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Prognostic Significance of Stability in Slipped Upper Femoral Epiphysis: A Systematic Review and Meta-Analysis

Theodoros Tosounidis, MD, Dirk Stengel, MD, PhD, MSc, George Kontakis, MD, Brian Scott, FRCS, Peter Templeton, FRCS, and Peter V. Giannoudis, BSc, MB, MD, EEC (Ortho)

Objective To examine associations of major complications after surgical treatment of slipped upper femoral epiphysis (SUFE) with condition- and treatment-related risk factors.

Study design This systematic review and meta-analysis of observational studies used an electronic literature search of Embase and Medline supplemented by a manual search of bibliographies. The studies enrolled children and adolescents with SUFE, defined stable and unstable disease, and reported at least 3 primary endpoints: avascular necrosis (AVN), chondrolysis, and reoperation. Random-effects meta-regression analysis was performed when possible.

Results The weighted risk for AVN, derived from intercept-only meta-regression, was estimated as 5.3% (95% confidence interval [CI], 3.4%-7.2%). Patients with unstable slips had a 9.4-fold greater risk of developing AVN. Instability proved to be an independent predictor for AVN. The weighted risk of chondrolysis was 0.8% (95% CI, 0.2%-1.4%), associated with unstable slips and osteotomies. The risk of reoperation was estimated at 5.5% (95% CI, 1.7%-9.3%). Loss of fixation was the primary reason for reoperation.

Conclusions Current evidence indicates that unstable slips are at a significantly higher risk for AVN than stable slips, regardless of the attempted surgical approach. Little clinical information is available regarding chondrolysis and reoperation in relation to the stability of the physis. *(J Pediatr 2010;157:674-80)*.

Slipped upper femoral epiphysis (SUFE) is one of the most common orthopedic emergencies in adolescence. Incidence in the United States has been estimated at 11/100 000,[1] with some seasonal variation.[2] Most experts agree that once SUFE is diagnosed, surgical stabilization is required to restore the normal proximal femur anatomy.[3]

Common criteria for classifying SUFE include acuity and radiologic slip severity.[4,5] The concept of stability of the physis, introduced by Loder et al[6] in 1993, changed our understanding of the disease considerably. Differentiating SUFE into stable and unstable cases based on the child's ability to ambulate with or without crutches is straightforward and simple, and might predict the prognosis and the risk of typical complications, such as avascular necrosis of the femoral head (AVN).[7]

It remains unclear to which degree instability (compared with stability) explains the onset of AVN, and what other variables may contribute to the risk of this event. With no clear guidance from the literature regarding the treatment of stable and unstable SUFE, and in the light of the potential complications of surgical treatment, we thoroughly searched and reviewed published articles in which the concept of stability was evidently utilized. The aim of this study was to collect and present the existing data for 3 major complications—AVN, chondrolysis, and reoperation after the surgical treatment of stable and unstable SUFE—and functional outcomes. We set out to provide summary estimates for orthopedic trauma surgeons, pediatric orthopedic surgeons, general practitioners, and pediatricians to better counsel patients and families about the individual prognosis.

Methods

Clinical Question Addressed by This Review

We posed the following question: In patients with slipped upper femoral epiphysis (SUFE), compared with stable slips, does the presence of instability lead to clinically relevant and statistically significant worse outcomes in terms of common complications, such as AVN of the femoral head, chondrolysis, and reoperation?

Literature Search

Two of the authors (T.T. and D.S.) searched the PubMed Medline, Ovid Medline, and Embase databases for January 1993 to June 2009 to retrieve relevant ar-

AVN	Avascular necrosis
BMI	Body mass index
CI	Confidence interval
SUFE	Slipped upper femoral epiphysis

From the Academic Department of Trauma and Orthopaedics, Leeds General Infirmary, University of Leeds, Leeds, UK (T.T., B.S., P.T., P.G.); Center for Clinical Research, Department of Trauma and Orthopaedics, Unfallkrankenhaus Berlin and University of Greifswald, Berlin, Germany (D.S.); Academic Department of Trauma and Orthopaedics, University of Crete, Iraklio, Greece (G.K.)

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ticles. We deliberately refrained from tracing studies published before the introduction of the stability concept in 1993. We manually searched the bibliographies of identified articles, and also used the "related articles" options in PubMed Medline. We restricted our search to studies published in English, French, Spanish, Italian, Greek, and German.

The Medical Subject Headings, equivalent keywords in other databases, and wild card terms (indicted by "*" or "$") were slipped capital femoral epiphys*/$, slipped upper femoral epiphys*/$, stab*/$, unstab*/$, instab*/$, funct*/$, complication*/$, necros*/$, surg*/$, fixation, outcome*/$, function*/$. Keywords were connected by Boolean operators (AND/OR).

Criteria for Eligibility

Studies selected were original articles that fulfilled the following eligibility criteria: (1) more than 10 adolescent patients were included; (2) articles were published in a Roman language; (3) the full text of each article was available; (4) the specific issue of stability (stable/unstable epiphysis), as described by Loder et al,[6] was used in each study to classify the slips; (5) there was a clear relationship of the outcome with the initial stable/unstable classification of the slips in most of the cases in each study; (6) surgical treatment was implemented; (7) complications were declared and related to the preoperative status; and (8) minimum follow-up was 1 year postoperatively, or until closure of the physis.

All articles that did not meet the foregoing criteria were excluded. Particular attention was paid to identifying in which articles the stability of the physis was not implemented either directly or indirectly for classification of slips. No clear demonstration of classification and outcomes/complications constituted an exclusion criterion.

Extraction of Data

Relevant information on publication year, recruitment interval, numbers of patients and hips, sex, age, body mass index (BMI), duration of follow-up, history of trauma, stability (stable or unstable), acuity (acute, acute on chronic, or chronic), severity grading according to Southwick,[8] type of surgical procedure (eg, screw fixation, osteotomy), and number of screws used were carefully extracted. Cases with bilateral hip involvement were included, although prophylactic fixation of the contralateral hip was not evaluated in data analysis. Functional outcomes assessed by a validated score, such as the Harris Hip Score[9,10] or the American Academy of Orthopedic Surgeons hip score.[11] We used information on raw scores and categories (excellent, good, fair, or poor).

We considered AVN, chondrolysis, and reoperation to be major complications. Studies not dealing with any of these major complications were excluded. Pin removal performed on a routine basis was not estimated in the total number of reoperations. Intraoperative complications and minor complications, such as superficial infection, that were managed nonsurgically also were not included.

Statistical Analysis

Information from individual studies was extracted independently by two of the authors (T.T. and D.S.) and entered into an electronic database. In addition to aggregated information presented in texts and tables, we used individual patient data whenever available. According to the underlying distribution, data were expressed as means, medians, and proportions together with their appropriate measures of uncertainty. When ranges were provided, they were approximated by the range/4 rule of thumb (http://math.uprm.edu/wrolke/esma3015/summaries2.htm#4).

A first review of the available studies found that most represented retrospective case series. This level of evidence is inherently biased and limits both statistical pooling and clinical inferences. All reviewers discussed whether the results should be tabulated in a systematic review fashion or aggregated by quantitative methods. A consensus was reached that some quantitative information and trends are more useful for clinicians, researchers, policy makers, and, of course, patients and their relatives.

Consequently, we investigated several analysis strategies. First, we conducted a classic meta-analysis of studies that reported the risk of AVN stratified for slip stability. We computed χ^2 and I^2 statistics of heterogeneity, and assessed publication bias using Egger's regression test. An I^2 value >50 was considered indicated the presence of heterogeneity. Pooled risk ratios were calculated using a random-effects model to obtain a robust estimate of the risk of AVN with stable and unstable disease.

Second, we computed weighted estimates and 95% confidence intervals (CIs) of functional scores and the risk for AVN, chondrolysis, and revision surgery by random-effects meta-regression analysis. In contrast to classic regression, in meta-regression the smallest unit of observation is the individual study, not the individual patient. Random-effects modeling accounts for both within- and between-study variability. We a priori selected publication year, mean age, mean BMI, sex, bilateral disease, stability, acuity, severity, number of screws, and osteotomies as possible predictors of function and adverse events. Variables with $P < .20$ in univariate analysis were entered into a multivariate meta-regression model.

All analyses were conducted in a nonconfirmative fashion, and P values should be interpreted descriptively. Stata 10.0 (StataCorp, College Station, Texas) was used for all analyses.

Results

Literature Search

The initial electronic search yielded 718 articles, 170 of which were potentially eligible based on a scan of the title and the abstract. After obtaining the full text, we found that a total of 29 articles met the inclusion criteria.[6,12-40] The study selection procedure is illustrated in **Figure 1**, and study details are given in **Table I** (available at www.jpeds.com). The vast majority of studies were

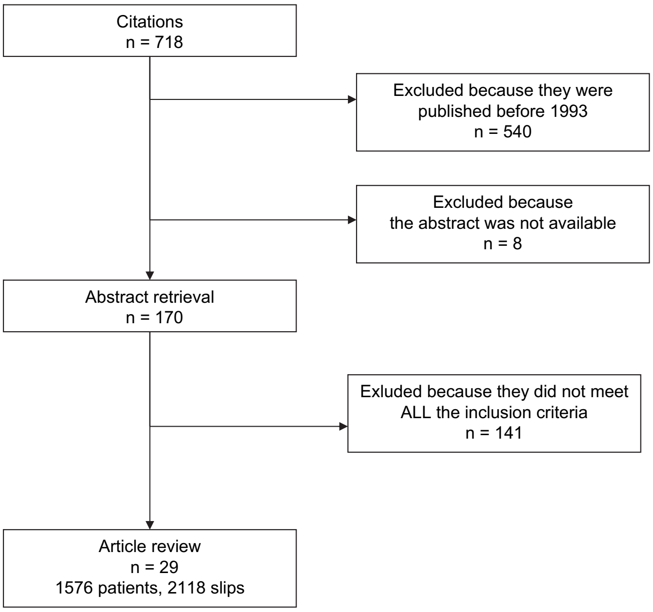

Figure 1. Study selection procedure.

retrospective case series, with subset analyses allowing for some cohort comparisons between stable and unstable disease.

The study included 1576 patients who underwent a total 2118 hip operations. There was a male predominance (1071/1576; 68%). The median age at the time of surgery was 12.7 years (range, 11 to 14 years). A total of 225 slips were bilateral (11%; 95% CI, 9%-12%). One-quarter of all slips were classified as unstable (26% [544/2118]; 95% CI, 24%-28%). Of the 1653 reported cases, 586 (35%; 95% CI, 33%-38%) were acute, 190 (11%; 95% CI, 10-13%) were acute on chronic, and 877 were chronic (53%; 95% CI, 51%-55%). Of 1511 slips, 639 (42%; 95% CI, 40-45%) were classified as mild, 407 (27%; 95% CI, 25%-29%) were moderate, and 465 (31%; 95% CI, 28%-33%) were severe. Two hundred forty of 1896 slips (13%; 95% CI, 11%-14%) were preceded by a traumatic event. Single screw fixation was the most common surgical treatment (65% [1284/1963]; 95% CI, 63%-68%). More than one screw was used in 103 cases (8%; 95% CI, 7%-10). Slips were fixed by Knowles and other pins 209 times (16%; 95% CI, 14%-18%) and by K-wires 99 times (8%; 95% CI 6%-9%). Intertrochanteric or cuneiform osteotomies were performed in 171 of 2027 hips (8%; 95% CI, 7%-10).[18,20,24-26,28,29,33,34] Reduction was attempted or occurred unintentionally in 188 of 838 slips (22%; 95% CI, 20-25%).[17,19,20,28,30,32,38,41,42]

Other baseline and treatment variables (eg, BMI, duration of prodromal symptoms, interval between symptom onset and hospital admission, lag time to surgery, preoperative traction) were reported infrequently. Patients were followed-up for a median of 36 months (range, 10-100 months).

Outcomes

AVN occurred after 127/2118 surgical procedures for SUFE (Table II). The crude risk, derived from raw numbers, was 6.0 (95% CI, 5.0-7.1%). The weighted risk, derived from intercept-only meta-regression, was estimated as 5.3% (95% CI, 3.4%-7.2%).

A total of 14 studies allowed for estimating the weighted risk ratio between stable and unstable cases.[6,12,15,18,19,27,29,31-34,38,39,43] There was significant heterogeneity across studies (I^2 = 68%; P = .001), but no evidence of publication bias (intercept, 80.8; P = .15). Patients with unstable slips had a 9.4-fold greater relative risk of developing AVN compared with patients with stable slips (Figure 2).

After multivariable adjustment, unstable slips and female sex remained independent predictors of AVN (Table III). In contrast to AVN, chondrolysis was a rare complication. The crude risk was 32/1808 (1.8%; 95% CI, 1.2%-2.5%), and the weighted estimate was 0.8% (95% CI, 0.2%-1.4%). Table II presents the incidence of chondrolysis reported by individual studies. In stable cases, chondrolysis occurred in 1 hip treated with single screw fixation,[15] in 4 hips treated with intertrochanteric osteotomy,[26,29,34] in 8 hips treated with cuneiform osteotomy,[24] and in 2 hips treated with epiphysiodesis.[16] In unstable slips, chondrolysis occurred in 1 slip treated with single screw fixation,[38] in 4 slips treated with double-screw fixation,[27,40] and in 2 slips treated with epiphysiodesis.[14,16]

Osteotomy has been previously recognized as a predisposing factor to chondrolysis.[24,26,29,34,44] In only 3 slips was chondrolysis resulting from previous trauma elicited from the patient's history.[40] Material penetration during the operation was reported in only 2 cases that developed chondrolysis.[6,38] Multivariate meta-regression identified higher numbers of unstable slips and osteotomies as potential independent predictors of chondrolysis (Table III).

The incidence of reoperation was 57/1085 (5.2%; 95% CI, 4.0-6.8%), with the weighted estimate indicating a revision risk of 5.5% (95% CI, 1.7%-9.3%). The distribution of reoperation rates across studies is summarized in Table II. Thirty-eight reoperations were related to inadequate fixation or loss of reduction.[6,15,18,24,27,34,35,41] Eighteen reoperations were performed to improve decreased function.[14,16,26,29,30,41] AVN was the reason for 10 reoperations,[6,20,27,40,43] whereas fracture and infection accounted for 3 reoperations and 1 reoperation, respectively.[14,16,30] In most cases, the time interval between the initial and secondary operation could not be estimated. Meta-regression failed to reveal clear predictors of reoperation (Table II).

Ten studies reported outcomes in categories from excellent to poor, with 460 of 622 patients (73.9%; 95% CI, 70.3%-77.4%) achieving excellent or good hip function.[12,14,20,22-24,29,35,41,42] The predicted estimate was 79.4% (95% CI, 72.3%-86.5%). Only 5 studies allowed for modeling 100-point functional scales, with weighted overall mean scores of 93.9 (95% CI, 87.8-100.0).[20,22,23,25,45] Of note, the likelihood of excellent and good functional outcomes did not

Table II. Results of univariate and multivariate meta-regression analysis of variables associated with adverse events

	AVN			Chondrolysis			Revisions		
Incidence	5.3%	3.4%	7.2%	0.8%	0.2%	1.4%	5.5%	1.7%	9.3%
Univariate	*β*	95% CI	*P*	*β*	95% CI	*P*	*β*	95% CI	*P*
Publication year	0.00	-0.01 to 0.00	.591	0.00	0.00 to 0.00	.484	0.00	-0.02 to 0.00	.257
Follow-up	0.00	0.00 to 0.00	.383	0.00	0.00 to 0.00	.507	0.00	0.00 to 0.00	.759
Mean age	0.01	-0.02 to 0.04	.511	0.01	0.00 to 0.02	.148	0.01	-0.04 to 0.06	.662
Male patients	-0.19	-0.43 to 0.04	.102	-0.02	-0.15 to 0.10	.700	0.05	-0.42 to 0.51	.835
Bilateral slips	-0.05	-0.17 to 0.06	.367	-0.02	-0.05 to 0.01	.197	-0.06	-0.29 to 0.18	.610
Unstable hips	0.07	0.02 to 0.13	.008	0.03	0.00 to 0.06	.047	0.05	-0.05 to 0.15	.325
Acute cases	0.06	-0.01 to 0.13	.114	0.03	0.00 to 0.06	.047	-0.01	-0.17 to 0.14	.852
Severe grades	0.02	-0.04 to 0.07	.605	0.02	-0.02 to 0.05	.306	-0.06	-0.21 to 0.10	.458
Single screws	-0.02	-0.07 to 0.02	.334	-0.02	-0.04 to 0.00	.016	-0.05	-0.12 to 0.02	.131
Osteotomies	0.04	-0.05 to 0.12	.369	0.07	0.02 to 0.12	.011	-0.01	-0.12 to 0.10	.908
Multivariate									
Unstable hips	0.07	0.03 to 0.13	.003	0.03	0.00 to 0.06	.032			
Male patients	-0.22	-0.42 to 0.02	.033	0.07	0.02 to 0.12	.008			
Constant	0.17	0.04 to 0.29		0.00	-0.01 to 0.01				

decrease with increasing proportions of unstable slips included in individual studies ($\beta = 0.19$; 95% CI, -0.01 to 0.38).

Discussion

Although the typical patient with a SUFE is an obese male adolescent age 9-16 years,[46,47] the condition often poses a diagnostic dilemma.. Hip or groin pain in a limping child directs the physician's attention to the affected hip. Referred pain to the ipsilateral knee or thigh and external rotation of the limb are clinical signs pointing to the correct diagnosis.[48] The multifactorial etiology (the bilaterality which manifests either at presentation[47] or later[47,49-51]) the risk of progression if left untreated, and the natural history of the disease leading to degenerative joint disease (which has been questioned) underscore the need for diagnostic vigilance and prompt management.[52-56] There is evidence that physican-related delays in diagnosis may average 3-4 months.[57]

The stability concept of classification of SUFE was originally proposed by Loder et al[6] in an effort to predict reliably potential complications, especially AVN, after the treatment of this common adolescent disorder. The idea of instability has been conceptualized as acuity of the slip up to that time, and many authors have commented on this topic.[58,59] Up to 1993, the clinical classification of SUFE was based primarily on the duration of the patient's symptoms and was accordingly described as acute, acute-on-chronic, or chronic.[3,4,60,61]

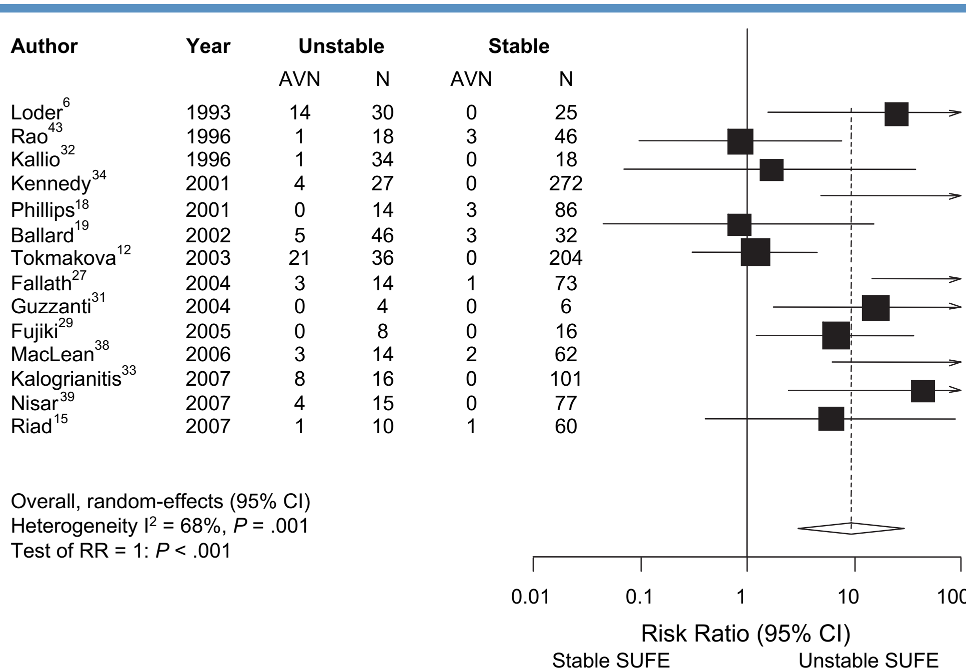

Figure 2. Random-effects meta-analysis of the risk of AVN in stable and unstable slips.

Table III. Individually reported rates of AVN, chondrolysis, and reoperation

			AVN		Chondrolysis		Reoperation	
Author	Year	Hips	n	Incidence (95% CI)	n	Incidence (95% CI)	n	Incidence (95% CI)
Ballard and Cosgrove[19]	2002	110	8	7% (3%-14%)	0	0 (0-3%)		
Biring et al[20]	2006	25	3	12% (3%-31%)	4	16% (5%-36%)	1	4% (0-20)
Carney et al[21]	2003	46	0	0 (0-8%)	0	0 (0-8%)	0	0 (0-8%)
DeLullo et al[23]	2006	38	6	16% (6%-31%)				
DeRosa et al[24]	1996	27	4	15% (4%-34%)	8	30 (14%-50)	3	11% (2%-29%)
Diab et al[25*]	2006	10	0	0 (0-31%)	0	0 (0-31%)		
Diab et al[25†]	2006	10	0	0 (0-31%)	0	0 (0-31%)		
Diab et al[26]	2004	26	3	12% (2%-30)	1	4% (0-20)	2	8% (1%-25%)
Fallath and Letts[27‡]	2004	92	1	1% (0-6%)	0	0 (0-4%)	2	2% (0-8%)
Fallath and Letts[27§]	2004	14	3	21% (5%-51%)	1	7% (0-34%)	2	14% (2%-43%)
Frangnière et al[28]	2001	64	3	5% (1%-13%)				
Fujiki et al[29]	2005	24	0	0 (0-14%)	2	8% (1%-27%)	0	0 (0-14%)
Gordon et al[30]	2002	16	2	13% (2%-38%)	0	0 (0-21%)	3	19% (4%-46%)
Guzzanti et al[31]	2004	10	0	0 (0-31%)	0	0 (0-31%)	0	0 (0-31%)
Kalogrianitis et al[33]	2007	117	8	7% (3%-13%)				
Kennedy et al[34‡]	2001	272	0	0 (0-1%)	1	0 (0-2%)	0	0 (0-1%)
Kennedy et al[34§]	2001	27	4	15% (4%-34%)	0	0 (0-13%)	1	4% (0-19%)
Kumm et al[35]	2001	29	0	0 (0-12%)	0	0 (0-12%)	11	38% (21%-58%)
Lee and Chapman[36]	2003	15	0	0 (0-22%)	0	0 (0-22%)	0	0 (0-22%)
Loder et al[6‡]	1993	25	0	0 (0-14%)	1	4% (0-20)		
Loder et al[6§]	1993	30	14	47% (28%-66%)	1	3% (0-17%)		
MacLean and Reddy[38]	2006	76	5	7% (2%-15%)	1	1% (0-7%)		
Nisar et al[39]	2007	92	4	4% (1%-11%)	0	0 (0-4%)	0	0 (0-4%)
Parsch et al[40]	2009	64	3	5% (1%-13%)	3	5% (1%-13%)	2	3% (0-11%)
Peterson et al[17]	1997	91	13	14% (8%-3%)				
Philips et al[18]	2001	100	4	4% (1%-10)	2	2% (0-7%)	3	3% (1%-9%)
Rao et al[43]	1996	64	4	6% (2%-15%)	3	5% (1%-13%)	8	13% (6%-23%)
Riad et al[15]	2007	70	2	3% (0-10)	1	1% (0-8%)	3	4% (1%-12%)
Schmidt et al[14]	1996	40	1	3% (0-13%)	1	3% (0-13%)	4	10 (3%-24%)
Seller et al[41]	2006	32	2	6% (1%-21%)	0	0 (0-11%)	12	38% (21%-56%)
Tokmakova et al[12]	2003	240	21	9% (5%-13%)	0	0 (0-2%)		
Lim et al[42]	2007	38	2	5% (1%-18%)	0	0 (0-9%)		
Castaneda et al[22]	2009	129	6	5% (2%-10)	1	1% (0-4%)		
Kallio et al[32]	1995	55	1	2% (0-10)	1	2% (0-10)		

*No osteotomy.
†Osteotomy.
‡All stable slips.
§All unstable slips.

According to Loder et al,[6] stability is a clinical diagnosis indicating that the child is able to walk, whereas in an unstable slip, the child is unable to walk with or without crutches.[6] In adolescence, femoral head displacement through the physis may compromise the tenuous blood supply of the vessels along the femoral neck. The paucity of traversing vessels at the physis level, and the fact that the main vessels that supply the adolescent femoral head, are periosteal further increase the risk of avascular necrosis.[62] In essence, instability denotes increased mobility at the level of the physis, which potentially compromises the precarious blood supply to the femoral head through a tear or pressure in the periosteal sleeve.

AVN was recorded as the most common complication in our review. Most cases occurred in unstable slips, and a statistically significant difference was evident between the unstable and stable slips that developed AVN. Early reduction has been implicated as a causative agent for AVN by many authors.[17,18,44,58,60] It was not possible to extract specific information regarding the relation of stability and reduction of the slip and the development of AVN. Similarly, no useful information concerning the timing and the magnitude of reduction could be drawn. One of the many concerns surrounding the potential risk of AVN is its relationship to the treatment method. Our review found little comparative information between the treatment of the slip and subsequent AVN. Records about specific treatment were available from 111 slips. We traced 22 (19.8%) cases of AVN in slips treated with osteotomy (intertrochanteric or cuneiform) or epiphysiodesis, 86 (74.5%) cases in slips treated with 1 screw/2 screws or pin/wire fixation, and in 3 (2.7%) cases in slips treated with a spica cast. Evacuation or aspiration of hematoma has been proposed in cases of unstable slip treatment.[3] We compiled no data regarding evacuation of intracapsular hematoma. Although SUFE is in essence a Salter type I fracture (epiphysiolishesis), the incidence of previous injury in children with an unstable acute slip seems to be underreported; only 5 studies commented on a traumatic event in slips that developed AVN.[12,19,33,39,40]

Our review found a low overall incidence of chondrolysis. Joint penetration and an autoimmune reaction are considered causative factors in chondrolysis.[63-67] Penetration from fixation material was described in only 2 unstable cases.[6,38] Istability and osteotomy possibly contributed to the development of chondrolysis.

Secondary surgery is a relatively common complication. A recent analysis reported a 34% rate of inplant removal in SUFE.[68] Routine extraction of hardware was reported in 84 slips in 3 studies,[27,35,41] but these were not calculated in the total number of patients who underwent secondary surgery for a complication. No statistically significant difference in the rate of reoperation was found between stable and unstable slips. The risk of progressive SUFE persists as long as the physis remains open.[69,70] In this review, loss of fixation was the primary reason for reoperation. AVN was the third most common reason for reoperation, confirming its status as one of the most devastating complications of SUFE.[52,71]

The present study has some limitations. The classification of SUFE as stable or unstable narrowed the total number of studies and patients that were evaluated. Consequently, the results (incidence and potential prognosis of complications) can be applied only when this classification scheme is used. Most of the studies identified through our literature search were retrospective case series. We felt that the quality and quantity of information that could be gathered by contacting the corresponding authors did not justify the extra effort, given the lack of publication bias, the long intervals of patient recruitment, and publication dates back to 1993.

Because of the inherent bias of the original studies, our analysis was limited to descriptive statistics, which provide rough estimates of results. In addition, variable outcome measures limited our ability to compare results among studies. Nonetheless, we attempted to minimize selection bias through predetermined inclusion and exclusion criteria. We believe that the results of the present review set the benchmark of possible major complications of the surgical treatment of SUFE. All of the available information in relation to the stability of physis, surgical treatment, and complications is provided; thus, this represents the current best possible summary of potential complications and provides a measure against which treatment and future studies should be compared. Adoption of a standardized preoperative assessment approach considering the child's ability to walk and history of previous traumatic event, standardized postoperative functional and quality of life evaluations, clear description of all outcomes, and, most importantly, a standardized treatment protocol in a multicenter trial will provide a better understanding of the true incidence of major complications after the treatment of stable and unstable slipped upper femoral epiphysis. ■

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Reprint requests: Peter V. Giannoudis, BSc, MB, MD, FRCS, Academic Department of Trauma and Orthopaedics, A Floor, Clarendon Wing, Leeds General Infirmary, Great George Street, Leeds LS1 3EX, UK. E-mail: pgiannoudi@aol.com.

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Table I. Study profile: Baseline demographic data

							Hips		Acuity			Severity			Screws					
Author	Year	Patients	Mean age, years	Males	Mean follow-up, months	Trauma	Stable	Unstable	Acute	Acute on chronic	Chronic	Mild	Moderate	Severe	Single	≥2	Pins	K-wires	Osteotomy	Epiphyseodesis
Ballard and Cosgrove[19]	2002	78	13.2	50	30	18	64	46	49	0	61	80	22	8	109	1	0	0	0	0
Biring et al[20]	2006	24	13.8	15	99	0	2	23	0	25	0	0	0	25	0	0	0	0	25	0
Carney et al[21]	2003	37	12.3	28	24	0	46	0							46	0	0	0	0	0
Castaneda et al[22]	2009	105		62	66		129	0				0	0	129	129	0	0	0	0	0
DeLullo et al[23]	2006	29	13.9	13	91	0	35	3				22	14	1	38	0	0	0	0	0
DeRosa et al[24]	1996	23	13.6	15	10	0	27	0	0	0	27	0	0	27	0	0	0	0	27	0
Diab et al[25]	2006	10	13.0	5	82	0	10	0	0	0	10	0	0	10	10	0	0	0	0	0
		10	13.9	5	96	0	10	0	0	0	10	0	0	10	10	0	0	0	10	0
Diab et al[26]	2004	25	12.6	12	64	0	26	0	0	0	26	0	0	26	0	0	0	0	26	0
Fallath and Letts[27]	2004	73	12.4	49	33	11	92	0	14	4	70				58	29	3	0	0	0
		14	12.8	7	35	11	0	14	7	7	0				10	1	3	0	0	0
Frangnière et al[28]	2001	49	12.7	26	36	3	55	9	18	12	34	25	27	12				0	11	0
Fujiki et al[29]	2005	24	13.0	10	62	0	16	8	0	18	6	0	0	24	0	0	0	0	24	0
Gordon et al[30]	2002	16	11.1	8	27	0	0	16	16	0	0	2	8	6	0	16	0	0	0	0
Guzzanti et al[31]	2004	10	11.5	9	44	0	6	4				6	4	0	10	0	0	0	0	0
Kallio et al[32]	1995	45	13.3	34			18	34	12	8	32				23	0	32	0	0	0
Kalogrianitis et al[33]	2007	82	12.5	43	18	10	101	16	26	0	56	62	9	11	117	0	0	0	2	0
Kennedy et al[34]	2001		11.7	92	24	0	272	0			225				251	0	0	0	17	4
			11.3	10	24	0	0	27	10	17	0	3	5	19	7	19	0	0	0	1
Kumm et al[35]	2001	25	12.8	17	84	0	26	3	3	0	25	29	0	0	26	0	0	3	0	0
Lee and Chapman[36]	2003	13	10.5	9	12	0	15	0							15	0	0	0	0	0
Lim et al[42]	2007	30	11.0	22	34		24	14	8	16	14	27	10	1	36	1	1	0	0	0
Loder et al[6]	1993	25	13.0	13	36	6	25	0	21	4	0	12	7	6	18	7	0	0	0	0
		30	12.0	14	36	27	0	30	17	13	0	2	9	19	7	23	0	0	0	0
MacLean and Reddy[38]	2006	60	12.5	42		9	62	14	18	20	38	43	25	8	75	1	0	0	0	0
Nisar et al[39]	2007	73	11.9	38	33	14	77	15	16	43	30	53	34	5	87	5	0	0	0	0
Parsch et al[40]	2009	64	12.1	37	59	63	0	64	64	0	0	20	24	20	0	0	0	64	0	0
Peterson et al[17]	1997	87	13.0	60		0	0	91	91	0	0	5	67	19						46
Phillips et al[18]	2001	100	13.0	69		0	86	14	100	0	0	37	27	36	2	0	66	0	29	0
Rao et al[43]	1996	43	12.4	25	35	0	46	18				28	19	10	0	0	0	0	0	64
Riad et al[15]	2007	70	13.0	45		0	60	10							67	0	3	0	0	0
Schmidt et al[14]	1996	33	13.0	20	24	0	34	6	7	3	30	31	9	0	0	0	0	0	0	40
Seller et al[41]	2006	29	12.5	19	42	0	3	29	32	0	0	19	7	6	0	0	0	32	0	0
Tokmakova et al[12]	2003	240	12.8	148	54	68	204	36	57	0	183	133	80	27	133	0	101	0	0	0