

## Case Report Article

# Bilateral osteonecrosis of the femoral head in an oocytes donor: A case report

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## Abstract

We report the case of a 31-year-old, previously healthy woman, with bilateral hip pain six months after ovarian stimulation for oocytes retrieval. Plain radiographs of both hips as well as clinical examination at that time, which were performed at a different hospital, showed normal findings. Three months later, however, the patient presented to our department with progressive hip pain. MRI examinations were performed on both hips and revealed bilateral osteonecrosis of the femoral head (Ficat I). Conservative treatment was recommended but the patient failed to complete the suggested clinical reevaluations during this conservative management period and reappeared 17 months after her last visit to our department. At that time, radiographs revealed remarkable collapse of both femoral heads. Consequently, cementless ceramic - ceramic total hip arthroplasty was performed, first on the right hip and three months later on the left.

**Keywords:** Osteonecrosis, Femoral head, Assisted fertilization, Ovarian hyperstimulation

## Introduction

The most common condition of the hip that results in the need for prosthetic replacement even in the young adult population is osteonecrosis of the femoral head. Femoral head osteonecrosis is bilateral in up to 75% of cases<sup>1</sup>. Risk factors include fractures of the femoral neck, long-term steroids use, Cushing's syndrome, alcoholism, smoking, a history of slipped femoral capital epiphysis and systemic lupus erythematosus. Additional factors include other connective tissue disorders such as autoimmune disease, vasculitides, hemoglobinopathies (like sickle cell anemia), clotting disorders such as thrombophilia or disseminated intravascular coagulation and furthermore, hyperlipidemia, fat embolism syndrome, chemotherapy and radiation, organ transplantation, chronic liver disease, Gaucher disease, gout, as well as bone metabolic diseases<sup>2-6</sup>.

Intravascular coagulation is the final common pathway that correlates with osteonecrosis. Patients with idiopathic osteonecrosis may have a hypercoagulable state that should be seriously taken into consideration whenever they undergo an operation<sup>7</sup>. Regardless of the primary cause, several studies suggest a common pathophysiological pathway involving apoptosis of osteoblasts and osteocytes<sup>2-3</sup>.

In addition to vascular injury and programmed cell death, decreased bone formation is a key component of osteonecrosis<sup>5</sup>.

## Assisted reproductive technology (ART)

The process of assisted reproductive technology or in vitro fertilization has as its main purpose to achieve cycle control, stimulate the ovaries and finally support implantation by using exogenous hormones. The procedure begins the month preceding the IVF, by the recipient receiving oral contraceptives or gonadotrophin releasing hormone analog (GnRH). GnRH is given so as to block the production of endogenous reproductive hormones, thus permitting only

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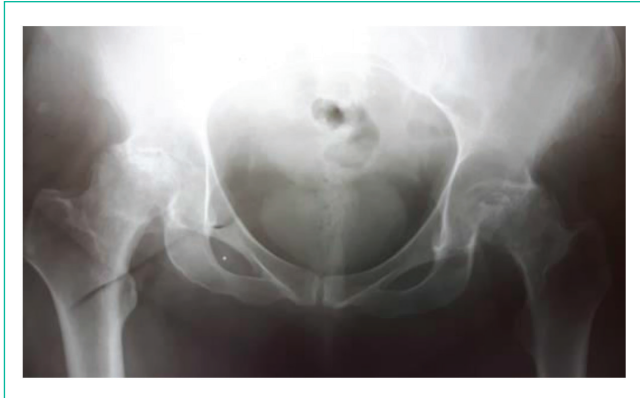
the action of exogenous hormones on the ovaries. The next step includes the administration of exogenous hormones including gonadotrophins (LH and FSH), human menopausal gonadotrophin (hMG), human chorionic gonadotrophin (hCG), or clomiphene citrate, the usage of which as well as its dosage differs according to IVF centre and protocol<sup>8</sup>. The follicle stimulating hormones are usually administered in the first half of the cycle for a period of 7 to 10 days. During this time the development of the follicles and the levels of serum estrogen and progesterone are measured. When both the optimum size of follicles and serum level of estradiol are reached, hCG is administered, and oocyte retrieval is performed 36 hours later.

### Case report

We report the case of a 31 year old woman, who presented to the orthopaedic outpatient department of our clinic in 2009, 3 months after visiting another clinic, complaining of progressive bilateral hip pain. The patient had no history of trauma; she was a smoker (1 pack/day), and refused excessive coffee and alcohol intake. In addition, she did not receive any medication apart from occasional use of over-the-counter painkillers and NSAIDs for her current condition. Her past medical history comprised of a normal delivery when she was 20, one year later an abortion and an ovarian cyst removal.

In 2008 she had been subjected to a controlled ovarian hyper stimulation regimen, including human menopausal chorionic gonadotropin (hMG) over a period of 7 days in the first half of the cycle, followed by human chorionic gonadotropin (hCG). Two days later, oocyte retrieval was performed. 6 months after that the patient started to have hip pain bilaterally. Initial work up performed to another hospital did not include MRI of the hips, so an early diagnosis of osteonecrosis was not made. Three months later, the patient presented to our hospital with worsening of symptoms. MRI of both hips revealed a band pattern of low signal intensity for both hips on T1 and T2 weighted images. Therefore the diagnosis for bilateral hip osteonecrosis was established. The primary therapeutic approach was conservative with frequent follow up visits. The patient was lost to follow up and presented 17 months after her last visit to our department. A new radiological examination revealed marked collapse of both femoral heads, subchondral sclerosis and joint space narrowing (Ficat IV).

On clinical examination the patient had significant reduction in the range of movements of both hips and walked with marked limp using crutches. Laboratory examinations including ESR, CRP, lipidemic profile, coagulation tests were all within the normal range. The patient initially had a right total hip arthroplasty (press fit, ceramic-ceramic) and three months later a similar left total hip arthroplasty was performed (Figure 2). The patient failed to complete the recommended postoperative follow-up course (three, six and twelve months) three months after the second procedure.



**Figure 1.** Anteroposterior view revealing bilateral osteonecrosis of both hips with marked collapse seventeen months after the ovarian hyperstimulation regimen.



**Figure 2.** Postoperative anteroposterior radiograph after press fit bilateral total hip arthroplasties.

### Discussion

Osteonecrosis of the femoral head in its incipient stages is commonly passed by or confused with other hip pathology due to the subtle non typical symptoms. The sudden onset of groin pain is a characteristic clinical finding which is aggravated by ascending and descending stairs. The pain persists, does not subside with NSAIDs, is still present without weight-bearing and reaches its peak two to three months after the initial presentation. When the patient reports pain while walking, the disease may be already at stage II. In advanced stages, reduced range of motion and in particular limitation of internal rotation is observed.

Stage I of osteonecrosis according to Ficat (1980) does not present any radiographic changes and diagnosis is based on bone biopsy and the measurement of endosseous pressure.

In stage II, the contour of the femoral head is unaffected and a reparative process is observed in subchondral bone. Stage III is characterized by radiographic changes characteristic of osteonecrosis including impaired bone contour and structural damage. In stage IV, there is collapse of the articular surface and secondary osteoarthritis<sup>9</sup>. Steinberg's modified classification, introduces parameters related to the extent and location of lesions found on MRI. Steinberg's classification has a prognostic value for femoral head osteonecrosis.

Treatment options for femoral head osteonecrosis include monitoring, decompression, rotational osteotomy, vascularized fibula graft and finally hip arthroplasty. Decompression is indicated in the initial stages of the disease before collapse of the subchondral bone occurs. However, even when it is performed early, decompression may not prevent subchondral bone collapse<sup>10</sup>.

In literature most cases of peripartum osteonecrosis are related to assisted fertilization. Pregnancy is a condition that favours the development of femoral head osteonecrosis due to the action of the following factors: accentuated hormonal alterations, mechanical stress on hips due to extra weight and fetus pressure on the pelvic arterio-venous network.

A well-known complication of IVF is the ovarian hyperstimulation syndrome<sup>11</sup>. This frequently occurs when the ovaries are stimulated with exogenous gonadotrophins in order to acquire oocytes for fertilization. The clinical expression of this syndrome comprises of a spectrum of symptoms ranging from mild to severe or even fatal conditions like acute renal failure, ARDS and hematological abnormalities. Risk factors for the establishment of the syndrome include the patient's young age, high and rapidly increasing estradiol levels, the increased size and number of follicles being stimulated, the presence of polycystic ovarian syndrome and certain protocols for ovarian hyperstimulation<sup>12</sup>. A state of hypercoagulability which leads to arterial and venous thrombotic complications are associated with this syndrome. It is known from current studies that both the coagulation and fibrinolytic systems are activated with ovarian stimulation. During the treatment cycle, hemostatic, prothrombotic and clot lysis markers were measured before the administration of exogenous hormones to just before induction of ovulation with hCG. This measurement corresponded to the minimal to maximal estradiol levels period within the cycle. From these studies, it is evident, that when ovarian stimulation occurs coagulation factors like vWF, factors VIII, V, fibrinogen as well as activated protein C resistance are increased. On the other hand the activity of anti- thrombin, proteins C and S is decreased. Furthermore, markers promoting fibrinolysis like tissue plasminogen activator and plasminogen activator inhibitor type I displayed a decrease<sup>13,14</sup>. All the above mentioned changes demonstrate that a prothrombotic state can occur. Indeed, there are numerous published reports of thromboembolic complications associated with the use

of assisted reproductive technology. Osteonecrosis of the femoral head during or just after assisted pregnancy, although rare, is a clearly described clinical entity<sup>12</sup>.

In our case report a probable causal factor is ovarian hyperstimulation. The adverse effects of hyperviscosity and hypercoagulability after a course of ovarian hyperstimulation drugs seem to be a possible cause of hip osteonecrosis. According to Hasegawa et al.<sup>12</sup> supra-physiological levels of estradiol as in ovarian hyperstimulation may result in a prothrombotic state leading to femoral head osteonecrosis in predisposed individuals.

The initial treatment for pre-collapse avascular osteonecrosis of the femoral head (Ficat O - I - II) is conservative<sup>15</sup>. It includes lipid lowering agents, anticoagulants, prostacycline (as a vasoactive agent), bisphosphonates (to reduce osteoclast activity), biophysical treatments (extracorporeal shockwave therapy) and hyperbaric oxygen. Early instituted conservative treatment may improve pain and functional outcomes, delay the progression of the disease and prevent collapse. Early intervention prior to collapse is critical in view of native joint preservation. Late intervention usually leads to some form of arthroplasty.

The rotational osteotomy is indicated in cases of small necrotic lesions in which the necrotic part can be moved outside the loading area. In an intact lateral part of the femoral head the indication is varus osteotomy, while at an intact medial part the indication is valgus osteotomy. The successful operative outcome is inversely proportional to the size of necrotic area. The vascularized fibula graft is a relatively new technique which includes decompression of the femoral head and placement of vascularized bone graft. This process prevents collapse of the subchondral bone and it has been proved as an effective treatment even though some degree of collapse has occurred, since there is porosis at the remnant of the autologous graft<sup>16</sup>.

Hip arthroplasty is recommended in advanced stages of the disease with extensive destruction of the femoral head. The choice of hemiarthroplasty versus total hip arthroplasty depends on the age, the level of patient's physical activity and possible pre-existing osteoarthritis of the hip. Active and young patients submitted to hip hemiarthroplasty are usually associated with worse outcome due to the rapid wear of the articular cartilage of the acetabulum and the manifestation of pain in the groin and acetabular protrusion. Instead, hemiarthroplasty hip is considered as better treatment for older patients who cannot comply with the instructions and precautions required in total hip arthroplasty and whose osteonecrosis is caused by alcohol abuse.

## Conclusions

To date, the mechanisms leading to osteonecrosis after ovarian hyperstimulation syndrome are still unclear. Assisted reproductive technology may result in ovarian hyperstimulation syndrome. This is related to a state of

hypercoagulability which may lead to arterial and venous thrombotic complications. In patients receiving ART and complaining of hip pain, a high index of suspicion must be maintained regarding the development of osteonecrosis of the femoral head. Incipient osteonecrosis is usually asymptomatic. When the patient finally reports symptoms the condition is advanced. In these cases, early diagnosis with MRI is of paramount importance, since radiographic signs lag in appearance behind MRI signs. Early diagnosis with MRI leads to early implementation of conservative treatment that might prevent future femoral head collapse and subsequent surgery.

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