Primary Bilateral Tubal Pregnancy: A Case Report and Review of Literature*

Maria Reichenber C. Arcilla MD, Marietta S. Sapaula, MD, FPOGS, FPSRM;
Marites A. Barrientos MD, FPOGS, FPSRM and Ma. Asuncion A. Fernandez MD, FPOGS, FPSRM
Section of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, St Luke's Medical Center

Ectopic pregnancy is one of the leading causes of maternal morbidity and mortality worldwide, as seen in 9 to 13% and up to 30% of maternal deaths in developed and developing countries, respectively. Bilateral tubal pregnancy is an exceedingly rare condition with an even greater risk of rupture and hemorrhage than that of the unilateral type. This is a case of a 32 year-old G4P3 (4004) who presented with amenorrhea of 5 weeks, vaginal bleeding, and abdominal pain. The triad of symptoms, elevated serum β-HCG levels, along with a transvaginal ultrasound finding of a right adnexal mass led to the impression of a ruptured ectopic pregnancy, probably tubal. Patient underwent laparoscopy and intraoperative findings revealed bilateral tubal pregnancy for which bilateral salpingectomy was done. Oftentimes, as in this case, bilateral tubal pregnancy is diagnosed intraoperatively. However, it is possible, as seen in a review of cases, that a combination of history, symptoms, and clinical findings may point to a probable diagnosis which is imperative in treatment planning. Bilateral tubal pregnancy is rare, but due to a rise in pelvic inflammatory disease, its consequences, and the advent of assisted reproductive techniques, the risk for this condition increases with important clinical implications.

Key words: bilateral tubal pregnancy, ectopic pregnancy

Introduction

Normal blastocyst implantation occurs in the endometrial lining of the uterine cavity. One to two percent of implantation occurring elsewhere is considered ectopic. Over 98% of these implants in various segments of the fallopian tube, more commonly in the ampullary segment, with the remainder occurring in the cervix, ovary, and abdominal cavity.[1,2]

Ectopic pregnancy remains as one of the leading causes of maternal morbidity and occasional mortality due to risk of tubal rupture and hemorrhage. Annually, 11.5 cases per 1000 pregnancies are reported in the UK with 0.4 per 1000 tubal ectopic pregnancies leading to maternal death.[3] In the USA, the annual incidence of ectopic pregnancy is now nearly 2%.[4] Locally, the incidence of ectopic pregnancy is 75,000 cases per year based on nationwide statistics data of the Philippine Obstetrics and Gynecological Society.[5] Between 2005 and 2009, the cases of ectopic pregnancy increased from 13% to 17%. In a government hospital setting, the incidence has been reported at 1.3-1.5% per year compared to a private institution of 0.5% per year.[6,7] Based on the Department of

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Health's annual report of 2013 and 2015, the maternal mortality rate in the Philippines is 73.71 per 100,000 livebirths with a mortality rate of 0.1 per 1000 livebirths (10.4%) attributable to pregnancies with abortive outcomes, inclusive of ectopic pregnancies.[8,9]

Ciliary dysfunction leading to defective transport as a result of previous tubal surgery, a history of ectopic pregnancy, and assisted reproductive techniques have been implicated as the main etiopathogenesis of ectopic pregnancies.[1,10] Cigarette smoking and infections caused by Chlamydia trachomatis, for example, contribute to altered tubal microenvironment and smooth muscle contractility.[11] Six to sixteen percent of all pregnant patients presenting at the emergency room complaining of vaginal bleeding and/or abdominal pain have ectopic pregnancies. Without high index of suspicion, these cases lead to maternal morbidities and mortalities in the first trimester as seen in 9 to 13% and up to 30% of maternal deaths in developed and developing countries, respectively.[12]

Bilateral tubal pregnancy is a rare clinical entity with an incidence of 1 in 200,000 pregnancies.[13] A review of ectopic pregnancy case reports in the Philippines since 1976 yielded only one citation of a local occurrence of bilateral tubal pregnancy.[14] Experience with this condition is limited, therefore, the authors present a rare case of bilateral tubal pregnancy and its management. Cases reported since 2007 were also reviewed to stimulate a broader understanding of the pathogenesis of bilateral tubal pregnancy, in order to facilitate prompt diagnosis and timely intervention in instances confronted with this diagnostic and therapeutic challenge that is often associated with significant maternal morbidity.

The Case

A 32 year-old G4P3 (4004) nurse from Caloocan City, Metro Manila, was admitted on February 8, 2017 due to right lower quadrant pain. History started one week prior to admission when the patient noted vaginal bleeding, amounting to less than 1 pad per day, accompanied by an initially vague, non-radiating right lower quadrant pain. Due to increasing severity of pain, she consulted with her obstetrician.

Patient has no known co-morbidities and unremarkable family history. She had regular menses occurring every 30-32 days, lasting for 3 to 5 days, and amounting to 3 pads per day accompanied by episodes of dysmenorrhea. She had no history of oral contraceptive use and was not on any form of family planning at the time of consult. She delivered vaginally to a full term, live baby girl in 2013 and to a full term, live baby boy in 2015. Her third pregnancy was a spontaneous twin gestation delivered via primary low transverse cesarean section for a malpresented first of twin. She delivered to a term baby boy and girl with no growth discordancy. Bilateral tubal ligation was contemplated during her last pregnancy.

Upon consult, patient was ambulatory with a blood pressure of 110/70 mmHg, pulse rate of 75 beats per minute, respiratory rate of 20 breaths per minute, and temperature of 37.1°C. She had pink palpebral conjunctiva and no signs of pallor. The abdomen was soft with slight tenderness on deep palpation of the right lower quadrant. Speculum examination revealed brownish discharge in the vaginal vault and a bluish cervix with no active bleeding per os. On bimanual examination, the cervix was soft, long, closed with no cervical motion tenderness. The uterus was not enlarged. There was a palpable right adnexal mass, approximately 4cm x 4cm, movable and slightly tender. There were no masses nor tenderness on the left adnexa. A urine pregnancy test kit revealed positive results. Impression at the time was G4P3 (4004) to consider ectopic pregnancy, 5 weeks AOG. Complete blood count, blood typing with RH screening, routine coagulation profile, and serum β-HCG were requested. Results showed a serum β-HCG level of 9,382 mIU/mL, hemoglobin of 11.2 g/dL, and a normal coagulation profile. Transvaginal ultrasound revealed a normal-sized anteverted uterus with a slightly thickened endometrium, 0.69cm, with no intrauterine gestational sac. The right ovary was normal in size and echotexture with a 1.6cm x 1.0cm corpus luteum. The left ovary was likewise normal in size and echotexture. A 4.3cm x 3.0cm x 1.8cm

heterogenous mass with well-defined borders was noted medial to the right ovary. There was a slightly echogenic free fluid at the cul-de-sac that amounted to approximately 49.9mL (Figure I, A-I).

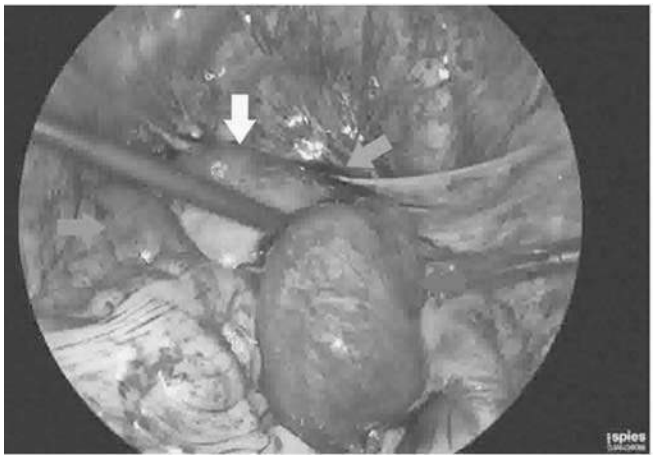


Figure I, A-I. On admission (February 8, 2017): A - Cervix 3.4cm 3.4cm x 2.5cm, intact canal, no lesion; B - Endometrium 0.69cm, hyperechoic, with fluid flow, no intrauterine gestational sac seen; C - Uterus 5.6cm x 5.1cm x 4.5cm, normal in size and anteverted with no myometrial lesion; D - Right Ovary 2.6cm x 1.6 x 1.9cm, normal in size and echotexture; E - corpus luteum, right ovary = 1.6cm x 1.1cm; F - Left Ovary 2.9cm x 2.4cm x 1.6cm, normal in size and echotexture; G, H - Medial to the right ovary is a 4.3cm x 3.0 cmx 1.8cm heterogenous mass with well-defined borders, could be tubal pregnancy; I - Cul-De-Sac: (+) slightly echogenic free fluid noted, most likely hemoperitoneum = 8.3cm x 4.3cm x 2.7cm, (vol. 49.9cc).

Admitting impression was G4P3 (4004) ectopic pregnancy, right, 5 weeks AOG, probably tubal, probably ruptured. After a thorough discussion of her clinical condition, patient was informed of treatment options that included salpingectomy of the pathologic tube versus bilateral salpingectomy for permanent tubal sterilization via either laparotomy or laparoscopy. Patient consented for laparoscopic bilateral salpingectomy.

Intraoperative findings revealed approximately 400 mL of hemoperitoneum. The uterus was normal in size, with smooth, pink serosal surface. The right fallopian tube was distended by ectopic products of conception, measuring 5cm x 3cm x 2cm at the dark brown, thinned-out ampullary segment down to the fimbrial end from which brownish, spongy tissues and blood clots were seen protruding. A 0.5cm point of rupture was noted at the antimesenteric border of the proximal portion of the dilated ampullary segment. The left fallopian tube was likewise distended to a violaceous 4cm x 3cm x 2cm portion of the ampullary area with no point of rupture. Both ovaries were grossly normal, as well as the liver surface, appendix, and the rest of the abdominal organs (Figures 2-4). Bilateral salpingectomy was done. Specimen was submitted for histopathologic examination. Postoperative diagnosis was G4P3 (4014) bilateral tubal pregnancy, 5 weeks AOG, ruptured right ampullary segment, unruptured left ampullary segment. Histopathologic examination confirmed the diagnosis (Figures 5-8). The postoperative course was uneventful and patient was discharged on the 2nd day post surgery.

Discussion

Definition

In 1959, Fishback first established the histologic criteria for diagnosis of bilateral tubal pregnancy and required the presence of fetuses or fetal parts and placental material in both tubes.

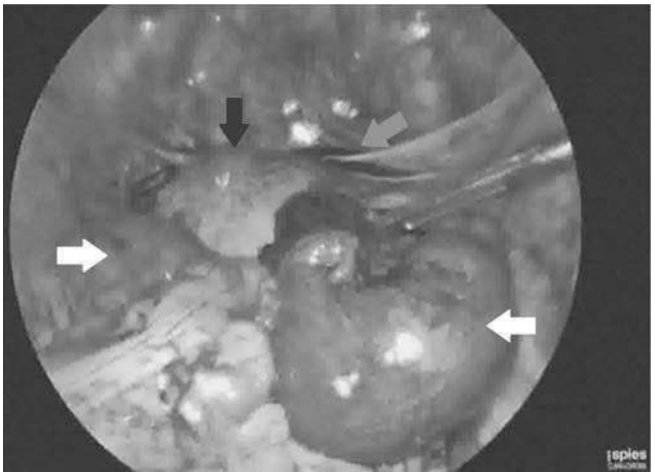


Figure 2. There was approximately 400cc of hemoperitoneum (gray arrow). The uterus was normal in size with smooth surface (black arrow). The left (arrow) and right (arrow) fallopian tubes were both distended by ectopic products of conception.

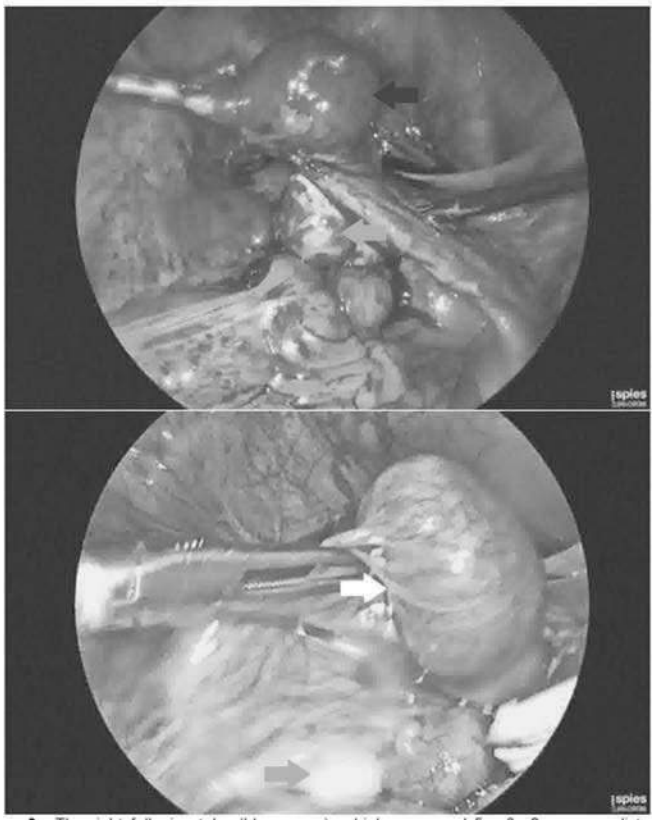


Figure 3. The right fallopian tube (black arrow), which measured 5cm x 3cm x 2cm, was distended and thinned out at the ampullary segment down to the fimbrial end. The left fallopian tube (white arrow) was likewise distended to a violaceous 4cm x 3cm x 2 cm portion of the ampullary area with no point of rupture. Both ovaries were grossly normal (gray arrow).

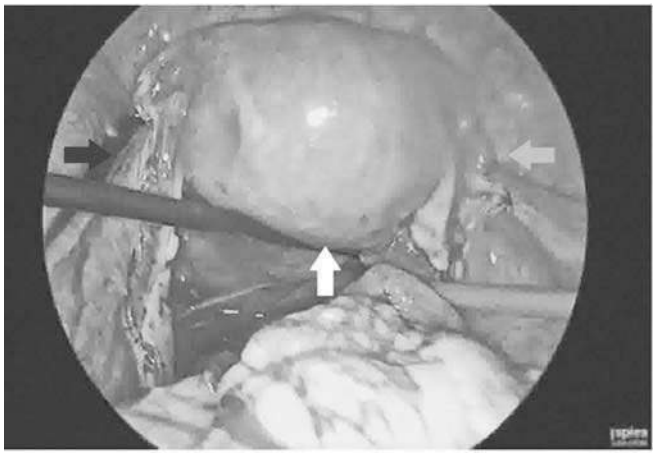


Figure 4. View of the uterus (white arrow) and left and right adnexa (black and gray arrow) after bilateral salpingo-oophorectomy.

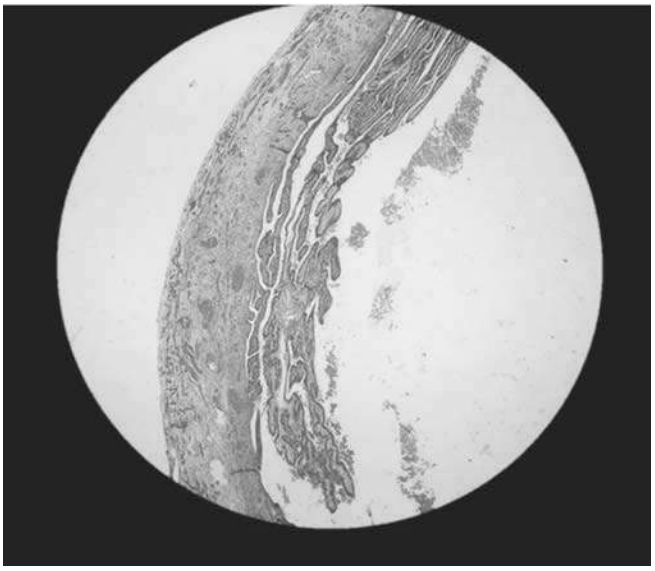


Figure 5. A scanning view of the ampullary portion of the right fallopian tube.

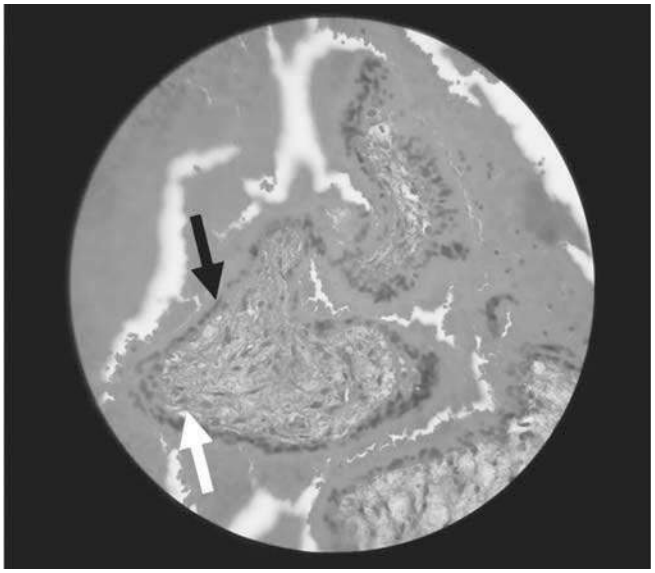


Figure 6. Under high power field, chorionic villi are found in the blood-filled and dilated lumen of the right fallopian tube. Syncytiotrophoblast (black arrow) and Cytotrophoblast (white arrow)

Norris later reported that microscopic identification of chorionic villi in each fallopian tube is sufficient for diagnosis.[15] In 2007, De Los Rios, et al. clinically defined primary bilateral ectopic pregnancy as a condition wherein at least 2

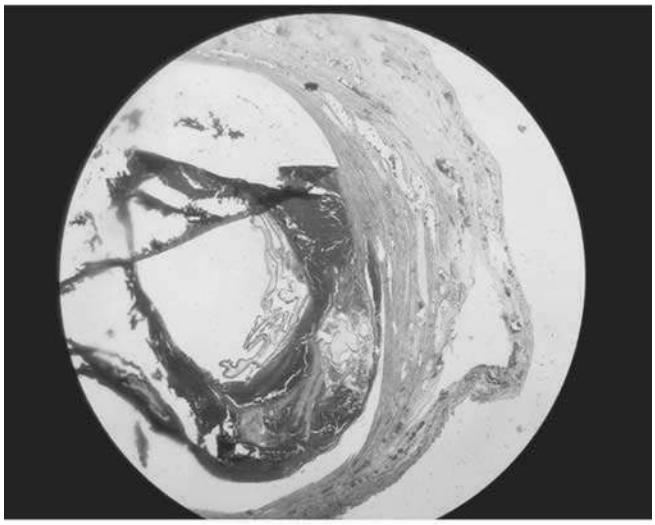


Figure 7. A scanning view of the ampullary portion of the left fallopian tube.

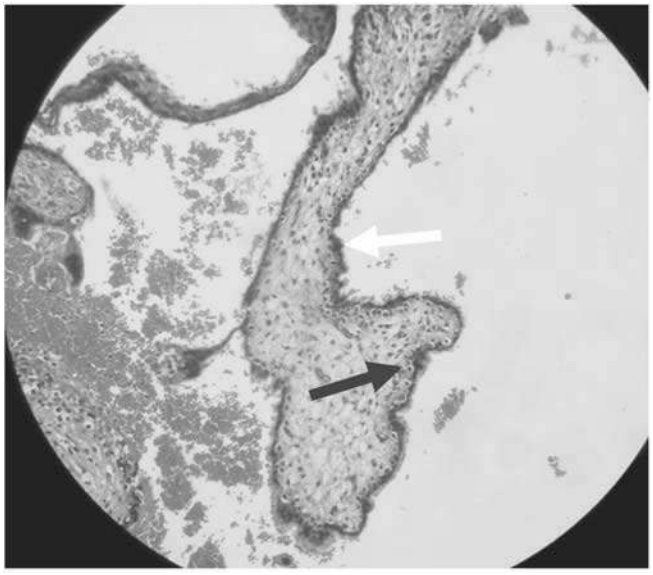


Figure 8. On higher magnification of a section of the left fallopian tube, shows intraluminal immature chorionic villi and extravillous trophoblast composed of syncytiotrophoblast (white arrow) and cytotrophoblast (black arrow).

concomitant spontaneous pregnancies are present in the same patient, each located on structures of the contralateral side, in the absence of an intrauterine pregnancy. Secondary bilateral ectopic pregnancy, on the other hand, is that condition occurring as formerly described as a result of ART. Only 43% of the reported cases of bilateral ectopic pregnancies are primary events.[13] The case described here is that of a primary bilateral ectopic pregnancy, an exceedingly rare type of extra-uterine pregnancy.

Incidence

Bilateral tubal pregnancy is one of the rarest forms of extra-uterine pregnancy, with an incidence of 1 in 725-1580 ectopic pregnancies.[16] The occurrence of heterotopic pregnancies - from 1 in 30,000 50 years ago to currently 1 in 3900 spontaneous pregnancies and 1.5 out of 1000 after ART - and twin pregnancies in the same fallopian tube, 1 in 200 ectopic pregnancies, are even thought to be more common.[17-20]

Collins was the first to describe a case of simultaneous bilateral tubal pregnancy in 1912 and since, more than 200 case reports have been published, with a third of the cases having been documented in the last decade alone.[21-23] This, however, is the first known case to have occurred in a natural cycle in a patient who previously spontaneously delivered to twins and is the second case reported locally.

Risk Factors

The risk for ectopic pregnancy increases as much as 10-fold in women with a previous ectopic pregnancy, three-fold for those with documented tubal pathology - salpingitis secondary to sexually-transmitted infections, two-fold for diethylstilbestrol (DES) exposure in utero, infertile women, those conceiving via ART, and smokers, and a mildly increased risk for those with history of early age intercourse. Sterilization failure and pregnancy occurring with IUD in-situ are also associated with ectopic pregnancy.[19] These same risk factors are implicated for cases of bilateral tubal pregnancy, however, were not present in this case.

Risk factors for primary bilateral ectopic pregnancy are the same as those for unilateral ectopic pregnancy. However, it is important to note there is a distinct pathophysiologic mechanism inherent to each of the two subgroups of bilateral ectopic pregnancy.[24] Hence, cases of secondary

bilateral pregnancy may occur in the presence of other risk factors. Several hypotheses have been described to explain the increased rates of ectopic pregnancy after ART. Authors have examined techniques of embryo transfer, the number and quality of embryos, pelvic and tubal conditions, hormonal milieu, and superfecundation. A deficient transfer technique, presence of endometrial secretions that could push the embryo regressively into the tubes, and the "spray and drift effect" as a result of excessive medium and improper catheter insertion leading to dispersion of embryos have been associated with increase tubal pregnancy rates. An ectopic pregnancy incidence of 9.4% versus 2.1% has been described when embryos are transferred with 20-50 microliters of medium versus 10-20 microliters. Risk of extra-uterine pregnancy is concluded to be greater when more embryos are transferred as evidenced by case reports describing bilateral ectopic pregnancies after IVF-ET involving transfer of more than 2 embryos. The smooth muscle relaxant effect of progesterone, ovulation induction with clomiphene citrate and GnRH agonist use in the IVF population have also been linked to higher rates of ectopic pregnancy.[13,25]

Pathophysiology

Several theories have been postulated to explain the pathophysiologic mechanism underlying the occurrence of bilateral tubal pregnancies. The three most commonly cited explanations for bilateral ectopic pregnancy are simultaneous multiple ovulation, sequential impregnation or superfetation, and transperitoneal migration of trophoblastic cells from one site of extra-uterine pregnancy to the contralateral site with implantation.[26]

First, multiple ovulations are thought to occur with subsequent fertilization and implantation at sites of tubal ciliary deficiency in bilateral tubal gestation. Secondly, consistent growth discordance in early twin gestations, as seen in published case reports, may suggest superfetation, an otherwise extremely rare event in humans and only thought to have known to occur in mares. An interval as long as or longer than a menstrual cycle intervenes between fertilizations in superfetation and maybe a plausible mechanism for bilateral tubal pregnancy. Thirdly, upon findings of fetal tissue in one tube and only villi in the other, Tabachnikoff, et al. stated that a possible etiology is transperitoneal migration of trophoblastic cells resulting in unequal growth of two gestations and abnormal or arrested development.[1,27,28]

Another explanation posed by Andrews, et al. is that a second tubal pregnancy as a result of a second ovulation may have occurred after spontaneous abortion of the first tubal gestation. Hormone levels - serum estradiol, progesterone, and serum β-HCG levels have been demonstrated to be lower in extra-uterine gestations compared to intrauterine pregnancies and may be insufficient to inhibit a subsequent ovulation, though there is limited evidence.[27]

In the background of a spontaneous dizygotic twinning in the patient in this case, a probable multiple ovulation may have again spontaneously occurred in a single natural cycle. Dizygotic twinning being much more common than monozygosity, 6 per 1000 versus 4 per 1000 births in Asia, is influenced by race, heredity, maternal age, parity, and fertility treatment.

The risk factor for twinning in this patient would be maternal age, risk of 4-fold between ages 15 and 37, and increasing parity.[1,29] Mothers of multiples also were found to have a 39% increased risk of conceiving another set of multiples.[30] However, it is difficult to discount the other theories that may explain spontaneous bilateral tubal gestation in this patient.

Clinical Presentation and Diagnosis

Review of cases indexed in Pubmed / Medline and other search engines using the keywords Bilateral Ectopic Pregnancy and Bilateral Tubal Pregnancy yielded 45 articles with full access and 9 abstracts published between 2007 and 2017, with exclusion of 3 titles with inadequate patient data (Table 1).[15,16,23-27,31-73] Fifty-three cases of bilateral tubal pregnancy in the past decade were studied and were found to have occurred in women between ages 22 to 40 years old, with

almost equal incidence in nulliparous (25) and multiparous (26) patients (with 2 reports lacking these data). Thirty-one of the cases (58%) occurred spontaneously, as in the case presented here. Similarly, according to a review of 42 cases of bilateral ectopic pregnancies reported between January 1997 and October 2006 by De Los Rios, et al., 50% of cases were primary and 45% of cases occurred after ART.[13] Zhu, et al. reviewed 16 cases of bilateral ectopic pregnancy between 2008 and 2012 and found half to have occurred spontaneously and 43% after ovulation induction. Bustos, et al. reported an incidence of 36% (14 of 38) for the primary cases between 1980-1997.[50] The increasing incidence of spontaneously occurring bilateral tubal pregnancies may be explained by increasing prevalence of pelvic inflammatory disease.

In the present review of cases, mean age of diagnosis for primary bilateral ectopic pregnancy was 7.5 weeks with an expected earlier age of gestation at diagnosis in the ART group - 6.6 weeks. This also concurs with previous studies describing mean age of diagnosis for primary cases at 7.5 weeks versus 6.7 weeks for secondary cases.[13] The higher index of suspicion and closer monitoring of serum β-HCG results in prompt diagnosis in cases following ART. In the case presented, early diagnosis is attributed to patient awareness and ease of access to medical care.

Patients with bilateral tubal pregnancies may present with non-specific symptoms, as in this case, and thus, appear similarly to those patients with the unilateral type, in theory though, the authors may conclude that there is a greater risk of rupture and hypovolemic shock in patients with bilateral ectopic pregnancies. Fourteen patients (26%) in this review presented with signs of acute abdomen and/or hemorrhagic instability, therefore facilitating diagnosis.

In other cases, and often times when ultrasound findings are equivocal and symptoms may point to

Table 1. Reported Cases of Bilateral Tubal Pregnancy from 2007 to 2017.

	Author & Year of publication	Age	OB score	Conception Method	AOG	vaginal bleeding	abdominal pain	β-HCG mIU/mL	Ultrasound finding	Intervention	Exact procedure
1	This case (2017)	32	G4P3 (4004)	Spontaneous	5	(+)	(+)	9382	unilateral	Laparoscopy	Bilateral salpingectomy
2	Funamizu et al (2017)	29	G1P0	Gonadotropins	7 2/7	(+)	(-)	33,000	unilateral	Laparoscopy	Bilateral salpingectomy
3	Abi et al (2016)	28	G1P0	Spontaneous	6	(+)	(+)	8240	unilateral	Laparoscopy	Bilateral salpingectomy
4	Calagna et al (2016)	34	G1P0	Spontaneous	8	(+)	(+)	4954	unilateral	Laparoscopy	Salpingectomy + Salpingostomy
5	Gerli et al (2016) readmission	32	G1P0	Clomiphene	5 8	(-) (-)	(+) (+)	4370 40,440	unilateral	Laparoscopic Laparoscopic	Right salpingectomy Left salpingotomy
6	Hoffman et al (2016)	39	G2P1	Spontaneous	8 4/7	(-)	(-)	6615	unilateral	Laparoscopy	Bilateral salpingotomy
7	Sheeba et al (2016)	28	G3P2 (2002)	Spontaneous	8	(+)	(+)	-	unilateral	Laparotomy	Bilateral salpingectomy
8	Jena et al (2016)	23	G2P1	Clomiphene + Gonadotropins IUI	7 5/7	(+)	(+)	9602	unilateral	Laparotomy	Bilateral salpingostomy
9	Sim et al (2016)	31	G1P0	Gonadotropins	5	(+)	(-) → (+)	4123	unilateral	MTX → Laparoscopy	Bilateral salpingectomy
10	Baghdadi et al (2016) readmission	32	G1P0	Agonist protocol ICSI-ET	4 5/7 6	(-)	(+) (+)	7722 3520	unilateral unilateral	Laparoscopy Laparoscopy	Left salpingectomy Right salpingectomy
11	Arab et al (2015)	30	G1P0	Clomiphene + Gonadotropins	9	(+)	(+)	19435	unilateral	Laparotomy	Bilateral salpingostomy
12	Kaur et al (2015)	30	G3P2 (2002)	Spontaneous	6	(+)	(+)	6887	unilateral	laparotomy	Bilateral salpingectomy
13	Ghomian et al (2015)	33	G1P0	Spontaneous	8	(+)	(+)	5700	unilateral	laparotomy	Left salpingectomy Right salpingostomy
14	Amine et al (2015)	33	G8P3	Spontaneous	9 2/7	(+)	(+)	positive	unilateral	laparotomy	Bilateral salpingectomy

	Author & Year of publication	Age	OB score	Conception Method	AOG	vaginal bleeding	abdominal pain	β-HCG mIU/mL	Ultrasound finding	Intervention	Exact procedure
15	Petersen et al (2015) readmission	---	G3P2	Spontaneous	--- + 3 wks	---	---	---	unilateral		Salpingectomy Salpingectomy
16	Buca et al (2015)	37	G1P0	ICSI-ET	5?	(-)	(-)	1916	Intrauterine + bilateral	Laparoscopy	Bilateral salpingectomy
17	Das et al (2015)	24	G1P0	Spontaneous	6	(+)	(+)	positive	unilateral	Laparotomy	Salpingostomy + Salpingectomy
18	Grechukhina et al (2015)	39	G4P2 (2012)	Spontaneous	4 2/7	+	+	1270	unilateral?	Laparoscopy → Laparotomy	Bilateral salpingostomy
19	Dasari et al (2015)	39	G4P3	IVF-ET	8 ?	-	+		bilateral	MTX + Mifepristone	
20	Algaithy et al (2015)	31	G5P2	Spontaneous	8		(+)	4000	unilateral	Laparotomy	Salpingectomy, Salpingostomy
21	Rakshit et al (2014)	28	G1P0	Spontaneous	6	(+)	(+)	positive	PUL	Laparotomy	Salpingectomy + Salpingostomy
22	Jamilian et al (2014)	25	G1P0	IUI	6	(+)	(+)	3605	PUL	Laparotomy	Salpingectomy + Salpingostomy
23	Nwali et al (2014)	37	G10P5 (5045)	Spontaneous	12	(+)	(+)	-	Not done	Laparotomy	Bilateral salpingectomy
24	Fukuda et al (2014)	32	G1P0	Clomiphene + Gonadotropin IUI	9	(+)	(+)	165,395	Intrauterine + unilateral	Laparoscopy	Salpingectomy + Salpingotomy
25	Zhu et al (2014) readmission	25	G1P0	COH-IUI	5 ? + 3 wks		(+)	1204 1049	unilateral	Laparoscopy MTX → Laparoscopy	Right salpingectomy Left salpingectomy
26	Li et al (2014) readmission	33	G2P0 (0010)	Spontaneous	6	(+)	(-)	13721	unilateral unilateral	Laparoscopy Laparoscopy	wedge resection + partial (isthmus) resection of the right tube Left salpingostomy Curettage
27	Polat et al (2014) a	37	G1P0	Agonist protocol ICSI-ET	6	(-)	(-)	1721	bilateral	MTX	
28	Polat et al (2014) b	35	G1P0	Agonist protocol ICSI-ET	6	(-)	(-)	6013	bilateral	Laparoscopy	Salpingotomy + Salpingectomy
29	Ghosh et al (2014) a	37	G3P1 (1011)	Spontaneous	6	(+)	(-)	2512	PUL	Laparoscopy	Left salpingectomy + MTX for right tube
30	Ghosh et al (2014) b	34	G1P0	IUI	5	(+)	(+)	9691	PUL	Laparoscopy	Bilateral salpingectomy
31	Seol et al (2014)	29	G1P0	Spontaneous	8	(-)	(-)	1886	bilateral	2 cycles MTX →Laparoscopy	Bilateral salpingostomy
32	Kelekci et al (2014)	33	G5P0 (0040)	Spontaneous	---	(+)	(+)	7001	bilateral	Laparoscopy	Bilateral salpingostomy
33	Moradan et al (2014)	33	G3P1	Spontaneous	6 6/7						
34	Kovachev et al (2013)		---	Antagonist Protocol ICSI-ET	6-7 ?		(+)	---	Hemoperi-toneum	Laparotomy	Bilateral salpingectomy
35	Othman et al (2013)	29	G2P0 (0010)	Spontaneous	7	(+)	(+)	7487	unilateral	MTX → Laparotomy	Salpingectomy + Salpingostomy
36	Ali et al (2013)	35	G7P5	Spontaneous	8	(+)	(+)	positive	unilateral	Laparotomy	Salpingectomy + Salpingostomy
37	Vyas et al (2013)	40	G4P2	Spontaneous	7	(-)	(+)		unilateral	Laparotomy	Bilateral salpingectomy
38	Mandal et al (2013)	32	G3P2	Spontaneous	8	(+)	(+)		Not done	Laparotomy	Bilateral salpingectomy
39	Pramanick et al (2013)	24	G2P1 (1001)	Spontaneous	6	(+)	(+)	-	Intrauterine + unilateral	Laparotomy	Salpingectomy + Fimbriectomy
40	Eze et al (2012) a	23	G1P0	Spontaneous	9 5/7	(+)	(+)			Laparotomy	Bilateral salpingotomy

	Author & Year of publication	Age	OB score	Conception Method	AOG	vaginal bleeding	abdominal pain	β-HCG mIU/mL	Ultrasound finding	Intervention	Exact procedure
41	Eze et al (2012) b	30	G4P3	Clomiphene	-	(+)	(+)		-	Laparotomy	Salpingectomy + Salpingotomy
42	Wali et al (2012)	23	G1P0	Spontaneous	8	(+)	(+)	1218→ 1041		MTX→ Laparotomy	Bilateral salpingectomy
43	Azzam et al (2012)	28	G1P0	ICSI-ET	5 ?			1840	PUL	Laparotomy	Bilateral salpingectomy
44	Pehlivanov et al (2012)	32	G1P0	Clomiphene IUI	6	+	+	18022	bilateral	Laparotomy	Bilateral salpingectomy D&C
45	Mbarki et al (2010)	33	G1P0	Spontaneous	8	(+)	(+)	7765	bilateral	laparoscopy	Salpingectomy + Salpingotomy
46	Jeong et al (2009)	34	G3P2	Clomiphene	8 1/7					Laparoscopy	Bilateral salpingectomy D&C
47	Sentilhes et al (2009)	33	G4P1	Spontaneous	7	(-)	(+)	3186	bilateral	laparoscopy	Bilateral salpingectomy
48	Martinez et al (2009)	31	---	Spontaneous	6	(+)	(-)		bilateral	laparoscopy	Bilateral salpingectomy
49	Issat et al (2009)	33	G2P1	IVF-ET	6	(+)	(+)	6327	bilateral	laparoscopy	Bilateral salpingectomy
50	Yu et al (2008)	25	G2P0	Clomiphene	---	(+)	(+)	17000	unilateral	laparoscopy	Bilateral salpingostomy
51	Greenberg (2008)	22	G1P0	---	---	(+)	(+)	200,000	unilateral	laparoscopy	Salpingectomy + Salpingostomy
52	Altinkaya et al (2008)	27	G1P0	Agonist protocol IVF-ET	7	(+)	(+)	3,091	bilateral	laparoscopy	Bilateral salpingostomy
53	Andrews et al (2008)	25	G3P0	Spontaneous	9 2/7	(+)	(+)	242	unilateral	laparoscopy	Bilateral salpingostomy
54	Al-Quraan et al (2007)	35	G7P5	Spontaneous	8	(+)	(+)	-	PUL	laparotomy	Salpingectomy + Salpingostomy

other conditions such as abortion, biochemical assessment becomes necessary in 8-31% of patients suspected of ectopic pregnancy.[12] But due to the wide range of serum β-HCG during normal gestation, there is difficulty in making a diagnosis of bilateral ectopic pregnancy based on the concentration of this hormone. Out of those who presented with hemodynamic stability, only 15% had serum β-HCG levels that did not correlate with the age of gestation, clinical, and ultrasound findings, hence leading to a probable diagnosis of ectopic pregnancy. The serum β-HCG level of the patient was also markedly elevated for age of gestation and did not concur with the ultrasound findings in terms of sonographic size and tubal contents. A correlation of serum β-HCG with other clinical findings could have raised suspicion of a bilateral ectopic pregnancy in this case.

Recent studies have focused on serum biomarkers to help aid the diagnostic process in cases of ectopic pregnancy, particularly in determining location or viability of early pregnancy, or in determining which case is best managed surgically, medically, or expectantly. These biomarkers have been classified as to markers of trophoblast function - hCG, hyperglycosylated hCG, activin A, pregnancy-associated plasma protein A, pregnancy-specific beta glycoprotein 1 (SP-1), human placental lactogen, A Disintegrin and Metalloprotease-12 (ADAM-12), placental mRNAs; markers of luteal function - progesterone, inhibin A; markers of angiogenesis - vascular endothelial growth factor (VEGF), placenta like growth factor (PlGF); markers of endometrial function - leukemia inhibitory factor (LIF), glycodelin, mucin-1 (MUC1), adrenomedullin; markers of inflammation and muscle damage; and markers of impaired tubal transport.[12] Though promising, most of these markers are still being developed for clinical use. The assays are not readily available, if not expensive. Perhaps, due to rarity of bilateral pregnancy, none of the studies reviewed mentioned the use of these biomarkers in aiding diagnosis apart from serum β-HCG.

The presence of ectopic pregnancy in the contralateral tube was not visualized by sonography in this case, as commonly seen in instances where a working diagnosis of a unilateral ectopic pregnancy has already been made. Preoperative diagnosis by transvaginal ultrasound was correct

in identifying bilaterality in only 19% (10 out of 53) of cases reviewed. This low predictive value of transvaginal ultrasound in diagnosing bilateral ectopic pregnancies was also seen in reviews by De Los Rios et al and Zhu, et al. with only 2 out of 42 cases and 6 out of 16 cases accurately diagnosed, respectively.[13,50] Sonographic visualization of a unilateral ectopic pregnancy often leads to complacency in assessing the contralateral tube, therefore resulting in misdiagnosis. Aside from a thorough examination, Sentilhes et al and other authors have suggested to base a diagnosis of bilateral tubal pregnancy on the presence of live embryos in both tubes or the visualization of adnexal masses at the least, instead of merely confirming the absence of an intra-uterine gestational sac.[68]

Intraoperative Findings

In the majority of cases of bilateral ectopic pregnancy, diagnosis is made intraoperatively.[23] Thorough surgical exploration with meticulous inspection of both adnexae helps prevent maternal morbidity. In the case presented, immediate assessment was focused on the side of pathology as suggested by preoperative transvaginal ultrasound. A systematic approach and vigilance to execute a thorough pelvoabdominal inspection enabled recognition of the presence of ectopic pregnancy on the contralateral side. This is in contrast to that reported by Petersen, et al. wherein the presence of adhesions from a previous cesarean section hindered the surgeon to fully determine with certainty the presence of a healthy contralateral tube. Li, et al. reported a case wherein the slightly inflamed appearance of the contralateral tube was dismissed in the background of a previous tubal pregnancy. Both patients were subsequently readmitted for a repeat surgery.[40,51] Unequal development of the tubal gestations could have also contributed to delayed diagnosis, thus, surveillance is warranted in cases wherein intraoperative findings are suspicious and conservative management is employed.

In 60% of the cases reviewed, there was ampullary involvement, as seen in the present case. There was one case of interstitial involvement reported by Li, et al. and one case of bilateral isthmic pregnancy reported by Pehlivanov, et al.[51,65] Tubal rupture in at least one of the tubes were confirmed in 36% of the cases. Due to earlier diagnosis, there are fewer cases of secondary bilateral tubal pregnancies presenting with tubal rupture compared to the primary bilateral tubal pregnancies (7.5% vs. 26%). A greater proportion of tubal rupture was also seen in the primary cases cited in the study by De Los Rios, et al.[13]

Management

The aforestated data highlights the importance of a combination of patient history, symptoms, clinical findings, serum β-HCG, and sonography in diagnosing bilateral tubal pregnancies.[50] However, despite a thorough preoperative assessment, cases of bilateral tubal pregnancies are more often diagnosed intraoperatively, thereby, subsequently posing a management dilemma. The patient presented here was no longer desirous of future childbearing and had contemplated tubal sterilization in the past. The decision to do bilateral salpingectomy was an easy one in this case. But in instances where fertility is to be preserved, several factors have to be taken into consideration in order to define the best management option.

In cases where diagnosis is definite, patient is stable, and future fertility is to be preserved, medical management of bilateral tubal pregnancy may be an option.[48] Early diagnosis permits medical management using methotrexate, with 14% requiring multiple doses and another 10% ultimately requiring surgery.[44] Polat, et al. reported a case of a 37 year-old nullipara who underwent an ICSI-ET cycle with transfer of 2 embryos and sonographically diagnosed at 6 weeks with bilateral empty extrauterine sacs. Serum β-HCG was 1721 mIU/mL at time of diagnosis. A single dose of methotrexate 50mg/m^2 was administered intramuscularly and β-HCG levels progressively decreased over the course of 3 weeks. Patient conceived after third ICSI-ET attempt and had an unremarkable pregnancy.[52] Dasari, et al. reported another successful medical management of

bilateral tubal pregnancy, a triplet ectopic with 2 gestational sacs on one side and another on the contralateral tube as seen on ultrasound. Patient was on a multi-dose protocol of methotrexate 50mg/m^2 and was also given a total of 3 doses of mifepristone 200mg/tab during the course of treatment.[44] Ghosh, et al. reported successful use of 2 cycles of single-dose methotrexate and 2 doses of mifepristone for conservative treatment of the contralateral tube diagnosed at time of laparoscopic left salpingectomy.[53]

Use of methotrexate for the management of bilateral tubal pregnancy was also reported in 6 other cases in this review. Sim, et al. reported a case of incorrectly diagnosed unilateral ectopic pregnancy managed with methotrexate, but which eventually required surgery for acute abdomen.[37] Seol, et al. reported a case of primary bilateral tubal pregnancy with β-HCG of 1886 mIU/mL, and 3cm bilateral adnexal masses, with persistently elevated β-HCG despite 2 cycles of methotrexate.[54] Wali, et al. reported a similar case of failed medical management of bilateral tubal pregnancy that underwent bilateral salpingectomy.[63] The remaining 3 cases employed use of methotrexate as prophylaxis for persistent tubal pregnancy after salpingostomy.

In select cases wherein diagnosis of bilateral tubal pregnancy is assured, medical management may be an option for conservative treatment of patients desirous of pregnancy. Pregnancy rate has been reported at 80% after 1 year with live birth rate of 30%.[44] At the time of reviews done by De Los Rios, et al. and Zhu, et al. there were no published cases of successful medical management of bilateral tubal pregnancies. But despite recent reports, because of a greater risk of tubal rupture and maternal morbidity, proper case selection and monitoring of patients is extremely warranted, as medical treatment of this condition is not yet clear.[13,50]

When management entails surgery, a radical or a conservative approach via a minimally invasive procedure or a laparotomy may be considered.[48] When available, laparoscopy is employed as a diagnostic and therapeutic tool. Laparoscopy was the therapeutic modality of choice for the patient in this case, as was also seen in a majority of patients in the review (27 cases). Li, et al. proposed that the most proper and safest way to deal with bilateral tubal pregnancy may be laparoscopic salpingostomy, with salpingectomy as an option for intractable bleeding or damaged tubes.

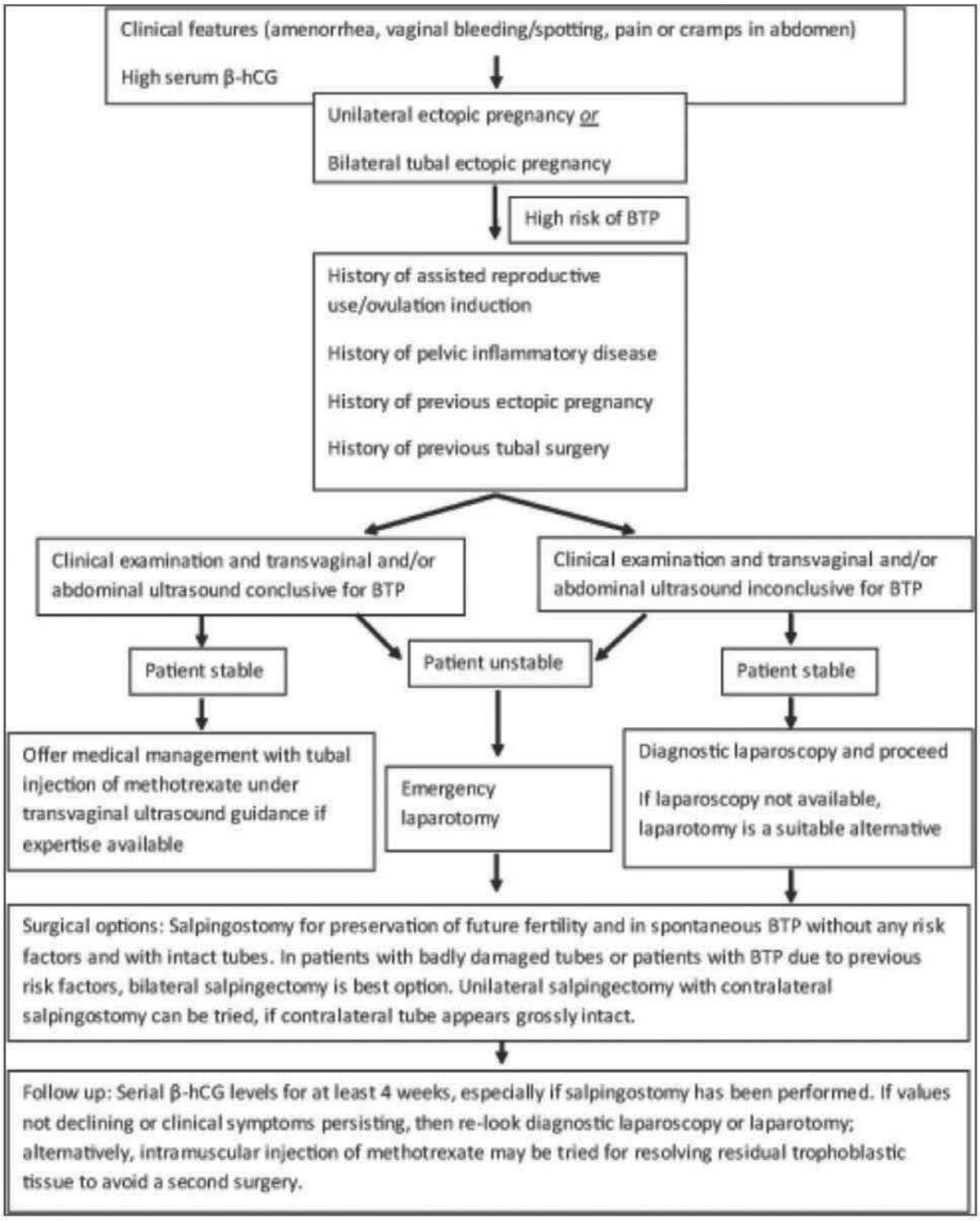
For secondary bilateral tubal pregnancy, removal of both tubes was suggested.[51] In the absence of management guidelines, Jena et al proposed a systematic approach to a patient with possible bilateral tubal pregnancy (See Appendix).[36]

Conclusion

Prompt diagnosis and timely intervention are of paramount significance in preventing maternal morbidity and mortality in patients with ectopic pregnancy. Though an exceedingly rare condition, diagnosis and management have an even greater clinical implication in patients with bilateral tubal pregnancy. As seen in the case presented, serum β-HCG may sometimes provide clues to diagnosis. Sonographic visualization of a unilateral ectopic pregnancy should also not prevent a complete assessment of the contralateral structures. A high index of suspicion and, when possible, arrival at a correct diagnosis, facilitates a full discussion of management options with the patient. Maternal morbidity can be prevented with thorough surgical exploration and inspection of both tubes as was done in the case. When intraoperative findings are equivocal for a contralateral ectopic pregnancy, close surveillance is warranted to assure patient safety.

With proper patient selection, a medical approach may also be an option for conservative treatment of bilateral tubal pregnancy in patients desirous of fertility preservation. The case presented and the review of literature offers a guide for case recognition and provides a management algorithm. Further studies and research are needed to set the recommendations for the optimum medical management protocol of bilateral tubal pregnancy, a rare condition of increasing incidence.

Appendix. Algorithm for management of bilateral tubal pregnancy[36]



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