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Complications of medically assisted conception in 3,500 cycles

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Objective: To investigate the incidence of complications in the use of assisted reproductive technology in the management of infertile couples.

Design: Retrospective study.

Setting: The Egyptian IVF & ET Center, Maadi, Cairo, Egypt.

Patient(s): Two thousand nine hundred twenty-four patients underwent IVF-ET or intracytoplasmic sperm injection (ICSI) in 3,500 cycles.

Intervention(s): IVF-ET, ICSI, ejaculate sperm, epididymal sperm aspiration, and testicular sperm extraction.

Main Outcome Measure(s): Complications of the procedure and complications of pregnancy in 702 patients.

Result(s): Fifteen hundred ovum pickups for IVF-ET and 2,000 ovum pickups for ICSI were performed. Clinical pregnancy occurred in 1,078 patients (30.8%). Four groups of complications were identified. Complications of the procedure occurred in 291 patients (8.3%). Complications of pregnancy included ectopic pregnancy in 1.9%, heterotopic pregnancy in 0.2%, abortion in 20.6%, multiple pregnancy in 28%, pregnancy-induced hypertension in 10%, preterm labor in 21.5%, low birth weight in 30.5%, and intrauterine death in 2%. Coincidental complications occurred in five patients (0.15%). Other complications that were difficult to measure included psychological breakdown and socioeconomic problems.

Conclusion(s): Assisted reproductive technology is effective for the management of infertility and has an acceptable incidence of complications. Complications rarely endanger the life of the patient. When this line of treatment is offered, the indications should be definitive. Patients should be monitored properly and measures should be taken to minimize the incidence of complications. (Fertil Steril® 1998;70:638–42. ©1998 by American Society for Reproductive Medicine.)

Key Words: IVF-ET, ICSI, ART complications, TESE, PESA

Assisted reproductive technology (ART) has made great strides since the birth of Louise Brown 20 years ago. Today, ART has become a well-established and accepted method for the treatment of female and male infertility and is practiced widely in almost every country in the world. However, debate continues regarding its safety and risks. Although an enormous number of publications have appeared on the various complications and sporadic risks of ART, only a few (1–3) have discussed the complications of the procedure as a whole. Furthermore, these few publications were mostly reviews of the literature, with reference to some complications encountered by the authors.

We present a retrospective analysis of the complications encountered in ART at one center during an 11-year period and discuss measures to minimize the incidence of these complications.

MATERIALS AND METHODS

Data pertaining to complications encountered at the Egyptian IVF-ET Center, Maadi, Cairo, were extracted from the permanent records of the patients. The study was approved by the Egyptian IVF-ET Center Institutional Review Board.

The study included patients undergoing conventional IVF-ET or intracytoplasmic sperm injection (ICSI) using either ejaculated or surgically retrieved sperm. Follow-up was accomplished by chart review, by mailed questionnaires, by telephone communication, and by home visits by a social worker and a physician when necessary. A total of 3,852 charts

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were sought and thoroughly reviewed, resulting in a final study group of 3,500 consecutive ovum pickups performed on 2,924 patients. For the purpose of this study, we included only patients who underwent ultrasonically guided vaginal oocyte pickup and who received GnRH analogue (GnRH-a) and hMG protocols, as described previously (4, 5).

All patients received prophylactic doxycyline (100 mg twice daily for 10 days) and metronidazole (200 mg) once they started GnRH-a therapy. All patients received fluconazole (150 mg) on the first day of administration of hMG. The vagina was prepared by repeated painting with povidone iodine 10%, followed by repeated irrigation with distilled water. Only two vaginal punctures were performed in most patients; in a few cases, more than two were necessary. Before aspiration of any peripheral follicle, it was visualized in a cross-section to differentiate follicles from blood vessels.

The complications encountered were classified into four groups: those of the procedure itself, pregnancy complications of women who had follow-up until delivery, coincidental complications, and other side effects. Coincidental complications were defined as complications that occurred while the patients were under treatment or follow-up that could not be proved to be due to ART. However, from the patients' point of view, they were linked to the procedure because they were diagnosed while the patients were under treatment or follow-up. The last group of complications included side effects, which were difficult to measure; psychological breakdown; and socioeconomic problems such as financial constraints and divorce.

The χ^2 test was used to compare the pregnancy complications in the different groups of ICSI. Analysis of variance was used to compare mean values. $P < .05$ was defined as statistically significant.

RESULTS

The study group included 1,500 ovum pickups for conventional IVF-ET and 2,000 ovum pickups for ICSI. The indications for ART were severe male factor infertility, tubal factor infertility, and unexplained infertility in 1,720 (49%), 1,410 (40%), and 370 (11%) cycles, respectively. In the ICSI group, 1,425 cycles were performed with ejaculated sperm and 575 cycles used surgically retrieved sperm; the latter involved testicular sperm extraction and epididymal sperm aspiration in 498 and 77 cycles, respectively, as described previously by us (6). Clinical pregnancy, as detected by a rising β-hCG level and ultrasonically demonstrable and viable pregnancy sac, was diagnosed in 1,078 patients. The overall pregnancy rate was 30.8% per ovum pickup.

Complications of the procedure are shown in Table 1. Ovarian hyperstimulation syndrome (OHSS) occurred in a moderate form in 206 cycles (5.9%) and in a severe form in 60 cycles (1.7%) using the criteria described previously (7).

TABLE 1

Complications of ART performed in 3,500 treatment cycles.

Complication	No. (%) of complications
OHSS	
Moderate	206 (5.9)
Severe	60 (1.7)
Vaginal bleeding	3 (0.09)
Deep vein thrombosis	4 (0.1)
Hemiparesis	2 (0.06)
Pelvic infection	10 (0.3)
Acute abdomen	3 (0.09)
Anesthetic complications	2 (0.06)
Mortality	1 (0.03)
Total	291 (8.3)*

* Overall complication rate.

Other complications included vaginal bleeding in three patients (0.09%), deep vein thrombosis in four patients (0.12%), hemiparesis in two patients (0.06%), acute abdomen necessitating laparotomy in three patients (0.09%), and anesthetic complications in two patients (0.06%). The laparotomies were performed for ruptured heterotopic pregnancies in two patients and torsion of an adnexal cyst in one patient.

Complications of anesthesia included severe bradycardia and cardiac arrhythmia in one patient and asystole in another patient following deep abdominal pressure on very high ovaries. Both patients had taken β-adrenergic blocking drugs. Both patients responded to administration of atropine and deepening of the level of anesthesia and recovered quickly. Death in one patient was due to hepatorenal failure following moderate OHSS. A retrospective review of the medical records of this patient revealed a history of hepatitis C with residual impairment of liver function. Unfortunately, this information was not revealed by the patient when she was scheduled for ART. In the male partners, testicular infections occurred in four patients among the 575 surgical retrievals of sperm (0.7%).

The pregnancy complications included 21 cases of ectopic pregnancy (1.9%) and two cases of heterotopic pregnancy (0.2%). Only 702 pregnant patients (65%) could be followed up until late in pregnancy, and this group was used to assess the incidence of abortion and pregnancy complications (Table 2). Abortion (both first- and second-trimesters) occurred in 145 patients (20.6%), multiple pregnancy in 196 patients (28%), pregnancy-induced hypertension in 70 patients (10%), preterm labor in 151 patients (21.5%), low birth weight (<2 kg) in 214 patients (30.5%), intrauterine death in 14 patients (2%), and congenital malformation in 15 patients (2.1%). Analysis of the multiple pregnancies revealed twins in 139 patients (71%), triplets in 42 (21.5%), and quadruplets or more in 15 (7.5%). The high rates of

TABLE 2

Complications of pregnancy among 702 pregnancies achieved by ART.

Complication	No. (%) of complications
Abortion	145 (20.6)
Multiple pregnancy	196 (28)
Pregnancy-induced hypertension	70 (10)
Preterm labor	151 (21.5)
Low birth weight	214 (30.5)
Intrauterine death	14 (2)
Congenital malformation	15 (2.1)

preterm labor and low birth weight were related to the high rate of multiple pregnancy in this study.

Analysis of the 15 cases of congenital malformation revealed ventricular septal defect in six infants (40%), inguinal hernia in three (20%), mesenteric cysts and polydactyly in two each (13.3%), and anencephaly and urethral atresia in one each (6.6%) (Table 3). Karyotyping was performed in 80 infants resulting from ICSI and revealed normal karyotypes in 78 (97.5%), Turner/mosaic (XX/XO) in one (1.25%), and a balanced translocation in another (1.25%).

The group of coincidental complications included two cases of invasive ovarian adenocarcinoma (0.06%) as well as breast duct carcinoma, recurrent thyroid adenoma, and breast fibroadenoma in one patient each (0.03%).

Socioeconomic complications included psychological breakdown of the wife, financial constraints, and divorce. Although many of these problems arose during the past 11 years, it was difficult to analyze the incidence of these complications on a retrospective basis.

DISCUSSION

ART is now considered a reasonable solution for most male and female infertility problems. However, ART is not risk free, and several complications have been reported in the literature. Often, the severity of these complications was exaggerated and used in the argument against ART without reference to the rate of complications in large series. The present study has shown that among 3,500 ovum pickups, the overall rate of complications was 8.3%. Most of these complications (5.9%) involved moderate OHSS, which resolved spontaneously without the need for medications or hospitalization. The management and prevention of this complication are described in a previous publication (7).

In the present study, the incidences of vaginal bleeding and pelvic infection were very low (0.09% and 0.3%, respectively) compared with those reported by other investigators, varying between 1.8% and 4.2% (1, 8–10). The use of prophylactic antibiotics and antimycotics, thorough vaginal preparation before vaginal puncture, use of the fewest possible vaginal punctures, and careful visualization of peripheral follicles before puncture played a major role in reducing these complications. Meldrum (11), Borlum and Maiggard (12), and Evers et al. (13) reported similar low rates of pelvic infection and vaginal bleeding, but in much smaller series.

Thromboembolic disease associated with ART is considered extremely rare. In the present study, four cases of deep vein thrombosis and two cases of hemiparesis were reported (total of 0.17%). All cases were associated with severe OHSS. Stewart et al. (14) reported four confirmed cases of thromboembolic disease directly related to treatment in more than 1,000 cycles of ART. However, three of these cases were upper-limb deep vein thrombosis, and the investigators questioned the argument that lower-limb thrombosis occurring in cases of complicated or severe OHSS represents the likeliest thromboembolic disorder in this situation.

Hignett et al. (15) suggested that in pregnant patients with severe OHSS, consideration be given to treatment with low-dose heparin throughout the first trimester to prevent the serious complications of thrombosis and thromboembolism. After reviewing the world literature, Stewart et al. (16) suggested that this treatment be continued throughout any resultant pregnancy because short-term prophylactic measures may not be sufficient.

The two anesthetic complications of cardiac, arrhythmia and asystole could be explained by the reflex increase of vagal tone resulting from stretching of the peritoneum due to ovarian enlargement, which was increased by abdominal pressure used to push the ovaries down in the pelvis. This mechanism is similar to what happens during laparoscopy (17). This vagal stimulation was accentuated because both patients had taken β-adrenergic blocking drugs. When abdominal pressure is necessary to push the ovaries down in the pelvis, this should be done very gently and the patient's pulse should be monitored carefully to detect and correct this complication immediately.

The only patient in this series who died was a 39-year-old

TABLE 3

Congenital malformations in 702 pregnancies achieved by ART.

Congenital malformation	No. (%) of complications
Ventricular septal defect	6 (0.85)
Inguinal hernia	3 (0.42)
Mesenteric cyst	2 (0.28)
Polydactyly	2 (0.28)
Anencephaly	1 (0.14)
Urethral atresia	1 (0.14)
Total	15 (2.1)

TABLE 4

Guidelines for reducing the risk of complications in ART.

Risk	Measures to reduce risks
General	Blood tests
	Kidney function tests
	Liver function tests
	Blood sugar assessment
	Abdominal and pelvic ultrasound scan
OHSS	Individualization of dose of hMG or FSH
	Coasting for high-risk patients
	Cancellation of ET in hyperstimulated cycles
	Withhold the use of hCG for luteal phase support
Thromboembolic disease	Exclusion of past or family history of deep vein thrombosis
	Early ambulation and abundant fluid intake
	Prevention of OHSS
	Coagulation profile assessment for OHSS patients
	Low-dose heparin throughout pregnancies associated with OHSS
Cardiac arrhythmia at ovum pickup	Exclusion of history of cardiac disease
	Exclusion of history of intake of β-adrenergic blocking drugs
	Routine electrocardiogram
	Avoidance of deep abdominal pressure on very high ovaries
Hemorrhage	Vaginal punctures should be limited whenever possible to two punctures only
	Ultrasound visualization of peripheral follicles in a cross-section before punctures
	Use of color Doppler if available
Infection	Prophylactic use of antibiotics and antimycotics before ovum pickup
	Proper vaginal sterilization with povidone iodine 10%
	Minimum number of vaginal punctures
Multiple pregnancy and pregnancy wastage	Reduce number of transferred embryos
	Selective fetal reduction for high-order multiple pregnancies
Chromosomal anomalies in ICSI	Karyotyping of male partners before ICSI for severe oligoasthenospermia or azoospermia
	Cystic fibrosis testing in both partners before ICSI for CAVD
Psychological breakdown and socioeconomic problems	Proper informative and supportive counseling of the couple before, during, and after treatment

Note: CAVD = congenital absence of the vas deferens.

woman who developed moderate OHSS. After ovum pickup, she was drowsy and never regained full consciousness. She deteriorated quickly over a 10-day period and died of hepatorenal failure. Retrospective review of her medical records revealed a history of hepatitis C with residual impairment of liver function. Because of this unfortunate event, it has become our policy to check liver and renal functions of all patients before starting stimulation protocols.

The incidences of ectopic pregnancy and heterotopic pregnancy in the present study are lower than those reported by other investigators (1, 2). This may be explained by the fact that almost 60% of the women in this series had healthy tubes.

Only 65% of the pregnant patients could be followed up until either miscarriage or delivery because many of them came from either distant areas in Egypt or from the neighboring middle eastern countries. The incidences of abortion and other pregnancy complications, including pregnancy-induced hypertension, preterm labor, low birth weight, and intrauterine death, were high compared with those following natural conception but were similar to those reported in other studies (1, 2, 18). There was no statistically significant difference in the incidence of pregnancy complications among patients who underwent ICSI with either ejaculated, epididymal, or testicular sperm. In addition, we found no significant difference in the incidence of complications of pregnancy between acquired obstructive azoospermia or congenital absence of the vas deferens.

The average age of the female patients in this study was rather high (34.2 years; range, 21–44 years), and the multiple-pregnancy rate was also high (28%). This may explain the high incidence of some pregnancy complications, particularly preterm labor, low birth weight, and related perinatal morbidity.

The high multiple-pregnancy rate was due to the high number (range, 1–6) of embryos transferred. In a controlled study, Reubinoff et al. (19) showed that when controlling for maternal age, parity, ethnic origin, and location and date of delivery, singleton IVF pregnancies did not carry an increased risk for prematurity, low birth weight, or maternal or fetal complications. It seems that the most logical solution to reduce pregnancy complications in ART is to prevent the high frequency of multiple gestations by limiting the number of embryos transferred to a maximum of two or three,

regardless of the age of the patients, as suggested by Roest et al. (20) and Senoz et al. (21).

Chromosomal karyotyping of 80 infants born as a result of ICSI for severe male factor infertility revealed abnormal karyotypes in two (2.5%), which is similar to the rate reported by Van Steirteghem and Devroey (2.4%) in a much larger series (22). One infant was a Turner-mosaic XX/XO and another had a balanced translocation of chromosomes 17 and 19. A much larger study of chromosomal karyotyping and a study of the Y chromosomes of male infants born as a result of ICSI are currently being conducted at our center.

The group of coincidental complications, although small (5 patients, 0.14%), included serious diseases such as ovarian malignancy (2 cases) and breast carcinoma (one case). It was hard to convince these patients and, sometimes, the referring physician that the development of these diseases probably had nothing to do with the treatment of infertility at our center. The patients with ovarian carcinoma, in particular, believed that the condition was related to the ovarian enlargement induced by the ovarian superstimulation protocol. In both patients with ovarian cancer, the pretreatment ultrasound scan revealed normal-looking ovaries with no evidence of enlargement or cyst formation.

In a recent case-control study, Mosgaard et al. (23) showed that among parous as well as nulliparous women, treatment with infertility drugs did not increase the ovarian cancer risk compared with untreated infertile women. In another case-control study, Parazzini et al. (24) provided evidence of the absence of a strong association between fertility drugs and the subsequent risk of developing epithelial ovarian cancer.

Among those patients who failed to get pregnant after ART, it was extremely difficult to analyze retrospectively the incidence of the last group of complications, namely psychological breakdown and socioeconomic problems including financial constraints and divorce. These complications were common, especially among the lower socioeconomic class. In Egypt, ART is provided almost totally on a private basis, and it is not a state- or insurance-funded line of treatment. The cost of ART is relatively high considering the average annual income in Egypt. Our findings emphasize the importance of proper counseling before scheduling patients for ART. Supportive counseling, particularly if pregnancy does not occur, is extremely important to minimize the incidence of these complications. We are currently conducting a prospective study to assess this group of complications.

In conclusion, ART is a significant advancement in the management of both male and female infertility. However, it has the potential for complications before and during pregnancy. These complications are usually not serious and only rarely endanger the life of the patient. Definitive criteria should be used to select patients for the procedure. Precautions should be taken at every step to reduce the risks to a minimum. Table 4 shows a checklist to achieve this objective.

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