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The incidence of major clinical complications in a Dutch transport IVF programme

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Four different major clinical complications were identified in a retrospective analysis of 2495 in-vitro fertilization (IVF) cycles resulting in oocyte retrieval. The severe form of ovarian hyperstimulation syndrome (OHSS) occurred in 18 patients, giving a prevalence for this complication of 0.7%. Seven (39%) of these 18 patients had previously been diagnosed as having polycystic ovaries. Eleven patients were admitted with moderate OHSS. Adnexal torsion was diagnosed in two patients. Ovariectomy was considered necessary in both cases. Complications of the transvaginal procedure occurred in seven cases (0.3%): one patient had an acute appendicitis with puncture holes in the appendix, six patients were admitted shortly after oocyte retrieval with a pelvic inflammatory disease. Of the 624 pregnancies obtained, 13 were ectopic, giving an ectopic pregnancy rate of 2.1%. It is concluded that serious clinical complications of IVF treatment are rare. However, patients should be counselled for the occurrence of serious procedure-related complications before entering an IVF programme.

Key words: clinical complications/ectopic pregnancy/ IVF/OHSS

Introduction

In-vitro fertilization (IVF) treatment is an elective procedure. Clinical complications caused by the procedure are therefore always iatrogenic. Although complications are reported to occur infrequently, counselling of patients on possible complications of IVF treatment is necessary before informed consent can be obtained. The incidence of complications appears to differ between programmes and could depend on various factors such as methods used for ovarian stimulation, criteria used for cancellation of cycles, and techniques used for follicle aspiration and embryo transfer. Therefore, it seems advisable to inform patients about the incidence of clinical complications in the actual IVF programme they are about to join. To obtain data concerning the incidence of clinical complications leading to hospital admission in our transport IVF programme at the Zuiderziekenhuis, Rotterdam, The Netherlands, a retrospective analysis was carried out. In the population studied, four different major complications were identified: ovarian hyperstimulation syndrome (OHSS), adnexal torsion, pelvic inflammatory disease (PID) and ectopic pregnancy. The occurrence of high-order pregnancies is not discussed here since this will be the subject of a separate paper. Detailed reports have been published elsewhere on the occurrence of a hepatitis-B infection related to the IVF laboratory procedure (van Os *et al.*, 1991). Psychological complications resulting from procedure-related stress or disappointing treatment results can occur in IVF treatment. Although this aspect certainly needs attention, psychological reactions were not a subject of this study. Publications on assisted reproduction that include information concerning complications are reviewed, and the findings of our retrospective study are compared with these reports.

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Materials and methods

In a retrospective analysis of 2495 consecutive cycles resulting in oocyte retrieval, the incidence of major clinical complications of IVF treatment was assessed. A major complication was defined as a complication resulting from IVF treatment leading to hospital admission. The organizational aspects of our transport IVF programme with satellite clinics have been described previously (Roest *et al.*, 1995a). Patients were accepted for the programme after serological tests (HBsAg, syphilis, human immunodeficiency virus) and routine physical examination. Ovarian stimulation consisted of human menopausal gonadotrophin (HMG) 150–450 IU i.m./day (Humegon; Organon, Oss, The Netherlands), depending on age, starting on cycle day 3. The standard starting dose of HMG for patients aged <35 years was 150 IU/day; above this age 225 IU/day was used. Patients diagnosed as having polycystic ovaries, or known to have had a previous explosive ovarian response during ovarian stimulation, started with 75–150 IU/day. Since the introduction of gonadotrophin-releasing hormone agonists (GnRHa) the short flare-up regime was used in most cases, starting on cycle day 1 until the day of human chorionic gonadotrophin (HCG) injection. Plasma oestradiol measurements were not carried out during ovarian stimulation. Monitoring of follicle growth was performed by vaginal ultrasound measurements only. When >35 developing follicles were seen during monitoring, the cycle was cancelled in most cases by withholding HCG and continuing GnRHa to reduce the chance of development of OHSS.

Oocyte retrieval was planned 35 h after i.m. injection of 10 000 IU HCG (Pregnyl; Organon) on the day the leading follicles reached a diameter of 18–20 mm, measured in three dimensions. Follicle aspiration was carried out by ultrasound-guided vaginal puncture under local anaesthesia. Preventive antibiotics were not used. Chemical disinfection of the vagina was not used in view of possible harm to the oocytes. Before oocyte aspiration the vagina was soaked twice with sterile isotonic saline solution. The ultrasound transducer was covered with a sterile plastic sheet. The patient was covered with a sterile, single-use surgical sheet and the gynaecologist wore sterile surgical gloves. Bilateral ovarian puncture was carried out with the same one-way needle. Evacuated follicles were not rinsed. Luteal support was given with 1500 IU HCG on the day of ovum retrieval (day 0) and on days 3, 6 and 9. When ≥15 follicles were retrieved, progesterone (200 mg vaginally twice daily; Progestan; Organon) was prescribed for 15 days. In these cases HCG for luteal support was withheld. Replacement of embryos was carried out 2–5 days after oocyte retrieval. Embryos (initially a maximum of four) were replaced to the midcavity position. The amount of culture fluid used varied from 30 to 60 µl. No routine consultation was planned during the first 2 weeks after embryo transfer. Patients were instructed to contact the clinic if signs and symptoms of possible complications occurred. For the assessment of OHSS the classification of Golan *et al.* (1989) was used. All patients with severe OHSS or presenting with signs of PID were routinely admitted for clinical observation and treatment.

Ovarian hyperstimulation syndrome

The severe form of OHSS was diagnosed in 18 patients, giving a prevalence per oocyte retrieval of 0.7%. A total of 12 cases were diagnosed as grade 4 and six cases were grade 5. The median length of hospital stay was 11 days (range 4–25). Five patients underwent abdominal paracentesis for relief of symptoms. In one case with extensive pleural effusion bilateral thoracal drainage was necessary. In 13 out of 18 patients (72%), the IVF cycle resulted in a pregnancy; including two sets of triplets and seven twins, giving a multiple pregnancy rate of 69%. Although moderate OHSS was not routinely followed by hospital admission, 11 patients with this condition were admitted. The median duration of admission for moderate OHSS was 8 days (range 4–12). Four patients (36%) were pregnant, all multiple pregnancies: two triplets and two twins.

The OHSS is the most frequent complication of ovarian stimulation. Reports of OHSS developing after all methods of ovulation induction have been published (Schenker and Weinstein, 1978). In rare cases, the severe form of OHSS can result in a life-threatening condition (Mozes *et al.*, 1965). The characteristic clinical components of OHSS are ovarian enlargement with multiple cyst formation and oedema of the stroma, and an acute fluid shift from the intravascular space to the extravascular compartment, associated with ascites, hydrothorax and generalized tissue oedema. The latter component of the syndrome is the main cause of the morbidity and mortality related to it. The fluid accumulation in the peritoneal and pleural cavities leads to hypovolaemia and haemoconcentration. Without correction, renal perfusion can be modified, with resultant oliguria. Increased haemoconcentration may lead to thrombosis and thromboembolism.

The pathogenesis of OHSS is still poorly understood. Several substances, e.g. oestradiol, prostaglandins and histamine, have been proposed as mediators for the pathogenesis but were rejected later (Pride *et al.*, 1986; Bergh and Navot, 1992; Pellicer *et al.*, 1991; Brinsden *et al.*, 1995). Evidence exists that the activation of the renin–angiotensin–aldosterone system is a primary event in the

development of OHSS. A vasoactive substance produced by the ovaries, which had already been proposed by Polishuk and Schenker (1969), was shown by Frederick *et al.* (1984) to induce angiogenesis in the rabbit cornea. Fernandez *et al*. (1985) found high renin-like activity in preovulatory follicular fluid, and a correlation between plasma renin activity and severity of OHSS has been demonstrated (Navot *et al.*, 1987).

Prevalence and factors influencing the incidence of OHSS after ovarian stimulation

In IVF treatment, the development of mild ovarian stimulation, allowing recruitment of a cohort of mature follicles, is a primary goal. The incidence of severe OHSS is relatively rare in patients undergoing ovarian stimulation for IVF when compared with ovulation induction cycles. Schenker and Weinstein (1978) reported the occurrence of severe OHSS after ovarian stimulation for ovulation induction in ~2% of the cycles. The incidence of severe OHSS after ovarian stimulation ranges from 0.5 to 1.8% (Padilla *et al*., 1990; Smitz *et al*., 1990; Rizk and Aboulghar, 1991; MacDougall *et al*., 1992; Aboulghar *et al*., 1993; Pattinson *et al*., 1994). The prevalence of 0.7% found in our population is comparable with these reports. Puncture and aspiration of the ovarian follicles is apparently an effective way to avoid ovarian hyperstimulation (Golan *et al*., 1989).

Several factors have been reported to influence the incidence of OHSS. The importance of polycystic ovaries (PCO) as a risk factor has been stressed (Schenker and Weinstein, 1978; MacDougall *et al*., 1992; Rizk and Smitz, 1992; Wada *et al*., 1993). Among the 18 patients with severe OHSS in our population, seven (39%) had been diagnosed as having PCO. A high ovarian response during ovarian stimulation, resulting in a high oocyte yield, is associated with a higher incidence of OHSS (Delvigne *et al*., 1991; Sher *et al*., 1993; Wada *et al*., 1993). An increased prevalence of OHSS is seen when GnRHa is used during ovarian stimulation (Golan *et al*., 1988; Forman *et al*., 1990; MacDougall *et al*., 1992). The administration of ovulatory HCG has been proposed as the most important factor in inducing OHSS (Smitz *et al*., 1990; Wada *et al*., 1993). The pregnancy rate in OHSS cycles is reported to be 3- to 4-fold higher when compared to cycles without signs of hyperstimulation (Golan *et al*., 1988). Oocyte donors in donor programmes have a very low risk of OHSS, probably because of the absence of pregnancy after ovarian stimulation (Morris *et al*., 1995). These reports suggest a positive role of endogenous HCG in the development of OHSS. Dahl Lyons *et al.* (1994) differentiated between early OHSS, presenting 3–7 days after HCG administration, and late OHSS, presenting 12–17 days after HCG administration. Early OHSS was predicted by the number of oocytes retrieved and the oestradiol concentration on the day of HCG administration, while late OHSS was associated with the number of gestational sacs seen on ultrasound 4 weeks after embryo transfer. The authors concluded that early OHSS was an effect of the HCG administered prior to oocyte retrieval and late OHSS was induced by the rising serum concentration of HCG produced by the early pregnancy. In cases where a high ovarian response occurs, the use of exogenous HCG for luteal phase supplementation increases the risk of development of OHSS (Rizk and Smitz, 1992).

Prevention of OHSS

Several methods have been proposed to lower the incidence of OHSS. Patients who previously developed OHSS, or who are known to have PCO, should be treated with a low-dose gonadotrophin protocol (MacDougall *et al*., 1992; Rizk and Smitz, 1992). In our IVF programme, patients with PCO are treated with two ampoules (150 U) HMG per day, and patients who previously had OHSS with 1–2 ampoules. The condition did not recur in the severe form in the same patient.

Oestradiol peak concentration and rate of increase during ovarian stimulation, number and size of follicles developing, and number of oocytes collected are parameters used for prediction of the development of OHSS. In view of this, close monitoring of ovarian stimulation as a method for prevention of OHSS has been advised (Rizk and Smitz, 1992). However, a considerable overlap of distribution of these values between OHSS and control populations has been found (Delvigne *et al*., 1991). Therefore, the value of intensive monitoring for prevention of OHSS has been debated (Tan, 1994; Roest *et al*., 1995b).

Monitoring for impending OHSS is carried out by transvaginal ultrasound examination, frequently combined with measurements of serum oestradiol concentration during ovarian stimulation. In case an explosive ovarian response occurs, ovulatory HCG can be withheld and the IVF cycle cancelled. However, precise criteria for impending OHSS and subsequent cancellation of the IVF cycle are lacking. There is wide variation between authors in the oestradiol concentrations above which they advise HCG to be withheld. Forman *et al.* (1990) withheld HCG at an oestradiol serum concentration >2000 pg/ml. In these cases the administration of gonadotrophins was stopped and GnRHa continued. After a period of desensitization follicular stimulation was recommenced with a lower dose of gonadotrophins. Other authors (Chenette *et al*., 1990) developed less strict criteria and reported that cycles with oestradiol levels

≤5000 pg/ml need not be cancelled and can proceed to oocyte recovery and embryo transfer. Morris *et al*. (1995) found only one case of OHSS among 10 patients with oestradiol concentration >6000 pg/ml and >30 oocytes recovered. They concluded that the risk of OHSS at high levels of stimulation is lower than previously believed. In contrast, Asch *et al*. (1991) found OHSS in 80% of the patients with peak oestradiol >6000 pg/ml and >30 oocytes collected. The same authors found no cases of OHSS with serum oestradiol concentrations <3500 pg/ml, and only one case in a group of 67 patients with levels between 3500 and 6000 pg/ml.

In several IVF programmes, monitoring of ovarian stimulation is carried out by transvaginal ultrasound examinations only (Tan, 1994; Wikland *et al*., 1994; Roest *et al*., 1995b). In these programmes the number of developing follicles is used as the criterion to cancel the cycles or proceed to oocyte retrieval. The development of >30–35 follicles, corresponding with a serum oestradiol concentration of ~6000 pg/ml (Asch *et al*., 1991), has been mentioned as the criterion for cancellation (Sher *et al.*, 1993; Roest *et al*., 1995b).

Besides cancellation of the cycle, several other approaches are possible in cases of impending OHSS. Withholding the ovulatory dose of HCG is one option. It was postulated that the longer half-life, higher affinity and longer intracellular effect of exogenous HCG compared to endogenous HCG results in a more extensive luteinization of hyperstimulated ovaries. Therefore, Gonen *et al*. (1990) used the initial flare-up effect of GnRHa to achieve the final follicle maturation. Discontinuation of gonadotrophin therapy and deferring HCG administration until the plasma oestradiol concentration drops below 3000 pg/ml, called 'prolonged coasting', has also been proposed (Sher *et al*., 1993).

Elective cryopreservation of all embryos of patients at high risk of development of OHSS, to avoid a pregnancy and subsequent production of endogenous HCG in the stimulation cycle, is another option for prevention. It has been reported that this procedure reduces the severity of OHSS, but not its incidence (Wada *et al*., 1993). However, a lower incidence of OHSS after cryopreservation of all embryos, with good results from subsequent thaw cycles, has been described (Pattinson *et al*., 1994).

The use of progesterone instead of HCG for luteal support is advised to reduce the risk for OHSS (MacDougall *et al*., 1992). However, support with progesterone during the luteal phase does not prevent OHSS. Progesterone (200 mg vaginally twice daily; Progestan; Organon) is nowadays routinely used in our programme when ≥15 follicles are retrieved during oocyte aspiration. Despite this, severe OHSS developed in eight cases.

In an effort to prevent third space fluid accumulation, Asch *et al*. (1993) treated high-risk subjects for OHSS with albumin so as to increase the serum oncotic pressure, and possibly reverse the leakage of fluids from the intravascular space. The patients received 50 g of human albumin i.v. at the time of oocyte retrieval. Among 36 high-risk patients no case of severe OHSS occurred. In a prospective placebo-controlled study, Shoham *et al*. (1994) confirmed the possible role of albumin in the prevention of OHSS. The authors postulated that, apart from the plasma-expanding effect of albumin, the binding and transport properties of human albumin may play the main role in the prevention of severe OHSS by binding certain factor(s) that are possibly members of the renin–angiotensin cascade. However, absolute prevention of OHSS is not achieved with albumin administration. Two cases of OHSS occurring despite the administration of albumin have been described (Mukherjee *et al*., 1995).

The key to prevention of OHSS is early identification of patients at risk. To increase the predictability of OHSS, Delvigne *et al*. (1993) developed a formula for pre-oocyte retrieval conditions in a multiple discriminant analysis. A prediction rate for the development of moderate or severe OHSS of 76.1% with a false-negative rate of 18.1% was found. The use of this formula calls for an intensive and expensive monitoring procedure and cannot prevent OHSS in all cases.

Management of OHSS

Once OHSS develops, treatment should be aimed at prevention of serious complications, relief of symptoms and shortening of hospital stay. The treatment of individual patients with OHSS varies according to its severity. Patients with moderate OHSS can be kept under surveillance as outpatients; cases of severe OHSS should be admitted. The patient should be carefully examined and the circulatory condition assessed. Vaginal examination is to be avoided because of the risk of injury to the ovaries. The ovaries should be screened by ultrasonography and the presence of ascites and pleural effusion noted. Basic laboratory investigations such as full blood count, serum electrolytes and renal function tests should be carried out. The main line of treatment is to correct the circulatory volume and the electrolyte imbalance, which will improve renal perfusion and prevent coagulation disorders. Colloidal plasma expanders such as dextran or albumin can be used to correct the hypovolaemia. The haematocrit can serve as

a guide during the treatment of the syndrome. Recording of the fluid balance is important, and urinary output must be carefully monitored. The use of heparin should be considered in severe OHSS in view of the risk of coagulopathy due to haemoconcentration. We used heparin 5000 IU twice daily for prophylactic reasons in eight out of 18 cases of severe OHSS. Paracentesis is indicated when serious abdominal discomfort or breathing difficulties are caused by extensive ascites (Smitz *et al*., 1990). Five of our patients underwent abdominal paracentesis with marked relief of symptoms. To avoid injury to the enlarged ovaries, drainage of ascites may be performed via the transvaginal route under ultrasound guidance (Aboulghar *et al*., 1993). A marked positive effect of paracentesis on the diuresis has been reported (Padilla *et al*., 1990; Aboulghar *et al*., 1993). One of our patients had an extensive pleural effusion for which bilateral thoracal drainage was necessary. It was remarkable that in this patient only a small amount of ascites was found. Hydrothorax has been described by others as the only extra-ovarian manifestation of OHSS (Daniel *et al*., 1995).

As prostaglandins have been suggested to be important mediators of the increased vascular permeability in OHSS, prostaglandin synthetase inhibitors, like indomethacin, have been used for the treatment of the syndrome (Schenker and Weinstein, 1978). However, Pride *et al*. (1986), found no effect of the use of indomethacin on ascites formation in animal experiments. Balasch *et al*. (1990) reported a case of severe OHSS complicated by prerenal oliguria and liver dysfunction due to indomethacin therapy. In view of the doubtful benefit of therapy with prostaglandin synthetase inhibitors and the possible side-effects, these drugs should not be used for the treatment of OHSS.

Secondary complications of OHSS

Although secondary complications of OHSS are rare, the severe form of OHSS should be considered a potentially life-threatening condition. Thromboembolism, acute pulmonary failure, hypovolaemic shock, hepatocellular damage and renal failure (Mozes *et al*., 1965; Balasch *et al*., 1990; Forman *et al*., 1990; Padilla *et al*., 1990; Rizk *et al*., 1990; Waterstone *et al*., 1992) are some of the complications that have been reported to occur in association with the syndrome. Mozes *et al*. (1965) reported two cases of arterial thromoembolic complications. One patient died after a carotid arteriotomy and another underwent a leg amputation. Cases of deep cerebral venous thrombosis as a complication of severe OHSS have been described (Waterstone *et al*., 1992). Deep venous thrombosis in the absence of signs of haemoconcentration in a patient with a low level of antithrombin III was reported by Kaaja *et al*. (1989). Hepatocellular damage may occur as a result of high oestrogen concentrations (Balasch *et al*., 1990). Forman *et al*. (1990) described a patient with severe OHSS who had a marked and prolonged elevation of liver enzymes, declining only after the pregnancy ended in a spontaneous abortion.

Among the cases of severe OHSS in our population, no major complications occurred. In one patient with moderate OHSS, a ruptured ovarian cyst with intra-abdominal bleeding was diagnosed during a diagnostic laparoscopy for suspected adnexal torsion. Treatment remained conservative and the clinical course was uneventful.

Adnexal torsion

In the 2495 IVF cycles studied, adnexal torsion occurred in two cases. In one case a torsion and rupture of an ovary was diagnosed. After unwinding the ovary, suturing of the rupture (necessary because of bleeding) was not possible because the ovarian tissue was too friable. An adnex extirpation was carried out. In the other case an ovariectomy was carried out because the ovary was considered too necrotic to justify a conservative approach.

Adnexal torsion is an infrequent but serious complication of ovarian stimulation and should be considered in every patient with complaints of abdominal pain and nausea during or after ovarian stimulation. Kemmann *et al*. (1990) described four cases of adnexal torsion among 648 menotrophin-induced pregnancies. Ovarian cysts are the main cause of adnexal torsion (Hibbard, 1985). Therefore the incidence of this complication can be expected to be higher among patients with OHSS. Maschiach *et al*. (1990) found 15 cases of adnexal torsion in 201 cases of OHSS, 12 of whom were pregnant. The authors advised unwinding of the ovary regardless of its morphological appearance. This procedure was carried out in 11 of 12 patients. In three patients suture of the ruptured ovary was performed; in two cases ovarian cystectomy was necessary.

Oelsner *et al*. (1993) expanded on these data by reviewing the outcomes of 40 cases of adnexal torsion managed with detorsion only. In 26 cases laparotomy was carried out, and the remaining 14 were managed with operative laparoscopy. The postoperative course was uneventful in all cases. In 35 of the 37 patients available for follow-up, a normal ovary with follicular development was noted on ultrasound examination. It appears that the sparing approach should be used in the management of adnexal torsion.

Complications of the transvaginal procedure

In the population studied, one serious visceral injury occurred in 2495 oocyte retrievals; this has been reported elsewhere (Van Hoorde *et al*., 1992). The patient developed

signs of appendicitis during the week after the IVF procedure. On the eighth day after oocyte retrieval, a laparotomy was performed because of suspected peritonitis. A perforated appendix was removed. On histological examination the appendix showed several puncture holes. Intra-abdominal vascular injuries did not occur in our population.

PID was diagnosed in six patients after transvaginal oocyte retrieval, giving an incidence of 0.24% for this complication. The diagnosis was established by a rise in body temperature to >38°C and signs of pelvic peritonitis on physical examination, together with an elevated leukocyte count and erythrocyte sedimentation rate. All patients were hospitalized for i.v. antibiotic treatment. In none of the cases was a surgical approach necessary. The mean duration of hospital admission was 13 days (range 4–21).

Oocyte retrieval for IVF was initially carried out by laparoscopy. The complications of this procedure were related to the anaesthesia, pneumoperitoneum and visceral and vascular injuries caused by trocar insertion (Schenker and Ezra, 1994). Transvaginal ultrasound-guided follicle aspiration has replaced laparoscopy nowadays and has been used in our programme since 1988. This procedure is carried out under local anaesthesia and is less time-consuming. Complications are infrequent but potentially serious. Pelvic visceral and vascular injuries have been reported (Berg and Lundkvist, 1992; Van Hoorde *et al*., 1992). PID is another potential hazard. Dicker *et al*. (1993) reported five symptomatic injuries needing a surgical approach among 3656 ovum retrievals: two patients with ruptured endometriotic cystic masses and three cases of intra-abdominal bleeding. A case of infected endometriotic cysts secondary to oocyte aspiration was described by Yaron *et al.* (1994).

The risk of pelvic infection was initially seen as a disadvantage of the transvaginal approach. To reduce this risk, administration of preventive antibiotics and vaginal disinfection have been proposed (Meldrum, 1989; van Os *et al*., 1992; Peters *et al*., 1993). However, the efficacy of these measures has not been established. Børlum and Maigaard (1989) reported two pelvic infections after 400 vaginal procedures using the semi-sterile technique and concluded that acceptable safety is achieved without the use of rigorous disinfection or preventive antibiotics. The low incidence of PID in our population supports this. Reports from large series show a low incidence of PID after transvaginal follicle aspiration. Ashkenazi *et al*. (1994) found 28 cases among 4771 patients, and Bennett *et al*. (1993) reported 18 cases after 2670 procedures, giving incidence rates of 0.58 and 0.68% respectively. Pelvic infection after IVF treatment is not necessarily the result of transvaginal ovum retrieval, since a case of PID as a result of embryo transfer in an oocyte donation cycle was reported by Sauer and Paulson (1992).

Table I. Rate of ectopic pregnancy according to indication for in-vitro fertilization. Values in parentheses are percentages

Indication	Pregnancies	Ectopic pregnancies
Tubal	297	8 (2.7)[a]
Non-tubal	327	5 (1.5)[a]

[a]The rate of ectopic pregnancy was not significantly different between the two groups.

Ectopic pregnancy

Out of the 624 pregnancies obtained in the IVF population studied 13 were ectopic, giving an ectopic pregnancy rate of 2.1%. The incidence of ectopic pregnancy was analysed according to indication for IVF. The results are shown in Table I. In one case an ectopic pregnancy was found in both Fallopian tubes, and in two cases a heterotopic pregnancy, the combination of an ectopic with an intra-uterine pregnancy, was diagnosed.

The first pregnancy obtained after IVF was an ectopic (Steptoe and Edwards, 1976). The reported incidence of ectopic pregnancy after IVF–embryo transfer varies from 2 to 11% (Lopata, 1983; Azem *et al*., 1993). In view of the 1.2–1.4% incidence for all reported pregnancies (Chow *et al*., 1987), the risk for an ectopic pregnancy after IVF is high and apparently related to the high incidence of tubal dysfunction in the IVF population. The incidence reported in multicentric studies is ~5% (Cohen *et al*., 1986; Ezra and Schenker, 1993). The incidence for ectopic pregnancy of 2.1% in our population is low when compared with results of multicentric studies. No statistically significant higher incidence was found in the group with tubal dysfunction (Table I). Conflicting data have been reported on the risk factors associated with ectopic pregnancies after IVF. Tubal dysfunction appears to be a risk factor (Cohen *et al*., 1986; Herman *et al*., 1990; Dubuisson *et al*., 1991; Azem *et al*., 1993; Verhulst *et al*., 1993; Marcus *et al*., 1995), and preventive measures prior to IVF treatment have been proposed. Steptoe *et al*. (1980) advised occlusion of the utero-tubal junction on each side if diseased tubes are present but stated that removal is not required. The same suggestion was made by other authors (Tucker *et al*., 1981). However, Karande *et al*. (1991) reported two interstitial pregnancies after IVF, one in a patient with a previous bilateral salpingectomy and the other in a patient who had a salpingectomy on the side of the ectopic. Apparently, during embryo transfer embryos can be flushed into the Fallopian tubes. When tubes are normal, the embryos return to the uterine cavity, simulating the physiological journey of the fertilized ovum. This transport may be thwarted when the tubes are dysfunctional.

The embryo transfer technique has been suggested as a factor for the occurrence of ectopic pregnancies. Knutzen *et al*. (1992) injected 40 µl of radiopaque fluid in a mock embryo transfer and found flux into the Fallopian tubes in 38% of patients. They advised transfer of embryos in a small amount (10–20 µl) of culture fluid in an attempt to prevent reflux. Yovich *et al.* (1985) inserted the delivery catheter 55 mm only and concluded that this gives an embryo transfer to a standard midcavity position, resulting in a lower ectopic pregnancy rate.

Evidence exists that ovarian stimulation is associated with an increased incidence of ectopic pregnancy (Fernandez *et al*., 1991). McBain *et al*. (1980) found a high rate of ectopic pregnancy following ovulation induction in the absence of predisposing factors. They found an association between the occurrence of ectopics and an elevated urinary oestrogen excretion in the peri-ovulatory phase of induced ovulatory cycles, and concluded that high oestrogen concentrations influence tubal embryo transport. The use of clomiphene citrate combined with HMG for ovarian stimulation has also been reported to be a risk factor (Cohen *et al*., 1986; Verhulst *et al*., 1993). Other authors could not confirm this (Dubuisson *et al*., 1991; Marcus and Brinsden, 1995).

The incidence of combined intrauterine and extrauterine pregnancy is evidently higher after IVF than in spontaneous pregnancies. Rizk *et al.* (1991) reported a frequency of 1% in clinical pregnancies after IVF. Marcus *et al.* (1995) found 20 heterotopic pregnancies among 2650 clinical IVF pregnancies, giving a frequency of 0.75%. A heterotopic pregnancy can give diagnostic difficulties (Fisch *et al.*, 1995; Mooseburger and Tews, 1996) and should always be included in the differential diagnosis of symptomatic patients with an intrauterine pregnancy after IVF.

Conclusion

In conclusion, our data and those reported in the literature show that IVF treatment, performed under good medical and laboratory practice conditions, carries an acceptable risk of complications. Strict prevention of OHSS is not possible; however, sharp attention to its symptoms and adequate treatment can lead to a less severe course of disease. Adnexal torsion occurs infrequently and ovariectomy is hardly ever indicated in these cases. Symptomatic visceral lesions and PID as a result of follicle aspiration are rare. The risk for an ectopic pregnancy is higher when compared with the general population. Despite the low incidence of serious complications, counselling of patients on this aspect of IVF treatment appears necessary.

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