

# Bilateral ectopic pregnancy

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**Abstract.** Bilateral simultaneous ectopic pregnancy is a very rare clinical condition. Two different subsets of patients can be distinguished: women presenting with the disease as a result of spontaneous conception and those with the condition after undergoing assisted reproduction procedures. This article reviews and analyzes 42 cases of bilateral ectopic pregnancies reported in the last 10 years, proposes a new classification of the disease, and presents some data that should be useful for the clinician who confronts this difficult entity.

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The implantation of a trophoblast outside the endometrial cavity occurs in 1.5% to 2% of all pregnancies. In more than 90%, this occurs in the fallopian tubes, and 8 of every 10 tubal pregnancies are located in the ampullar region.<sup>1</sup>

According to most reports coming from developed countries, the incidence of ectopic pregnancies has grown in the last 30 years.<sup>2</sup> Some clearly recognizable facts account for this growth, such as the increase in the incidence of sexually transmitted diseases, the increases in tubal surgery in developed countries, and the more frequent use of ovulation inductors and assisted reproduction technologies (ART). Its impact on maternal death is still considerable, representing almost 10% of the deaths that follow all pregnancy-related complications in developed countries.<sup>3</sup>

However, bilateral tubal ectopic pregnancy is a rare clinical entity.<sup>4</sup> The reported instance is 1 in 200 000 pregnancies.<sup>5</sup>

Since 1918, more than 200 cases of simultaneous bilateral ectopic pregnancies have been reported,<sup>6</sup> 38 of which took place between 1980 and 1997. The last review of the

literature on this subject was published by Bustos et al<sup>7</sup> in 1998. Somewhat more than half of those cases were the result of ART, including ovulation induction,<sup>8</sup> intrauterine insemination,<sup>9</sup> in vitro fertilization and embryo transfer (IVF-ET),<sup>10,11</sup> transfer of gametes to the fallopian tubes,<sup>12</sup> and intracytoplasmic sperm injections (ICSI).<sup>13</sup>

Besides describing the first case of spontaneous bilateral ectopic pregnancy in Colombia and its management by means of bilateral laparoscopic salpingostomy,<sup>14</sup> the purposes of this study are to review the cases of bilateral ectopic pregnancies reported since 1997, to propose an etiologic classification of the entity, and to present some information from case analyses that might enable the clinician to confront with greater security this entity, so difficult to diagnose and treat.

## Incidence and classification

Regarding the incidence of spontaneous bilateral ectopic, all articles reviewed state that it oscillates between 1/725 and 1/1580 of the ectopic pregnancies. This information is based on reports written in 1948 to 1950 and has been used since then as reference by the authors of all latter articles, without submitting the data to either scrutiny or review.<sup>5,15,16</sup> As is common in medicine regarding all dis-

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eases, there is a considerable amount of unrecorded data that have impeded a true calculation of the actual rate of incidence of the entity. In our country, the record of diseases does not function adequately, which makes it impossible to obtain reliable data regarding the occurrence of this disease. Nevertheless, we know the history of the Clínica del Prado, and we are certain that this is the second case of bilateral ectopic pregnancy that has occurred during the past 20 years of our institution. To date of writing this article, 60 983 deliveries have been completed. In our country, the rate of ectopic pregnancy is similar to that of the rest of Latin America, about 1.5% of all pregnancies.<sup>17</sup> With these data, an incidence of spontaneous bilateral ectopic pregnancy could be estimated as 1:914 ectopic pregnancies.

In most of the articles reviewed, it is stated that bilateral ectopic pregnancies are probably the result of the use of ART. However, after an exhaustive quest in Medline, Embase, PubMed and SciELO (Latin-American database), as well as in different Internet search engines, we found 42 cases of bilateral ectopic pregnancy published in medical literature since 1997, 21 of which (50%) reported spontaneous bilateral ectopic pregnancies.<sup>7,14,18-35</sup> In 19 cases (45%), the bilateral ectopic pregnancy was the result of ART that involved ovarian stimulation,<sup>7-9,11,13,36-49</sup> and in 2 cases (5%), the authors do not explain the origin of the condition.<sup>50,51</sup> Therefore, although logic would seem to suggest that the occurrence of this disease probably does increase with hormonal manipulation and induced superovulation during ART, evidence found in cases of the last 10 years shows a different reality, which, although possibly not exact because of incomplete records, does at least lead to doubting the categorical observation made by some authors. Bustos's 1998 review<sup>7</sup> shows that of the 38 cases of bilateral ectopic pregnancy published between 1980 and 1997, 14 (36%) were spontaneous. Taking into account all the cases reported since 1980, we might conclude that in the last 26 years, 43% of the reported bilateral ectopic pregnancies have been spontaneous.

Ectopic pregnancies produced during a woman's natural cycle and those that place as a result of assisted reproduction hormonal manipulation should be studied separately because of the fact that physiopathologic mechanisms clearly circumscribe 2 different entities. This is also applicable in the case of bilateral ectopic pregnancy.

Theories regarding the genesis of spontaneous ectopic pregnancy are well known, such as damage to the endosalpinx produced by sexually transmitted infections, distortion of pelvic anatomy caused by diseases like endometriosis or by adhesions after previous interventions as appendectomy, surgery performed in the fallopian tubes, müllerian malformations, hormone concentration imbalance during the menstrual cycle, late ovulations, tubal transmigration of the fertilized ovum, history of previous ectopic pregnancy in one of the tubes and its sequelae, etc. Obviously, to produce a spontaneous bilateral ectopic pregnancy, in addition to any of the factors previously mentioned, a double sponta-

neous ovulation should also take place, a circumstance that is quite infrequent in human beings.

On the other hand, in cases of bilateral ectopic pregnancies related to ART, the occurrence of multiple ovulations is common and predictable and, indeed, is part of the treatment to which the woman was submitted. Although cases of ovulation induction or intrauterine insemination have many intervening factors that share physiopathology with those of spontaneous bilateral ectopic pregnancies, in advanced procedures such as in vitro fertilization, intracytoplasmic sperm injection or transfer of gametes or embryos to the tubes, other theories might explain the appearance of bilateral ectopic pregnancies. Therefore, for the sake of analysis, we have decided to separately assess the results of spontaneous bilateral ectopic pregnancies and those that are the result of ART; additionally a terminology and classification are proposed that will make it possible in the future to independently improve the study of both conditions.

## Primary bilateral ectopic pregnancy

### Definition

Primary bilateral ectopic pregnancy is a condition in which there are at least 2 concomitant spontaneous pregnancies in the same patient, none of which are intrauterine, with both being located in structures of the opposite side. The first case of primary bilateral ectopic pregnancy described was published by Bledsoe in 1918.<sup>52</sup> The first one described in Latin America was reported in Mexico in 1993.<sup>53</sup>

### Diagnostic criteria

To substantiate the anatomic-pathologic diagnosis of bilateral ectopic pregnancy, in 1939 Fishback<sup>54</sup> proposed that 2 embryos should be observed in any portion of the tubes, accompanied by chorionic tissue. Fourteen years later Norris<sup>55</sup> argued that the aforementioned diagnosis could be reached just by finding chorionic villi in surgical specimens obtained from both tubes.

### Diagnosis

Of the 42 bilateral ectopic pregnancies reported between January 1997 and October 2006, 21 (50%) were primary.<sup>7,14,18-36</sup> In 10 of the cases,  $\beta$ -human chorionic gonadotropin ( $\beta$ -hCG) values were reported at the moment of the presumptive diagnosis of ectopic pregnancy (range 539–113 102 mIU/mL).<sup>7,14,20,21,25,26,30,31,33,35</sup> The gestational age at the moment of diagnosis was reported in 17 cases, with an average of 7.5 weeks since the last menstruation (range 5–13 weeks).<sup>7,14,21-23,25-35</sup>

**Table 1** Correlation between the concentration of  $\beta$ -hCG at the moment of diagnosis and gestational weeks, considered from last menstruation in patients with primary bilateral ectopic pregnancy 1997–2006

Author and year of publication	Concentration of $\beta$ -hCG in mIU/mL	Gestational weeks
Bustos et al <sup>7</sup>	2.000	5
Rondeau et al <sup>21</sup>	6.398	7
Sommer et al <sup>25</sup>	1.800	6
Ardevino et al <sup>26</sup>	25.217	6
Ryan, Saldana <sup>35</sup>	14.939	6
Walter, Buckett <sup>30</sup>	44.253	8
Nikolic et al <sup>31</sup>	113.102	8
Marpeau et al <sup>33</sup>	69.725	6
De Los Rios et al <sup>14</sup>	15.445	7

$\beta$ -hCG =  $\beta$ -human chorionic gonadotropin.

In 9 cases, it was possible to establish a correlation between  $\beta$ -hCG values and the gestational age measured in weeks, beginning with the date of the last menstruation<sup>7,14,21,25,26,30,31,33,35</sup>; it was found that only in 1 of the cases  $\beta$ -hCG values were higher than those considered normal for the gestational age.<sup>33</sup> In the 8 remaining cases, the values of the hormone subfraction lay within the ranges recognized for the corresponding gestational ages.

The well-known ample range of the hormone during normal gestation makes it difficult to recognize a bilateral ectopic pregnancy only on the basis of the concentration of the beta portion of gonadotropin. In the review made, only 1 (12.5%) of the 9 values found and correlated with gestational age was abnormally high, although all the other cases showed the presence of trophoblast tissue in both tubes, which would lead to considering that the concentrations should at least approach the higher range of what was to be expected per gestational week, something that did not happen, as can be seen in Table 1. None of the 21 cases reported was correctly diagnosed by ultrasound scanning.

Ultrasound findings were described in 12 cases.<sup>7,14,20–22,25–27,30,31,33,35</sup> Four of them correctly diagnosed at least 1 ectopic pregnancy.<sup>7,30,31,33</sup> In 1 of the cases,<sup>21</sup> the ultrasound was absolutely normal; in 6 other cases, the ultrasound specialist reported adnexal masses<sup>20,22,25–27,35</sup>; and in 1 publication, a pseudo sac was described.<sup>14</sup> Besides, in the case of Nikolic et al,<sup>31</sup> a viable intrauterine pregnancy was reported, culminating in vaginal delivery at 39 weeks.

None of the 21 patients was correctly diagnosed before surgery. This reflects the great difficulty in diagnosing such a condition, in which the level of  $\beta$ -hCG was not useful, given its ample range of normality, nor did transvaginal ultrasound scanning lead to determining the bilateral character in any of the cases; on the contrary, in 66%, the diagnosis of ectopic pregnancy failed to be conclusive, suspected because of indirect signs and chorionic gonadotropin values above the discriminatory zone in patients with an empty uterus.

## Clinical findings

The clinical findings of primary bilateral ectopic pregnancy do not differ very much in its symptoms from that of unilateral ectopic pregnancy. However, it may be there is a greater risk of rupture and hemorrhagic shock in this case, because both tubes are in danger of presenting the complications mentioned. When reviewing the reported cases, we found, of the 18 cases being analyzed for this matter, 9 (50%) were diagnosed from a lack of correlation between ultrasound findings and  $\beta$ -hCG levels and were symptom free or were due to the presence of some minor clinical signs such as vaginal bleeding or mild abdominal pain.<sup>7,14,22,25–27,30,34</sup> On the other hand, 9 (50%) of the patients arrived with a clinical picture of acute abdomen or hypovolemic shock.<sup>20,21,23,28,29,31–33,35</sup>

## Intraoperative findings

Regarding the location of ectopic pregnancies, of the 21 cases reported information was obtained on 19 patients,<sup>7,14,18–35</sup> that is, on 38 ectopic pregnancies. Of these, 31 (73%) were ampullar, of which 10 (32%) were ruptured, and 21 (68%) ruptured. Three (7%) of the total number of ectopic pregnancies were isthmic, and unruptured. One (2%) ectopic pregnancy was cornual and ruptured. Three (7%) of the ectopic pregnancies were fimbrial, and the 3 were ruptured at the moment of diagnosis. Of the 17 cases reporting the condition of the tube, it was found 5 patients (29%) had a rupture of 1 of the ectopic pregnancies at the moment of presentation,<sup>20,21,23,29,32</sup> and 5 (29%) had a bilateral rupture.<sup>27,28,31,33,35</sup> One case of ampullar bilateral ectopic with ruptured tubes was found in an HIV-positive patient with previous tubal ligation.<sup>28</sup> In 7 patients (41%), there were no ruptures.<sup>7,14,22,24–26,30</sup>

## Treatment

For treating a primary bilateral tubal ectopic pregnancy, when it comes to choosing a therapeutic modality, the same considerations must be taken into account as when the ectopic pregnancy is unilateral. However, medical treatment of this disease does not yet seem clear. In only 1 case reported, methotrexate was used with the usual doses for handling unilateral ectopic pregnancies, although a therapeutic failure. Four days after the drug was given, the patient presented a rupture of 1 of the tubal pregnancies. It must be noticed that in this case, when the medication was prescribed, the presence of bilateral ectopic pregnancy was unnoticed, because this condition became apparent only during the emergency laparotomy the patient required after the rupture. Under different conditions, if previous bilateralism is suspected, the authors would probably have varied the dose of the medication, as they themselves explain in their article.<sup>20</sup> At the time of this review, there was no published proof of therapeutic success of treating primary bilateral ectopic pregnancy with methotrexate.

All cases described required surgical management. Of the 19 analyzable cases, 12 (63%) were treated with laparoscopy,<sup>7,14,22–26,30,31,33,34</sup> and 7 (37%) required laparotomy.<sup>20,21,27–29,32,35</sup>

Although in most of the articles no specific reason was given for using radical or conservative surgery and none of them expressed the patient's desire for future fertility, it seems implicit that the latter was present when, at least on one of the tubes, conservative surgery was practiced. Of the 12 cases operated through laparoscopy, bilateral salpingostomy was performed in 5 (42%),<sup>7,14,22,24,25</sup> bilateral salpingectomy in 4 (33%),<sup>23,30,31,33</sup> and in 3 cases (25%), salpingectomy was done on a damaged tube, whereas salpingostomy was practiced on the contralateral one.<sup>26,34</sup>

In the cases of laparotomy, a combination of salpingostomy and salpingectomy was practiced in 3 patients (43%),<sup>20,29,32</sup> bilateral salpingectomy in 3 cases (43%),<sup>27,28,35</sup> and 1 patient required salpingostomy on one side and cornual resection in the other because of the rupture of the pregnancy located in this place.<sup>21</sup>

## Reproductive prognosis

When salpingostomy is performed, it is expected by preserving the tube the patient should have a new spontaneous and, it is hoped, intrauterine pregnancy. This is the main expected advantage of such a procedure, as proven by studies of laparoscopic salpingostomy in patients with only 1 tube, with rates of postsurgical intrauterine pregnancy oscillating between 47% and 60% and rates of recurrent ectopic going from 12% to 42% in different reports.<sup>56–59</sup>

However, none of the 21 articles on primary bilateral ectopic pregnancies describes pregnancies subsequent to the surgery in any of the 13 unilateral or bilateral salpingostomies by laparoscopy or laparotomy practiced on the 18 patients analyzed. It would be very helpful if the authors would review these cases and report on the obstetric outcome after surgery. This would provide information regarding the advantages and disadvantages of one technique over another and might be especially important in the case of the 5 patients whose disease was treated through bilateral salpingostomy.<sup>7,14,22,24,25</sup>

Only 2 studies report bilateral tubal patency after laparoscopic bilateral salpingostomy.<sup>7,14</sup> It is important to emphasize that there are also no reports on the recurrence of ectopic pregnancies in tubes undergoing conservative surgery for primary bilateral ectopic pregnancy.

## Conclusions

$\beta$ -hCG levels do not lead to a diagnosis of primary bilateral ectopic pregnancy; however, this entity should always be kept in mind in patients with concentrations of the subfraction of the hormone with levels above those established for a determined gestational age.

Although in the cases studied transvaginal ultrasonography did not make the correct diagnosis in any of the patients, 90% of them did have some pathologic finding that guided the clinician in decision making. This is also true in cases of unilateral ectopic pregnancies, in which studies like those of Mahoney et al<sup>60</sup> reported that, in a series of confirmed cases of ectopic pregnancies, 20% showed apparently normal adnexa in transvaginal ultrasound scanning. It must also be remembered that ultrasound scanning is an operator-dependent examination.

Because there was no case in which an accurate preoperative diagnosis was obtained, it can be said that laparoscopy is the gold standard for diagnosing primary bilateral ectopic pregnancy. Therefore an adequate evaluation of both tubes during surgery becomes mandatory because there have been cases described in which the second ectopic pregnancy is diagnosed days or weeks after laparoscopic treatment of the first one.<sup>35,61</sup>

As happens in unilateral ectopic pregnancies, the most frequent location is the tubal ampulla (73%). In primary bilateral ectopic pregnancies there is a high risk of rupture and hemodynamic consequences deriving from it (50%). Bilateral rupture was observed in up to 23% of the cases. There is no report of successful treatment with methotrexate or other substances for this disease; therefore there is no known dose nor any percentage of success that should be explained to patients before any medication is given for therapeutic purposes.

Laparoscopy is not only the ideal diagnostic method but also the preferred way for treatment, under the condition that it is permitted by the patient's status, the hospital facilities, and the surgeon's training. Neither postsurgical results nor the reproductive prognosis of any of the interventions accomplished in treating primary bilateral ectopic pregnancy are known, because nothing has been published on this matter.

## Secondary bilateral ectopic pregnancy

### Definition

Secondary bilateral ectopic pregnancy is the condition in which 2 simultaneous gestations take place, neither of them eutopic, localized in structures of the opposite side and after manipulation of the physiology by means of drugs used for assisted reproduction. From the beginning of ART, its potential to generate ectopic pregnancies has been known. In fact, the first procedure described on IVF-ET, accomplished by Steptoe and Edwards<sup>62</sup> in 1976 resulted in an ectopic pregnancy.

But the first case of bilateral ectopic pregnancy after IVF-ET was published in 1983 by Trotnow et al.<sup>63</sup> In 1985, Dr. Bledsoe, who had reported the first case of spontaneous bilateral ectopic in 1918, accompanied Hewitt et al<sup>64</sup> in the

publication of the second case of such a complication, after manipulation in human reproduction.

## Cause

There are several different hypotheses regarding why an ectopic gestation can occur after assisted reproduction procedures. Among them, some authors mention the possibility of this risk being increased by the use of certain ovulation induction protocols.<sup>65</sup>

In fact, clomiphene citrate has always been blamed as one of the factors contributing to the genesis of this anomalous gestation. Other authors, however, have not corroborated this hypothesis.<sup>66,67</sup>

Some authors<sup>63,68,69</sup> have found higher rates of ectopic pregnancies when larger amounts of culture medium are used during the transfer of embryos. Marcus et al<sup>68</sup> described an ectopic incidence of 2.1% when embryos are transferred with 10 to 20  $\mu$ L of the medium versus 9.4% when transferred with 20 to 50  $\mu$ L.

In 1985, Yovich et al<sup>70</sup> attributed an increase in the rate of ectopic pregnancies to having introduced the transfer catheters too far into the uterine cavity; after his investigation he recommended that these should not penetrate more than 55 mm past the external cervical orifice. Other authors consider that neither the transfer technique, the patient's position, the type of catheter, the number of embryos transferred, nor the amount of transfer medium have an effect on the posterior incidence of ectopic pregnancies.<sup>67,71</sup>

Although the cause of bilateral ectopic pregnancy after ART is clearly different from one occurring spontaneously, it seems that previous tubal disease is a common risk factor in both situations. In fact, authors like Azem et al<sup>72</sup> consider fallopian tube disease to be the most relevant risk factor in relation with the presence of ectopic pregnancies after IVF-ET.

Although IVF-ET was theoretically developed to avoid the use of defective or useless tubes during the reproductive process, when there is permeability of the tubes and the embryos enter a diseased tube, they reproduce the physiopathologic process of the spontaneous or primary ectopic pregnancy, being incapable of returning to the endometrial cavity. Already in 1991, Dubuisson et al<sup>69</sup> had demonstrated that, in the case of those patients for whom IVT-ET was indicated because of tubal factors, there was a rate of ectopic pregnancies of 11%, whereas patients who had the same technique applied because of endometriosis had an incidence of only 2%, similar to that of the general population. These data were comparable with the study by Zouves et al,<sup>73</sup> who found a 12% incidence of ectopic pregnancies in patients undergoing IVF-ET for tubal reasons versus 2.6% when the indication differed.

Three theories have been outlined by Hewitt et al<sup>64</sup> to explain the origin of bilateral ectopic pregnancy after assisted reproduction procedures. First, the embryos might be directly injected into the tubes because of a deficient transfer technique. Second, embryos correctly transferred to the

endometrial cavity could regressively migrate to the tubes as a consequence of endometrial secretions that push them in that direction. The third theory is the so-called "spray" effect produced during transfer: when emptying the hypodermic syringe, the embryos could possibly "be pushed" toward the tubal portions. However, in spite of any of these mechanisms, in the presence of normal tubes, the embryos should return to the endometrial cavity, simulating the normal journey of a fertilized egg in that direction, but in dysfunctional or damaged tubes, their implantation outside the eutopic endometrium can occur more frequently.<sup>64</sup>

From this point of view, patients with tubal disease and permeable ostia seem to have a higher risk of ectopic pregnancy, either unilateral or bilateral, no matter how careful the transfer technique, the length of the catheter introduced, the quantity of transfer medium, the number of transferred embryos, or the type of ovulation induction used.<sup>36</sup>

## Diagnosis

Of the 42 bilateral ectopic pregnancies reported between January 1997 and October 2006, 19 (45%) happened after ART.<sup>7-9,11,13,36-49</sup> These data contradict the assertion of many authors who consider that most bilateral ectopic pregnancies occur because of this mechanism. Regarding the ART used, both intrauterine insemination and IVF-ET share an equal percentage of presentation, being responsible of more than 70% of the cases reported (Table 2). In 15 of the cases,  $\beta$ -hCG values were reported at the moment of a presumptive ectopic diagnosis (range 27–226.768 mIU/mL).<sup>7,8,11,13,36-38,40-45,47,49</sup>

The gestational age in weeks at the moment of diagnosis was reported in all the cases, and on average it was 6.7 weeks after the last menstruation (range 5 to 9 weeks). In 15 cases it was possible to correlate the  $\beta$ -hCG values with the age of gestation in weeks from the date of the last menstruation; it was found in only one of the cases (6.6%) that  $\beta$ -hCG was above the value regarded as normal for the gestational age. In 5 of the cases (33.3%), values ranked below expectations for gestational age as estimated by amnorrhea. In the remaining 9 cases (60%), hormone subfraction values were within ranges recognized for the corre-

**Table 2** Distribution of patients with bilateral ectopic pregnancy after assisted reproduction procedures according to technique used 1997–2006

Assisted reproduction procedure	No.	%
Ovulation induction with clomiphene <sup>48,49</sup>	2	10.5
Ovulation induction with gonadotropins <sup>7,8,39,44,47</sup>	5	26.3
Ovulation induction + intrauterine insemination <sup>9,43,46</sup>	3	15.7
In vitro fertilization + embryo transfer <sup>11,36-38,40,41,45</sup>	7	36.8
Intracytoplasmic sperm injection <sup>13,42</sup>	2	10.5

**Table 3** Correlation between concentration of  $\beta$ -hCG at the moment of diagnosis and weeks of gestation counted from last menstruation in patients with bilateral ectopic pregnancy after assisted reproduction 1997–2006

Author and year of publication	Concentration of $\beta$ -hCG in mIU/mL	Weeks of gestation
Bustos et al <sup>7</sup>	27	7
Kasum et al <sup>36</sup>	5.133	8
Chang et al <sup>37</sup>	6.350	8
Klipstein, Oskowitz <sup>38</sup>	1.724	8
Yarali et al <sup>8</sup>	85	6
Mock et al <sup>13</sup>	1.724	6
Campo et al <sup>40</sup>	2.170	6
Pan et al <sup>41</sup>	366	7
Sergent et al <sup>11</sup>	3.669	6
Hoopmann et al <sup>42</sup>	13.296	6
Shiau et al <sup>43</sup>	856	6
Bettocchi et al <sup>44</sup>	226.768	7
Myoungseok et al <sup>45</sup>	62.520	6
Mahmood et al <sup>47</sup>	4.486	6
Shenoy et al <sup>49</sup>	4.234	6

$\beta$ -hCG =  $\beta$ -human chorionic gonadotropin.

sponding gestational ages (Table 3). Of the 19 cases reported, 2 (10.5%) were recognized and correctly diagnosed by ultrasonography.<sup>13,42</sup>

In the case described by Mock et al,<sup>13</sup> the second ectopic pregnancy was diagnosed by ultrasound scanning 5 days after the first was diagnosed and treated with a local injection of methotrexate. Findings were quite heterogeneous in this group of patients, and some of the cases merit special comments. In 7 of the 17 cases that reported the ultrasound findings (41%), the diagnosis was that of unilateral ectopic pregnancy.<sup>7,9,11,13,37,39,44</sup>

Three of the cases (17.6%) found empty uteri, and it was this finding, plus the correlation with  $\beta$ -hCG values, that led to suspect diagnosis.<sup>8,40,45</sup> In one of the cases, the ultrasound scan was reported as normal.<sup>47</sup>

Four ultrasound examinations (23.5%) found either adnexal mass or free fluid in the pelvis.<sup>36,38,41,49</sup> Four of the cases (23.5%) corresponded to heterotopic pregnancies whose ectopic component was bilateral.<sup>41,42,44,46</sup> In only one of them (5.8%), the diagnosis of heterotopic pregnancy with bilateral ectopic was fully made by means of ultrasound scanning.<sup>42</sup> In 2 of these cases the intrauterine pregnancies continued uneventfully until term.<sup>41,44</sup>

One of the cases reported bilateral ovarian cysts corresponding to a bilateral ovarian ectopic pregnancy.<sup>45</sup> One case reported the presence of 3 gestational sacs in the left tube, but then, when laparoscopy was done, it was found that the other tube also had an ectopic pregnancy, and when submitted to anatomic pathologic study, it was discovered that this tube also contained 3 gestational sacs.<sup>37</sup>

In one of the heterotopic cases, after gonadotropin ovarian stimulation and spontaneous conception, the ultrasound scan showed 5 intrauterine sacs and an adnexal one; during

surgery it was found that in addition to the 5 intracavitary embryos, the patient had a bilateral ectopic embryo.<sup>44</sup>

Unlike what happens in a primary bilateral ectopic pregnancy, in cases where the condition is produced by the manipulation of the reproductive process, it seems possible, with some good sense and a high degree of suspicion, to reach a correct diagnosis by means of ultrasound scanning, because of the strict follow-up of patients made by most groups.

## Clinical findings

Of the 19 cases, 13 (68.4%) were diagnosed because of the lack of a correlation between ultrasound scan findings and  $\beta$ -hCG levels and because of some minor clinical signs,<sup>7,9,13,36,37,39,40,42–45,47,49</sup> whereas 6 others (31.6%) arrived with a clinical picture of acute abdomen and hypovolemic shock.<sup>8,11,38,41,46,48</sup> The difference between these findings and those encountered when reviewing primary bilateral ectopic pregnancies seems to be explained by the better care given, from the paraclinical point of view, to patients undergoing assisted reproduction (Table 4).

## Intraoperative findings

Regarding the location of ectopic pregnancies, information was obtained in 18 patients, that is to say 36 ectopic pregnancies. Of these, 28 (77.7%) were ampullar: Six were ruptured (21.4%) and 22 (78.6%) were not ruptured. Two (5.5%) of all ectopic pregnancies were ovarian, and none were ruptured. One (2.7%) ectopic was cornual, not ruptured. Two of the ectopic pregnancies were fimbrial (5.5%), with 1 ruptured. Another was an intact isthmic pregnancy. Of the 18 cases susceptible of analysis, 5 patients (26.3%) had a rupture of 1 of the ectopic pregnancies at the moment of presentation.<sup>8,11,41,47,48</sup> There were no cases of bilateral rupture.

**Table 4** Comparison between findings in primary and secondary ectopic pregnancies

Variable	Primary bilateral ectopic (n = 21)	Secondary bilateral ectopic (n = 19)
Mean gestational age at diagnosis	7.5 weeks	6.7 weeks
Correct preoperative diagnosis	0	2
Diagnosis while asymptomatic	9	13
Diagnosis with acute symptoms (hypovolemic shock or acute abdomen)	9	6
Unilateral rupture	5	5
Bilateral rupture	5	0
Laparoscopic management	12	12
Treatment by laparotomy	7	6
Successful medical management	0	1
Reported pregnancies after treatment	0	1

## Treatment

Treatment of secondary bilateral ectopic pregnancy should not leave any room for doubt for the clinician about performing bilateral salpingectomy, especially when such techniques of assisted reproduction as IVF-ET or ICSI are used, because, when such a diagnosis is confirmed, bilateral salpingectomy would not only be the treatment of choice but, according to some authors, a condition for the realization of these techniques.<sup>74</sup> However, when checking cases, we found the following: 18 of the 19 publications reported surgical management, whereas 1 reported a case of medical treatment.

Therefore, 36 ectopic pregnancies were managed by surgery, 23 of which (63.8%) were treated with laparoscopy<sup>7-9,11,37-40,42,44,46</sup> and 13 (36.1%) with laparotomy.<sup>36,41,43,45,47,49</sup> Odd numbers are explained because in 1 case the patient presented with an acute abdomen, and salpingectomy by laparotomy was performed, but 1 month later pain recurred, and ultrasound scanning showed an adnexal mass. In laparoscopy a contralateral ectopic pregnancy was found and managed by salpingectomy.<sup>48</sup> One of the cases reported refers to a bilateral ovarian cystectomy, because laparotomy revealed 1 ectopic pregnancy in the mentioned location.<sup>45</sup>

Regarding the 23 tubes treated with laparoscopy, linear salpingostomy was performed in 10 tubes (43.5%); 12 tubes (52.2%) were removed and in the last 1, a milking maneuver was done. Eleven tubes were managed by means of laparotomy. Seven (63.6%) of them were removed; 2 (18%) underwent "tubal milking"; and, in the remaining 2, a lineal salpingostomy was done.

In 2001, it was<sup>13</sup> reported the first case of successful medical treatment of a bilateral ectopic pregnancy after ICSI with ET. In this patient, they made a correct ultrasound diagnosis of a 34-mm left tubal ectopic with no signs of rupture and decided to apply methotrexate 1 mg/kg directly in the sac, under ultrasound guidance. Five days later, because of an abnormally slow descent in  $\beta$ -hCG, a new ultrasound was obtained, in which a second adnexal mass was detected; it was located in the right side and measured 19 mm. Once again, guided by ultrasonography, methotrexate 1 mg/kg was injected directly in the adnexal mass. After this handling,  $\beta$ -hCG levels became negative in 34 days. In their article the authors emphasize that it is possible to reach a bilateral ectopic diagnosis by means of ultrasound scanning if an adequate examination takes place. In cases in which medical treatment is made, an ultrasound scan for control after the application of the medication is important and should include an adequate assessment of the contralateral adnexa, especially in cases in which assisted reproduction procedures have been used. They propose as a strategy obtaining an ultrasound 1 week after the medical or surgical treatment of ectopic pregnancy. The article also concludes that the dose to use is 1 mg/kg on each of the ectopic pregnancies to be treated.

## Reproductive prognosis

There is only 1 report of a successful intrauterine pregnancy after treatment of a secondary bilateral ectopic pregnancy.<sup>49</sup> In this case, a symptom-free patient treated with clomiphene after tubal anastomosis and anovular cycles underwent laparoscopy because of a  $\beta$ -hCG level of 4.234, an empty uterus, and an echogenic mass in the right adnexa measuring 2.5 cm. The intraoperative finding of dense adhesions motivated the surgeon to convert the procedure into a minilaparotomy in which a left salpingectomy and a milking procedure of the right tube were done.  $\beta$ -hCG levels became negative 3 weeks later. Fifteen weeks after surgery the patient got pregnant again, had an uneventful course, and delivered a term baby.

Paradoxically, the only data on successful outcome, after treating an ominous reproductive condition such as bilateral ectopic pregnancy, corresponds to a case not treated by laparoscopy, with dense adhesions, with clearly recognizable and persistent risk factor (tubal anastomosis) and managed by "milking" the sole remaining tube, procedure that for some authors should not be used.<sup>75,76</sup> Again we insist on the necessity of having authors report on the reproductive prognosis of patients treated, to substantiate, in terms of future fertility, which would be the best therapeutic approximation for handling this disease.

## Conclusions

A preoperative diagnosis of secondary bilateral ectopic pregnancy was made in 2 (10.5%) of 19 patients, and this was possible in 1 of the cases thanks to a control ultrasound obtained 5 days after treatment. Therefore an important diagnostic strategy could be that, in addition to monitoring the normal descent of hCG in patients treated for ectopic pregnancies that follow assisted reproduction, an ultrasound examination be performed, making an adequate assessment of the treated side, to observe its evolution; of the uterine cavity, to exclude a heterotopic pregnancy; and of the contralateral adnexa, to avoid letting a contralateral ectopic go by unnoticed, which, as has been demonstrated by several reports in literature, can have a natural history and evolution of its own, different from what was initially treated.

However and in spite of the preceding statement, to this day, laparoscopy is still the gold standard for a diagnosis of secondary bilateral ectopic pregnancy. As happens in unilateral ectopic pregnancies, their most frequent location is the tubal ampulla (77.7%).

No patients with bilateral rupture were reported, and the percentage of women presenting an acute abdomen or hypovolemic shock was 31.6%. These 2 datasets show a difference against what was observed in cases of primary bilateral ectopic pregnancies, in which the values were significantly greater. A possible explanation for this difference is the fact that almost all patients involved in assisted

reproduction programs follow preestablished protocols after the intervention that help to raise the level of suspicion of any complication such as ectopic pregnancy.

After an adequate diagnosis of a secondary bilateral ectopic by means of ultrasound scanning, medical management can be attempted with a local injection of methotrexate 1 mg/kg in each of the ectopic pregnancies. However, in most cases diagnosis is still intraoperative.

If the assisted reproduction procedure after treating the bilateral ectopic is going to require the presence of the tubes (i.e., induction of ovulation, intrauterine insemination) and their condition allows it, bilateral salpingostomy could be attempted. If, by all means and because of other indications, the patient requires the use of other techniques, such as ICSI or IVF-ET, then a good choice is the practice of bilateral salpingectomy. Postoperative results are not well known yet, nor are the reproductive prognoses of any intervention made for the treatment of secondary bilateral ectopic pregnancy.

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