

## Research Letter

# Aseptic necrosis of bilateral femoral heads after pregnancy

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Aseptic necrosis, also known as avascular necrosis, ischemic necrosis, and osteonecrosis, is a pathological process caused by impaired blood supply to the affected bone that results in the death of osteocytes and bone marrow cells. Osteoclastic resorption of dead bone induces demineralization, trabecular thinning, and subsequent collapse of the joint surface with fracture of subchondral bone. A clinical diagnosis is made appropriately according to the patient's symptoms, physical findings, and imaging results compatible with this disease. The precise prevalence of avascular necrosis is unknown; but in the United States, the number of newly diagnosed patients is estimated to be 10,000 to 20,000 per year [1].

Generally, most avascular necrosis of the femoral head is because of alcoholism, steroid use, and trauma. Excessive alcohol intake and usage of prolonged high doses of glucocorticoids are reported to account for more than 90% of cases [1]; other risk factors or conditions associated with avascular necrosis include Gaucher's disease, pancreatitis, chemotherapy, decompression sickness (Caisson disease), and blood disorders, such as sickle cell disease and polycythemia. However, little is known about whether pregnancy is an etiological factor in femoral head osteonecrosis. We report the cases of two patients with bilateral osteonecrosis of the femoral head after pregnancy after ovulation induction and include a review of the literature.

A healthy 27-year-old Taiwanese woman presented with right groin pain for 1 month after giving birth to a 2.8 kg female baby by normal spontaneous delivery (Gravida 1, Para 1, Abortion 0) at 40 weeks' gestation 6 weeks before this episode. She had been treated with clomiphene citrate to increase the chance of becoming pregnant. The patient had no history of contraceptive drug use, trauma, alcohol drinking, steroid usage, hyperlipidemia, or ovarian hyperstimulation syndrome. Her weight gain during this pregnancy was 15 kg

(pregnant body weight = 84 kg; body height = 158 cm; BMI = 33.65).

The patient complained of no symptoms other than a deep ache in the right groin, which forced her to use a wheelchair. On physical examination, range of motion was found to be limited with a positive Patrick's (FABER) test in the right, whereas the left side also showed positive for Patrick's test but movement was pain-free.

Radiographs of the pelvis showed slight irregularity in the density and articular surface of both femoral heads (Fig. 1), and magnetic resonance imaging (MRI) indicated a band pattern of low signal intensity of both hips on T1- and T2-weighted images (Fig. 2).

Percutaneous core decompression was performed for both hips, and pathological examination of the specimen revealed empty lacunae and necrosis of the trabecular bone. The pain subsided after the operation, but unfortunately returned 6 months after core decompression surgery, and the patient subsequently underwent simultaneous bilateral total hip replacement in another hospital.

A healthy 26-year-old Taiwanese woman (Gravida 2, Para 1, Abortion 1) presented with bilateral hip and buttock pain for 6 months. Because preeclampsia occurred at 35 weeks of gestation, a 1.72 kg male baby was delivered by cesarean section 1 year ago. The patient underwent artificial insemination using her husband's semen after three cycles of ovulation induction with clomiphene citrate, recombinant human FSH, and human chorionic gonadotropin hormone to achieve a viable pregnancy. The patient's weight gain during this pregnancy was 17 kg (pregnant body weight = 79 kg; body height = 156 cm; body mass index = 32.46).

Bilateral hip and buttock pain was noted 6 months after childbirth; the soreness and pain became more and more severe and made it difficult for the patient to walk. On physical examination, the range of motion was found to be limited with positive Patrick's (flexion abduction external rotation) tests in both hips. There was no history of steroid usage, alcohol drinking, or trauma.

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Radiographs of the hips showed collapse of the articular surface of both femoral heads (Fig. 3), and bilateral MRI of the femoral head showed the presence of double-line signs, subchondral bone fracture, deformed joint surface, and bone marrow edema (Fig. 4). Bilateral osteonecrosis of the femoral head was diagnosed and core decompression surgical treatment was suggested, but as the patient wished to receive a second opinion, she has accepted medical treatment only to date.

Pregnancy-associated femoral head osteonecrosis is very rare, although at least 42 cases have been reported in the literature [2–4]. In 1999, Montella et al [4] reported the largest known series (13 cases), in all cases of which osteonecrosis affected the left hip and only 4 cases were bilateral. Our cases series is the third in which bilateral involvement subsequent to ovarian hyperstimulation medication is reported [3,5], and the periods between symptoms onset and diagnosis in our cases are much shorter than previously reported. Osteonecrosis of the femoral head during or just after pregnancy, although rare, is clearly a clinical entity.

Usually, osteonecrosis of the femoral head is attributed to alcoholism, steroid therapy, or trauma. Some other etiologies that may contribute are coagulopathy, autoimmune disorders, infection, cryoglobulinemia, Gaucher's disease, pancreatitis, chemotherapy, or after radiation; however, many cases are considered idiopathic. Fat embolism, ischemia, and increased intraosseous pressure are known to be associated with osteonecrosis of the femoral head. The etiology and the pathogenetic mechanism of postpartum osteonecrosis of the femoral head are still controversial and probably multifactorial. Hormonal influences, increased coagulability, mechanical stress, and impaired venous stasis are some speculative mechanisms that have been proposed [4,6,7].

Many hormonal modifications occur during pregnancy and are suspected to be possible factors of osteonecrosis, and some molecules have been shown to be involved. The unbound maternal cortisol level is elevated to three times that in



Fig. 2. Coronal T1-weighted magnetic resonance imaging of the hips showing a band pattern of low signal intensity within the femur heads (white arrows).

nonpregnant women [8]. Estrogen and progesterone production by the placenta may promote the evolution of osteonecrosis by fat embolism via inducing fat metabolism in the liver and destabilizing endogenous plasma lipoproteins. Progesterone and synthetic progestins are known to exert glucocorticoid-like effects in humans [4,7].

Another factor inducing osteonecrosis of the femoral head is ischemia. It is well known that pregnancy produces a hypercoagulable state, with an overall monthly prevalence of 0.01 thrombotic events per 1,000 women. This prevalence tends to be higher in the third trimester [9]. Hypercoagulability may result in thromboembolism of vessels, which leads to vascular occlusion or venous congestion, or both, with subsequent ischemic necrosis of the bone [4]. Ovulation induction, moreover, may be another cause. From the results of current studies, it is clear that both coagulation and fibrinolytic systems are activated with ovulation induction [10–13]. Hasegawa et al [5] reported such a case in 1999, and the adverse effects of ovarian hyperstimulation drugs, which include hyperviscosity and hypercoagulability, were hypothetically associated with the osteonecrosis, but no definite evidence was found to support the



Fig. 1. Anteroposterior radiographs of the pelvis showing abnormal density patterns and irregularity in the articular surface of both femoral heads (white arrows).

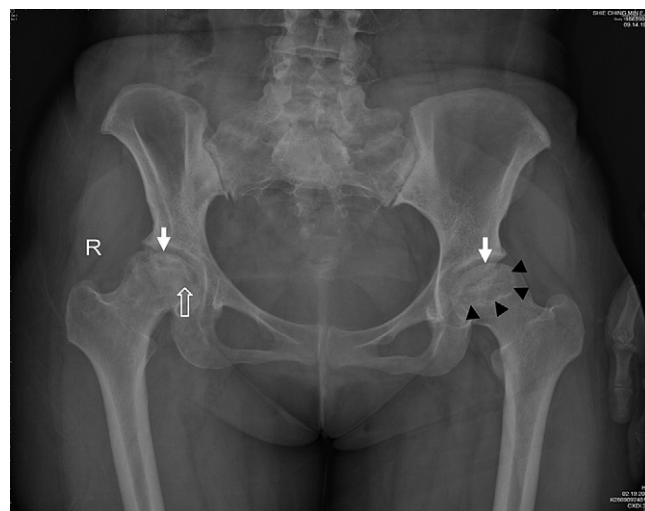


Fig. 3. Anteroposterior radiographs of the hips showing collapse of the articular surface of both femoral heads (white arrows). New subchondral fracture lucencies of the right-side femoral head area (white open arrow) and curvilinear sclerosis of the left femoral head (black arrowheads) were also noted.

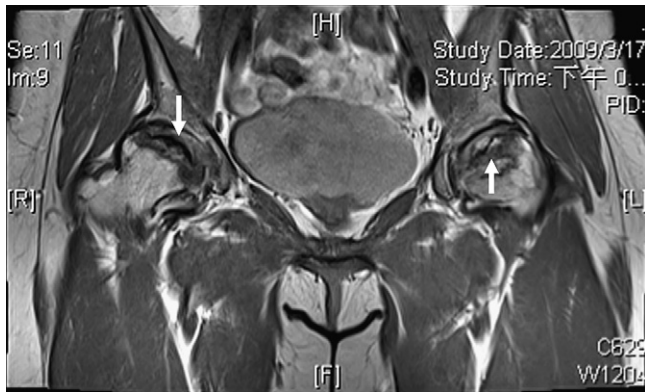


Fig. 4. Coronal T1-weighted magnetic resonance imaging of bilateral femoral heads showing the presence of double-line signs, subchondral bone fracture, deformed joint surfaces, and bone marrow edema (white arrows).

argument. In our cases, the biochemical and coagulation parameters of the patients' blood, including Protein C and Protein S, showed no abnormalities; anticardiolipin antibodies and antiphospholipin antibodies were also negative. The laboratory data did not indicate that osteonecrosis in our patients was induced by hypercoagulability.

Mechanical stress induced by excessive weight gain during pregnancy may be another etiological factor for osteonecrosis of the femoral head, especially in women with a small body frame [2–4]. Our two patients were small in stature, which may have increased the risk of femoral head osteonecrosis postpartum.

Diagnosis of pregnancy-associated osteonecrosis is often delayed as hip pain during pregnancy and postpartum is not uncommon. Compression and stress of the pelvis, ligamentous laxity induced by relaxin, transient osteoporosis of hips, sciatica or sacroiliac strain, referred pain from the spine or genitourinary tract, osteonecrosis of the femoral head, and other mechanical factors may all result in hip pain [8,14]. Because osteonecrosis and osteoporosis of the hip associated with pregnancy have distinctly different natural histories and prognoses, a differential diagnosis is important. Differentiation of history, standard radiographs, and MRI can help to make a diagnosis [2,4,5,15,16].

The optimum treatment for osteonecrosis associated with pregnancy is controversial. Accepted treatment options include restricted weight bearing, osteotomy, use of a nonvascularized or vascularized structural graft, electrical stimulation, core decompression, and arthroplasty. Core decompression is frequently suggested as a less technically demanding procedure with less operative morbidity, and satisfactory short-term results of this surgery were observed in our patients. Although surgical

options can help to reduce the symptoms, secondary osteoarthritis is often a prognostic result, and almost all patients require total hip arthroplasty in the end stages of osteonecrosis.

In conclusion, pregnancy-associated hip avascular necrosis is relatively rare, and reports of more cases are required to identify a relationship between pregnancy and this disease. We hope that this article will enlighten medical staff as to a high index of suspicion for the diagnosis and treatment of this disease.

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