Surgical Treatment before Assisted Reproductive Technologies

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Abstract

Advances in technology have transformed surgery from a major approach into an art of science capable of treating many diseases and conditions in a less risky way. This advance let physicians perform surgery commonly in their practice. Today, surgery in reproductive medicine has become so customary that evidence has not been questioned commonly. Therefore, this review will help reproductive endocrinologists to read the most recent evidence for surgery to improve in vitro fertilization outcome. This will also help them to inform their patients with the most recent evidence.

Keywords

- Asherman
- endometrial polyp
- endometriosis
- hydrosalpinx
- hysteroscopy
- infertility
- leiomyoma
- uterine septum

The scope of reproductive surgery could be summarized under three general titles:

1. A primary treatment for infertility
2. Surgery to improve in vitro fertilization (IVF) outcome
3. Surgery for fertility preservation[1]

Contrary to the initial expectations, the scope of reproductive surgery has been widening after the era of IVF dawned in 1978. The main reason is, while the paradigm is shifting away from surgery as a primary treatment of infertility, reproductive surgery is now thought to play an important role in improving IVF outcomes.[1] In this review, we tried to analyze the role of reproductive surgery, which is performed to enhance the IVF outcome.

Tubal Surgery

Accounting for 25 to 35% of female infertility, tubal pathologies are one of the most frequent causes of infertility.[2,3] Initially, IVF has been effectively practiced for tubal infertility.[4] However, surprisingly, it has been recognized that IVF in women with tubal factor infertility was associated with lower pregnancy, implantation, and delivery rates than after IVF in other subfertile patients.[5,6] Hydrosalpinges are responsible for this deleterious effect on IVF outcome. This lowered efficacy of IVF alone has raised the question whether tubal surgery before IVF improves results and, therefore, different types of surgical interventions have been suggested: (1) salpingectomy,[7] (2) salpingostomy,[8,9] (3) aspiration of hydrosalpinx fluid with or without subsequent sclerotherapy,[10–13] (4) tubal ligation,[14] and (5) tubal occlusion by means of clips,[15] hysteroscopic electrocautery,[15] Adiana (Hologic, Inc., Bedford, MA)[16] or Essure (Conceptus Incorporated Mountain View, CA) microinserts,[17–20] or laparoscopic electrocautery.[21]

Randomized controlled trials comparing reproductive outcome after IVF for women with hydrosalpinges, with or without prior laparoscopic salpingectomy, reported that salpingectomy restores ongoing pregnancy rates similar to those of women without hydrosalpinx.[7,22,23] A Cochrane meta-analysis has concluded that laparoscopic salpingectomy or occlusion should be considered before IVF in patients with hydrosalpinx.[24] This meta-analysis shows that the clinical pregnancy rate for patients with hydrosalpinges that are

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managed by laparoscopic salpingectomy or proximal tubal occlusion is more than twofold higher than in the nonintervention controls.[24] The American Society for Reproductive Medicine (ASRM), along with the Society of Reproductive Surgeons (SRS), citing three randomized controlled trials in the meta-analysis,[7,22,23] recommends salpingectomy or proximal tubal occlusion before IVF in patients with hydrosalpinges to improve pregnancy rates.[25] Based on these data and recommendations, a recent survey of Society for Reproductive Endocrinology and Infertility/SRS members revealed that 89% pursued laparoscopic salpingectomy or proximal tubal occlusion before IVF.[26] Among these physicians, the most common method of managing hydrosalpinges was salpingectomy (80%) or laparoscopic proximal tubal occlusion (14%), while the latter was especially reserved for patients with history of multiple surgeries.[26]

Although commonly performed, both these methods have been implicated as causes of diminished ovarian reserve.[27,28] There are however reassuring data to suggest that ovarian reserve is not affected.[29,30] While performing salpingectomy, the plane of dissection should be close to the base of the tube. Similarly, less thermogenic modalities such as scalpel or mechanical clips may be the preferred method for tubal surgery to avoid any probable damage to the ovarian blood supply during cauterization.[27] There is also a theoretical concern that proximal tubal occlusion may lead to an increase in the size of the hydrosalpinx due to the bilateral blockade of the fluid in the tube. Therefore, wide fenestration of the fimbrial end should be considered during proximal occlusion. Other possible adverse effects following salpingectomy are interstitial or ovarian pregnancy, formation of cornual fistulae, and cornual rupture, which have been reported in rare cases.[31–34] A case of adnexal torsion after tubal occlusion for hydrosalpinx has been reported.[35]

However, salpingectomy remains a destructive procedure that, when bilateral, renders a woman dependent entirely on IVF. The psychological impact of such surgery should therefore not be underestimated.[36] Therefore, blind victimization of the fallopian tube has been questioned previously and functional surgery by means of salpingostomy has been suggested in selected cases.[37–40] Vasquez et al,[41] in a prospective study, concluded that the abundance of mucosal adhesions were the most important factor in determining the fertility outcome. Following salpingostomy, the intrauterine pregnancy rate was 22% when mucosal adhesions were present, and was 58% when adhesions were absent.[41] However, salpingoscopy is the most accurate method for identifying mucosal adhesions,[38,39] but, although it has been available for many years, it is still not part of normal clinical practice in most centers. Also, to our knowledge, its effectiveness before IVF has not been studied in a randomized trial. Although, reocclusion and high ectopic pregnancy rates (4–7%) are drawbacks of this procedure,[42–44] these may not be an immediate concern if an IVF cycle follows the procedure.

When laparoscopy may be neither safe nor possible, hysteroscopic occlusion of tubes using microinserts may prove beneficial. There are two different brands of microinserts, both of which have been developed for contraception: Adiana and Essure. Since the latter has been approved by the Food and Drug Administration 7 years earlier than the former, it has been more widely studied as a treatment option for hydrosalpinx before IVF.[16–20] Live birth rates (per embryo transfer) between 20 and 57% have been reported in small case series.[17,20,45] Adiana, as a new device, uses radiofrequency energy to stimulate interstitial scarring followed by insertion of a small silicone elastomer matrix. Data for Adiana in the treatment of hydrosalpinx before IVF are much more limited, and only individual case reports have been reported.[16] Yet, the number of published cases for both Essure and Adiana is small, and the effects of these devices on the pregnancy still need to be studied in large series. Today, this approach could be an acceptable alternative in women at risk of laparoscopy, that is, women with a history of multiple laparotomies or bowel surgery.[1]

Transvaginal aspiration of the hydrosalpingeal fluid either before the start of IVF or during egg collection has been suggested as a less invasive means of treating a hydrosalpinx.[11,12] Hammadieh et al,[13] in a small randomized trial, have suggested an improvement in the clinical pregnancy and implantation rates, which however were not of statistical significance. The recent Cochrane review judged this study as underpowered.[24] In a recent randomized trial after this review, a larger group of patients have been analyzed, and a statistically significant improvement in the ongoing pregnancy and implantation rates has been reported.[10] Infection and reaccumulation of fluid during the same cycle are potential risks of this approach. Reaccumulation of hydrosalpingeal fluid was observed in 25 to 30% of cases after 14 days in these studies.[10,13] There was no infectious morbidity in these studies.[10,13] This approach may be especially useful when hydrosalpinx becomes visible during IVF treatment.[13,36] Recurrence may be avoided by performing sclerotherapy with 98% ethanol following aspiration.[12] However, if addition of sclerotherapy is planned, the procedure should be performed before the IVF cycle.[12]

In conclusion, each treatment has its own pros and cons. Eliminating the risk of abscess formation or torsion and increasing the accessibility of the ovary during ovum pickup in IVF are the advantages of salpingectomy.[23] However, the invasiveness of the procedure and eliminating any probability of conceiving spontaneously are the main drawbacks of the procedure.[24] Alternative approaches, that is, salpingostomy, aspiration, and tubal occlusion appear to be safer, less invasive with shorter hospital stays, and easier to perform in case of dense adhesions.[24] It is not an easy decision for a woman with infertility to have a surgery to remove the fallopian tubes and surgery is not free of risks.[24] Therefore, it is important to inform the woman with the best available evidence for these interventions.[24]

Endometrioma

Before suggesting any surgical approach for the management of endometrioma before IVF treatment, two questions should be answered. First, does the presence of the endometrioma impair the IVF outcome? Results of studies evaluating this issue have been mixed.[46–51] Indeed, it is difficult to truly

Table 1 Surgery for endometrioma before assisted reproductive technology; main results of a Cochrane meta-analysis[54]

A total of 312 participants in four eligible studies have been analyzed in the Cochrane meta-analysis
None of these trials have reported live birth outcomes
Surgery (aspiration or cystectomy) vs. expectant management showed no evidence of a benefit for clinical pregnancy
Cystectomy was associated with a decreased ovarian response to controlled ovarian hyperstimulation

assess the effect of an endometrioma per se on IVF outcome, since most of these lesions are likely to present with concomitant peritoneal disease that could have an independent effect.[52] However, it seems that endometriomas of 4 cm or less in diameter do not affect IVF outcome.[48,49]

Second, does surgery improve the IVF outcome? A recent meta-analysis of the effect of surgical treatment of endometriomas or expectant management on subsequent IVF cycles concluded that there is no benefit in surgical intervention.[53] Another meta-analysis confirmed this and has shown that surgery versus expectant management showed no evidence of a benefit for clinical pregnancy with either of the two techniques; aspiration or cystectomy (►**Table 1**).[54]

In addition to this lack of any beneficial effect, cystectomy was associated with a decreased ovarian response to controlled ovarian hyperstimulation compared with expectant management, but aspiration was not.[54] Another review has concluded that excision is more favorable than drainage with regard to recurrence of the endometrioma and of pain, and with regard to spontaneous pregnancy.[55] There is consistent evidence demonstrating that the ovarian reserve is diminished following surgical excision of ovarian endometriomas, especially in women with bilateral disease.[56–60] Therefore, there is a growing consensus that ovarian endometriomas should not be routinely removed in asymptomatic women before IVF.

A consensus appears to be present to suggest surgery for the histological confirmation of the diagnosis, for women with progressive pain, for those of a large size enough to create concern for rupture, and an inability to access the remainder of the ovary and for those with masses that necessitate exclusion of any associated ovarian cancer, that is, that exhibit rapid enlargement and/or have suspicious ultrasound signs of malignancy.[58,61,62] Based on these considerations, ASRM and European Society of Human Reproduction and Embryology suggest surgery for large endometriomas unless the patient has a previous ovarian surgery (►**Table 2**).[63,64] There is a need for more randomized controlled trials to answer the question as to whether small ovarian endometriotic cysts should be removed before assisted reproductive technology.[64] However, when surgery should be undertaken, an effort should be made to avoid any damage to healthy ovarian tissue. Suturing and use of vasopressin have been suggested in limited studies.[65–67] Also, a combination of excision and ablation and a three-step procedure have been suggested.[68–70]

Endometrial Polyp

Endometrial polyp is the most common acquired uterine abnormality. Polyps can be found in up to 25% of the subfertile population.[71–73] The rate appears to be increased in infertile women with endometriosis.[74] Both the association between endometrial polyps and fertility and the mechanism by which polyps may negatively affect fertility are poorly understood. However, mechanical or biochemical interference with sperm transport or embryo implantation may play a role.[72,73,75] The only randomized trial analyzing whether hysteroscopic polypectomy improves fertility outcome have included 215 infertile women, who have been randomized to one of two groups before intrauterine insemination (IUI); hysteroscopic polypectomy or diagnostic hysteroscopy and polyp biopsy.[76] Women, who had undergone polypectomy, had a better probability of conceiving than the patients, who did not undergo polypectomy (relative risk [RR], 2.1; 95% confidence interval [CI], 1.5–2.9).[76] The cumulative pregnancy rate was 51.4% in the polypectomy group and was significantly higher than that in the control group (25.4%).[76] More important, 65% of women, who have had polypectomy, have conceived spontaneously within 3 months after surgery.[76] This was independent of the dimension of the polyp, and the pregnancy rate improved even after very small (< 5 mm) polyps were removed.[76] Two recent observational studies also have concluded that hysteroscopic polypectomy appears to improve

Table 2 European Society of Human Reproduction and Embryology recommendations with their level of evidence for the surgical management of endometrioma in women with infertility[64]

Recommendation	Level of evidence
Cystectomy for an endometrioma larger than 3 cm in diameter before in vitro fertilization treatment does not improve the reproductive outcome	A[a]
Cystectomy for an endometrioma larger than 3 cm in diameter before in vitro fertilization treatment can only be justified for the relief of endometriosis-associated pain or the improvement of accessibility of follicles	GPP[b]
Physicians should inform women with endometrioma regarding the risk of decreased ovarian reserve after surgery, especially in the presence of a history of previous ovarian surgery	GPP

[a]Supporting evidence is of high quality based on meta-analysis, systematic review, or multiple randomized controlled trials.
[b]Good practice point (GPP) based on clinical expertise.

fertility outcome in women undergoing IUI treatment.[77,78] However, it has been suggested that small (< 1.5–2 cm) polyps do not affect IVF outcome.[79,80] In a retrospective study, excision of polyps, which were located at the uterotubal junction (8% of polyps), improved cumulative pregnancy rates to a higher level than excision of those at other locations.[81] Mean (± standard deviation) diameter for the polyps were 9.4 ± 2.5 mm in that study, that is, most probably, its size was smaller than 2.0 cm in all cases.[81] Therefore, excision of small polyps, which are located at the uterotubal junction may help improve fertility outcome for expectant or IUI treatment, but may not affect the outcome in IVF treatment.

Uterine Septum

Among congenital uterine anomalies, the uterine septum is the most common anomaly and 35% of uterine anomalies consists of a septate uterus.[82] It is associated with a high overall spontaneous abortion rate (44 to more than 60%) and term delivery rates of only 40%.[82–84] Hysteroscopy made the management of the septate uterus extremely easy. In a recent meta-analysis of 29 published studies, the overall pregnancy rate was 63.5% and live birth rate was 50.2% after hysteroscopic metroplasty.[85] In an earlier review of 12 published retrospective studies, Homer et al[83] compared reproductive outcome before and after hysteroscopic surgery and showed a pooled postoperative pregnancy rate of 80% in women with miscarriage or infertility. In addition, the term birth rate increased from 0 to 7% to 73 to 100% after the operation. In another systematic review and pooled analysis of 1,501 women in 18 studies, Nouri et al[86] reported an overall pregnancy rate of 60.1% and a live birth rate of 45% after hysteroscopic metroplasty. Based on these acceptable rates for the reproductive outcome, hysteroscopic metroplasty is a common practice in many countries. However, all these studies are observational studies. Observational studies are biased because women treated by hysteroscopic metroplasty served as their own controls in these studies and making these before and after comparisons will always favor the intervention.[87,88] A randomized controlled trial (TRUST trial) is currently underway and was planned to end in 2014 (http://www.studies-obsgyn.nl/trust/page.asp?page_id=674). This study includes 68 women with two or more abortions before 20 weeks of gestation.

Most studies of metroplasty for a septate uterus in the above meta-analyses combine women with recurrent pregnancy loss and infertility. Although metroplasty after poor obstetric outcome seems justified, controversy exists as to whether infertile women should undergo metroplasty. A rough pregnancy rate of 48% was obtained after metroplasty in 84 infertile patients gathered from seven reports.[83] Recent observational studies also support that hysteroscopic metroplasty improves reproductive outcome in patients with septate uterus and unexplained infertility.[89–93] In the only randomized controlled trial, 60 women, who have been diagnosed to have uterine septum but no history of poor obstetric outcome, have been randomized to either hysteroscopic metroplasty or expectant management.[94] However, it has not been mentioned whether these women had infertility, in the article.[94] Authors have observed comparable pregnancy, abortion, preterm delivery, and term delivery rates between groups.[94]

Tomaževič et al have investigated the effect of uterine septum on IVF outcome.[95] The authors have analyzed reproductive outcome after 289 embryo transfers before and 538 embryo transfers after hysteroscopic septum resection and compared the results to two consecutive embryo transfers in the control group. In women with a large septum, the live birth rate was 2.7% before surgery, 15.6% after surgery, and 20.9% in the control group.[95] In those with a small septum, the corresponding rates were 2.8, 18.6, and 21.9%, respectively.[95] Two other observational studies also support the beneficial effect of septum resection on reproductive outcome after IVF.[96,97] Despite the lack of any randomized controlled studies, current evidence suggests the efficacy of hysteroscopic septoplasty before IVF.

Leiomyoma

The frequency of leiomyoma in women with fertility treatment is estimated to be between 5 and 10%.[98] Studies demonstrated that submucosal and intramural myomas that distort the uterine cavity are associated with decreased pregnancy, implantation and ongoing pregnancy/live birth rates, and a significantly higher spontaneous abortion rate.[99] In the only randomized trial, Casini et al[100] reported that excision of a submucous myoma led to a significant increase in the pregnancy rate, from 27.2% (6/22) to 43.3% (13/30), in 52 patients and the miscarriage rate decreased, although the difference was not significant. However, Bosteels et al[101] have reported that recalculation of the available data in the study by Casini et al[100] failed to demonstrate statistically significant difference in pregnancy rates. A recent Cochrane meta-analysis, which included only the above study, also reported a comparable outcome.[102] This statistical error raises questions about the validity of the published data. Another randomized trial has been retracted after publication.[103] However, observational studies evaluating the role of myomectomy for submucous fibroids suggest the procedure may be beneficial.[104]

There is more uncertainty about the effect of intramural fibroids without uterine cavity involvement on reproductive outcome than those distorting the cavity. In a meta-analysis of 19 observational studies involving 6,087 IVF cycles, the authors reported a significant decrease in both clinical pregnancy and live birth rates in women with noncavity distorting intramural myomas compared with those without myomas (►**Table 3**).[105] However, Metwally et al[106] addressed several methodological problems related to study selection and dealing with confounding factors in that meta-analysis. They reported another analysis and suggested no negative impact for intramural fibroids on the clinical pregnancy rate, the live birth rate, or miscarriage rate, although their initial analysis including low-quality studies suggested a negative effect on the clinical pregnancy rate.[106] A recent Cochrane meta-analysis of only one limited study demonstrated no

Table 3 The effect of intramural fibroids without uterine cavity involvement on the outcome of IVF treatment; main results of a meta-analysis[105]

A total of 19 observational studies involving 6,087 IVF cycles have been analyzed
Both the live birth rate (RR, 0.79; 95% CI, 0.70–0.88; $p < 0.0001$) and the clinical pregnancy rate (RR, 0.85; 95% CI, 0.77–0.94; $p = 0.002$) were decreased in women with noncavity–distorting intramural fibroids compared with those without fibroids, following IVF treatment

Abbreviations: CI, confidence interval; IVF, in vitro fertilization; RR, relative risk.

beneficial effect of myomectomy of intramural myomas.[100,102] Observational studies also support the lack of benefit for myomectomy of intramural myomas not encroaching the cavity.[99,104]

Intrauterine Adhesions

Joseph Asherman described obliteration of the uterine cavity secondary to trauma to the endometrium and the term Asherman syndrome was ascribed.[107,108] The prevalence rate of intrauterine adhesions (IUA) in the general population is estimated to be 1.5%.[109] Hysteroscopy, when performed before the initial IVF attempt, will identify IUA in 3 to 16% of women.[110,111] Randomized or controlled studies on reproductive outcome after hysteroscopic adhesiolysis are absent. The available observational studies are of very low quality.[112–116] In an observational study of 89 women with infertility, Roy et al[114] have reported that the pregnancy rate after hysteroscopic removal of mild adhesions (58%) was higher than that of moderate adhesions (30%) and severe adhesions (33.3%). Fernandez et al[116] have reported that hysteroscopic adhesiolysis led to a live birth rate of 32.8% in 64 women with severe adhesions. In a recent study of 43 women, an overall pregnancy rate of 51.2% and a live birth rate of 32.6% have been reported after the removal of adhesions.[113] Although the evidence is poor, hysteroscopic adhesiolysis is a common and logical practice to restore a sufficient cavity before any type of infertility treatment.

Screening Hysteroscopy before IVF

Evaluation of endometrial cavity by using hysteroscopy has revealed rates of abnormal findings changing from 11% before the first IVF cycle to 26% among women who had two or more IVF failures.[117–119] Thirty-five to 50% of these pathologies were polyps, and others were leiomyomas, adhesions, and septum.[117,118] Treatment of these lesions may enhance the IVF outcome, and approach to these pathologies was mentioned above.

Meta-analysis of the two available studies has shown that hysteroscopy before IVF improves the outcome among women, who had two or more IVF failures.[119–121] Women in these studies were randomized into two groups to study the effect of hysteroscopy on pregnancy outcome. Office hysteroscopy has not been performed before IVF treatment in group I. In group II, hysteroscopy has been performed and women have been divided into group IIa with normal findings and group IIb with uterine pathology, which has been treated during the same procedure. The clinical pregnancy rate in group II was significantly higher than that in group I (RR, 1.6; 95% CI, 1.3–1.9).[121] A recent meta-analysis of these two randomized studies and one nonrandomized study supports the former meta-analysis.[119,120,122,123]

The results of the above-mentioned randomized studies show that screening hysteroscopy before IVF is beneficial. Another randomized controlled trial among women with recurrent implantation failure is ongoing.[124] However, it should be emphasized that the study population in these studies included women with at least two IVF failures.[119,120] In a recent meta-analysis of one randomized and four nonrandomized studies, Pundir et al[125] have analyzed the role of routine hysteroscopy before the first IVF cycle. The authors have reported that the clinical pregnancy rate improved significantly (RR, 1.44; 95% CI, 1.08–1.92).[125] An other randomized study is ongoing.[126]

In the intervention group of the above-mentioned two randomized studies,[119,120] there was no significant difference in treatment effect between women with normal findings and women with uterine pathology.[121] Meta-analysis of the three nonrandomized studies, in which screening hysteroscopy has been performed before the first IVF cycle, also revealed that the live birth rate in women with normal hysteroscopic findings was comparable to those with abnormal findings, which have been subsequently corrected.[125] This suggests that diagnostic hysteroscopy alone also improves the IVF outcome. Although it is unknown which patients in the control group had intrauterine pathology in these studies,[119,120] this beneficial effect cannot be ignored. It is acceptable that cervical dilatation facilitates embryo transfer.[127] Moreover, hysteroscopic manipulation or the effect of the distension medium on the endometrium, similar to the therapeutic effect of tubal flushing during hysterosalpingogram, might play a role.[128]

Local Injury to Endometrium during Screening Hysteroscopy

In a randomized controlled trial, which included 200 infertile women with a history of repeated implantation failure, Shohayeb and El-Khayat[129] have compared women, who underwent hysteroscopy and endometrial biopsy, with those, who underwent hysteroscopy without endometrial scraping in the cycle preceding the intracytoplasmic sperm injection cycle. The endometrial biopsy performed during hysteroscopy has statistically significant higher implantation rate (12 vs. 7%), clinical pregnancy rate (32 vs. 18%), and live birth rate (28 vs. 14%) than hysteroscopy without endometrial scraping.[129] The effect of hysteroscopic biopsy, which has been performed during the ongoing ovarian stimulation, also has been analyzed in a limited observational study, and higher pregnancy and implantation rates have been reported when compared with the no intervention group.[130] The

Table 4 Conclusions

Procedures which improve the reproductive outcome when performed before IVF
Salpingectomy or proximal tubal occlusion
Removal of submucous leiomyomas
Hysteroscopy after failed IVF
Procedures which have insufficient evidence to recommend before IVF to enhance the reproductive outcome. And therefore, performing these procedures remains controversial
Removal of intramural leiomyomas
Removal of endometrioma
Septum resection (excluding women with poor obstetric outcome)
Removal of endometrial polyps
Removal of adhesions

Abbreviation: IVF, in vitro fertilization.

beneficial effect of local injury to endometrium has been suggested previously, but blind endometrial sampling devices have been used for the endometrial injury in these initial studies.[122,131–136] A recent meta-analysis[122] of two randomized[131,137] and two nonrandomized studies[133,134] has shown that endometrial scratch in the cycle preceding IVF improved the clinical pregnancy and live birth rates in women with recurrent implantation failure. Therefore, addition of a biopsy procedure, in case of absence of any intrauterine pathology during a screening hysteroscopy, appears to be an acceptable choice.

Conclusion

In conclusion, very few reproductive surgeries have good evidence for their benefit in enhancing reproductive outcome, when performed before IVF (►**Table 4**). Most surgical treatments lack good evidence to perform before IVF. However, it should be emphasized that performing good-quality studies may have some ethical and practical issues that will prevent their conduct in some cases such as removal of large polyps, resection of endometrial adhesions, or septum. Ease of hysteroscopy and available observational studies let these procedures be adapted into common practice even at academic institutions.

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