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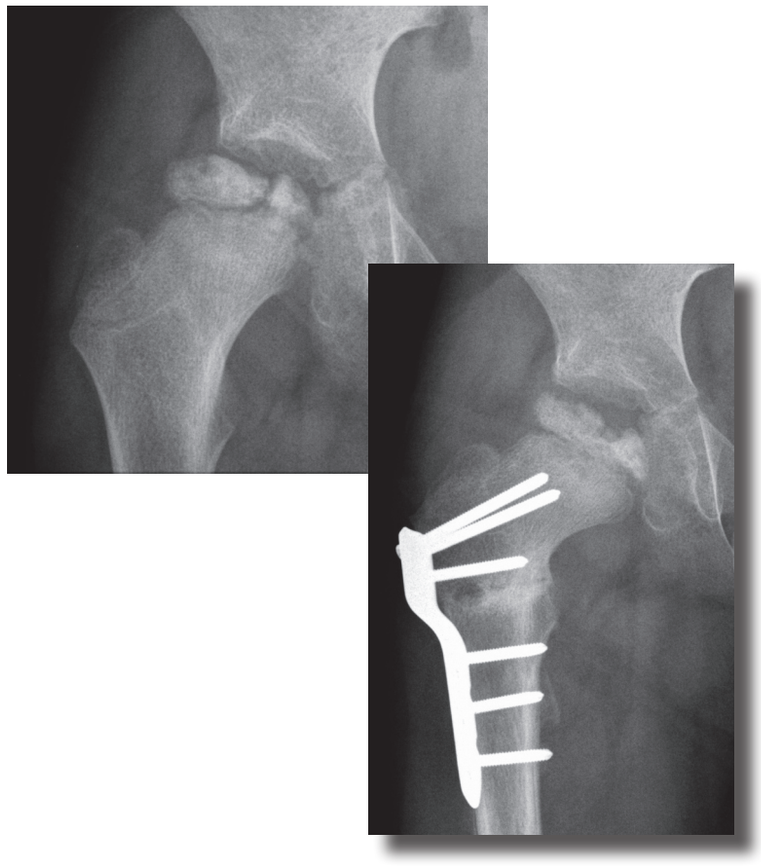
Perthes' disease in Norway

A prospective study on 425 patients

Ola Wiig



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Thesis

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Contents

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Oslo, June 25th
2008,

Ola Wiig

List of papers

This thesis is based on the following papers, which will be referred to by their roman number in the text:

I Wiig O, Terjesen T, Svenningsen S, Lie S A. The epidemiology and aetiology of Perthes' disease in Norway: A nationwide study of 425 patients. *J Bone Joint Surg (Br)* 2006; 88-B: 1217-23.

II Wiig O, Terjesen T, Svenningsen S. Inter-observer reliability of radiographic classifications and measurements in the assessment of Perthes' disease. *Acta Ortop Scand* 2002; 73: 523-30.

III Wiig O, Svenningsen S, Terjesen T. Evaluation of the subchondral fracture in predicting the extent of femoral head necrosis in Perthes' disease. A prospective study of 92 patients. *J Pediatr Orthop B* 2004; 13(5): 293-8.

IV Wiig O, Terjesen T, Svenningsen S. Inter-observer reliability of the Stulberg classification in the assessment of Perthes' disease. *J Child Orthop* 2007; 1: 101-5.

V Wiig O, Svenningsen S, Terjesen T. Prognostic factors and outcome of treatment of Perthes' disease. A prospective study of 368 patients with 5 year follow-up. *J Bone Joint Surg (Br)* 2008; 90-B: 1364-71.

What is Perthes' disease?

Perthes' disease is still an enigmatic disease nearly 100 years after it was first described almost simultaneously by Legg and Waldenström in 1909, Calvé and Perthes in 1910.

The disease has had many different names over the years, either referring to the above authors (Legg-Calvé-Perthes' disease, Legg-Perthes' disease, Calvé-Legg-Perthes' disease, Perthes' disease), or in more descriptive terms such as coxa plana, osteochondritis coxa juva, artritis deformans juvenilis, osteochondritis deformans coxae juvenilis among others.

Perthes' disease is a condition of the hip affecting children between 2 and 12 years of age, but it is more prevalent among children between 5 and 6 years of age, and more common in boys. The femoral head becomes partially or completely necrotic and gradually deformed during the active stages of the disease. This is followed by new bone formation (reossification) in the epiphysis and eventually healing. The femoral head becomes deformed to a varying extent. The hip is a functional and anatomical entity and is subject to remodelling during growth; thus a deformed femoral head will contribute to a varying degree of acetabular deformation during the course of the disease. The final deformity can vary from nearly normal joint configuration to an extensive deformation with severe flattening and subluxation of the femoral head, broadening of the femoral neck, and a deformed and dysplastic acetabulum which in turn can lead to early onset osteoarthritis and need of total hip replacement.

The initial symptoms are usually a limping gait, pain in the hip, thigh or knee, and reduced range of hip motion. Later in the course of the disease, leg length discrepancy as well as atrophy of musculature about the hip can be observed. The active phase of the disease can last for several years and interferes with the daily life and activities of the child and the family, and is often of great concern for the parents.

The epidemiology, etiology, radiological classifications, prognostic factors and treatment of Perthes' disease have been an object of controversy, and it is still heavily disputed.

Historical overview

Tuberculosis reached epidemic proportions during the 19th century, and thus bone and joint tuberculosis was fairly common at the beginning of the 20th century. Bone and joint tuberculosis was a serious disease that often was fatal or healed with considerable sequelae. However, there exist occasional reports of children thought to have hip tuberculosis that recovered quickly without loss of function (Brodie 1834, Lébert 1849 and Barwell 1861). This type of non-suppurative hip disease was termed pseudocoxalgie. Duplay (1896) reported on a mild form of hip disease in a child which may have been the first report of Perthes disease. In 1895, Wilhelm Röntgen presented his discovery of a new kind of rays that provided orthopaedic surgeons with a new diagnostic tool. Köhler (1905) presented a case of flattening and later fragmentation of the femoral head that, in his opinion, was non-tuberculous in origin, and could resemble an infarction of bone. In 1907, Preiser reported a similar case, but he thought it was a congenital dysplasia of the hip.

In 1909, Jaques Calvé spoke of a kind of hip disease in children where the severe radiological changes did not correspond with the clinical picture. One year later, he published his article "Sûr une forme particuliere de pseudocoxalgie", a classic that linked his name to the disease. He presented 10 patients, and believed the cause of the disease was an abnormal osteogenesis resembling rickets combined with a low grade infection. Waldenström (1909) presented 7 otherwise healthy patients with intermittent limp and slight pain, and suggested that a benign form of tuberculosis was present that interfered with the blood supply of the femoral head. He explained the pathology as a softening of the medial portion of the femoral neck and head, where the mechanical pressure against the articular cavity flattened the femoral head. In his opinion, the degree of flattening depended on the degree, extent, and duration of the softening. In 1922, he stated that the primary cause was an irregular cell proliferation in the cartilage and bone cells of the epiphysis and the medial parts of the femoral neck, resulting in softening and deformation. Arthur Legg (1910) reported on 5 children with an "obscure affection of the hip joint" that he believed was caused by trauma where a minimal displacement of the epiphysis disrupted the blood flow to the femoral head. This in turn caused a hyperemia with subsequent broadening of the femoral neck.

In 1910, Georg Clemens Perthes presented his paper "Über Arthritis Deformans Juvenilis" with 38 patients. He believed that the disease was caused by a bacterial infection, most likely staphylococci (retrieved from one case). Phemister supported the infective theory from a histological study of human material. Perthes later revised his etiological theory after retrieving biopsy specimens from another of his patients, and in 1913 he stated that the disease most likely was due to interruption of the blood supply to the femoral head of unknown origin.

In the twenties, several authors (Fragenheim, Liek, Lieshied and Sellheim, Muhlbrandt, Sandoz, Schmidt, Sundt) suspected an underlying hormone disturbance to be an etiological factor, based upon the radiological resemblance of severe hypothyroidism.

The theory of one or more infarctions (Jønsæter 1953, Inoue et al. 1976) of the femoral head due to interruption of vascular supply eventually causing the deformity has emerged during the last decades. Joseph Trueta (1953, 1957, 1960) developed a technique of post mortem bone angiography, and thus provided the scientific basis for the hypothesis of epiphyseal infarction in Perthes' disease. Most authors have agreed on the dependence of the epiphysis on the single vascular supply between the third and eight year, but there have been different theories on how the interruption of the vascular supply had come about. Several authors (Soto-Hall 1964, Kemp 1973 and Tachdjian 1968) suggested that an intracapsular tamponade could interrupt the blood flow through the vessels lying on the femoral neck. Kemp, like Trueta, believed that the vascular interruption was transient and of varying duration, so that total necrosis within the epiphysis

would not necessarily occur. This assumption was supported by Sanchis et al. (1973) who found that serially applied diathermy of the lateral epiphyseal vessels produced Perthes-like changes in dogs. At present, there seems to be a consensus that the epiphysis of the affected femoral head in a child with Perthes' disease would reveal necrotic bone if we were able to examine it histologically (Harrison and Burwell 1981).

Salter and Thompson (1984) believed that an ischemic episode of obscure origin occurred in the epiphysis, causing a temporary cessation of growth followed by revascularisation and ossification from the periphery. The condition at this point was termed "potential" Legg-Calvé-Perthes' disease and was clinically "silent", and the development of a subchondral fracture in the vulnerable femoral head caused by normal activity, would herald the "true" clinically evident disease. The subchondral fracture would be followed by resorption of underlying bone, replacement with biologically plastic bone, subluxation and development of the deformity.

In recent years, there has been increasing evidence of Perthes' disease being a more widespread disease expressing itself through necrosis of the femoral head. Several authors have suggested different contributory factors including delayed skeletal maturity (Harrison et al. 1976), impaired and disproportionate growth (Burwell et al. 1978), short stature (Harrison et al. 1976, Weiner and O'Dell 1970), low birth weight (Molloy and MacMahon 1967, Lappin et al. 2003), social and economic deprivation (Barker et al. 1978, Hall and Barker 1989, Kealey et al. 2000, Hall et al. 1983), trauma, as well as an association with congenital anomalies (Katz 1959, Catterall et al. 1971, Wynne Davies and Gormley 1978, Hall et al. 1979).

From the late eighties and until present, several authors (Mankin 1992, Ura et al. 1992, Liu and Ho 1991, Gregosiewich et al. 1999, Choi et al. 1995, Clueck 1994, 1996, 1998) have speculated on whether disorders in the coagulation system could cause thrombophilia and/or hypofibrinolysis, and that this in turn leads to thrombotic venous occlusion with subsequent necrosis of the femoral head in children. In 1994, Glueck et al. presented 8 patients with Perthes' disease in which 4 had thrombophilia caused by protein C and protein S deficiency, and one had hypofibrinolysis caused by low levels of tissue plasminogen activator activity. Two years later (1996) he reported that 8 of 64 patients with Perthes' disease, versus 1 of 101 healthy controls, had resistance to protein C and a mutation of the Factor V Leiden gene. A mutation of the Factor V Leiden gene is responsible for resistance to protein C, which is the most common thrombophilic trait. Matsuo (1999) disputed Glueck's theory as he did not find any relation between the factor V Leiden gene and Perthes' disease in a Japanese population. Koo et al. (2002) found no evidence of a relationship between Perthes' disease and thrombolytic or fibrinolytic disorders in a Korean population.

The long forgotten hormone trace from the twenties (Fragenheim 1920, Liek 1922, Lieshied and Sellheim 1924, Muhlbrandt 1929, Sandoz 1928, Schmidt 1927, Sundt 1921) and fifties (Beiler and Love 1956, Katz 1955) was brought into light again by some authors (Neidel et al 1993, Roy 1991), inspired by the fact that the radiological appearance of the capital femoral epiphysis in a hypothyroid child can mimic the appearance of Perthes' disease. Moreover, the recent speculations that Perthes' disease was a manifestation of a generalized condition with impaired and disproportionate growth resulting in femoral head necrosis, actualized these theories.

Thyroid hormones (TSH, T4, T3) play an important role in skeletal maturation (Ramos-Remus et al. 1996, Burman 1997), and deficiencies in these hormones lead to delays in both diaphyseal and epiphyseal ossification. The assumed short stature of children with Perthes' disease has brought about studies of insulin-like growth factor (IGF) and somatomedins (Burwell et al. 1986, Grasemann et al. 1996, Kitsugi et al. 1989, Neidel et al. 1993). The results of these studies have differed, and no definite conclusion has been reached. In a study of Kealey et al. (2004) TSH, free T4, IGF 1 and urinary cortisol/creatinine ratio from children with Perthes' disease was compared to healthy controls. They found no significant differences between the study and control children and they reported that the Perthes children were of normal body habitus compared with the general pediatric population.

Abnormally large collagen fibrils in cartilage from children with Perthes' disease was reported by Ponseti (1963). In 1983 he found areas of hypercellular and fibrillated cartilage with promi-

nent blood vessels and irregularly oriented large collagen fibrils beneath the normal articular cartilage in affected hips. He suggested that the disease could be a localized expression of a generalized, transient disorder of epiphyseal cartilage that is responsible for delayed skeletal maturation. Moreover, he stated that it was plausible that collapse and necrosis of the femoral head may result from abnormal cartilage, but whether this was a primary or secondary event in relation to ischemia remained uncertain. Recently, evidence linking mutations in the gene for type II collagen has been linked to familial avascular necrosis of the femoral head (Liu 2005) and Perthes' disease (Miyamoto et al. 2007). Collagen type II is the most abundant protein found in cartilage, and it forms a grid of fibres that traps proteoglycans which in turn absorbs large amounts of water, distending this grid. This makes the cartilage resilient to compression. Abnormal collagen and subchondral trabeculae caused by mutations in the gene for collagen type II could make the femoral head vulnerable to a subchondral stress fracture resulting in Perthes' disease.

Since Perthes' disease was first described, there have been numerous reports regarding treatment. In 1921, Bankart, Platt, and Roth stated that the disease should be treated conservatively to avoid a poor end result. Perthes and Welsch (1922) thought that treatment had little effect on the outcome and that operative treatment was contraindicated. This was confirmed by Waldenström (1922), who stated that the treatment was of no real importance for the development of the disease. Sundt (1949) found that treatment could not alter the natural history and that the development of osteoarthritis depended on the sphericity of the femoral head.

Early methods of treatment comprised non weight bearing and strict recumbency (Eyre-Brook 1936, Katz 1967, Gossling 1973, Brotherton and McKibbin 1977) until the femoral head was reossified, so that there would be no mechanical deformation of the femoral head (Brotherton and McKibbin 1977, Kelly et al. 1980).

Until the 1960s, the treatment of Perthes' disease was based on the concept that the affected femoral head was "soft" due to the avascular necrosis. Consequently all treatment involved non-weight bearing of the affected hip to decrease load and prevent femoral head deformity. This led to strict long-term bed rest, often in hospital, depriving the children of regular contact with their parents and family (Helbo 1953, Meyer 1977).

The concept of containment of the femoral head in the acetabulum in order to enhance its sphericity was first introduced by Eyre-Brook (1936), and further established by Harrison (1966), Salter (1966), and Petrie and Bitenc (1971). Sommerville (1971) stated that the ishaemic femoral head could develop in a satisfactory way provided containment of the head in the acetabulum. Petrie and Bitenc (1971) introduced an above knee weight-bearing cast fixed in abduction and internal rotation and joined with a broomstick. A number of different braces have been in use, some non-weight bearing (Birmingham Splint), weight bearing abduction braces permitting limited motion of the hip (Petrie cast, Newington brace), and weight bearing abduction braces permitting free motion of the hip except from adduction (Atlanta Scottish Rite Orthosis, Toronto brace).

The surgical containment of the femoral head within the acetabulum was first proposed by Soeur and De Racker (1952). The treatment involves varus osteotomy of the proximal femur, which centers the femoral head more deeply within the acetabulum. Some authors have advocated different kinds of innominate osteotomies (Sponseller et al. 1988, Paterson et. al 1991, Salter 1984, Bennet et. al 1991), which redirect the acetabulum hence containing the femoral head in the acetabulum.

The Seaside Hospitals in Norway and Denmark

The Seaside Hospitals in Norway and Denmark were built when the belief in fresh air and rest as treatment for tuberculosis was strong in the medical community. As the tuberculosis epidemic declined, the seaside hospitals started treating other diseases, mainly Perthes' disease and other diseases of the hip joint. In the beginning of the 20th century the treatment for Perthes' disease consisted of long time recumbency in hospital with or without traction. Consequently both time and patient material were abundant thus making large studies possible.

In 1920 Halvdan Sundt (Figure 1), head of the Seaside Hospital in Stavern, Norway, presented his monograph on Perthes' disease where he reported on 48 unilateral cases. He divided the patients into three groups of treatment: immobilisation (14 cases), immobilisation and traction (15 cases), and no treatment (18 cases), which was the largest material presented at that time. He found no difference in outcome between these groups and hence propagated a nihilistic attitude towards the treatment of Perthes' disease. He stated that some kind of hereditary dysendorchism most likely was the cause of this "universal malady". Later, in 1949, he published "Further investigations respecting Malum Coxae Calvé-Legg-Perthes" where he had collected a material of 153 hips with 10–52 year follow-up. 16 cases were bilateral, the male:female ratio was 3.6:1 and the peak age at diagnosis was between 7 and 8 years. He found that younger children had more favourable prognosis regardless of whether the patient had been treated or not. Moreover, he stated that the shape of the femoral head after healing was decisive of the long term prognosis. Furthermore, treatment had no effect on neither the final shape of the head, subluxation, degree of mobility or the late occurrence of osteoarthritis. He was convinced that the cause of the disease was a circulatory disturbance in the upper end of the femur.

Helbo (1953) at the Seaside Hospital in Refsnæs, Sjælland in Denmark, presented 52 unilateral cases examined after more than 25 years. The patients were either untreated or received only symptomatic treatment. He found an incidence of 0.44 per 1000 children, with a peak age at diagnosis between 5 and 9 years. As Sundt (1949), he concluded that the radiological shape of the femoral head at the time of primary healing played a decisive role in the development of secondary osteoarthritis. He found no effect of symptomatic treatment. After 25 years, 85% of the patients had hip pain or discomfort. However, patients that received bed rest early in the course of the disease had considerably better long-term prognosis compared with those who did not.

In 1966, Helbo's chief at the Seaside Hospital at Refsnæs, Johannes Meyer, published a series of 220 patients receiving 3 modalities of treatment; ambulatory relief from weight- bearing, relief from weight bearing with traction and relief without traction in strict bed rest. He found that relief from weight bearing with traction gave the best radiological results with respect to femoral head shape and thus long time prognosis. In a study from 1977, Meyer supplemented his material from 1966 with 114 patients treated at the orthopaedic hospital in Århus for 2 years with non-weight bearing in a wheelchair. He found that traction treatment in bed gave 1.5 times as many satisfactory results as bed rest or wheelchair treatment.

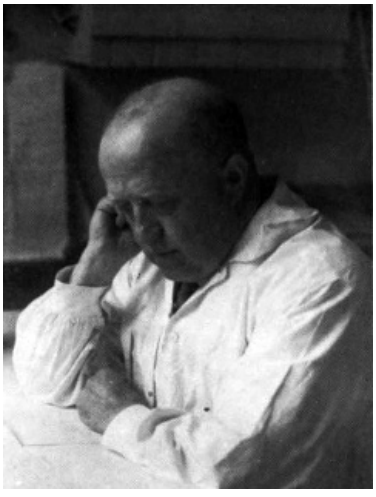

Figure 1. Halvdan Sundt, MD, PhD

Introduction to the present studies

Epidemiology

The published studies on epidemiology were carried out in different parts of the world, among different populations living under quite unlike economical and social conditions. The statistical methods differ among the studies making comparison difficult. Consequently, there is no uniform understanding of the epidemiology of Perthes' disease and to the best of my knowledge no nationwide prospective study on the subject has yet been published.

In Scandinavia, epidemiological studies have been carried out in parts of Denmark (Faroe Islands and Sjælland) and Sweden (Uppsala) but there has been no study of the epidemiology in Norway.

Etiology

As the historical overview shows, even though the majority of pathogens in man have been considered, the etiology of Perthes' disease has still not been revealed. From the early 20th century, different kinds of infectious diseases were believed to be the cause of the disease, via theories that vascular occlusion was the sole reason, to the later parts of the century and up to present, where more complex theories involving genetic and environmental factors are more popular. During the 20th century a so called epidemiological transition has occurred, where the industrialized world has undergone a shift from infectious to chronic degenerative, genetic, and man made (environmental) diseases as prevailing causes of disease and death (Omran 1971). The search for pathogens in Perthes' disease mirrors this trend and shows how our diagnostic tools govern our search for causes of disease. Thus further studies concerning the etiology of Perthes' disease are needed.

Radiographic classifications

Several radiological classifications during the active stages of the disease have been proposed (Sundt 1949, O'Garra 1959, Ponseti 1961, Catterall 1971, Salter and Thompson 1984, Herring 1992 and 2004) and much confusion still exists concerning their use, reliability and ability to predict long-term prognosis.

One possible prognostic sign is the extent of the necrosis of the femoral head. The most commonly used classification is probably the Catterall classification (1971). Catterall used the studies of Sundt (1949) as a foundation for his four group classification. Salter and Thompson (1984) simplified this classification, dividing the hips into 2 groups, based on the extent of the subchondral fracture first described by Waldenström (1938). In 1992 Herring et al. presented a 3-group classification based on the grade of resorption of the lateral femoral head pillar during the fragmentation phase.

The degree of deformity after healing of the disease is a prognostic factor, and has been classified by a number of methods. Mose (1980) used concentric circles 2 mm apart which he placed over the radiographs of the femoral head in both planes to determine the deviation from sphericity. Stulberg et al. (1981) proposed a 5-class classification based on the shape of the femoral head and acetabulum to predict long-term prognosis.

As this overview shows, there have been several radiographic classifications in use. There is, however, no agreement in the literature regarding their predictive value and there are few studies that ascertain their inter-observer reliability.

Prognostic factors

Several factors have been proposed to be of prognostic importance in Perthes' disease, but their relative significance remains unclear.

The extent of femoral head involvement has been used to predict long-term outcome (O'Garra 1959, Catterall 1971, Salter and Thompson 1984, Herring 1992). O'Garra (1959) introduced the concept of partial or complete involvement of the femoral

head, where those with less than 50% necrosis had good prognosis, and those with more than 50% had worse prognosis. Catterall (1971) found a correlation between his 4-group classification system and the radiographic end result. Several authors have supported this finding (Dickens and Menelaus 1978, Hardcastle et al. 1980, Kahmi et al. 1975); however, the literature differs concerning this association. Herring's 3-group classification (1992) based on the involvement of the lateral pillar, has also been shown to have prognostic significance as it predicts the degree of femoral head deformity and hip joint congruity at skeletal maturity (Herring et al. 1992 and 2004, Ritterbush 1992, Farsetti et al. 1995, Ismail et al. 1998). Sugimoto et al. (2004), however, reported that an accurate prediction of the prognosis was not possible with the lateral pillar classification alone.

A subchondral fracture can be seen in approximately 25% of children with Perthes' disease on the initial radiograph (Salter and Thompson 1984, Ismail et al 1998) and represents a trabecular fracture due to an initial avascular phase followed by cessation of epiphyseal growth. Salter and Thompson (1984) found that the extent of the fracture correlated with the extent of the subsequent necrosis according to the Catterall classification, and thus had prognostic significance, but this has not to my knowledge been evaluated in other studies.

Increasing degree of femoral head uncovering has been linked to poor prognosis by several authors (Murphy and Marsh 1977, Dickens and Menelaus 1978, Mukherjee et al. 1990, Gigante et al. 2002), but further studies are needed to evaluate what degree of femoral head coverage that is needed for a favourable prognosis.

The deformity of the femoral head at healing has been shown to correlate with the long time prognosis. In 1981 Stulberg et al. established a relationship between the residual deformity of the hip joint and occurrence of osteoarthritis in later life. However, the inter-observer reliability of the Stulberg classification has been questioned (Neyt et al. 1999).

Most long-term studies conclude that the patient's age at diagnosis is a prognostic factor (Danielsson and Hernborg 1965, Ratliff 1967, Catterall 1971, Mose 1977, Kelly et al. 1980, Stulberg et al. 1981, Perpich et al. 1983, McAndrew and Weinstein 1984, Ippolito et al.1987, Ismail et al. 1998) in the sense that the younger the child at the time of diagnosis, the better the outcome. However, studies with somewhat different experience have been published (Snyder 1975, Fabry 2003) where the outcome in younger children (< 5 years) was not uniformly good.

Catterall (1971) found that girls had a worse prognosis than boys. This has been confirmed by some authors (Dickens and Menelaus 1978, Mukherjee et al. 1990, Herring et al. 1992) but not by others (Mose 1977, Guille et al. 1998).

As this overview indicates, many factors have been considered to have prognostic significance in Perthes' disease. It has been difficult to identify specific criteria due to lack of uniformity of the different radiological classifications making comparison between studies difficult. Thus, further studies are needed

Treatment

The objectives of treatment are to reduce pain by non-weight bearing or analgetics, and maintain or improve the range of motion during the active phase of the disease. Furthermore, treatment may attempt to prevent hip joint deformity by containment of the femoral head in the acetabulum during the active phases. The most widely used methods of containing the femoral head in the acetabulum are abduction orthosis (Curtis et al. 1974, Bobechko 1974, Purvis et al. 1980, Martinez et al. 1992) and femoral or pelvic osteotomies (Axer et al. 1980, Heikkinen et al. 1976, Sponseller et al. 1988, Paterson et al. 1991, Salter 1984). The operative containment treatment has consisted of varus osteotomy of the proximal part of the femur, which centers the femoral head more deeply within the acetabulum. This allows the femoral head to mould within the acetabulum, increasing its sphericity at healing. Similarly, a pelvic osteotomy covers the femoral head by redirecting the acetabulum.

The major underlying problems are the indications for treatment and how to treat. What treatment (if any) is most likely to alter the natural history of the disease? The large body of literature on this subject consists of retrospective case series or comparative studies where the indications for

treatment and treatment method differ within the groups studied. Still, nearly 100 years after Perthes' disease was first described, there are controversies and hence no uniform guidelines for treatment. To the best of my knowledge, no large prospective randomized studies were available when the present study was started.

Aims of the study

As the introduction shows, nearly all aspects of Perthes' disease (epidemiology, etiology, radiological classifications, prognostic factors and treatment) are still an object of controversy. On these grounds, the Norwegian Paediatric Orthopaedic Society initiated a nationwide prospective study on Perthes' disease that started in 1996. This thesis is based on different aspects of this study.

The aims of the present study were to:

1) investigate the epidemiology of Perthes' disease in Norway and explore differences in incidence between different regions and population areas (paper I);
2) explore etiological features of Perthes' disease by linking the patient cohort to The Medical Birth Registry in Norway (paper I);
3) evaluate the inter-observer reliability of the most commonly used radiographic classifications, assessments and measurements (papers II, III, and IV);
4) assess the subchondral fracture as a predictor of femoral head necrosis in Perthes' disease and its clinical significance (paper III);
5) determine radiographic and clinical prognostic factors and their relative importance in Perthes' disease (paper V);
6) evaluate and compare the outcome of three modalities of treatment in Perthes' disease: physiotherapy, abduction orthosis, and proximal femoral varus osteotomy (paper V).

Summary of papers I–V

Paper I

Wiig O, Terjesen T, Svenningsen S, Lie S A. The epidemiology and aetiology of Perthes' disease in Norway: A nationwide study of 425 patients. J Bone Joint Surg (Br) 2006; 88-B: 1217-23.

As part of a nationwide study on Perthes' disease in Norway, orthopaedic surgeons in 28 hospitals in 19 counties were instructed to report all new incidents over a 5- year period. 425 patients were registered, which represents an average annual incidence of 9.2 per 100 000 per year in subjects under 15 years of age, and an attack-rate of 1:714 for the country as a whole. There were marked countywise and regional variations in incidence. The lowest incidence was found in the northern region (5.4 per 100 000 per year) and the highest was registered in the central and western part (10.8 and 11.3 per 100 000 per year). There was a trend towards higher incidence in urban areas (9.5 per 100 000 per year) compared with rural parts of the country (8.9 per 100 000 per year). The male/female ratio was 3.3:1, and mean age at onset for both sexes combined was 5.7 years.

402 patients were linked to data from the Medical birth registry of Norway and compared to a matched control group of non-affected children (n = 1 025 952). We analyzed several maternal data (age at delivery, parity, length of pregnancy), birth length and weight, presentation (breech birth, transverse lie or other malposition), head circumference, and presence of congenital anomalies. Children with Perthes' disease were significantly shorter at birth and had increased frequency of congenital anomalies. Applying Sartwell's logarithmic normal model of incubation periods to the distribution of age at onset of Perthes' disease showed a good fit to the lognormal curve. Our findings point toward a single cause acting prenatally, genetic or environmental, in the etiology of Perthes' disease.

Paper II

Wiig O, Terjesen T, Svenningsen S. Inter-observer reliability of radiographic classifications and measurements in the assessment of Perthes' disease. Acta Ortop Scand 2002; 73:523-30.

This study was undertaken to assess the inter-observer agreement of radiographic methods when evaluating patients with Perthes' disease. The radiographs were assessed at the time of diagnosis and at the 1-year follow-up by local orthopaedic surgeons (O) and 2 experienced pediatric orthopaedic surgeons (TT and SS). The Catterall, the Salter-Thompson, and the Herring lateral pillar classifications were assessed, and the femoral head coverage (FHC), Center-Edge angle (CE-angle), and articulo-trochanteric distance (ATD) were measured in both the affected and normal hips.

At the primary evaluation, the lateral pillar classification and the Salter-Thompson classification had a higher level of agreement among the observers than the Catterall classification, but none of the classifications obtained good agreement (weighted kappa values between O and SS 0.56, 0.54, 0.49, respectively). Combining Catterall groups 1 and 2 into one group, and groups 3 and 4 into another gave a higher level of agreement (kappa 0.55) than the original 4 group system. There was better agreement (kappa 0.62–0.70) between experienced than between less experienced examiners for all classifications.

The femoral head coverage was a more reliable and accurate measure than the CE-angle to quantify the acetabular covering of the femoral head, indicated by higher intraclass correlation coefficients (ICC) and smaller inter-observer differences. The ATD obtained good agreement in all comparisons and had low inter-observer differences.

We conclude that all classifications of femoral head involvement are adequate in clinical work if the radiographic assessment is performed by experienced examiners. For less experienced examiners, a 2 group classification or the lateral pillar classifi-

cation is more reliable. For evaluation of containment of the femoral head, FHC is more appropriate than the CE-angle.

Paper III

Wiig O, Svenningsen S, Terjesen T. Evaluation of the subchondral fracture in predicting the extent of femoral head necrosis in Perthes' disease. A prospective study of 92 patients. J Pediatr Orthop B 2004; 13(5): 293-8.

The aim of this study was to evaluate the subchondral fracture as a predictor for the extent of femoral head necrosis in Perthes' disease. Out of 392 patients, 92 (23.5%) had a detectable subchondral fracture at the time of diagnosis. There was concordance between predicted Catterall groups on the basis of the extent of the subchondral fracture and the actual Catterall groups at the time of maximal resorption in 61% of the cases, when assessed by an experienced observer. When using the extent of the subchondral fracture to predict Salter-Thompson groups, this observer obtained 89% concordance with the actual Salter-Thompson groups at the time of maximal resorption.

The inter-observer agreement between the experienced and a less experienced observer regarding the presence or absence of a subchondral fracture was moderate (weighted kappa 0.59, 87% agreement). When using the extent of the subchondral fracture as a measure of femoral head involvement (Catterall groups), the inter-observer agreement was moderate (weighted kappa 0.46). Patients with detectable subchondral fracture were significantly older (mean 6.5 years) at the time of diagnosis than those without visible fracture (mean 5.2 years). The delay in diagnosis was significantly shorter in the group with subchondral fracture (mean 3.2 months) than among patients without visible fracture (mean 4.9 months).

We conclude that the subchondral fracture is a relatively rare early sign in Perthes' disease. When present, it is a useful sign when assessed by an experienced observer as its extent was in fairly good concordance with the extent of femoral head involvement at the time of maximal resorption. Awareness of this radiographic sign will aid the orthopaedic surgeon to establish diagnosis and, to some degree, to predict prognosis early in the course of the disease.

Paper IV

Wiig O, Terjesen T, Svenningsen S. Inter-observer reliability of the Stulberg classification in the assessment of Perthes' disease. J Child Orthop 2007; 1: 101-5.

The radiographic classification of Stulberg is widely used as a predictor of long-term outcome. We used this classification to assess the radiographs of 101 hips in 2 separate sessions (55 and 46 hips respectively), interfered by an educational intervention where the classification algorithm was discussed and clarified.

We obtained good agreement between experienced examiners (weighted kappa 0.65 and a percentage agreement of 71%). We obtained weighted kappa values of 0.51 and 0.57 (moderate agreement) and percentages agreement of 62% and 65% between the least experienced observer and the two experienced examiners. Combining Stulberg class I and II, and IV and V, into a simpler 3-group classification, gave better agreement between all observers. The agreement between the two experienced observers improved to 81%.

We conclude that the reliability of the Stulberg classification is acceptable when the radiographic assessment is done by experienced examiners. A simpler 3-group classification based on the shape of the femoral head (spherical, ovoid, and flat) gave better agreement and is therefore recommended for routine clinical use.

Paper V

Wiig O, Svenningsen S, Terjesen T. Prognostic factors and outcome of treatment in Perthes' disease. A prospective study of 368 patients with 5 year follow-up. J Bone Joint Surg 2008; 90-B: 1364-71.

The treatment of Perthes' disease is controversial. This nationwide prospective study was designed to determine prognostic factors and to evaluate the outcome of different treatment modalities.

28 hospitals with pediatric orthopaedic service throughout Norway were instructed to report all new incidents of Perthes' disease over a period of 5 years. 425 patients were reported and followed for 5 years. 368 children had unilateral affection and were included in the present study. The hips were radiographically classified according to a modified 2-group Catterall classification and the lateral pillar classification. 358 of 368 patients (97.3%) attended the 5 year follow-up. A modified 3-group Stulberg classification was used as radiographic outcome measure. For patients above 6.0 years of age at the time of diagnosis with more than 50% necrosis of the femoral head (152 patients), the surgeons at the different hospitals had chosen one of three methods of treatment: physiotherapy (55 patients), the Scottish Rite abduction orthosis (26 patients), and proximal femoral varus osteotomy (71 patients). 146 of these hips (96.1%) were available at the 5-year follow-up.

The strongest predictor of outcome was femoral head affection more or less than 50% (Odds Ratio (OR) = 7.76, 95% Confidence Interval (CI) 2.82–21.37), followed by age at diagnosis (OR = 0.98, 95% CI 0.92–0.99), and the lateral pillar classification (OR = 0.62, 95% CI 0.40–0.98). In children above 6.0 years at the time of diagnosis with more than 50% femoral head necrosis, proximal femoral varus osteotomy gave significantly better outcome compared with orthosis ($p = 0.001$) and physiotherapy ($p = 0.001$). There was no significant difference between the physiotherapy group and the orthosis group ($p = 0.36$). We found no difference in outcome of treatment in children less than 6 years ($p = 0.73$).

We recommend proximal femoral varus osteotomy in children aged 6 years and older at the time of diagnosis with hips with more than 50% femoral head necrosis. The abduction orthosis should be abandoned as treatment method.

General discussion

Patients

In January 1996 the Norwegian Pediatric Orthopaedic Society started a nationwide study on Perthes' disease. All hospitals with pediatric orthopaedic service (6 university clinics, 16 county hospitals and 6 local hospitals) throughout Norway were instructed to report all new incidents of Perthes' disease over a period of 5 years. The diagnosis was established by the treating orthopaedic surgeon on the basis of clinical examination and recognized radiographic changes. 399 patients were reported primarily and registered. In order to find new unreported cases we carried out an audit in 2003. The diagnosis registries of all the participating hospitals were checked by the local orthopaedic surgeons to ensure that the reported incidence was as close to the true incidence as possible. All cases referred to the different hospitals were identified through either the radiographic archives or the computerized diagnosis systems. In this way 26 previously unreported children were detected. Thus, a total of 425 patients were included in the study.

Diagnosis

Bilateral disease

Bilateral Perthes' disease poses several problems with regard to diagnosis, treatment, and outcome compared to unilateral disease. The distinction between bilateral Perthes' disease from the generalized skeletal dysplasias (multiple epiphyseal dysplasia, pseudoachondroplasia, spondyloepiphyseal dysplasia) and Meyers dysplasia can be a challenge in clinical practice (Crossan et al. 1983). Rosenfeld et al. (2007) found that a group of children with concurrent bilateral disease did not fit the typical Perthes' disease pattern that might represent a yet undescribed disorder of the femoral head. Van den Bogaert et al. (1999) reported inferior outcome in patients with bilateral involvement, but a larger retrospective study by Guille et al. (2002) showed that the disease tended to be milder in patients with bilateral disease. Also, questions have been raised on whether treatment of one hip can affect the disease process in the other hip in bilateral disease, or if the development and outcome of the disease in each hip is an independent event (Guille et. al 2002, Futami et. al 1997). In paper V we chose to omit children with bilateral disease when comparisons between treatment groups were made, so that our results would be in less risk to be skewed in any direction.

Meyer's dysplasia and multiple epiphyseal dysplasia (MED)

Meyer's dyplasia is a rare and symptomless developmental disorder of the hip first reported by Karup Pedersen (1960) and later more thoroughly described by Meyer (1964). The disease is manifested by a delayed, irregular ossification centre of the femoral epiphyseal nucleus. Meyer's dysplasia is more prevalent in the younger children (below 4 years of age), and is more frequently bilateral, in 50–59% (Khermosh and Wientroub 1991, Rowe et al. 2004) than Perthes' disease. Unlike Perthes' disease, Meyer's dysplasia develops in a pathologic nucleus (delayed and irregular ossification), and the initial radiographic finding is characterized by a small ossification centre, and a "cracked" ossific nucleus. However, there is no subchondral fracture, no condensation or collapse of the epiphysis, and no subluxation, as is the case in Perthes' disease (Meyer 1964, Rowe et al. 2004). The hip heals completely and leaves no trace except a slight loss of epiphyseal height, and the duration of the disease is shorter (< 3 years) than for Perthes' disease.

Pedersen (1960) analyzed 672 patients diagnosed as Perthes' disease, and found 42 (6%) patients in whom the disease pattern was atypical. Meyer (1964) reviewed 300 patients treated for Perthes' disease at the Seaside Hospital at Refsnæs, Denmark, and found that at least 10% of these children actually had epiphyseal dysplasia. In our material we found 4 patients out of 425 (1%) with possible Meyer's dysplasia. Nevertheless, they were included in the study.

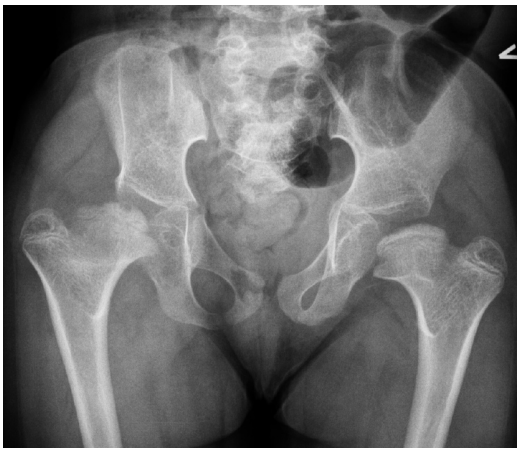

Figure 2. Spondyloepiphyseal dysplasia.

Multiple epiphyseal dysplasia (MED) is a genetically determined disorder characterized by abnormal ossification of multiple epiphyses (Fairbank 1947, Kaufmann 1976). Diagnostic criteria are abnormal ossification of two or more pairs of epiphyses in the absence of features suggestive of other diagnoses. Vertebral end-plate irregularity especially at the thoraco-lumbar junction can exist. Both hips are frequently affected and the condition is thus a differential diagnosis for bilateral Perthes' disease. MED is heterogenous with both mild and severe forms and can cause early osteoarthritis (Treble et al. 1990). No patient in our material met these criteria.

Other conditions primarily affecting epiphyseal growth can mimic Perthes' disease, such as pseudoachondroplasia, spondyloepiphyseal dysplasia congenita (Figure 2) and tarda and hypothyreoidism. We found no patients in our material that fitted the criteria of any of these diagnoses.

Congenital dislocation of the hip and late Perthes' disease

We found an unexpectedly high incidence of congenital dislocation of the hip (9 children) in our cohort (425 children) in children with Perthes' disease (paper I). All of the children had been treated with Frejkas pillow for at least 4 months just after birth, and they had recovered before developing Perthes' disease several years later. Hence it is not likely that these children developed avascular necrosis as a complication of congenital dislocation of the hip resembling Perthes' disease later in childhood.

To the best of my knowledge, only 17 cases of late Perthes' disease after congenital dislocation of the hip has been reported in the literature: Lindholm et al. 1978 (3 cases), Williams et al. 1982 (1 case), Koczewski and Napiontek 2001 (10 cases), and Theodorou et al. 2004 (3 cases). Koczewski and Napiontek (2001) stated that the course of Perthes' disease in their patients was typical of Perthes' disease, contradictory to Lindholm (1978) and Theodorou (2004) who found that the disease usually was more severe, with extensive involvement of the upper end of the femur (broader) and the acetabulum (more dysplastic) and a flat and anteverted femoral head.

Methods

Epidemiology

The average annual incidence and attack-rate were calculated for the country as a whole and for each county based on population data from Statistics, Norway. The average annual incidence rate was calculated as the number of cases registered to the sum of the person-years for individuals below 15 years of age for each year from 1996 to 2000. The occurrence rate measures cases appearing in a group of children followed through the period of risk (Molloy and MacMahon 1966). The total occurrence rate was computed by adding the annual incidence rates over the total period of risk. The occurrence rate for Perthes' disease was the sum of the incidence rates for individual years up to age 15 years.

Urban and rural incidence rates were calculated separately, where the 4 largest cities (Oslo, Bergen, Trondheim and Stavanger) were considered as urban areas, and the rest of the country as rural. This dividing line could be questioned because there is no clear difference between the larger cities and the somewhat smaller ones.

Etiology

The Medical Birth Registry

The Medical Birth Registry of Norway provided the data necessary to carry out the investigation concerning the presence of congenital anomalies and other parameters at birth among the Perthes children. The Medical Birth Registry is a national

health register of all the newborns in Norway established in 1967. It conducts epidemiological surveillance of birth defects and other perinatal health problems. In addition to complete identification of the mother and the father in terms of their national identification numbers, the register holds demographic information on the mother and father, mother's health before and during pregnancy, including chronic diseases, complications during pregnancy and delivery as well as information on the infant, including birth defects and other perinatal problems.

Sartwell's logarithmic normal model

The Gaussian (normal) distribution is most often assumed to describe the random variation that occurs in the data from many scientific disciplines. Skewed distributions, however, is particularly common in biology (growth of bacteria, survival times after cancer diagnosis). This is also the case with incubation periods of disease. Sartwell's biometrical model is useful to test potential causal factors at the origin of biological phenomena of unknown etiology. Sartwell (1950) showed that the incubation periods of a number of infectious diseases formed a consistent pattern. All of the diseases studied (bacterial food poisoning, streptococcal sore throat, measles, typhoid fever, chickenpox, amoebic dysentery, hepatitis, malaria, and common cold), although having a great variance in incubation period, possessed the similar skewed curve when the incubation period (x-axis) was plotted against the cumulative percent of symptomatic individuals (y-axis). Similarly, when he used the logarithm of the incubation period on the x-axis plotted against the cumulative percent of symptomatic individuals, all of the diseases studied produced a straight line. He stated that the shape of the curve gave clue to whether a particular epidemic was due to practically simultaneous exposure of the infective agent to a group (i.e. when contaminated food is served at a social gathering), or whether successive infections took place over time (when a milk supply contains streptococci, shed by a cow with mastitis, over a period of weeks). The frequency curve of incubation time of a particular infection occurring simultaneously, took the form of a logarithmic normal curve, as was not the case in infection occurring over a long time span (i.e. waterborne epidemics). Later, it has been suggested that the relative etiologic importance of genetic and environmental factors for a disease can be determined by how well the distribution of age at disease onset fits Sartwell's incubation period model. Assuming that the age at onset for well defined genetic diseases corresponded with the incubation period of the disease, Armenian and Khoury (1981) found that for disease with strong environmental influences or ill defined genetic etiology, the distribution of age at onset (incubation period) did not fit the logarithmic normal curve, whereas diseases with genetic etiology did. This model has been used to study the incubation periods of a number of infectious, non-infectious, neoplastic-, and genetic diseases (Armenian and Khoury 1981) such as Rett's syndrome (Kozinets et. al 1997), and Alzheimer's disease (Horner 1987). In all of these applications, both the model and the measures of incubation period that it generated were found to be robust. The major attraction of this method is its simplicity, as well as its applicability to a broad spectrum of diseases.

However, several concerns have been raised regarding the use of Sartwell's incubation period model in etiologic investigations of chronic diseases (Horner and Samsa 1992). It is important to recognize some underlying assumptions of the model. First, the pathologic process being studied is one of multiplicative growth of the causative agent or its toxic by-products, and that there is a threshold at which symptoms appear, and that the time from exposure to symptom is the incubation time. Secondly, we assume that variation in incubation time is a natural phenomenon reflecting variation in the host. A third concept is that lognormality of the distribution argues for a common source of the agent and/or a common time of exposure, and hence that a disease with a lognormal distribution of incubation periods supports certain conclusions concerning the etiology. These underlying assumptions have been criticized (Horner and Samsa 1992), and it has been suggested that the age at onset distribution for all or most chronic diseases will be lognormal because of disease and population dynamics. Secondly, the model can not distinguish between prenatal and age-related postnatal exposure because the latter also will have a lognormal distribution of age at onset. Finally,

Sartwell's model is most appropriate in population based case series where the population is stable and the incubation period is relatively brief, thus minimizing the risk of missed cases due to migration, truncation (cases not yet observed), and other causes of loss to follow-up.

Imaging methods

Papers II, III, and IV deal with different radiographic aspects of Perthes' disease and are mainly concerned with inter-observer reliability of radiological classifications and measurements. In paper II and III, we assessed the radiographs at time of diagnosis and at short-term follow-up (1 year after diagnosis in paper II, at the time of maximal resorption in paper III). In paper II, we investigated the inter-observer reliability of certain radiographic classifications and measurements between the treating orthopaedic surgeon and two experienced pediatric orthopaedic surgeons. Paper III had a similar design, were two observers (experienced and less experienced) evaluated the subchondral fracture as a predictor for the extent of femoral head necrosis.

This thesis is based on a nationwide study where a large number of hospitals (28) and departments of radiology have participated. We have not been able to standardize the radiographs due to differing local traditions, which might have resulted in variable quality both with regard to projection angles, contrast and size. A correct placement of the centre of the femoral head is essential to decide the CE-angle and whether the shape of the surface of the epiphysis is spherical or ovoid. We found it difficult to observe the outline of the femoral head, acetabulum and pelvis clearly in some low contrast radiographs. The measurements were especially difficult to make when the radiographs showed small scale and poor quality images of the hip. The early radiographs were mostly projected onto film, whereas the more recent ones (from 2000–2001 and onward) were recorded digitally. In our opinion, the overall quality of the digital images was somewhat better, and the ability to improve and magnify these images by computer software was an advantage.

It was our intension to evaluate the skeletal age and to assess the role of MRI in Perthes' disease. However, only a limited number of hand radiographs and MRI's were carried out and no sound assessment could be made.

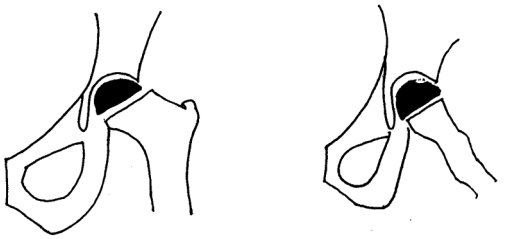

Figure 3. Catteral group 1.

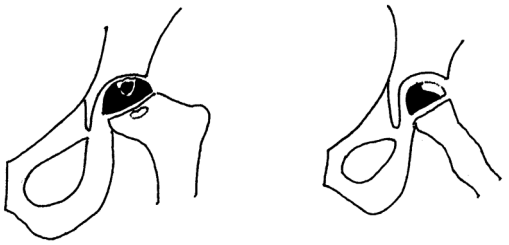

Figure 4. Catterall group 2.

Radiographic phases

In paper II and V, the radiographic phases were determined at the time of diagnosis according to Waldenström (1922), where the initial phase was characterized by difference in epiphyseal height, width and bone structure compared with the normal hip. The fragmentation phase included the hips where the necrotic bone was partly or totally resorbed. Hips with obvious signs of reossification were classified as being in the reossification phase, and those who had been fully rebuilt were classified as being in the healed stage.

The Catterall classification

In papers II, III, IV and V the classification of Catterall (1971) was used. In group 1 (Figure 3) only the anterior part (25%) of the epiphysis is involved. There is no collapse of the involved segment and no sequestrum formation. The height of the epiphysis is maintained on the anteroposterior projection. In the Lauenstein projection only the anterior part of the femoral head is involved.

Up to 50% of the anterior part of the epiphysis is involved in group 2 (Figure 4), and there is collapse and increased density of the involved segment with formation of a sequestrum. On the

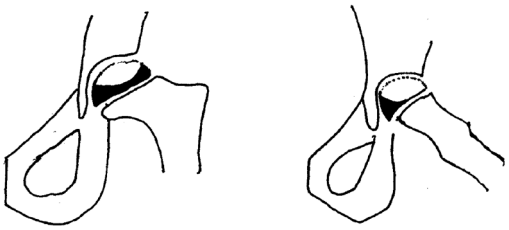

Figure 5. Catterall group 3.

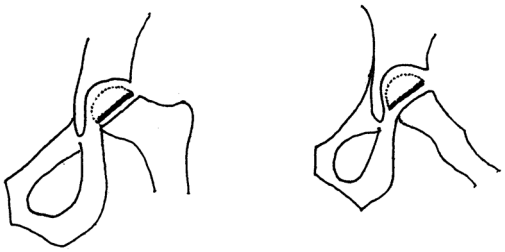

Figure 6. Catterall group 4.

anteroposterior radiograph there are viable lateral and medial fragments, and the height of the epiphysis is maintained.

Group 3 (Figure 5) involves 50–75% necrosis of the femoral head and only very small normally textured segments are observed on the lateral and medial sides (AP plane). In the Lauenstein projection, only a small part of the posterior epiphysis appears uninvolved.

In group 4 (Figure 6) the whole epiphysis is necrotic (sequestrated). In the AP plane, a total collapse of the epiphysis is observed. On the Lauenstein projection, there is no posterior viable portion, and the epiphysis is replaced by an irregular linear opacity.

Based on the original Catterall classification, we combined Catterall groups 1 and 2 (less than 50% necrosis of the femoral head), and Catterall groups 3 and 4 (more than 50% necrosis of the femoral head) classifying the hips into a simpler 2-group classification. Our motive was based on our previous experience that the original Catterall classification had been difficult to apply. Moreover, insufficient inter-observer reliability with the Catterall classification had been reported (Christensen et al. 1978, Hardcastle et al. 1980). Additionally we assumed that the agreement would be better when comparing classifications with fewer categories (Altmann 1999).

Catterall's five head at risk signs (1971) consists of Gage's sign (small osteoporotic segment which forms a transradiant "V" on the lateral side of the epiphysis on the AP view), calcification lateral to the epiphysis, lateral subluxation seen as an increase of the inferomedial joint space, and a transverse growth plate seen on the AP view. The literature differs considerably on the prognostic significance regarding the "head at risk signs" (Mukherjee et al. 1990, Murphy and Marsh 1977, McAndrew and Weinstein 1984, Fulford et al. 1993). We therefore thought they would hardly provide reliable additional information regarding prognosis, and thus we did not evaluate the "head at risk signs" in our study.

The Salter-Thompson classification

In papers II and III the Salter-Thompson classification was used. Group A included hips with less than 50% involvement of the femoral head and group B included those with more than 50% involvement of the femoral head. Originally this classification was based on the presence of a subchondral fracture visible early in the course of the disease on a limited number of hips. This classification can be applied in the early stages of the disease when the subchondral fracture is still detectable as well as throughout the ensuing resorptive stage (Salter and Thompson 1984). The presence of the subchondral fracture is not an absolute condition to use the classification, but rather it is to be considered a prognostic sign in the very early phase of the disease, since the extent of the fracture correlates with the involvement of the femoral head in later phases.

The subchondral fracture

Salter and Thompson (1984) described the subchondral fracture and found that this was of prognostic significance. Because this has not been supported by others, we thought it would be interesting to evaluate this radiographic sign (paper III). The extent of the subchondral fracture was predicted as being in group 1, 2, 3 or 4 of the Catterall classification in the ensuing stage of maximal resorption. Group 1 consisted of hips where the subchondral fracture was not visible in the anteroposterior radiograph, but where the extent of the fracture was clearly visible in the lateral radiograph. Group 2 included hips where the fracture was visible on the

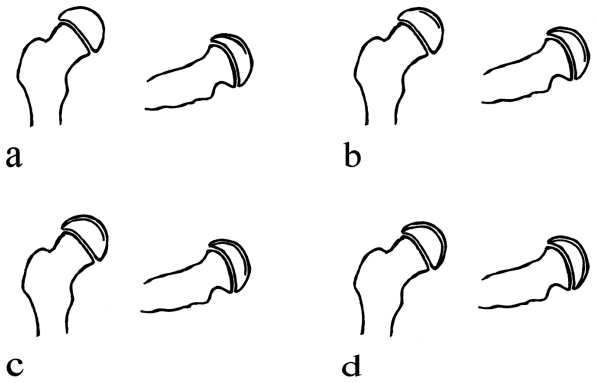

Figure 7. Subchondral fracture groups 1–4 (a-d).

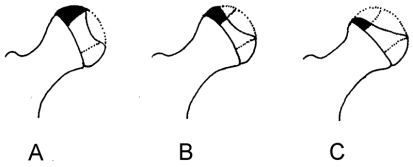

Figure 8. The lateral pillar classification.

anteroposterior radiograph but did not involve the lateral or medial margin, and on the lateral radiograph the fracture began at the anterior margin and extended posteriorly slightly beyond the midline of the femoral head. In group 3 hips the subchondral fracture involved almost all of the epiphysis in both planes, and in group 4 the subchondral fracture extended over the entire surface of the epiphysis on both the anteroposterior and lateral radiograph (Figure 7).

In paper III the extent of the subchondral fracture was used to classify the hips as being in Salter-Thompson group A or B. Group A consists of hips in which less than one half of the capital femoral epiphysis is involved, and in group B more than one half of the epiphysis was involved.

The lateral pillar classification

In papers II and V we used the lateral pillar classification (Herring et al. 1992) (Figure 8): group A with no height reduction of the lateral pillar of the femoral head, group B hips with more than 50% height of the lateral pillar maintained, and group C hips with less than 50% height maintained.

This classification was used because there were promising reports concerning its reliability and prognostic significance (Simmons et al. 1990, Herring et al. 1992, Ritterbush et al. 1993, Podeszwa et al. 2000). We did not use the B/C border group as this group was introduced by Herring et al. in 2004, several years after the inclusion period of our study.

Residual hip joint deformity

Stulberg et al. (1981) proposed a 5-class classification to predict long-term prognosis and the onset of degenerative joint disease after Perthes' disease. In paper IV and V we used the Stulberg classification as modified by the algorithm of Neyt et al. (1981). Class I hips are spherical with normal femoral head, neck and acetabulum. Class II hips have spherical femoral head with either coxa magna, short neck, or steep acetabulum. Class III hips have ovoid (not flat) femoral head contour, in the sense that they do not fall within 2 mm of the Mose concentric circles (Figure 9) in both anteroposterior and Lauenstein projections. Class IV hips have flat outline of the femoral head (at least 1/3 of the contour of the femoral head resembles a straight line on at least 1 projection), and there is congruency between the femoral head and the acetabulum. Class V hips have flat femoral head and normal acetabulum.

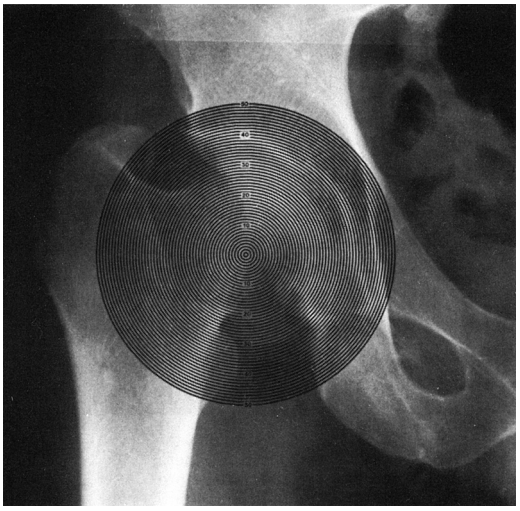

Figure 9. Mose's concentric circles.

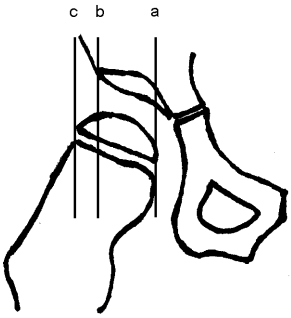

Figure 10. FHC = ab/ac x 100.

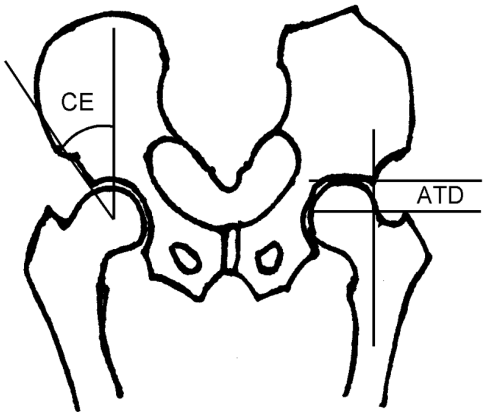

Figure 11. CE-angle (right hip) and the ATD (left) hip).

Class I and II have spherical congruency, class III and IV have aspherical congruency, and class V has aspherical incongruency.

In paper IV we modified the Stulberg classification, reducing the 5 groups to 3 groups (A, B, and C), based on the shape of the femoral head. Group A hips were defined to be spherical (femoral head contour within 2 mm of the Mose concentric circles in both projections), group B to be ovoid (contour outside 2 mm of the Mose concentric circles in both projections), and group C to be flat (at least 1/3 of the contour of the femoral head resembles a straight line on at least 1 projection). This was done in order to test whether a simpler classification would give better agreement. We believed that this was possible without reducing the prognostic value of the classification.

Uncovering of the femoral head

The femoral head coverage (FHC) (Figure 10) was obtained by calculating the percentage of the femoral head medial to Perkin's line to the width of the femoral head parallel to Hilgenreiner's line (paper II and V).

The CE-angle (Wiberg 1939) (Figure 11) is the angle between the perpendicular through the centre of the femoral head and the line connecting the centre of the femoral head and the lateral edge of the acetabulum. We measured this angle as described by Müller (1971) (paper II and V).

Containment of the femoral head in the acetabulum can be measured as the FHC and the CE-angle on plain AP radiographs. Increasing degree of femoral head uncovering at the time of diagnosis has been linked to poor prognosis (Dickens and Menelaus 1978, Gigante et al. 2002, Mukherjee and Fabry 1990). On these grounds we wanted to investigate the reliability of these measurements (paper II) as well as their prognostic significance (paper V).

Articulo-trochanteric distance (ATD)

The articulo-trochanteric distance (ATD) (Figure 11) was measured as the distance between 2 lines perpendicular to Perkins' line: the line through the proximal tip of the greater trochanter and that through the most proximal point of the femoral head. ATD describes the degree of trochanteric overgrowth and length of the femoral neck and is a simple measure on the deformation of the proximal femur. We wanted to evaluate the inter-observer reliability (paper II) and prognostic significance (paper V) of this measurement.

Other imaging methods

Fulford et al. (1993) found that arthrographic evaluation in four views was more predictive in relation to outcome than the Catterall grouping and head at risk signs. This was confirmed by Ismail et al. (1998), who found arthrographic shape of the femoral head (in addition to age at diagnosis and lateral pillar classification) to be a strong predictor of prognosis. We have not assessed arthrography in this thesis.

Terjesen (1993) found that ultrasound was reliable in diagnosing Perthes' disease when the surface of the ossified epiphysis was irregular and when fragmentation had occurred. Furthermore, he stated that ultrasound and radiography was com-

plementary, and that ultrasound provided useful information regarding synovitis, lateral and anterior protrusion, and femoral anteversion angles. Ultrasound has not been included as a diagnostic tool in our studies.

There are several reports concerning the use of radionuclide bone scanning for diagnostic and prognostic purposes. The appearance of Perthes' disease on bone scan has been demonstrated to be characteristic with a marked void in activity in the femoral epiphysis at a very early stage, and signs of revascularisation have been demonstrated later in the course of the disease (Danigelis 1975, 1976, Sutherland et al. 1980, Calver 1981). With bone scan, it is possible to classify Perthes' disease into stages of revascularisation (Tachdjian 1984, Tsao et al. 1997), and serial bone scan have been shown to have prognostic significance regarding later femoral head involvement and degree of deformity at healing (Tsao et al. 1997). However, bone scan lacks the ability to describe the shape of the femoral head and its relationship with the acetabulum. The increased radiation compared with conventional radiography is concerning. I have not evaluated radioisotope scanning in this thesis.

MRI is useful for monitoring overall changes of the epiphysis and is reported to be more sensitive for early detection compared to plain radiographs and radionucleide bone scans (Scoles et al. 1984, Toby et al. 1985). The technique describes the progression of the necrosis, the ensuing reparative processes as well as the shape and condition of the cartilage (Tsuchida et al. 2005). However, no uniform MRI-based classification with prognostic significance has to date gained popularity, and MRI has been shown to be less effective in assessing hip deformity (Jaramillo et al. 1999). MRI should not be regarded as a non-invasive procedure, as many children require sedation to be able to cooperate sufficiently to obtain adequate imaging, and it is yet a costly procedure. More research is required to explore the role of MRI in the assessment of Perthes' disease.

Treatment

Study design

The randomized clinical trial (RCT) is regarded as the gold standard for research designed to answer questions in relation to medical treatment (Rudical and Esdaile 1984), but there is a considerable lack of such studies comparing surgical procedures. The traditional RCT design poses several problems when surgical treatment methods are evaluated. In clinical practice, the surgeon aims to treat each patient individually. A RCT, however, forces the surgeon to submit to a specific treatment regime where the aim is to solve a clinical dilemma to the good of future patients. The surgeon may feel that the trial may allocate his or her patient to an inferior treatment, hence the surgeon is confronted by an ethical dilemma. Moreover, it is difficult to compare surgical procedures as the surgeons may be more familiar and skilled with one procedure than another. Different surgeons usually have diverse surgical philosophies based on their interpretations of the available literature and the surgeons' own experience. Thus the individual surgeon's belief in a certain procedure represents a possible bias.

In paper V, the study design was similar to the randomized surgeon design described by Rudical and Esdaile (1984) in the sense that surgeons and hospitals were assigned to the treatment of their own choice. Patients were treated in their local hospital and only rarely referred to a hospital outside the county. Prior to the study, orthopaedic surgeons at each hospital were given the opportunity to choose one of the three methods according to their treatment philosophy. We believe that this contributed to eliminate the patient selection bias and enhanced surgeon compliance by allowing the surgeons to be committed to their favoured treatment. This study design eliminated performance bias as the orthopaedic surgeons at each hospital had chosen the treatment with which they were most familiar. The net result of this design is probably as adequate as the RCT and it solves some of the problems with randomized surgical trials.

Ethical considerations

At the time the study was initiated (1996), there were no prospective randomized study published that ascertained that treatment with femoral varus osteotomy or abduction orthosis gave better outcome than physiotherapy or no treatment. Reports comparing different treatments were mainly retrospective case series with a relative small number of patients without a control group. We enrolled patients in our study from January 1996 to Decem-

ber 2000. As far as I know the only prospective randomized study on this subject published to date is the one of Herring et al. (2004), which was published after inclusion of patients for the present study. Thus, we did not think that offering physiotherapy to older children with more than 50% femoral head necrosis represented an ethical dilemma. Recruitment to the study was done through informed consent, and the study was approved by the Norwegian Data Inspectorate and the Norwegian Directorate of Health and Social Affairs.

Age

There are contradictory reports regarding what exact age at diagnosis that seems to be the watershed with regard to the long-term prognosis (Ippolito et al. 1987, Stulberg et al. 1981, Perpich et al. 1983, Herring et al. 1992, McAndrew and Weinstein 1984, Mukherjee et al. 1990, Brotherton et al. 1977, Kelly et al. 1980). After carefully reviewing the literature, the protocol was designed with 6 years of age at time of diagnosis as the dividing line with regard to treatment.

Choice of treatment methods

We wanted to compare the outcome of three modalities of treatment; non-surgical containment, surgical containment, and a treatment which was as close to the natural history of the disease as possible. The choice of treatment methods were based on the available literature at the beginning of the study and the established treatment in Norway.

As opposed to several other braces, the Scottish Rite abduction orthosis (Figure 12) permitted free motion (except adduction) of the hips. It is engineered on the principle that weight-bearing in itself is not detrimental as long as the femoral head is contained in the acetabulum (Purvis et al. 1980). This put fewer limitations on the child's daily activities and thus it was chosen over other braces to represent non-surgical containment treatment in our study.

For surgical containment treatment pelvic osteotomy or proximal femoral varus osteotomy were considered. Pelvic osteotomies redirect the acetabulum and hence improve the femoral head coverage. Femoral osteotomy (Figure 13), which centers the femoral head more deeply within the acetabulum, is believed to trigger biologic healing as the osteotomy heals (Axer 1980, Stulberg 1981), improve venous drainage (Heikkinen 1976 and 1980), and decrease biomechanical load on the femoral head due to the resultant varus (Heikkinen 1980).

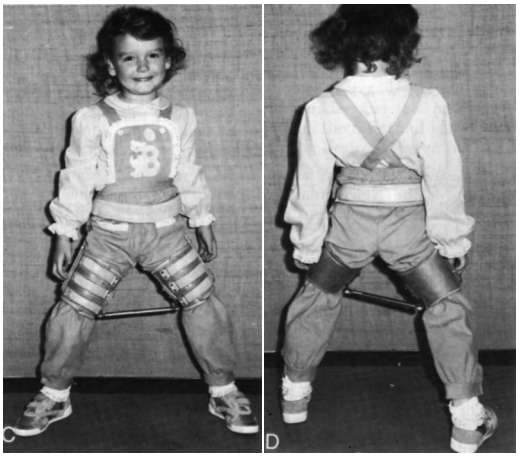

Figure 12. The Scottish Rite orthosis.

Both surgical procedures were in an equal degree documented with acceptable results in retrospective case series (Sponseller et. al 1988, Paterson et. al 1991, Salter 1984, Bennet et. al 1991, Coates et al. 1990, Lloyd-Roberts 1976, Hoikka 1986, Mc Elwain 1985). However, femoral osteotomy was by far the most common surgical procedure for Perthes' disease in Norway, and most orthopaedic surgeons find it easier to perform compared with some kind of pelvic osteotomy. A nationwide study that involved pelvic osteotomy would have been difficult to carry out as few orthopaedic surgeons were familiar with this procedure in Norway. Thus, proximal femoral varus osteotomy was selected as surgical containment method.

An ideal study design would be to compare non-surgical and surgical containment treatment with the natural history of the disease. Physiotherapy would in theory allow dynamic moulding of the epiphysis, and as the joint cartilage receives its nourishment from the surrounding tissues, the range of motion exercises would facilitate the nutrition of the cartilage. Maintaining or increasing the range of motion of the hip and preventing joint contracture could relieve certain parts of the femoral head of constant pressure from the acetabulum, thereby decreasing the risk of deformation. However, to the best of my knowledge, no study has

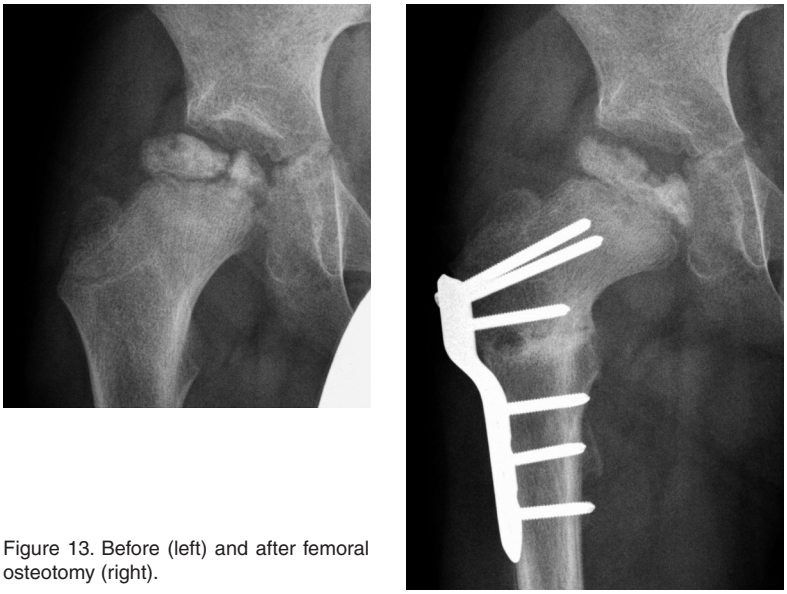

Figure 13. Before (left) and after femoral osteotomy (right).

been published that evaluated the efficacy of physiotherapy as treatment of Perthes' disease. Prior to the study it was our general impression that the majority of children with Perthes' disease received physiotherapy at some point during the course of the disease and that there was a strong belief in the benefit of physiotherapy for any orthopaedic condition among the parents. When the study was initiated in 1996, there existed no prospective randomized study evaluating the outcome of treatment and no firm conclusion could be drawn regarding the efficacy of any treatment. However, to offer no treatment at all would probably not have been accepted by the parents and could possibly pose an ethical dilemma. We considered that treatment with physiotherapy would be both acceptable ethically and acceptable to the parents and at the same time as close as we could get to the natural history of the disease. Thus physiotherapy was chosen as the third treatment method.

Statistics

For the statistical analyses in paper I, we used logistic regression with Perthes' disease as the dichotomous outcome. The numeric variables were categorized according to standards given by the Medical Birth Registry in Norway. All explanatory variables were run in simple models, only estimating the effect for the single variable one at the time. Thereafter a multiple logistic regression was done for the explanatory variables that were statistically significant in the simple analyses. The categorical data were analyzed by the chi-square test. The Kolmogorov-Smirnov test was used to assess the fit to Sartwell's logarithmic normal model.

Inter-observer agreement, categorical data

Inter-observer agreement between categorical variables is considered as the ability of different examiners to agree upon the classification of subjects into one of several groups.

There are several possible methods to quantify agreement. The simplest and most intuitive method is percentage agreement, where one simply observes the number of exact agreements between two observers given in percentage. This method, however, does not take into account between which categories the agreement was obtained or the agreement reached by pure chance. Nevertheless, this method to quantify agreement is probably the most intelligible method among non-statisticians (orthopaedic surgeons).

A more reasonable measure is obtained if we consider the agreement as the agreement in excess of the amount of agreement that we would expect by chance, as the kappa (k) measure provides (Altmann 1999). Kappa is a function of the ratio of agreements to disagreements in relation to

Table 1. Interpretation of kappa values

Value of kappa	Strength of agreement
< 0.20	Poor
0.21–0.40	Fair
0.41–0.60	Moderate
0.61–0.80	Good
0.81–1.00	Very good

expected frequencies. It has a maximum of 1.00 when agreement is perfect, a value of 0.00 when the agreement is no better than chance, and negative values when agreement is worse than chance. There are no uniform definitions as to what value is considered poor, fair, moderate, good or very good agreement. We have used Altmann's (1991) adaptations of Landis and Koch (1977) guidelines for interpreting the kappa values (Table 1).

The simple kappa statistics does not take into account the degree of disagreement and hence all disagreements are treated equally. In medical practice, a big disagreement in e.g. categorizing a certain illness will be more serious than a slight disagreement. If one considers the disagreement of only one category (near the diagonal of the cross-table) as less serious, and disagreement of more categories (farther from the diagonal) as more serious, it is preferable to give different weights to disagreements according to the magnitude of discrepancy. This yields the weighed kappa (kw) (Altmann 1999), which in my opinion is preferable over simple kappa statistics of the above mentioned reasons. Different cross-tables can give the same kappa values, and the value of kappa depends on the prevalence in each category. Thus, it can be difficult to compare kappa values from different studies as the prevalence of the categories often will differ. Additionally, the kappa value is dependent on the number of categories, giving better kappa values for classifications of fewer categories. Nevertheless, despite its shortcomings, I consider the weighed kappa statistics to be the most appropriate measure of agreement among observers concerning categorical variables.

Inter-observer agreement, numerical data

In order to evaluate agreement among observers regarding numerical data, I have used the intraclass correlation coefficient (ICC) (McGrav and Wong 1996), which is an index of reliability or agreement for two or more observers (paper II). Conceptually, ICC can be regarded as the ratio of between-group variance to the total variance. ICC will approach 1.00 when there is no variation within the target measured, meaning all observers give the same measure, indicating that the total variation in measurements is due solely to the target measured (i.e. radiograph), and not due to disagreement among the observers. Thus, an ICC of 1.00 indicates perfect agreement.

To evaluate the accuracy of the measurements, mean and standard deviation (SD) of the differences between observers and the range which includes 95% of the inter-observer differences (mean ± 2SD, 95% limits of agreement) (Altmann 1999) were used in paper II.

As in paper I, the statistics in paper V were performed in collaboration with a statistician. In paper V we evaluated the risk factors regarding radiographic outcome and all variables were run in simple models, only estimating the effect of the single variable one at a time. Outcome was the modified 3-group Stulberg classification. The categorical data were analyzed by the Pearson chi-square test, and continuous variables using a one-way analysis of variance (ANOVA). A multinomial proportional odds logistic regression analysis was performed with the 3-category Stulberg classification as outcome. Variables were excluded from the multivariable model one at a time using a backwards stepwise procedure. A mixed model repeated measures ANOVA was performed to assess the change of femoral head coverage over time. All p-values below 0.05 were considered significant.

Results

Epidemiology

Basic population data needed for the calculations regarding incidence and occurrence rates were provided by Statistics, Norway. This autonomous institution is the central body responsible for collecting and analyzing official statistics in Norway.

The average annual incidence of Perthes' disease in Norway was 9.2 per 100 000 per year in subjects under 15 years of age, and the total occurrence

rate was 1: 714. The incidences varied from 3.6 in Finnmark county to 16.7 in Sogn og Fjordane county. When using the highest populated county (Akershus) as reference category, Sogn og Fjordane, Møre og Romsdal and Sør-Trøndelag county had significantly higher incidence ($p = 0.001$, 0.003 and 0.013 respectively). Occurrence rates varied from 1:1818 in Troms to 1: 384 in Sogn og Fjordane. There were 325 boys and 100 girls, giving a ratio of 3.3:1.

The incidence rate of 9.2 is higher than that reported in Massachusetts (Molloy and MacMahon 1966) with 5.7 per 100 000 per year, and Yorkshire (Hall and Barker 1989) with 6.1 per 100 000). Our incidence was similar to that of the Trent region in England (Barker et al. 1978) with 7.6 per 100 000, in Uppsala, Sweden (Moberg and Rehnberg 1992) with 8.5 per 100 000) and in the white population of South Africa (Purry 1982) with 10.8 per 100 000. The incidence in Norway was considerably lower than in the Faroe Islands (Nicklasen 1974) with 29.4 per 100 000, Liverpool (Hall et al. 1983) with 21.1 per 100 000 and Northern Ireland (Kealey et al. 2000 with 11.6 per 100 000). The lowest incidences have been reported in China (Thompson et al. 1978) with 1 in 0.45 million, and British Colombia (Gray et al 1972) with 5.1 per 100 000. As reported in some English studies (Barker et al. 1978, Hall and Barker 1989, Hall et al. 1983), we found a somewhat higher incidence in urban (9.5 per 100 000) compared to rural (8.9 per 100 000).

We found significantly higher incidences in the central ($p = 0.015$) and western ($p = 0.014$) regions (11.3 and 10.9 per 100 000) compared to the east region, whereas the northern region had the lowest incidence rate (5.4 per 100 000). As the northern part of Norway is the most sparsely populated part of the country, one could argue that patients living at some distance from hospitals are less likely to be referred to an orthopaedic surgeon for treatment. However, it is unlikely that general practitioners will treat a child with a painful limp (92% of the patients in the present study) without consulting a specialist. We therefore assume that the variation in the occurrence of Perthes' disease reflects variations in true incidence.

The male/female ratio (3.3:1) was lower than that found in Massachusetts (5:1, Molloy and MacMahon 1966) and British Colombia (5.2:1, Gray et al. 1972). We found a frequency of bilateral disease of 13%. The reported incidence of bilateral disease varies from 8% to 24% (Guille et al. 2002, Harrison and Blakemore 1980, Salter and Thompson 1984). The mean age of onset was 5.8 years which is in accordance with Kealey et al. (2000) and comparable with Barker et al. (1978) who found a peak age at onset between 5 and 6 years.

Genetics and population in Norway

The northern part of Norway has a different ethnical composition compared to the rest of the country, as there exist a large Saami population and a strong element of Finnish immigrants especially in Finnmark county (Hinderaker and Reikerås 1988). The Saami people and the Finns (together with the Sardinians, the Greeks, and the Basques) are genetically distinct from other Europeans (Sajantila et al. 1995). Analyses of classic chromosomal marker variation have demonstrated that the genetic distances between the Saami population and other European populations are significantly larger than between any other pair of European populations (Cavalli-Sforza et al. 1997). It has been proposed that the genetic composition of the Saami people arose from extensive admixture between Caucasoid and Mongoloid populations, and thus that the Saami people has its origin in Asia (Zerjal et al. 1997 and 2001). The rest of the Norwegian population, however, has its genetic origin in Central and Western Europe (Passarino et al. 2002).

In paper I, we found significantly higher incidences in the central and western regions of Norway compared to the northern region (5.4 per 100 000 per year). Finnmark county had the lowest incidence in the country (3.6 per 100 000 per year). In this respect, the incidences in the Northern region, and especially in Finnmark county are comparable to incidences recorded among Asians (0.2–4.4 per 100 000 per year as reported by Rowe et al. (2005)). Similarly, the incidences recorded in central and western parts of Norway are comparable to incidences recorded in among Caucasians in western Europe (5.5–29.4 per 100 000 per year).

Etiology

Impaired and disproportionate skeletal growth

Several reports have concluded that Perthes children have delayed skeletal maturity at the time of

diagnosis, and that this persists during the course of the disease (Goff 1954, Weiner and O'Dell 1970, Harrison et al. 1976, Katz and Siffert 1977. Bohr (1979) studied 223 children with Perthes' disease over a period of 4–5 years and observed that the delay in skeletal age increased below the age of 5 years, whereas in children over the age of 8 years it gradually decreased. Harrison (1976) and Bohr (1979) observed a "standstill" in skeletal maturation in which no new carpal bones were formed, but bones already ossified became gradually larger. The skeletal age remained constant for as long as 3 years, especially in boys below 5 years of age. Harrison (1976) found the same delay in skeletal age in 93 unaffected siblings of patients with Perthes' disease.

Our intention was to determine the skeletal age of the patients in our study but we were not able to collect a sufficient amount of radiographs to obtain a meaningful analysis.

In their study on skeletal immaturity in Perthes' disease, Harrison et al. (1976) suggested that children with Perthes' disease may have a generalized disorder of growing bones, and Burwell et al. (1978) did an anthropometric study on 232 children with Perthes' disease. They found a significant reduction in standing, sitting and subischial height, reductions in total arm, forearm, hand and foot length, tibial length, biacromial and biiliac width. The head circumference was normal in children with Perthes' disease compared with normal children. The impaired growth affected various regions of the body differently. The circumference of the head was disproportionately large relative to the standing height, the growth of the upper and lower limb was disproportionate but symmetrical, and the growth of the foot was more impaired than the tibia. Hall et al. (1988) reached similar conclusions when they examined 73 children from Liverpool with Perthes' disease, as they found short stature and retarded limb growth, most evident in their small feet compared with unaffected children.

Allometric growth is a term that is applied to the normal differential growth rates in mammals, and the process of allometric growth may start at different times in different organs during early embryonic development. The growth in the embryo shows a cephalocaudal progression in the head and trunk, and a proximodistal development in the limb buds. Burwell et al. (1978) implied that Perthes children may have an abnormality in allometric growth starting in early embryonic life. Wynne-Davies and Gormley (1978), Hall et al. (1988) and Lappin et al. (2003) among others, have reported short stature in Perthes children compared with unaffected children at the time of diagnosis. In paper I, we showed that in Perthes children short stature and disproportional growth is present already at birth.

Molloy and Macmahon (1967) found significantly lower birth weight among 74 white children with Perthes' disease compared with a matched control group, and Lappin et al. (2003) observed an association between low birth weight and Perthes' disease in five sets of twins. We found no association between low birth weight and Perthes' disease (paper I).

Congenital anomalies

Katz (1959), Catterall et al. (1971), Wynne-Davies and Gormley (1978), and Hall et al. (1979) have reported an increased frequency of congenital anomalies in children with Perthes' disease and this was supported by the results in paper I. Our findings agree with the assumption of Catterall et al. (1971) that there is a higher incidence of anomalies in the pelvic region in children who later in life develop Perthes' disease.

In paper I we applied the Sartwell's log-normal model to the ages at onset of Perthes' disease and found that the lognormal distribution of age at onset, combined with short stature and disproportional growth at birth and an increased frequency of congenital anomalies, pointed toward a single agent, genetic or environmental, acting prenatally causing a susceptibility to Perthes' disease later in childhood. Additionally, we found a male:female ratio of 3.3:1, indicating that Perthes' disease could be an y-linked trait . The above indices, combined with the striking similarity of incidences reported in Asian countries origin and the population of Finnmark county, which has a strong element of people with Asian origin (the Saami and the Finns), further strengthen the importance of a genetic agent in the etiology of Perthes' disease.

Radiographic classifications

All three studies (papers II, III, and IV) showed that the classifications and measurements were more

reliable and had a more acceptable inter-observer reliability when assessed by experienced observers which is in accordance with Simmons et al. (1990), but opposed to Podeszwa et al. (2000). In addition, we found that the simpler the classification and the fewer groups it comprised, the better inter-observer reliability was obtained (papers II and IV). This is in accordance with Altmann (1999) who stated that kappa values will be higher when comparing classifications with fewer categories. For routine clinical use, when radiographic assessment is performed by a less experienced observer, we recommend classifications involving few groups (2-group Catterall classification, 3-group Stulberg classification).

Femoral head involvement

Several authors have reported relatively poor inter-observer reliability when the Catterall classification was applied (Christensen et al. 1978, Hardcastle et al. 1980, Ritterbush et al. 1993). Better inter-observer agreement was found with the Salter-Thompson or the lateral pillar classification (Simmons et al. 1990, Herring et al. 1992, Ritterbush et al. 1993, Farsetti et al. 1995, Podeszwa et al. 2000). This is in accordance with our results.

Paper II showed that the lateral pillar classification (kappa 0.56) and the Salter-Thompson classification (kappa 0.54) had a higher level of agreement among the observers than the original Catterall classification (kappa 0.49), but none of the classifications obtained good agreement. Combining Catterall groups 1 and 2 into one group, and groups 3 and 4 into another gave a higher level of agreement than the original 4 group system (kappa 0.55). We found that all classifications of femoral head involvement are adequate in clinical work if the radiographic assessment is performed by experienced examiners (kappa 0.62–0.70). For less experienced examiners, a 2-group classification or the lateral pillar classification seems to be more reliable.

Our work confirmed that of Salter and Thompson (1984), as we found that the subchondral fracture was a relatively rare early sign (23.5% of the hips) in Perthes' disease. Paper III showed that there was 61% concordance between predicted Catterall groups on the basis of the extent of the subchondral fracture and the later Catterall groups at the time of maximal resorption when assessed by an experienced observer (SS). However there was 89% concordance between the predicted Salter-Thompson groups and the later actual involvement according to this 2 group classification. Assessed in the Lauenstein projection alone, we found a nearly complete concordance (95%) between the extent of the subchondral fracture and the later necrosis. This indicates that the necrosis develops directly beneath the subchondral fracture.

Femoral head coverage

Paper II showed that the femoral head coverage (FHC) was a more reliable (ICC 0.91) and accurate measure than the CE-angle (ICC 0.51) to quantify the acetabular covering of the femoral head. The articulo-trochanteric distance (ATD) obtained good agreement (ICC 0.81–0.92) and had low inter-observer differences. As in paper IV, the inter observer reliability was better when radiographs were assessed by experienced observers.

Residual hip joint deformity

Paper IV showed that we obtained good agreement between experienced examiners (weighted kappa 0.65 and an agreement of 71%) when we evaluated the Stulberg classification. The agreement was less (moderate) between the least experienced observer and the two experienced observers, which is in accordance with our findings in papers I and II. Combining Stulberg classes I and II, and classes IV and V, into a simpler 3-group classification, gave better agreement between all observers. The agreement between the two experienced observers improved to 81%.

Agus et al. (2004) and Farsetti et al. (1995) both reported excellent inter-and intra-observer reliability, whereas Neyt et al. (1999) found that the inter-observer variance was marked and they called into question the usefulness and reliability of the Stulberg classification. Herring et al. (2004) found 91% agreement and a weighted kappa of 0.82 when they used a redefined Stulberg classification and found it sufficiently reliable and accurate for routine clinical use. We found that the reliability of the Stulberg classification was acceptable when the radiographic assessment was done by experienced examiners (weighed kappa 0.65). A simpler 3-group classification based on the shape of the femoral head (spherical, ovoid, and flat) gave better

agreement (weighed kappa 0.70) and was therefore recommended for routine clinical use.

Prognostic factors

In paper V we investigated several radiographic prognostic factors on basis of the initial radiographs and the radiographs from the 1- and 3-year follow-up that were submitted to the study group.

The Stulberg classification and our 3-group modification were used as radiographic outcome measures at the 5-year follow-up (paper V). We found a highly significant association ($p = 0.0001$) between the modified 2-group Catterall classification and radiographic outcome according to the 3-group Stulberg classification at the 5-year follow-up. As shown in some previous studies (Herring et al. 1992 and 2004, Ismail and Macnicol 1998, Farsetti et al. 1995), we found significant association ($p = 0.001$) between the lateral pillar classification and radiographic outcome. There was a similar association when the lateral pillar classification was applied 1 year after diagnosis. Herring et al. (2004) reported that the lateral pillar classification was the strongest single predictor of outcome. Our results did not confirm this as the multinomial proportional odds logistic regression analysis showed that the lateral pillar classification was the third strongest predictor after the modified 2-group Catterall classification and age at diagnosis.

Age at diagnosis correlated strongly with outcome in the sense that outcome in children under 6 years of age was markedly better than the outcome in those aged 6 years and older ($p < 0.0001$). It is believed that the younger the child is at onset of the disease, the more time is available to remodel the residual deformity of the femoral head and acetabulum after healing is completed. The ability of the acetabulum to remodel, and thereby conform to the altered shape of the femoral head, seems to diminish after the age of 8 years (Lindström et al. 1979). However, there are contradictory reports regarding what exact age at diagnosis that seems to be the watershed with regard to the long term prognosis. Ippolito et al. (1987) found that patients who had been under 5 years of age at the onset of the disease had better prognosis, and that children over 9 years at onset had worse prognosis. Stulberg et al. (1981), Perpich et al. (1983) and Herring et al. (1992), reported similar results as they found that children over the age of 9 at onset had the worst prognosis. McAndrew and Weinstein (1984) reported that children under the age of 8 at onset had a stable Iowa hip rating during the 47.7 year follow-up period, whereas the rating decreased for patients over that age. Others (Brotherton et al. 1977, Kelly et al. 1980, Ippolito 1987, Mukherjee et al. 1990) have found that recovery is most likely if the child is under 5 or 6 years at onset.

Studies with somewhat different experience have been published. Snyder (1975) found that no less than 32% of patients with age at onset 5 years or younger and Catterall hips 3 or 4 had radiographically poor results at healing. Likewise, Fabry et al. (2003) reported 48% poor results according to a modified Stulberg classification and Schoenecker et al. (1993) reported that 24% of children under 6 years of age with hips in Catterall groups 3 or 4 had poor results. Our study did not support these findings, as the poor results in this group were only 12%, which is in accordance with the 12% poor results reported by Rosenfeld et al. (2007).

Femoral head coverage in patients treated with physiotherapy decreased during the first years of the disease. The mean at the time of diagnosis was 92% (95% CI 90.8–93.2) and decreased with 9% (95% CI 6.7–11.6) to 83% (95% CI 81.7–84.8) after one year ($p < 0.0001$). Three years after diagnosis the FHC decreased by 4% (95% CI 2.0–5.8) to a mean of 79% (95% CI 77.8–80.9), which was significantly less than at one year ($p < 0.0001$). From 3 to 5 years there was a slight increase in mean FHC to 80 % but the difference was not significant ($p = 0.38$). Increasing degrees of femoral head uncovering at the time of diagnosis has been linked to poor long-term prognosis by several authors (Dickens and Menelaus 1978, Mukherjee and Fabry, Gigante et al. 2002). This was not supported by the present results, as the femoral head coverage (FHC) at the time of diagnosis was not associated with the radiographic outcome. However, there was a strong significant association between FHC 1 year after diagnosis and the 5-year outcome, indicating that good femoral head coverage during the course of the disease predisposes to favourable long-term results. This supports the containment concept of Salter (1966).

Table 2. Long-term results of non-operative treatment in Perthes' disease

Author (year)	n	F-up years	Treatment	Radiographic results (%) Good	Fair	Poor	OA	THR %
Brotherton et al. (1977) [a]	87	17	Prolonged recumbency	88	10	2	1	-
Kelly et al. (1980) [a]	80	22	Weight-relieving sling or harness	80	11	2	5	2.5
Ippolito et al. (1987)	61	25	Traction, spica, calliper	-	-	-	28	
Ratliff (1967) [a]	34	30	Immobilisationor no treatment	44	32	24	-	
Perpich et al. (1983)	40	30	Spica	33	23	43	5	7
Danielsson and Hernborg (1965)	35	33	Bed rest/plaster	17	46	37	49	-
Yrjonen et al. (1992)	96	35	Non-containment	-	-	61	49	4
Gower and Johnston (1971)	30	36	Non-surgical (spica, bed rest)	-	-	-	77	8
Stulberg et al. (1981)	88	40	Conservative			-		
McAndrew and Weinstein (1984)	35	48	Non-surgical	14	-	86	50	40
Mose (1977)	19	57	No treatment				>85	-

n is number of patients, F-up is follow-up, OA is osteoarthritis, THR is total hip replacement,.
[a] Grading consists of a combination of radiographic and clinical scores.

In my experience, most hips have good femoral head coverage at the time of diagnosis regardless of femoral head involvement or age at diagnosis. In this respect it is hardly surprising that the femoral head coverage at the time of diagnosis was not associated with outcome. In children treated with physiotherapy we found that the greatest reduction in femoral head coverage was between the time of diagnosis and the 1-year follow-up. This is probably close to the expected development in untreated hips.

We found a significant association between sports activity and walking ability in relation to Stulberg outcome at 5 years, as hips classified as Stulberg groups IV–V had more often limited walking distance ($p < 0.001$) and reduced ability to participate in sports activities ($p = 0.002$). However, longer term follow-up using walking tests, validated activity questionnaires and pain scales is required to better understand the level of association between radiographic outcome following Perthes' disease and reported pain, walking ability, and participation in sporting activities.

Long-term results

Most studies concerning prognostic factors evaluate the ability of specific radiographic signs at diagnosis to predict the radiographic outcome at skeletal maturity. This is not necessarily identical with the long-term prognosis. The ability of the Mose (1977) and Stulberg (1981) classifications to predict occurrence of early osteoarthritis are based on retrospective long-term follow-up studies where patients were included regardless of epiphyseal involvement, age at onset of the disease, age at beginning of treatment and treatment modality, and control groups often were absent.

Several long-term studies of Perthes' disease have been published. Most of these studies suffer from several weaknesses. Different radiological classifications have been used to evaluate clinical and radiological results, without information of inter- or intra-rater reliability. Nevertheless, these studies are at present perhaps the closest we can get to the end point of the disease, and much is to be learned from these studies.

As Table 2 shows, the results are increasingly poor as the follow-up time increases, and follow-up studies beyond 40 years show marked decrease in hip function and the majority of patients have developed osteoarthritis over the age of 50–60 years.

Treatment

Incomplete follow-up probably makes the results of a trial less reliable, and this is exaggerated when there are different drop-out rates between the study groups or when patient characteristics of drop-outs are different from those who complete the follow-up. 5% loss to follow-up probably leads to little bias, whereas greater than 20% loss most likely will reduce the validity of the results considerably (Rudical and Esdaile 1984). In paper V, we obtained a follow-up of 97% 5 years after diagnosis, thus bias due to loss to follow-up is not

likely. This high follow-up rate has been possible partly because only 12.8% of Norwegians move per year, most of them within the same county (Statistics, Norway). Thus the large majority of patients belonged to the same hospital and resided at the same address 5 years after inclusion in the study. In contrast, 17% of Americans move each year and they frequently change physicians (Smith et al. 1998). We experienced some problems in locating certain children due to name changes after their parent's marriage or divorce. We invested much time making requests by mail and phone to the treating orthopaedic surgeons that both radiographs and clinical information were to be submitted to the study group. The remaining missing patients were contacted by phone, and the lacking radiographs were obtained by direct request to the radiology departments at the different hospitals. Thus our follow-up rate (97%) was considerably higher than in other similar studies (Herring et al. 2004, Joseph et al. 2003).

What is a good result?

In paper V we used a modified Stulberg classification as outcome measure 5 years after diagnosis. There are different opinions on what should be regarded as a good radiographic result. Some authors regarded only Stulberg class I and II to be a good result (Thompson et. al 2002, Herring et al. 2004), whereas others considered Stulberg class I, II, and III to be a good result (Mc Andrew and Weinstein 1984, Hall 1981). Herring et al. (2004) considered Stulberg class III to be intermediate, and class IV to be a poor result. Stulberg (1981) stated that severe osteoarthritis developed before the age of 50 years in the class V hips, in contrast to the class III and IV hips, where mild to moderate arthritis developed in late adulthood. Weinstein (1997) stated that class V hips deteriorated in the end of the fourth decade of life, whereas patients with class III and IV hips undergo significant functional deterioration one decade later. In paper III we argued that it was reasonable to consider that class IV and V hips for all practical purposes have quite similar prognosis, as these hips deteriorated functionally when the patients were in their thirties and forties.

Stulberg classes I and II have good outcome, as arthritis does not develop (Stulberg 1981). Ippolito et al. reported that 37% of Stulberg class III hips, and 70% of class IV hips had osteoarthritis at the ages of 30–40 years. Consequently, as Herring et al. (2004), we consider the Stulberg class III to be fair and Stulberg class IV and V to be a poor result.

Outcome of different treatment methods

The treatment of Perthes' disease is controversial, and many treatment methods have been applied over the years. This has been discussed earlier in this thesis and in paper V. Table 3 shows an overview of retrospective studies comparing different treatment methods.

Non-containment treatment

Before the seventies the customary treatment of Perthes' disease was long time recumbency with or without traction. This was probably encouraged by promising results of this kind of treatment reported by several authors such as Eyre-Brook (1936), Helbo (1953), Meyer (1966), Katz (1967) and Ratliff (1967), and on the conception that the femoral head was rendered "soft" after the avascular necrosis. Consequently all treatment involved non-weight bearing of the affected hip to decrease load and prevent femoral head deformity. This led to strict long-term bed rest often in hospital, depriving the children of regular contact with their parents and family, causing social and emotional distress. Complications included muscular atrophy, osteopenia, shortening of the involved extremity, loss of thoracal kyphosis, and urinary caliculi. (Harrison and Menon 1966, Harrison et al. 1969, Curtis et al. 1974, Brotherton and Mc Kibbin 1977, Martinez et al. 1992). Fortunately, long-time recumbency treatment is currently considered as malpractice and abandoned altogether.

Eventually, studies disputing the good outcome of long-term recumbency or other conservative treatment were published. Gower and Johnston (1971) reported on 30 non-surgically (hip spica, bed rest) treated hips with an average of 36 years follow-up. 23 of 30 patients had signs of osteoarthritis, and 8% of the patients had had an arthroplasty. McAndrew and Weinstein (1984) reviewed 35 patients with a follow-up of 48 years. 50% of the patients had disabling OA by the time they had reached their sixth decade of life, which was reported to

Table 3. Results of retrospective studies of various treatment methods in Perthes' disease

Author (year)	n	Treatment	Conclusion
Lloyd-Roberts et al. (1976)	109	Femoral osteotomy / no treatment	Femoral osteotomy indicated Catt 2–4
Marklund, Tillberg (1976)	58	Femoral osteotomy/Thomas splint	Equal results
Brotherton, McKibbin (1977)	102	Recumbency/femoral osteotomy	Recumbency not justified in Catt 1/2, Recumbency in Catt 3/4
Jani, Dick (1980)	83	Orthosis/femoral osteotomy	Immediate osteotomy recommended > 6 years
Laurent, Poussa (1980)	67	Femoral osteotomy/Thomas splint	Osteotomy in Catt 4
Edvardsen et al. (1981)	58	Femoral osteotomy/conservative	Highlights advantages with osteotomy
Cooperman, Stulberg (1984)	248	Crutches/Scottish Rite orthosis/ Newington abduction orthosis/ femoral osteotomy	Osteotomy better than orthosis < 8 years when subluxed
McElwain et al. (1985)	32	Femoral osteotomy/plaster/splints	Femoral osteotomy indicated in severe disease
Evans et al. (1988)	36	Femoral osteotomy/bracing	Equal results, certain advantages with surgery
Poussa et al. (1993)	112	Femoral osteotomy/non-containment	Femoral osteotomy in subluxed hips and Catt 2–4
Wang et al. (1995)	124	Orthosis/non-weight-bearing/ pelvic/ femoral osteotomies	Equal results. Orthosis not recommended
Lahdes-Vasama et al. (1997)	56	Femoral osteotomy/Thomas splint	Ostetomy not necessarily better when limited involvement
Kamegaya et al. (2004)	36	Conservative/femoral osteotomy	Surgical treatment better in severe disease
Aksoy et al. (2004)	51	Brace/non-brace	Similar result, inconclusive

n is number of patients, Catt is Catterall classification

be 10 times that found in the general population in the same age group. Mose (1980) observed 19 patients for an average of 57 years. All patients with irregular femoral heads at healing had OA in their seventh decade of life. Even the hips that were classified as normal and ball shaped in the patients third and fourth decade of life, had slight (33%) to severe (67%) osteoarthritis at an average of 65 years of age. Yrjonen et al. (1992) reviewed 96 patients who had non-containment treatment with an average follow-up of 35 years. 61% had a poor result according to Mose, and 48% had evidence of OA. However, only 4% had a total hip replacement in addition to 13% having symptoms warranting a total hip replacement. Stulberg et al. (1981) followed 88 patients in an average of 40 years who had been treated conservatively, and reported that about 6% of the spherical heads, 60% of the ovoid heads, and 78% of the flat heads at healing had developed osteoarthritis

Although there are no study published that assesses the effect of physiotherapy in the treatment of Perthes' disease, it is my impression that physiotherapy has been used both as sole or adjuvant treatment. Maintaining or increasing the range of motion of the hip and preventing joint contracture could relieve certain parts of the femoral head of constant pressure from the acetabulum, thereby decreasing the risk of deformation. However, physiotherapy is not to be considered as a treatment that contains the femoral head in the acetabulum, and it is in this respect different from the two other methods of treatment considered in this thesis. As stated previously, one of the reasons why we chose physiotherapy to be a treatment option was that it was in our opinion as close to the natural history of the disease as we could get without offering the patient any treatment at all. However, in the patient group with the assumed worst prognosis (above 6 years of age with more than 50% femoral head necrosis), our study showed that 33% of the hips treated with physiotherapy obtained good results (spherical femoral heads). In my opinion, this is probably not due to the treatment given, but rather to the nature of the disease. Further studies are required to reveal the characteristics of this subgroup of patients in order to avoid unnecessary surgery.

Containment treatment

Varying results have been reported with the Scottish Rite orthosis. Curtis et al. (1974) reported 84% good or fair, and 16% poor results, and Herring et al. (2004) also had quite good outcome with 52% of the hips in Stulberg classes I–II, 31% in Stulberg class III, and only 17% poor results in Stulberg class IV–V. We found, however, that patients above 6.0 years at the time of diagnosis with hips with more than 50% femoral head necrosis obtained inferior results, with 18% of the patients in Stulberg classes I–II, 37% in Stulberg class III, and 44% of the patients in Stulberg class IV–V. Thus, our results in this age group with femoral head necrosis more than 50% were worse than those of Martinez et al. (1992) and Meehan et al. (1992) who had 33% and 21% poor Stulberg results, respectively. Price et al. (1988) concluded that patients treated with bracing had a more significant deficit with regard to social and sexual behaviour and academic disability than children who had been treated by surgery. In addition, bracing created a sense of being different and handicapped. Thus, based on the literature and the present study, we recommend that the use of abduction orthosis should be abandoned in the treatment of Perthes' disease.

Several case series have shown favourable outcome after femoral osteotomy in Perthes' disease (Lloyd-Roberts et al. 1976, Hoikka et al. 1986, Coates et al. 1990). Favourable results were confirmed in the present study. In patients above 6.0 years of age and Catterall 3–4, we found that 43% of the hips had good outcome in Stulberg classes I–II and only 11% had poor outcome in Stulberg classes IV–V at the 5 year follow-up. We registered complications in 4 patients. 1 had postoperative infection with staphylococcus aureus that resolved with antibiotics. 3 patients had complications due to surgical failure. In one patient non-intended inward rotation of the femoral shaft occurred, and one patient had too large varisation of the proximal femur postoperatively. In 1 patient the osteotomy dislocated, resulting in too large varisation but the osteotomy healed uneventfully.

Some studies comparing treatment methods show better results of surgery than of other treatment methods, whereas others have reported equal results (Table 3). However, it is difficult to draw firm conclusions from these studies, as they were not prospective, patient numbers were small, and the criteria for inclusion, severity of the disease, age groups treated, and indications for surgery varied considerably.

In addition to the present study, the only prospective multicenter study on the effect of treatment published is that of Herring et al. (2004). They found that children with age over 8 years at diagnosis with hips classified as lateral pillar B or "B/C border" benefited from surgery compared with bracing or range of motion exercises. Our present results are in accordance with these findings because proximal femoral varus osteotomy gave significantly better outcome than those of treatment with the Scottish Rite orthosis or physiotherapy in children more than 6.0 years at the time of diagnosis with hips with more than 50% femoral head necrosis. Thus, we recommend proximal femoral osteotomy in this group which has the worst prognosis without treatment. There was no significant difference in outcome between the orthosis and physiotherapy groups which also supports the findings of Herring et al. (2004).

Comparison between the treatment methods with regard to outcome could not be reliably performed in children below 6 years with more than 50% femoral head necrosis because the worst hips, i.e. those with femoral head coverage below 80%, were treated with femoral osteotomy or orthosis in those hospitals that had chosen these two treatment modalities, whereas the remaining patients (with better femoral head coverage) were treated with physiotherapy. With this reservation, no significant differences between the treatment methods were found ($p = 0.73$). This is in accordance with the experience of Coates et al. (1990) and Rosenfeld et al. (2007).

Statistical analysis comparing treatments could not be reliably performed in children with less than 50% femoral head necrosis as 38 of 45 children were treated with physiotherapy according to our protocol. 5 children were treated with osteotomy and 1 with orthosis due to protocol departure probably because the treating orthopaedic surgeons considered these hips to be in Catterall group 3 rather than group 2.

Future research

Prospective cohort studies are notoriously difficult to carry out due to practical, financial or other restraints. Most surgical randomized trials require long follow-up in order to determine outcome, making their performance both logistically difficult and expensive.

National quality registries have been established to improve health care in several areas in medicine. They are designed to collect information prospectively of all cases of a certain disease and hence provide epidemiological and etiological features of the disease as well as to detect inferior treatment. The Norwegian Hip Arthroplasty Registry started in 1987 after inferior results associated with some hip prosthesis designs had been detected in the early 1980's .The aim was early detection of inferior results caused by implants, cements, or surgical techniques (Engesæter et al. 1992). Of the 104 316 primary total hip arthroplasties performed in Norway from 1987 through 2006, 1 316 (1.3%) was due to either Perthes' disease or slipped capital femoral epiphysis (Norwegian Hip Arthroplasty Registry, report 2007). This information is not sufficiently reliable as the data were collected retrospectively and hence is subject to considerable bias.

A nationwide paediatric hip registry based on a continuous report system is currently under planning in Norway. Hopefully it will provide us with useful information regarding Perthes' disease and other paediatric hip diseases. However, some questions still have to be addressed by properly designed randomized controlled trials.

Long-term follow-up is essential, and the cohort on which this thesis is based on should be re-examined at a later date.

Pelvic osteotomies are not frequently used to treat Perthes' disease in Norway. Only future prospective randomized trials or registry based studies can decide whether this treatment gives a better outcome compared with proximal femoral varus osteotomy.

Technical advances in gene sequencing have enhanced our ability to detect causes of disease, and thus better understand the role of genetic alterations in musculoskeletal disease.

Gregory et al. (1984) found known genetic conditions in over 50% of patients admitted to a paediatric orthopaedic hospital. As pointed out by Dobbs (2007) genetics in orthopaedic surgery will become increasingly important, and in light of recent research (Miyamoto 2007), large scale screening for collagen type II mutations in children with Perthes' disease should be considered.

Conclusions

1) The annual incidence of Perthes' disease in Norway was 9.2 per 100 000 per year in subjects under 15 years of age. There were marked countywise and regional variations in incidence where the lowest incidence was found in the northern region (5.4) and the highest was registered in the central and western part (10.8 and 11.3) (paper I).
2) Children with Perthes' disease were significantly shorter at birth and had increased frequency of congenital anomalies. Our findings pointed toward a single cause acting prenatally, genetic or environmental, in the etiology of Perthes' disease (paper I).
3) All radiographic measurements and classifications of femoral head involvement and residual hip joint deformity were adequate in clinical practice if the assessment was performed by experienced examiners. For less experienced examiners, classifications including fewer groups were more reliable (papers II, III, and IV).
4) The subchondral fracture was a rare (23% of the patients) but useful early sign in Perthes' disease when present as it's extent was in fairly good concordance with the extent of later femoral head involvement (paper III).
5) The strongest predictor of outcome was the extent of femoral head necrosis, followed by the age at diagnosis and the lateral pillar classification (paper V).
6) Proximal femoral varus osteotomy gave significantly better 5-year radiographic outcome in children aged 6 years and older at the time of diagnosis with hips with more than 50% femoral head necrosis compared with physiotherapy and orthosis. The abduction orthosis should be abandoned as treatment method (paper V).

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Abbreviations

AP	anteroposterior
ASD	atrial septal defect
ATD	articulotrochanteric distance
CE-angle	centre-edge angle
CI	confidence interval
FHC	femoral head coverage
ICC	intraclass correlation coefficient
ICD	international classification of injuries and causes of death
n	number(s)
OA	osteoarthritis
OR	odds ratio
OW	Ola Wiig
RCT	randomized controlled trial
SD	standard deviation
SS	Svein Svenningsen
TT	Terje Terjesen
VSD	ventricular septal defect