

## Research Article

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# Ectopic pregnancy treatment by combination therapy

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**Abstract:** Detectability of early stages of ectopic pregnancies has increased due to improvements in ultrasonographic and biochemical techniques. Since the patients' future procreative plans must be taken into consideration when commencing treatment, the goal of this work was to compare the effects of treatment methods and their impact on fertility. The study included 91 patients treated surgically for ectopic pregnancy. The choice of treatment depended on patients' general condition, ultrasonographic evaluation and serum level of beta-hCG. A combination of laparoscopic and conservative systemic treatment was applied in 70% of cases. More rapid beta-hCG reduction was noted when laparoscopy and intra-oviductal injection of hyperosmolar glucose or methotrexate (MTX) were combined with intramuscular administration of MTX at a dose of 50 mg/m<sup>2</sup>. Follow-up examination of 66 patients revealed that the greatest number of spontaneous pregnancies (48%) resulted after this combination therapy. We conclude that this combination treatment is safe and provides satisfactory results in terms of future fertility.

**Keywords:** Ectopic pregnancy; Laparoscopy; Hyperosmolar glucose; Methotrexate injection.

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## 1 Introduction

In recent years we have noted an increased incidence of ectopic pregnancies. They result from increasingly more frequent inflammatory conditions of the lesser pelvis, which is, in turn, related to changing sexual behaviors, including numerous partners. Other factors that increase the risk of ectopic pregnancy include a history of surgery on the oviducts, history of tubal pregnancy, smoking, age more than 35 years and use of intrauterine devices.

In 95% of cases ectopic pregnancy is located in the oviducts. Less frequent locations include the ovaries, abdomen, cervix or a cesarean section scar. There are isolated cases of coexisting eutrophic and ectopic pregnancies (heterotopic pregnancy), most often associated with use of assisted reproductive technology techniques.

In the past many patients presented with ruptured salpingeal pregnancy and symptoms of hemorrhage and hypovolemic shock, leading to radical surgical treatment, which was laparotomy with salpingectomy. Currently, detectability of this pathology in the early stages has increased due to constantly improving ultrasonographic and biochemical techniques, which has created new possibilities for conservative management and increased chances of normal pregnancy in the future.

While planning the treatment for ectopic pregnancy, we must take into consideration the patient's current clinical condition and her future procreative plans.

After considering all of these aspects, we have to choose between several therapeutic methods:

Expectant management, where effectiveness varies between 47.7% and 75% depending on the beta-hCG levels [1].

Pharmacological treatment, with a single dose of methotrexate (MTX) (effectiveness between 63% and 94%) [2] or multiple doses of MTX. If the beta-hCG level decreases by 15% or more on the 4th and 7th day following drug administration, the effectiveness reaches 98% [3].

Surgical management (laparoscopy or laparotomy), sparing or radical.

Combination therapy consisting of joint pharmacological and surgical methods: laparoscopy and intramus-

cular MTX (at a dose of 50 mg/m<sup>2</sup>) or surgery intra-oviductal hyperosmolar glucose, MTX, prostaglandins and KCl.

## 2 Purpose

Evaluation of risk factors for extrauterine pregnancy.

Comparison of effectiveness of applied methods.

Assessment of the effect of the surgical treatment on the type and proportion of complications.

Assessment of the effect of the surgical treatment on future fertility.

## 3 Material and methods

Ninety-one patients with ectopic pregnancy were hospitalized and treated surgically at the Department of Gynecological Surgery and Gynecological Oncology of the Pomeranian Medical University in Szczecin in years 2011-2014. The study included only those patients who had undergone surgery (it did not include patients who were treated conservatively).

Patient characteristics are presented in Table 1. The mean age of patients in our study was 29 years. The average body mass index (BMI) was 22.42. Ectopic pregnancies were significantly more common in multiparous women.

The choice of treatment depended on:

- the patient's general condition (with or without active bleeding)
- ultrasonographic assessment

**Table 1:** Patients characteristics.

Patients	
Age	average 29 (20-40)
Less than 30 yrs old	45
More than 30 yrs old	46
BMI	average 22,42 (19-32)
No risk factors	28
1 risk factor	51
2 or more risk factors	19
Births	46

- serum beta-hCG levels.

The operating surgeon assigned individual patients to various types of treatment.

The following surgical techniques were used:

- Laparoscopic excision of fertilized ovum with or without intramuscular MTX in patients with interrupted tubal pregnancy, sac diameter not exceeding 15 mm and beta-hCG level below 3000 mIU/mL.
- Laparoscopic salpingectomy, in the presence of tube injury.
- Combination treatment: Laparoscopy (intra-oviductal injection of hyperosmolar glucose or MTX) + intramuscular MTX administration at a dose of 50 mg/m<sup>2</sup> in patients with gestational sac > 2 cm and beta-hCG level elevated above 2000 mIU/mL.
- Laparotomy in patients with significant intraperitoneal bleeding.

All ultrasonographic examinations were performed using an ultrasonograf Medison, SonoAce 9900 device with 7.5 MHz probe. Serum beta-hCG levels were assessed with electrochemiluminescence method (ECILA), from Roche running on the cobas e 601 analyzer. Ten µL of the sample was incubated with both biotinylated, monoclonal hCG specific antibody and a ruthenylated, monoclonal hCG specific antibody to sandwich complex. Streptavidin was added to the reaction mixture. Chemiluminescence is measured by a photomultiplier and the concentration of hCG +beta within the sample is calculated using a calibration curve. The range was -0,100-10,000mIU/mL, and the functional sensitivity < 0,6mIU/mL. Statistical analysis was conducted using variance analysis. All statistical analyzes were performed with Statistica 10. Results of beta-hCG in the various groups and subgroups are presented as mean values. To calculate each fraction, cumulative percent was used. Comparisons between groups were completed using a nonparametric U Mann-Whitney test.

1. Ethical approval: The research related to human use has been complied with all the relevant national regulations, institutional policies and in accordance the tenets of the Helsinki Declaration, and has been approved by the authors' institutional review board or equivalent committee.

2. Informed consent: Informed consent has been obtained from all individuals included in this study.

## 4 Results

Main risk factors for extrauterine pregnancy in the study group included: medical history of surgery (34.1%), in vitro pregnancy (20.9%), history of extrauterine pregnancy (7.7%) and implanted intrauterine device (13.2%). No cases of endometriosis or prior inflammation of uterine adenexa were noted. After analyzing the cases, we found that the surgery was not only the most common but the most important risk factor. Surgery in 10 cases led to such damage to the oviduct that salpingectomy was performed [Table 2].

In three cases we performed laparoscopic excision of a tubal hematocele without further treatment. These were the cases of interrupted tubal pregnancy with a hematocele approximately 15 mm in diameter. In a small proportion of cases (4%), we placed hypertonic glucose into the oviduct during laparoscopy without further adjuvant treatment. In 10% of cases (9 patients) laparoscopy was performed with the administration of MTX into the hematocele and no further treatment. Combination laparoscopic and systemic conservative treatment was administered in 70% of cases (66 patients), including 20% where the hematocele was surgically extruded from the oviduct. Due to the intermediate beta-hCG level oscillating above 6000 mIU/mL in this group of 43 patients, intramuscular MTX (50 mg/m<sup>2</sup>) was administered after the procedure. Intra-oviductal injection of hyperosmolar glucose with subsequent intramuscular MTX administration was performed in 25% of cases (23 patients) when the beta-hCG level exceeded 2000 mIU/mL and the mean sac diameter was 22 mm. Intra-oviductal MTX injection with subsequent systemic MTX administration was conducted in 18% of patients (16 patients). In this group the mean beta-hCG level did not exceed 2000 mIU/mL and the mean sac diameter ranged above 2.5 cm.

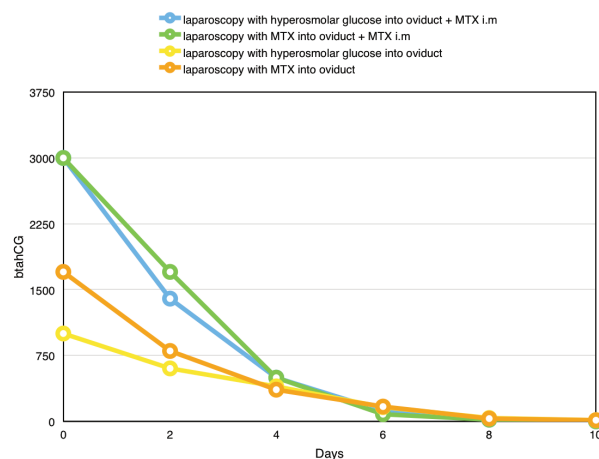
**Table 2:** Risk factors for ectopic pregnancy.

	n	%
Pregnancy after in vitro	19	20.9
History of ectopic pregnancy	7	7.7
Inflammation of the appendages in interview	0	0
Past operations	31	34.1
Infertility in an interview	1	1.1
Endometriosis in an interview	0	0
The IUD	12	13.2

Salpingectomy was performed in one patient when intraperitoneal bleeding was diagnosed during laparoscopy. The medical history of this patient included extrauterine pregnancy in the oviduct several years before. At that time, the gestational sac was 28 mm in diameter. Surgical management through laparotomy was implemented in 16% of cases (15 patients); the oviduct was removed in 56% of cases (9 patients), whereas 44% (6) procedures involved excision of an embryo from the oviduct only. Laparotomies were performed in patients diagnosed with intraperitoneal bleeding and a beta-hCG level above 3000 mIU/mL (Table 4). There were no statistically significant differences with regard to reduction of beta-hCG level between subgroups of patients subjected to excision of the ovum during laparoscopy with or without adjuvant intramuscular MTX administration (at a dose of 50 mg/m<sup>2</sup>) ( $p < 0.3$ ).

Faster beta-hCG reduction was noted in patients undergoing laparoscopy with intra-oviductal injection of hyperosmolar glucose or MTX and intramuscular MTX (50mg/m<sup>2</sup>) compared to patients who were not given systemic MTX. However, these results did not reach statistical significance ( $p < 0.06$ ) (Figure 1).

Repeated laparoscopy was necessary in two cases due to persistently high beta-hCG levels (initial level, 1800 mIU/mL) and ongoing pain. In the first case, following laparoscopic extrusion of the hematocele (approximately 12 mm in diameter) from the oviduct due to interrupted tubal pregnancy. In the second case, persisting disease was diagnosed after two weeks from intra-oviductal MTX administration without adjuvant treatment. As the concentration of beta-hCG decreased from 1400 mIU/mL to only 1310 mIU/mL, we decided to repeat the laparoscopy [Table 3]. No statistically significant differences in the number of



**Figure 1:** Decrease beta-hCG value, depending on the type of operation

**Table 3:** (n=91) Beta-hCG level, gestational sac size, intraabdominal bleeding and reoperation necessity depends on treatment.

	Medium beta-hCG (range) [mIU/ml]	Medium gestational sac size (range) [mm]	Presence of fluid in cave Douglasi in USG [n / %]	Reoperation [n / %]
Laparotomy / extrusion of hematocele (n=6)	4211 (330-15000)	23 (16-50)	4 / 100	0 / 0
Laparotomy / Salpingectomy (n=9)	3189 (703-10000)	25 (10-45)	9 / 100	0 / 0
Invasive laparoscopy / extrusion of hematocele (n=3)	3350 (1700-5000)	15 (5-35)	3 / 100	1 / 0.9%
Invasive laparoscopy / extrusion of hematocele with MTX im (n=19)	6325 (115-21964)	15 (4-20)	6 / 50	0 / 0
Invasive laparoscopy / salpingectomy (n=1)	12500	28	1 / 100	0 / 0
Laparoscopy MTX injection into oviduct (n=9)	341 (99-1250)	17 (16-32)	0 / 0	1 / 0.9%
Laparoscopy MTX injection into oviduct with MTX im (n=16)	2096 (365-14000)	26 (7-50)	7 / 63	0 / 0
Laparoscopy Hyperosmolar glucose injection into oviduct (n=4)	981 (173-1788)	9 (4-17)	2 / 100	0 / 0
Laparoscopy Hyperosmolar glucose injection into oviduct with MTX im (n=23)	2085 (104-5349)	22 (14-46)	6 / 40	0 / 0

**Table 4:** Type of operation depending on the fulfilled parameters of categorisation.

	Laparoscopy / hyper- osmolar glucose into oviduct	Laparoscopy / hyper- osmolar glucose into oviduct with MTX i.m	Laparoscopy / MTX into oviduct with MTX i.m	Laparoscopy / MTX into oviduct	Laparoscopy extrusion of hemotecele with MTX i.m	Laparoscopy / extrusion of hemote- cele	Laparotomy / salpingec- tomy	Laprotomy / extrusion of hemotecele
betahCG > 3000 size < 15mm fluid (-)	2	16	8	2	10	2	-	2
bethCG < 3000 size > 15mm fluid (-)	1	4	5	7	3	1	-	-
betahCG > 3000 size > 15mm fluid (+)	1	6	3	-	6	-	9	4

complications were noted between less invasive laparoscopic techniques and conventional methods involving excision of extrauterine pregnancy through laparotomy.

Patient interviews show that as many as 70 patients confirmed attempts to become pregnant within five years from the time of surgery.

The average time to become pregnant was 9.2 months. Follow-up conducted on 66 patients treated for ectopic pregnancy demonstrated that the greatest number of spontaneous pregnancies occurred after combination treatment involving laparoscopy and intra-oviductal administration of glucose or MTX. As well, 31 of the 66 patients (48%) had spontaneous pregnancies after surgery intra-oviductal with intramuscular injection of MTX at a dose of 50 mg/m<sup>2</sup>. Fifteen patients (23%) were observed to have spontaneous pregnancies following administration of hyperosmolar glucose into the oviduct or MTX into the oviduct without subsequent adjuvant treatment with 50 mg/m<sup>2</sup> of intramuscular MTX. Spontaneous pregnancies were also noted among 18% of patients after laparoscopic extrusion of hematocele from an oviduct and administration of MTX. Among all spontaneous pregnancies, 8 ended in miscarriage, and 4 in the demise of the fetus (3 early cases and 1 at week 16). Six patients had live births following in vitro fertilization, including one patient who had undergone laparotomy with salpingectomy. A significantly greater proportion of pregnancies was noted after sparing laparoscopic procedures combined with intramuscular MTX compared to abdominal surgery.

## 5 Discussion

Van Mello emphasizes that, historically, diagnostics and treatment of extrauterine pregnancies were based on surgical procedures, first through laparotomy and later through laparoscopy. Attempts at nonsurgical treatment of extrauterine pregnancy through systemic MTX administration have been made since 1970. Van Mello quotes an article by Mashiach *et al.* (1982) that reported a high proportion of early extrauterine pregnancies that were self-limiting through reabsorption or resulted in tubal abortion [4]. In 2013, Van Mello re-visited this topic and questioned the point of systemic administration of MTX in comparison to watchful waiting. Analyzing the studies, which included one group of patients receiving intramuscular MTX and the other subjected to watchful waiting, van Mello concluded that patients with low beta-hCG levels should not receive systemic MTX, as it does not affect the results of treatment [5].

Tzafettos *et al.* reported that a single intra-oviductal administration of large dose of MTX (100 mg), either through laparoscopy or under ultrasound guidance, is safe and gives satisfactory results in as many as 88.98% of cases. In their study group viable tubal pregnancy was

noted in 7 out of 118 subjects despite MTX administration [6].

In the analyses by Mol *et al.* and Beall *et al.*, the authors found that MTX administered as an intramuscular injection contributes to shorter hospitalization time and faster recovery, but does not influence future spontaneous fertility or recurrent ectopic pregnancies [7, 8].

However, other authors emphasize that with systemic administration of MTX, one should remember that a side effect of this drug, which is a folic acid antagonist, is displacement of folic acid from its bonds within deoxyribonucleic and ribonucleic acids. Rodriggues *et al.* noted that only one dose of MTX cannot always be administered. According to their studies, one dose is beneficial in only those patients with a beta-hCG level below 1500 mIU/mL. However, patients with a beta-hCG concentration above 3000 mIU/mL should receive multiple doses of the drug, as it is more effective and protects from recurrence of ectopic pregnancy [9].

Yang *et al.* divided 96 patients with ectopic pregnancy into two groups: one group received MTX as intramuscular injection in combination with prostaglandins (Mifepristone) and traditional Chinese medicines, and the second group was given the same drugs through the posterior vaginal wall, straight into the oviduct.

These authors demonstrated greater efficacy (*i.e.*, through faster beta-hCG reduction) of MTX, mifepristone and traditional Chinese medicines administered directly into the oviduct through the posterior vaginal wall in comparison to intramuscular injections [10].

Sadan *et al.* studied the differences in the effects of MTX and hyperosmolar glucose administered via the oviduct. Patients included in that study fulfilled the same inclusion criteria as ours: the diameter of the embryo did not exceed 4 cm, no intraabdominal bleeding was present, and the beta-hCG level was stable.

It was demonstrated that intra-oviductal injection of MTX was more beneficial than the administration of hyperosmolar glucose, as it led to faster reduction in the beta-hCG level. These differences were not statistically significant, and some authors suggest that **they** might be due to a small size of the study group [11]. In our study, we observed more rapid reduction of beta-hCG concentration among patients subjected to intratubal injection of MTX or hyperosmolar glucose with subsequent adjuvant intramuscular administration of 50 mg/m<sup>2</sup> compared to patients who had not received additional intramuscular MTX. However, there were no differences with regard to the rate of beta-hCG reduction between patients treated with MTX and hyperosmolar glucose administered via the oviducts.

Gjelland et al. studied whether ultrasound-guided administration of hyperosmolar glucose through the posterior vaginal wall is as effective as direct administration of glucose into the oviduct. They found that ultrasound-guided glucose injection results in a statistically significant reduction in repeated procedures due to a further increase in beta-hCG in comparison to administration during laparoscopy. Difficulties in intra-oviductal glucose administration often resulted from technical difficulties, such as adhesions caused by previous surgeries or inflammatory conditions [12].

The same authors also compared intra-oviductal administration of hyperosmolar glucose through laparoscopy and under ultrasound guidance. In a group of patients, the treatment was successful in 82% of patients who had received glucose through the posterior vaginal wall under ultrasound guidance compared to 52% who had undergone laparoscopic administration. However, the authors emphasized that in this study laparoscopic administration of hyperosmolar glucose failed due to technical difficulties in as many as 6 out of 20 patients [13]. In their study, they noted that more patients conceived without the use of assisted reproduction techniques after intra-oviductal administration of hyperosmolar glucose [13]. In the follow-up phase of our study, we found a significant number of spontaneous pregnancies in 36% of patients who had received hyperosmolar glucose by intra-oviductal injection during laparoscopy with or without adjuvant intramuscular MTX. Hordnes suggests that the ratio of persistent disease is so high that it is preferable to perform laparoscopic salpingectomy and administer hypertonic glucose under ultrasound guidance [13]. Lang et al. found that oviduct-sparing surgery results in satisfactory effects [14].

Lehner et al. reported that a non-ruptured extrauterine pregnancy with a beta-hCG level ranging between 1000 mIU/mL and 2500 mIU/mL may be treated with local intra-oviductal administration of MTX, prostaglandins, hyperosmolar glucose and NaCl or KCl [15]. Verma et al. cited an example of a 37-year-old multiparous woman who presented with pelvic pain. Right-sided extrauterine pregnancy with heartbeat was diagnosed, and the gestational age was assessed at 9 Hbd with a beta-hCG level of 58423 mIU/ml. Under ultrasound guidance, 1 cm<sup>3</sup> of [2mEq/ml] KCl was injected into the oviduct, followed by systemic MTX administration at a standard dose of 50 mg/m<sup>2</sup>. Ninety days after the procedure, the beta-hCG level was 14 mIU/ml [16]. Likewise, Verma described a case of a 29-year-old patient with a left-sided tubal pregnancy of 7 weeks' duration. The initial beta-hCG level was 102953 mIU/ml. The concentration of 1940 mIU/ml was achieved

35 days after administration of KCl into the oviduct and intramuscular MTX injection [16]. Our experience is similar. We conclude that, besides local intra-oviductal injection, it is necessary to administer MTX systemically to protect patients from persistent disease. In 2009, Dadhwal et al. diagnosed left-sided extrauterine pregnancy in a 27-year-old nulliparous woman after laparoscopic salpingectomy due to extrauterine pregnancy 4 years previously. The initial beta-hCG concentration was 89200 mIU/ml. There was no intraabdominal fluid. She was treated with 2 mEq/ml of KCl injected into the embryo and intramuscular administration of 50 mg/m<sup>2</sup> of MTX. No surgical treatment was undertaken. The beta-hCG test was negative 70 days after the procedure [17]. In our Clinical Center we are trying to perform as few surgical procedures involving salpingectomy as possible, as most extrauterine pregnancies occur in young women, who are concerned with preservation of fertility.

Giuliani analyzed future outcomes of 124 patients who had received intra-oviductal hyperosmolar glucose. As many as 70% of patients who had received this treatment became pregnant without assistance and had live births. Among the remaining 39 women with fertility problems, salpingeal occlusion was diagnosed during hysterosalpingographic examination in 69% of them [18].

In our follow-up studies, the greatest proportion of spontaneous pregnancies was noted among patients who had been given hyperosmolar glucose or MTX via the oviduct with a single intramuscular dose of 50 mg/m<sup>2</sup> of MTX. Spontaneous pregnancies were also noted in 23% of women after the administration of MTX or hyperosmolar glucose into the oviduct without adjuvant 50 mg/m<sup>2</sup> of MTX administered intramuscularly, as well as among patients following laparoscopic extrusion of hematocele with simultaneous administration of intramuscular MTX (18%).

The results from our Center suggest that combination treatment consisting of laparoscopy and a single dose of MTX (50 mg/m<sup>2</sup>) gives satisfactory results.

## 6 Conclusions

The main risk factors for extrauterine pregnancy in our study included a history of surgery and extrauterine pregnancies. The fastest reduction of the beta-hCG level and absence of persistent tubal disease was noted after combination treatment with invasive and conservative methods: intra-oviductal injection of hyperosmolar glucose or MTX with subsequent intramuscular administration of 50 mg/

m<sup>2</sup> of MTX in a single dose. There were no repeated laparoscopies in a group receiving combination treatment. The highest number of pregnancies was also noted after surgically conservative treatment. We conclude that the combination therapy in use at our Clinical Center is safe and gives satisfactory results with regard to preservation of future fertility.

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## References

- [1] Trio D, Strobelt N, Picciolo C, Lapinski RH, Ghidini A. Prognostic factors for successful expectant management of ectopic pregnancy. *Fertil Steril* 1995;63:469-472
- [2] Glock JL, Johnson JV, Brumsted JR. Efficacy and safety of single-dose systemic methotrexate in the treatment of ectopic pregnancy. *Fertil Steril* 1994;62:716-721
- [3] Barnhart KT, Gosman G, Ashby R, Sammel M. The medical management of ectopic pregnancy: a meta-analysis comparing „single dose” and „multidose” regimens. *Obstet Gynecol* 2003;101:778-784
- [4] van Mello NM, Mol F, Ankum WM, Mol BW, van der Veen F, Hajenius PJ. Ectopic pregnancy: how the diagnostic and therapeutic management has changed. *Fertil Steril* 2012;98:1066-1073
- [5] van Mello NM, Mol F, Verhoeve HR, van Wely M, Adriaanse AH, Boss EA, et al. Methotrexate or expectant management in women with an ectopic pregnancy or pregnancy of unknown location and low serum hCG concentrations? A randomized comparison. *Hum Reprod* 2013;28:60-67
- [6] Tzafettas JM, Stephanatos A, Loufopoulos A, Anapliotis S, Mamopoulos M, Kalogeropoulos A. Single high dose of local methotrexate for the management of relatively advanced ectopic pregnancies. *Fertil Steril* 1999;71:1010-1013
- [7] Mol BW, Hajenius PJ, Ankum WM, van der Veen F, Bossuyt PM. Conservative versus radical surgery for tubal pregnancy. *Acta Obstet Gynecol Scand* 1996;75:866-867
- [8] Beall S, DeCherney AH. Management of tubal ectopic pregnancy: methotrexate and salpingostomy are preferred to preserve fertility. *Fertil Steril* 2012;98:1118-1120
- [9] Rodríguez L, Takacs P, Kang J. Single-dose methotrexate for the management of interstitial ectopic pregnancy. *Int J Gynaecol Obstet* 2004;84:271-272
- [10] Yang XL, Cao YP, Liu ZH. Therapeutic effect of pelvic methotrexate injection via the posterior fornix for treatment of tubal pregnancy. *Nan Fang Yi Ke Da Xue Xue Bao* 2011;31:377-379
- [11] Sadan O, Ginath S, Debby A, Rotmensch S, Golan A, Zakut H, et al. Methotrexate versus hyperosmolar glucose in the treatment of extrauterine pregnancy. *Arch Gynecol Obstet* 2001;265:82-84
- [12] Gjelland K, Hordnes K, Tjugum J, Augensen K, Bergsjø P. Treatment of ectopic pregnancy by local injection of hypertonic glucose: a randomized trial comparing administration guided by transvaginal ultrasound or laparoscopy. *Acta Obstet Gynecol Scand* 1995;74:629-634
- [13] Hordnes K. Reproductive outcome after treatment of ectopic pregnancy with local injection of hypertonic glucose. *Acta Obstet Gynecol Scand* 1997;76:703-705
- [14] Lang JH. Conservative surgery in tubal pregnancy. *Zhonghua Fu Chan Ke Za Zhi* 1989;24:206-208, 251
- [15] Lehner R, Kucera E, Jirecek S, Egarter C, Husslein P. Ectopic pregnancy. *Arch Gynecol Obstet* 2000;263:87-92
- [16] Verma U, Jacques E. Conservative management of live tubal pregnancies by ultrasound guided potassium chloride injection and systemic methotrexate treatment. *J Clin Ultrasound* 2005;33:460-463
- [17] Dadhwal V, Deka D, Ghosh B, Mittal S. Successful management of live ectopic pregnancy with high beta-hCG titres by ultrasound-guided potassium chloride injection and systemic methotrexate. *Arch Gynecol Obstet* 2009;280:799-801
- [18] Giuliani A, Hoenigl W, Schoell W, Tamussino K, Arikian G, Lang PF. Reproductive outcome after laparoscopic instillation of hyperosmolar glucose into unruptured tubal pregnancies. *Fertil Steril* 2001;76:366-369