



Abdominal Pregnancy and *In Vitro* Fertilization with Embryonic Transfer

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Abstract

Background: Pregnancies achieved by assisted reproduction techniques have doubled in the last decade occupying 1% of annual births, but have maternal complications such as ectopic pregnancy, which should be suspected mainly in patients in sterility management.

Objective: A case of abdominal pregnancy related to *in vitro* fertilization and review of the literature is presented.

Case Presentation: A 40-year-old woman with controlled hypothyroidism and infertility, who achieved pregnancy with *in vitro* fertilization and embryo transfer, quantified the beta fraction of hCG serial with levels of 150/IU considering biochemical pregnancy; During its follow-up the transvaginal ultrasound finding an extrauterine amniotic sac, without fetal vitality of 12 weeks, compatible with abdominal pregnancy. The exploratory laparotomy was performed, finding a peritoneal cavity with multiple adhesions to the intestine, extracting the gestational sac with the fetus and placenta in a partial manner due to adherence to the omentum and left salpinge, presenting severe haemorrhage under hemodynamic control and during the postoperative period developing partial occlusion and ileum which was resolved with conservative management and is released a month in good condition.

Conclusion: Abdominal pregnancy is rare; with low incidence and absence of specific symptomatology that makes diagnosis difficult, there are no criteria for diagnosis or therapeutics. These will be adapted to the site of implantation, gestational age in an individualized way, the management requires the surgical extraction of the fetus, leaving the placenta in situ and adjuvant metotrexate. This is the first report in our country, of an abdominal bladder associated with *in vitro* fertilization that is diagnosed opportunistically with proper management.

Keywords: Ectopic pregnancy; *In vitro* fertilization and Embryo transfer; Ultrasound; Conservative management; Methotrexate

Introduction

Ectopic pregnancy is the main cause of maternal morbidity and mortality during the first trimester; it represents 5 to 10% of all maternal deaths [1] or is 7.7 times greater than in tubal ectopic pregnancy and 90 times higher than intrauterine pregnancy. Fetal mortality occurs in 75% - 90% of cases [2,3]; *in vitro* fertilization (IVF) and embryo transfer (ET), (IVF-ET) is a risk for developing it and the incidence increases 2-3 times that observed in the general population; affects 1% of patients under and these procedures have increased dramatically, doubling in the last decade. At least 12% of women have sought treatment for infertility at some point, and infertility is a problem that affects 8% -12% of couples worldwide.

Many risk factors related to IVF-ET and the causes of infertility have been documented. The combination of transvaginal ultrasound and levels of the beta subunit of human chorionic gonadotropin (hCG) is the most reliable diagnostic tool for the early diagnosis of pregnancy and, if ectopic, allows conservative management; It is estimated that spontaneous ectopic pregnancy occurs in 1% to 2% of pregnancies; However, it increases the risk of developing it after fertility management, which is due to the effects of the treatment or the preexisting disorder [4].

The frequency of ectopic implantation sites related to FIV-TE, are tubal pregnancy 90% to 95%; in the ampulla 80%, isthmic 5% to 10%, interstitial 2.5%, ovarian 0.15% to 3%, abdominal 1.3%, cervix 0.15%; the rarity of implantation in these sites, much of the information related to the

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diagnosis and treatment of these pregnancies has been derived from small observational studies and case reports. This makes the optimal approach to its evaluation and management difficult to determine [5].

Ectopic pregnancy is defined when the embryo is implanted outside the uterine cavity, when an abdominal pregnancy is located it may reach its term; but, these fetuses are usually severely compromised in their development and rarely survive; When it is not detected, it will continue to grow and may cause severe fatal hemorrhage, if not treated. The monitoring of pregnancies by laboratory and ultrasound allows to prevent the complications associated with ectopic pregnancies allowing a management that has evolved the radical surgical treatment due to obstetric urgency to the doctor mainly with metotrexate, reducing the high morbidity and mortality rates associated with this condition. when diagnosed early. When an ectopic pregnancy occurs after assisted reproduction techniques with FIV-TE, regardless of the various strategies to reduce the risk, ectopic pregnancies occur [5,6].

The levels of the beta subunit of human chorionic gonadotropin (hCG), normally doubles in a normal intrauterine pregnancy, when they do not duplicate suggest impending abortion or ectopic pregnancy. The transvaginal ultrasound detects an ectopic pregnancy before rupture or if it is already broken it will be detected by the presence of free fluid in the abdominal cavity, which is an adverse sign and allows to identify its location and vitality for its timely management [5,6].

Abdominal Pregnancy

Abdominal pregnancy is a rare but clinically significant form of ectopic pregnancy with high maternal morbidity and mortality; which refers to implantation in the peritoneal cavity, external to the uterine cavity and uterine or fallopian tubes. Potential sites include omentum, pelvic sidewall, broad ligament, posterior cul-de-sac, abdominal organs (eg, spleen, intestine, liver), large pelvic vessels, diaphragm, and uterine serosa [7,8]. The estimated incidence is 1 for every 10,000 births. There are reports of abdominal pregnancy that occur after hysterectomy [8,9]. The risk factors of ectopic pregnancy have been studied after IVF-TE, very little is known about the specific risk factors for abdominal pregnancy. Spontaneous abdominal pregnancies represent 1.4% of all ectopic pregnancies [6]. The risk increases with assisted reproduction techniques and the true incidence in this population is not well established. The diagnosis depends on the visualization of an extra-uterine, extra-adnexal or extraovarian pregnancy in the abdomen or pelvis by imaging, which is generally visualized as the supply of nutrients is through the omentum and abdominal organs. It is unknown whether spontaneous abdominal pregnancies are the result of the secondary implantation of an aborted tubal pregnancy or the result of intra-abdominal fertilization of the sperm and the ovum, with primary implantation in the abdomen [6,7] or it is likely to be the result of a uterine contraction, causing an embryo to be expelled from the uterine or fallopian tube.

In Vitro Fertilization and Embryo Transfer

IVF-TE is usually considered in pairs where the woman has absence or blockage of the fallopian or uterine tubes; male factor with severe oligospermia, advanced reproductive age, no response to treatment for infertility, hereditary genetic disease that prevents its transmission prior to preimplantation genetic diagnosis, or through gamete donation in ovarian failure; IVF-TE has a high success rate, but some disadvantages, costs, risks and invasive procedures used, as

well as an increase in the rate of multiple gestation, higher risk of complications and ectopic pregnancies.

The first pregnancy achieved by *in vitro* fertilization (FIV-TE) [8] in 1976. Data from a US registry of more than 550,000 FIV-ET pregnancies found that the pregnancy rate ectopic decreased from 2.0 percent in 2001 to 1.6 percent in 2011; A higher risk of ectopic and heterotopic pregnancy has been associated, with IVF-ET its frequency is 6%, corresponding to 0.3% of all pregnancies and the incidence ranges from 2.1% to 8.6% according to various studies, all pregnancies and reaches 11% in women with a tubal factor of [7,9] compared to spontaneous ectopic pregnancy of 2%.

Risk Factors for Ectopic Pregnancy

In ectopic pregnancy after IVF-ET, the passage of the embryo along the uterine or fallopian tube does not occur and additional factors prevent intrauterine implantation by developing the ectopic pregnancy; as the alteration of the tubal function and the endometrial receptivity that occur after the failure of the normal biological interactions between endometrium, uterine or fallopian tube and the embryo due to the controlled ovarian stimulation and the subsequent alteration in the hormonal environment [10,11].

Additional risk factors for ectopic pregnancy include advancing maternal age (especially >40 years), smoking, history of ectopic pregnancy, endometriosis, salpingitis or tubal surgery. The risk of ectopic pregnancy increases with advancing age, especially in women over 35 years of age [12,13]; with the increase of 6.9% in women of 44 years or more. An explanation of this trend with age could be the existence of a greater probability of exposure to most other risk factors with advancing age, increased chromosomal abnormalities in trophoblastic tissue and age related to changes in tubal function, other reports have not been able to detect an association between maternal age and the risk of developing it [14-19].

Recent studies have attempted to identify risk factors for ectopic pregnancy after IVF-ET, including tubal factor infertility, endometriosis, transfer to the blastocyst stage, increased number of embryos transferred, decreased endometrial thickness, variation in means of culture and the transfer of fresh embryos, there are few data on the risk factors for abdominal pregnancy after IVF; uterine perforation during embryo transfer has also been suggested, and the embryo transfer technique; in addition, of the large volume of transfer media, induction of abnormal uterine contractions, location of the embryo transfer in relation to the fundus of the uterine cavity. All these factors have been associated with the retrograde flow of both the transfer medium and the embryo to the uterine or fallopian tube [5,20], see Table 1.

	Maternal factors	By factors of the IVF-ET
Defined Risks	Tubal Infertility High	Volume of transfer media
	Pelvic inflammatory disease	Multiple embryo transfer
	History of tuba surgery	
	Previous ectopic pregnancy	
	Smoking	
	Endometriosis	
Undefined risks	Maternal age	Control of ovarian stimulation
	Uterine abnormalities	Activation of oocyte maturation
	IVF / maturation	Luteal phase support
		Assisted development
		Embryonic stage in the transfer
		Embryo fresh vs. frozen
		Embryo transfer technique

Table 1: Risk factors for ectopic pregnancy during FIV-ET.

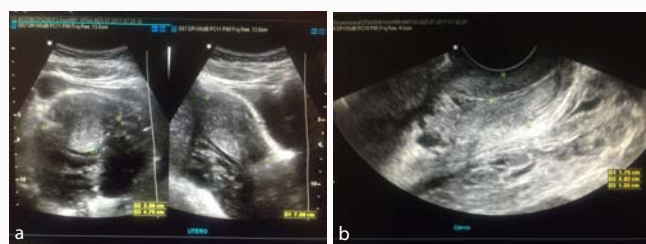


Figure 1: Pelvic Ultrasound with trans abdominal approach, where the uterus is identified in cross section and the presence of a heterogeneous collection in the bottom of the sac of Douglas which is related to organized bleeding.

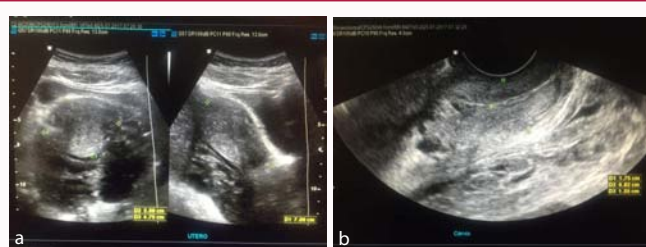


Figure 2: Pelvic ultrasound with trans abdominal, and endovaginal approach. Uterus in transverse and sagittal (transabdominal) projection (a), presents normal dimensions. Normal cervix (trans-vaginal) (b).

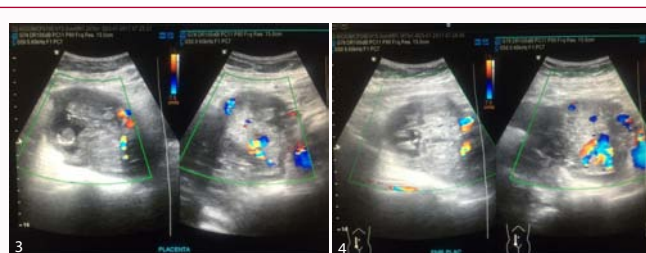


Figure 3 and 4: At the abdomino-pelvic level and towards the left iliac fossa, a lobulated image with irregular edges is seen that loses its interface with mesenteric fat, heterogeneous, predominantly echogenic, which projects acoustic shadow, exhibits vascularity to the color Doppler modality, said image is in relation to the placenta.

Material and Methods

A systematic literature search was conducted to identify cases of abdominal pregnancies after IVF, in a report of 28 cases of abdominal pregnancy after IVF, in ages between 23 and 38 years (average = 33.2 years). The causes of infertility included tubal factor 13 (46%), endometriosis 4 (14%) cases, male factor 4 (14%), pelvic adhesions 2 (7%), anatomical findings of structural alterations of the uterus by exposure to diethylstilbestrol 2 (7%), of unexplained cause 4 (14%), and 1 without specifying the cause. In general, anatomical / structural factors represented 17 (61%), antecedents of ectopic pregnancy 11 (39%), tubal surgery 14 (50%), 9 (32%) of them were bilateral salpingectomy. The transfer of more than two embryos was reported in 15 (54%), two embryos were transferred in 7 (25%), while the transfer of a single embryo was reported in 2 (7%). There was no information on the number of transferred embryos available in 4 (14%). The transfer of fresh embryos represented 20 (71%), frozen in 3 (11%) and 5 (18%) nonspecific. The heterotopic abdominal pregnancy occurred in 13 (46%), and 15 (54%) were abdominal pregnancies. The 5 retroperitoneal ectopic pregnancies, with abdominal fetal death at 28 weeks and 4 viable one at 30 weeks, two at 32 weeks and one at 34 weeks of gestation [5,10,20].

As the number of IVF procedures performed continues to increase, the incidence of ectopic and abdominal ectopic pregnancy will probably also increase. Although there are still relatively few reported cases of abdominal ectopic pregnancies after IVF-ET, our systematic review demonstrates several trends among reported cases. First, the majority of cases (61%) reported a history of anatomical/ structural etiology of infertility with a history of tubal factor infertility (46%), the most frequent [5,7].

In other reports, four cases of viable abdominal pregnancies were identified, which is an extremely rare result. Three of these cases were identified at 19 weeks or more, and all three had adherence of the abdominal placenta to the peritoneal surface of the uterus without the involvement of other abdominal organs. The placental site to the uterus has been associated with the viability of abdominal pregnancies, and with a lower risk of bleeding and lower probability of fetal growth retardation. Three of these cases were identified at 19 weeks or more, and all three had adherence of the abdominal placenta to the peritoneal surface of the uterus without the participation of other abdominal organs, abdominal ectopic pregnancies were much more common in the transfer of fresh embryos (71% of cases) than in the transfer of frozen embryos (11% of cases). This may be due to the fact that frozen embryo transfer has been widely used recently, and we can begin to see a higher frequency with frozen embryo transfers over time. However, several recent studies indicate that ectopic pregnancy rates are higher for fresh compared to frozen IVF cycles [21,22]. The clinic is variable according to the location and the evolution of the picture. It can be asymptomatic in 50% of cases by spontaneous resorption. On the other occasions, pain may appear accompanied by signs of initial pregnancy [5,7].

Clinical Case

A 40-year-old female patient with a history of controlled hypothyroidism, and sterility, which is managed with IVF-ET with two blasts, genetically normal, after embryo biopsy on day 3 for genetic diagnosis preimplantation and embryo transfer, quantification of beta fraction of hGC at 8 days and weeks after finding values of 150/ IU considering a biochemical pregnancy and follow-up with pelvic ultrasound control with trans-abdominal approach, where the uterus is identified in the transverse and the presence of a heterogeneous collection in the bottom of a bag of Douglas, which is related to organized bleeding (Figure 1), a uterus with normal dimensions in transverse and sagittal (trans-abdominal a) and normal cervix (trans-vaginal b), Figure 2; At the abdominopelvic level and towards the left iliac fossa, a lobulated image with irregular edges is seen that loses its interface with mesenteric fat, heterogeneous, predominantly



Figure 5: Trans-abdominal ultrasound showing a poorly defined hypoechoic image to the cephalic region corresponding to the fetal pole, without cardiac activity when applying Doppler window.



Figure 6 and 7: Pelvic ultrasound where fluid is observed in the bottom of a Douglas sack of anechoic predominance with linear echogenic areas and fine septa to which the Doppler color modality does not present vascularity, this collection extends to pelvic egg and iliac fossa where it acquires dimensions 118x108x38mm.

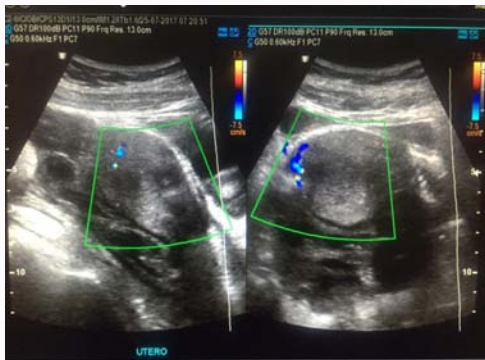


Figure 8: Uterus in longitudinal and transverse where hypo echoic images of regular and defined edges are identified, located towards the fundus, which are in relation to myomas.



Figure 9: Trans-vaginal ultrasound, it is not possible to identify the right ovary in its topography of the anatomical site.

echogenic, which projects acoustic shadow, exhibits vascularity to the color Doppler modality, said image is in relation to the placenta. Figures 3 and 4, in the trans-abdominal ultrasound shows a poorly defined hypoechoic image corresponding to the fetal pole, without cardiac activity when applying Doppler window, Figure 5, in other pelvic ultrasound images where liquid is observed in the background of Douglas sack of anechoic predominance with linear echogenic areas and fine septa to which, in color Doppler modality, do not present vascularity, this collection extends to pelvic egg and iliac fossa where it acquires a size 118x108x38mm, Figures 6 and 7, in another image, the uterus in longitudinal and transverse section identifies hypo echoic images of regular and defined borders, located towards the fundus, which are related to leiomyomas, figure 8, in the image



Figure 10: Trans-vaginal ultrasound The left ovary with regular and defined edges with dimensions 37x22x24mm in its major axes and an approximate volume of 13.4cc its parenchyma shows a normal follicular pattern.



Figure 11: Exploratory laparotomy with the presence of a complete amniotic sac adhered to the omentum.



Figure 12: Rupture of the amniotic sac and presence of dead fetus.

by trans-vaginal ultrasound, it is not possible to identify the right ovary in its topography of the anatomical site, Figure 9, and the left ovary with regular and defined borders with dimensions 37 x 22 x 24 mm in its major axes and an approximate volume of 13.4 cc its parenchyma shows a normal follicular pattern, Figure 10; Integral ultrasonographic diagnosis of abdominal pregnancy is integrated, without fetal vitality, with heterogeneous free fluid in the pelvic cavity,

suggesting hematoma, abdominal free fluid and uterine myomatosis. Hospitalization is entered in good asymptomatic health status, for surgery programming through exploratory laparotomy, finding the following findings: peritoneal cavity, with multiple adhesions to the intestine, and abdominal pregnancy by extracting a gestational sac of 15 x 15 cm with embryo, Figure 11 and the placenta partially by adherence to the omentum and left salpinx that is removed, Figure 11, rupture of the amniotic sac and presence of dead fetus, Figure 12, severe hemorrhage of 2000 cc is presented, with hemodynamic control with hemotransfusion of three packages globular and management in intentional therapy where partial occlusion and postoperative ileus was developed with conservative treatment and resolution in two days; the quantification of beta sub-unit of hCG at 24 hours after surgery with figures of 9385.79 Mu / ml and 3 doses of metotrexate of 75 mg alternated with folinic acid 7.5 mg and it is delivered with total recovery at month of admission in good clinical conditions, with negative hCG and without data and placenta remains.

Discussion

Since the birth of the first newborn with successful *in vitro* fertilization (IVF) [20] in 1978, there has been an increase in the demand for assisted reproductive technologies (ART) [24]. Abdominal pregnancies comprise less than 1% of all ectopic pregnancies, but have a maternal mortality rate eight times higher than tubal pregnancies, [7] early recognition and timely management is decisive, with the case presented; in general, the atypical presentation highlights the need to consider abdominal pregnancy in the differential diagnosis of any gestation of unknown location after IVF-ET [5].

The rate of ectopic pregnancies after the assisted reproduction techniques are higher, compared with spontaneous ectopic pregnancy rates [22-27]. Pregnancies achieved by assisted reproduction techniques have doubled in the last decade in more than 1% of births each year, which will probably increase; with maternal complications; There are few reported cases of abdominal pregnancies after IVF, the systematic review shows several trends among the reported cases, the majority of cases (61%) report antecedents of anatomical / structural etiology of infertility with a history of tubal factor (46%) as the most frequent; being a known risk factor for ectopic pregnancy after FIV-TE; where, the risk ratio (OR) is 3.99 (95% CI: 1.23 to 12.98) [28]. In another report on assisted reproduction techniques, among all the diagnoses of infertility, the tubal factor was the main factor of risk of ectopic pregnancy (relative risk (RR) 1.25, 95% CI 1.16-1.35) [29], compared with those with other causes infertility. The antecedents of ectopic tubal pregnancies are reported in 37% of abdominal pregnancies as reported in the literature; The risk of ectopic pregnancy after IVF-TE in women with a previous ectopic pregnancy increases the risk compared to 45 times in women with other causes of infertility. The reported prevalence of ectopic pregnancy was 8.95% compared to 0.75% in the control group [30]. The history of previous tubal surgery is also common (50%) in abdominal pregnancies, tubal or pelvic surgery is another important risk factor for the development of ectopic pregnancy after IVF-TE. The quotient of possibilities for the development of ectopic pregnancy was 8.52 (95% CI: 5.91-12.27) for the previous adnexal surgery, 11.02 (95% CI: 5.49-22.15). for a previous surgery of tubal infertility, 5.16 (95% CI: 1.25-21.21), surgery for endometriosis and for abdominal / pelvic surgery 17.70 (95% CI: 8.11-38.66) 29,31, bilateral salpingectomy was the most common reported; our patient did not present any risk factor, although the exact mechanism of abdominal cling after bilateral salpingectomy

is not clear, many authors have proposed that it may be due to the development of a micro-fistulous tract after salpingectomy [31]. Uterine perforation during embryo transfer has also been suggested as a mechanism for abdominal pregnancy, and the embryo transfer technique also increases the risk of ectopic pregnancy a large volume of transfer media, induction of abnormal uterine contractions, and location of the embryo transfer in relation to the uterine fundus, the location of the pregnancy was attributed to uterine perforation by the IVF transfer catheter [25]; probably some of these factors were associated with the case of our patient. All these factors are associated with the retrograde flow of both the transfer medium and the embryo to the uterine or fallopian tubas. Many suggestions have been made regarding the location of optimal transfer within the endometrium, ranging from 5 mm to 20 mm from the fundus surface, while others recommend placement in the median cavity to avoid the proximity of the fallopian uterine tubules [5].

Conclusion

Ectopic pregnancy, including abdominal pain, is a known risk factor for IVF-ET. The reported case highlights that the diagnosis and timely management of this rare form of ectopic pregnancy, avoids morbidity but not morbidity, are patients who have severe hemorrhage due to surgical management. The systematic review of the literature has revealed several known risk factors for ectopic pregnancy after IVF, including tubal factor infertility, antecedents of tubal ectopic pregnancy, tubal surgery, increased number of embryos transferred and transfers of fresh embryos, without that his relationship with our case has been proven.

The growing demand for assisted reproduction techniques such as IVF-ET will increase the likelihood of associated complications when they become pregnant and requires the development of a biomarker/diagnostic algorithm that can predict pregnancy outcomes with high sensitivity and specificity before IVF. -ET to prevent and/or administer adequately to those who are at higher risk of ectopic pregnancy; follow-up and diagnosis with timely management will avoid the potentially fatal consequences of ectopic pregnancies that are relatively more common after IVF-ET.

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