

Case Report

Dangerous Methotrexate-Indispensable Abdominal Pregnancies in A Developed Country

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Abstract

Objectives: Methotrexate (MTX)-indispensable abdominal pregnancies (APs) represent problematic ectopic pregnancies in developed countries. We explored these problems by performing a review of reported cases.

Methods: We searched the literature using the Japanese medical-article research service Japana Centra Revuo Medicina, with search terms “peritoneal pregnancy” and “abdominal pregnancy”. We identified 95 cases in 69 articles between 1983 and 2014.

Results: A total of 86 early (before 20 weeks) and 9 advanced (after 20 weeks) APs were reported, including 6 live births. Among the early (E) APs (EAPs), MTX was administered in eight cases because of no or impossible or incomplete resection of pregnancy contents.

Conclusion: MTX-indispensable EAPs should be regarded as dangerous. Operative treatment is usually difficult. Some EAPs cannot be managed only by operative dissections: MTX administration is required as additional therapy.

Keywords: Abdominal Pregnancy, Methotrexate

Introduction

In normal pregnancy, a fertilized egg is implanted in the endometrial gland area of the uterine corpus. In ectopic pregnancy (EP), however, implantation occurs elsewhere, including in the tubal, ovarian, cesarean scar, cervical or abdominal area. EPs comprise 1% of all pregnancies, and abdominal pregnancies (APs) comprise 1% of all EPs; APs thus account for only 0.01% of all pregnancies and are considered very rare. Although most

APs show similar symptoms and signs to other EPs during the early stages, some undergo abrupt clinical course and massive intra-abdominal bleeding with rupture of the pregnancy mass because the pregnancy contents are not covered by the tube or uterus.

A few reported APs may have migrated far from the uterus within the pelvic cavity, and may have adhered to and invaded neighboring tissues or organs. There may thus be problems

associated with surgical invasiveness, surgical danger and surgical incompleteness. Additional methotrexate (MTX) administration may be necessary in these cases.

We review the dangerous types of MTX-indispensable abdominal pregnancies, reported in Japan between 1983 and 2014 [1].

Methods

Igaku Chuo Zasshi (Centra Revuo Medicina Japana) [1] is issued by the NPO Japan Medical Abstracts Society, and all Japanese medical articles and congress abstracts are included in this review system, similar to PubMed. We searched this system using the terms “peritoneal pregnancy” and “abdominal pregnancy”, and identified 94 Japanese articles concerning humans from 1983 to 2014. A review of the original papers identified 69 articles, including 95 cases of AP with sufficient clinical information, including our previously reported case [2].

There were 86 EAPs (i.e. 19 weeks or less; longest 13 weeks), and 9 AAPs (i.e. 20 weeks or longer; shortest 20 weeks). There were eight MTX-indispensable EAPs.

Results

AAPs were reported in 10% (9/95) of all APs during the period of 1983 to 2014. MTX was administered mainly postoperatively in 9% (8/86) of EAPs. The characteristics are described in Table 1 [3-10] and Figure 1 [4-8].

The patient's background, pregnancy method, pregnancy weeks, hCG (human chorionic gonadotropin) level, implantation site, operation, blood loss, blood transfusion, reason for MTX therapy and MTX schedule are shown. Pregnancy weeks were documented on articles in six cases and were 5 (2 cases), 6, 7, 8, and 10 weeks respectively. But, fetal heart beat were not positive in all cases. Implantation sites varied. Blood loss ranged from 225–2,000 g in five of the eight cases, and blood transfusion was performed in one case.

MTX was administered to one patient (12.5%) who did not undergo surgical extraction because of liver pregnancy [4], one patient (12.5%) without tumor extraction for fear of massive bleeding [6], and to the remaining six patients (75%) because of incomplete extraction or residual pathological changes [3,5,7-10]. Miwa et al. [5] reported retroperitoneal pregnancy in a hematoma in which complete pregnancy content resection was impossible (Figure 1). Suzuki et al. [7] reported five to seven-centimeter omentum pregnancy with surrounding scattered lesions in which complete pregnancy content resection was impossible (Figure 1). Umesaki et al. [8] reported three-centimeter soft bulging tumor in the right posterior broad ligament pregnancy in which complete pregnancy content resection was impossible (Figure 1). MTX was mostly

administered according to the standard regimen for trophoblastic disease (10–30 mg MTX for 5 days or 50 mg/m² administered intramuscularly).

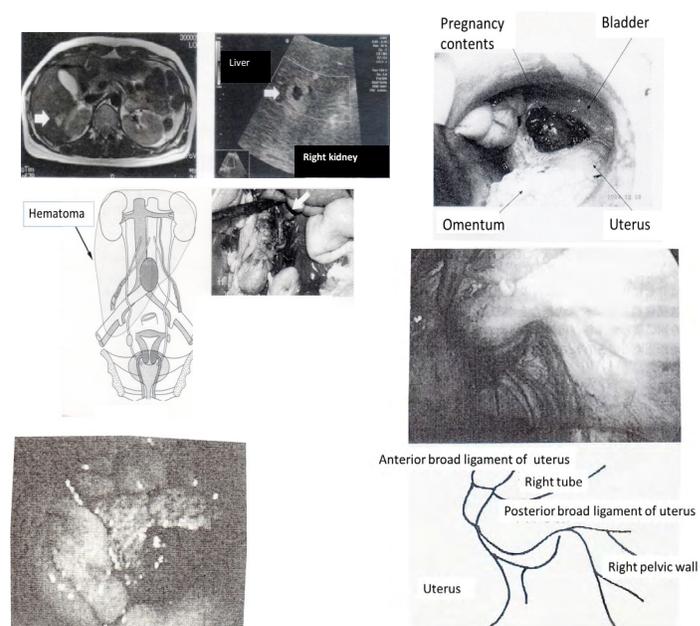


Figure 1 Figures from reports of methotrexate-indispensable abdominal pregnancies (reproduced with the authors' and publishers' permission). Top left. Liver pregnancy. Left: MRI. Right: TAUS. Modified from Ichihara et al., 2010 [4].

Top right. Left vesico-uterine pouch pregnancy. Modified from Isobe et al., 2005 [6].

Middle right. Retroperitoneal pregnancy in a hematoma. Modified from Miwa et al., 2005 [5].

Bottom left. Five to seven-centimeter omentum pregnancy with surrounding, scattered lesions. Modified from Suzuki et al., 2004 [7].

Bottom right. Three-centimeter soft bulging tumor in the right posterior broad ligament. Modified from Umesaki et al., 2013 [8].

Discussion

AP in ectopic pregnancy

AP shows various pathophysiologies. It is important to consider AP as a differential diagnosis in clinical practice, and to diagnose it correctly by hCG examination, vaginal and abdominal ultrasound, CT, and MRI. Because the pregnancy contents are not enclosed within the oviduct or uterine wall, it is necessary to be aware that rapid bleeding into the abdominal cavity may occur.

According to several sources, primary and secondary APs in which the chorionic tissue presents near the tube and in

Table 1. Eight cases of early abdominal pregnancy without surgical resolution who received methotrexate (MTX)

Reference	Maternal age (y.o.) Gravity (G) Parity (P)	Pregnancy weeks	Pregnancy method	hCG level (IU/L)	Implantation site	Operation method & range	Blood loss and blood transfusion	Reason for MTX therapy	MTX schedule
Higa et al. 2013 [12]	Not described	Not described	Not described	Not described	Abdominal	Laparotomy	Not described	Postoperative persistent ectopic pregnancy	Postoperative 6th day, 50 mg intramuscularly
Iehihara et al. 2010 [13]	35 y.o. 0G0P	10 weeks	Ovulation induction, AIH	Urine: 7599	Liver	Exploratory laparotomy and D&C. Diagnosed by abdominal CT. No liver surgery because of high risk	2000 g Blood transfusion, RCC 10 U, FFP 10 U	No liver surgery	General administration
Miwa et al. 2005 [14]	34 y.o. 3G1P	8 weeks	IVF-ET	Urine: 5629	Right retro-peritoneal cavity to the right hypochondriac region	Only biopsies were performed	225 g	Persistence of chorionic tissue	20 mg, 4 days, intramuscularly
Isobe et al. 2005 [15]	28 y.o. 3G1P	6 weeks	Ovulation induction, Timing method	Urine: 4000	Left vesico-uterine cavity	Only coagulae exfoliation was performed. No chorion exfoliation		Persistence of chorionic tissue	15 mg, 5 days, intramuscularly, 2 courses
Suzuki et al. 2004 [16]	32 y.o. 1G0P	5 weeks	Spontaneous	Urine: 3298	Omentum	Laparoscopy, omentectomy	Not described	Persistence of pregnancy lesion in the omentum	70 mg, postoperative 2nd day, intravenously. MTX 20 mg/day, 5 days, intramuscularly, postoperative 1 week
Umesaki et al. 2003 [17]	32 y.o. 3G1P	7 weeks	Spontaneous	Blood: 155,700	Posterior surface of the right broad ligament	Laparoscopy changed to laparotomy. Hemorrhage stopped only. Ligation only. Incomplete chorionic tissue resection.	1000 g No blood transfusion	Persistence of chorionic tissue	MTX-leucovorin, 4 courses, MTX 640 mg/body
Saito et al. 1996 [18]	28 y.o. 2G1P	Not available	Spontaneous	Urine: 64	Posterior peritoneum of the left ovary	Laparotomy. Left salpingectomy, wedge resection of left ovary, confirmation of chorionic tissue. D&C	400 g	Incomplete resection of chorionic tissue	15 mg, 5 days, intramuscularly
Kurobe 1993 [19]	34 y.o. 2G2P	5 weeks	Spontaneous	Urine: positive	Left utero-sacral ligament	Laparotomy. Partial resection of the tumor. Bleeding blood vessel ligation. Peritoneum suturing.	450 g	Suspicion of persistence of chorionic tissue	20 mg, 4 days

D&C: dilatation and curettage, CT: computed tomography, RCC: red cell concentrates mannitol adenine phosphate, FFP: fresh frozen plasma, AIH: artificial insemination with husband's semen, IVF-ET: in-vitro fertilization and egg-transfer

the cul-de-sac are easy to diagnose as APs, while cases in which the chorionic tissue presents far from the tubes, such as in the greater omentum, liver, or spleen, are harder to diagnose [2,11-15]. In the case of EAP, diagnosis and treatment is relatively easy and similar to that for ectopic tubal and ovarian pregnancies [11-16].

AAPs in APs

AAPs (20 weeks or later) have formed the focus of discussions of APs in textbooks and reviews, and account for 49–81% of all abdominal pregnancies [11-14]. Maternal mortalities of 20% [11], 5–20% [12], seven to eight times greater than tubal EPs and 90 times greater than intrauterine pregnancy [13], and 0.5–18% and eight times greater than other ectopic pregnancies [14] have been reported. But, there were no Japanese AAP cases reported in the current study [2].

An AAP is defined as a pregnancy of 20 weeks' gestation or over with a living fetus, or a fetus showing signs of having lived and developed in the mother's abdominal cavity. A total of 163 AAPs have been described in 22 reports from 13 countries since 1946, according to a journal search and PubMed review. It may be assumed that potential AAPs are likely to be diagnosed and terminated in early pregnancy in resource-rich countries, resulting in the apparently higher incidence in non-industrialized countries. Non-industrialized countries lack medical facilities, medical personnel and ultrasound facilities near the pregnant women [15]. In our literature review, we found no article published after 2002 dealing with AAPs in Japan up to the end of the study period.

AP in developed countries

The level of diagnosis and treatment of abdominal pregnancies may be expected to depend on the medical insurance system, medical facilities, medical personnel, and the gross domestic product per person of the country concerned. Everyone in Japan was covered by the national health insurance system during the study period (1983–2014). Clinical use of transvaginal ultrasound, computerized tomography (CT) and magnetic resonance imaging (MRI) were introduced into obstetrical and gynecological practice and have spread widely. In Japan, most pregnant women try self-administer commercial pregnancy-testing kits if their period is 1 or 2 weeks late, and the first visit to an obstetrical clinic occurs at an average of 6 weeks of gestation. All pregnant women then undergo ultrasound examination to rule out miscarriage, EP, multiple pregnancy, and fetal anomalies. Fourteen vouchers for regular checkups and three for prenatal blood examinations are distributed to all pregnant women. In most developed countries, the medical circumstances are supposed to be almost similar with our country.

Methotrexate-indispensable abdominal pregnancies

The abdominal cavity is much larger than the uterine or tubal cavity, an AP may infiltrate to neighboring tissue or organs or spread far from the pelvic cavity. In such cases, complete resection of the pregnancy contents became invasive, dangerous and difficult. This condition resembles persistent trophoblastic disease after conservative tubal surgery, which is treated with MTX. Some APs therefore also require MTX administration. MTX-indispensable APs are therefore recognized as dangerous forms of abdominal pregnancy.

MTX is usually administered for trophoblastic disease and EP at a dose of 10–30 mg for 5 days intramuscularly, or 50 mg/m² MTX with leucovorin rescue. After 5 weeks of pregnancy, chorionic invasion of the neighboring tissue or organs is likely to have occurred. In the case of EAPs, it is therefore important to recognize that the pregnancy contents may not be able to be resected perfectly, unlike in ectopic tubal or ovarian pregnancies.

MTX is usually administered when operative dissection is not performed (such as in liver pregnancy), when operative dissection is considered to be a high-risk procedure because of massive bleeding (such as in a feticide case [17]), and when operative dissection is performed but entire resection is difficult and dangerous (such as in chorionic invasion into the retroperitoneal space or omentum). MTX may be administered postoperatively in these instances. However, it is necessary to decide on the extent of the operation and to prescribe MTX after assessing the risks and the AP conditions [2]. Although postoperative MTX should be administered under these circumstances, MTX administration in EAP patients without surgical resolution is poorly documented [2]. No unsuccessful MTX cases were reported in this study, because most of the pregnancy contents had already been resected or the MTX-targeted lesion was small and inactive.

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