Ovarian stimulation and embryo banking for fertility preservation in a woman with severe mixed connective tissue disease: is it safe?

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Received: 26 October 2011 / Accepted: 13 December 2011 / Published online: 29 December 2011
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Abstract

Objective To report the first case of using assisted reproductive technologies (ART) for fertility preservation in a patient with mixed connective tissue disease (MCTD), secondary pulmonary hypertension (PH) and antiphospholipid syndrome (APS).

Design Case-report and review of the literature.

Setting Academic infertility practice and tertiary care center.

Patient(s) A 25-year-old woman with MCTD, complicated with PH and APS, who was scheduled for gonadotoxic therapy

Intervention(s) Controlled ovarian hyperstimulation, egg retrieval, embryo banking.

Main outcome measure(s) Successful ART cycle leading to embryo banking without worsening her underlying disease.

Result(s) Following successful embryo cryopreservation, the patient experienced respiratory failure and other severe complications, resulting in a prolonged hospital stay.

Conclusion(s) Controlled ovarian hyperstimulation for embryo banking in women with MCTD, PH and APS may pose a risk for potentially catastrophic complications. A

multidisciplinary approach to these patients is necessary to optimize the outcomes of such procedures. More data are needed regarding the safety of fertility preservation technologies in patients with complex medical diseases.

Keywords Ovarian stimulation · Fertility preservation · Mixed connective tissue disease · Pulmonary hypertension · Antiphospholipid syndrome

Introduction

Mixed connective tissue disease (MCTD) is an overlap syndrome that shares features of systemic lupus erythematosus (SLE), systemic sclerosis (scleroderma) and polymyositis, in the presence of a high titer of anti-ribonucleoprotein (RNP) antibody [1]. The prevalence of MCTD in the population is 10 cases per 100,000, with women being predominantly affected [1]. Although MCTD itself does not seem to alter reproductive potential, some treatments are gonadotoxic. Furthermore, pregnancies may be complicated by maternal disease flares, fetal loss, pregnancy-induced hypertension, preeclampsia, preterm delivery, small for gestational age infants and neonatal lupus [2]. Pulmonary hypertension (PH), a significant cause of death in MCTD [1], remains an absolute contraindication for getting pregnant [3]. Given the risks of pregnancy, in vitro fertilization (IVF) with gestational surrogacy may be an option for patients with MCTD and PH to have biologic children.

Moreover, young women with autoimmune diseases who face imminent gonadotoxic treatment may preserve their fertility potential through oocyte or embryo banking [4]. Our aim was to describe a case of assisted reproductive technologies (ART) for embryo banking in a woman with a history of MCTD and secondary manifestations of PH and

Capsule A woman with severe mixed connective tissue disease experienced serious complications after ovarian stimulation and embryo banking for fertility preservation. The multidisciplinary team approach to these patients is critical to optimize the outcomes of such procedures.

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antiphospholipid syndrome (APS), scheduled for highly gonadotoxic therapy.

Case report

A 25-year-old woman was referred to our center for counseling regarding fertility preservation. Her medical history was significant for MCTD, PH, interstitial lung disease, esophageal reflux, anxiety, depression and antiphospholipid antibody complicated by a history of bilateral pulmonary embolism. Medical therapies at the time of consultation included azathioprine, hydroxychloroquine, sildenafil, ambrisentan, metoprolol, esomeprazole magnesium, bupropion, sertraline HCl and therapeutic warfarin. Due to her worsening pulmonary status, high dose alkylating agent administration and autologous bone marrow transplantation had been recommended to the patient as an experimental therapy for her disease. Given the high risk of gonadotoxicity related to bone marrow transplantation [5], she was referred to discuss fertility preservation options. After extensive consultation and review of all of her options, the patient decided to proceed with controlled ovarian hyperstimulation and embryo cryopreservation with her long-term partner, with plans to use a gestational carrier for childbearing in the future.

After evaluation by a pulmonologist, azathioprine was discontinued and anticoagulation was converted to therapeutic doses of enoxaparin. To prevent ovarian hyperstimulation syndrome (OHSS), a major adverse outcome of IVF cycles in women with autoimmune rheumatologic diseases [6], a protocol based on the use of a GnRH antagonist was favored so that leuprolide acetate could be employed for final oocyte maturation if deemed necessary [7]. Baseline laboratory values included FSH of 4.5 IU/L, E_2 of 77 pg/ml and antral follicle count of 17. Her BMI was 29 kg/m². On cycle day 2, the patient was started on recombinant FSH at 150 IU daily. On stimulation day 5, cetorelix was initiated at dose of 0.25 mg and 75 IU highly purified human menopausal gonadotropin (HMG) was substituted for 75 IU of recombinant FSH during the last four days of ovarian stimulation. E_2 /LH levels and follicles were monitored every 24–48 h. Final oocyte maturation was triggered with 10,000 IU human chorionic gonadotropin (hCG) on stimulation day 15 since the patient was not deemed at high risk of OHSS. The maximum serum E_2 concentration on that day was 1,519 pg/mL and 13 follicles were noted to be at least 14 mm in mean diameter.

A total of 16 oocytes were retrieved vaginally 36 h after the hCG administration. The anesthetic protocol consisted of IV propofol (100 mg), midazolam (5 mg) fentanyl (200 µg) and local vaginal anesthetic. The patient was

awake and communicative during the entire surgical procedure. Intravenous doxycycline (100 mg) was administered at the time of surgery. The immediate recovery period was uneventful and the patient was discharged with instructions of restarting enoxaparin 12 h after the procedure and transitioning to warfarin. Of the collected oocytes, six were fertilized conventionally and were cryopreserved at the 2 pronuclear stage.

Two days after oocyte retrieval, the patient reported a fever of 102.2°F and shortness of breath. She was instructed to go to the emergency room where the initial work-up revealed a WBC of 14.2/uL with 83.2% neutrophils. Bibasilar atelectasis and small pleural effusions were noted on chest x-ray and a pelvic ultrasound revealed bilaterally enlarged ovaries and moderate amount of free fluid without definite evidence of hemoperitoneum. She was admitted to the hospital and promptly placed on levofloxacin/metronidazole for a possible pelvic infection. Warfarin was stopped and enoxaparin reinitiated for anticoagulation. Four days later, she was transferred to the MICU for worsening hypoxia presumably secondary to multifocal pneumonia, hemoptysis and underlying pulmonary hypertension and pulmonary fibrosis. Prolonged INR of 4.9 was detected and reversed with vitamin K administration. Her pulmonary status deteriorated to ventilator-dependent respiratory failure. Her course was further complicated with fevers, lower gastrointestinal tract bleeding likely due to ischemic colitis, left common femoral vein thrombosis and ICU myopathy. All cultures failed to yield any specific pathogen. Mixed connective tissue disease was controlled with the use of hydroxychloroquine and methylprednisolone, a combination converted later to prednisone. Eventually, tracheostomy and gastrostomy-jejunostomy tube placement were required for prolonged respiratory failure and enteric access. The patient was discharged three months after her admission and transferred to an acute rehabilitation facility.

Given the life-threatening nature of the patient's complications, the planned bone marrow transplantation was cancelled. The patient was treated with oral cyclophosphamide for mixed connective tissue disease and has been without evidence of relapse for the past year. During that period of time, the patient had a spontaneous pregnancy that ended in miscarriage. Given the risk of pregnancy, she pursued permanent sterilization by laparoscopic bilateral tubal ligation. She is considering having her embryos thawed and transferred to a gestational carrier.

Discussion

In this report, we describe a patient with MCTD and secondary PH and APS who experienced serious complications

after ovarian stimulation for embryo banking. In this case we suspect that increased serum estradiol levels coupled with oocyte retrieval under sedation may have exacerbated esophageal reflux causing aspiration pneumonia [8]. Infection subsequently precipitated respiratory failure and a cascade of multi-organ system dysfunction, typical of patients with severe rheumatologic disorders [9]. There are limited data on the safety of ovarian stimulation and oocyte retrieval in patients with MCTD.

Ovarian stimulation is marked by elevated serum E_2 levels that may exceed menstrual values by 2- to 10-fold [6]. It is well-known that estrogen plays a crucial role in immune system modulation and, thus, expression of autoimmune diseases. However, its effects on cell proliferation, cytokine production and differentiation of hematopoietic cells varies in different tissues depending on the type of the estrogen receptor (ER), ER- α or ER- β , present [10, 11]. Therefore, there is reason for concern regarding increased risks of complications in women with autoimmune diseases undergoing IVF.

Most data on the relationship between ART and systemic rheumatic diseases are based on patients with SLE. Although the induction, unmasking or exacerbation of pre-existing SLE and various medical complications have been described with ovulation induction [6], the results of the two large series seem to be reassuring. The first included 68 cycles of ovulation induction (OI) or IVF. Increased lupus activity or OHSS were diagnosed in 43% and 29% of SLE patients, respectively, and were generally mild. No adverse events were reported in any woman with primary APS [12]. The second study included women with SLE or APS undergoing a total of 114 OI or IVF cycles. In this study, 30% of patients had a SLE flare when the underlying disease had not been previously diagnosed. Two cases of venous thromboses and none of OHSS were reported [13]. In this context, planned ovarian stimulation during a remission phase, use of protocols to avoid high serum E_2 levels, concomitant therapy with medications such as anticoagulants, corticosteroids, or immunosuppressants, prevention of OHSS [7], single embryo transfer and natural progesterone administered vaginally for luteal phase support may optimize the outcomes of women with SLE or APS undergoing ovarian stimulation [6].

The effects of infertility treatments on other systemic rheumatic diseases remain largely unknown. Successful outcomes have been described in a small series of patients with Sjögren syndrome after IVF and low-dose prednisolone administration [14] and in case reports of ovulation induction in women with either rheumatoid arthritis [15], or Takayasu's disease [16]. On the other hand, there has been a case of acute polymyositis and vasculitis which occurred during GnRH analogue administration for IVF [17]. Given

the immunostimulating properties of GnRH [18], it is possible that GnRH may exacerbate autoimmune diseases, an association that merits further research.

PH, a major concern in our patient, has been defined as a mean pulmonary arterial pressure (PAP) ≥ 25 mmHg at rest as assessed by right heart catheterization [19]. It is estimated that connective tissue diseases account for up to 30% of all adults with pulmonary arterial hypertension (PAH) and are associated with worse prognosis as compared to its idiopathic form [20]. Interstitial lung disease and diastolic left heart dysfunction represent other mechanisms for PH development in patients with MCTD [21]. Although new medications and updated guidelines are now available [19], the reported overall maternal mortality rate of 25% is still prohibitively high [3]. The physiologic changes related to pregnancy make it extremely risky for women with significant PH.

However, while pregnancy is risky in women with PH, animal data indicate that estrogen may actually be beneficial in PH. This phenomenon has been referred to as the "estrogen paradox" [22, 23]. Estrogen-induced rescue of severe pre-existing PH seems to be associated with stimulation of cardiopulmonary neoangiogenesis, suppression of inflammation, fibrosis and right ventricular hypertrophy, most likely mediated through ER- β [23]. Human studies in postmenopausal women also suggest a protective role of estrogen in PH [24, 25]; nevertheless, contradictory data exist [26, 27]. Interestingly, the only publication on the use of ART in a patient with primary pulmonary hypertension did not report any complications [28]. While it is unclear if our patient's worsening PH was related to hyperestrogenism, we suspect that infection was the precipitating event.

The perioperative management of patients with PH planning oocyte retrieval poses a clinical challenge for the anesthesiologist. Noncardiothoracic, nonobstetric surgery may lead to death or complications in 7% and 29% of patients with mild-to-moderate PH, respectively [29]. Anesthesiologists should have a clear understanding of the underlying pathophysiology of PH and pay special attention to the prevention of possible right heart failure and, subsequent, systemic hypotension [30]. Chronic therapies should be continued during the entire perioperative period [30].

In our patient, mild conscious sedation combined with local anesthesia was used to minimize risk. While anticoagulation was warranted in this patient during ART given her history of APS, there may be a role for anticoagulation in patients with idiopathic, heritable, or anorexigen-related PAH [19]. Anticoagulation was achieved with enoxaparin during the ovarian stimulation and transitioned to warfarin after the oocyte retrieval. The supratherapeutic INR levels, along with the relevant clinical symptoms observed during

the first days of her hospitalization, may be partly attributed to the interaction between recent warfarin exposure and levofloxacin/metronidazole [31] and highlight the complexity that characterizes the management of such patients.

As fertility preservation strategies improve and become more accessible, more young women with complex medical diseases requiring gonadotoxic therapies such as MCTD will seek them to expand their reproductive options. Embryo and oocyte cryopreservation in particular offer patients the option of using a gestational carrier in situations where pregnancy is not considered safe. Indeed, since patients with medical problems may be ineligible for adoption, these techniques or the use of donor gametes may be the only realistic options for having future children. This report highlights the fact that women with MCTD undergoing ART may be at risk for serious complications. Given the uncertain risks of these procedures, we recommend a multidisciplinary team approach to the care of these patients, including clinicians with broad expertise in the medical management of complex patients, reproductive endocrinologists, and psychosocial counselors. In addition, care should be provided in a highly specialized health care facility with the capability to care for complex and critically ill patients. More data on the safety of ovarian stimulation and other fertility preservation strategies in such populations are needed to improve patient counseling and determine appropriate candidates for these procedures.

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