

II. 原 著

II. 2 Therapy for cesarean scar pregnancy in Japan during the past five years

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Abstract

[Objectives] Cesarean scar pregnancy (CSP) is a dangerous condition that will cause uterine rupture and hemorrhagic shock. In this report, therapy for CSP was reviewed in order to obtain a consensus regarding therapy guidelines for easy reference in treating future cases.

[Methods] The cases of CSP were collected using the document retrieval system to identify cases. The management of these cases was then reviewed in detail.

[Results] There were 46 cases reported by 39 authors including 4 cases of our own. There was 1 case in which the pregnancy continued up to 24 weeks, and a baby was delivered by a cesarean section following supravaginal amputation of the uterus. There were 45 cases in which pregnancy intervention was performed. There were 5 cases in which hysterectomy were performed and 40 cases in which pregnancy contents were extracted from the uterus. In 40 patients with uterine preservation, pregnancy contents were surgically extracted with operation in 26 cases and not surgically extracted in 14 cases. The approaches in 21 cases were vaginal, in 3 cases laparoscopic, in 1 case laparotomic and in 1 case hysteroscopic. Systemic administration of MTX (methotrexate) and/or local administration of MTX and/or UAE (uterine artery embolization) were performed before extraction of the pregnancy contents and in cases in which the pregnancy contents were not extracted.

[Conclusion] It is important to recognize the disease as early as possible. If the disease is diagnosed, discontinuation of the pregnancy is the safest option. Choices of treatment modality depend on the status of diagnostic time and pregnancy viability. If it is in the early stage, a vaginal approach to extracting the pregnancy contents is easy and can be safely performed under abdominal ultrasound guidance. MTX administration and UAE are also useful in cases managed with or without surgery. Depending on the situation, laparotomic, laparoscopic or hysteroscopic surgery can also be useful. When required, doctors should not hesitate to perform prompt hysterectomy.

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帝王切開癒痕部妊娠の治療について

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要 旨

[目的] 帝王切開癒痕部妊娠は気づかれずに妊娠が継続されると、子宮破裂が起こり出血性ショックになる危険な疾患である。また、最近の帝王切開の増加に伴って報告例も増えてきている。それに伴い、帝王切開癒痕部妊娠という概念は周知されるようになり、治療法は確立されてきたと考えられるが、いまだコンセンサスは得られていないと考えられる。今回、医療従事者が参考にしやすい治療法のコンセンサスを得る目的で、帝王切開癒痕部妊娠に適用された最近の治療方法について検討してみた。

[方法] 医療環境が均一であるわが国の症例を文献検索システムを使って集め、帝王切開癒痕部妊娠の治療法について検討した。

[結果] 最近5年間のわれわれの施設と同様の状況下にある医療機関で、治療された帝王切開癒痕部妊娠報告例は、自験例の4例を含めて39著者による46例である。24週まで妊娠継続して、帝王切開後に膈上部切断術を行い、母児ともに経過順調な例が1例ある。妊娠継続していない例は45例である。子宮を摘出した例は5例であり、子宮を摘出しなかった例は40例である。子宮を摘出した例の内訳は、子宮温存を希望せずに最初から子宮を摘出した例が3例、経膈的に内容除去を試みたが大量出血して子宮を摘出した例が1例、詳細が不明であるが子宮を摘出した例が1例である。子宮を摘出しなかった例の内訳は、妊娠内容除去術を行ったのが26例、妊娠内容除去術を行わなかったのは14例である。妊娠内容除去術は、経膈的に21例、腹腔鏡下に3例、開腹術により1例、子宮鏡下に1例が行われた。妊娠内容除去術の前後に、MTXの全身投与、局所投与、UAEなどが行われていた場合もある。妊娠内容除去術を行わない場合には、MTXの全身投与、局所投与、UAEなどが行われていた。前治療でhCGが下降しなかったり、出血が減少しなかったりした場合には、次の段階の治療方法が試みられている場合が多かった。MTXの投与方法は、添付文書の絨毛性疾患に対する用法の記載どおり、1クールを5日間とし、1日に15~20mgが投与されている場合が多かった。休薬期間は7~12日間としていることが多かった。局所投与する場合は、胎嚢を穿刺して、内容液を吸引した後に、50mg/2mlを局注している場合が多かった。

[結論] 帝王切開癒痕部妊娠についてもっとも必要なことは、まず疾患の存在を認識し、疾患を疑うことである。次に、早期に診断することが大切である。診断できれば、危険を犯して妊娠継続を期待せずに、妊娠の中断をはかるのが安全である。治療は、診断時期、病巣の状態などにより異なる。初期であれば経腹的あるいは経膈的超音波観察下に経膈的な妊娠内容除去術手術が行われている。MTXの全身投与、局所投与、UAEなどもよく行われている。状況によっては、開腹術、腹腔鏡手術、子宮鏡下手術も行われている。必要であれば、子宮摘除もためらうべきではない。いずれにしろ、さまざまな起こりえる状況を予測して、時機を逸することのないように治療法を選択するのがよいと考える。

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Objectives

Cesarean scar pregnancy (CSP) is a dangerous condition that will cause uterine rupture and hemorrhagic shock, if CSP continues without being detected. Moreover, the number of reported cases has been increasing with the increased rate of cesarean section in the recent years. Although the risks of CSP have become well-known, and therapeutic modalities for CSP have been developed, a general consensus regarding therapy for CSP has not yet been established.

Generally, therapy for a disease is not universal but rather individually tailored to the medical environment, legal restrictions, ethical restrictions, medical insurance system, socio-economic situation and time. Moreover, therapy is impacted by the wealth of residents in the area, which affects the hygiene environment and traffic environment. The cases of CSP in this series were collected from an area with a unified medical environment using the document retrieval system to identify cases treated in the past five years. In this report, therapy for CSP in Japan is reviewed in order to obtain a consensus regarding therapy for easy reference in treating future cases.

Methods

The Japanese literature between 2002 and 2007 was searched using Japan Centra Revuo Medicina (<http://www.jamas.gr.jp>) and the key words : cesarean scar pregnancy. There were thirty-nine papers describing cesarean scar pregnancies including our four previously published case reports. The management of these cases was then reviewed in detail.

Results

There were 46 cases reported by 39 authors (Figure 1) including our own four cases^{1) 2)}. There was one case in which the pregnancy continued until 24 weeks, and a baby was delivered by a cesarean section following supravaginal amputation of the uterus. The mother and the baby followed an uneventful postoperative course. There were 45 cases in which pregnancy intervention was performed. There were five cases in which hysterectomy were performed and there were forty cases in which pregnancy contents were extracted from the uterus, allowing the uterus and fertility to be preserved. In three cases, the patients did not desire uterine or fertility preservation because they already had a sufficient number of children. In one case, dilatation and curettage was attempted but massive bleeding occurred and hysterectomy was subsequently performed¹⁾. In one case, the details were not documented, but

hysterectomy was performed. Among forty patients with uterine preservation, pregnancy contents were surgically extracted in twenty-six cases (surgical treatment group) and not surgically extracted in fourteen cases (medical treatment group). The most frequent therapy in CSP was pregnancy intervention and vaginal extraction of the pregnancy content. Twenty of the total 46 cases accounts for 43.5%. Forty-five of 46 cases (97.8%) failed to obtain a baby. The uterine or fertility preservation rate was 87.0% in 40 of 46 cases.

In cases of uterine preservation, surgical extraction of the pregnancy content was performed in 26 of 40 cases (65.0%) and non-surgical extraction in 14 of 40 cases (35.0%). In fourteen cases undergoing medical treatment, the weeks of gestation at the start of therapy were documented in eight cases. Medical therapy was initiated at five weeks of gestation in four cases, six weeks in one case, seven weeks in two cases and eight weeks in one case. There were 10 viable fetuses, two non-viable fetuses and viability was not documented in two cases. Fourteen cases in the medical treatment group and 26 cases in the surgical treatment group showed almost the same background with regard to mother's age, obstetrical history, timing of therapy initiation, presence of fetal heart beat (FHB) and hCG level. (Table 1)

In the medical treatment group, systemic administration of Methotrexate (MTX) was performed in only one case, in which FHB was not detected at seven weeks of gestation. Local injection of MTX was administered in thirteen cases. Only local injection of MTX was administered in eight cases. Under vaginal ultrasound guidance, the gestational sac (GS) was punctured with a 16 to 19G needle, GS fluid was aspirated and then 15 – 50mg/2ml of MTX was injected in many cases. At that time, feticide was performed in many cases. In one case, trans-arterial embolization (TAE) of the uterine arteries was performed and then systemic and local administration of MTX was performed simultaneously. In one case of massive bleeding with tumorous and hematoma-like appearance without clear GS, TAE was performed and blood transfusion was prescribed, then two courses of local injections of MTX were administered for 5 days. In cases showing enlargement at 8 weeks and 4 days of gestation, the fetus was punctured under vaginal ultrasound guidance, 2ml of saline was injected and then disappearance of FHB was observed and GS fluid was aspirated. Thereafter 30mg of MTX was injected and systemic MTX was administered for four days. In a case of bleeding, TAE was performed and local MTX was administered. In a

case at five weeks of gestation, the fetus continued to grow after systemic administration of MTX. At seven weeks of gestation under transvaginal ultrasound guidance, the GS was punctured with a 19G needle, 2ml of GS fluid was aspirated and then feticide was performed which was followed by local administration of 50mg/5ml of MTX.

In the surgical treatment group, a vaginal procedure were performed in 20 cases, laparoscopic surgery was performed in 4 cases, hysteroscopic surgery was performed in 1 case and laparotomy was performed in 1 case.

Both pre-surgical and post-surgical therapy were administered in 6 cases, only pre-surgical therapy were administered in 14 cases, only post-surgical therapy were administered in 3 cases and there was no other therapy administered in 3 cases.

In 6 cases receiving both pre-surgical and post-surgical therapy, the pre-surgical therapy was vaginal intrauterine dilatation and curettage in 2 cases, systemic MTX administration in 3 cases and a combination of local and systemic MTX administration along with TAE were performed in one case.

As post-surgical therapy, systemic MTX was administered in 2 cases, local MTX in 2 cases, a combination of local and systemic MTX in 1 case and a combination of blood transfusion, hemostatic drugs and anti-DIC drugs were administered in 1 case.

In 14 cases receiving pre-surgical therapy only, laminaria insertion was performed in 2 cases, TAE was performed in 1 case, systemic MTX was administered in 2 cases, vaginal intrauterine dilatation and curettage was performed in 1 case, local MTX was administered in 1 case, a combination of local and systemic MTX were administered in 2 cases, a combination of systemic MTX was administered in combination with TAE in 1 case, combination therapy with general and local MTX along with TAE were performed in 3 cases and local MTX was combined with TAE in 1 case. In 3 cases receiving post-surgical therapy only, general MTX were administered in 2 cases and TAE was performed in 1 case. In some cases, ligations of the uterine and internal iliac artery were performed followed by blood transfusion as well as administration of both hemostatic drugs and anti-DIC drugs. (Table 2)

Regarding chemotherapy, MTX were administered in all cases and only one case received a combination of MTX and VP-16. When the hCG value remained high, bleeding persisted after the initial therapy or mass persisted, further medical treatment was attempted in many cases. Systemic MTX at a dose of 15-20mg/day was administered for five days according to

the approved usage for treatment of trophoblastic disease. The interval until administration ranged from 7 to 12 days in many cases. Local administration of MTX was 50mg/2ml in many cases after puncturing the GS and extracting the GS fluid.

Comments

I. Incidence, diagnosis and treatment of cesarean scar pregnancy

Cesarean scar pregnancy is an ectopic pregnancy in a previous cesarean scar, it occurs in about 1 in 2000 pregnancies and accounts for 6 percent of ectopic pregnancies among women with a prior cesarean delivery in developed countries^{3) 4)}.

The diagnosis is made by sonographically visualizing an enlarged hysterotomy scar with an embedded mass, which may bulge beyond the anterior contour of the uterus. Many ultrasonographic photographs and magnetic resonance imaging photographs have been reported in textbooks and journals^{4) - 6)}.

There are too few reported cases on which to base a specific treatment recommendation. Treatment should be tailored to the individual patient. Desire for future fertility, size and gestational age of the pregnancy, and hemodynamic stability should be considered when determining a treatment plan. Options include wedge resection of the ectopic pregnancy via laparotomy or laparoscopy, hysteroscopic excision, local injection of 5 mEq potassium chloride into the sac, and local or systemic methotrexate administration (local administration is preferable if fetal cardiac activity is present).⁴⁾

Local methotrexate injection to the gestational sac (GS), general administration of methotrexate^{7) 8)} and TAE to uterine arteries⁹⁾ are also widely used as therapeutic modalities. Medical treatment using systemic MTX therapy has been used extensively in the management of tubal and cervical ectopic pregnancies. It is well recognized that a higher failure rate of medical treatment is associated with a gestational age of ≥ 9 weeks, a fetal pole >10 mm, the presence of embryonic cardiac activity and a serum HCG concentration of ≥ 10000 IU/L.

II. Surgical treatment of early CSP is easy

A vaginal procedure consisting of dilatation with laminaria tent insertion and curettage under abdominal ultrasound guidance with uterine gauze packing is considered a simple and easy method in Japan. It is widely performed as therapy for spontaneous missed abortion and pregnancy intervention before twelve weeks of gestation.^{1) 2) 10) 11) 12)}

In CSP, the fertilized ovum arrives at the cesarean scar site

space via a route through the intrauterine cavity. It adheres to the endometrial membrane, and then is implanted in the lining membrane and grows. If in the early stage of pregnancy, the pregnancy content is small and the chorion has not invaded the myometrium, the pregnancy content can be easily removed from the uterus by surgery. Therefore, it is rational to approach CSP from the intrauterine side, that is to say, a vaginal approach. A vaginal approach with laminaria tent insertion under abdominal ultrasound guidance to extract the pregnancy contents is easy and can be safely performed under abdominal ultrasound guidance with ample anesthesia²⁾.

The uterus of adult nulliparous woman ranges from 6 to 8 cm in length compared with 9 to 10 cm in multiparous woman. Uteri of nulliparous women average 50 to 70 g, and those of parous women average 80 g or more. In nulliparous women, the body of the uterus and the cervix are about equal in length. In multiparous women, the cervix only comprises slightly more than one third of the total length of the organ¹³⁾. The volume of GS calculated from the diameter of the GS is 0.06ml at 4 weeks of gestation, 0.78ml at five weeks, 2.98ml at six weeks, 7.84ml at seven weeks, 15.72ml at 8 weeks, 27.63ml at 9 weeks, 45.51ml at 10 weeks and 69.80ml at 11 weeks.

Surgical resection of GS appeared to be easy before seven weeks because the GS volume comprises under 10% of the uterus, but not easy after 9 weeks because the GS volume comprises over 30% of the uterus. At 8 weeks, surgical resection is controversial because the GS volume is about 20% of the uterus.

One article documented that insertion of a Shirodkar cervical suture during the evacuation of a cesarean scar pregnancy is an effective method of securing hemostasis; it minimizes the need for blood transfusion and ensures preservation of fertility. Thirty-three cesarean scar pregnancies were diagnosed, and 28 (85%) underwent surgical evacuation. A cervical suture was necessary to achieve hemostasis in 22/28 (79%) cases. In the remaining 6/28 (21%) cases, the bleeding was minimal and the suture was not tied. The median estimated intraoperative blood loss was 50 mL. Six of 28 (21%) women demonstrated blood loss \geq 300 mL and two (7%) required blood transfusion. One woman (5%) required repeat surgery because of retained products of conception. There were no other significant complications and the uterus was preserved successfully in all cases.¹⁴⁾

III. "Recent criteria for judgment of dilatation and curettage appropriate or not"

Recent criteria for judgment of dilatation and curettage appropriate or not are as follows (Figure 2)²⁾; ① Regarding the entry course of the laminaria tent for dilatation at the time of insertion, laminaria remaining in the cervical and uterine cavity is appropriate for D&C. Laminaria perforated the uterine wall and reaching to the extra uterine space is not appropriate for D&C because of uterine perforation. ② Regarding the position of the GS after insertion of laminaria, GS remaining in the uterus is appropriate for D&C. Pushing GS into the extra uterine space is not appropriate for D&C which because the thinning of uterine wall. ③ Regarding the position of the GS after removing the laminaria, GS subsequently moving to the center of the uterine cavity is appropriate for D&C. GS remaining in the anterior uterine wall is not appropriate for D&C because chorionic invasion to the uterine wall is to suspected.

Conclusion

Our proposed therapy for cesarean scar pregnancy for easy reference in treating future cases is as follows:

1. To prevent a catastrophic outcome of CSP, it is important to recognize the conditions as early as possible.
2. When CSP is diagnosed, discontinuation of the pregnancy is the safest option. Choices of treatment modality depend on the status of diagnostic time and pregnancy viability.
3. If the pregnancy still in the early stage (4–8 weeks of gestation), a vaginal approach with laminaria tent insertion to extract the pregnancy contents is easy and can be safely performed under abdominal ultrasound guidance with ample anesthesia. Criteria for judging whether dilatation and curettage is appropriate or not (Figure 3)²⁾ are very useful.
4. Systemic and/or local MTX administration and/or UAE are also useful in cases managed with or without surgery. Systemic MTX at a dose of 15–20mg/day should be administered for five days according to the approved usage for treatment of trophoblastic disease. The interval until the next MTX administration should range from 7 to 12 days. With local MTX administration, the GS should be punctured with a 16 to 18G needle under vaginal ultrasound guidance, GS fluid should be aspirated then 50mg/2ml of MTX should be injected.
5. Depending on the situation, laparotomic, laparoscopic or hysteroscopic surgery can also be useful.
6. When required, physicians should not hesitate to perform

prompt hysterectomy.

Part of the data in this paper was presented at 14th International Conference on Prenatal Diagnosis and Therapy. 1-4 June 2008, Vancouver, Canada.

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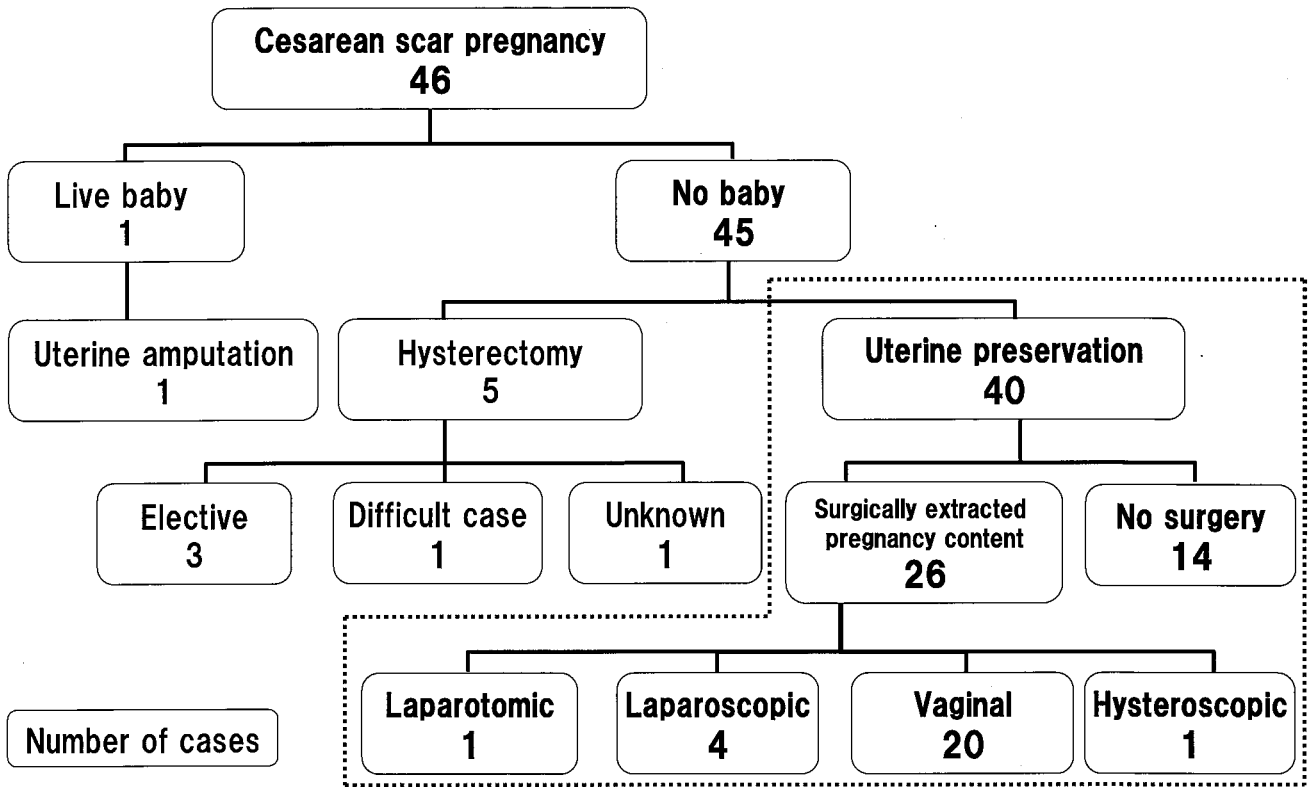
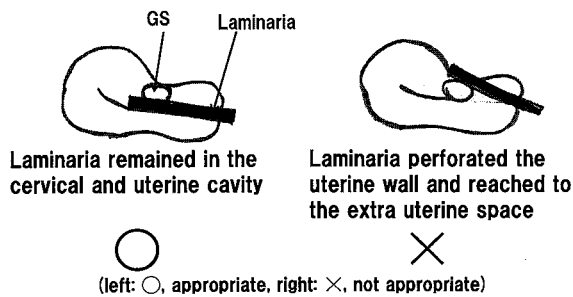


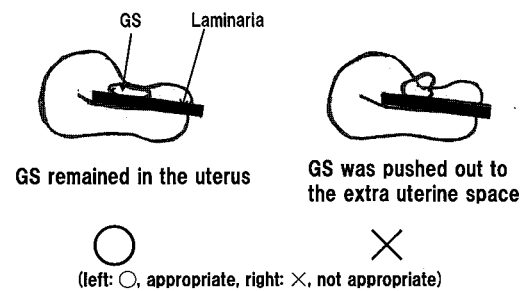
Figure 1. Forty six cases of cesarean scar pregnancy in Japan
(Japan Centra Revuo Medicina, 2002~2007)

Criteria for judgment of dilatation and curettage²⁾

① Entry course of Laminaria tent for dilatation



② Position of the GS after insertion of Laminaria



③ Position of the GS after pulling out of Laminaria

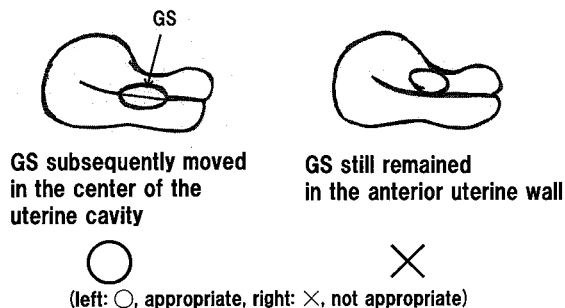


Figure 2. Criteria for judging whether dilatation and curettage has been appropriate for treatment of cesarean scar pregnancy. (left : ○, appropriate, right : ×, not appropriate)

① Entry course of Laminaria tent for dilatation. Left : Laminaria remaining in the cervical and uterine cavity. Right : Laminaria perforating the uterine wall and reaching to the extra uterine space.

② Position of the GS after insertion of Laminaria. Left : GS remaining in the uterus. Right : GS pushed out into the extra uterine space.

③ Position of the GS after removal of Laminaria. Left : GS subsequently moved into the center of the uterine cavity. Right : GS still remaining at the anterior uterine wall.

Table 1. 40 cases of uterine preservation in cesarean scar pregnancy 2002–2007 in Japan

14 cases of non-surgical extraction of pregnancy content (medical treatment group)

	documented cases	range	average
age (years)	9	24~38	32
number of previous pregnancies	9	1~4	2.56
number of previous deliveries	9	1~3	1.89
number of previous cesarean sections	6	1~3	2
timing of therapy (weeks)	8	5~7	5.75
fetal heart beat	12	positive : 10, negative : 2	
hCG(mIU/ml) in positive FHB	4	12490~80982	34819
hCG(mIU/ml) in negative FHB	1	25869	25869

26 cases of surgical extraction of pregnancy content (surgical treatment group)

	documented cases	range	average
age (years)	24	28~41	32.5
number of previous pregnancies	20	1~8	3.35
number of previous deliveries	21	1~3	1.62
number of previous cesarean sections	17	1~3	1.71
timing of therapy (weeks)	18	4~8	6.22
fetal heart beat	20	positive : 12, negative : 8	
hCG (mIU/ml) in positive FHB	10	8000 ~ 205440	62470
hCG (mIU/ml) in negative FHB	3	2304 ~ 26000	13421

Table 2. Number and type of treatment modality

Group		Average	Type	
Medical treatment (14 cases)	—	1.43	Local MTX=65%, Systemic MTX=20%, TAE=15%	
Surgical treatment (26 cases)	Both pre-surgical and post-surgical therapy (6 cases)	Pre	1.33	Systemic MTX=50%, D&C=25%, Local MTX=12.5%, TAE=12.5%
		Post	1.17	Local MTX=43%, Systemic MTX=43%, Other=14%
	Only pre-surgical therapy (14 cases)	1.29	Systemic MTX=28%, TAE=22%, Laminaria=11%, D&C=11%	
	Only post-surgical therapy (3 cases)	1	Systemic MTX=67%, TAE=33%	
	No other therapy (3 cases)	0	—	