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Imaging of the JIA Hip

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Abstract:	Hip involvement in JIA is common and estimated to occur in approximately 35-63% of cases. It is more prevalent in the aggressive systemic subtypes, with irreversible changes occurring as early as within 5 years of diagnosis. Whilst clinical parameters and joint examination can be useful for assessing disease severity, subclinical disease is known to exist and delayed treatment may herald a lifetime of disability and pain. Early recognition of JIA changes is therefore crucial in determining treatment options. The development of validated scoring systems in the radiological assessment of the hip for clinical drug trials may inform treatment outcomes, although robust tools for analysis are still lacking. This review article details the various modalities utilised for imaging the hip in JIA with particular efforts focussed upon reliability and validity in their assessment of joint disease. We conclude with a short literature review on the potential future techniques being developed for hip joint imaging in JIA.
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Author Comments:	Dear Dr. Oystein Olsen, We should be grateful if you would consider our enclosed manuscript entitled "Imaging of the JIA Hip" for publication in Pediatric Radiology intended for the 'Imaging of Juvenile Idiopathic Arthritis' minisymposium issue. We believe that this article complements the other suggested titles for the minisymposium as it highlights the available data within the medical literature on work performed in repeatability, clinical and construct validity of imaging JIA of the hip. This manuscript is being submitted only to Pediatric Radiology, and has not been previously submitted for publication. All authors have participated sufficiently in this submission and take responsibility for its content. All authors have approved the final version for submission, and none of the authors have any conflict of interest to

	disclose. Yours sincerely, Susan Shelmerdine Paediatric Radiology Research Fellow Great Ormond Street Hospital and UCL Institute of Child Health, London, UK On behalf of all authors
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Minisymposium: Imaging in juvenile idiopathic arthritis

Imaging of the hip in juvenile idiopathic arthritis

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Abstract

Hip involvement is common and estimated to occur in approximately 35-63% of children with juvenile idiopathic arthritis (JIA). It is more prevalent in the aggressive systemic subtypes, with irreversible changes occurring as early as within 5 years of diagnosis. Whilst clinical parameters and joint examination can be useful for assessing disease severity, subclinical disease is known to exist and delayed treatment may herald a lifetime of disability and pain. Early recognition of JIA changes is therefore crucial in determining treatment options. Validated scoring systems in the radiologic assessment of the hip for clinical drug trials may inform treatment outcomes, although robust tools for analysis are still lacking. This review article details the modalities utilised for imaging the hip in children with JIA with particular efforts focused upon reliability and validity in their assessment of joint disease. We conclude with a short literature review on the potential future techniques being developed for hip joint imaging in JIA.

Keywords Children, Hip, Juvenile idiopathic arthritis, Radiology, Scoring, Validity

Introduction

The prevalence of juvenile idiopathic arthritis (JIA) is estimated between 16 and 150 per 100,000 [1], with hip involvement occurring in approximately 20-50% of cases [2, 3]. Even when the hip is not the primary joint affected at the time of diagnosis, a threefold increase in cases with hip involvement has been observed in a cohort of JIA patients over

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a 5-year follow-up period, despite being on medical therapy [4]. In addition, it has been shown that destructive hip disease, in particular, is more frequent in patients with the aggressive "very early-onset systemic" subtype of JIA [5]. The majority of children with hip involvement can develop irreversible changes within 5 years of diagnosis [6], and approximately 26-44% will require a total hip replacement within the first 10 years of disease onset [7], at least in the prebiological era. Hip joint involvement is therefore a marker that heralds future disability with the potential to incite a reduced sense of personal independence and deterioration in overall health, partially from lack of exercise and subsequent depression [8].

Whilst clinical parameters and joint examination in cases of JIA are useful for assessing severity and extent of disease, hip involvement can be easily missed given the difficulty both in palpating the inflamed hip joint synovium [9] and in observing joint malformation due to effusion or synovial hypertrophy, which is relatively easier to identify in smaller joints, such as the wrist and knee. It is also now known that with improved therapeutic agents, joint destruction can be prevented especially when initiated promptly, underpinning the importance of detecting inflammation in subclinical disease [10].

With these factors in mind, imaging of the hip joint, particularly in early disease, holds great potential for accurately assessing disease progression, determining escalations for medical therapy and the need for targeted steroid injections and counseling with regard to future surgical management. It is worth noting that imaging of the hip also provides a role in determining differential diagnoses for hip joint pain such as leukemic involvement, avascular necrosis, trauma or underlying osseous malignancy [11].

In this review article, we highlight imaging modalities that can be used to assess the hip joint in JIA including radiography, ultrasound (US) and magnetic resonance imaging (MRI). Particular efforts have been made to focus on the feasibility, reliability, and construction of a clinical validity for published scoring systems in each imaging modality.

Progression of changes seen in juvenile idiopathic arthritis of the hip

Before determining the imaging modality and radiographic features to assess, it is important to understand the natural history of JIA disease's involvement of the hip joint. Whilst papers focusing specifically on changes in the hip are scarce and longitudinal imaging studies are lacking, it is generally believed from long-term and short-term studies of various joints that destruction follows a reasonably predictable pattern.

The progression is thought to start primarily with inflammatory soft-tissue changes (synovitis, tendinitis, bursitis) and effusions before periarticular osseous changes (bone marrow oedema). Eventually, further disease progression may lead to growth disturbances (caused by reduction in bone mineral density, epiphyseal enlargement and early physeal closure) with destructive osteocartilagineous changes (cartilaginous thinning, joint space reduction and bone erosions) and degenerative features (ankylosis, joint malalignment) and growth disturbances leading to leg length discrepancy [12] (Fig. 1).

The order and presence of the features are not absolute or prerequisites for other destructive changes. The rapidity of development may be different between patients and dependent both on JIA subtype and on treatment response. In addition, the peculiarities of

the growing skeleton, including incomplete ossification and age-related variation in cartilage thickness, make the evaluation of children's joints a real challenge. These are all factors one must bear in mind whilst interpreting the imaging and devising scoring systems.

Conventional radiography

Conventional radiography of the hips is available in most health care centres, and is relatively inexpensive and quick to acquire. Traditionally, it has been the mainstay of imaging in JIA, although given the degree of cartilage in the developing hip joint, early erosive changes can be overlooked with this modality [13]. Whilst radiographic scoring systems for rheumatoid arthritis in adults have been used to define outcomes in clinical trials for therapies [14], they are not directly translatable to children given the growth disturbances and changes in anatomy with age (Fig. 2).

The only validated radiographic scoring system available for JIA of the hip is the Childhood Arthritis Radiographic Score of the Hip [15], developed by a panel of five paediatric rheumatologists and based on clinical experience and known radiographic features of hip disease in JIA. In this system, each hip is scored separately on a single frontal radiograph of the pelvis and awarded points based on the subjective assessment of joint space narrowing, erosive change, growth abnormalities, subchondral cysts, joint malalignment, sclerosis of the acetabulum and avascular necrosis of the femoral head. A maximum possible score of 16 for all variables can be assigned per hip joint (i.e. 32 per patient). In terms of repeatability scores, the intraclass correlation coefficients ranged between 0.76–0.98 for interobserver repeatability (in 2 observers scoring 381 hip

radiographs) and 0.82-0.96 for intraobserver repeatability (1 observer of a random selection of 37 patients, 3 months apart).

A test of clinical and construct validity between the Childhood Arthritis Radiographic Score of the Hip and clinical markers (such as the Childhood Health Assessment Questionnaire, physician and parent's global assessment of child's well-being) did not show any predictable correlation, although a change (not an absolute value) in the Childhood Arthritis Radiographic Score of the Hip between a baseline assessment and follow-up after approximately 1 year was able to give some measure of long-term destructive hip changes.

As this scoring system was only tested by two experienced radiologists, further work is needed to determine how user-friendly the system can be and whether it is appropriate across a wider range of patient abnormalities. The increasing use of biological agents that prevent rapid destruction has stimulated the need for imaging modalities more sensitive in detecting inflammatory pre-erosive changes. Early soft-tissue changes seen at the onset of JIA in the hip are not well determined on radiographic imaging and the use of ionising radiation (particularly to the gonadal regions in a predominantly early pubertal age group) may limit the widespread usage of this technique.

Ultrasound

The lack of ionising radiation, low cost, ability to detect soft-tissue changes and dynamic real-time scanning of the hip joint makes US a useful tool for joint assessment and guidance of steroid injection therapy in the setting of JIA. Several joints can be assessed

at the same sitting, and previous studies have suggested that US may be more accurate at detecting synovitis than physical examination [16]. These factors together with the lack of sedation (which may be required in MRI for some children) make US examination an attractive modality for hip joint assessment (Fig. 3).

There are no standardized US imaging protocols specific to the hip in the setting of JIA; however, the European Society of Musculoskeletal Radiology provides an excellent free online guide [17] with anatomical correlation and sonographic features of the hip joint, detailing insertion sites of the surrounding musculature and probe location for optimal imaging of hip joint effusions.

Caution should, however, be taken when translating adult musculoskeletal sonographic findings to the paediatric hip, as age-related variations in thickness of cartilage, and the appearances of ossification centres and normal epiphyseal and metaphyseal vessels can mimic pathology [18]. Normal values for hip joint capsule and synovial cavity thickness have now been established in apparently healthy children by Zuber et al. [19], based on 816 US hip studies in 408 patients ages 0–18 years old. Notably, the data set was drawn from a cohort of children referred to a rheumatological centre, but without musculoskeletal disease being found. Neither images demonstrating the US appearances nor measurement sites were presented. The authors reported a reasonable inter- and intraobserver mean precision of approximately 1.8% and 12.5%, respectively, based on 3 sonographers assessing 34 randomly selected patients in this cohort.

Standardized US scoring systems for the hip joint in JIA have not been established and studies thus far have mostly detailed correlations of sonographic

appearances and clinical symptoms in small joints. In one retrospective study of 92 JIA patients, 31.5% of patients demonstrated abnormal hip US findings (i.e. the presence of effusion and/or synovial thickening), which were highly associated with clinical symptoms of limited joint movement, but not with disease activity or subtype [20]. Another study comparing bilateral hand, wrist, ankle, hip and elbow ultrasounds in 27 JIA patients in clinical remission against 36 healthy controls discovered that there was a significant difference in the proportion of children with subclinical synovitis in the JIA group (41.7% vs. 11.1%). Unfortunately, hip involvement was not common in this subgroup and the majority of the abnormalities were seen in the elbows and ankles [21]. Finally, it has also been shown that US assessment after intra-articular steroid injection can monitor a response to treatment by showing reduction in joint effusion, although this was based on only four hips in one study [22].

Despite these interesting observations, true population-based reference standards as well as papers relating to the reliability and reproducibility of abnormalities with respect to the hip joint in JIA are lacking. US technique relies heavily on operator experience, patient cooperation, the depth of joint for adequate sonographic penetration (which may be harder to assess in larger, potentially obese and immobile children) and possible reduced visualization of the entire joint if pain limits patient movement of the joint. These factors may limit repeatability of further studies.

Magnetic resonance imaging

MRI is the only modality that can assess both the soft-tissue and bone marrow changes seen in JIA. Nevertheless, caution must be applied during MR interpretation as the

developing skeleton in children can pose several pitfalls. One such area includes understanding the predictable marrow transformation pattern from haematopoietic (red) to fatty (yellow) marrow, which starts in the peripheries (fingers and toes) before moving centrally (axial skeleton). Within long bones, the epiphyses first undergo fatty transformation, followed by the diaphysis and lastly the proximal metaphyses [23]. This pattern can sometimes lead to erroneous overcalling of abnormal marrow signal in the proximal femora on pelvic MRI studies. In addition, a rich, branching vascular network of epiphyseal vascular canals is normal in younger children and can result in diffusion of intravenous MR contrast agents into the surrounding cartilage. This can persist for several minutes after injection and easily fool the inexperienced interpreter into over-calling synovial enhancement and hypertrophy. As children develop and epiphyseal ossification ensues, the canals become less numerous [24].

Interpretation of imaging in child athletes and gymnasts should also be broached with caution given the subtle differences in normal developmental appearances, which include increased incidence of coxa valga, tendinous hypertrophy and oedema within the greater trochanter [25]. Whilst it is acknowledged that joint space narrowing is a feature of JIA, and that a small amount of joint fluid may be within normal limits, studies that provide absolute quantification of these parameters on MRI are lacking and still require subjective judgment by the experienced radiologist.

Different hospital departments usually have their own protocol for imaging an inflamed joint, although in general, the assessment of the hip joint includes the whole pelvis to allow visualization of both hips. The patient is imaged supine with the legs straight and the feet together in a neutral position. At the very least, MRI sequences will

usually include one T1-weighted sequence (not fat saturated) to assess for appropriate bone marrow fatty conversion, a STIR (short tau inversion recovery sequence) to assess for bone marrow oedema and joint effusion and at least one contrast enhanced T1-weighted sequence to assess for synovial enhancement and thickening (Fig. 4). To ensure accurate comparison between previous and present examinations, timing of post-contrast images should be standardized. Based on the existing, but sparse literature, we would suggest an interval of 3-5 min [26]. To aid diagnostic interpretation, imaging in two planes of view (axial and coronal) is preferential [27]. The MRI protocol used at Great Ormond Street Hospital is given in Table 1, performed on a 1.5-T MRI system with gadolinium-based contrast agent administered intravenously at standard dose.

As yet, a validated and universally utilised MRI scoring system for the hips has not been established. Whilst some studies have devised their own scoring systems, these were performed primarily with the intent of observing how imaging appearances correlate to clinical parameters than for standardizing their usage across clinical trials. In a study by Argyropoulou et al. [28], a six-point hip scoring system was created based on the presence and extent of synovial enhancement, thickening and bone erosions (1=no enhancement to 6=diffuse enhancement with villonodular synovial thickening and subchondral bone erosions). An assessment of 28 patients using this scoring system showed significant differences between patients classified clinically with active disease vs. inactive disease and between different subgroups of arthritis (systemic arthritis vs. oligoarthritis; systemic arthritis and polyarthritis).

Nistala et al. [29] further developed this system to identify whether clinical assessment could predict features of hip arthritis in 34 children with JIA. In their MRI

scoring system, they divided imaging appearances into those of active synovitis (one point each for synovial effusion, enhancing synovium of thickness >2 mm and periarticular bone oedema) and damage (one point each for bony erosions, cartilage loss, acetabular protrusion and bony remodeling). Clinical assessment was based on physicians' global assessment, Childhood Health Assessment Questionnaire score and visual analogue scales for patient overall well-being. The final results reported the clinical assessments to yield a sensitivity of 25.7% and specificity of 91% for detecting MRI diagnosed arthritis. The greatest limitation of the study, however, was their use of MRI features as the gold standard in diagnosing arthritis, which, without validated tools, may not necessarily be true.

Kirkhus et al. [30] utilised MRI to identify differences in appearances of hip joint in hip arthritis. Their scoring system was created to apply across all affected joints rather than be specific to the hip joint, and more descriptive in nature. This encompassed a score of 0 to 3 for the degree of joint fluid present (0=none to 3=distention of the joint capsule), presence of synovitis (enhancement or thickening of >2 mm), bone marrow oedema (none, less than or greater than one-third of the epiphysis), bone erosions (yes/no), soft-tissue oedema (none, trace, marked) and maximal short-axis diameter of the largest regional lymph node. In their prospective imaging review of 59 patients, it was found that four patients with infectious arthritis (two of whom had hip joint imaging) had abnormally low contrast enhancement in the hyaline cartilage. This finding was statistically significant compared to imaging features in children with JIA, although the overall numbers of participants in the different arthritis groups and those with hip imaging were very small overall to generalize the conclusions.

El-Azeem et al. [31] more recently performed a retrospective study assessing clinical JIA parameters with hip imaging findings in 30 patients using the same scoring system as Kirkhus et al. [30]. In addition, they also scored the amount of joint damage by awarding one point each for the presence of cartilage loss, bony remodeling and acetabular protrusion. In this study, a statistically significant difference was seen in the MRI scores between patients with clinically active and inactive hip disease (3.5±1.5 vs. 2.1±0.9, respectively), although the confidence intervals were wide. The presence of joint effusion and synovial enhancement were also found to be significantly higher in active hip disease.

Although it is interesting to note MRI differences between arthritis subgroups, the scoring for the above mentioned studies was only performed once (either by a single or group of radiologists together) and at one time meaning repeatability data for MRI imaging scoring systems are also lacking. The scoring systems also do not take into account all changes that can be seen in JIA (e.g., growth disturbances) and may be simplistic for clinical trial usage. Information on reliability, repeatability and correlation of imaging findings with treatment outcomes is still largely unknown.

Future work

New imaging techniques provide exciting possibilities for the future of hip imaging in the setting of JIA. Within the field of ultrasonography, preliminary work relating to volumetric rendering of the femoral head surface may better inform us of erosive changes and increased usage and acceptance of contrast-enhanced US techniques may help in

better characterizing synovial inflammation, although these hypotheses are yet to be evaluated in children [32].

Advances in MRI techniques for JIA imaging are mainly focused on identifying early cartilaginous damage. Changes in T2-relaxation times for cartilage can be processed to give a T2-map, with age-related differences in results believed to reflect changes in the inherent collagen content in children [33]. Preliminary studies have shown some promise for differentiating healthy and JIA affected knee joints [34, 35], although hip changes are yet to be evaluated. Diffusion tensor imaging maps may also be created from MRI studies to better identify the microarchitecture in the cartilage [36]. This work is still to be tested in the setting of JIA; however, work on depicting early cartilage damage in adult knee joints has been encouraging [37].

One other potential technique is dynamic contrast enhancement MRI; alterations in healthy children have been seen with this technique [38]. Malattia et al. [39] did not find any correlation between dynamic parameters and clinical markers of inflammation in 10 children with hip involvement of JIA (despite changes being apparent in children with wrist involvement). The authors proposed that this may be due to lower levels of disease activity in the hip group compared to the wrist group. Nevertheless, the reproducibility of the dynamic imaging parameters for enhancement curves between the two observers was high and further work with a greater number of patients with varying levels of hip disease activity may be required to fully assess utility of this technique.

Other imaging alternatives may include near infrared spectroscopy. This technique is already utilised in various areas of medicine such as in pulse oximetry and functional neuroimaging and has the added benefit of not requiring ionizing radiation.

Hyun et al. [40] have developed cartilage-specific contrast agents for this technique, although to our knowledge, they have so far only been tested on mice in preclinical studies.

Conclusion

Although radiographic assessment has traditionally been the mainstay of JIA hip imaging, early disease changes are not well depicted. Thus, this method should be reserved for cases with known chronic changes and where there has been a significant deterioration in symptoms and pain. MRI and US are useful imaging techniques for early detection of hip involvement in JIA and also for avoiding the use of ionizing radiation. Novel imaging techniques for both these modalities hold some promise for identifying early cartilaginous changes, although they are yet to be used in standard imaging protocols. Regardless of modality, few reliability and reproducibility studies exist for the hip joint and validated scoring systems. Reference standards also are lacking. The fundamental principles of reliability and validity should not be ignored when taking these techniques forward for use in clinical trials and knowledge of imaging findings in healthy children is also mandatory to avoid misinterpretation.

Compliance with ethical standards

Conflicts of interest None

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Legends

Fig. 1 Changes in hip radiographic appearances over time in the same boy with polyarticular juvenile idiopathic arthritis. **a** Frontal pelvic radiograph in an 8-year-old boy demonstrates enlarged fovea bilaterally (*arrowheads*). **b** Radiograph of the pelvis at age

10 reveals bilateral proximal femoral epiphyseal sclerosis, with erosive changes more predominantly affecting the right femoral head and loss of femoral epiphyseal height. **c** A radiograph of the pelvis at age 13 demonstrates further irreversible destruction with bilateral loss of joint space, further erosive changes, shortening of the femoral neck distance and superolateral displacement of the left hip joint

Fig. 2 Radiographs demonstrate subtle growth disturbances in the left hip in a boy with juvenile idiopathic arthritis (enthesitis-related arthritis subtype). **a** Normal frontal pelvic radiograph at age 7 years. **b** Repeat imaging at 9 years of age demonstrates abnormalities of the left hip joint with enlargement and squaring of the proximal femoral epiphysis and possible erosion at the medial proximal femoral metaphysis (*arrowhead*)

Fig. 3 Comparative ultrasound and radiographic imaging in a 9-year-old boy with polyarticular juvenile idiopathic arthritis demonstrates subtle findings shown on sonographic assessment. **a** A longitudinal sonogram of the right hip joint anteriorly reveals increased synovial thickening with capsule femoral neck distance of 8 mm (between calipers), and a focal erosion at the proximal femoral metaphysis (*arrowhead*). **b** Colour Doppler imaging of this region does not reveal any synovial hyperaemia. **c** The frontal pelvic radiograph performed within 3 months of the ultrasound did not demonstrate any abnormality

Fig. 4 Pelvic MRI study in an 11-year-old girl with polyarticular juvenile idiopathic arthritis and left hip pain at initial diagnosis. **a** Coronal shout-tau inversion recovery

(STIR) spin echo sequence reveals high signal abnormality (*arrowheads*) in the left hip joint. **b** Post-contrast coronal T1-weighted fat-saturated images show that this predominantly represents a left hip joint effusion, with enhancement of the mildly thickened synovium (*arrowheads*)

Table

Table 1 Suggested MRI imaging protocol for the hips in children with suspected or established juvenile idiopathic arthritis

Sequence	Echo time/repetition time (ms)	Voxel size (mm)	Field of view (mm)	Number of averages	Plane	Slice thickness (mm)	Slices	Flip angle (°)	Time (min)
STIR, high resolution	95/5,000	1.0 x 0.9 x 5.0	300	2	Coronal or axial	5	23	150	6.5
T1-weighted spin echo	9 /328	0.8 x 0.8 x 4.0	250	3	Coronal	5	16	90	6.5
T1-weighted spin echo, fat suppressed	17/584	1.0 x 1.0 x 5.0	250	2	Coronal or axial	5	20	90	3
Post-gadolinium T1-weighted spin echo, fat suppressed[a]	17/584	1.0 x 1.0 x 5.0	250	2	Coronal or axial	5	20	90	3

STIR short tau inversion recovery

[a] The time interval between administration of intravenous gadolinium and post-contrast sequence acquisition is as short as achievable

Figure 1a

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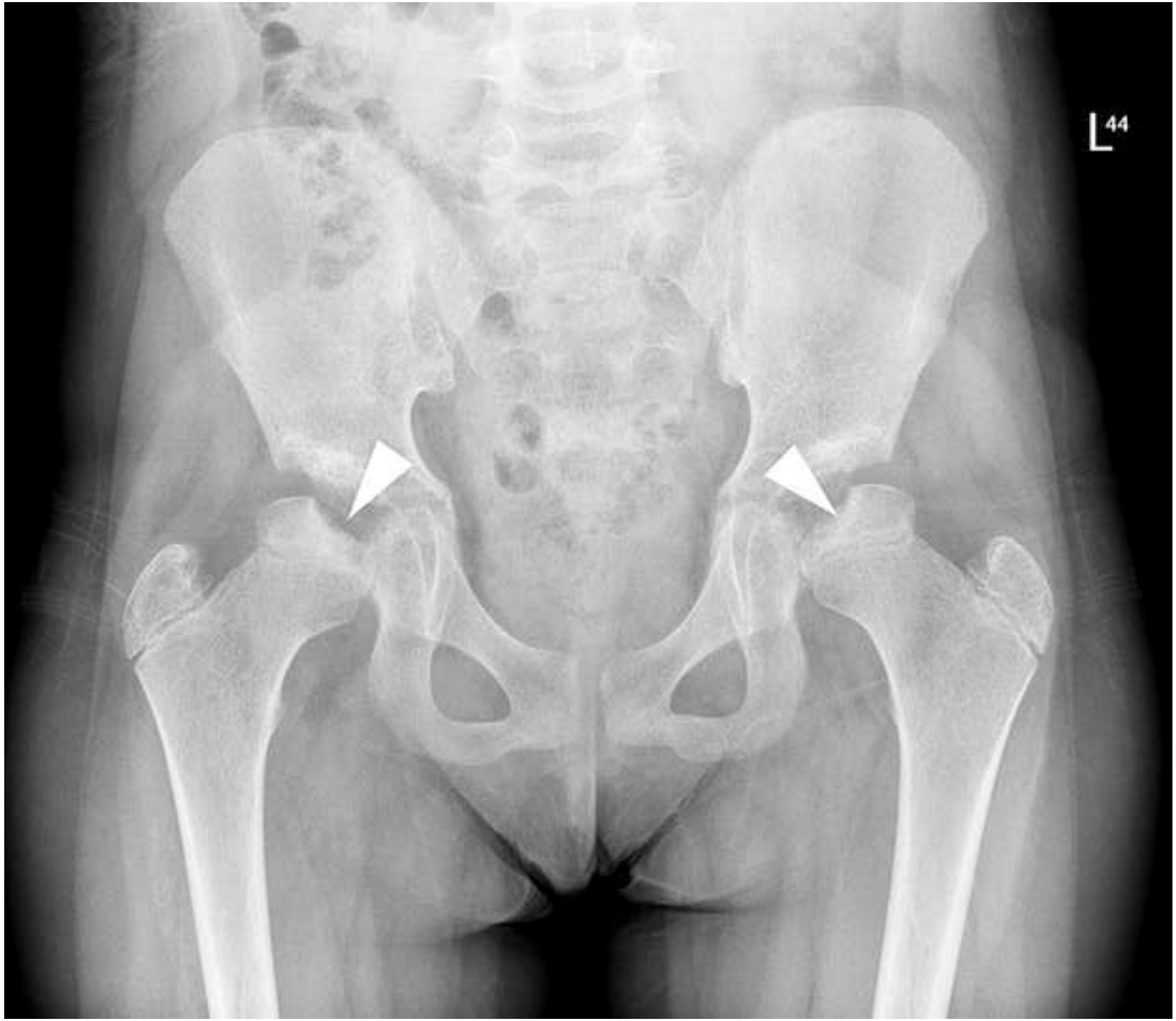

Figure 1b

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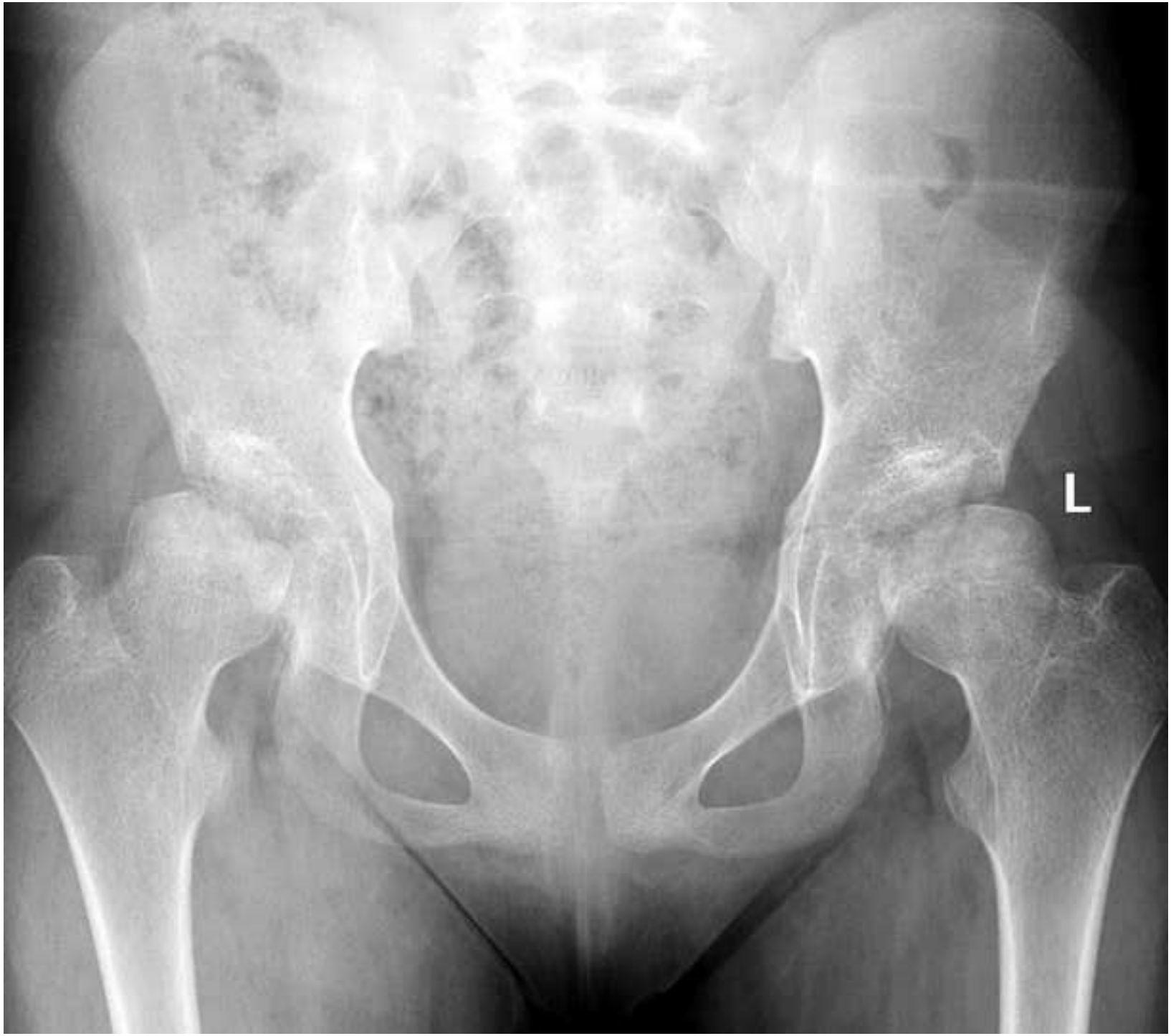

Figure 1c

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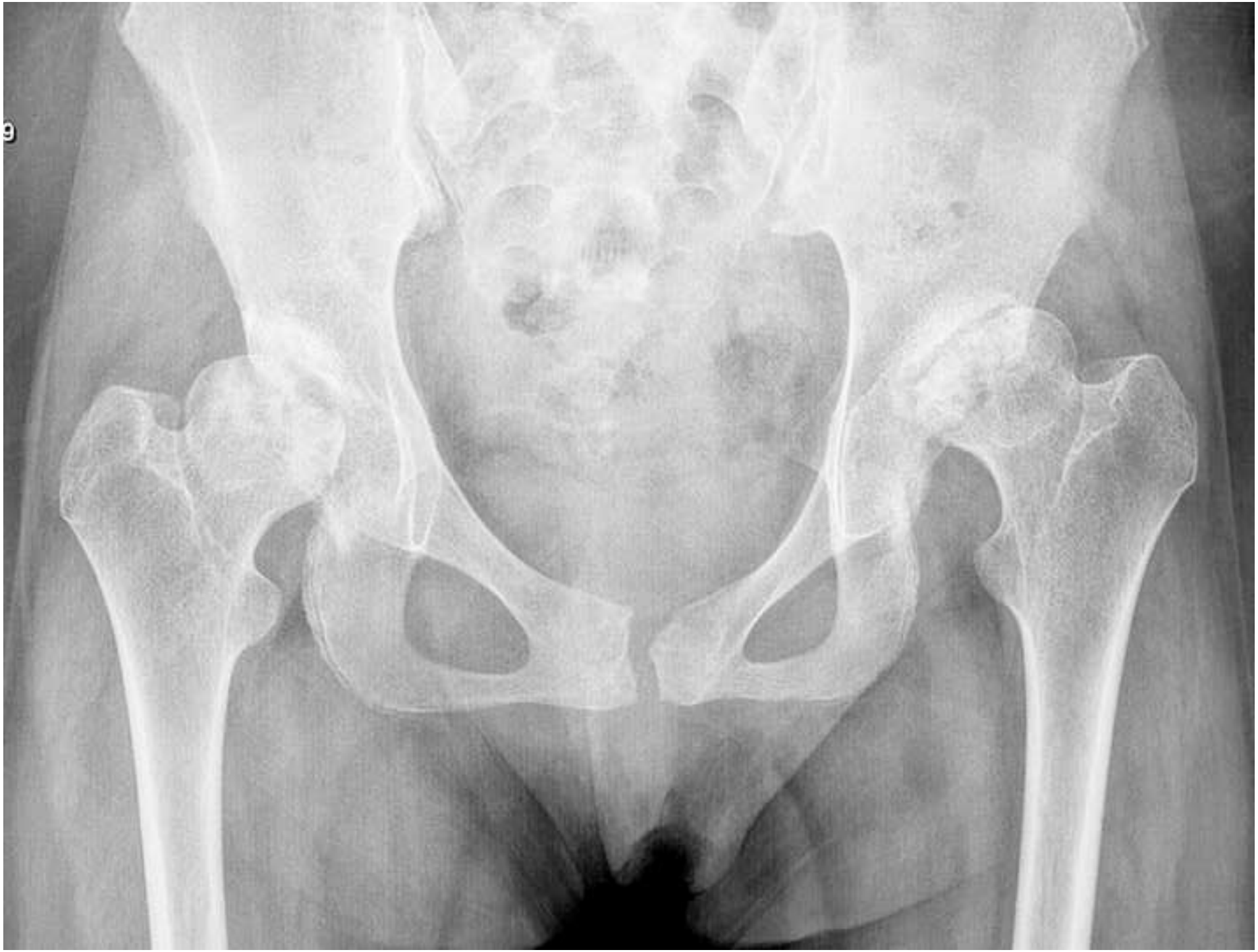

Figure 2a

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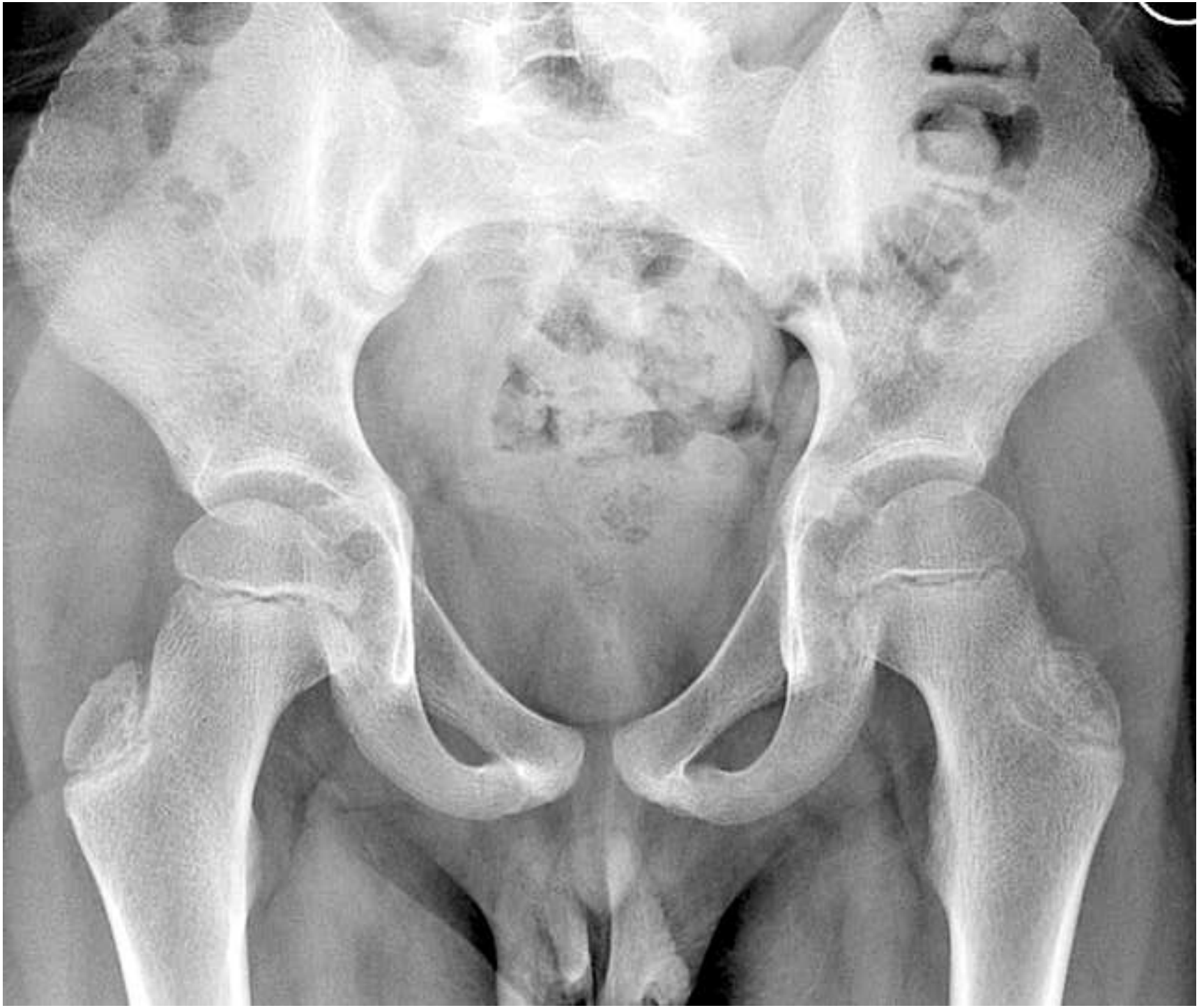

Figure 2b

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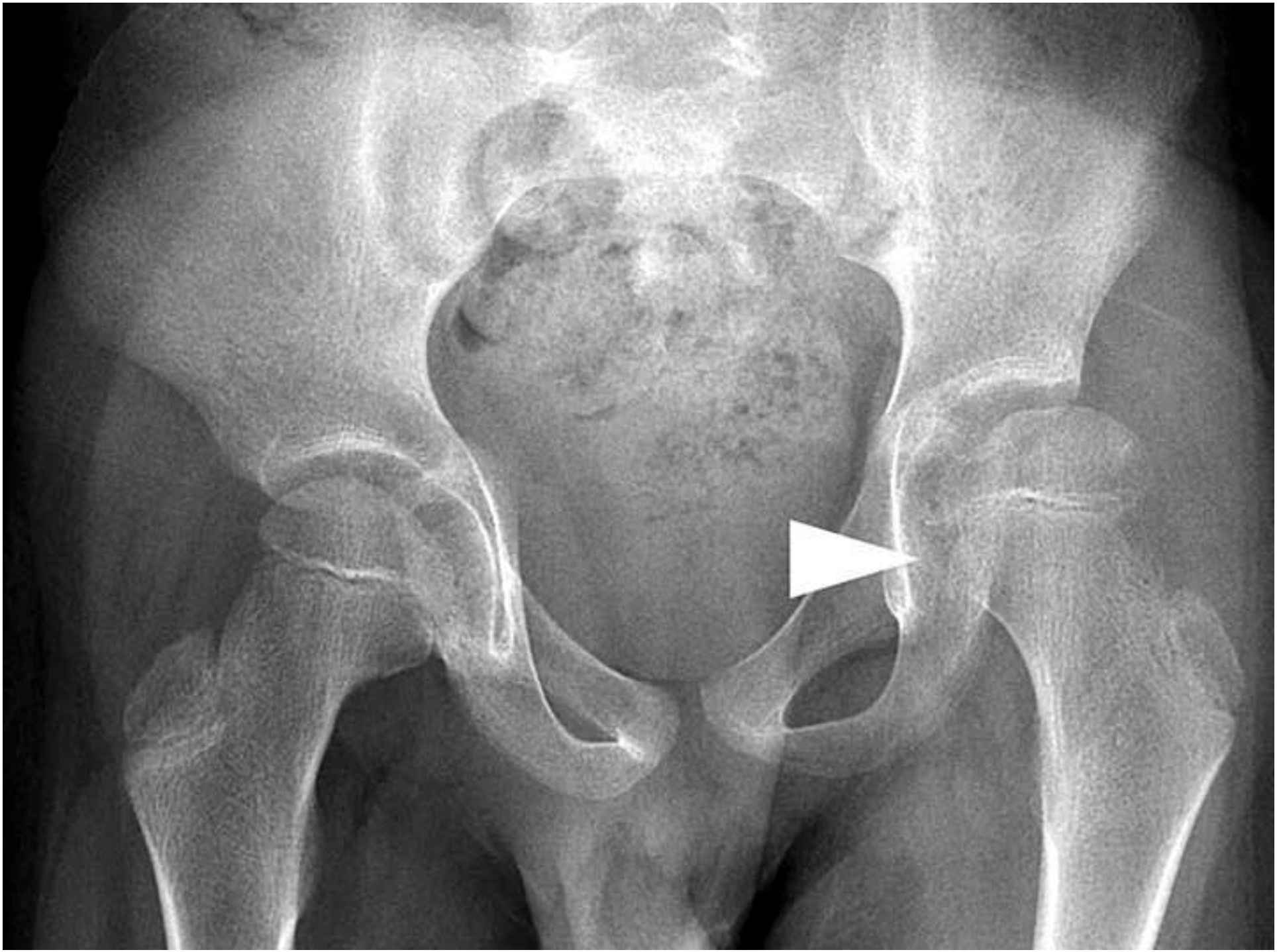

Figure 3a

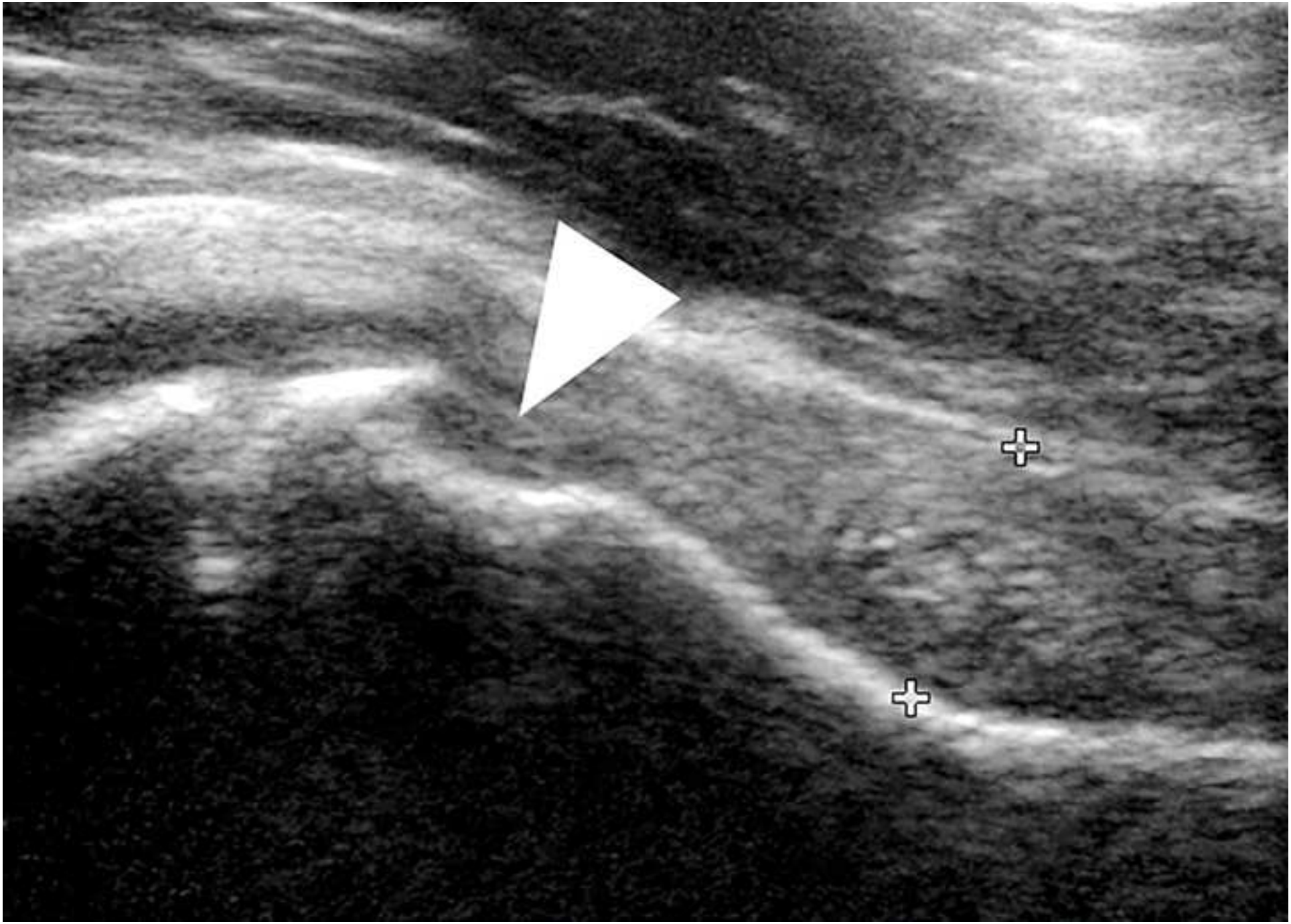

Figure 3b

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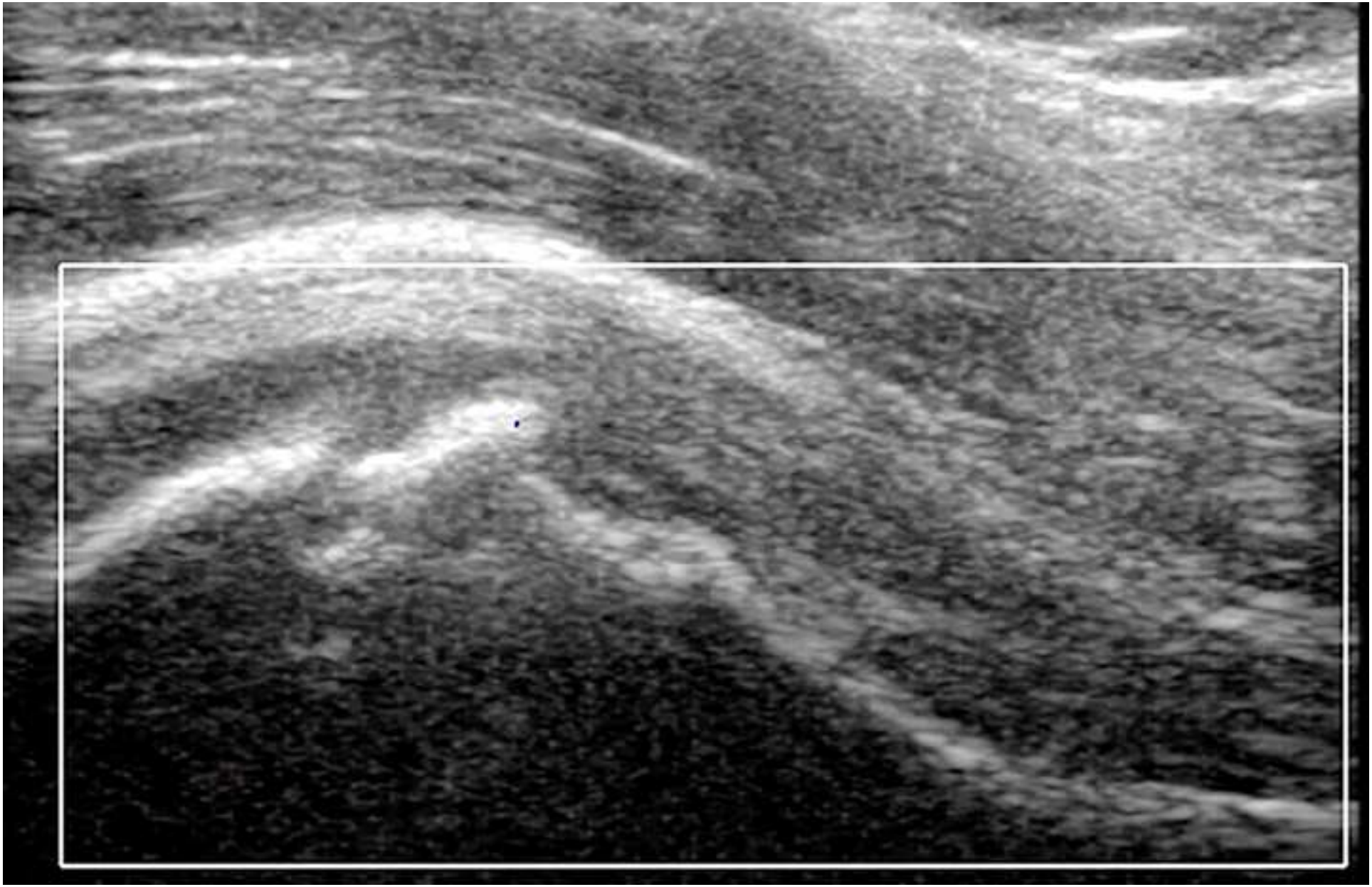

Figure 3c

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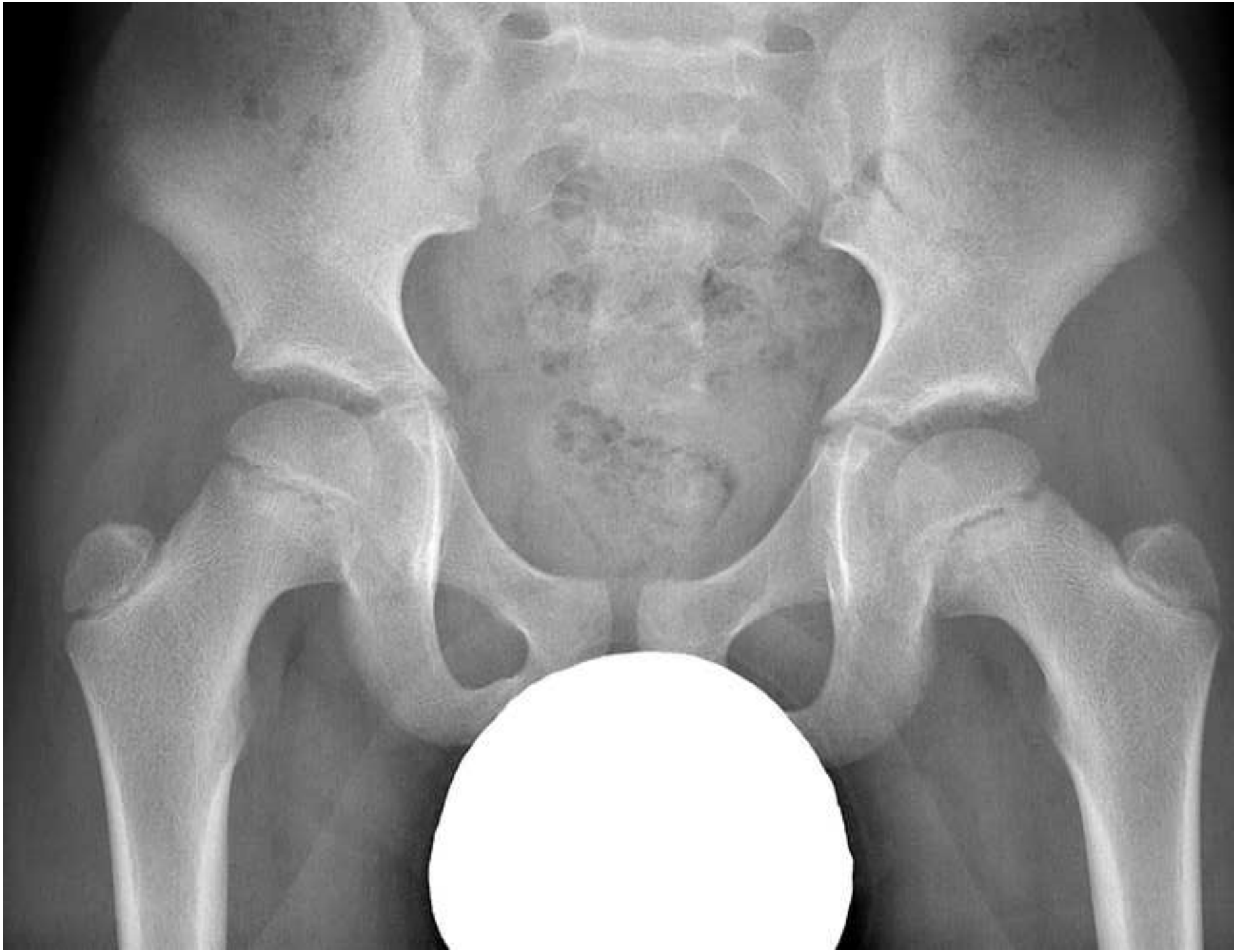

Figure 4a

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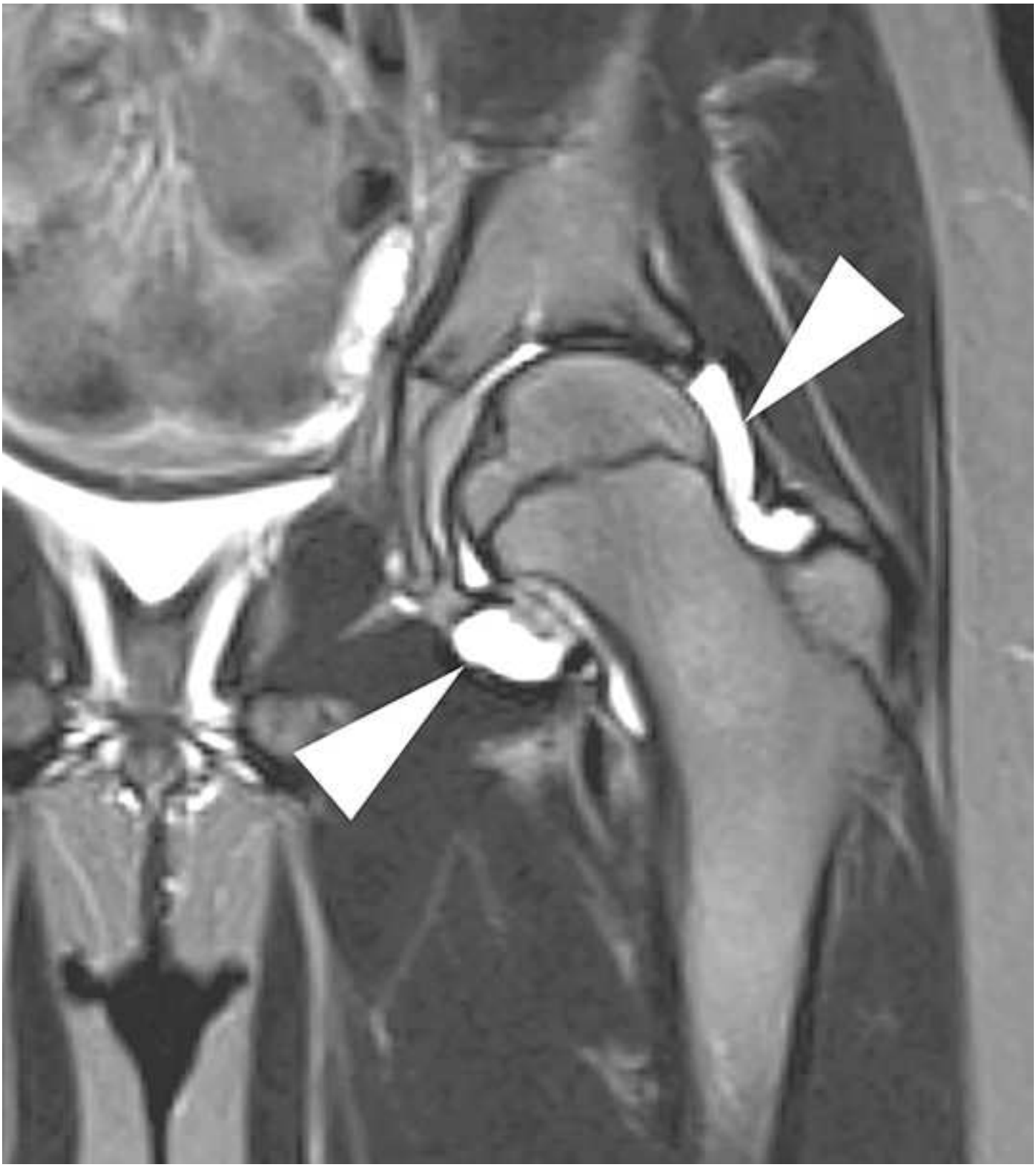

Figure 4b

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