Assisted Reproductive Technique Complications in Pregnancy

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10.1 Introduction

The sterility uses, currently, two techniques of treatment, the homologous insemination (Fig. 10.1) and intracytoplasmic sperm injection (ICSI) (Fig. 10.2). This chapter presents the complications of pregnancy after in vitro fertilization (IVF). These complications are presented as they arise during the process of ovarian stimulation (Fig. 10.3a, b). Mainly, meta-analytic studies have been used with priority, where available. The majority of complications during IVF or ICSI are presented as case reports. Differences have been observed in management options, especially the surgical management. Complications may be due to three main causes: pharmacologic stimulation, previous illnesses that complicate medical treatment, and surgical complications due to ovarian follicular pickup (Fig. 10.4). Pathophysiologic studies associated with these complications have been reported in a concise form.

10.2 Before IVF and During Patient Selection

10.2.1 Diseases That Pose Specific Risks in IVF Treatment

Severe mixed connective tissue disease (MCTD) mixes features of systemic lupus erythematosus (SLE), systemic sclerosis (scleroderma) polymyositis, and a high titer of anti-ribonucleoprotein (RNP) antibody. Pregnancies of women with MCTD may be complicated by maternal disease flares, fetal loss, pregnancy-induced hypertension and preeclampsia, preterm delivery, and small-for-gestational-age babies with neonatal lupus. In case pulmonary hypertension (PH) develops, a significant cause of death in MCTD, it is an

In memory of Prof. Dimitrios Hassiakos, Aretaieion University Hospital, 1st Department of Obstetrics and Gynecology, Athens, Greece, a true inspirational leader in obstetrics and gynecology.

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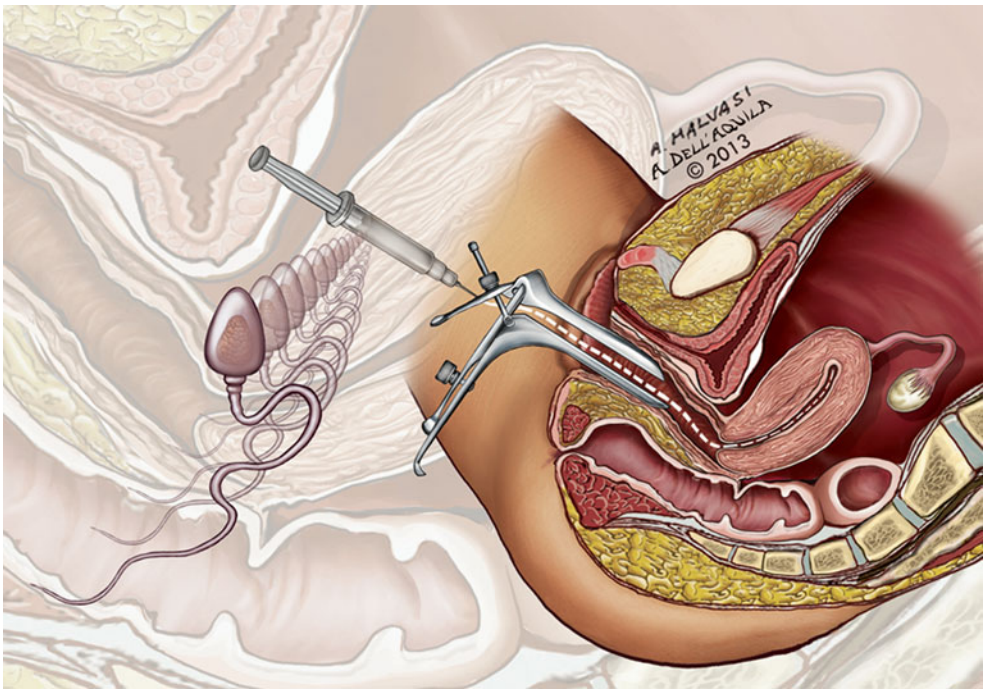

Fig. 10.1 The figure represents an intrauterine insemination

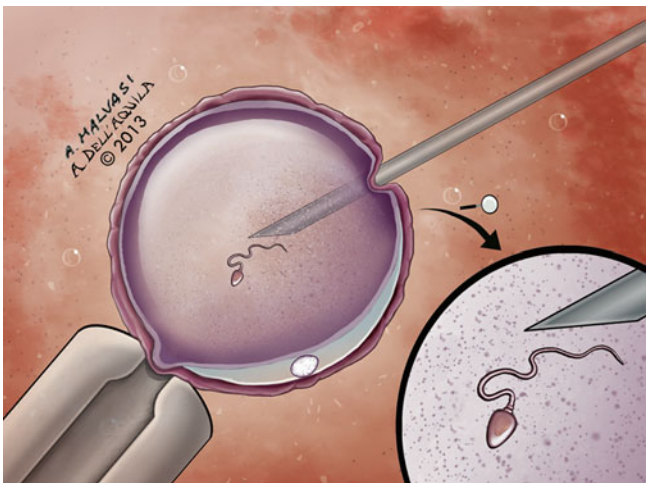

Fig. 10.2 The figure shows the intracytoplasmic sperm injection (ICSI) technique

absolute contraindication for carrying a pregnancy and in vitro fertilization and surrogacy are advised.

In a case, a 25-year-old woman referred to an IVF clinic underwent controlled ovarian hyperstimulation and embryo cryopreservation because she is planning autologous bone marrow transplantation. Her clinical situation was severe, with pulmonary hypertension and antiphospholipid antibody with a history of bilateral pulmonary embolism. She underwent mild ovarian hyperstimulation with a GnRH antagonist protocol and hCG trigger for final oocyte maturation. Two days after oocyte retrieval, she developed signs of infection, bibasilar atelectasia, and small pleural effusions. Obviously, in the pelvis, enlarged ovaries and moderate amounts of free fluid were observed. After 4 days, she developed hypoxia after multifocal pneumonia, hemoptysis, pulmonary hypertension, and fibrosis. Eventually, she developed ischemic colitis and left common femoral vein thrombosis. Because of prolonged respiratory failure, she had a tracheotomy. After 3 months of treatment, patient was discharged. The patient remained in stable condition for the next year and, at that time, had a spontaneous pregnancy that ended in miscarriage. After all these events, patient performed sterilization with laparoscopic bilateral tubal ligation and opted for a gestational carrier [1].

10.2.2 PCOS and Obstetric Complications After ART

Women with PCOS, after IVF, experience early pregnancy loss at a rate of 17 %, when compared with normally conceiving women at 15 %. Increased frequency of cervical incompetence has been found in pregnant PCOS women. In addition, PCOS women with CI were also more probable to have received gonadotrophin therapy, but it is still not recognized whether factors, like race and fertility drugs, play a part.

Likewise, women with PCOS, when pregnant, carry a significantly higher chance to develop gestational diabetes mellitus. A strong association between PCOS and preeclampsia has been established, and this is augmented by the fact that

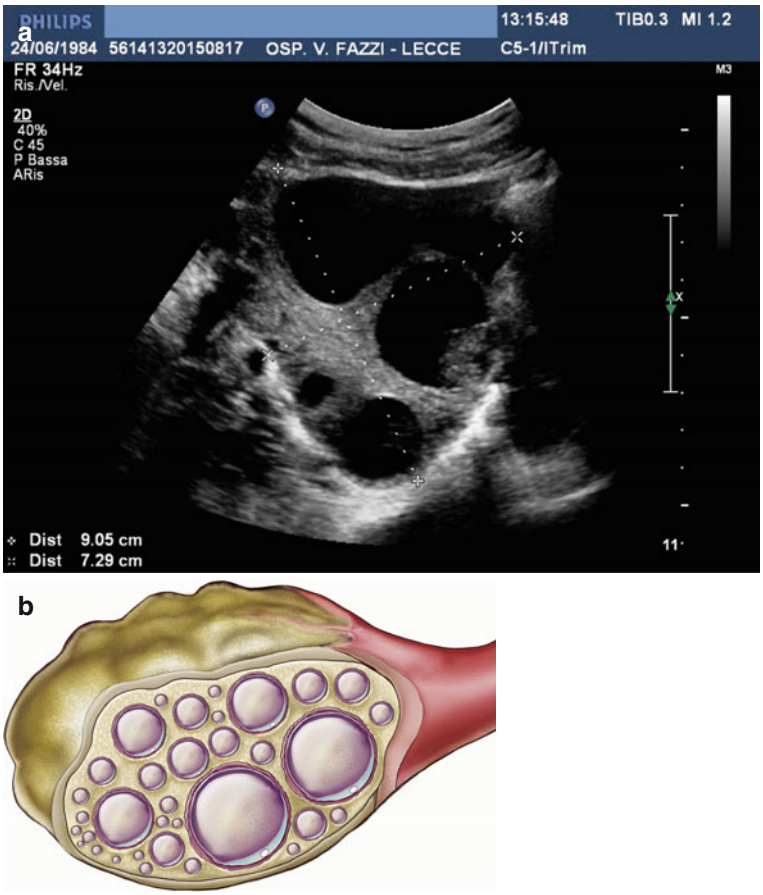

Fig. 10.3 (**a**, **b**) On the *left*, ultrasonographic transvaginal scan of an ovarian hyperstimulation; on the *right*, the corresponding draw

women undergoing ART have an increased risk of hypertensive disorders [2].

On the contrary, women on PCOS do not deliver small-for-gestational-age offspring, except secondary to pre-eclampsia. They usually deliver large-for-gestational-age babies, even in the absence of GDM.

Patients with the combination of PCOS and obesity have smaller oocytes [3]. Lean Chinese PCOS women present with higher clinical pregnancy rate after IVF than obese PCOS women of the same ethnicity [4]. Increased abdominal obesity is associated with increased lipid peroxide levels, and it is independent from PCOS but it is exacerbated by its presence [5].

10.2.3 Obesity and ART Pregnancy Complications

10.2.3.1 Maternal Obesity

Obese women are affected by metabolic syndrome (Fig. 10.5) and do not need higher FSH doses [6]. No significant difference has been found for euploid embryos, among overweight/obese women, when compared with normal weight women [7]. Also, pill administration for ovarian downregulation and follicle synchronization, in obese women, increases antral follicle count [8].

On the other hand, bariatric surgery that decreases BMI significantly reduces the amount of gonadotrophin needed; however, no other observed stimulation parameters change [9].

Overweight women with BMI between 25.0 and 29.9 kg/m^2 present with low offspring birthweight (<2500 g) [10]. Very early preterm birth is increased from maternal obesity [10]. The same applies for morbidly obese women (≥35.0 kg/m^2), both in singleton and twin pregnancies [11].

Obese poor responders, with BMI (≥30.0 kg/m^2), showed significantly lower fertilization and clinical pregnancy rates [12]. Metabolomic profiling from day 3 embryos culture media is different among obese and nonobese women [13]. In obese women, the number of COCs retrieved and MII oocytes are lower after IVF, but this does not apply to women with minimal stimulation [14]. It seems that oocyte mitochondria play a role [15] on obesity-related birth defects. With a mouse experimental model, fed with high-fat diet, maternal obesity is associated with oocyte meiotic aneuploidy and abnormal processes distinct from meiotic aneuploidy that both leads to early embryonic loss [16].

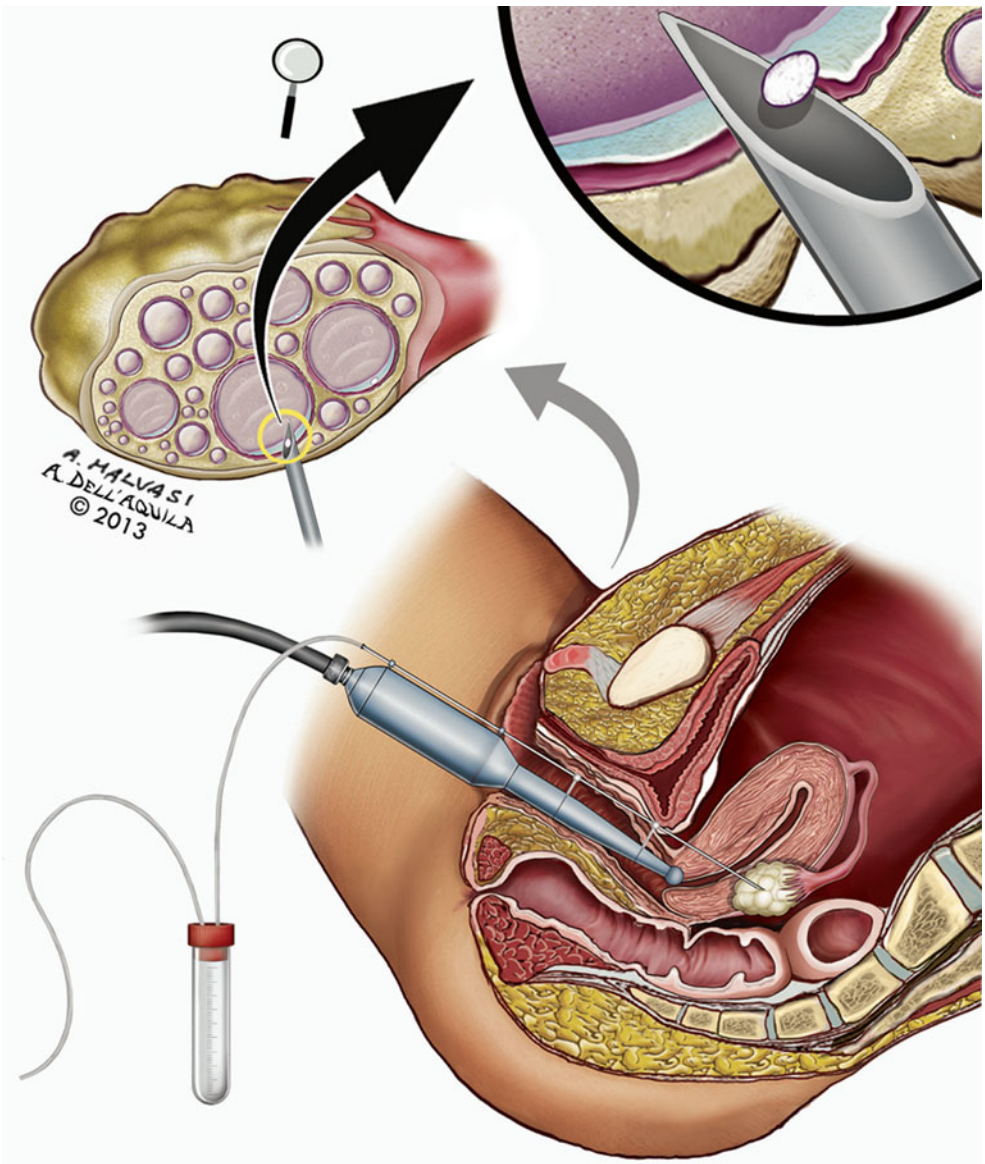

Fig. 10.4 An ovarian follicular pickup guided by transvaginal ultrasonography

10.2.3.2 Paternal Obesity

On the other hand, paternal obesity is associated with infertility (OR = 1.66, 95 % CI 1.53–1.79), reduced live birth per cycle (OR = 0.65, 95 % CI 0.44–0.97), and increased pregnancy embryo lethality [17]. Furthermore, offspring that came from high-fat diet mouse males and continues in the same diet shows a reduction in sperm motility, decreased sperm oocyte binding, and impaired overall parameters [18]. Preconception paternal obesity increases the incidence of metabolic disorders in offsprings [19]. Global methylation is significantly increased on female placentas that came from obese fathers [20], while preconception diet/exercise in these males normalizes sperm profile and metabolic status in female offspring [21]. Obviously, a lot more can be documented for obesity and IVF, but remains outside the scope of this chapter.

10.3 GnRH Downregulation and Ovarian Stimulation

10.3.1 Organ Dysfunction and Damage from GnRH Administration

10.3.1.1 Bowel Dysmotility

After GnRH analog downregulation, gastrointestinal complaints and bowel dysmotility have been described. In one study, the majority of patients experienced bowel dysmotility and suffered from endometriosis, while two patients have been homozygous for minor allele G, at the single nucleotide polymorphism. Another three patients expressed IGM antibodies against GnRH1 [22]. From animal studies, increased apoptosis of submucous and myenteric neurons in the fundus, ileum, and colon has been observed and possibly by

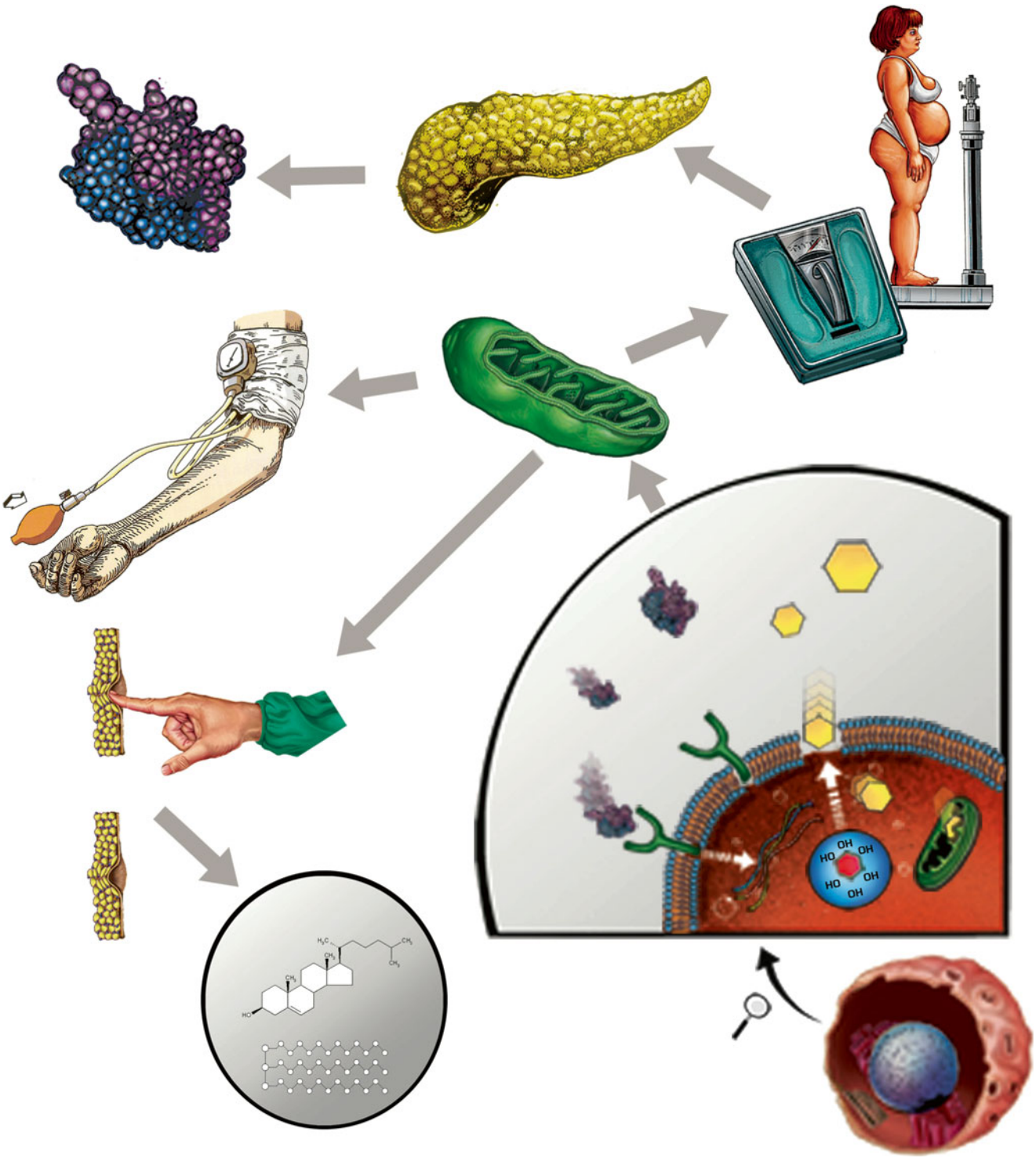

Fig. 10.5 Obesity is often associated with the metabolic syndrome: glucose intolerance, diabetes, hypertension, and dyslipidemia. Women with the metabolic syndrome to be submitted to ART are prepared with light therapy (inositol, secondary messenger of insulin)

neuron LH-receptor hyperactivation. These experimental data are associated with bowel dysmotility [23]. In humans, patients with dysmotility had depletion of gonadotrophin-releasing hormone (GnRH) receptors in the enteric nervous system (ENS) and serum antibodies against GnRH [24].

10.3.1.2 Bowel Obstruction

Small bowel obstruction, secondary to ovarian torsion after OHSS, has been observed at 12 weeks of gestation. Ovary was removed due to necrosis. Pregnancy viability was confirmed and patient discharged [25].

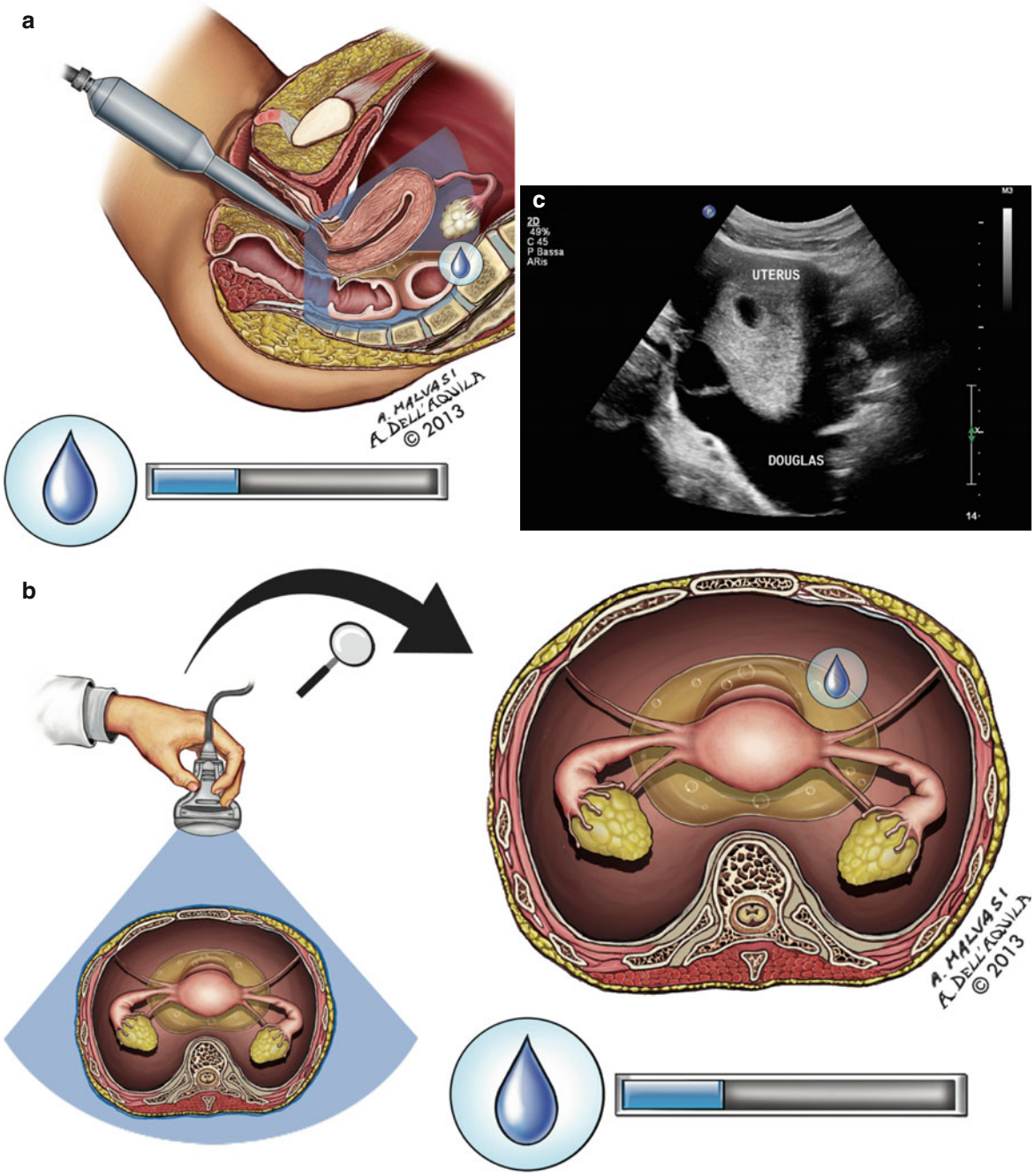

Fig. 10.6 (**a**, **b**) The mild ovarian hyperstimulation syndrome (OHSS) is represented, on the *left*, by a transvaginal ultrasonographic (US) scan and, in the *middle*, a transabdominal (US) examination, on the *right* an ultrasonographic photo

In another case, a 31-year-old woman after GnRH agonist administration and the flare-up effect revealed endometriosis recurrence from a deep endometriosis lesion, affecting the sigmoid and colorectal junction, eventually leading to bowel occlusion. Surgical resection of this laceration was necessary before treatment continuation [26]. A rare late complication from ileus has been reported after oocyte retrieval, at 28 weeks of gestation [27].

10.4 Ovarian Stimulation

The ovarian hyperstimulation syndrome (OHSS) is classified as mild, moderate, and severe, as American Fertility Society (AFS) reports:

1. Mild OHSS (Fig. 10.6a–c) is classified as follows:
Grade 1 – Abdominal distention and discomfort

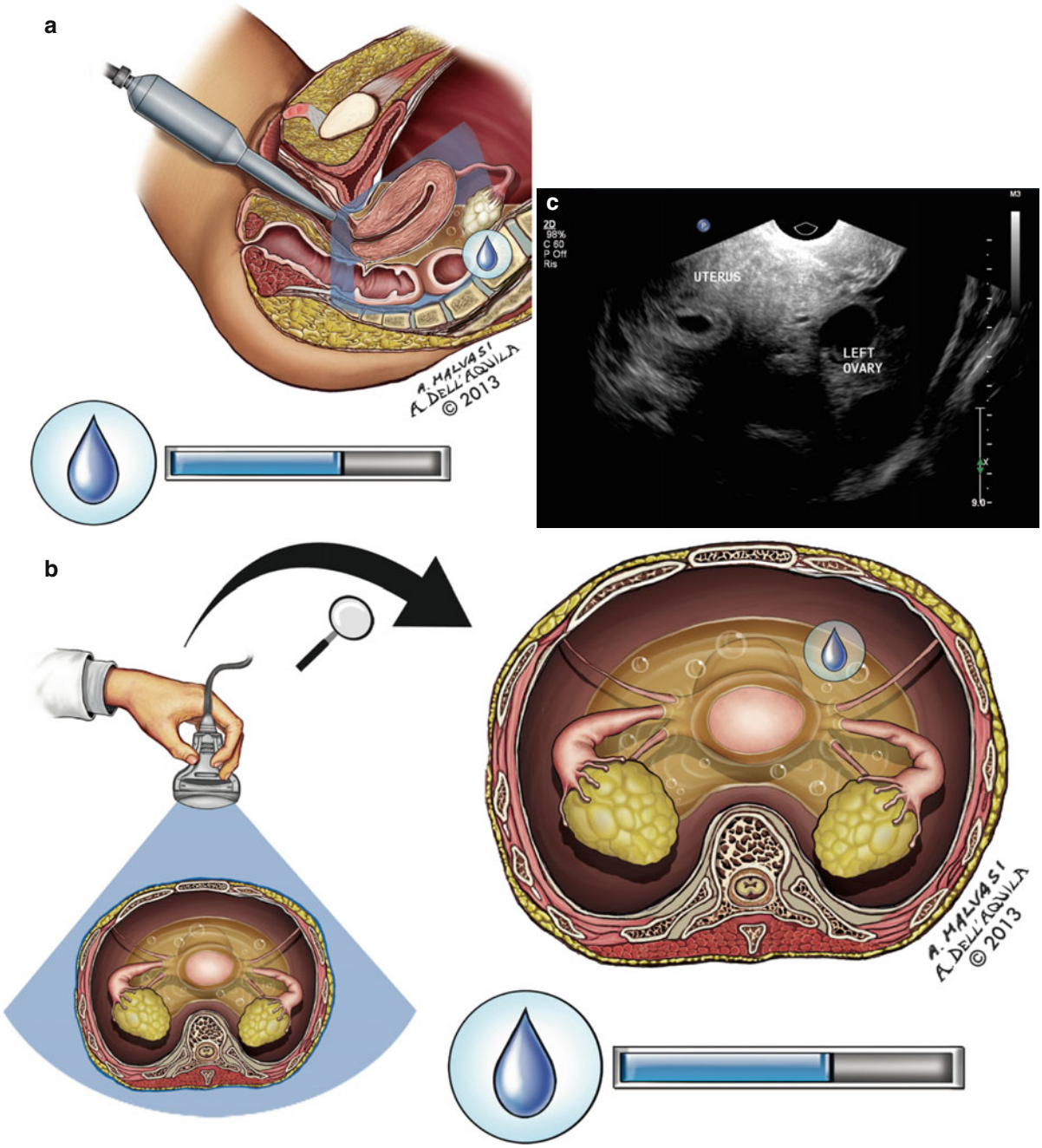

Fig. 10.7 (**a**, **b**) The moderate ovarian hyperstimulation syndrome (OHSS) is represented, on the *left*, by a transvaginal ultrasonographic (US) scan and, in the *middle*, a transabdominal (US) examination, on the *right* an ultrasonographic photo

Grade 2 – Grade 1 disease plus nausea, vomiting, and/or diarrhea, as well as ovarian enlargement of 5–12 cm

2. Moderate OHSS (Fig. 10.7a–c) is classified as follows:

Grade 3 – Features of mild OHSS plus ultrasonographic evidence of ascites

3. Severe OHSS (Fig. 10.8a–c) is classified as follows:

Grade 4 – Features of moderate OHSS plus clinical evidence of ascites and/or hydrothorax and breathing difficulties

Grade 5 – All of the above plus a change in the blood volume, increased blood viscosity due to hemoconcentration, coagulation abnormalities, and diminished renal perfusion and function

10.4.1 Ovarian Stimulation Neurological Symptoms

A 21-year-old woman underwent ovarian stimulation. The first day after oocyte retrieval, difficulty in speaking, mild disorientation, motor aphasia, and right-sided hypoesthesia

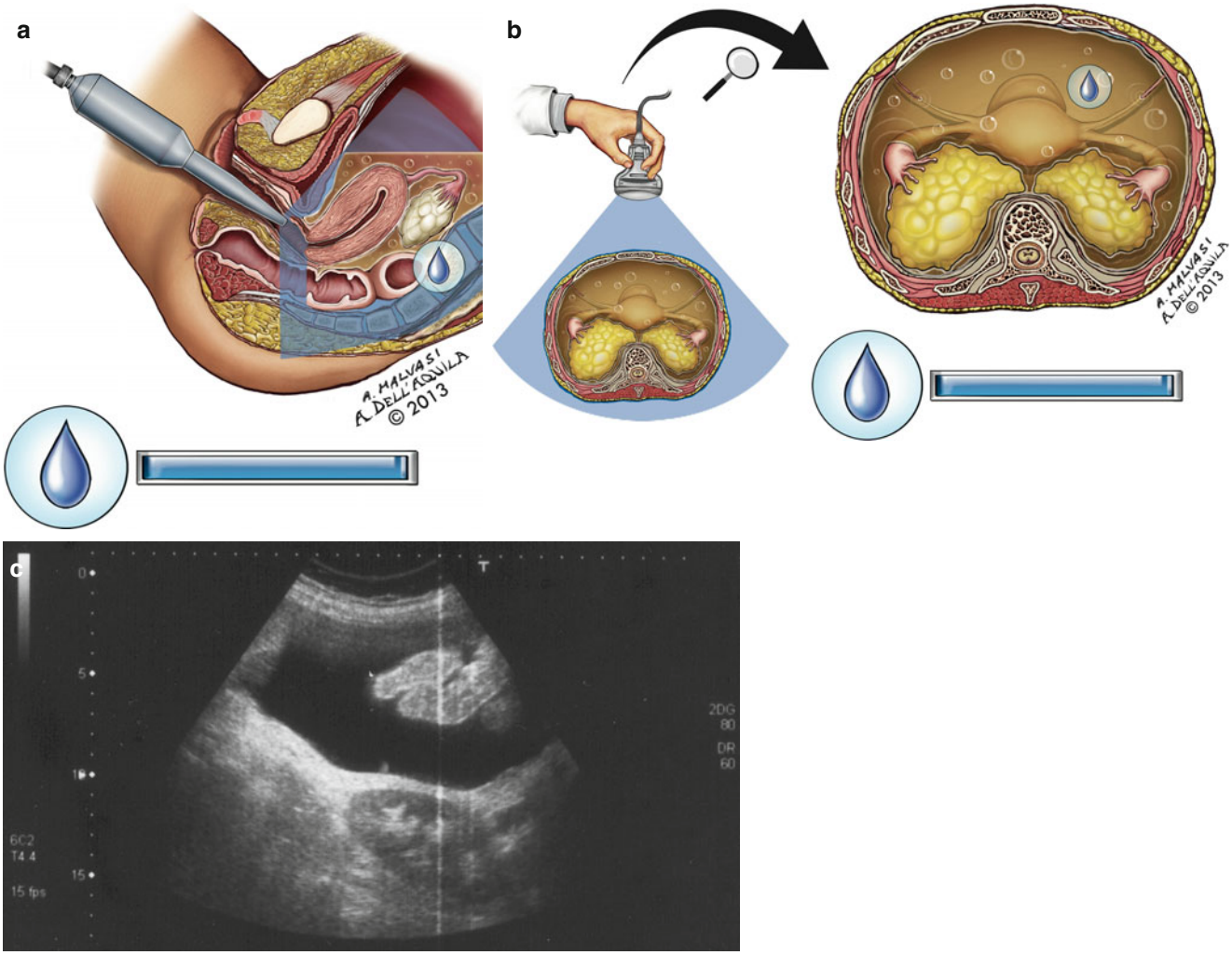

Fig. 10.8 (**a**– **c**) The severe ovarian hyperstimulation syndrome (OHSS) is represented, on the *left*, by a transvaginal ultrasonographic (US) scan and, in the *middle*, a transabdominal (US) examination, on the *right* an ultrasonographic photo

were noted. Brain-computed tomography scanning without contrast, magnetic resonance imaging (MRI), MRI angiography (MRA), and perfusion MRI were performed and showed left parietal lobe infarct with an infarct of the posterior division of the left middle cerebral artery (MCA). Patient recovered within 8 months and had a spontaneous pregnancy after 1 year. She had a vaginal delivery at 38 weeks of gestation. Ovarian hyperstimulation syndrome was not evident [28]. Another patient developed ischemic stroke after receiving clomiphene citrate and gonadotrophins [29].

More cases of thrombosis exist in the presence of ovarian hyperstimulation syndrome (OHSS). These case reports present with infarction as they have developed ovarian hyperstimulation syndrome. Main reason for arterial and venous occlusion is the hemoconcentration from the large fluid passage from the intravascular to the peritoneal cavity and subsequent increased blood viscosity.

In the first case, a female with OHSS presented with ischemic stroke due to right middle cerebral artery (MCA) occlusion. Eventually, left central hemiparesis occurred suddenly within a few days after the ET. She had magnetic resonance imaging diffusion-weighted images and a magnetic resonance angiography (MRA) that showed infarction in the right basal ganglia and revealed the occlusion of the M1 segment of the right MCA. She started the treatment, and 24 h after the stroke onset, MRA showed MCA recanalization. As a good prognosis patient, the neurological deficit resolved completely within 3 months. Eventually, she delivered two healthy infants at term [30].

The second case, after IVF, presented with sudden onset of left hemiplegia. CT scan showed a full thickness right MCA territory infarct, while a repeat MRI showed hemorrhagic conversion of infarct [31].

In the third case, a patient was already hospitalized, because she suffered from nausea and progressive abdominal distension, 8 days after ET, and all signs of ovarian hyperstimulation syndrome. She showed some improvement whereas she was treated with hypertonic solution, albumin

infusion, and paracentesis. Unfortunately, 11 days after ET and on the 4th day of hospitalization, she suddenly developed left hemiparesis, and dysarthria occurred. She progressed to complete hemiplegia within a few hours. Computed tomography and magnetic resonance angiography showed infarction of the right middle cerebral artery and occlusion of the main trunk of the right middle cerebral artery. Unfortunately, clinicians had to terminate the pregnancy because of progressive tachycardia, dyspnea, and increased abdominal girth despite supportive treatment. The neurologic deficits remained stationary at the time of discharge [32].

A 26 year old patient undergoing hMG/hCG therapy presented with multiple cerebral infarctions associated with ovarianhyperstimulation syndrome. She showed hemoconcentration, increased plasma levels of D-dimer and thrombin-antithrombin III complex, and decreased protein S activity, a hypercoagulable activity that is the base for thromboembolic events [33].

10.4.1.1 Early Diagnosis of Neurological Thromboembolic Events

Cerebral infarction associated with mild neurologic deficits may be overlooked in patients with ovarian hyperstimulation syndrome. Immediate recognition of neurologic symptoms will lead to treatment of thrombosis and brain damage minimization. On the other hand, clinicians should be aware that thrombosis may arise without ovarian hyperstimulation syndrome.

10.4.2 Ovarian Stimulation Psychiatric Symptoms

Psychotic symptoms have been described, after mild ovulation induction with clomiphene. Certain cases have been presented with transient psychosis after stimulation with a combination of clomiphene and bromocriptine [34]. The majority of them have a previous history of psychiatric disorders.

In a specific case, a 32-year-old woman developed symptoms 3 days after the start of the stimulation. On the next day, the patient had pronounced changes in her personality. Further, in the course of treatment, severe rational thought disturbances and perceptual and sensory deceptations arose. The patient was admitted to the psychiatric ward. From her medical history, it was evident that the patient had a history of psychic instability in stressful situations. After symptoms ceased after several weeks, treatment continued with human menopausal gonadotrophin plus hCG, without any psychiatric symptoms, at this time [35].

From the previous case reports, it is evident that previous psychiatric history should be taken into account, before starting ovarian hyperstimulation. In addition, rapid changes of estrogen levels due to clomiphene treatment may lead to an increased sensitivity of dopamine receptors [36].

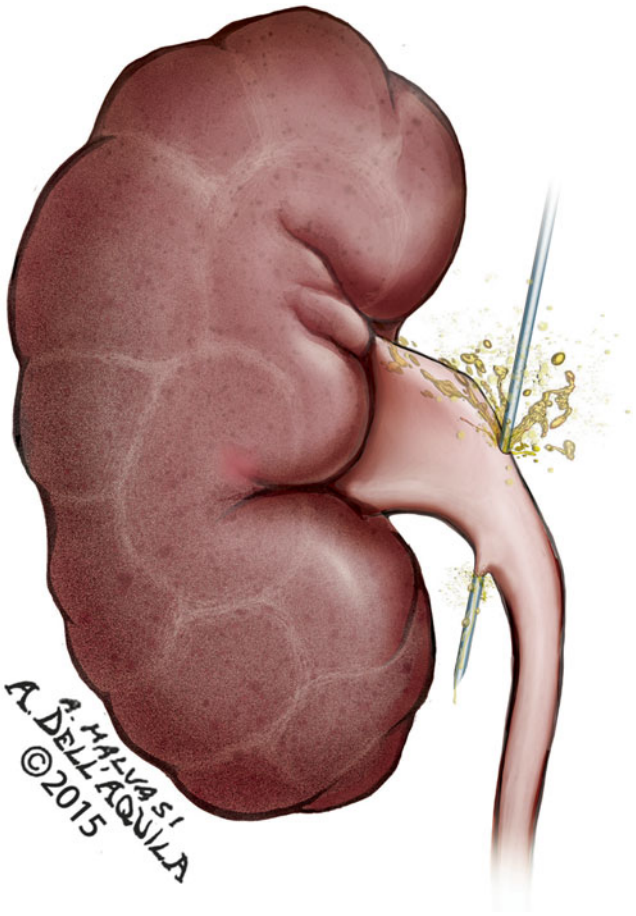

Fig. 10.9 The image shows a ureteral accidental injury during ovarian pickup

10.5 Oocyte Retrieval

10.5.1 Trauma During Oocyte Retrieval

10.5.1.1 Ureteral Injury

Ureteral injuries are rare (Fig. 10.9), but they are more possible in patients with ectopic kidney (Fig. 10.10a, b).

A 26-year-old patient presented, after oocyte retrieval, with acute pain and mild OHSS. Using computed tomography, it was found a right pelvic-ureter lesion. A right ureteral stent was placed. Patient delivers a healthy baby [37]. Another patient had a ureteric injury after OPU and treated also with ureteral stents. Stent was inserted in the next oocyte retrieval and better ureteral visualization was allowed, thus avoiding a repeat injury. A pregnancy occurred [38].

A 34-year-old patient received her second IVF attempt and 19 oocytes were retrieved after OPU. After 7 days, she presented with right lower quadrant pain. Using abdominal/pelvic computerized tomography, right hydronephrosis and mild hydroureter were found. Patient underwent cystoscopy and right ureteroscopy. Scope could not pass beyond 1 cm of the ureterovesical junction. A thrombus with underlying

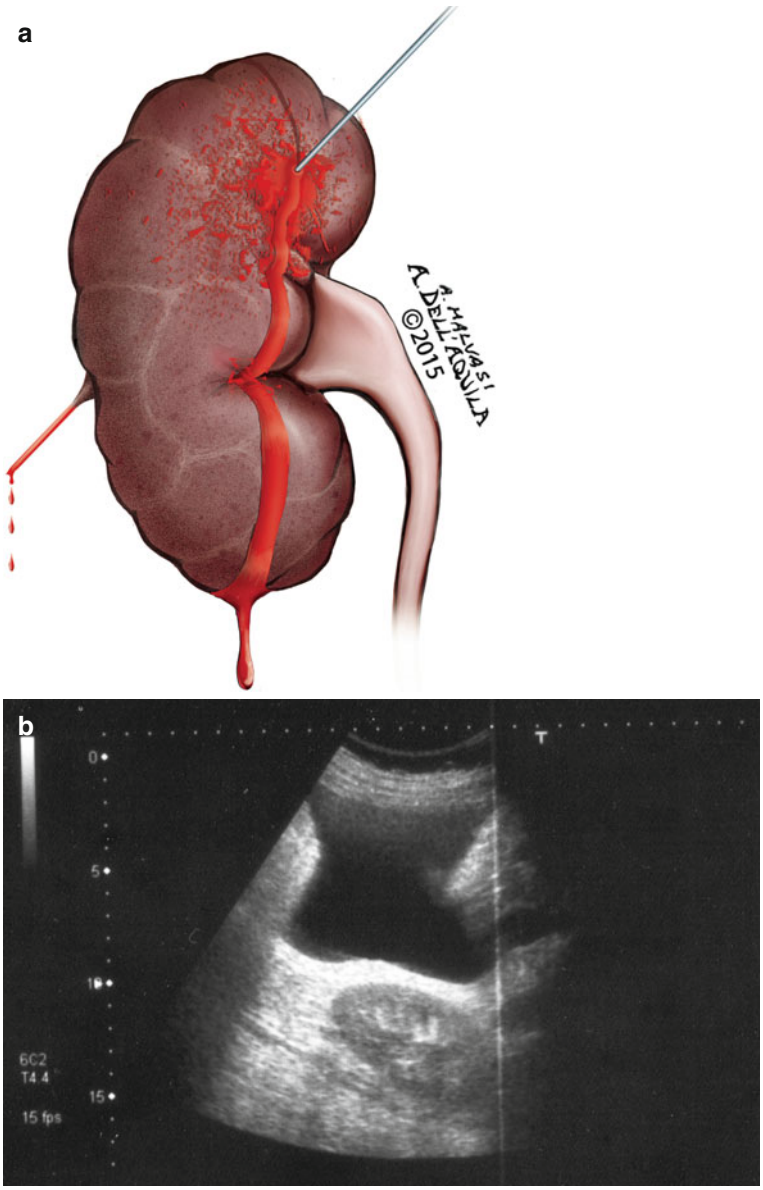

Fig. 10.10 (**a**, **b**) On the *left*, it is represented as an accidental puncture of the kidney; on the *right*, a transabdominal ultrasonographic image, showing an ectopic kidney in a patient with a severe OHSS

mucosal disruption was detected. A stent was placed and after symptoms resolved was removed with an office cystoscopy after 3 weeks. Unfortunately, this patient had a negative pregnancy test [39]. Another patient presented after OPU, with massive hematuria [40]. Immediate cystoscopy performed and revealed pseudoaneurysm. Consequent hemodynamic instability was stabilized with blood transfusion. Pseudoaneurysm was resected and cauterized.

Ureteric injuries are rare complications after OPU. Certain measures include the use of color Doppler technique to preview the needle path to avoid vessels [41] and maintain a needle lateral position than a anterior one. Have in mind that pelvic adhesions may exist due to endometriosis or pelvic infection and distort ureteric structures, ensuring that the aspiration needle do not pass through the ovary. Operators should know that symptom presentation may be early or late; they do present with compromised ureteral function. Differential diagnosis includes adnexal torsion, intraovarian hemorrhage or torsion, hematoma formation from pelvic blood vessels injury, and OHSS. Administration of antibiotics prevents infection. Stent insertion is the therapeutic solution. Stents should be inserted before repeat OPU also, to avoid another trauma.

During ovarian pickup, it is possible also to detect bladder lesions (Fig. 10.11a, b).

10.5.1.2 Vessel Injuries

Vessel punctures are possible during ovarian pickup (Fig. 10.12a, b). A patient presented with a pseudoaneurysm of left inferior pudendal artery. Diagnosis was set by US and angiography and treated with embolization. A cesarean section was performed at 32 weeks and a healthy infant was

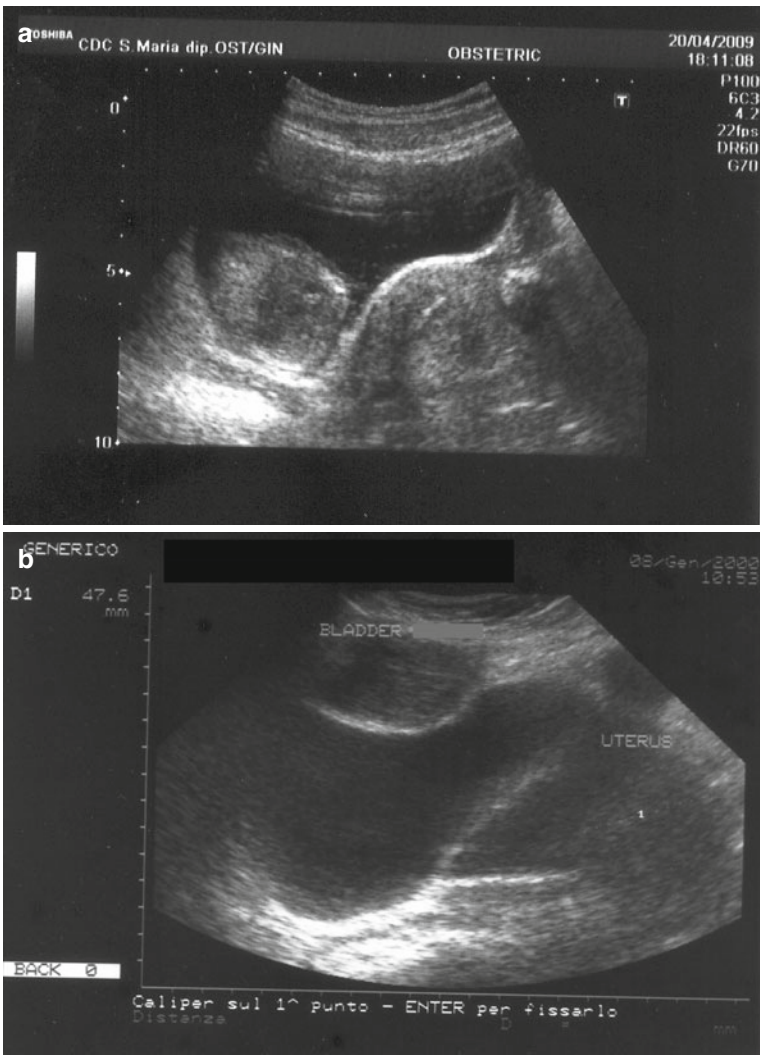

Fig. 10.11 (**a**, **b**) On the *left*, a transabdominal ultrasonographic scan showing coats into the bladder after an accidental puncture during an ovarian pickup; on the *right*, the image shows a hematoma of bladder dome, after an accidental puncture during ovarian pickup

delivered [42]. Late presentation takes place also. A pelvic pseudoaneurysm developed after an OPU 6 years earlier. It was treated by arterial embolization [43].

10.5.2 Specific Oocyte Retrieval (OPU)

10.5.2.1 OPU for In Vitro Maturation

Except oocyte retrieval of IVF, patients may undergo OPU for in vitro maturation. No serious complications have been seen for this technique. In a retrospective cohort study, 188 women underwent OPU for this reason. Only one patient presented with pelvic infection. Another patient had severe abdominal pain after retrieval. It seems that this technique is well tolerated although requires more punctures per ovary [44].

10.5.2.2 Transabdominal Oocyte Retrieval

When ovaries are not accessible through vaginal approach, then transabdominal retrieval should be undertaken. In a study [45], in 12 years, only one complication arose that needed hospitalization. Otherwise, this technique is safe and presents no statistical difference, with vaginal oocyte retrieval, between treatment parameters except the lower number of oocytes retrieved.

10.5.2.3 Hydrosalpinx Fluid Aspiration

In one of the first studies for hydrosalpinges ultrasound-guided aspiration [46], positive significant difference has been observed for clinical, ongoing pregnancy and the implantation rates, while patients with presence of hydrosalpinges had poor IVF outcomes.

In another study, aspiration took place after all oocyte retrieval, if hydrosalpinges are still present. Implantation and pregnancy rates are increased, if fluid reaccumulation takes place after the first 2 weeks of aspiration. This technique is simple safe and effective under ultrasound-guided aspiration [47].

Another clinical trial that tested aspiration of hydrosalpinx before oocyte collection found no difference in pregnancy rates between the two groups except biochemical pregnancy rate, favoring the aspiration group. Although the effectiveness of this technique is not established, on improving pregnancy rates, it is considered safe [48].

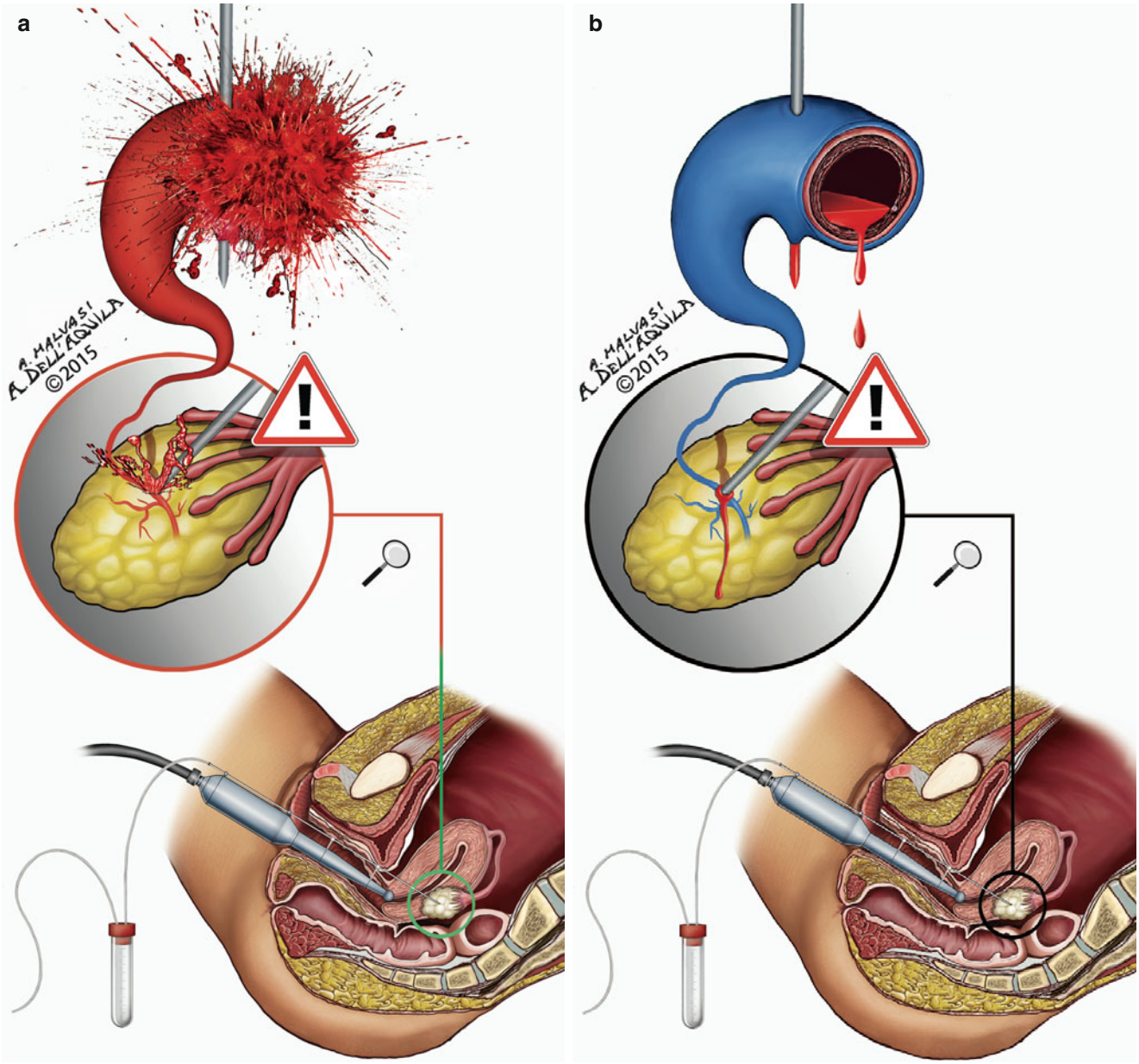

Fig. 10.12 (**a**, **b**) Accidental puncture of ovarian artery (requiring an urgent laparotomy), on the *left*, and ovarian vein (solving spontaneously, generally without problems), on the *right*

10.5.3 Strategies for OPU Injury

Although it was proposed as a method to reduce blood vessel injury risk, it is not entirely clear yet that transvaginal color Doppler ultrasound may achieve it. When it was routinely tested, it was found that it did not predict 45 % of moderate peritoneal bleeding [41]. Coagulation screening was proposed because of the risk of bleeding, after oocyte retrieval, for patients that plan an IVF cycle. The numbers needed to test to prevent one case of bleeding, associated with abnormal coagulation test, were 534 tests [49].

10.5.4 Infections After Oocyte Retrieval

10.5.4.1 Infection at Various Sites

Oocyte retrieval is considered a safe technique, but case reports associate this technique with various complications. In a case report, a 16-week pregnant woman that had undergone oocyte retrieval and ET had developed infectious spondylitis in the second and third lumbar vertebrae. Blood and spinal biopsies revealed *S. aureus*. The patient was treated with IV cefazolin (6.0 g/day) for 6 weeks. The patient delivered at 38 weeks and 4 days [50].

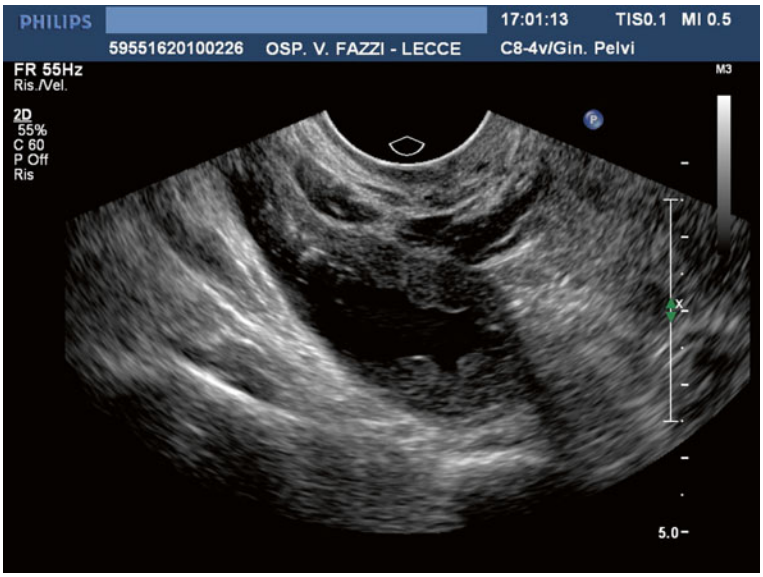

Fig. 10.13 An ultrasonographic transvaginal scan of a pyometra during first trimester after IVF

10.5.4.2 Pyometra

Two case reports of pyometra (Fig. 10.13) have been reported after oocyte retrieval. The first woman, 43 years old, presented with infection signs that eventually developed to septicemia. Pyometra was diagnosed and endometrial cavity biopsy showed vancomycin-resistant enterococci. The situation was partially resolved, and after infection recurrence, patient underwent hysterectomy. Autolyzed endometrium and subserosal and intramural abscesses have been found on the specimen [51].

The second case was detected during embryo transfer. At this patient, pyometra treatment was successful and was followed by a frozen embryo transfer. Authors conclude that the use of ultrasound during embryo transfer is essential for the diagnosis of pyometra and the change of treatment plan [52].

10.5.4.3 Ovarian Abscess

The ovarian abscess (Fig. 10.14) is a possible complication of ART. A 35-year-old woman developed pelvic infection, 16 days after oocyte retrieval. By transvaginal ultrasound, a solid mass was found between left ovary and the uterus. Both ovaries contained several follicles. The clinical situation was continuously deteriorating even with the administration of IV clindamycin and gentamicin. Consumption coagulopathy was developed. The patient underwent a midline laparotomy, and a large amount of pus was drained when incising the capsule of each ovary [53].

In a case series, three cases of tubo-ovarian abscess have been described after OPU. The first patient had a history of right ovarian cystectomy and bilateral ovarian endometriomas that were not punctured. The second one had a 3 cm ovarian endometrioma that was punctured and the third one with a history of right ovarian cystectomy for endometriosis. All three patients developed pelvic abscesses after OPU, even after antibiotic prophylaxis. Pelvic abscess had a size of 8–9 cm and the third one at 4 cm. All three cases required surgical drainage after antibiotic treatment, while the third one received right adnexectomy [54].

Rare Ovarian Abscesses

Bacteremia with *Actinomyces urogenitalis* has been described after oocyte retrieval, in parallel with tubo-ovarian abscess formation [55]. In another rare case, tuberculosis was diagnosed after histology of an ovarian abscess, after an unsuccessful IVF cycle. It is not clear whether this was initially infected or reactivated [56].

Ovarian Abscess and Pregnancy

A case of ovarian abscess that existed in parallel with the pregnancy is presented after a 35-year-old nulliparous woman underwent oocyte retrieval. Vaginal discharge was presented at a 13 weeks of pregnancy with no other symptoms. At 30 weeks of pregnancy, she developed an ovarian abscess, and for this reason, she was hospitalized and received broad-spectrum antibiotics. This woman delivered by cesarean section and at this time percutaneous drainage of abscess was performed [57].

Another case developed infection after oocyte retrieval. Although broad-spectrum antibiotics have been administered, an abscess was formed that needed transvaginal ultrasound-guided drainage after 9 days from OPU. In addition, posterior colpotomy and T-drain into the cul-de-sac was placed. Improvement was observed with a viable pregnancy. Drain was removed after 3 weeks. Eventually, patient had a successful completion of pregnancy and she delivered vaginally at 38 weeks of gestation [58].

Ovarian Abscess: Conclusion

Pelvic infections after OPU are rare. The percentage of tubo-ovarian abscess after OPU ranges from 0.6 % till 1.3 %. It is

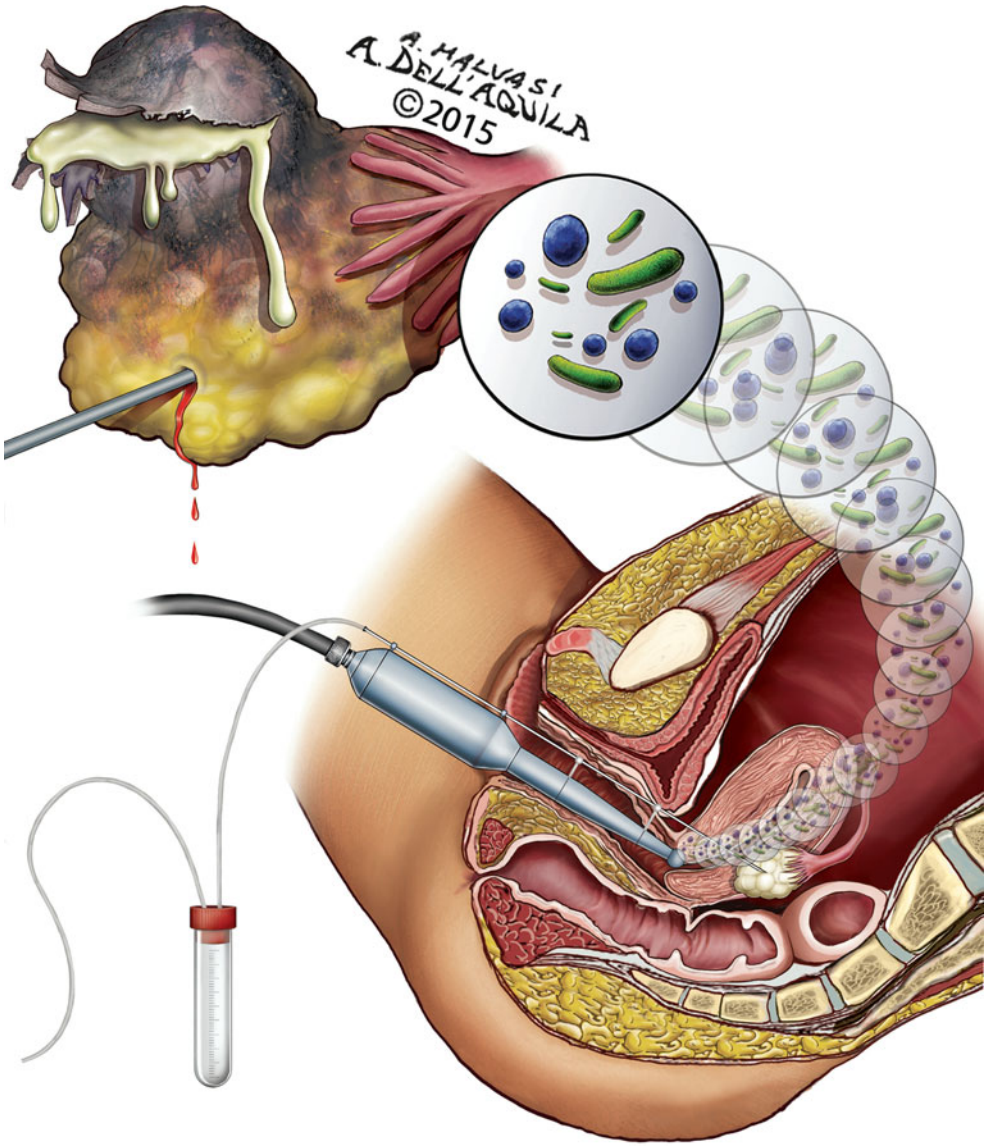

Fig. 10.14 The image shows an ovarian abscess after vaginal bacterial infection, during an ovarian pick up

not clear yet whether vagina cleaning with povidone iodine or chlorhexidine solution adds any real benefit. In addition, antibiotic prophylaxis remains controversial. Only for endometriosis patients, antibiotic prophylaxis is recommended during OPU, but this also remains controversial about its effectiveness [54]. From the other side, endometriosis is currently considered as a major risk factor for pelvic inflammation (33 %), especially after IVF but also a factor for higher percentage of antibiotic treatment failure (48 %) [59].

Pelvic infections after oocyte retrieval take place in patients with endometriosis, PID, pelvic adhesions, or pelvic surgery so these patients are recommended to receive prophylactic antibiotics.

Pelvic infection presentation takes place from a few hours to 56 days with the majority of cases to be presented within 3 weeks. Consumption coagulopathy may be developed and as such should be monitored. Increasing INR, APTT, D-dimers, and decreasing HB are the signs of it. Treatment may be medical alone (34–87, 5 % successful) or with a combination of surgical treatment (laparoscopically or by laparotomy). Incising the capsule of the ovary (if ovarian abscess), abscess drainage, and excision of infected tissue are performed. Severe pelvic adhesions are a limitation for laparoscopy.

Ultrasound-guided drainage of pelvic abscess has a value in the clinical setting. Residual abscess remains at 6.6 % and requires further surgery.

10.6 OHSS

10.6.1 OHSS: Clinical Symptoms

Ovarian hyperstimulation syndrome (OHSS) is observed with two distinct clinical presentations, the "early" and "late" forms (Fig. 10.15). "Early" OHSS takes place

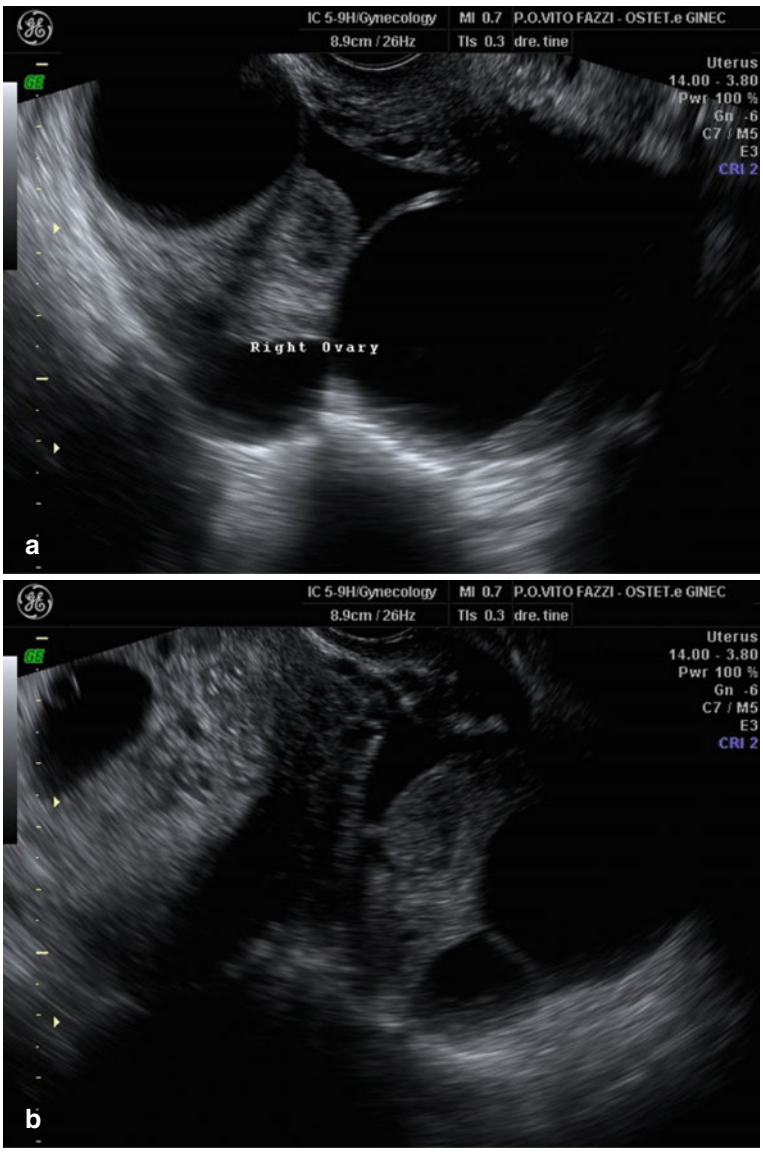

Fig. 10.15 (**a**, **b**) On the *left*, an ultrasonographic scan of "early" ovarian hyperstimulation (OHSS); on the *right*, a "late" OHSS

within 9 days of hCG administration while "late" OHSS presents more than 10 days after hCG. Obviously hCG plays an important role as it is recognized as a trigger for the syndrome. Pregnant patients produce high levels of hCG and take a longer time to recover [60]. OHSS is presented with enlarged ovaries, ascites, hemoconcentration and thrombosis, hypoalbuminemia and hypoproteinemia, electrolyte imbalances, and acute renal failure. Ascites may persist for a long time if not aspirated [61] and may extend to pleural effusion [62]. It may coexist with molar pregnancy [63, 64] with peritonitis due to perforation [62, 65], tuberculosis [66], ectopic pregnancy [67], and vulvar edema [68]. Hemoconcentration is produced from increased vessel permeability and hypovolemia. Disturbed balance between various clotting factors has been reported [69]. Thrombotic incidences and treatment have been reported previously.

10.6.2 OHSS: Prediction

Several efforts have been tried to associate various parameters of ovarian stimulation with OHSS, as measures of prediction for this. An antral follicle count (AFC) ≥ 24 seems to be to correlate with an increased risk of moderate to severe OHSS in comparison to an AFC < 24 (8.6 % versus 2.2 %) [70]. Other authors consider this is much lower at AFC (2–8 mm) ≥ 12. AMH > 0.47 pmol/L (3.36 ng/mL) shows a sensitivity of 90.5 % and specificity of 81.3 % predicting OHSS. Estradiol alone could not predict ovarian hyperstimulation, and various studies that tried to combine the number of follicles and estradiol levels on the day of hCG administration presented with low sensitivity and specificity. Young age and PCOS combined with low weight (thin PCOS) are important general factors predicting OHSS.

10.6.3 OHSS Treatment

The majority of efforts for OHSS prevention and treatment focus on the modification of protocols currently in use. None of these modified protocols have offered an entirely OHSS free practice, despite the claims of advocates of each protocol. Treatment remains largely empirical, although new medications like everolimus and kisspeptin offer possible future therapies. These modifications have been focused on the following:

10.6.3.1 OHSS: Treatment Before Ovarian Stimulation

Metformin, as adjuvant therapy has been used extensively to reduce the incidence of OHSS (OR 0.29; 95 % CI 0.18–0.49) [71]. No negative effect was observed in the number of oocytes yielded, serum estradiol levels, but reduced length of the stimulation and total amount of gonadotrophins have been used. Extensive use of metformin is needed for OHSS prevention (3–16 weeks at various doses) [72] and may be administered also during ovarian stimulation.

Pill pretreatment (OCP pretreatment) has been used in the past as a method to extensively downregulate the ovary for the 21 days before starting GnRH agonist. Sometimes it could be used both for overlapping each other. One of the benefits is that it homogenizes follicular development, so follicles develop in synchrony, without having a large number of small follicles. It is only used in the long GnRH agonist protocol. It is not clear yet whether pill pretreatment reduces pregnancy rates in GnRH antagonist cycles, so it is not used until now [73, 74].

10.6.3.2 OHSS: Treatment During Ovarian Stimulation

Low-dose hCG administration when combine with a GnRH antagonist protocol significantly reduces OHSS (OR 0.30; 95 % CI 0.09–0.96) [75]. Also observation of a steep rise of estradiol levels may incline the clinician to reduce gonadotrophin levels (step-down regimen). An extreme form of that is called coasting-withholding gonadotrophins, but it has adverse effects on pregnancy rates, if used for more than 4 days [76, 77].

Minimizing dose for hCG administration has been found to play a role. Doses at 5000 IU, 2500 [78] and 2000 IU [79] have been used without affecting the pregnancy outcomes.

Utilization of GnRH antagonist protocol has significantly reduced OHSS (OR 0.43, 95 % CI 0.33–0.57) [80]. In PCOS patients undergoing IVF, downregulation with GnRH antagonist reduces the risk of OHSS, when compared with long agonist (RR 0.60; 95 % CI 0.48–0.76) [81, 82]. The same applies for normal responders [83].

Long-acting and weekly administrated corifollitropin alfa, which is recombinant FSH (rFSH), is associated with increased ovarian response and risk of OHSS [84], so it needs to be administered with GnRH antagonist and not in good responders.

Coadministration of the dopamine agonist cabergoline has been found also to reduce the risk of moderate to severe ovarian hyperstimulation (RR 0.38, 95 % CI 0.29–0.51) [85] by inhibiting VEGF [86]. It may be better than the use of albumin infusion [87] and coasting [88].

Aromatase inhibitors may be used for two purposes. First, one is to reduce estradiol levels in breast cancer patients undergoing IVF before chemotherapy [89] and thus may be used for the same purpose in a hyperresponsive patient, although it is not clear yet the appropriate dose [90]. Second, to reduce total gonadotrophins administration, as long as they administered before cycle cancelation, is the last option, but with extensive psychological impact to the patient.

10.6.3.3 OHSS: Treatment During Oocyte Retrieval

Oocyte retrieval can be planned earlier when follicles are at 12–15 mm diameter and estradiol levels at ≥2500 pg/ml and mature in the laboratory, a technique that is called in vitro maturation. This is especially effective in PCOS, but it presents with lower pregnancy rates [91]. It is even more effective than GnRH antagonist protocol for preventing OHSS [92]. It may be combined with a freeze-all embryo strategy [93].

It is a promising technique under continuous development [94].

Albumin infusion (OR 0.67, 95 % CI 0.45–0.99) and hydroxyethyl starch infusion (OR 0.12, 95 % CI 0.04–0.40) are two methods of fluid replacement during OPU that seems to be effective preventing abdominal ascites [95]. For albumin infusion, opinions differ and certain authors speak about pregnancy rate reduction while in parallel does not reduce the incidence of OHSS [96, 97].

Given the possibility of viral transmission through albumin minimizes its use.

10.6.3.4 OHSS: Treatments for Oocyte Maturation

One method of OHSS prevention is to avoid hCG injection, but administering GnRH agonist for final oocyte maturation in GnRH antagonist cycles. Although there is a significant reduction of OHSS by GbRH agonist oocyte triggering in fresh (OR: 0.06; 95 % CI: 0.01–0.33) and donor cycles (OR: 0.06; 95 % CI: 0.01–0.27), there is a significant reduction in ongoing pregnancy rates in fresh autologous cycles (OR: 0.69; 95 % CI: 0.52–0.93), while no difference existed between the two regimens in oocyte donor cycles (OR: 0.91; 95 % CI: 0.59–1.40) [98].

10.6.3.5 OHSS: Treatment After Ovarian Stimulation

Transvaginal ascitic fluid aspiration has been proven effective to reduce further exacerbation of the symptoms. It may

take place one or more times in case of severe OHSS. It reduces the hospitalization time by dramatic symptom improvement, decreases abortion, and improves clinical pregnancy rates [99]. hCG as luteal phase support has long been abandoned with the use of progesterone. Obviously, it cannot be used in cases of ovarian hyperresponse.

It is not clear yet the role of embryo cryopreservation, alone, for avoiding OHSS. Embryos produce hCG and exacerbate OHSS phenomena. Issues like the pregnancy rates in a frozen-thawed cycle, the extensive storage capacity that is needed, and the labor-intensive use of embryo vitrification that is needed, mandate its use only within a GnRH antagonist protocol with agonist triggering.

10.6.4 OHSS: Pathophysiology

Ovarian hyperstimulation syndrome is associated with various genetic polymorphisms in AMH, AMHR2 [100], ESR1 AND 2 [101], VEGF receptors [102], and BMP15 [103]. It is not clear which pathways are involved in the syndrome presentation except that hCG activates P13K/mTOR signaling pathway and activates VEGF [104]. Till now VEGF-A is considered as the molecule that is responsible for OHSS, because it increases vascular permeability. From other studies, other pathways (mTOR) may be considered more effective because pathway inhibition has more effects on ovarian weight reduction and abdominal albumin concentration [105]. VEGF pathway inhibition has no effect in any of these parameters [106]. In parallel, calcium modulation is very effective in reducing abdominal fluid accumulation by either calcium pathway inhibition [106] or calcium infusion [107–109]. Also, kisspeptin-64 has been tested instead of hCG in oocyte maturation and it is very promising in reducing OHSS [110]. Overall, more research is needed to define the exact pathways responsible for the different phenotypes of OHSS.

10.7 Thrombosis

10.7.1 General

In a large cohort Swedish study of 964.532 deliveries, there was a 0, 2 % incidence of first trimester VTE in IVF patients compared with the normal population, while in IVF-OHSS patients, it showed a 100-fold increase of VTE. There was no increase in risk in frozen embryo transfer patients and after the first trimester of pregnancy [111].

In a retrospective study of [112] 65 patients with thrombosis after IVF, 10 had lower extremity thrombosis, 11 had upper extremity thrombosis,19 with neck thrombosis,18 with intracranial thrombosis, and 7 with thrombosis in other sites. In all cases, hematocrit rise >42 was in 62 % of the cases, estradiol rise >3000 pg/ml was at 54 % of the cases, and inherited thrombophilia existed in 23 % of the cases. Two deaths have been observed (both with intracranial thrombosis) and neurologic sequela was left at 18 % of the patients. Neurological sequelae included permanent hemiparesis (two patients) and impairment of daily activity (seven patients). Overall onset of the thrombotic event took place at 25.5 ± 20.1 days, while intracranial thrombosis took place at the earliest (10.2 ± 4.6 days) from all other cases [112].

Specific cases will be analyzed below.

10.7.1.1 Portal Vein Thrombosis

A 39-year-old woman, several days after oocyte retrieval, had an acute portal vein thrombosis with extension into the splenic and superior mesenteric veins. This was presented as a right upper quadrant pain [113].

10.7.1.2 Jugular Vein Thrombosis, Subclavian Vein, and the Right Brachiocephalic Vein Thrombosis

Nine days after the embryos were transferred, the patient had ascites, hydrothorax, and fluid of pelvic cavity accumulating. Her right neck had pain 43 days after the embryo transfer. B scan ultrasound showed jugular vein thrombosis, subclavian vein, and right brachiocephalic vein thrombosis [114].

Internal jugular vein thrombosis and subclavian vein thrombosis have been reported in a 26-year-old patient with OHSS. She was treated for OHSS, but after 2 days, she presented with left arm edema and neck pain. The abovementioned diagnosis was set up [115].

Right internal jugular vein may be presented as a neck lump [116], as a complication of OHSS [117, 118], in conjunction with a resistance to activated protein C (APC) or Dahlbäck disease [117] that usually is diagnosed later, even after low-dose heparin prophylaxis [118], and with factor V Leiden mutation (FVLM) either homozygous [119, 120] and the other heterozygous [120]. Also, infraction to the maternal side after an extensive placental infraction has been observed [120]. Two cases have been reported with internal jugular vein infraction and prothrombin 3 UTR mutations [119, 121], despite therapeutic anticoagulation.

Bilateral internal jugular vein thrombosis may take place after OHSS [122, 123], and without OHSS [124] may present at a rather late (8–9 weeks) pregnancy [124, 125], be evolved in pulmonary emboli [125], despite prophylactic albumin administration [123], negative thrombophilia screening [124], with twin pregnancies [126].

Subclavian vein thrombosis may be associated with OHSS [115, 127], may be presented at 7–10 weeks of gestation [128], and may already have received thromboprophylaxis [128].

In a patient with several risk factors (smoking, immobilization, a positive family history of thrombosis, protein S

deficiency, APC resistance), 5 weeks after IVF, complete obstruction of the subclavian and brachiocephalic vein on the right side and clots in the superior vena cava, left subclavian vein, bilateral internal jugular veins, and the right axillary vein, as revealed by magnetic resonance imaging (MRI), have been developed [129].

10.7.1.3 Cerebral Thrombosis

A 37-year-old woman presented to the emergency room with abdominal pain and tenderness. She had an IVF cycle 38 days ago. An ectopic pregnancy diagnosis and partial salpingectomy was performed. Two days after discharging from the hospital, she was presented with syncope and generalized tonic-clonic seizure. By cranial tomography, generalized edema and cerebral venous thrombosis were established [130].

In another case, a 30-year-old woman developed left middle cerebral thrombosis after IVF. Anticoagulation treatment was successful but patient left with neurologic sequelae [131].

A 38-year-old nulliparous woman on 7th day after OPU developed a severe headache and neck pain. Before 2 days, she had developed severe ovarian hyperstimulation syndrome, but was corrected. By MRI, extensive cortical vein and dural sinus thrombosis, including the superior sagittal sinus and transverse sinuses, were revealed. The thrombophilia test was negative. The patient was treated with low molecular weight heparin. She left the hospital 15 days after oocyte retrieval. After 2 months, a repeat MRI revealed patency in superior sagittal sinus and transverse sinuses and no evidence of flow obstruction while patient had no signs of neurological sequelae [132].

Another patient after her second cycle experienced ovarian hyperstimulation syndrome with progressive abdominal distention, 13 days after the embryo transfer. The next day, she developed mild difficulties in writing and generalized seizure. After MRI, a lesion found over the left high frontal lobe. Evidence of mild vasogenic edema at the brain white matter was found that pointed to small subacute hematoma. Eventually, diagnosis of cavernous angioma with hemorrhage was set up. The patient was set under observation while on treatment for neurological symptoms. After a positive pregnancy test, she had a paracentesis to improve symptoms. Unfortunately, after 1 week, the patient developed pain in left hip with mild edematous calf. A thrombus has been formed in the left common femoral vein extending into the left external iliac vein. Also, extensive venous thrombosis, up to the infrarenal portion of the inferior vena cava, was revealed. Both situations required a combined assessment, and decreased flow in the cortical vein was found that corresponds to the subacute hematoma previously mentioned. Termination of pregnancy was requested from the patient and eventually performed. Thrombophilia screen was negative, and no neurological sequelae were left. Complete solution of the intracerebral hemorrhage was established [133].

Two other cases have been presented. The first patient developed mild ovarian hyperstimulation 7 days after embryo transfer. The patient advised to monitor herself and return to hospital if symptoms worsen. Unfortunately, she presented with left hemiparesis, with loss of power in the left arm and leg. A hypodense cortical area was evident after computed axial tomography. After treatment, hemiparesis improved gradually in a week, but this patient did not get pregnant. She continued to improve her left motor weakness.

The second patient developed ovarian hyperstimulation 3 days after embryo transfer, with mild abdominal distension. During the admission to the hospital, she had a convulsive fit and left hemiparesis with motor power loss in both left arm and leg. A hypodense area was found in the left parieto-occipital lobe, both cortical and subcortical, and the diagnosis of acute infarction was made. After treatment, the situation improved in 36 h. On the third and fourth day, improvement continued and left leg and arm became normal. After 6 days, patient was discharged with no symptoms. Both patients have been normal for anticardiolipin IgG/IgM antibodies, protein C and S, and antithrombin III [134].

After OHSS, in parallel with cerebral infarction, myocardial infarction and death have been reported [135].

10.7.1.4 Carotid Thrombosis

It is a rare complication associated with OHSS. Three cases have been presented [136], associated with cardiovascular risk factors. In another case, in a 33-year-old patient, after OHSS, a floating thrombus located in the internal carotid artery has been found. The patient developed left hemiparesis and with open surgery avoided recurrent sequelae [137].

10.7.1.5 Mesenteric Vein Thrombosis

A 33-year-old patient developed abdominal pain after ET, and a CT scan showed a superior mesenteric vein thrombosis. The patient underwent therapeutic anticoagulation and finally the situation resolved [138].

A 39-year-old woman developed acute portal vein thrombosis with extension into the splenic and superior mesenteric veins, after oocyte retrieval. ET was postponed. Eventually, the situation was also partially resolved [113]. In another case [139], after mesenteric vein thrombosis, fatal outcome was reported.

10.7.2 Prevention and Treatment

Due to the life-threatening complications of jugular vein thrombosis, prevention and fast diagnosis are needed. Diagnosis is confirmed by Doppler ultrasound of the neck after symptom presentation. Prevention of ovarian hyperstimulation syndrome (OHSS) may reduce the incidence. Also increased APC resistance may contribute, but it is not clear

whether general screening for resistance to APC before admission to the IVF program should be performed. All patients should be counseled before treatment about the rare possibility of thrombosis thus to avoid immobilization. Also, recurrent episode in a next pregnancy, especially for cerebral infarction and intracerebral hemorrhage, is rare, if patient is under preventive antithrombotic treatment [140]. Although low molecular weight heparin anticoagulation could be administered in OHSS, the inclusion of other preventive measures, such as low molecular weight dextran expansion and albumin infusion, might not help avoiding it. In an experimental basis, procoagulable detection has been tested with the use of thrombin generation measurement and overall hemostasis potential. Both they increase during ovarian stimulation in IVF [141]. On the other hand, screening for the Factor V Leiden (FVL) and prothrombin gene G20210A mutation (PGM) genes does not offer any benefit, because they do not add to the thrombosis risk [142]. Also, thrombophilia mutations, in patients, may demand for a natural cycle process than ovarian stimulation IVF [143]. Systemic lupus erythematosus and/or antiphospholipid syndrome, although rare, may have up to 5 % risk for thrombosis and OHSS [144].

In case patients at risk of thrombosis need to take prophylactic antithrombotic therapy with LMWH, before and during ovulation induction, risk of bleeding is not increased [145].

Survival of pregnancy can be achieved, but progressive thrombosis may demand for termination of it [126], so a decision on continuation of early pregnancy upon progressive thrombosis should be made.

The timely cesarean section should be decided according to the patient's clinical picture.

10.8 Ovarian Complication

10.8.1 Adnexal Torsion

Many cases of adnexal torsion have been presented. It occurs at various points, mainly in the first trimester. From the pregnant women who had a torsion, it is evident that this takes place at 11.5 (7.7) weeks of gestation, while 56 % of them developed after IVF treatment [146].

There is a case report of 32-year-old woman who developed left adnexal torsion 2 days after embryo transfer. She also developed a right adnexal torsion, at 7 weeks of gestation. Again, at 10 weeks of pregnancy, right adnexal torsion occurred again. At all times, laparoscopic detorsion of adnexa was performed, and in the third case, shortcoming of the uteroovarian ligament was performed [147].

Another case of a second episode of adnexal torsion after IVF was observed after IVF, at 7 weeks of gestation. At 19 weeks of gestation, a contralateral adnexal torsion was performed. In the first time, laparoscopic adnexal detorsion was performed, and in the second time, this laparotomy with salpingo-oophorectomy was the treatment choice. Pregnancy was successful, even after salpingo-oophorectomy [148].

Adnexal torsion in a twin pregnancy after IVF was presented at 25 weeks. Diagnosis was established after the use of color Doppler that compared the ovarian blood flow between the two ovaries. A three-port laparoscopy was employed to unwind left adnexa [149]. In another case of an IVF twin pregnancy, a left adnexal torsion at 25 weeks of pregnancy was presented and treated with single-port laparoscopy [150].

Bilateral megalocystic ovaries have been observed at 36 weeks of gestation of a twin pregnancy, as the remains of IVF. This woman has developed deep vein thrombosis at 32 weeks of pregnancy. During cesarean section, both adnexa were markedly enlarged with minimal ascites in the abdominal cavity. After an ovarian biopsy, the diagnosis of bilateral follicular cyst was revealed. Although a rare case, pregnant IVF patient's close follow-up will ensure the existence of such pathological events and subsequent ovarian torsion [151].

Another twin pregnancy after IVF presented at 23 weeks with maximal tenderness in the right lower abdominal quadrant and guarding. A right-sided adnexal mass of 5–6 cm with free fluid in the pouch of Douglas was revealed. Laparoscopic detorsion of the right adnexa that was twisted three times was successful. Eventually, she delivered at 35 weeks of pregnancy two healthy children [152].

From a large retrospective study, the incidence of ovarian torsion in 10,583 cycles was 9 ovarian torsion cases and 104 ovarian hyperstimulation syndrome (OHSS) cases, which are susceptible to ovarian torsion. Only three of them had torsion of the adnexa and two of them have been pregnant.

At diagnosis time, five of the patients were clinically pregnant and one was chemically pregnant. Only in one of these patients, laparoscopic detorsion was failed and followed by laparotomy. This was due to the large ovary [153].

After IVF, ovarian torsion is one of the major complications but rare. Pregnancy and ovarian hyperstimulation are the two main factors, coexisting with ovarian torsion. Immediate diagnosis with Doppler ultrasound for absence of flow [154] and emergency laparoscopic intervention are needed, to preserve the ovary(ies). In case of laparoscopic failure, laparotomy is needed. Recurrence of torsion is also rare, but it associated with pregnancy [146].

10.9 Ectopic Pregnancy (EP)

10.9.1 Heterotopic Pregnancy

Heterotopic pregnancy is considered as rare (1/30,000) and could be seen especially after IVF (<0.01) [155, 156]. It has been presented in literature in various forms: (1)

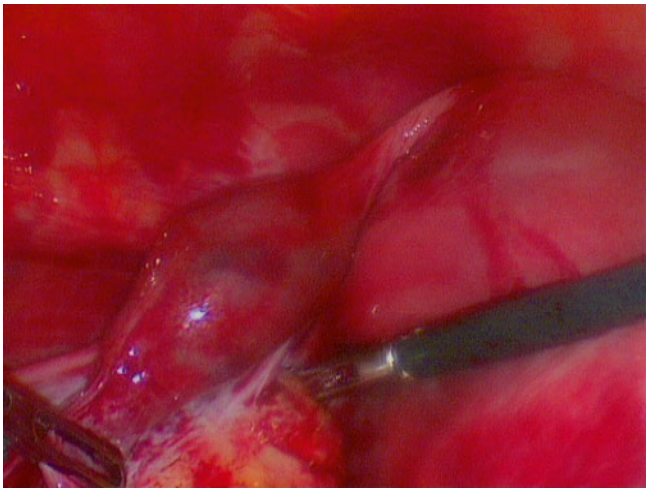

Fig. 10.16 A laparoscopic image of a tubal pregnancy

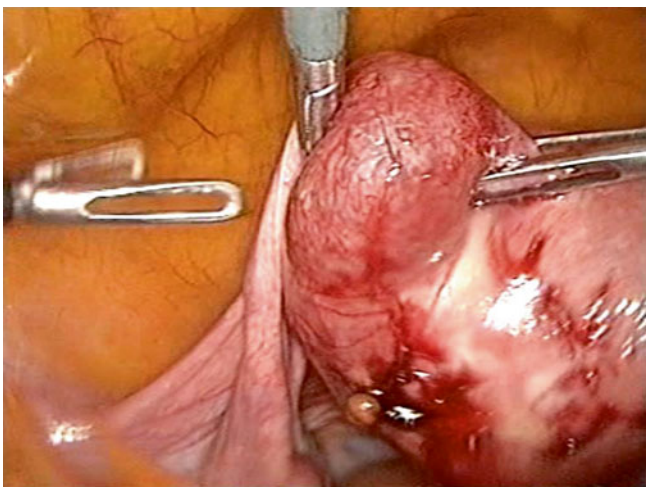

Fig. 10.17 A laparoscopic image of corneal pregnancy

Heterotopic triplet pregnancy: (a) in a cesarean scar with an intrauterine pregnancy, (b) tubal singleton pregnancy (Fig. 10.16) and two intrauterine pregnancies combined with an ovarian abscess, (c) bilateral tubal and intrauterine pregnancy. (2) Cornual pregnancy (Fig. 10.17): (a) recurrent cornual pregnancy, (b) cornual pregnancy combined with twin intrauterine pregnancy, (3) heterotopic pregnancy and intrauterine dizygotic twins after blastocyst transfer. (4) Heterotopic cervical pregnancy (Fig. 10.18): (a) twin cervical and intrauterine pregnancy, (b) cervicoisthmic pregnancy. (5) Heterotopic pregnancy combined with ovarian hyperstimulation syndrome. (6) Heterotopic pregnancy ruptured after spontaneous abortion. The presence of an intrauterine gestation sac in a patient without symptoms should not exclude the diagnosis of a concomitant extrauterine pregnancy until the pelvis is carefully visualized [157].

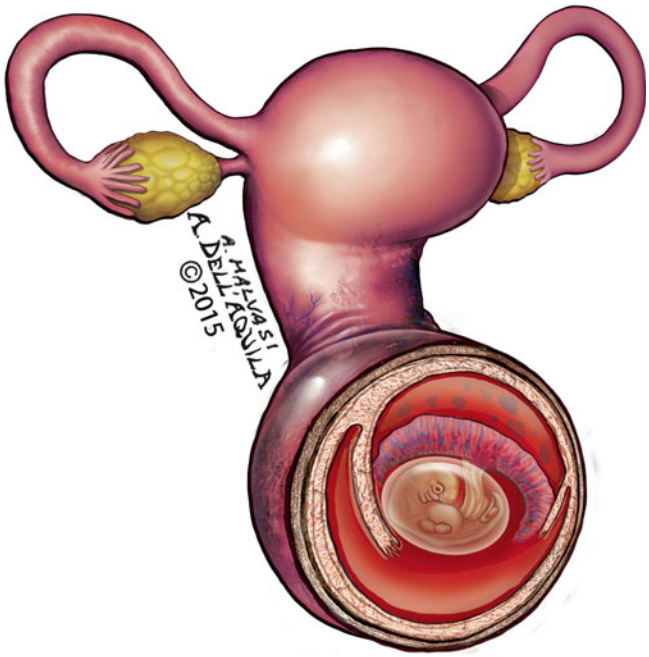

Fig. 10.18 The image shows a cervical pregnancy post-ART

10.9.1.1 Differences in the Prevalence in Different Countries of the World

EP complicates about 2 % of all pregnancies. Although no studies exist that describe the prevalence of the EP, in different countries, especially after IVF treatment, many studies present prevalence of the EP, as a secondary outcome. From specific studies, in Nigeria, prevalence for the EP, after IVF, was 7.8 %, while in the general population, EP rate was 1.74 % [158].

For other countries like Jordan, EP percentage is 0.005 % [159], while in Cameroon, this percentage is 0.72 % [160]. In a large follow-up study in Sweden, ectopic pregnancy rates were compared between women from different countries of birth, but small differences were found [161]. In New York, ectopic pregnancy rates in black women are 4.78 % [162].

10.9.1.2 Contraception as a Risk Factor

It is discussed that LNG contraception leads to ectopic pregnancy. In a case report, Ghosh et al. described a right ampullary ruptured ectopic pregnancy after levonorgestrel failure as emergency contraception [163], while Fabunmi and Perks reported a case of cesarean section scar pregnancy after LNG failure [164]. From retrospective cohort studies, no association of LNG failure with ectopic pregnancy was found.

10.9.1.3 Ectopic Pregnancy Rates in Fresh Versus Frozen Cycles

There is still controversy in this issue. Jun et al. found no difference in ectopic pregnancy rates between fresh and frozen cycles, whereas Yanaihara et al. found a significant

difference in ectopic pregnancies when two frozen blastocysts were transferred, compared to one [165, 166]. From the other side, Ishihara et al., in a retrospective study, found that frozen-thawed single blastocyst transfer significantly reduced EP rates [167]. EP rates varied when data were stratified for age, but remained low.

10.9.1.4 Day 3 Versus Day 5 Embryo Transfer

Milki et al. found no difference in ER rates between blastocyst and day 3 embryo transfers [168]. Important confounding factors have been checked between the two groups (like tubal disease between the two groups, cryopreserved transfers, but not number of embryos transferred) but no significant difference was found.

10.9.1.5 Blastocyst (Single Versus Double Blastocyst Transfer)

A heterotopic abdominal pregnancy was reported, after the transfer of two blastocysts [169]. Intrauterine pregnancy miscarried first while abdominal pregnancy ruptured 2 weeks later and ectopic pregnancy removed by laparoscopy. EP rates are significantly lower with the single frozen-thawed blastocysts transfer as compared with two blastocysts [166].

10.9.1.6 Oocyte Donation and Ectopic Pregnancy Rates

Cohen et al., in an oocyte donation program, found that hydrosalpinx patients present with higher ectopic pregnancy rates than patients without hydrosalpinx [170]. Chronic alteration of endometrium rather than direct embryotoxic effect of hydrosalpinx fluid is a possible cause. If after oocyte donation an ectopic takes place, minimal monitoring may allow rupture of ectopic with significant complications [171]. Mantzavinos et al. reported three cases of ovarian pregnancy after oocyte donation [172]. Patients have been treated laparoscopically, with removal of ovarian pregnancy tissue. Pantos et al. found only one ectopic pregnancy in a large series of donation patients [173]. Rosman et al. found that there is no difference in ectopic pregnancy rates between donor and IVF cycles, in a large retrospective study (4186 non-donor IVF cycles vs. 884 donor ET cycles) [174]. From the other side, donor patients showed significant lower incidence of tubal disease than standard IVF patients.

10.9.1.7 The ICSI Role

From a large retrospective study, that use of ICSI was found not to be associated with EP, while male factor infertility was associated more with EP with all other races than white non-Hispanic [175].

10.9.1.8 Ultrasound-Guided Embryo Transfer

In a meta-analysis of clinical trials (on 5968 ET cycles), comparing ultrasound-guided ET vs. clinical touch ET [176], no difference was found in ectopic pregnancy rates between the two groups. In another meta-analysis of 17 studies [177], same results have been found, even though that EP is relatively rare and study sample sizes limit the ability to detect such differences. When a single clinician performs all guided embryo transfers (Fig. 10.19), [178], no difference in EP rates has been found.

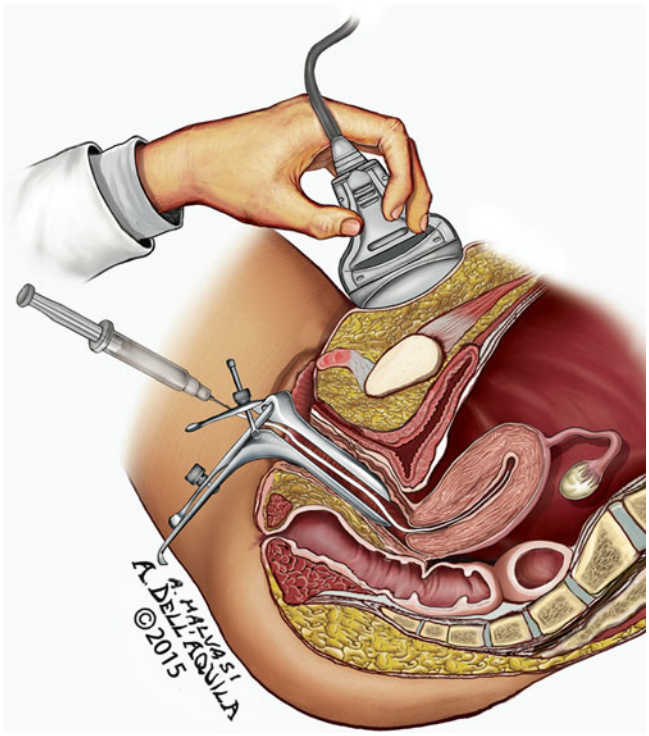

Fig. 10.19 An echo-guided embryo transfer

10.9.1.9 Assisted Hatching

Hagemann et al. found no difference in ectopic pregnancy rates after embryos that had assisted hatching or not [179]. On the other hand, Jun et al., in a large series of retrospectively examined patients, saw that a significant higher ectopic pregnancy rate was found in cases where assisted hatching (AH) was performed when compared with cases where hatching was not preformed [180]. Pathophysiologic explanations include (1) assisted hatching may accelerate embryo implantation; (2) a mechanism exists that prevents embryos that reached the fallopian tube to divert back to the uterus, and (3) the much higher embryo transfer volume used in certain IVF programs.

10.9.1.10 Air Bubble Position After Embryo Transfer

No difference in ectopic pregnancy rates has been observed with different distances of embryo deposition, as measured, from the uterine fundus (10–15 mm or < 10 mm) [181].

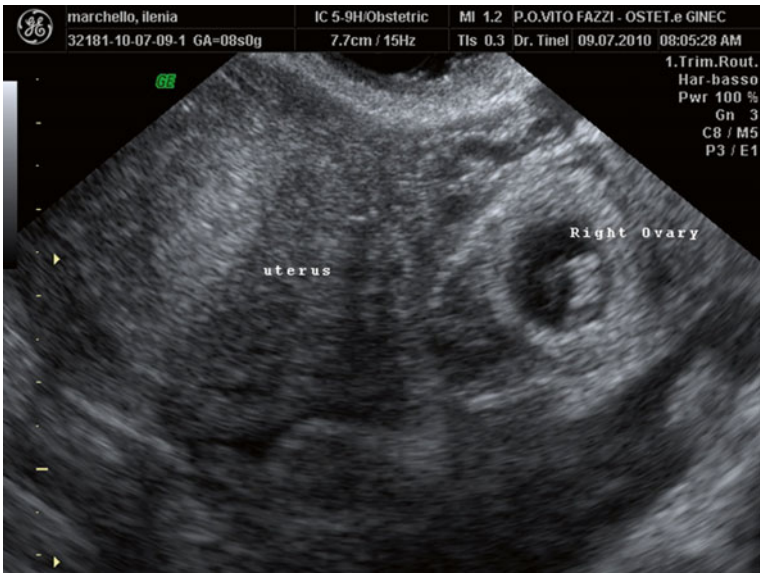

Fig. 10.20 The ultrasonographic image shows a *right* ovarian pregnancy

10.9.1.11 Reanastomosis

Tubal infertility patients, after former sterilization, may undergo microsurgical reconstructive surgery of the fallopian tubes for adhesiolysis, anastomosis, fimbrioplasty, and salpingostomy. These patients, which follow the microsurgical approach, present with higher ectopic pregnancy rates after a single IVF trial [182]. In a small series of patients, higher incidence of ectopic pregnancies has been observed when previous tubal sterilization was reversed by laparoscopy compared with open microsurgical reversal [183]. By using a serosamuscular fixation/biological glue technique, a sutureless laparoscopic tubal reanastomosis can be performed, but ectopic pregnancy rate remains high at 3.9 % [184]. When robotic tubal reanastomosis is performed [185], more ectopic pregnancies have been observed when compared with open reanastomosis.

10.9.1.12 Other Complications of Ectopic Pregnancies

After a ruptured ectopic pregnancy, Rh immunization could be observed.

10.9.2 Rare Cases of Ectopic Pregnancies

Ectopic pregnancies after IVF and subsequent clinical picture will be presented in this section. Case studies will be categorized according to anatomical location.

10.9.2.1 Ovarian Ectopic Pregnancies

In a large series of patients, Raziel et al. found that ovarian ectopic pregnancy (Fig. 10.20) rate comprises 2.7 % of all ectopic pregnancies, is highly associated with the use of intrauterine device, and is treated with laparoscopic wedge resection [186]. Ultrasound use in hemoperitoneum diagnosis makes culdocentesis not essential. Case reports presenting ovarian ectopic pregnancies present (1) ovarian heterotopic pregnancy after IVF [187], (2) bilateral ovarian pregnancy after IVF and previous tubal pregnancy after reanastomosis [188], (3) left ovarian pregnancy after empty follicle syndrome in IVF treatment [189], and (4) ovarian pregnancy from cornual fistulae after bilateral salpingectomy and IVF treatment [190].

Management of a Late Ectopic Pregnancy

A case of a cervical intrauterine pregnancy after IVF has been reported [191]. At the 13th week of gestation, two pregnancies have been diagnosed, a viable intrauterine pregnancy and a nonviable cervical pregnancy. The cervical pregnancy was restricted anteriorly, near a thick cervical blood vessel that presented at Doppler ultrasound with the low resistance flow. There was increased risk of bleeding associated with a cervical pregnancy expulsion, due to the proximity to the cervical venous vessel. After hospitalization and observation, cervical pregnancy was expulsed at 15th week + 6 days of gestation. Hemorrhage was managed through cervical curettage and multiple cervical stitches under general anesthesia. Subsequently, intrauterine pregnancy expulsed also, some hours later, leading to a curettage. Another case of heterotopic pregnancy after IVF and diagnosed at 16 weeks gestation was presented by the late Hassiakos [192]. When it was ruptured, intra-abdominal bleeding and hemorrhagic shock were a consequence.

Maternal-Embryo Complications from Use of Potassium Chloride

A cervical heterotopic pregnancy (one in the intrauterine cavity and the other in the upper portion of the cervix) was

treated with KCl (3 mL) injection and aspiration of the gestational sac [193]. A blood supply was seen at 19 weeks, separate from that of the remaining pregnancy by color Doppler. Remaining trophoblastic tissue did not resolve, leading to obstetric hemorrhage at 31 weeks of gestation. An emergency cesarean hysterectomy took place, with a viable infant, as the patient waited for an elective CS (cesarean section) at 32 weeks. Another possible complication of this technique is that KCL diffuse in the target amniotic sac may lead to diffuse to adjacent sac, thus contributes to harm to the intrauterine embryo.

10.9.2.2 Cervical Pregnancies

A heterotopic cervical pregnancy developed uterine varices at the cervical site and treated with TVS-guided aspiration 34 days after ET. Bilateral hypogastric artery occlusion was used, while a fundal classic cesarean section at 37 weeks was used to give birth to an infant [194]. Uterine varices were diagnosed at 28 weeks gestation, as prominent vessels associated with the empty sac located anteriorly and posteriorly occupying a significant portion of the myometrium at the lower uterine segment and cervical stroma. In Doppler studies, venous waveforms have been observed. To avoid entry into the gestational tissue and vasculature that occupied the lower uterine segment, a fundal cesarean section was planned. After delivery, the patient went for pelvic angiography and possible embolization to diminish the risk of bleeding.

Another heterotopic cervical pregnancy was treated with TVS-guided aspiration and instillation of hypertonic solution of sodium chloride, while, in parallel, ligation of descending cervical branches of the uterine arteries was performed [195]. The latter took place before TVS-guided aspiration. By vagina retraction, two DEXON sutures were placed bilaterally on the cervix, high below the fornix vaginae, thus reducing hemorrhage, significantly. Twin pregnancy in the uterine cavity continued to grow till 12th week of pregnancy, but no data exist thereafter.

A cervical twin ectopic pregnancy has been also described [196]. Treatment consists of TVS-guided aspiration plus systemic methotrexate injection. A 37-year-old woman developed severe ovarian hyperstimulation syndrome, after IVF. Two gestational sacs with one viable fetus located below the internal cervical os at 7 weeks of gestation have been revealed. Doppler imaging demonstrated a cervical mass with numerous tortuous and dilated blood vessels, including vascular communication beds at the implantation site, and established abundant peritrophoblastic arterial flows. Two days later, vaginal bleeding developed and intracervical Foley catheter tamponade was performed. Persistently active gestational tissue and bleeding is followed by hysteroscopic endocervical resection (with a 12° resectoscope with an outer diameter of 8 mm) in combination with temporary balloon occlusion of bilateral common iliac arteries (CIA).

When gestational tissue was removed, electrocoagulation for hemostasis was performed, using the rollerball. As a second measure for hemostasis, a 24-Fr Foley balloon catheter was placed at the cervical canal and methotrexate (50 mg i.m.) was injected on the next day. The 24-Fr Foley balloon catheter was removed 3 days after [197]. Same method of treatment was used by Peleg et al. [198].

A 45-year-old woman was diagnosed by ultrasound with a triplet gestation 7 weeks following IVF. Transvaginal ultrasound showed a triplet heterotopic pregnancy consisting of two gestational sacs in the cervix and one in the uterine cavity. Termination of pregnancy with catheterization and methotrexate treatment was performed, for future fertility preservation. The right femoral artery was catheterized with catheter and uterine arteries have been cannulated; 42 mg of methotrexate was injected into the right and left uterine arteries (at a total dose of 84 mg (50 mg/m^2). After that, both artery embolization was performed with pledgets of Gelfoam. Follow-up by ultrasound scan (after 48 h) revealed an absence of cardiac activity in both embryos. A gradual shrinkage of the cervical and intrauterine sacs was seen later [199]. On a 37-year-old woman that had an ICSI cycle, due to severe oligoasthenoteratospermia, two gestational sacs with embryonic heartbeats have been diagnosed, one in the cervical region and the second intrauterine. To preserve the intrauterine pregnancy, a hysteroscopic removal of the cervical gestational sac was decided. The gestational sac was observed on the left side of the endocervical canal, 2 cm away from the internal cervical ostium. The tip of the resectoscope remained below the internal cervical os at the operation, and the uterine cavity was not touched. Rollerball electrocautery was used to cauterize the conception products. Continuous ultrasound guidance with an abdominal probe was used during the entire procedure [200].

After four IVF attempts, a viable intrauterine and cervical pregnancy was diagnosed in a 34-year-old woman. With transabdominal scanning guidance, the needle was inserted transcervically and maneuvered into the embryo fetal heart that ceased. After that, KCl was injected. With 3 cm^3 of saline injection in the cavity, better visualization of the cervical fetus was achieved, and absence of heart beat was confirmed. The intrauterine pregnancy was delivered at 36, 5 weeks [201].

A heterotopic cervical pregnancy was diagnosed 25 days after ET with the patient complaining of mild vaginal bleeding. Confirmation of the suspected heterotopic cervical pregnancy was achieved by transvaginal ultrasound and for the vascular blood flow with use of Doppler. Cervical pregnancy was treated with transvaginal ultrasound-guided aspiration and KCL injection in the heterotopic pregnancy cavity.

Hemostatic synthetic absorbable sutures were placed high on the cervix at 1, 3, 9, and 10 o'clock, ultimately

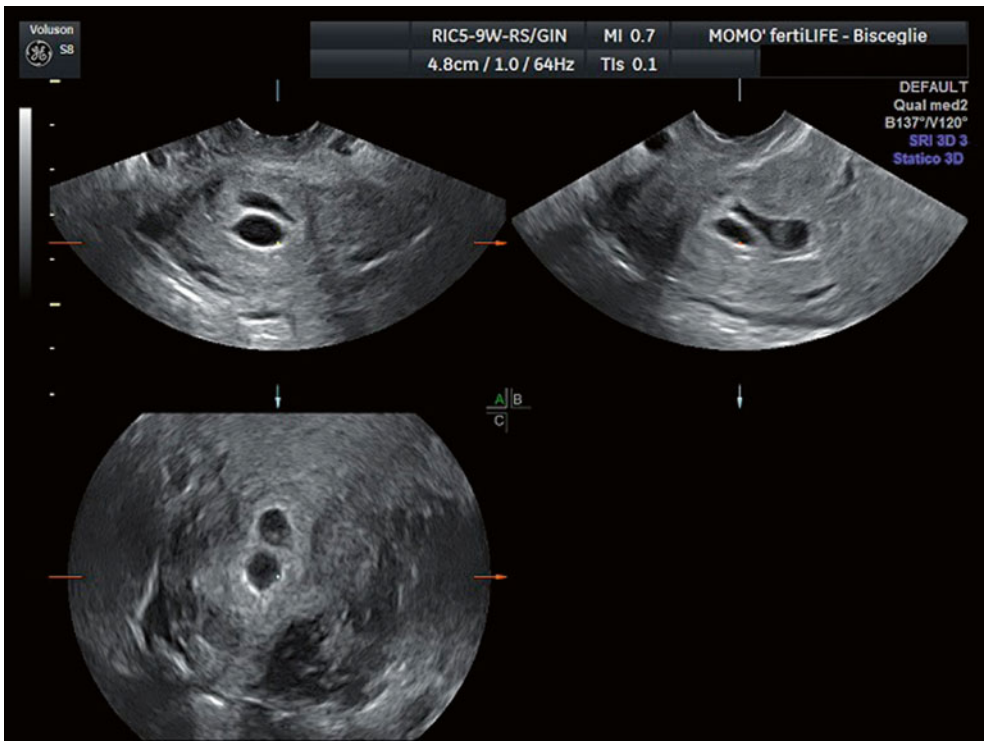

Fig. 10.21 An ultrasonographic image of a twin cesarean pregnancy scar

circumferentially tying the cervix after a period of 16 days after the first procedure and under epidural anesthesia. Cervical-stay sutures were dissolved by the 18th–20th weeks of gestation. No cervical incompetence was observed. At 38 weeks of gestation, an infant was delivered via cesarean section. For safety precautions, during the procedure, interventional radiologists were on standby to perform uterine artery embolization if necessary [202].

10.9.2.3 Ectopic Pregnancies Developed in a Scar

Previous Myomectomy Scar

Although pre-IVF myomectomy is not a necessity to achieve an ongoing pregnancy [203], other authors prefer to perform it, especially when repeated implantation failures take place [204] or uterine cavity involvement exists [205]. In a retrospective study for laparoscopic myomectomy outcomes, Paul et al. mentioned a 5.2 % EP rate [206]. In the same year, Seracchioli et al. reported an EP rate of 2.6 % [207]. From the other side, Campo et al. found no ectopic in their series after laparoscopic [208]. None of the ectopic pregnancies developed in the scar of the previous myomectomy.

Previous Cesarean Scar pregnancy (CSP)

Cesarean scar pregnancy (Fig. 10.21) carries the risk of uncontrollable bleeding requiring hysterectomy, so management has to include this risk in its treatment options. Wang et al. described a heterotopic pregnancy combined with intrauterine pregnancy after IVF [209]. Embryo reduction was performed with transvaginal ultrasound-guided KCL injection (0.2 ml) at 10 weeks of gestation. A mass 3×3 cm remained till 32 weeks of gestation. A male was delivered at 35 weeks by CS. Remaining gestational tissue leads to massive blood loss after CS, blood transfusion, and bilateral internal iliac arteries ligation. Another author [210] found a cesarean scar pregnancy (within the isthmic area of the lower anterior wall of the uterus) and an intrauterine pregnancy after IVF. At this time, management was performed by hysteroscopy evacuation at 7 weeks of gestation and coagulation of the implantation vessel site. Cervix was dilated to 11 mm, not beyond the endocervical canal, and gestational sac was pulled out, under sonographic guidance. Suction curettage was used to clear the residual gestational tissue and a hysteroscopic rolling ball was used to stop the bleeding point. A healthy infant was delivered by CS at 39 weeks of gestation. From the other side, two different cases were presented by Chueh [211]. Both cases were a twin cesarean scar pregnancy. Ectopic pregnancies were treated either by laparotomy excision of the scar twin pregnancy (first case) and hysteroscopic resection (second case) with resectoscopic coagulation of placenta bed vessels. In both cases, no fluid was seen in the cul-de-sac.

More pregnancies could be observed in cesarean scar. Litwicka et al. described a triplet heterotopic cesarean scar pregnancy after IVF, a twin pregnancy in the anterior isthmic wall, close to the CS scar (separated from the bladder wall by a thin myometrial layer) and one intrauterine

gestational sac [212]. Cesarean scar gestation sacs have been diagnosed, 1 week later than the intrauterine sac. Transvaginal ultrasound-guided potassium chloride (2 ml) and methotrexate (15 mg) were injected in the ectopic gestational sacs while the intrauterine pregnancy continues ongoing pregnancy.

In another case, described by Hsieh et al., a heterotopic triplet pregnancy was evident after an IVF treatment; the two have been intrauterine pregnancies and one cesarean scar pregnancy [213]. Color Doppler sonography revealed proliferated peritrophoblastic vessels around the cesarean scar pregnancy and the intrauterine twin pregnancy. CSP was treated with embryo aspiration under vaginal ultrasonography with preservation of intrauterine twin pregnancy. Due to preterm labor, two infants were delivered at 32 weeks of gestation. Rare CSP may exist in different forms after IVF treatments and previous CS. The management of these pregnancies may be performed with laparotomy or hysteroscopic resection of CS ectopic tissue after KCL injection to embryo. Also, MTX may be used for the second case. Complications of the second treatment include spontaneous abortion and congenital abnormality of MTX or diffuse KCL in the target amniotic sac that may lead to diffuse adjacent sac.

10.9.2.4 Live Twin Pregnancy in the Same Fallopian Tube

A left fallopian tube twin pregnancy has been described, an isthmic pregnancy and another ampullary sac in the same tube [214]. Both were treated with a left laparoscopic salpingectomy.

10.9.2.5 Cul-De-Sac Pregnancy

A case of a cul-de-sac ectopic pregnancy after IVF has been described [215]. After 4 weeks from ET, an ectopic gestational sac was found with the fetal heart beat in the left adnexa. By performing a diagnostic laparoscopy, it was revealed that an ectopic mass in the congenital blind pouch was connected to the posterior cul-de-sac. Laparotomy was performed for removal of conceptus and homeostasis.

10.9.2.6 Hepatic Pregnancy

Although a lot of case reports exist for a hepatic pregnancy in the literature [216], none of them is reported after IVF, so they were mentioned as primary hepatic pregnancy. Chlamydia infections may be involved also in this type of ectopic because adhesions between the liver and the diaphragm (Fitz-Hugh-Curtis Syndrome) were demonstrated in 34 % of those with EP [217]. Treatment of this type of pregnancy included direct methotrexate injection [218], laparoscopic suctioning, and hemostasis [216] or laparotomy. In case an advanced week's live pregnancy is diagnosed, then laparotomy with intact placenta may be performed [219].

10.9.2.7 Interstitial Pregnancy

Intrauterine and Twin Bilateral Tubal Pregnancy

Pan et al. report a case of bilateral tubal pregnancy and intrauterine pregnancy [220]. Because of cervical stenosis, a right tubal embryo transfer of four embryos was performed. After 5 weeks of gestation, a laparotomy showed a ruptured right tubal pregnancy, hemoperitoneum, and a dilated left tube. Bilateral salpingectomy was performed, with preservation of intrauterine pregnancy and delivery of a male at term.

Intrauterine and Interstitial Heterotopic Pregnancy After Bilateral Salpingectomy

After two previous unsuccessful IVF cycles and both tubes removal for bilateral hydrosalpinges and a successful third IVF cycle, the patient had an intrauterine pregnancy and an interstitial pregnancy. Interstitial pregnancy ruptured at the left salpingectomy site by its lateral position to the insertion of the ipsilateral round ligament. After laparotomy and left cornual resection, intrauterine pregnancy survived 2 more weeks and eventually miscarried. In aborted fetus, trisomy 21 was revealed [221].

Cornual Pregnancy

Two studies exist that describe cornual pregnancy after IVF. The first case was a heterotopic triplet pregnancy after in utero transfer of three embryos [222]. Cornual pregnancy was treated with resection by laparotomy. A special technique was presented in this patient. A Vicryl string with a tight knot was inserted at the base of the implantation site. The base of the uterine wall above this string was sectioned. Cornual scar was closed with the same stitches in X form while a base knot left in place. The patient delivered two girls with cesarean section at 31 weeks of gestation. The site of the corneal pregnancy was well vascularized and not ruptured.

The second case was a recurrent spontaneous cornual pregnancy 2 years after a heterotopic cornual pregnancy occurred after IVF cycle [223]. Previous corneal heterotopic pregnancy was treated with an injection of 0.5 ml of 15 % potassium chloride into the fetal heart while normal pregnancy was delivered at 39 weeks of gestation by elective cesarean section. Spontaneous cornual pregnancy was treated by injection of 40 mg methotrexate in the gestational sac and systemic methotrexate (1.0 mg/kg orally alternated with 15 mg folinic acid).

Interstitial Pregnancy

A unilateral triplet ectopic pregnancy has been reported on a woman with a history of right salpingectomy [224]. After IVF, in the left fallopian tube, a triplet pregnancy was found (two pregnancies at interstitial and one at ampullary location). Color flow Doppler sonography revealed intensive

peritrophoblastic blood flow around the two gestational sacs with live embryos, while TVS showed three gestational sacs, in the left interstitial area, in the isthmic part of the fallopian tube, and in the ampullary part next to the left ovary. After methotrexate multiple doses, hCG levels have been lowered. Ectopic pregnancies have been ruptured, so a laparotomy was performed with the removal of the left tube and cornual part of the uterus. Another case of previous bilateral salpingectomy and IVF was described [225]. An intrauterine monozygotic twin and an interstitial monozygotic twin pregnancy have been reported. By laparotomy, interstitial pregnancy was removed and intrauterine pregnancy was allowed to deliver at 38 weeks of gestation. Another intrauterine monochorionic diamniotic twin pregnancy and an interstitial pregnancy were reported [226]. Also, after bilateral salpingectomy and IVF, interstitial heterotopic pregnancy was developed that ruptured [221]. A recurrent interstitial pregnancy in uterine horn was seen after IVF [227].

Qin et al. used laparoscopic loop ligature, for heterotopic interstitial pregnancy [228]. Perez et al. reported medical therapy in two cases of interstitial pregnancy, one with transvaginal ultrasound-guided injection of methotrexate and second with potassium chloride into the ectopic sac of the heterotopic twins [229]. As a conclusion, interstitial pregnancies are always possible after tubal occlusion.

10.9.3 Rare Cases of Mild Ovarian Hyperstimulation and Ectopic Pregnancy

The coexistence of ovarian hyperstimulation and ascetic fluid accumulation enlarged ovaries after IVF, and a right tubal ectopic pregnancy has been reported [67]. Right salpingectomy was performed. Same case was presented by Fujii et al., which ended in a bilateral salpingectomy and continuation of intrauterine pregnancy till 32 weeks of gestation [230].

10.9.4 Consecutive Recurrent Ectopic Pregnancies

Three consecutive recurrent pregnancies have been reported in the same patient with pelvic inflammatory disease, two in the right and one on the left fallopian tube. The laparotomy option was chosen in all three cases, to preserve the tubes while removing conceptus [231]. Another case of two consecutive ectopic pregnancies after IVF has been reported [232]. Three consecutive cases of ectopic pregnancy on the same patient were presented [233]. The first involved simultaneous intrauterine and left tubal pregnancy, the second was a right tubal pregnancy, and the third was a right interstitial pregnancy. Another case of two ectopic pregnancies in consecutive menstrual cycles was presented [234]. Left distal ectopic pregnancy was seen and treated with left partial salpingectomy. In the next cycle, a right distal ectopic pregnancy was observed, which treated with right partial salpingectomy. Except the second case, the other two patients were conceived by coitus, so cases are presented in this review because they are rare. Another report of recurrent cornual ectopic pregnancies has been presented [235].

10.10 Chorioamnionitis

10.10.1 *Candida glabrata* and *Candida lusitaniae*

Chorioamnionitis with *Candida glabrata* represents a rare but catastrophic entity after in vitro fertilization. It takes place, usually, during the second trimester. There is increased probability of stillbirth of neonatal death [236]; early recognition and initiation of antifungal treatment may assist us in delivery of a baby once fetal maturity is achieved [237]. By this way, premature rupture of membranes may be avoided [238]. *Candida glabrata* chorioamnionitis can be developed after amniocentesis; thus, the women of increased age should be monitored for this event.

Another case report presented chorioamnionitis in pregnancy after infection with *C. glabrata*. The patient had undergone in vitro fertilization and eventually delivered after systemic antifungal treatment [237].

In another case report, a 41-year-old woman who was treated with combined in vitro fertilization with immunosuppressive therapy had sepsis at 18 weeks of pregnancy. She gets antifungal therapy with amphotericin, but she had premature rupture of membranes and preterm twin delivery at 23 weeks. The dichorionic diamniotic twins did not survive. After that, treatment changed to high dose fluconazole, for weeks. In our case the immunosuppressive therapy is the main factor for infection [239].

In a triplet pregnancy (after IVF) of a 33-year-old woman, premature rupture of membranes at 16 weeks of gestation ended to oligohydramnios in all three fetuses. After pregnancy termination and fetuses' examination, a *Candida lusitaniae* chorioamnionitis was observed. All three fetuses had developed pneumonia and granulomatous intraplacental inflammation [238].

Another 30-year-old patient, with a dichorionic diamniotic pregnancy after IVF, presented with vaginal bleeding at 15 weeks of pregnancy and eventually delivered both twins at 16 weeks. She had developed chorioamnionitis with *Candida glabrata*. She received boric acid. In subsequent IVF cycle, she had a dichorionic diamniotic pregnancy that delivered at 38 weeks of pregnancy. Obviously, complete

eradication of all *Candida glabrata* colonies ensures a successful subsequent IVF cycle.

10.11 Uterine Rupture and Pathophysiology

10.11.1 Uterine Rupture

Uterine rupture after laparoscopic myomectomy and subsequent IVF pregnancy (Fig. 10.22) is a rare complication that takes place in the third trimester of pregnancy. In the first case, the patient had a uterine rupture at 30 weeks of gestation on a twin pregnancy. She had IVF after 14 months after a laparoscopic myomectomy although she had an open myomectomy beforehand. It was presented as a sudden abdominal pain [240]. In another case after laparoscopic removal of a pedunculated fibroid, she had an IVF and conceived in 6 weeks after laparoscopy. She had uterine rupture at 35, 5 weeks of gestation at the uterine wall of the myoma site [241]. Also, a patient that had removal of adenomyosis and got pregnant in 5 months after the operation had a ruptured uterus at 33 weeks of gestation. At emergency CS, rupture was recognized at the posterior wall of the uterus, at the site of the scar. A healthy male was delivered and scar repaired by suture [242].

From a large retrospective study of 635 patients with 1170 fibroid that has been laparoscopically removed, 105 patients achieved pregnancy and no uterine rupture at the site of the scar was observed [243]. In a smaller retrospective study of 202 patients, 65 pregnancies took place with no uterine rupture at all. In 21 pregnancies, IVF was performed. Cesarean section was performed in 80 % of the cases [244].

Uterine rupture may take place at second trimester of gestation. In a Turner patient that received an oocyte donation, she had a uterine rupture at 14 weeks of pregnancy. After laparoscopy, operators have seen uterine rupture, partial pregnancy exteriorization, and placenta percreta. Due to hemodynamic instability, urgent laparotomy and hemostatic hysterectomy was performed [245]. Placenta percreta, which invades myometrium, can be a cause of uterine rupture. A case report of a woman after ten IVF cycles had a uterine rupture at 24 weeks of gestation. After ultrasound pregnancy confirmation, the location of placenta percreta and myometrial thinning was revealed. Confirmation with MRI revealed also that the full thickness of both myometrium and serosa was involved. Due to uterine contractions, a spontaneous vaginal delivery was performed. A decision was made to leave the placenta in situ, and pelvic arterial embolization was performed. Subsequently, hemorrhage occurred, and laparotomy with removal of placenta percreta and the closure of the perforated uterine wall were performed [246].

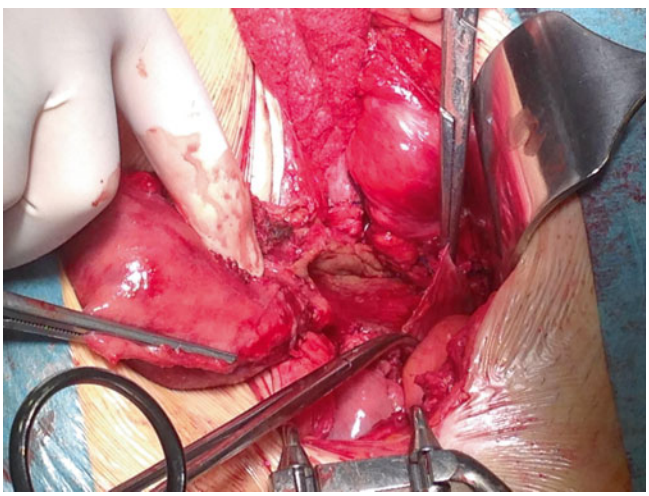

Fig. 10.22 Laparotomic image shows a spontaneous uterine rupture after ART

Intramyometrial pregnancy after IVF can cause uterine rupture at second trimester. A rare case of a twin intramyometrial pregnancy has been discussed, with pelvic pain, hemorrhage, and shock at 14 weeks of gestation. Surgical excision of pregnancy with adjust area of myometrium was performed [247]. In general, due to delayed diagnosis, intramyometrial pregnancy is managed by hysterectomy, but with early diagnosis of pregnancy with vaginal ultrasound, it may lead to early diagnosis and conservative management.

A uterine rupture was reported in a gestational carrier after embryo transfer. Although, a singleton pregnancy uterine rupture took place and the carrier had a hysterectomy [248].

Three rare cases of spontaneous rupture of subserous uterine veins have been reported after IVF achieved pregnancies. Rupture and intra-abdominal bleeding took place between 29 and 35 weeks of gestation. Exploratory laparotomy and appropriate treatment took place [249]. It is not clear whether this rupture of subserous uterine veins was due to in vitro fertilization or focal points of endometriosis that remained despite pregnancy. In pregnant patients that had endometriosis, awareness of such complication may lead to faster diagnosis and treatment, leading to uncomplicated pregnancy.

Spontaneous uterine rupture at 29 weeks has been observed during preterm labor of an IVF-conceived twin pregnancy. No risk factors have been observed and no explanation has been given for this [250].

10.11.2 Pathophysiology of Pregnancy That Leads to Uterine Rupture

Most of our cases involve a previous uterine trauma (from CS or myomectomy) that results in a sinus tract within the endometrium. Other mechanical reason includes false

passage creation through the cervix (difficult ET or dilatation and curettage) that leads to an ectopic embryo deposition in a later embryo transfer, thus leading to intramural pregnancy. Another pathophysiological factor is embryo penetration into the myometrium, because of increased trophoblastic activity and defective decidualization.

10.12 Laboratory Practices

10.12.1 Media Culture Effects

In a large retrospective study, the effect of media culture was analyzed on various newborn parameters, to minimize bias of investigating two different media (a commercially available, single-step culture medium and a commercially available sequential medium) on patients that undergo single embryo transfer. Also, fresh and frozen SET have been analyzed. From the results, it was found that there is no difference in all parameters of neonatal outcome, except the small-for-gestational-age (less than 10th percentile) babies born after frozen-thawed embryo transfer cycles that cultured with the single-step culture medium [251].

It was reported also that the age of the G-1 PLUS medium is inversely associated with birth weight, after controlling for all confounding factors. A difference of 234 g in birth weight is evident as the difference in age from media production to oocyte retrieval is up to 65 days [252].

In another retrospective study [253], the authors focused on the protein source of media for embryo culture. They compared two media, the GI-PLUS v5 media and the GI v5 media. They found differences in gestational age and infant gender-adjusted birth weight. More large-for-gestational-age infants are observed in the GI-PLUS v5 media group. They conclude that protein source affects birth weight in human.

Furthermore, in a prospective cohort study, two sequential culture media have been tested and found that in vitro culture of embryos in media from one company (Cook) resulted in singletons with a lower mean birth weight (adjusted mean difference 112 g) and more singletons with a LBW (2500 g) and LBW for GA ≥37 weeks, when compared with media from another company (Vitrolife AB). The same applied for twins [254].

It is questionable whether those differences exist in embryonic life. By measuring various parameters of fetal growth in the first and second trimester, researchers found that at around 8 weeks of gestation, fetal CRL showed no difference between the two different media compared while at 12 weeks of pregnancy, except nuchal translucency and PAPP-A that show no significance, but fB-hCG was significantly higher in the Vitrolife group.

At 20 weeks of pregnancy, head circumference and transcerebellar diameter were significantly higher in the Vitrolife group also. Increased fetal growth is associated with the Vitrolife group [255].

From animal studies, it is known that the addition of amino acids and protein in culture media leads to heavier offspring, but lack of serum inside these media leads to lighter offspring.

What about obstetric and perinatal outcomes after vitrification of oocytes? In a retrospective cohort study, they found no difference in all neonatal parameters, gestational age of delivery, birth weight and defects, perinatal mortality, and puerperal problems [256].

In another retrospective study, the authors compared the obstetric and neonatal outcomes between vitrified early cleavage embryos, slow freezing, and fresh transfers. They found that the mean birth weight of vitrified oocytes was higher (3455, 3 g) when compared to the other two groups. Perinatal mortality was the same in all transfer groups. No difference was observed in gestational age and preterm birth rate. In addition, fresh embryo transfers show the highest percentage of low birth weight white vitrified oocytes showed the lowest [257].

More studies are needed to better define the effect of culture media on embryo development. Further analysis of randomized controlled trials will lead to a conclusion.

10.13 Complications During Pregnancy

10.13.1 Preeclampsia

10.13.1.1 Preeclampsia: Male Factor

Several studies checked for preeclampsia in women that underwent ICSI. In a single-center, retrospective study, three groups have been compared, women that had ICSI with ejaculated or surgically obtained sperm, with women that underwent ICSI for female factor. There was 1.5 (0.67–3.22) times more risk for preeclampsia predisposition in male factor group, but no significant difference between the ejaculated and surgically obtained sperm. In parallel, there were significant differences between the two male factor subgroups and the female factor group [258].

In another retrospective study, 2392 single pregnancies that conceived either naturally or through IVF (4.5 %), when compared for preeclampsia, IVF pregnancies showed a percentage of 15.7 %. In addition, IVF pregnancies had significantly higher levels of sFlt-1 and lower levels of PIGF at 18 and 35 weeks of gestation. Increased antiangiogenic profile through gestation is associated with IVF pregnancies, and this might lead to abnormal placentation and preeclampsia.

In a large retrospective study of 3084 women that included IVF and not IVF pregnancies, preeclampsia was found in 15 (3.2 %) cases in the IVF group and 31 (1.2 %) cases in the non-IVF group. Patients with early-onset preeclampsia

(<32 weeks of gestation) was developed at two (13.3 %) for the IVF group and three (9.7 %) for the non-IVF group (NS). Preeclampsia severity was not different between the two groups (53.3 % versus 54.8 %, respectively). From this study, birth weight was significantly higher (3042.7 vs. 2988.1 g, $p=0.008$) in the IVF group, while no significant difference was observed between them. This is controversial, according to recent findings. Eventually, propensity score matching revealed no significant difference in preeclampsia in both groups [259].

No significant difference for preeclampsia was found between women that conceived after two or more failed IVFs [124] compared to the women that conceived after the first IVF [260].

10.13.1.2 Preeclampsia: Oocyte Donation

When examining donor oocyte cycles for preeclampsia, there is a significant difference for this pathologic entity in these cycles compared with autologous IVF [261].

In a retrospective, matched cohort study of 158 pregnancies, 77 ovum-donor recipient/81 autologous oocyte pregnancies were compared for preeclampsia or gestational hypertension in the third trimester. A significant difference was observed in ovum-donor recipients compared with women undergoing autologous IVF (24.7 % compared with 7.4 %, $P<0.01$, and 16.9 % compared with 4.9 %, $P=0.02$, for gestational hypertension and preeclampsia, respectively) [262].

10.13.1.3 Preeclampsia: Endometriosis

When it comes to endometriosis, a major factor for infertility, the incidence of preeclampsia was found in these women compared to normal woman (1.2 %) versus control (7.4 %) ($P=0.032$; OR = 6.6, 95 % CI: 1.2–37).

The odds of developing preeclampsia were 5.67 times higher in the normal women than in pregnancies after endometriosis-associated infertility, while on multiple gestation, no significant difference was found between the two groups. In both groups, there was an increased incidence of 1.93 times per additional child [263].

From another population-based study of 208,879 women with a singleton first delivery, 3239 had endometriosis. Of the 205,640 women without endometriosis, 4935 had an IVF cycle, and 841 of endometriosis women had IVF. The significant difference was found between the two groups for preeclampsia (OR 0.67 (0.4–1.1) $P=0.09$). When a regression model was built, there was no association between endometriosis and preeclampsia. The same applied for second or higher pregnancies following diagnosis of endometriosis [264].

10.13.1.4 Preeclampsia: Obesity

In a large hospital-based cohort study of 10,013 singleton pregnancies, which researchers controlled confounding factors for preeclampsia, the pregnancies after IVF, and obesity, higher risk of preeclampsia is observed compared to spontaneous nonobese pregnancies (OR 6.7, 95 % CI 3.3–13.8) [265].

When controlling for twin pregnancies in a population-based cohort study of twin deliveries, IVF treatment, parity, and maternal age are risk factors for preeclampsia. Also for women younger than 35 years that conceived following IVF treatments, an independent risk factor for the development of preeclampsia existed [266].

In another study, only in vitro fertilization was associated with an increased risk for preeclampsia (OR = 1.78, 95 % CI: 1.05–3.06), whereas intrauterine insemination (OR = 2.44, 95 % CI: 0.74–8.06) and ovulation induction (OR = 1.34, 95 % CI: 0.31–5.75) were not associated with the risk for preeclampsia [267].

Most importantly, IVF alone is statistically significantly associated with stillbirth, preterm birth, low birth weight, and low Apgar scores (<7 at 5 min), irrespective of the socioeconomic status of women that undertook it [268].

Another case report of preeclampsia in a 34-year-old woman was developed on a basis of lupus anticoagulant (LAC), anticardiolipin (ACL), and anti-dsDNA (ADD)-positive SLE and APLA syndrome, with multiple small cerebral infarcts. She had this pathological entity from 13. After her pregnancy conceived with IVF, she presented at 26 weeks of gestation with preeclampsia and HELLP syndrome. After CS, severe hypertension with CT confirmed multiorgan infarcts have been developed.

10.14 Twins and IVF

10.14.1 Chorionicity in Twins After IVF

In a large retrospective study, they found that ART twins were mostly dichorionic, and monochorionic twins were conceived either spontaneously or with ICSI [269].

A case of dichorionic triamniotic triplets was presented after blastocyst transfer in an IVF cycle. This pregnancy was complicated with twin anemia polycythemia that was diagnosed at 28 weeks of gestation. A single intraperitoneal transfusion was performed, thus extending pregnancy for 2 more weeks. In a recurrence anemia, cesarean section was performed [270].

In a small retrospective study, 17 cycles that ended to monozygotic pregnancies found that overall incidence is 1.3 %. No difference existed between women aged <35 years and ≥35 years (1.5 % and 0.8 %, respectively ($p=0.319$)). The same applied to ICSI and non-ICSI cycles (1.4 % vs. 1.0 %; $p=0.620$). Also, assisted hatching (AH) group showed no difference when compared to those without AH (0.9 % vs. 2.1 %; $p=0.103$). Blastocyst transfer did not contribute to the monozygotic pregnancies incidence when compared to

cleavage-stage embryo transfer (1.4 % vs. 1.3 %, respectively; $p = 1.000$). The incidence of each type of chorionicity, dichorionic-diamniotic, monochorionic-diamniotic, and monochorionic-monoamniotic was 33.3 %, 46.7 %, and 20.0 %, respectively [271].

The exact opposite picture is presented from a nested case control study of 6223 gestations. Although 131 monozygotic twins (2.1 % incidence; 2.0 % in autologous and 2.7 % in donor IVF cycles) have been diagnosed, 10 were dichorionic, and 121 were monochorionic. Young oocyte age, extended culture (non-cleavage embryos transferred on/after day 4), and year of IVF treatment cycle were significantly associated with monozygotic twins. Day 3-assisted hatching correlated more with dichorionic-monozygotic twins, whereas extended culture and day 5 blastocyst transfers correlated with monochorionic-monozygotic twins. Authors conclude that assisted hatching may play an important role in the type of chorionicity [272].

A slightly different outcome was presented after a large retrospective study of 4975 pregnancies after IVF, which combined autologous and donation cycles. Ninety-eight monozygotic pregnancies (2 %) have been diagnosed. When autologous oocytes have been transferred, MZT pregnancies have been at 1.7 and 3.3 % with donor oocytes. No significant difference was presented for younger women <35 years old either using their own oocytes (3.1 %) or donor oocytes. The majority of MZTs [79] occurred after the fresh blastocyst transfer (2.6 %), only 14 after day-3 transfer (1.2 %). Hatching did not pose any difference (1.3 % when hatching vs. 1.1 % with no hatching). ICSI also did not pose any difference when performed (2.4 % vs. 2.0 %) on monozygosity. Ninety-five percent of all monochorionic pregnancies have been confirmed as monochorionic-diamniotic [273].

From a large retrospective study from Japanese IVF registry, from 30,405 pregnancies conceived with ART technologies, 425 have been monozygotic. When blastocyst transfer was used (59,692 blastocyst transfers), 0.6 % (348) of monozygotic cases have been presented, while when the cleavage embryo transfer was used, 0.2 % [76] of such cases have been evident. Obviously, blastocyst embryo transfer significantly increases the incidence of monozygotic twins. All other parameters, like assisted hatching, maternal age, frozen-thawed embryo transfer, methods of blood stimulation, and whether ICSI was used, do not play a significant role in MZT.

In another large retrospective study of 9969 fresh-transfer cycles that ended in pregnancy, 234 MZT (2.4 %) have been observed. Of all transfers, 5191 were cleavage stage and 4778 were blastocyst stage. When analyzing, it was found that in the cleavage-stage group, 99 MZT (1.9 %) have been observed, while on the blastocyst ET group, there was 135 MZT (2.4 %). There was a significant difference for blastocyst transfer. As a confounding factor, increasing age was associated with a significant reduction in MZT, regardless of the transfer order. When controlling for patient age, other factors like the time period during which the cycle took place, the number and proportion of six- to eight-cell embryos, and the availability of supernumerary embryos did not result in significant difference in MZT rate when comparing blastocyst and day-3 embryo transfer [274].

10.15 Abnormal Placentation and IVF

10.15.1 Placenta Previa and IVF

There are not a lot of studies that directly associate placenta previa and IVF (Fig. 10.23). In most studies, placenta previa after IVF is presented as a parameter of the study. In addition, the numbers are low and either absolute or as a percentage.

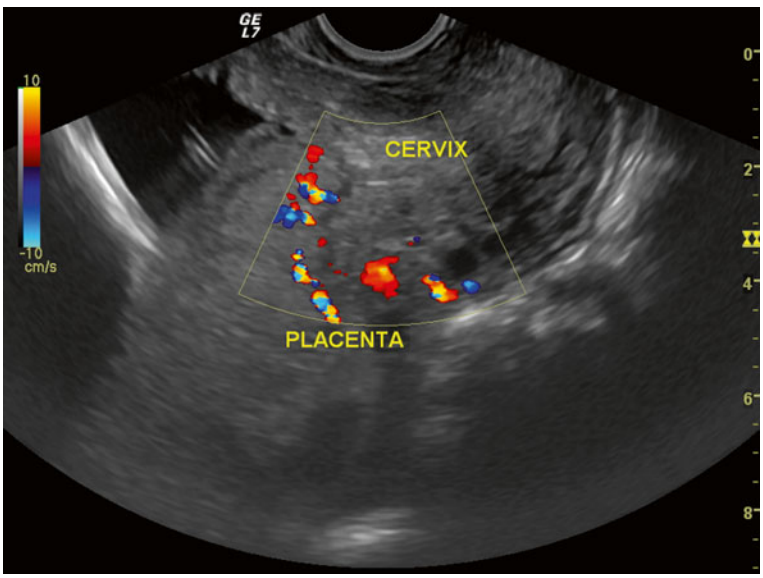

Fig. 10.23 An ultrasonographic image showing a central placenta previa after ART

Placenta previa represents a small % of overall pregnancies, ranging from 0, 22, to 0.54 % in normal conceived pregnancies but it rises to 1.59 % in singleton IVF pregnancies [275].

Vasa previa also is associated with in vitro fertilization [276]. Early associations between vasa previa and IVF exist in literature [277–279].

One of the earlier reports on twin pregnancies, when compared to spontaneous pregnancies with in vitro fertilization, found no difference in placenta previa [280]. Same results have been found from [281], in a case controlled study, that IVF does not appear to increase placenta previa. But in a meta-analysis for perinatal outcomes of singleton pregnancies after IVF, significant difference has been observed for this entity [282].

From a retrospective study of 47 patients with succenturiate lobes of placenta, IVF patients showed a significant higher incidence ($P<0.01$) for this placenta shape aberrations than unaffected controls [283].

Also for PCOS patients that undergone in vitro maturation and fresh ET, no difference has been observed in the rate of placenta previa, when compared with conventional IVF [284].

When performing a single embryo transfer, an increased risk for placenta previa has been observed when compared with the spontaneously conceived women ($n=15{,}037$). When comparing SET and DET for placenta previa, no difference was found [285].

In a population-based study in Norway, with 845,384 pregnancies, after IVF, a sixfold increase of the risk of placenta previa in singleton pregnancies was found compared with naturally conceived pregnancies [adjusted OR 5.6, 95 % confidence interval (CI) 4.4–7.0]. In parallel, for women with consecutive pregnancies, both natural and after assisted fertilization, the risk of placenta previa was nearly increased threefold in the pregnancy following assisted fertilization (adjusted OR 2.9, 95 % CI 1.4–6.1), when compared with the risk in the naturally conceived pregnancy [286].

After IVF, placenta previa was associated with first trimester intrauterine hematomas (OR, 8.7 95 %; CI 3.4–22.2) [287]. Also, from a retrospective study of 318 IVF pregnancies, it was found that endometriosis (odds ratio = 15.1; 95 % CI = 7.6–500.0) and tubal disease (odds ratio = 4.4; 95 % CI = 1.1–26.3) are significantly associated with placenta previa [288]. In general population, increased maternal age (≥30 year) is an independent risk factor for placenta previa [289].

When comparing pregnancies after fresh and frozen ET, significant differences for placenta previa and third trimester bleeding were observed ($p=0.002$). Placenta previa was more common after fresh ET [290]. In addition, birth weight was significantly lower after fresh ET.

10.15.2 Placenta Accreta and IVF

From another case control study, a strong association has been observed between cryopreserved embryo transfer and placenta accreta (Fig. 10.24) (adjusted OR 3.20, 95 % CI 1.14–9.02). Also, these patients with placenta accreta had the lowest endometrial thickness and estradiol levels [291]. Also, from a British case control study, IVF pregnancy is a risk factor for placenta accreta/increta/percreta (adjusted OR 32.13, 95 % CI 2.03–509.23) [292]. In a retrospective study of women with placenta accreta but without previous cesarean section, the rate of pregnancies obtained by IVF was higher (5/35 [15 %] vs. 2/63 [3 %], [$P=0.05$]) when compared to normal conceived pregnancies [293].

Furthermore, in a rare case report from a twin pregnancy of a 33-year-old patient, a sack was a complete mole; the other sack contained a fetus and placenta accreta. Embryo survived and was delivered at 37 weeks of gestation after CS, and subsequently with a hysterectomy for the placenta anomalies, the molar pregnancy, and the placenta accreta was performed [294].

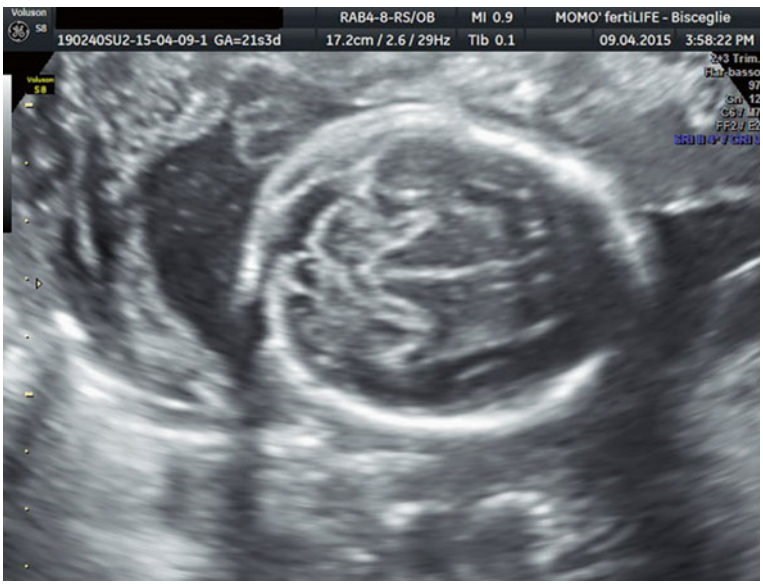

Fig. 10.24 A placenta accreta in a pregnant at 21 weeks; at 29 weeks, patient was urgently operated for cesarean section for massive bleeding, with a successive cesarean hysterectomy

10.16 Embryo, Child, and Delivery Effect After IVF

10.16.1 Sex Ratio

Children born after testicular sperm aspiration and ICSI when evaluated for singleton and twins outcomes together show a significantly lower sex ratio (♂/♀) against males (0.47 %) compared with conventional IVF (1.11; $P=0.017$) [295]. On the other hand, when this analysis transferred to singletons and twins only, no significant difference was observed.

10.16.2 Birth Defects

There is a great deal of controversy whether ART and especially ICSI are associated with birth defects. Studies include limited data and limited long-term follow-ups of infants born after IVF. Studies of special defects do not exist. Factors that may predispose to birth defects include the underlying infertility of couples, the ART procedures themselves, paternal subfertility with a genetic background, and female infertility itself, comparing ICSI with standard in vitro fertilization (IVF).

In a small retrospective study of 74 ART children born after the transfer of very poor-quality embryos compared with 1507 children born after the transfer of very good-quality embryos, no significant difference was found in the prevalence of birth defects, the rate of chromosomal abnormalities, and the perinatal mortality rate [296]. Congenital malformations are associated with the reason for infertility and not the ART technique [297].

From a large retrospective study of 978 births, 56 (5, 7 %) infants have been found with major malformations. An increase in the risk for these malformations has been observed (OR = 2.04), and the IVF group showed a 2.73 times higher prevalence than ICSI group, from major malformations. In this study, no other causes have been taken into account [298]. In a meta-analysis of Lie et al. [299], overall risk of a major birth defect after ICSI after comparing after standard IVF is estimated at 1.12, 95 % CI: 0.97–1.28, $P=0.12$, while no significant difference for cardiovascular defects, musculoskeletal defects, hypospadias, neural tube defects, or oral clefts was observed [299].

A very interesting study compared pregnancy outcomes from children conceived after ICSI both with ejaculated or aspirated sperm with normal IVF and naturally conceived pregnancies [295].

For singleton boys conceived with epididymal/testicular sperm, an increased rate of cardiac malformations (3.6 %) (such as Fallot's tetralogy and ventricular septal defects) was observed when compared with singleton boys after conventional IVF [295]. Also, twins that undergone ICSI with epididymal/testicular sperm showed an increase rate of neoplasms in bones and joints, thus indicating the role of imprinting related disorder [295].

However, in a large meta-analysis [300] involving 124,468 infants, the authors found no significant difference in birth defects between IVF and ICSI, but a significant risk difference has been found when compared with normal conceived children. It was evident for genitourinary, digestive, circulatory, myoskeletal, eye, ear, face, neck, and especially for the nervous system (RR ¼ 2.01, 95 % CI 1.27–3.20). They conclude the difference of the results from previous studies in the way data are collected. They do think that hospital-/clinical-based studies underestimate the rate of birth defects.

A retrospective study of 7120 IVF patients compared with 11,890 patients who received other fertility treatments and patients in the control group found that the relative risk for birth defects (RR 1.43 (95 % CI 1.19–1.72)) is increased for singleton infants. Specific defects associated with IVF/ICSI have been reported also in this study, like patent ductus arteriosus, hypospadias, and obstructive defect in the renal pelvis and ureter [301]. From the EVIAN decision group [302], no increased risk of birth defects and no difference in cognitive function were found in ART children. On the other hand, lower birth weight and higher fasting glucose concentrations have been observed in these children. No direct link could be established between IVF treatment and congenital anomalies, but rather an association of parents' age with these anomalies.

10.16.3 Perinatal Mortality

No difference was found at perinatal mortality rates [295, 303]. A recent study [304] focused in birth asphyxia. Singletons after IVF had an increased risk for low Apgar score (<4) (it can be more readable [OR] 1.29; 95 % CI, 1.14–1.46) and intrauterine fetal death (adjusted OR 1.61; 95 % CI, 1.35–1.91).

10.16.4 Neonatal Complications

Increased incidences of twin pregnancy and low birth weight ($P<0.01$) have been observed in IVF group, but decreased average birth weight ($P<0.05$) when compared with the control group [305].

10.16.5 Mother

In the IVF group, mother's age was increased [305] with higher incidence of cesarean section. This is also true for women over 35 years old [303]. When comparing for

testicular sperm aspiration, significantly, more cesarean sections have been performed after IVF (27.3 % for singletons) and ICSI (25.1 % for singletons) with ejaculated sperm compared with the aspirated sperm group (16.4 % for singletons) [295].

10.16.6 Pregnancy Complications

In pregnancy, complications considered are lower birth weight, very low birth weight, small for gestational age, and perinatal mortality.

When controlling factors contributing to adverse perinatal outcomes in singleton IVF, one is premature rupture of membranes [305], with spontaneous onset [303] and lower average birth weight. Preterm birth at different stages and intrauterine growth restriction are increased [306]. These singletons show a significant tendency for late preterm birth at 32–36 weeks (RR 1.52, 95 % CI 1.01, 2.30) [306], moderate preterm birth <32–33 weeks (RR 2.27, 95 % CI 1.73, 2.97), very LBW (<1500 g, RR 2.65, 95 % CI 1.83, 3.84), and a mean birth weight (−97 g, 95 % CI −161 g, −33 g).

Same findings are reported elsewhere. In a large Danish cohort study [307], mean birth weight was 65 g ([CI], 41–89] lower in all assisted reproductive technology children. Also, higher risk of low birth weight ([OR], 1.4; 95 % CI, 1.1–1.7]) and preterm birth (OR, 1.3; 95 % CI, 1.1–1.6]) was observed in IVF/ICSI children compared with spontaneous conception children.

In a meta-analysis [308], the factors for preterm birth in singleton pregnancies were examined. Might be eradicated that time to pregnancy (TTP) is one factor (spontaneous conception with (TTP) >1 year, IVF/ICSI singletons from subfertile couples with TTP > 1 year, IVF/ICSI singletons, singletons with a "vanishing co-twin," conception after ovulation induction, and/or intrauterine insemination). More specifically, when IVF/ICSI singletons have been examined, compared with spontaneous conception singletons from subfertile couples (for more than 1 year); preterm birth was significantly increased in the IVF group (OR 1.55, 95 % CI 1.30, 1.85). When it comes to conception after ovulation induction and/or intrauterine insemination compared with SC singletons (where time to pregnancy is ≤1 year), preterm birth is higher in the ART group (AOR 1.45, 95 % CI 1.21, 1.74).

In between ART technique comparison, ICSI versus IVF, lower risk of preterm birth was observed (AOR 0.80, 95 % CI 0.69–0.93) for ICSI. The same was applied for frozen embryo transfer when compared with fresh embryo transfer (AOR 0.85, 95 % CI 0.76, 0.94).

In the Chinese population, also increased incidence of low birth weight and decreased average birth weight was observed [305].

10.16.6.1 Vanished Twins and Pregnancy Complications

Vanished pregnancy (twins and triplets) is a different entity, but contributes to pregnancy complications. The risk of preterm birth in singletons with a "vanishing co-twin" versus a single gestation is against IVF siblings (AOR of 1.73 (95 % CI 1.54, 1.94) [308, 309].

In a retrospective study by Barton et al. [309], significantly lower mean birth weight (2192 g ($P=0.01$)) was observed in the vanished triplet group with a 64 % with at least one infant with LBW.

Preterm birth <37 weeks of gestation is affected at 83 % of the vanished triplets and 73 % of the non-varnished twins. However, vanished triplets had an increased risk of early preterm birth (<32 weeks) (OR 3.09, 95 % CI 1.63–5.87), and the length of gestation of these pregnancies was on average 1.5 weeks shorter [309].

In another study [310], preterm birth before 28 weeks was significantly increased by 7 % compared with 1, 2 % of normal singletons. In a study of vanishing twins in the Chinese population, lower mean birth weight and increased preterm delivery rate were observed [311].

10.16.6.2 Effect on Gestational Age

The mean gestational age (GA) for singletons delivered after testicular sperm extraction is (279 ± 12 days). This is significantly higher compared with the gestational age of IVF children (276 ± 18 days; $P=0.02$) [295]. In twin pregnancies, the duration of gestation (−0.5 weeks, 95 % CI −1.2 weeks, 0.2 weeks) was not significantly different compared to spontaneously conceived twins/IVF twins [312].

10.16.6.3 Low Birth Weight

IVF, prematurity, twin pregnancy, and pregnancy complications were risk factors for low birth weight [305] with IVF infants presenting the higher incidence of LBW. From two meta-analysis [306, 312], it is clear that IVF singletons present with LBW <2500 g (RR 1.60, 95 % CI 1.29, 1.98) and very LBW <1500 g (RR 2.65, 95 % CI 1.83, 3.84) when compared with spontaneously conceived singletons. The same is applied to twins. They present with LBW <2500 g (RR 1.14, 95 % CI 1.06, 1.22), very LBW <1500 g (RR 1.28, 95 % CI 0.73, 2.24), and extremely LBW <1000 g (RR 0.88, 0.04, 19.40) when compared with spontaneously conceived twins. When elective single embryo transfer is performed, the LBW is decreased (RR 0.25, 95 % CI 0.15–0.45) compared with double embryo transfers, but not when compared with spontaneously conceived singletons (RR 2.13, 95 % CI 1.26–3.61) [313]. When the sperm was extracted from the testes (TPT), the adjusted risk of LBW was significantly higher for offsprings that came from TPT versus NC singletons [adjusted odds ratio (AOR) = 0.67 (0.48–0.93)]; [295]. Vanishing twins may play an important role in low birth

weight. When vanishing twin pregnancy was diagnosed, the proportion of low birth weight (<2500 g) in remaining embryo was 33.3 % versus 11.7 % ($P=0.0001$) and very low birth weight (<1500 g) 3.5 versus 0.6 %, when compared with singleton IVF pregnancies, respectively [310].

Although children conceived with IVF showed significantly lower birth weight that may act as an important predictor of mental development, these children present with no differences on long-term growth and neurodevelopment of children compared with spontaneously conceived children [314].

Low birth weight is associated with a high number of oocytes (>20) retrieved (OR 1.17, 95 % CI 1.05–1.30), while no increased risk for LBW is found for normal response (10–15 oocytes) and poor response (≤3 oocytes) patients OR 0.92, 95 % CI 0.79–1.06 [315]. An association of media culture and the newborn birth weight is already indicated, but it will be further developed in the appropriate chapter.

10.16.7 Paternal Factor

Several factors have been implicated in male infertility. In infertile men with reciprocal translocation of autosomal chromosomes usually on their efforts to conceive, partners undergo abortions due to unbalanced translocations of the embryos. In a case report a male underwent testicular sperm extraction and IVF with preimplantation genetic screening [316] in a well-designed case control study, men with azoospermia and oligozoospermia (but without obstructive azoospermia, varicocele, cryptorchidism, hypogonadotropic hypogonadism, karyotype abnormalities, or complete deletion of AZF a, b, or c). SNPs rs7867029 and rs7174015 are associated with oligozoospermia; SNP rs12870438 is associated with azoospermia and oligozoospermia but no associations between rs724078 and azoospermia or oligozoospermia have been found [317]. A deletion mutation of adenine in location 11,337 of the Nsun7 gene in asthenospermic men has been found [318].

Advanced paternal age (PA) is associated with reduced semen volume; reduced sperm count, motility, and morphology; and a significant increase in the prevalence of both genomic and epigenomic sperm defects [319].

10.16.8 Explanations Given from Basic Sciences

10.16.8.1 DNA Methylation

DNA methylation differences observed between ART and in vivo conceptions are associated with some aspect of ART protocols [320]. Placental DNA methylation levels have been checked at 37 CpG sites in 16 candidate genes. Twenty of the 37 CpGs analyzed had been identified as differentially methylated between ART and fertile control groups. Also, differences in placental DNA methylation have been observed in 12 CpG sites, between oocyte donor offspring and fertile control groups.

Although children conceived through IVF have a higher incidence of preterm birth and lower birth weight, clinical follow-up for 7 months to 3 years showed that none of the children had clinical symptoms of any imprinting diseases. Also, all children had normal DNA methylation patterns at six DMRs (KvDMR1, SNRPN, MEST, MEG3, TNDM, and XIST) [321].

When it comes to ICSI evaluation, malformation rates in these offspring ranged from 3.5 to 6.2 %. At 3 years of age ($n=811$), the proportion of children at risk for developmental delays was 10.4 % in ICSI and 10.7 % in *IVF* singletons. For singleton pregnancies, obstetric and neonatal outcomes are dependent upon maternal age, while epigenetic analysis of these fetuses found minor imprinted gene expression imbalances [321, 322].

10.16.8.2 Maternal Factors

Placental Animal Studies Associated with Lower Birth Weight

Although placenta weight shows no difference between IVF (ICSI or IVF) and normal conceived mice, the levels of placental estriol were significantly lower in the ART group, thus showing the efficiency of total steroid production. Levels of steroid metabolites androstane-3alpha-17beta-diol glucuronide and dehydroepiandrosterone sulfate were higher in fetal compared to maternal blood in ART-conceived animals. The authors conclude that the ART placenta has greater capacity to metabolize and remove steroids through glucuronidation and that this phenomenon is associated with lower steroid hormone levels transiting the placenta to the fetal unit [323].

Based on the fact that since steroid hormones, especially progesterone, prevent oxidative stress and inflammation in pregnancy, the same authors proved that placental inflammation and oxidative stress exist in ART placenta and may mediate low birth weight.

Placentas from ART contained significantly less lipids, with greater levels of apoptosis and degraded nucleotides. No significant difference was observed in placenta reactive oxygen species between ART placenta and normal conceived embryos. In parallel, maternal livers from normal fertilization had less ROS than maternal livers from ART. Placentas from ICSI pregnancies had lower activities of superoxide dismutase (SOD), thioredoxin reductase (TrxR), xanthine oxidase (XO), catalase, glutathione-S-transferase (GST) glutathione peroxidase, and glutathione reductase (GR). Furthermore, GR, GST, and SOD were also lower in fetal livers from ICSI pregnancies. Placentas from IVF pregnancies had decreased levels of SOD, TrxR, and XO; only both ICSI and IVF pregnancy IL-6 levels were significantly increased. The authors conclude that IVF/ICSI is associated with placental inflammation (IL-6), oxidative stress, and apoptosis [324].

In another study [325], researchers examined the placental growth and function and its association with fetal weight. Although placental weights did not differ also, between IVF and natural mating embryos, proliferation was increased in IVF placentae. Both fetal weights and fetal-to-placental ratios were lower in the IVF group. Also in these placentas, the mRNA for selected glucose, system amino acid transporters, and imprinted genes was downregulated. Also, GLUT3 protein level was decreased in the IVF group. Fetal accumulation of glucose was not different, but the amino acid accumulation was significantly (36 %) lower in IVF fetuses.

The same working group tried to define whether changes in placental structure take place and assess the net flow of hormones between the maternal, placental, and fetal circulations. ART increased 3β-HSD activity in maternal livers, but there were no other changes in 3β-HSD- or CYP17-mediated steroidogenesis. Cholesterol levels were significantly lower in maternal livers of ICSI pregnancies and in placentas from both IVF and ICSI pregnancies. Progesterone levels were higher in maternal and fetal livers after IVF and ICSI, respectively, but were significantly lowered in ICSI placentas, compared to normal fertilization. No differences in E1 or E2 levels were observed in maternal livers but ICSI significantly increased both E1 and E2 levels in placentas, while both IVF and ICSI significantly lowered E1 but raised E2 levels in fetal livers. In summary, while steroid production was normal, steroid diffusion/flow from mother to fetus was altered in murine pregnancies conceived by ART [326].

Embryo biopsy (single blastomere removal from cleavage-stage mouse embryos) affected the levels of steroids (estradiol, estrone, and progesterone) in fetal and placental compartments, but in maternal tissues, decreased activities of steroid clearance enzymes (uridine diphosphate-glucuronosyltransferase and sulfotransferase) were observed in IVF placentas; the weights of fetuses derived from biopsied embryos were lower than those of their non-biopsied counterparts [327].

From placentas from biopsied cleavage embryos, the same authors found an activation of MMP9, activation of STAT1, and lower levels of SOCS2 and SOCS3, thus indicating that Janus kinase/signal pathway may be associated with premature rupture of membranes and preterm birth [328].

Abnormal placentation may be another cause for low birth weight in ART offspring. Also in a mouse model, fetuses from IVF blastocysts showed a modest but significant delay in development compared with normal blastocysts. In addition, IVF conceptuses were consistently smaller than normal blastocyst fetuses.

IVF mice have a higher abortion rate, smaller fetuses, and relative larger placentas. The fetal placentation area is smaller but morphologically normal in IVF mouse, so the placental-to-fetal ratio was larger in the IVF group [329].

Conclusion

One of the minor complications that literature neglects is the accidental puncture of the bowel (Fig. 10.25). Often the bowel is adherent to the internal genitalia, for diseases

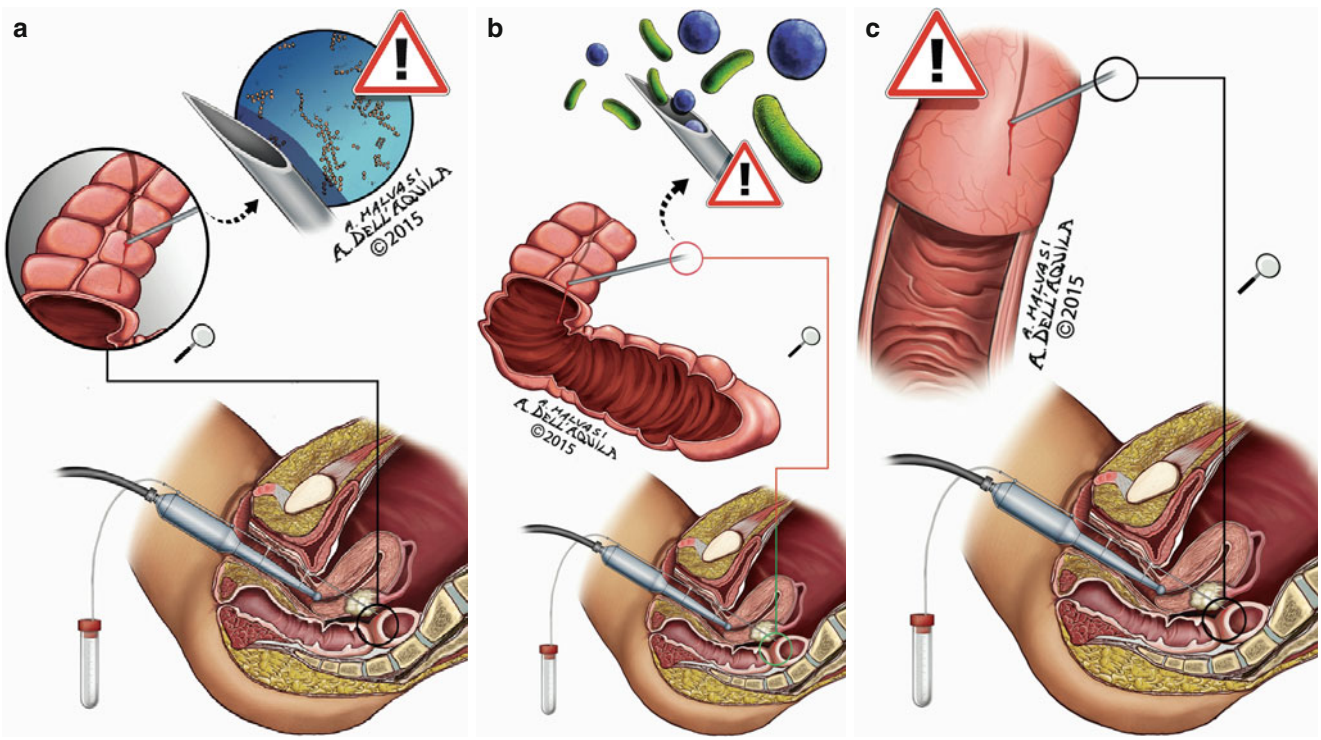

Fig. 10.25 (**a**–**c**) An accidental puncture of bowel with bacteria spreading: on the *left* is represented *streptococci*; on the *right*, *enterococci*

such as endometriosis, pelvic inflammatory disease outcomes, previous interventions, etc. Normally, after the accidental puncture of the intestine, nothing serious happens, since the drilling is minimal and closes again immediately. Sometimes, however, it may be that intraintestinal bacteria can spread in the abdominal and pelvic cavity and can cause abdominal infections.

Current notion is that complications of pregnancy depend rather on the pathophysiology and the genetic basis of infertility than on the technique of ART.

IVF complications may serve as a base to study pathophysiologic mechanisms of common gynecologic and obstetrics diseases.

This chapter might help viewers understand the complexity of in vitro fertilization and all possible complications that may arise even when the operator is very experienced.

Techniques may have a high accuracy and safety record, but underlying pathophysiology from infertility or from the pharmacological intervention may lead to more unstable condition.

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