Original Clinical Article

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The incidence of avascular necrosis following a cohort of treated developmental dysplasia of the hip in a single tertiary centre

Rahim Nawaz Hussain[1]
Darius Rad[2]
William John Watkins[3]
Clare Carpenter[2]

Abstract

Purpose Avascular necrosis (AVN) may occur following treatment for developmental dysplasia of the hip (DDH). The primary aim of this study was to identify the incidence of AVN in a cohort of patients treated for DDH. Secondary aims were to classify AVN using available classification systems, analyze the correlation between the systems and investigate their relationship with the age at diagnosis of DDH.

Methods An 11-year retrospective study was carried out at a single tertiary centre, using data from the clinical portal (patient records database) and IMPAX (system used to store plain radiographic images). Clinical details (patient demographics and outcomes) and plain radiographic images were used to identify cases of DDH and categorize cases of AVN using available classification systems: Tonnis and Kuhlmann, Kalamchi and McEwen, Bucholz and Ogden and Salter. Severin was used to assess final clinical outcome.

Results In total, 405 (522 hips) cases of DDH were identified, of which 213 resolved without treatment, 93 were treated conservatively and 99 surgically. Only treated cases were included in the analysis (n = 192). AVN (45/99; 45.5%) was found to occur only postoperatively. A positive correlation was present between age at presentation and severity of AVN as classified according to Salter's criteria (chi-squared p value < 0.01).

Conclusion AVN incidence was 23.4% (45/192) and only occurred in surgically treated patients. Older age at diagnosis was associated with a higher incidence of AVN, as defined according to Salter's criteria. The classification systems appeared to show no correlation amongst each other (p-value < 0.01).

[1] University Hospital of Wales, Cardiff, UK
[2] Children's Hospital for Wales, University Hospital of Wales, Cardiff, UK
[3] Cardiff University, Cardiff, UK

Correspondence should be sent to: Dr. Rahim Nawaz Hussain, Worcestershire Royal Hospital, Charles Hastings Way, Worcester, WR5 1DD, United Kingdom.
E-mail: rahimhussain13@yahoo.com

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Keywords: avascular necrosis; developmental dysplasia of the hip; Pavlik Harness; paediatric orthopaedics.

Introduction

True incidence of avascular necrosis (AVN) is variable within the literature. Previously, there has been an association reported between age at treatment of developmental dysplasia of the hip (DDH) and subsequent development of AVN,[1] with some studies suggesting an older age at treatment is more likely to lead to AVN, which may be because these patients tend to require more invasive treatment.[2,3] Historically, the rate of AVN has ranged between 4% and 60%, but a more recent systematic review concluded that 10% went on to develop significant AVN at mid-term postoperative follow-up.[4] Previous studies have been limited to small sample sizes and the use of differing classification systems. Pavlik harness has been reported as resulting in a low AVN rate in the literature, with some studies reporting no AVN in cases treated with Pavlik alone.[5,6]

All the available classification systems were used in this study to classify the cases of AVN and severin criteria was used to assess the final clinical outcome.[10] Statistical correlation between these systems was also assessed.

Salter's criteria[7] can be used to diagnose AVN, although it is limited only to cases where 'complete' AVN has occurred. In cases where there is fragmentation or irregular ossification of the femoral head it may not be as useful.[1] In such cases, other classification systems are available, such as Bucholz and Ogden, Kalamchi and MacEwen, Tonnis and Kuhlmann and Severin.[8-10] Nonetheless, these have been criticized for having low levels of interobserver and intraobserver reliability and also a degree of ambiguity which makes it difficult to use in clinical situations.[8,9] Severin was used as it is regarded as one of the most reliable, with low inter observer variability.[10]

This study aimed to qualify the incidence of AVN in a consecutive cohort of patients treated surgically and non-surgically for DDH over an 11-year period in a single tertiary centre.

Materials and methods

This was a retrospective cohort study which analyzed data collected between 1 February 2007 and 30 November 2017. The institution clinical portal was used to obtain clinical information (age at referral, sex, side affected, Graf type (where applicable), treatments received), clinical outcomes and complications for cases which were referred to a tertiary centre. Radiographic images were obtain using the IMPAX (Mortsel, Belgium; (DRAgfa picture archiving and communication system-proprietary software for use at medical facilities using a digital radiology imaging system) and analyzed by a post-Certification of Completion of Training Senior Paediatric Orthopaedic fellow (DR). Both databases were used to confirm the diagnosis of DDH, classify using the known systems and to analyze final clinical outcome using Severin.

Cases of AVN were classified using the available classification systems and the proportions of AVN in each group were calculated. A large series of follow-up radiographs were available and thus correlation between the classification systems or between other parameters could be identified if present. This is consistent with Tsukagoshi et al[11] who looked at correlation between Salter and Kalamchi. Subgroup analysis determined whether the rates of AVN were affected by the age of the individual at initial presentation, the severity of hip dysplasia (Graf grading (if applicable)) and treatment modality (i.e. Pavlik, closed *versus* open reduction (OR) *versus* pelvic osteotomy (PO)/femoral osteotomy (FO). Successful treatment was defined as one which did not lead to development of AVN, as this was the main aim of this study.

Data was classified into three groups according to the age at initial presentation. Group 1 included individuals less than three months, as this is the period of highest remodelling potential of the acetabulum, as suggested by Graf's Reifungskurve.[12] Group 2 included individuals aged three months up to, but not including, 18 months. Group 3 included individuals aged 18 months and older.

This age (18 months and older) has been the historical age at presentation/treatment variable for DDH as it guided management options such as the decision to carry out closed *versus* open reduction or the addition of osteotomy procedures. For the purpose of establishing categories of age at presentation *versus* treatment modality we decided to continue using this age model. However, perhaps this will need to be redefined or looked at from a broader perspective.[13,14]

Patients who presented at 12 weeks or less were classified as an early presentation; post-12 weeks patients were classified as late. This was similar to the criteria used by Senaran et al.[15] Infants below the age of six months were defined as having DDH according to the sonographic method described by Graf.[12] Infants above six months underwent a plain anteroposterior radiograph and evaluated as per Tonnis.[8]

The presence of AVN was assessed by identifying radiographic images taken at six-monthly intervals after treatment. Severity was categorized using the Tonnis and Kuhlman, Kalamchi and McEwen, Bucholz and Ogden and Salter classification systems. The Severin classification system was used to grade the final clinical outcome of the cases.

Age at diagnosis of DDH was defined as the date DDH was detected on ultrasound scan (where applicable) or plain radiograph. The subsequent age at diagnosis of AVN was obtained by calculating the age of the individual one year after their final procedure to allow classification according to Salter's criteria. Non-surgical treatment was defined as treatment with more conservative measures (double nappies, ossur brace, pavlik harness). Surgical treatment was defined as closed or open reduction with or without additional procedures, where applicable.

Inclusion/exclusion criteria

Patients with a confirmed diagnosis of DDH by clinical examination in conjunction with either an ultrasound scan or plain radiographs (infants aged over six months) were included in the study. Patients with complete clinical data regarding their treatment, clinical outcomes and complications were included. Only individuals who underwent treatment (whether surgical or non-surgical) were included in the statistical analysis. We excluded patients with no diagnosis of DDH, or who had an associated neuromuscular disorder.

Statistical analysis

This was performed using the statistics package IBM SPSS (Armonk, NY, USA) Statistics for Windows, Version 20.0. Data was expressed as ordinal categorical variables. Cross tabulation with chi-squared analysis was performed to evaluate the risk factors for AVN. Non-parametric Spearman's rho correlation tests were also used for subgroup analyses. The level of significance was set at $p < 0.05$. A p-value $0.05 < p < 0.1$ is regarded as near significant.

Results

In all, 1816 patients were initially screened for DDH, of which 1411 were discounted due to not meeting the inclusion criteria. A further 213 cases were excluded as they did not receive any intervention and self-resolved.

In total, 192 patients (247 hips) were included in this study (158 female and 34 male). The number of patients in each group and the demographics of the cohort are summaried in Tables 1 and 2.

Group 1

A total of 102 cases were present in this group. They were treated with double nappies, ossur brace, Pavlik harness, closed or open reduction. Figure 1 shows a summary of the cases treated in this group.

Six AVN cases were identified in group 1, of which three had closed reduction and three open reduction.

Group 2

A total of 54 patients received treatment in this group. This included ossur brace, Pavlik harness, closed reduction, closed reduction with additional procedures, open reduction and open reduction with additional procedures.

Additional procedures included: an adductor tenotomy in three children who underwent a closed reduction and a delayed pelvic and femoral osteotomy on the left side of one child whose right side resolved with closed reduction alone. Figure 2 diagrammatically summarizes the cases treated in group 2 along with the treatment modalities

Cases of AVN in group 2 and the treatments received by these cases are summarized in Table 3.

Group 3

A total of 36 patients were identified. Figure 3 summarizes the treatments received by this group diagrammatically.

Table 1 Summary of groups 1, 2 and 3

	Group 1	Group 2	Group 3
Patients	102	54	36
Hips	146	63	38
Side affected			
Left	33	27	21
Right	25	18	14
Bilateral	44	9	2
Male patients	23	6	5
Female patients	79	48	31
Mean age, wks (range)	5 (2.9)	28 (18.7)	122 (17.8)
Median age, wks (range)	5 (-1 to 11)	18 (12 to 69)	93 (73 to 354)

Table 2 Demographics of the cohort

Demographic	
Patients (hips)	192 (247)
Male:female	1:4.6
Mean age,* wks (range)	34 (54)
Median age,* wks (range)	10.5
Age range, wks (corrected for gestation)	-1 to 354
Side affected	
Left	80
Right	57
Bilateral	55

*corrected for gestation

Cases of AVN and the treatments received by each individual are summarized in Table 4.

Cases of AVN

All incidence of AVN occurred with cases treated under general anaesthesia (open or closed reduction +/- additional procedures). A total of 23.4% (45/192) patients developed AVN.

Three cases were in infants diagnosed with bilateral DDH, but only the hip which was affected by AVN was included in the analysis. In total, 31 cases had AVN on the left hip and 14 on the right.

Table 5 summarizes the cases of AVN into different age groups. The mean age at presentation of the DDH cases, later diagnosed with AVN, was 81 weeks (-1 to 354; sd 74.7).

Table 6 summarizes the number of cases of AVN in the different classification systems, including the Severin classification for final clinical outcome.

The supplementary material summarizes the treatment received by these individuals, the age at presentation and the length of follow-up.

Of those who underwent a successful closed reduction 28% (14/50) had signs of AVN. This included individuals with a simultaneous adductor tenotomy (n = 2) and a delayed pelvic osteotomy (n = 1) and combined pelvic and femoral osteotomy (n = 1).

The highest incidence of AVN was within the subgroup that underwent an open reduction (62%; n = 31/50). This group included individuals with an additional pelvic osteotomy (n = 11) or combined pelvic and femoral osteotomy (n = 9).

AVN severity: classification and correlation with Severin

A significant difference in age distributions was found across all Salter's criteria (chi-squared $p < 0.01$), but no such correlation was noted in the other classification systems (Table 5).

The classification systems appear to show a statistically significant correlation among one another: Kalamchi *versus* Bucholz and Ogden, Tonnis and Kuhlmann and Severin; Bucholz and Ogden *versus* Tonnis and Kuhlmann and Severin; Tonnis and Kuhlmann *versus* Severin; age at presentation *versus* index procedure (Table 7).

Salter has a significant relationship with age at presentation ($p < 0.01$).

Furthermore, Salter's criteria suggested a near significant relationship with Severin's ($p < 0.1$)

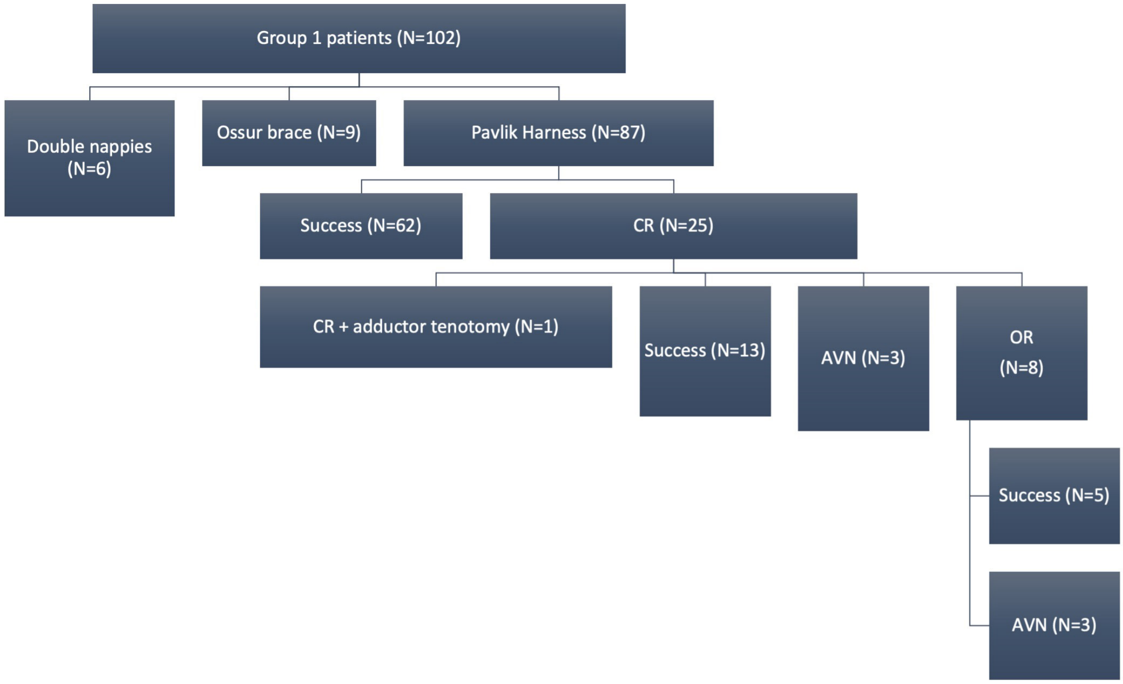

Fig. 1 Summary of cases in group 1. Total patients (hips) = 102 (146) (CR, closed reduction; AVN, avascular necrosis; OR, open reduction).

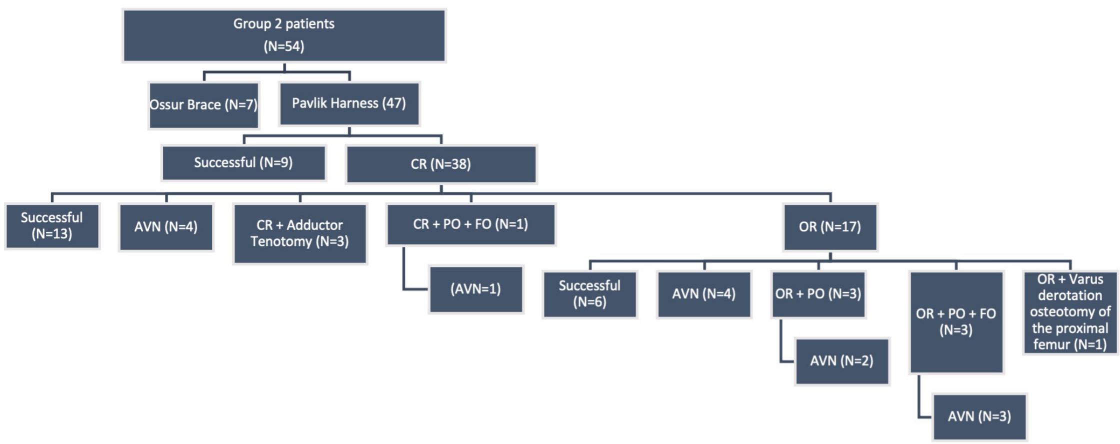

Fig. 2 Summary of cases in group 2. Total patients (hips) = 54 (63) (CR, closed reduction; AVN, avascular necrosis; PO, pelvic osteotomy; FO, femoral osteotomy; OR, open reduction).

Table 3 Avascular necrosis cases in group 2

Procedure	Number of cases
Closed reduction	4
Closed reduction, pelvic and femoral osteotomy	1
Open reduction	4
Open reduction and pelvic osteotomy	2
Open reduction, pelvic osteotomy and femoral osteotomy	3

We found no correlation between age at presentation and/or index procedure in any of the other classification systems.

A summary of the treatments received by patients in each group, age at diagnosis and the average age at which AVN was diagnosed is summarized in Table 7.

Graf grading versus AVN (age less than six months)

Table 8 summarizes the cases of DDH that were classified according to Graf.

No cases of AVN were seen in type 2a, 2b, 2c and D hips. In all, 10/45 (22%) cases of AVN were identified in Graf type 3 (n = 1) and Graf type 4 (n = 9).

The remaining cases presented after the age of six months and a Graf grading was not applied. Significant differences were observed across all the Graf types (chi-squared $p < 0.001$). The odds ratio for AVN comparing only Graf type 4 with 3 was 16.88 (1.96 to 145.34) and the Fisher's exact test gave $p < 0.003$ demonstrat-

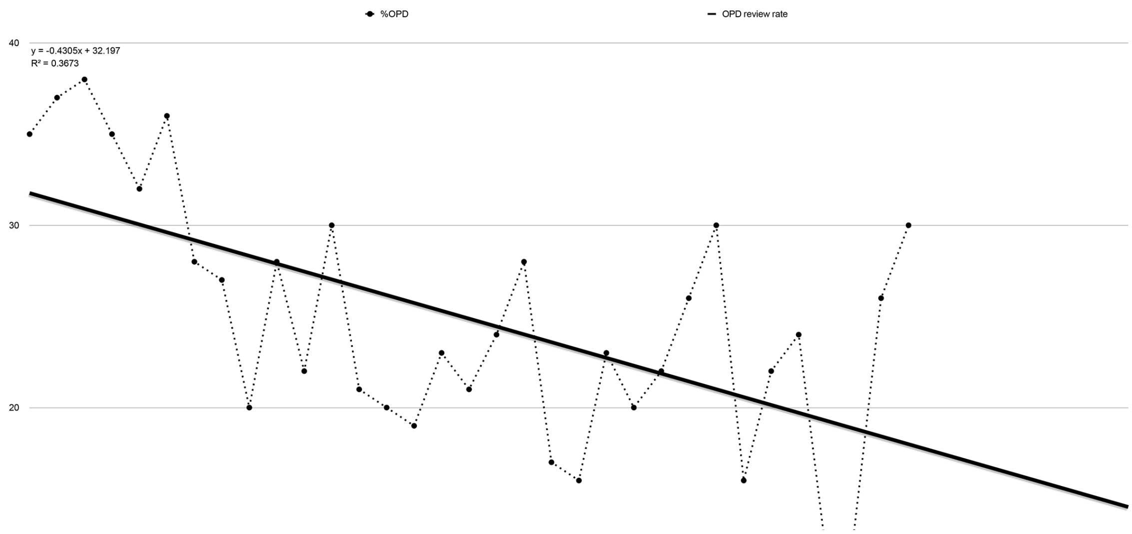

Fig. 3 Summary of cases in group 3. Total patients (hips) = 36 (38) (CR, closed reduction; AVN, avascular necrosis; OR, open reduction; PO, pelvic osteotomy; FO, femoral osteotomy).

Table 4 Avascular necrosis cases in group 3

Procedure	Number of cases
Closed reduction	3
Closed reduction with adductor tenotomy	2
Closed reduction with pelvic osteotomy	1
Open reduction only	4
Open reduction and pelvic osteotomy	9
Open reduction with pelvic and femoral osteotomy	5
Open reduction with pelvic, femoral and periacetabular osteotomies	1

ing the statistically significant difference between the two.

Age *versus* AVN

A logistic regression was implemented to analyze the effect of age at initial treatment on development of AVN. The model correctly predicted 83.9% of the cases. The overall model was found to be highly statistically significant ($p < 0.01$), meaning that the higher the age at initial treatment, the more likely the patient will develop AVN.

Discussion

The data above reveals that surgically more invasive treatment and higher Graf grades at initial presentation are also more likely to result in AVN. It may also reflect a late or suboptimal treatment protocol.

A few terminological clarifications at the beginning of this discussion are necessary, specifically the relationship between AVN and proximal femoral growth disturbance (PFGD) as used by Weinstein and Dolan.[16] The key question posed by their study (and others which use PFGD rather than AVN) concerns the aetiology of this disturbance seen at maturity, i.e. natural dysplasia progression or iatrogenic.[17] This study also suggests that the classification system most commonly used (Salter's) is potentially questionable due to characteristics not necessarily suggestive of vascular insult but increased vascularity following open reduction.[16] In keeping with Weinstein and Dolan's manuscript,[16] our findings using Severin's criteria did indicate a need to base our outcome conclusions on final follow-up radiographs and not rely on early changes with the ossific nucleusNon-surgical treatment led to a more successful outcome in groups with younger patients (group 1: 75%, group 2: 29.6%, group 3: 0%). We found that the younger the patient, the more likely that non-surgical treatment would resolve the DDH. No individuals who underwent non-surgical (double nappies, Ossur brace or Pavlik harness) treatment developed AVN. No child treated with Pavlik harness subsequently developed AVN. The success of Pavlik harness in this respect, which has been widely reported in the literature,[2,3] was found to be 100%. The oldest child to undergo treatment with Pavlik only in this study was 27 weeks. Previously it has been reported in the literature that in children above four months of age, the effectiveness of Pavlik is likely to be reduced,[18] however, in our study we found that it was preserved for a longer period. According to our findings, Pavlik seems to be beneficial up to the age of six months. However, the authors acknowledge that further studies are required to truly assess the significance of this finding.

Interestingly, the utilization of double nappies seemed to have resolved type 2a DDH in six cases within our cohort. Although these hips are well known to spontaneously resolve with no treatment, dysplasia may persist

Table 5 Age groups of avascular necrosis cases

Age at presentation, mths	Number of patients
< 6	10
6 to 12	6
12 to 18	8
18 to 24	10
24 to 36	5
36 to 48	1
> 48	5

Table 6 Classifications of avascular necrosis

	Grade					
Classification system	No grade	1	2	3	4	5
Salter	0	4	11	13	17	
Kalamchi and McEwen	1	17	8	11	8	
Bucholz and Ogden	1	17	10	11	6	
Tonnis and Kuhlmann	2	14	13	0	16	
Severin		3	24	13	4	1

in 5% to 10% of cases.[19] The literature is very limited on this treatment modality and the authors acknowledge that further studies should be carried out to determine its success rate.

The proportion of cases with AVN within the subgroup that underwent closed reduction was 28% (14/50). This included the use of additional procedures such as adductor tenotomy and Salter osteotomy, which is comparable with the current literature.[20-22] Malvitz and Weinstein[21] reported a higher rate of AVN in this group and, similar to this paper, we do not routinely employ preoperative traction within this unit, which may be a contributory factor. A prospective multicentre study found a 25% AVN rate, with older age and longer immobilization as predictors of further corrective surgery and development of AVN.[23] In our study, 25% of individuals who underwent closed reduction required further corrective surgery; this was more apparent as the age of the individual at initial presentation increased. An important point to note is that 6/14 of the above cases discussed were Severin I (n = 1) or Severin II (n = 5), which are not clinically relevant cases of AVN. A similar methodology was adopted by Terjesen and Halvorsen[22] in their study, whereby they Severin I or II was delineated as a satisfactory outcome. Therefore, the AVN rate in the group of individuals who underwent closed reduction with or without additional procedures is actually lower if the above is taken into account (12% *versus* 28%).

Of the 11 individuals who underwent closed reduction with adductor tenotomy, two developed AVN (18%). Although this is higher than in Tennant et al,[24] who described closed reduction with simultaneous adductor and psoas release in children under two and had comparatively better results, with an AVN rate of 1.5%. In our study, these two cases were found to be Severin type II which deems them as clinically non-significant. Adductor tenotomy with closed reduction has been mentioned several times in the literature as one of the risk factors for AVN.[7,25,26] However, Schur et al[27] report no significant difference in development of AVN. Overall, the correlation between adductor tenotomy and development of AVN appears minimal, as the aetiology of AVN in the context of closed reduction is multifactorial, so it is likely that later presentation at surgery is more statistically significant in our study.

Shin et al[28] compared the use of osteotomy *versus* no osteotomy in patients who underwent closed reduction. No significant difference was found in the outcome between the two groups. However, the authors do acknowledge that the use of acetabular index (AI) and centre edge angle (CEA) in DDH patients is reliable. In addition to this, the indication for osteotomy was not standardized in this study, therefore, reducing its relevance clinically when dealing with a patient with DDH. Nevertheless, AI and CEA at the age of three years are recommended as parameters predicting the success of this procedure. In our study, two patients required closed reduction with a subsequent osteotomy. They both developed AVN. This suggests that subsequent osteotomy is not beneficial, even though it is difficult to draw definitive conclusions based on such a small sample.

In the case of open reduction, the standard surgical approach used in the unit was a modified Smith Peterson. The AVN incidence for open reduction alone was 40.7% (11/27), which is comparable with the literature, although there is considerable variation.[29-34] Overall it is in agreement with the conclusion by Kothari et al[35] that open reduction alone provides the lowest risk of AVN compared with open reduction with additional procedures (11/27; 40.7% *versus* 20/23; 87%). In this review the group that underwent open reduction alone was younger than the other groups which underwent an additional pelvic osteotomy and, therefore, age may again be the confounding factor. In our study, we found that a large proportion of individuals who underwent open reduction with additional osteotomies subsequently developed AVN (20/23; 87%). It is important to note that quite a significant proportion of the cases which underwent open reduction alone or open reduction with additional procedures were Severin type I or II (32%; 16/50). Therefore, the high incidence of AVN recorded may not be clinically significant due to the Severin classification. Kothari et al[35] recorded AVN as clinically relevant if it was Kalamchi & MacEwen or Bucholz and Ogden 2 or greater. In the group that underwent open reduction alone, four cases fulfilled these criteria, therefore, they are not clinically relevant. Seven patients would be considered to have clinically relevant AVN. In the group that underwent open reduction with additional osteotomies five cases fulfil this criteria, resulting in total clinically relevant AVN cases of 15. Therefore,

Table 7 Summary of treatments, age at diagnosis and avascular necrosis (AVN)

Treatment	Average age at diagnosis of DDH, mths	Age at AVN diagnosis (1 yr after date of first procedure)
Closed reduction only	3.8	24
Open reduction only	4.4	25
Open reduction and pelvic osteotomy	11	45
Open reduction and femoral osteotomy	9	45

Table 8 Summary of cases with Graf grading

	Graf 2a	Graf 2b	Graf 2c	Graf D	Graf 3	Graf 4
Patients	35	11	27	2	31	25
Hips	35	15	36	3	41	34
Side affected						
Left	9	3	12	0	12	10
Right	9	4	6	1	9	6
Bilateral	17	4	9	1	10	9
Male cases	12	1	4	0	4	3
Female cases	23	10	23	2	27	22
Mean gestational age, wks	5.5	12	7.5	7.5	7.2	8
Median gestational age, wks (range)	4.6 (2 to 16)	13 (4 to 27)	5.7 (1 to 25)	7.5 (2 to 13)	5.9 (1 to 22)	7.3 (-1 to 22)
Cases of AVN	0	0	0	0	1	9

AVN, avascular necrosis

according to Kothari's methodology AVN incidence would be 44% (22/50). This is lower than the overall incidence of AVN in this group (open reduction alone or open reduction with additional osteotomies), which stands at 62% (31/50).

Generally, individuals older than six months at initial presentation were at greater risk of developing AVN compared with younger individuals (RR = 16.3). The age of the individual at initial presentation is dependent on a variety of factors that have changed within the unit over the years with the appreciation of the neonatal infant physical examination and the introduction of a selective screening programme in 2016. However, this had no impact on the number of patients presenting late to our institution.

Utilizing the Graf technique and grading is well established,[36] with studies demonstrating its superiority when compared with other ultrasonographic methods.[37-41] In this study, only Graf 3 or 4 hips developed AVN. These decentred hips by nature are more difficult to treat with a harness and required more intervention when compared with the lower Graf grades, hence increasing their risk of AVN.

This study sought to classify AVN cases using all the available classification systems. It was not possible to identify the inter- and intraobserver variability of these classification methods, which is one of the shortfalls of this study. We reviewed the literature to identify studies which have previously analyzed the interobserver reliability of the known classification systems, but were only able to find Omeroglu et al's[9] paper describing interobserver reliability in Kalamchi's criteria. In addition to this, there is another study describing the poor reliability of Severin's grades, calling into question the clinical conclusions of reports in which the Severin system has been used as the basis of proof.[10]

Moreover, all the classification systems commonly used showed strong elements of correlation among one another, but not with age at presentation or index of surgical intervention.

Tsukagoshi et al[11] pointed out that Salter's criteria are predictive of outcome and correlated with the Kalamchi grade of AVN at ten years after DDH treatment. In our study we observed no such correlation. This is potentially due to our smaller sample size (45 *versus* 123). Nonetheless, we did identify another near significant correlation between Salter's criteria and the severity of outcome through Severin's classification at skeletal maturity. This does confirm the notion that a poorer Salter grade could correlate with a more severe final radiological outcome as per Severin's classification. This statement is similar to the findings in Tsukagoshi et al,[11] however, no further correlation between Salter and other systems has been identified. Severin's criteria were measured on the final follow-up radiograph. The range of follow-up in our cohort of patients with AVN was from two to 12 years. Other similar studies looking into the outcome of open reduction, closed reduction and pelvic osteotomy had similar follow-up time and criteria for grading Severin's radiographic outcome.[42-44]

Furthermore, we found that Severin's classification at skeletal maturity has no correlation with the age at presentation. This finding was consistent with another study which found that the age at the time of closed reduction was not a risk factor for redislocation, AVN or poor radiographic outcomes according to the Severin grade.[36] There is a consensus in the literature that Severin grades I and II are not clinically relevant.[35] A total of 60% of our cases fit into this category. Therefore, the AVN which is clinically significant in this study (Severin grade III and IV), is actually 9.4% (18/192). Mean follow-up time for this cohort was 5.6 years, Range: 2-12 years

The strengths of this study include that this was a consecutive cohort of patients treated within a single unit. The sample size gave it adequate power to detect a statistically significant difference. All infants were treated according to a departmental protocol for intervention amongst all treating clinicians.

The limited sample used in this study is due to the fact that it was retrospective, thus relying on clear and consistent clinical records in order to collect the relevant data.

Conclusion

This study found the incidence of AVN in surgically treated late presentation DDH cases in a single tertiary centre to be comparable with the current literature. Salter's criteria were the most useful in defining early AVN. Age at diagnosis was the consistent factor associated with AVN, which highlights the need for earlier detection with less invasive treatment methods in order to reduce its overall incidence. Although the incidence of AVN in our study is towards the higher end of the spectrum, this is likely to occur as a result of a single observer assessing the classifications. In addition, it may reflect the overall practice in our institution which may need to be evaluated to improve outcomes.

One other important finding this study suggests is that perhaps we overclassify radiographs based on radiological changes found early after an intervention. We should certainly increase our follow-up time following any intervention and also incorporate patient-reported outcomes which are currently lacking in the paediatric population.

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COMPLIANCE WITH ETHICAL STANDARDS

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ETHICAL STATEMENT

Ethical approval: All the information analyzed in this study and procedures performed were compliant with the ethical standards of the ethical committee in our institution.

Informed consent: This article does not contain any studies with human participants or animals performed by any of the authors. Informed consent was not required.

ICMJE CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

RNH: Data collection, Analysis, Formulation of the original draft, Approval of the final manuscript.

DR: Data collection, Analysis, Formulation of the original draft, Approval of the final manuscript.

WJW: Statistical analysis of the data, Articulating the conclusions from the analysis, Approval of the final manuscript.

CC: Reviewed and edited the manuscript, Approval of the final manuscript.

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