

# Surgical Outcomes and Trends in Incidence of Ectopic Pregnancy

Hiroyuki Yazawa\*, Riho Yazawa, Ryo Matsuoka<sup>1</sup>, Miki Ohara

Department of Obstetrics and Gynecology, Fukushima Red Cross Hospital, <sup>1</sup>Department of Obstetrics and Gynecology, Fukushima Medical University, Fukushima, Japan

## Abstract

**Objectives:** We aimed to evaluate the surgical results for ectopic pregnancy (EP) treated at Fukushima Red Cross Hospital for over a 20-year period from 2002 to 2021.

**Materials and Methods:** We evaluated the incidence, surgical procedures, site of implantation, amount of hemoperitoneum, and the proportion of cases with risk factors of EP.

**Results:** Two hundred and fifty-nine cases of EP were treated surgically. The incidence of EP seemed to be gradually decreasing in recent years. By pregnancy site, 235 (90.7%) of EPs were tubal pregnancies (TPs), 13 in interstitial pregnancies (IPs), 7 in ovarian pregnancies, and 4 in peritoneal pregnancies. For IPs, human chorionic gonadotropin (hCG) levels were statistically higher than with TP and intraperitoneal bleeding was less than with other EP sites. Thirty-nine patients (15.0%) were with massive hemoperitoneum (>500 mL), and laparoscopic surgery was performed in all patients with massive hemoperitoneum except in two patients. The proportion of cases with risk factors for EP such as *Chlamydia trachomatis* infection or history of smoking was 5.4% and 40.6%, respectively. Epidemiological research shows that the number of patients with chlamydia infection, rates of smokers, or the occurrence of EP with assisted reproductive technology has been decreasing in recent years in Japan.

**Conclusion:** Appropriate surgical intervention should be selected while considering such as facility capabilities, context, and surgeon skill, especially in critical cases, such as cases involving massive hemoperitoneum and hemorrhagic shock. The recent presumed decrease in the occurrence of EP may partly be associated with the decrease in the occurrence of risk factors.

**Keywords:** Ectopic pregnancy, epidemiology, laparoscopic surgery, risk factors, serum human chorionic gonadotropin level

## INTRODUCTION

Ectopic pregnancy (EP) occurs in 1%–2% of all pregnancies<sup>[1]</sup> and is a disease that is not infrequently encountered in daily clinical care or in emergency medical care. In recent years, high-resolution transvaginal ultrasonography and highly sensitive serum human chorionic gonadotropin (s-hCG) tests have enabled earlier and accurate diagnosis in many cases of EP, but there are still cases of pregnancy of unknown location (PUL) that are difficult to differentiate from normal early pregnancy or intrauterine abortion,<sup>[1,2]</sup> and cases of severe conditions such as hemorrhagic shock.

We accumulated data of surgically treated cases of EP since 2002,<sup>[3-5]</sup> and in this article, we reported 259 cases of EP during the 20-year period, detailing the surgical technique, site of pregnancy, and amount of blood loss, and discussed the differential diagnosis of preoperative PUL based on evidence from recent literature and medical practice guidelines. We also discussed the decreasing trend in the occurrence of EP based on the results of epidemiological studies of risk factors.

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**Address for correspondence:** Dr. Hiroyuki Yazawa, Fukushima Red Cross Hospital, Yashima-cyo 7-7, Fukushima 960-8530, Japan.  
E-mail: [ikyoku12@fukushima-med-jrc.jp](mailto:ikyoku12@fukushima-med-jrc.jp)

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## MATERIALS AND METHODS

We evaluated the number of cases, surgical procedures, pregnancy sites, and blood loss in cases in which surgery was performed with a diagnosis or suspicion of EP, and the diagnosis of EP was confirmed at Fukushima Red Cross Hospital from 2002 to 2021.

This retrospective study was approved by the Institutional Review Board of our hospital (approval number: 2022-65). Informed consent (IC) for future use of medical records in scientific researches was obtained from all women at the time of admission.

### Diagnosis of ectopic pregnancy

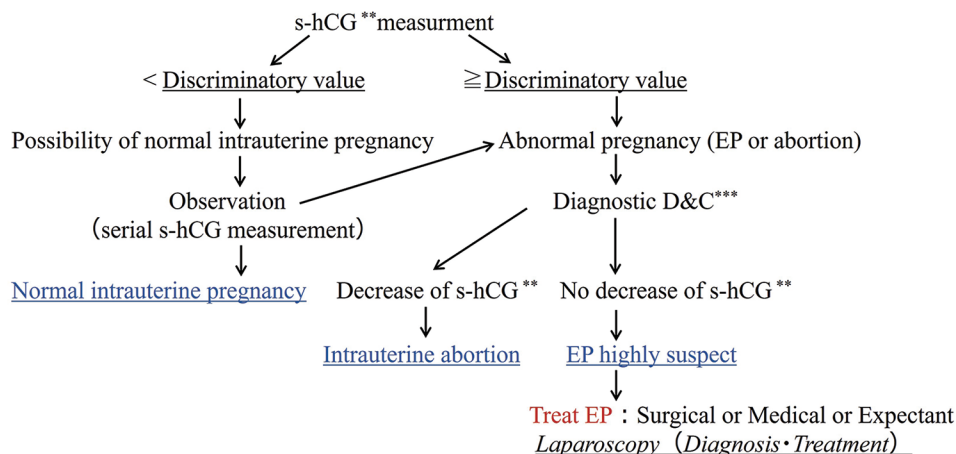
EP was diagnosed when the pregnancy test was positive, and a gestational sac (GS) or fetus is found outside the endometrium. If the pregnancy test was positive and no GS was found in the uterine cavity, a diagnostic laparoscopy was performed if a hematoma was found in the adnexal region, a moderate or large amount of bloody ascites was found in the abdominal cavity, or the patient had acute abdomen, to confirm the diagnosis of EP and to treat the patient once a definitive diagnosis of EP was obtained. In cases with no findings or symptoms suspicious of EP (preoperative PUL), s-hCG levels (discriminatory or serial) were evaluated according to the algorithm for EP diagnosis shown in Figure 1. Dilation and curettage (D and C) was performed when necessary to make a differential diagnosis of EP or intrauterine abortion. When an intrauterine abortion was ruled out and the possibility of EP was high, diagnosis and treatment by laparoscopy were performed. As the discriminatory value of s-hCG, although 2000 IU/L was conventionally adopted, the diagnosis was made based on the reports recommending a higher standard value (3510 IU/L)<sup>[6]</sup> in recent cases. If the case was preoperative PUL and the

s-hCG level was under discriminatory value, the diagnosis was made based on the serial changes in s-hCG levels and treated [Figure 1].

### Surgical treatments

If the diagnosis of EP was confirmed or EP was strongly suspected during the diagnostic process of PUL [Figure 1], surgical treatment being recommended as the first choice of therapeutic intervention in our clinic. The choice of laparoscopic surgery or laparotomy was made in consideration of the patient's condition, wishes, etc. Basically, laparoscopic surgery was chosen as the first choice based on our experience at our hospital. There are two main surgical methods for tubal pregnancy (TP): conservative surgery (salpingostomy) and radical surgery (salpingectomy). The decision of the surgical method is based on the indication conditions for fallopian tube preservation surgery in the Guidelines for Obstetric and Gynecologic Endoscopic Surgery,<sup>[7]</sup> namely, (1) desire to preserve fertility, (2) lesion size <5 cm, (3) s-hCG ≤10,000 IU/L, (4) first fallopian tube pregnancy, and (5) unruptured fallopian tubes. After IC was obtained regarding postoperative tubal obstruction, persistent EP, and the possibility of EP recurrence in the next pregnancy, salpingostomy was selected for those patients who consented. Patients undergoing salpingostomy were also treated with 20 mg of methotrexate injection into the mesentery of the fallopian tubes under IC. In all cases where surgical treatment was performed, postoperative histopathology confirmed the presence of chorionic villi and identified the site of pregnancy.

Because we recommend surgical treatment as the first-line treatment for EP, the number of patients who underwent medical or expectant treatment was limited and thus excluded them from this study.



**Figure 1:** Algorithm for evaluation of a patient with a suspected ectopic pregnancy (PUL\*). \*PUL: Pregnancy of unknown location, \*\*s-hCG: Serum human chorionic gonadotropin, \*\*\*D and C: Dilation and curettage, EP: Ectopic pregnancy

### Investigation of risk factors for ectopic pregnancy and epidemiological study results from websites

In 114 EP surgical cases since 2011, we investigated the proportion of chlamydia antigen-positive, infertile, smokers, previous smokers, and previous EP cases.

Among the risk factors associated with the occurrence of EP,<sup>[1]</sup> we investigated the annual trends of sexually transmitted diseases (*Chlamydia trachomatis* and gonococcal infection), smoking, and assisted reproductive technology (ART) treatment, which can be investigated based on the Ministry of Health, Labour and Welfare (MHLW) Sexually Transmitted Disease Report Count,<sup>[8]</sup> MHLW National Health and Nutrition Survey,<sup>[9]</sup> and ART Online Registry Data Book.<sup>[10]</sup> We also investigated the number of births in Fukushima City from the official Fukushima City website.<sup>[11]</sup> In addition, we investigated the number of births in Japan from the Vital Statistics of the MHLW.<sup>[12]</sup>

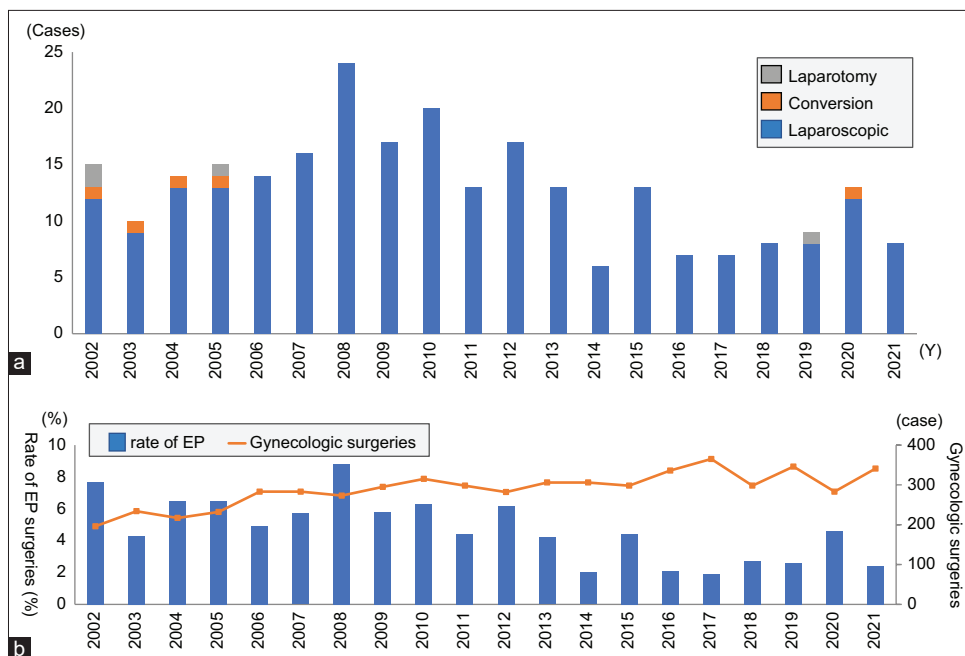
The Mann–Whitney *U*-test was used to test for significant differences, with *P* < 0.05 indicating a significant difference.

### RESULTS

The total number of surgical cases of EP during the 20-year period from January 2002 to December 2021 was 259. The annual trends in the number of surgical cases and details of the surgical techniques (laparoscopic or laparotomy) are shown in Figure 2a. The breakdown of surgical procedures was as follows: 4 (1.54%) were laparotomy, 5 (1.93%) were converted from laparoscopy to laparotomy, and 250 (96.5%) were laparoscopic. From 2006 to 2018, laparoscopic surgery

was performed in all EP cases, but there was one case in which laparotomy was opted for in 2019. This was a case of ovarian pregnancy (OP) with intra-abdominal bleeding (approximately 1000 mL) at 5 weeks and 1 day of gestation. The s-hCG level was 2058 IU/L. The possibility of normal intrauterine early pregnancy and ovarian bleeding could not be ruled out, and the patient wanted to have a baby, so the laparotomy under spinal anesthesia was selected for the patient.

The number and percentage of pregnancies by implantation site are shown in Table 1a. TPs accounted for 90.7%, interstitial pregnancies (IPs) for 5.0%, OPs for 2.7%, and peritoneal pregnancies (PP) for 1.5%. There was one case of cervical pregnancy that could be treated with medical treatment, but there were no cases of cesarean scar pregnancies or heterotopic pregnancies. The breakdown of surgical procedure for TP was as follows: salpingectomy in 140 cases (59.6%), linear incision of the fallopian tubes (salpingostomy) in 93 cases (39.6%), and other (removal of villi and washing) in 2 cases. IP is defined as an EP implanted in the tubal interstitial portion where it traverses through the uterine muscular wall to enter the cavity, and surgical management could be carried out with either cornual resection or cornuostomy.<sup>[13]</sup> The procedures used in this study for the 13 IPs were cornual resection in 7 cases and cornuostomy in 6 cases. The details of 13 IP, 7 OP, and 4 PP cases are shown in Table 2. IP had more cases with previous EP, higher hCG levels, less bleeding, and fewer symptoms than pregnancies at other sites, with significant differences in statistical studies.<sup>[5]</sup> The anatomical characteristics of the interstitial portion are said to be relatively resistant to rupture



**Figure 2:** (a) Annual trends of the number of surgeries and procedures for ectopic pregnancy (EP). (b) Annual trends of the number of gynecological surgeries and the rate of EP at our hospital. EP: Ectopic pregnancy

and prone to prolonged pregnancy, and the fact that there were no cases of rupture at our hospital may have contributed to this result.

The number and percentage of cases by intraoperative blood loss are shown in Table 1b. 48.3% of cases were <100 mL, 85.0% were <500 mL, and 2 cases were >2000 mL. The highest amount of blood loss during the study period was in a case with 2800 mL of intraoperative bleeding due to a ruptured TP at 11-week gestation.<sup>[4]</sup> The other case with blood loss exceeding 2000 mL was a patient with a 7-week gestation,

**Table 1: Number and percentage of ectopic pregnancy surgery cases by site of occurrence and intraoperative blood loss**

**Table 1a. Number and percentage of cases by site of occurrence**

Site of EP	Cases	%	Laparotomy
Tubal pregnancy	235	90.7%	6
Interstitial pregnancy	13	5.0%	2
Ovarian pregnancy	7	2.7%	1
Peritoneal pregnancy	4	1.5%	0

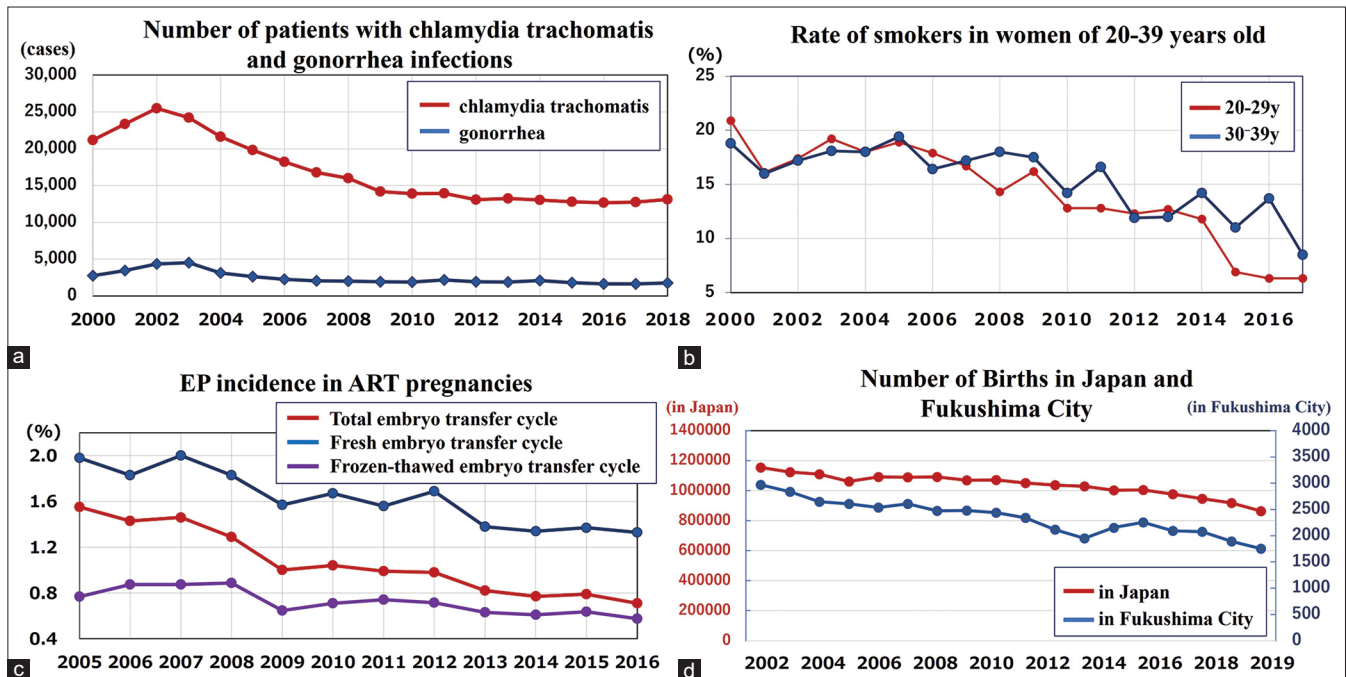
**Table 1b. Number and percentage of cases by intraoperative blood loss**

Blood loss during surgery	Cases	%	Laparotomy
0~99 ml	125	48.3%	3
100~499 ml	95	36.7%	4
500~999 ml	26	10.9%	1
1,000~1,999 ml	11	4.3%	1
≥ 2,000 ml	2	0.8%	0

s-hCG level of 1914 IU/L, and ruptured TP during follow-up after D and C with a diagnosis of PUL, with a blood loss of 2.720 mL. Both cases could have been treated by laparoscopic salpingectomy. The details of cases with blood loss ≥500 mL since 2011 are shown in Table 3. All patients with preoperative shock index (SI) >1 had bleeding of 1300 mL or more, but even in patients with bleeding volume ≥1500 mL, three of seven patients had SI <1. Statistical examination revealed no significant difference between the amount of blood loss and vital sign (systolic blood pressure and shock index), and a significant difference between the amount of blood loss and preoperative hemoglobin level.<sup>[4]</sup> In EP, bleeding often progresses slowly, and vital sign seems to be less variable for the amount of blood loss.<sup>[4]</sup>

The results of the prevalence of the main risk factors in the 114 EP cases from 2011 to 2022 were as follows. The rate of chlamydia antigen positivity was 5.4% (4 of 74), the rate of infertile patients was 10.5% (12 of 114), the rate of smokers and previous smokers was 30.0% (34 of 113) and 10.6% (12 of 113), respectively, and the rate of previous EP cases was 8.8% (10 of 114).

Annual trends of the number of EP surgeries, number of gynecologic surgeries, and the rate of EP are shown in Figure 2a and b. The annual trend in the number of EP at our hospital seemed to show a downward trend in recent years [Figure 2a]. The rate of EP surgeries to all gynecologic surgeries had decreased significantly in recent years [Figure 2b].<sup>[3]</sup> The



**Figure 3:** Risk factors for ectopic pregnancy and annual number of births. (a) Ministry of Health, Labour and Welfare (MHLW), Sexually Transmitted Diseases.<sup>[6]</sup> (b) MHLW, National Health and Nutrition Survey, MHLW.<sup>[7]</sup> (c) Data from ART Online Registry Data Book.<sup>[8]</sup> (d) MHLW, Vital Statistics, cited from the official Fukushima City website.<sup>[9,10]</sup> ART: Assisted reproductive technology

results of the survey of the four hospitals in Fukushima City also showed an overall downward trend in the number of EP surgeries as a whole, similar to the results of our hospital.<sup>[3]</sup> Furthermore, the results of the website survey on the number of chlamydial and gonococcal infections among women, the smoking rate among women aged 20–39 years, the incidence of EP by ART, and the number of births in Japan and Fukushima City all showed a downward trend in recent years [Figure 3a-d].

## DISCUSSION

EP can be treated by surgical, medical, or expectant treatments, the choice of which is determined by the patient’s symptoms, general condition, site of pregnancy, mass diameter, s-hCG level, and presence of a fetal heartbeat.<sup>[2,7]</sup> In a recent study involving 460 EPs, the success rate of medical treatment was

reported to be 90.2%.<sup>[14]</sup> In our hospital, surgical treatment was selected as the first choice for initial treatment, and laparoscopic surgery was currently selected in most cases (96.5%), including those with massive bleeding, in consideration of the minimally invasive nature of laparoscopic surgery.

Although there are nolarage-scale studies on the incidence of EP in Japan, a larage-scale survey conducted in 14 states in the United Steges from 2004 to 2008 reported an incidence of EP of 1.40% of all preganacies, with an incidence rate of 2.3 per 1000 women per year.<sup>[15]</sup> The incidence of EP is also known to increase in infertile patients, especially with ART.<sup>[16,17]</sup>

### Diagnosis of ectopic pregnancy, especially for the evaluation of discriminatory and serial serum human chorionic gonadotropin

In cases of preoperative PUL, the differential diagnosis between normal early pregnancy, intrauterine abortion,

**Table 2: Details of EP in unusual sites**

Interstitial pregnancies (IP)											
case	Pregnancy (w-d)	Surgical history	bleeding	pain	ascites	hCG	GS	FHM	Portion of pregnancy	Ope method	Bleeding
1	6w6d	EP1	-	-	+	5445	-	-	laparoscopy	Incision	150
2	6w0d	-	-	+	+	11315	-	-	laparoscopy	incision	85
3	6w3d	EP2	-	+	-	16000	+	-	laparoscopy	incision	0
4	6w2d	Appe	-	+	-	18401	+	+	laparoscopy	Incision	0
5	6w4d	-	-	+	-	19495	+	+	laparoscopy	incision	0
6	7w	EP1	+	+	-	16061	+	-	laparoscopy	excision	10
7	8w4d	-	-	-	-	14964	+	+	laparoscopy	excision	0
8	7w	-	+	-	-	1739	-	-	laparoscopy	excision	0
9	NA	-	-	-	-	13745	+	-	laparoscopy	excision	0
10	8w4d	CS1	+	-	-	24293	+	-	laparoscopy	excision	0
11	9w4d	EP1	-	-	+	2826	-	-	laparoscopy	excision	50
12	7w2d	-	+	+	+	7408	+	-	laparoscopy	incision	50
13	5w3d	EP2	+	+	-	3853	+	-	laparoscopy	Excision	5

Ovarian pregnancies (OP)											
case	Pregnancy (w-d)	Surgical history	bleeding	pain	ascites	hCG	GS	FHM	Laparoscope or laparotomy	Ope method	Bleeding
1	5w6d	-	-	+	+	1200	-	-	laparoscopy	excision	420
2	6w6d	-	-	+	+	5772	+	-	laparoscopy	excision	750
3	7w0d	-	+	+	-	8500	-	-	laparoscopy	excision	0
4	5w6d	Appe	-	+	-	5613	+	-	laparoscopy	excision	50
5	5w6d	-	+	+	+	8304	-	-	laparoscopy	excision	750
6	5w1d	CS3	-	+	+	2056	-	-	laparotomy	excision	960
7	7w1d	CS2	-	+	+	5118	+	-	laparoscopy	excision	500

Peritoneal pregnancies (PP)											
case	Pregnancy (w-d)	Surgical history	bleeding	pain	ascites	hCG	GS	FHM	Portion of pregnancy	Ope method	bleeding
1	6w	-	-	+	+	1617	-	-	Uterine body	excision	400
2	7w	-	-	+	+	13719	+	-	Tubal serosa	excision	300
3	6w3d	-	+	+	+	1405	+	-	Douglas pouch	excision	125
4	5w	-	-	+	+	5736	+	-	Douglas pouch	excision	500

hCG: Human chorionic gonadotropin, GS: Gestational sac, FHM: Fetal heart movement, EP: Ectopic pregnancy, Appe: Appendectomy, CS: Cesarean section, NA: Not available

**Table 3: Details of EP cases with intraoperative blood loss  $\geq 500$  ml (Study of cases since 2011)**

case	age	preg.	operation methods	bleeding (ml)	portion of preg.	rupture	CRC	s-hCG	SBP mmHg	DBP mmHg	Pulse (bpm)	Pre Hb (g/dl)	D1 Hb (g/dl)
1	31	6w1d	laparoscope: partial resection	500	OP	+	-	5,518	104	59	49	9.7	8.5
2	31	8w1d	laparoscope : salpingectomy	550	TP-a	+	-	282	110	70	100	10.5	8.5
3	31	6w3d	laparoscope : salpingectomy	1,708	TP-i	+	4U	973	94	67	111	5.0	8.0
4	25	5w	laparoscope : chorion resection	500	PP	+	-	5,736	96	63	83	13.4	9.5
5	39	5w1d	laparotomy : partial resection	960	OP	+	-	2,056	104	45	78	11.2	7.5
6	27	NA	laparoscope : salpingectomy	500	TP-a	-	-	357	104	65	83	10.1	9.0
7	35	8w5d	laparoscope : salpingectomy	1,670	TP-i	+	-	27,408	90	63	95	6.1	6.4
8	33	NA	laparoscope : salpingectomy	1,330	TP-i	+	6U	3,018	67	35	113	5.0	7.6
9	30	11w	laparoscope : salpingectomy	2,800	TP-a	+	6U	38,133	78	43	120	5.1	8.2
10	41	9w	laparoscope : salpingectomy	635	TP-a	-	-	95,122	113	77	67	10.3	8.5
11	35	5w-6w	laparoscope : salpingectomy	1,980	TP-i	+	-	4,658	63	31	100	6.4	5.8
12	32	8w4d	laparoscope : salpingectomy	2,720	TP-i	+	6U	1,604	100	70	90	5.0	7.6
13	38	NA	laparoscope : salpingectomy	1,955	TP-a	-	-	3,692	118	65	70	6.0	5.8
14	23	5w2d	laparoscope : salpingectomy	500	TP-a	+	-	9,306	125	68	115	11.6	9.1
15	38	7w0d	laparoscope : salpingectomy	600	TP-a	-	-	329	112	64	105	11.5	10.3
16	30	5w6d	laparoscope: partial resection	750	OP	+	-	8,304	108	68	85	10.7	8.2
17	30	6w1d	laparoscope : salpingostomy	750	TP-a	-	-	1,342	90	56	52	11.3	8.7
18	28	NA	laparoscope : salpingectomy	1,625	TP-a	+	-	25,964	110	58	62	6.3	6.3
19	30	4w6d	laparoscope : salpingectomy	1,685	TP-a	-	-	15,564	98	77	112	7.1	5.8

SBP: Systolic blood pressure, DBP: Diastolic blood pressure, Hb: Hemoglobin (g/dL), D1: Postoperative day 1, NA: Not available, OP: Ovarian pregnancy, PP: Peritoneal pregnancy, TP-i: Pregnancy of isthmus, TP-a: Pregnancy of ampulla, CRC: Concentrated red blood cell transfusion

and EP was made according to the algorithm shown in Figure 1, using the s-hCG level (discriminatory or serial) as an indicator. Until recently, we have used 2000 IU/L as the discriminatory value for s-hCG, but recently, there have been reports recommending higher discriminatory values,<sup>[6]</sup> so we try to make a more accurate diagnosis by referring to these reports. In normal intrauterine pregnancies, GS can usually be confirmed by transvaginal ultrasonography if the s-hCG level is 1500–2000 IU/L or higher.<sup>[2,18]</sup> However, there are some cases in which GS cannot be confirmed even if the s-hCG level exceeds 2000 IU/L, even in normal pregnancies, so caution is required.<sup>[2,6,19]</sup> It may not be appropriate to easily initiate treatment with s-hCG  $\geq 2000$  IU/L without GS. Connolly *et al.* reported that in 366 normal pregnancies, GS was confirmed in 99% at 3510 IU/L.<sup>[6]</sup> Since the most important thing is to ensure that a normal early pregnancy is ruled out before beginning treatment, it is important to look at serial s-hCG levels for a more accurate diagnosis if the patient has no symptoms and is amenable to follow-up. Barnhart *et al.* reported the serial s-hCG levels in 287 cases (only those with initial s-hCG < 5000 IU/L) in which the possibility of EP could not be ruled out at the time of initial examination but were later diagnosed as normal pregnancies. The elevation rates of s-hCG (minimum, mean, and maximum) were 24%, 50%, and 81% at 1 day and 53%, 124%, and 328% at 2 days, respectively, indicating that normal pregnancy could likely be excluded in cases that did not meet these elevation rates (when the elevation rate was less than the minimum value).<sup>[20]</sup> It should also be noted that if the patient was in multiple pregnancy, GS may not be confirmed even at  $>2000$  IU/L, because s-hCG levels are higher in multiple

pregnancies than in singleton pregnancies.<sup>[21]</sup> S-hCG levels are useful in diagnosing PUL but are not a predictor of risk for tubal rupture or massive bleeding. There have been case reports of tubal rupture and hemorrhagic shock with negative pregnancy test and s-hCG levels below sensitivity,<sup>[3,22]</sup> so caution is required.

### The choice of surgical procedure, laparoscopic or laparotomy

Laparoscopic surgery is clearly less invasive than laparotomy and is the gold standard for the treatment of EP.<sup>[7]</sup> Although there is some debate as to whether laparoscopic surgery is indicated when the patient’s general condition has deteriorated due to massive bleeding, at our hospital, laparoscopic surgery is the first choice based on the descriptions in the Guidelines for Obstetrics and Gynecology Treatment (Obstetrics Edition 2020)<sup>[2]</sup> and Guidelines for Endoscopic Surgery in Obstetrics and Gynecology (2019 Edition).<sup>[7]</sup> Although the selection criteria for laparoscopic surgery may vary from institution to institution, important factors in the selection of laparoscopic surgery in such cases with massive blood loss include stabilization of vital signs before surgery, preparation for blood transfusion, preparation for conversion to laparotomy, intraoperative management by a skilled anesthesiologist, and surgery performed by a skilled surgeon with extensive experience in laparoscopy.<sup>[4,23]</sup> In cases where these conditions are not met, or in cases where laparoscopic surgery is expected to be difficult due to severe obesity or suspected severe adhesions, or in cases where the surgeon has difficulty performing laparoscopic surgery, the patient

should be performed by laparotomy or promptly converted to laparotomy, without being wedded to laparoscopic surgery. It is important to select an appropriate surgical technique that can complete hemostasis more quickly and safely, taking into consideration the facilities and the skills of anesthesiologists and surgeons at each facility.<sup>[3,4]</sup>

### Risk factors for tubal pregnancy

The main risk factors for EP are listed in some articles.<sup>[1,24]</sup> It is well known that a history of EP is the most important of these factors, and pelvic inflammatory disease and history of induced abortion also were reported to be the most important etiological factors.<sup>[14]</sup> In our study, the percentage of infertility cases and previous EP cases was about 10%, but the percentage of smokers was 40.6% if previous smokers were included, which was considerably higher than the smoking rate among women in general (20–39 years old) shown in Figure 3b. Gaskins *et al.* reported a 1.73-fold increase in EP occurrence in smokers in their examination of risk factors in 411 EP patients.<sup>[24]</sup> Our results reaffirm the importance of smoking as a risk factor for the occurrence of EP. It is speculated that factors that contribute to the development of TP include the following: inflammation in the fallopian tubes caused by sexually transmitted diseases (especially chlamydial infection) and smoking, which results in contraction of the fallopian tube smooth muscle and disruption of ciliary movement of the fallopian tube epithelium, thereby disrupting intrafallopian transport of fertilized eggs, and inflammation in the fallopian tubes and arrested embryos that promote the expression of various implantation inducing factors and change the environment in the fallopian tubes to be suitable for implantation.<sup>[24,25]</sup>

It is also well known that the risk of EP is increased in infertile patients, especially in pregnancies with ART,<sup>[16,17]</sup> but the incidence of EP with ART has been declining in recent years, and changes in ART techniques are a major factor in this trend. Nowadays, a single frozen-thawed blastocyst transfer has become mainstream, and changes in these techniques have led to improvements in ART success rates (pregnancy rates and live birth rates) and a decrease in EP incidence rates.<sup>[16,17]</sup>

### The association between risk factors for ectopic pregnancy and the evolution of the number of ectopic pregnancies

Figure 2b shows that despite the increasing trend in total gynecologic surgeries in the past 20 years, the percentage of EP surgeries in the past 10 years showed a significant downward trend compared to earlier years at our hospital.<sup>[3]</sup> Since the number of EP cases with medical treatment throughout this period is limited, it can be said that the overall number of EP occurrences is decreasing. The approximate number of EP surgeries in Fukushima City as a whole surveyed in the questionnaire also showed

a downward trend similar to that of our hospital.<sup>[3]</sup> Although there are no reports of large-scale surveys in Japan on the incidence of EP, a long-term survey in the United States from 2000 to 2008 in the three states of Illinois, California, and New York reported a downward trend in the incidence of EP, and the possibility that this is the effects of prevention of sexually transmitted diseases, antismoking education, etc., is discussed in the discussion.<sup>[15]</sup>

Nationally, the number of births has been declining in recent years [Figure 3d], and naturally, it can be assumed that the total number of pregnancies also declining, which is one reason for the decline in the number of EP occurrences. Epidemiological study results show that the number of chlamydia infections [Figure 3a] and smoking rates [Figure 3b], which are cited as EP risk factors, have both shown a downward trend in recent years, and furthermore, the incidence of EP in ART pregnancies has also shown a steady downward trend in recent years in Japan [Figure 3c]. It is speculated that increases or decreases in the incidence of EP will vary primarily with trends in the number of pregnancies and risk factors. In future, even if the above factors are maintained at low levels, there is a possibility that the EP incidence will shift toward an increasing trend due to the influence of other factors. In particular, a significant increase in EP incidence has been reported in patients with endometriosis, which has been on a marked increase in recent years,<sup>[26,27]</sup> and there is a concern that this could be a factor in future increase in EP.

### CONCLUSION

For an accurate diagnosis of EP, especially in PUL, it is important to set and evaluate discriminatory and serial values for s-hCG based on the latest evidence. The results of epidemiological surveys in Japan confirmed that many factors involved in the occurrence of EP, such as the number of births, the number of cases of chlamydia infection, smoking rates, and the incidence of EP in ART, are changing in the direction of decreasing the occurrence of EP. However, we will continue to pay attention to the trends of factors involved in the increase of EP occurrence, such as endometriosis and the aging of pregnancy; we will continue to focus on trends in factors involved in the increased incidence of EP, new factors involved in EP development, as well as the results of future epidemiological studies on the incidence of EP.

### Data availability statement

All data generated or analyzed during this study are included in this published article.

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Nil.

## Conflicts of interest

There are no conflicts of interest.

## REFERENCES

- American College of Obstetricians and Gynecologists' Committee on Practice Bulletins-Gynecology. ACOG practice bulletin no. 193: Tubal ectopic pregnancy. *Obstet Gynecol* 2018;131:e91-103.
- Kawaguchi R, Matsumoto K, Ishikawa T, Ishitani K, Okagaki R, Ogawa M, *et al.* Guideline for gynecological practice in Japan: Japan Society of Obstetrics and Gynecology and Japan Association of Obstetricians and Gynecologists 2020 edition. *J Obstet Gynaecol Res* 2021;47:5-25.
- Yazawa H, Hobo T, Yazawa R, Sasaki R, Okabe C, Ohara M. Surgical results and current status of managements for ectopic pregnancy: A single-center study. *Fukushima Med J* 2021;71:69-80.
- Yazawa H, Hobo T, Yazawa R, Okabe C, Ohara M. Surgical results and current status of managements for ectopic pregnancy in patients with massive hemoperitoneum: A single-center study. *Jpn J Gynecol Endosc* 2021;37:30-7.
- Yazawa H, Hobo T, Yazawa R, Saito T, Okabe C, Ohara M. Surgical results and current status of managements for ectopic pregnancy in unusual sites: A single-center study. *Jpn J Gynecol Endosc* 2021;37:21-9.
- Connolly A, Ryan DH, Stuebe AM, Wolfe HM. Reevaluation of discriminatory and threshold levels for serum  $\beta$ -hCG in early pregnancy. *Obstet Gynecol* 2013;121:65-70.
- JSGOE Guidelines for Endoscopic Surgery in Obstetrics and Gynecology 2019, Ectopic Pregnancy, p65-76. Japan Society of Gynecologic and Obstetric Endoscopy and Minimally Invasive Therapy.
- Ministry of Health, Labour and Welfare Website, Number of Sexually Transmitted Diseases Reported. Available from: <https://www.mhlw.go.jp/topics/2005/04/tp0411-1.html>. [Last accessed on 2023 Apr 01].
- Ministry of Health, Labour and Welfare Website, Adult Smoking Rates (Ministry of Health, Labour and Welfare National Health and Nutrition Survey). Available from: <https://www.health-net.or.jp/tobacco/product/pd100000.html>. [Last accessed on 2023 Apr 01].
- Japanese Society for Reproductive Medicine, Subcommittee on Registration and Surveillance, ART Online Registration, Databook. Available from: <https://plaza.umin.ac.jp/~jsog-art/>. [Last accessed on 2023 Apr 01].
- Fukushima City Official Website, Fukushima City Open Data. Available from: <https://www.city.fukushima.fukushima.jp/jouhouka-toukei/shise/tokejouho/jinnkoudoutai.html>. [Last accessed on 2023 Apr 01].
- Annual Vital Statistics 2019, Ministry of Health, Labour and Welfare. Available from: <https://www.mhlw.go.jp/toukei/saikon/hw/jinnkou/suikei19/>. [Last accessed on 2023 Apr 01].
- Yen CF, Lin YS, Lin SL. Interstitial pregnancy. *Gynecol Minim Invasive Ther* 2019;24:199.
- Verma ML, Singh U, Solanki V, Sachan R, Sankhwar PL. Spectrum of ectopic pregnancies at a tertiary care center of Northern India: A retrospective cross-sectional study. *Gynecol Minim Invasive Ther* 2022;11:36-40.
- Stulberg DB, Cain LR, Dahlquist I, Lauderdale DS. Ectopic pregnancy rates and racial disparities in the Medicaid population, 2004-2008. *Fertil Steril* 2014;102:1671-6.
- Cirillo F, Paladino I, Ronchetti C, Busnelli A, Morengi E, Grilli L, *et al.* Ectopic pregnancy risk factors in infertile patients: A 10-year single center experience. *Sci Rep* 2022;12:20473.
- Zeng MF, Li LM. Frozen blastocyst transfer reduces incidence of ectopic pregnancy compared with fresh blastocyst transfer: A meta-analysis. *Gynecol Endocrinol* 2019;35:93-9.
- Practice Committee of American Society for Reproductive Medicine. Medical treatment of ectopic pregnancy: A committee opinion. *Fertil Steril* 2013;100:638-44.
- Doubilet PM, Benson CB, Bourne T, Blaivas M, Society of Radiologists in Ultrasound Multispecialty Panel on Early First Trimester Diagnosis of Miscarriage and Exclusion of a Viable Intrauterine Pregnancy, Barnhart KT, *et al.* Diagnostic criteria for nonviable pregnancy early in the first trimester. *N Engl J Med* 2013;369:1443-51.
- Barnhart KT, Sammel MD, Rinaldo PF, Zhou L, Hummel AC, Guo W. Symptomatic patients with an early viable intrauterine pregnancy: HCG curves redefined. *Obstet Gynecol* 2004;104:50-5.
- Póvoa A, Xavier P, Matias A, Blickstein I. First trimester  $\beta$ -hCG and estradiol levels in singleton and twin pregnancies after assisted reproduction. *J Perinat Med* 2018;46:853-6.
- Miuzta K, Miyoshi J, Kuroda K, Idegami T, Tanaka Y, Matsuoka S, *et al.* A case of ruptured ectopic pregnancy involving a negative urinary pregnancy test result. *Jpn J Gynecol Obstet Endosc* 2018;34:123-7.
- Odejimi F, Sangrithi M, Olowu O. Operative laparoscopy as the mainstay method in management of hemodynamically unstable patients with ectopic pregnancy. *J Minim Invasive Gynecol* 2011;18:179-83.
- Gaskins AJ, Missmer SA, Rich-Edwards JW, Williams PL, Souter I, Chavarro JE. Demographic, lifestyle, and reproductive risk factors for ectopic pregnancy. *Fertil Steril* 2018;110:1328-37.
- Shaw JL, Dey SK, Critchley HO, Horne AW. Current knowledge of the aetiology of human tubal ectopic pregnancy. *Hum Reprod Update* 2010;16:432-44.
- Yong PJ, Matwani S, Brace C, Quaiattini A, Bedaiwy MA, Albert A, *et al.* Endometriosis and ectopic pregnancy: A meta-analysis. *J Minim Invasive Gynecol* 2020;27:352-61.e2.
- Farland LV, Prescott J, Sasamoto N, Tobias DK, Gaskins AJ, Stuart JJ, *et al.* Endometriosis and risk of adverse pregnancy outcomes. *Obstet Gynecol* 2019;134:527-36.