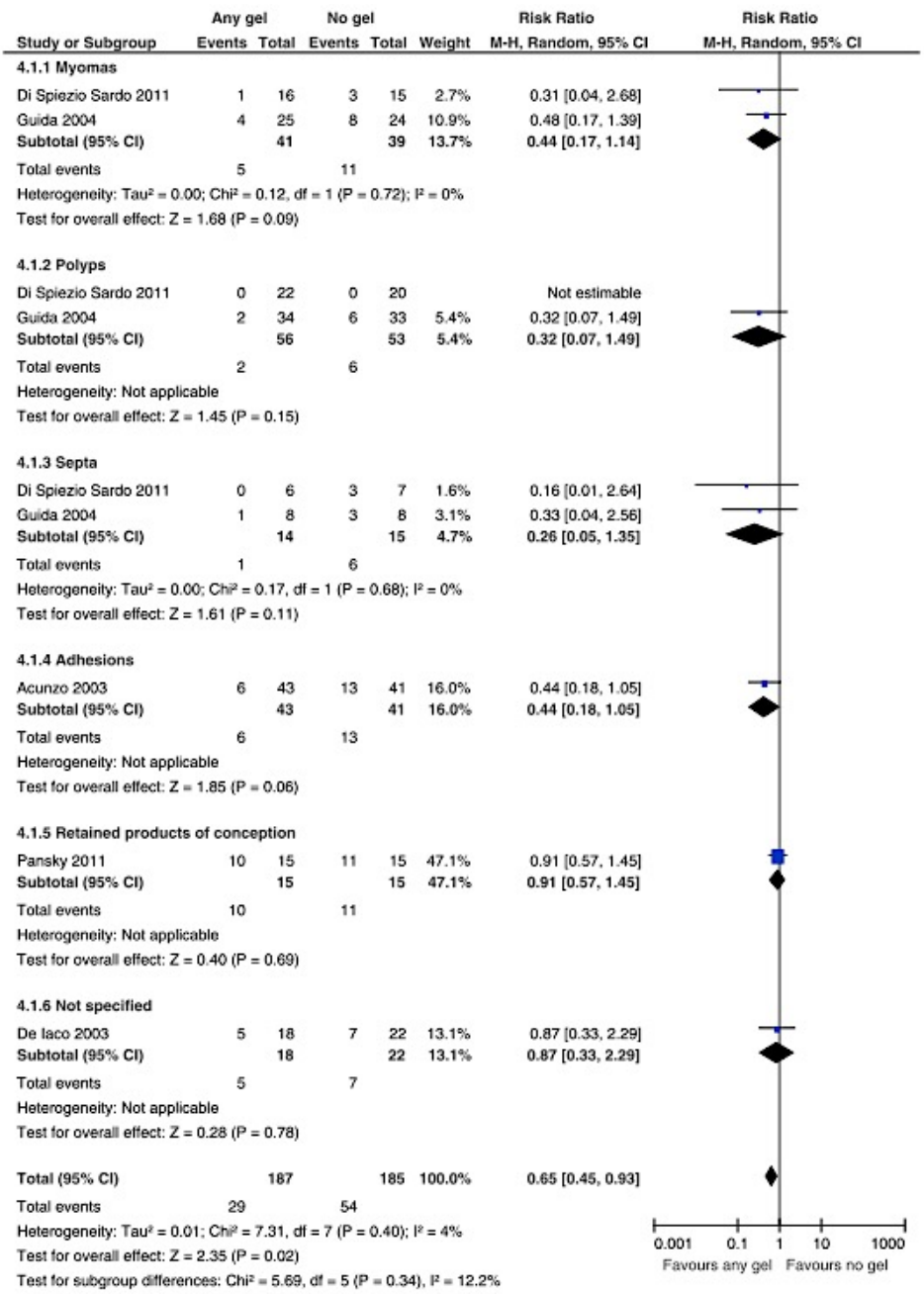

Any gel
No gel
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
4.1.1 Myomas
Di Spiezio Sardo 2011 1 16 3 15 2.7% 0.31 [0.04, 2.68]
Guida 2004 4 25 8 24 10.9% 0.48 [0.17, 1.39]
Subtotal (95% CI) 41 39 13.7% 0.44 [0.17, 1.14]
Total events 5 11
Heterogeneity: Tau² = 0.00; Chi² = 0.12, df = 1 (P = 0.72); I² = 0%
Test for overall effect: Z = 1.68 (P = 0.09)
4.1.2 Polyps
Di Spiezio Sardo 2011 0 22 0 20 Not estimable
Guida 2004 2 34 6 33 5.4% 0.32 [0.07, 1.49]
Subtotal (95% CI) 56 53 5.4% 0.32 [0.07, 1.49]
Total events 2 6
Heterogeneity: Not applicable
Test for overall effect: Z = 1.45 (P = 0.15)
4.1.3 Septa
Di Spiezio Sardo 2011 0 6 3 7 1.6% 0.16 [0.01, 2.64]
Guida 2004 1 8 3 8 3.1% 0.33 [0.04, 2.56]
Subtotal (95% CI) 14 15 4.7% 0.26 [0.05, 1.35]
Total events 1 6
Heterogeneity: Tau² = 0.00; Chi² = 0.17, df = 1 (P = 0.68); I² = 0%
Test for overall effect: Z = 1.61 (P = 0.11)
4.1.4 Adhesions
Acunzo 2003 6 43 13 41 16.0% 0.44 [0.18, 1.05]
Subtotal (95% CI) 43 41 16.0% 0.44 [0.18, 1.05]
Total events 6 13
Heterogeneity: Not applicable
Test for overall effect: Z = 1.85 (P = 0.06)
4.1.5 Retained products of conception
Pansky 2011 10 15 11 15 47.1% 0.91 [0.57, 1.45]
Subtotal (95% CI) 15 15 47.1% 0.91 [0.57, 1.45]
Total events 10 11
Heterogeneity: Not applicable
Test for overall effect: Z = 0.40 (P = 0.69)
4.1.6 Not specified
De Iaco 2003 5 18 7 22 13.1% 0.87 [0.33, 2.29]
Subtotal (95% CI) 18 22 13.1% 0.87 [0.33, 2.29]
Total events 5 7
Heterogeneity: Not applicable
Test for overall effect: Z = 0.28 (P = 0.78)
Total (95% CI) 187 185 100.0% 0.65 [0.45, 0.93]
Total events 29 54
Heterogeneity: Tau² = 0.01; Chi² = 7.31, df = 7 (P = 0.40); I² = 4%
Test for overall effect: Z = 2.35 (P = 0.02)
Test for subgroup differences: Chi² = 5.69, df = 5 (P = 0.34), I² = 12.2%
0.001 0.1 1 10 1000
Favours any gel Favours no gel

FIGURE 4

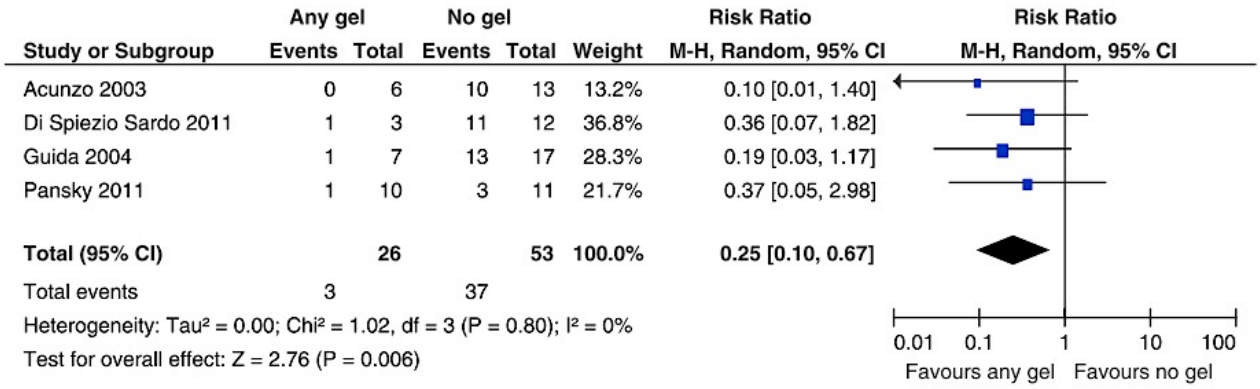

Any gel
No gel
Risk Ratio
Risk Ratio
Study or Subgroup
Events Total Events Total Weight
M-H, Random, 95% CI
M-H, Random, 95% CI
Acunzo 2003 0 6 10 13 13.2% 0.10 [0.01, 1.40]
Di Spiezio Sardo 2011 1 3 11 12 36.8% 0.36 [0.07, 1.82]
Guida 2004 1 7 13 17 28.3% 0.19 [0.03, 1.17]
Pansky 2011 1 10 3 11 21.7% 0.37 [0.05, 2.98]
Total (95% CI) 26 53 100.0% 0.25 [0.10, 0.67]
Total events 3 37
Heterogeneity: Tau² = 0.00; Chi² = 1.02, df = 3 (P = 0.80); I² = 0%
Test for overall effect: Z = 2.76 (P = 0.006)
0.01
0.1
1
10
100
Favours any gel
Favours no gel

FIGURE 5

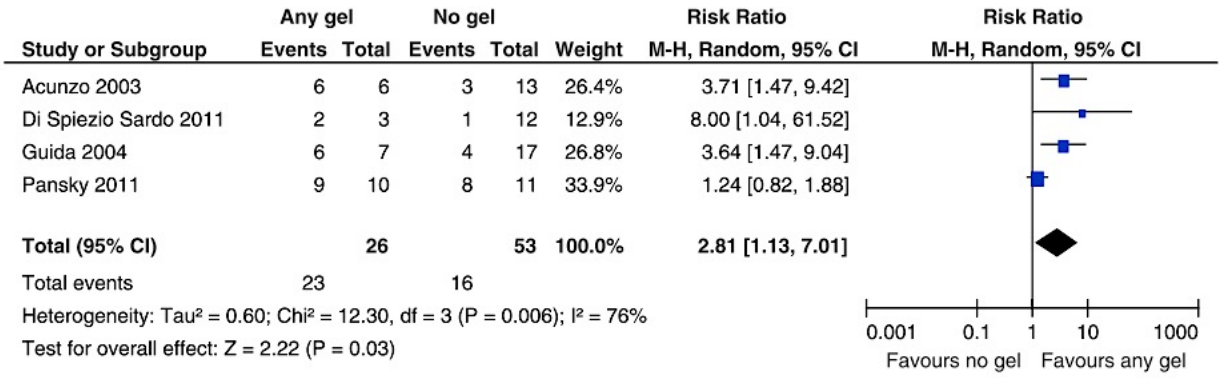
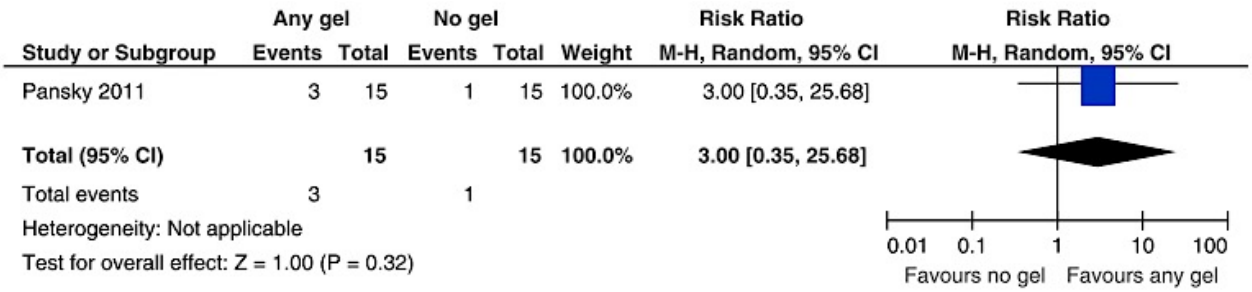

Any gel
No gel
Risk Ratio
Risk Ratio
Study or Subgroup
Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Acunzo 2003 6 6 3 13 26.4% 3.71 [1.47, 9.42]
Di Spiezio Sardo 2011 2 3 1 12 12.9% 8.00 [1.04, 61.52]
Guida 2004 6 7 4 17 26.8% 3.64 [1.47, 9.04]
Pansky 2011 9 10 8 11 33.9% 1.24 [0.82, 1.88]
Total (95% CI) 26 53 100.0% 2.81 [1.13, 7.01]
Total events 23 16
Heterogeneity: Tau² = 0.60; Chi² = 12.30, df = 3 (P = 0.006); I² = 76%
Test for overall effect: Z = 2.22 (P = 0.03)
0.001
0.1
1
10
1000
Favours no gel
Favours any gel

FIGURE 6


Any gel
No gel
Risk Ratio
Risk Ratio
Study or Subgroup
Events Total Events Total Weight
M-H, Random, 95% CI
M-H, Random, 95% CI
Pansky 2011 3 15 1 15 100.0% 3.00 [0.35, 25.68]
Total (95% CI) 15 15 100.0% 3.00 [0.35, 25.68]
Total events 3 1
Heterogeneity: Not applicable
Test for overall effect: Z = 1.00 (P = 0.32)
0.01 0.1 1 10 100
Favours no gel
Favours any gel