Review

Environmental Factors of Equine Osteochondrosis and Fetlock Osteochondral Fragments: A Scoping Review - Part 1

B. Van Mol [a, b, *], M. Oosterlinck [a], S. Janssens [b], N. Buys [b, 1], F. Pille [a, 1]

[a] *Department of Large Animal Surgery, Anaesthesia and Orthopaedics, Faculty of Veterinary Medicine, Ghent University Salisburylaan 133, 9820 Merelbeke, Belgium*
[b] *Center for Animal Breeding and Genetics, Department of Biosystems, KU Leuven, Kasteelpark Arenberg 30, 3001 Leuven, Belgium*

* Corresponding author. Tel.: +32 4725 25859.
E-mail address: bram.vanmol@ugent.be (B. Van Mol).
[1] These authors contributed equally as senior authors.

Abstract

Various environmental and genetic risk factors are linked to the pathogenesis of equine osteochondrosis and osteochondral fragments in the fetlock joint. Therefore, a scoping review was conducted to describe current evidence linking genetic factors and environmental factors of these osteochondral disorders. This article constitutes the first part of this scoping review and focuses on environmental factors, with the second part addressing genetic factors. To identify potentially relevant papers online bibliographical databases PubMed and Web of Science were utilised, supplemented with articles listed on the OMIA website (OMIA:000750-9796). After entry collection, removing duplicates, screening titles, abstracts, and full-text documents for eligibility, and manually searching reference lists of the remaining articles, a total of 212 studies was identified for this scoping review. First, an overview of the current understanding of the etiopathogenesis of equine osteochondrosis and osteochondral fragments in the fetlock joint is given. Subsequently, the article delves into the environmental factors associated with the prevalence of these disorders, which are categorized into foetal programming, biomechanical trauma and exercise, growth, anatomic conformation, nutrition, weaning, hormonal factors, bacterial infection, sex, date of birth, and other environmental factors. In conclusion, future research should adopt a multidisciplinary approach, emphasizing longitudinal studies and precise phenotype definitions. This strategy will help elucidate the complex relationships between environmental factors and OC, DOF, and POF, considering the dynamic nature, varying phenotypes, and scarcity of research in some domains of these osteochondral disorders. This approach will be crucial in developing effective management strategies aimed at improving equine orthopaedic health.

Keywords: Environmental factors; Horses; Osteochondrosis; Review

Introduction

Osteochondrosis (OC) refers to the focal failure of endochondral ossification whereby an area of growth cartilage is unable to properly transform into mature bone (Rejnö and Strömberg, 1978). This condition can manifest in both epiphyseal and physeal growth cartilage (Stromberg, 1979; Thorp et al., 1993). This review will specifically focus on articular osteochondrosis of the epiphyseal growth cartilage, which is highly prevalent across various horse breeds.

Over the decades, the understanding of the pathogenesis of OC and its associated terminology has evolved. König (1888) originally hypothesised a primary inflammatory aetiology, in some cases linked to trauma, causing joint cartilage lesions and the formation of loose osteochondral fragments. Based on this, they proposed the term 'osteochondritis dissecans'. Over time, alternative terms such as 'osteochondrosis'(Howald, 1942), 'metabolic bone disease' (Knight et al., 1986), and 'dyschondroplasia' (Jeffcott, 1993) were introduced as potentially more accurate. However, the term osteochondrosis became the most widely used, as it better captures the pathology and reflects the consensus that a primary inflammatory cause is not characteristic (Ytrehus et al., 2007). When a (partially) separated osteochondral fragment is present, the term osteochondrosis/osteochondritis dissecans is often used. In this context, dissecans refers to the osteochondral separation, osteochondrosis refers to the underlying disorder, and osteochondritis refers to a possible inflammatory response resulting from it (Rejnö and Strömberg, 1978; McCoy et al., 2013; McIlwraith, 2013).

The initial step leading to OC involves the focal failure of cartilage canal vessels that supply blood to the epiphyseal growth cartilage (Carlson et al., 1995; Jeffcott, 2004; Ytrehus et al., 2007; Olstad et al., 2013; Olstad et al., 2015a). Cartilage vessels are vulnerable to failure due to the physiological transition in blood supply from the perichondrium to the medullary cavity. This transition involves the formation of cartilage canal vessels that traverse through the ossification front from cartilage to bone. These vessels anastomose with subchondral bone vessels and are eventually incorporated into the ossification front (Olstad et al., 2008a; Olstad et al., 2008b; Olstad et al., 2013; Wormstrand et al., 2021).

Based on the new insights into the pathogenesis, new terminology was proposed. Ischemic necrosis caused by vascular failure within the growth cartilage was defined as osteochondrosis latens. This ischemic chondronecrotic growth cartilage can hinder physiological ossification when the ossification front progresses, leading to the formation of abnormal thickened, collapsed or separated necrotic subchondral bone, defined as osteochondrosis manifesta (Stromberg, 1979; Ytrehus et al., 2007; Olstad et al., 2015a). Alternatively, the area of ischemic necrosis can heal, resulting in the formation of healthy subchondral bone (GrØndahl, 1991; Carlsten et al., 1993; Carlson et al., 1995; Dik et al., 1999; Baccarin et al., 2012; Jacquet et al., 2013; Santschi et al., 2020). OC may develop at multiple predilection sites in a growing animal and commonly occur bilaterally symmetrical. Although different joints can be diseased, involvement of articular-epiphyseal cartilage at locations other than the joint-specific predilection sites is rare (Mcllwraith et al., 1991; McIlwraith, 1993; Pool, 1993; Barneveld and van Weeren, 1999).

Palmar- and plantarproximal osteochondral fragments of the proximal phalanx (POF) originate from an overload of physiological or pathological tensional forces at the distal attachment of the oblique and short sesamoid ligaments on the fragile, growing skeleton, leading to an avulsion fracture (Dalin et al., 1993; Pool, 1993; Nixon and Pool, 1995; Denoix et al., 2013). The primary cause of POF remains unclear, whether due to pathological tensile

forces causing a traumatic fracture (Pool, 1993; Barneveld and van Weeren, 1999), or physiological forces acting on focal areas of disturbed endochondral ossification, characteristic of OC, leading to a pathological fracture (Olstad et al., 2015). Histology of POF fragments revealed no signs of (disturbed) endochondral ossification activity at the facture borders or within the fragment, which is analogous to osteochondral fragments of known traumatic origin (Nixon and Pool, 1995; Theiss et al., 2010). However, since the POF fragments represent the end stage of the condition, this histological similarity does not definitively establish trauma as the sole cause (McCoy et al., 2013). Theiss et al. (2010) observed fibrous tissue at the fracture borders of most POF fragments, which is also typical of traumatic fractures. However, similar fibrous tissue can also be found in OC fragments, likely due to the remnants of necrotic epiphyseal cartilage and reactive fibrous tissue (McCoy et al., 2013).

Dorsoproximal osteochondral fragments of the proximal phalanx (DOF) seem to be the direct result of trauma, although there is still some ambiguity (Kawcak and Mcllwraith, 1994; Declercq et al., 2009). According to Declercq et al. (2009), DOF in warmblood horses are most likely the result of trauma at an early postnatal age. Histology revealed a bony structure covered with hyaline cartilage on one side and fibrous tissue on the other. There were no histological signs of OC such as retained cartilage cores and chondronecrosis (Pool, 1993; Henson et al., 1997b). In contrast, Theiss et al. (2010) could not clearly differentiate between a traumatic origin and OC, as they detected 12 DOF cases in a mixed population of breeds with signs of endochondral ossification activity at the fracture border and 4 cases without these signs, showing only fibrous tissue. Declercq et al. (2009) differentiated DOF in warmbloods from acute chip fractures in thoroughbreds because of the absence of clinical symptoms associated with fractures, the lack of sharp fracture lines on radiography, and the absence of histopathological signs of a recent fracture (Adams, 1966; Kawcak and Mcllwraith, 1994). The difference in the aetiology and histology of fragments at the dorsoproximal aspect of the proximal phalanx between breeds and possibly within breeds adds an extra layer of complexity to the research into predisposing factors of DOF.

While the etiopathogenesis differs among OC, DOF and POF, a shared aspect is the failure of the growing skeleton of the horse. Predisposing factors are multifactorial and can be divided into genetic and environmental factors, which may vary in relative importance depending on the clinical manifestation. The objective of this part of the scoping review is to provide a summary of the existing evidence regarding the involvement of environmental factors.

Methods

To conduct a scoping review that is rigorous, transparent and replicable, the recommendations of the PRISMA Extension for Scoping Reviews (PRISMA-ScR) protocol (Tricco et al., 2018) is followed and a detailed checklist is provided as Supplementary Checklist S1. To identify potentially relevant peer-reviewed literature, a search was performed in May 2023 by one author (BVM) with feedback on the process by all authors. The search was carried out on the bibliographic databases PubMed and Web of Science from 2003 to May 2023. The following search terms were used: (‘osteochondrosis’ OR ‘osteochondral fragment’ OR ‘developmental orthopaedic disease’ OR ‘juvenile osteochondral conditions’ OR ‘osteochondral lesion’) AND (‘equine’ OR ‘horse’ OR ‘pony’ OR ‘foal’ OR ‘yearling’ OR ‘warmblood’ OR ‘standardbred’ OR ‘trotter’ OR ‘thoroughbred’ OR ‘purebred’ OR ‘coldblood’). The bibliographic database search was supplemented with all (no publication date restrains) articles listed on the ‘online mendelian inheritance in animals’ website on osteochondrosis in Equus caballus (OMIA:000750-9796).

All the search results were exported in the reference manager EndNote for duplicate removal and study screening. For both parts of this scoping review, all unique titles and abstracts were screened for the eligibility criteria provided in Table 1. For this review, papers on subchondral bone cysts, identified by some as possible manifestations of OC (Stromberg, 1979; Olstad et al., 2015b; Ammann et al., 2022; Lemirre et al., 2022), as well as those referring to less common locations of OC, and types of fetlock fragments other than DOF and POF were excluded. Additionally, gene expression studies were excluded due to the recurrent uncertainty about whether changes in gene expression are related to the primary condition (OC, DOF, POF) or secondary responses. This uncertainty arises because the exact timing of natural lesion occurrence is unclear, and in experimental OC models, the aetiological background may differ. Furthermore, the review focused exclusively on *Equus ferus caballus* (horse). Although comparative studies with other species, such as pigs and humans (McCoy et al., 2013), could provide valuable insights, this criterion was applied to limit the scope to the already extensive literature available on horses.

Table 1
The eligibility criteria used in this two-part scoping review.

Criteria	Inclusion	Exclusion
Language	English	Other language
Publication type	Peer-reviewed primary literature	Non-peer-reviewed literature
Population	Horse (Equus ferus caballus)	Other animal species
Phenotype	Articular osteochondrosis of the fetlock, hock or stifle Palmar/plantar or dorsal osteochondral fragment of the fetlock	Osteochondrosis at other, less prevalent, locations Scientific papers discussing subchondral bone cyst Scientific papers about other types of fetlock fragments
Methods	Genome-wide association study based on single nucleotide polymorphisms Microsatellite-based genome-wide scan Pro- or retrospective study of environmental factors	Gene expression study
Concept	Description of genes potentially associated with the risk of developing the phenotype Description of environmental factors associated with an increased risk for developing the phenotype	Scientific papers that do not investigate genetic or environmental risk factors

Results

The literature search identified 565 articles on the Web of Science, 394 articles in PubMed and 168 articles in the OMIA database. After duplicate removal, 629 articles remained. Through analysis of article titles, abstracts, and full-text documents, 503 articles were excluded due to ineligibility. Through a manual search of reference lists, an additional 86 unique articles that met the eligibility criteria were identified and included for review. Ultimately, a comprehensive review was conducted on a total of 212 articles. This review is presented in two parts: 1) The current evidence implicating environmental factors of OC, DOF and POF; 2) The current evidence implicating genetic factors of these osteochondral disorders. A general limitation of this review is its scope, focusing exclusively on *Equus ferus caballus*, without considering comparative studies in other species, and covering findings only up to May 2023.

In the following sections, we first provide an overview of the general challenges and limitations in studies investigating the impact of environmental factors on the occurrence of OC, DOF, and POF. Subsequently, we categorized the results of these studies by the environmental factors researched in association with the prevalence or severity of these disorders. These categories include foetal programming, biomechanical trauma and exercise, growth, anatomic conformation, nutrition, weaning, hormonal factors, bacterial infection, sex, date of birth, and other environmental factors. Where possible, we discussed how these factors might be related to or even trigger vascular failure, which is currently considered a key element in the pathogenesis of OC.

Environmental factors

Numerous studies have investigated the impact of environmental factors on the occurrence of OC. However, there is a lack of research on how these factors influence the occurrence of DOF and POF. Comparative analysis of environmental studies faces challenges due to inherent methodological differences across these studies. Additionally, environmental studies in horses are susceptible to false-positive and false-negative associations due to limited sample sizes, recall bias in surveys and differences in ancestral origins and geographical regions.

For OC, most studies investigate the influence of environmental factors by comparing differences in OC prevalence or severity based on radiological screenings of animals over one year old. However, because OC is a dynamic condition that can heal during the first year of life (GrØndahl, 1991; Carlsten et al., 1993; Dik et al., 1999; Baccarin et al., 2012; Jacquet et al., 2013; Santschi et al., 2020), this approach raises questions about whether the environmental factors studied influenced the development of OC or its likelihood of healing. Both processes can reduce the incidence or severity of OC by the time of the radiological screening. Further complexity arises for POF and DOF, as these fragments can be arthroscopically removed without leaving any radiological trace, leading to false-negative controls.

Vascular failure of the epiphyseal growth cartilage is currently considered a key element in the pathogenesis of OC (Carlson et al., 1995; Jeffcott, 2004; Ytrehus et al., 2007; Olstad et al., 2013; Olstad et al., 2015a). Several direct and indirect factors potentially triggering this vascular failure will be discussed in this review. Consequently, the environmental factors that influence this vascular failure can only be studied during the window of time, known as the window of vulnerability, when the blood supply to the epiphyseal growth cartilage is still necessary. In the fetlock, the window for ischaemic necrosis closes at approximately 8 weeks of age (Carlson et al., 1995; Olstad et al., 2009). In the hock, the window of time closes around 10 weeks of age (Carlson et al., 1995). In the stifle, the window of time closes between two to seven months of age (Carlson et al., 1995; Shingleton et al., 1997; Olstad et al., 2008a), yet the precise time at which the articular epiphyseal growth cartilage becomes avascular remains unknown. During the prenatal period, the blood supply to the epiphyseal growth cartilage develops (Shingleton et al., 1997). Hence, it is equally important to explore environmental factors that may influence this development during conception and gestation.

Ideally, studies examining environmental factors should include longitudinal radiographic screenings. While radiographs have many limitations compared to advanced 3D imaging modalities like CT, particularly in detecting early OC lesions or those in complex areas like the axial skeleton due to superimposed structures (Olstad et al., 2008; Fontaine et al., 2013; Skarbek et al., 2020; Rovel et al., 2021), they remain the most practical choice for large-scale studies. The high costs and risks, including the need for anaesthesia, make 3D imaging less feasible for such studies at present. This approach would help to determine whether, for example, adverse environmental conditions increase the incidence of OC in horses younger than 8 weeks old (fetlock-OC), 10 weeks old (hock-OC) and 7 months old (stifle-OC), or rather affect the healing capacity of OC after the lesion has formed. This approach would also allow for deductions on whether a specific factor can lead to increased disease incidence, modify disease progression, or both. The period in which POF and DOF can develop and, if possible, heal remains uncertain. POF is reported to predominantly develop during the first few months of life and rarely after one year old (Carlsten et al., 1993; Pool, 1993). Due to the lack of literature that examines the impact of environmental factors on the occurrence of DOF and

POF, the following sections will primarily discuss the influence of environmental factors on the occurrence of OC.

Foetal programming

Prenatal conditions affect long-term postnatal health, a concept increasingly recognized in the expanding research field of developmental origins of health and disease (Chavatte-Palmer et al., 2015; Peugnet et al., 2016b; Clothier et al., 2020). This research highlights that the maternal environment can modulate the genetic potential of the foal, influencing characteristics such as osteoarticular health (Peugnet et al., 2016a; Peugnet et al., 2016b). The pre-and periconceptional periods are particularly important due to high epigenetic plasticity, which allows for easy modification of gene expression without altering underlying DNA sequence (Chavatte-Palmer et al., 2015; Chavatte-Palmer et al., 2017). Given the routine use of assisted reproduction techniques such as embryo transfer (ET) and ovum pick-up combined with intracytoplasmic sperm injection (ICSI), the potential long-term health effects of these techniques should be studied.

ET between breeds of different sizes has demonstrated variations in growth patterns, both pre- and postnatal, persisting into adulthood (Allen et al., 2004; Peugnet et al., 2014; Peugnet et al., 2016b). Foals experiencing intrauterine overgrowth through ET of pony and saddlebred embryos into draught horse mares, or growth retardation through ET of standardbred embryos into pony mares, have demonstrated abnormalities in blood pressure as well as in bone, glucocorticoid, thyroid hormone, lipid, and insulin homeostasis (Peugnet et al., 2014). Additionally, growth-retarded standardbred foals out of pony mares can show signs of dysmaturity, catch-up growth and disproportionate growth (Peugnet et al., 2016a; Peugnet et al., 2016b). Peugnet et al. (2016a) reported that all growth-retarded standardbred foals out of pony mares were affected with OC at 200 days old, with most lesions disappearing at 540 days old. Whether biomechanical overload due to an altered body conformation, the detected enhanced insulin sensitivity and hyperglycaemia up to 18 months old or other factors led to the significantly higher OC incidence at 200 days old is unsure. Various animal and human studies have associated assisted reproduction techniques such as ICSI and ET with epigenetic reprogramming abnormalities, postnatal phenotypic alterations, and disturbed glucose metabolism, cardiovascular function and fat deposition. Potential adverse effects have not been reported in horses, although this area remains little investigated (Peugnet et al., 2016b; Chavatte-Palmer et al., 2017).

Beyond reproduction techniques, maternal environment and management play an important role in the osteoarticular status of the foal (Peugnet et al., 2016b). Age and parity of the mare have been reported to significantly impact the initial height and weight of the foal at birth, as well as further weight and height gains after birth (Cymbaluk and Laarveld, 1996; Lepeule et al., 2009). Lepeule et al. (2009) reported that foals born to mares under 10 years old or over 15 years old have significantly higher odds of developing OC (*odds ratio of 2.3, 95% confidence interval: 1.0-4.7 and 2.7, 95% confidence interval: 1.1-7.0 in the respective categories*) compared to foals born to mares between 10 and 15 years old. In contrast, Sandgren et al. (1993a) did not find a relationship between the age and parity of the mare and the occurrence of OC, POF and DOF in the offspring. The administration of pharmaceuticals such as anti-inflammatories and antibiotics to the pregnant mare has not been associated with changed prevalence of osteochondral lesions in the foal, although only limited studies are available (Ellerbrock et al., 2020; Ellerbrock et al., 2021). The maternal diet and immunity can have an important influence on the osteoarticular status, as will be elaborated upon in the paragraph ‘nutrition’.

An adverse foetal environment leading to gestational immaturity and/or intrauterine growth retardation (IUGR) can have lasting consequences for equine health (Adams and Poulos, 1988; Rossdale and Ousey, 2002; Tauson et al., 2006; Clothier et al., 2020). Despite overlapping aetiological factors, there is a lack of research investigating the influence of IUGR on OC, DOF and POF. This is notable considering the high prevalence of these osteochondral disorders in thoroughbreds, which may experience IUGR more often than ponies (Rossdale and Ousey, 2002), in which the prevalence of these osteochondral disorders is low. Although other reasons for the breed discrepancy in OC prevalence between ponies and horses have been described (Hendrickson et al., 2015), as elaborated upon in the section on growth, horses may also be more susceptible to IUGR compared to other species (Tauson et al., 2006). Moreover, it is plausible that foals born with gestational immaturity remain undetected, leading to an oversight in establishing a relationship with orthopaedic health at a later age (Clothier et al., 2020). Despite important questions about the effects of foetal programming on OC, DOF, and POF, longitudinal research in this area remains scarce.

Biomechanical trauma and exercise

Numerous studies investigated the link between irregular, excessive, or insufficient exercise with the prevalence, location, and severity of OC. The suggested reason for this association is biomechanical overload, leading to the disruption of cartilage canal vessels. This disruption, in turn, can hinder the conversion of growth cartilage to bone (Carlson et al., 1995; Pagan and Jackson, 1996; Olstad et al., 2013). Alternatively, biomechanical overload could be a direct cause of traumatic osteochondral fragments leading to DOF and POF. Santschi et al. (2020) proposed that direct trauma could also induce OC-like radiographic abnormalities in the stifle. They observed two horses that developed bilateral fragmentation with adjacent lucencies and sclerosis of the lateral trochlear ridge of the femur (resembling OC) after the age of 10 months, thus after closure of the window of time (8 months) for ischaemic necrosis (Carlson et al., 1995; Shingleton et al., 1997; Olstad et al., 2008a).

The role of biomechanical disruption of cartilage vessels in OC is a subject of debate, mainly because most lesions tend to occur regionally rather than being generalized (Pool, 1993; Ytrehus et al., 2007). Several groups have therefore investigated the presence of regional differences in growth cartilage. Temporary (physiological) regional variations in matrix proteoglycan content, collagen content, and collagen structure at certain OC-predilection sites have been detected (van de Lest et al., 2004; Lecocq et al., 2008; Martel et al., 2016a; Hellings et al., 2017). Some of these structural variations are thought to result from biomechanical loading suggesting that inappropriate types and amounts of loading could lead to regional structural variations compromising the structural integrity of growth cartilage (Brama et al., 2000). Additionally, certain OC-predilection sites, such as the distal intermediate ridge of the tibia, the lateral trochlear ridge of the femur, and the dorsal half of the sagittal ridge of the distal third metatarsal bone, have a longer reliance on blood supply due to increased growth cartilage thickness and increased vascular density. These regions have more perichondral vessels not yet bridging to the subchondral bone at birth, compared to other regions within the joint (Lecocq et al., 2008; Olstad et al., 2008a; Olstad et al., 2008b; Olstad et al., 2009; Martel et al., 2016b). These regional differences could make certain cartilage vessels more susceptible to trauma, leading to an initiating vascular insult, thus explaining the focal distribution of lesions.

Appropriate types and amounts of biomechanical loading through moderate exercise can serve as a protective factor for foals, as this has been shown to decrease the fragility of bone and cartilage by influencing site-specific characteristics such as content, orientation and

topographical heterogeneity of collagen (Brama et al., 1999; van de Lest et al., 2002), glycosaminoglycan content (Brama et al., 1999), proteoglycan metabolism (van den Hoogen et al., 1999), number of viable chondrocytes (Robert et al., 2013), bone mineral density (Raub et al., 1989; Cornelissen et al., 1999; Firth et al., 1999) and cross-sectional area (Raub et al., 1989; Cornelissen et al., 1999). Moreover, exercise can positively and negatively influence risk factors such as energy intake, energy expenditure, and growth rate (van Weeren et al., 1999; Harris et al., 2004).

In the foetus, major changes in proteoglycan and collagen structure in the growth cartilage occur during the last two-thirds of the gestational period. Additionally, physiological indentations of the ossification fronts with an associated cartilage canal, areas of hypocellularity and the presence of necrotic chondrocytes are detected (Shingleton et al., 1997; van Weeren and Barneveld, 1999; Olstad et al., 2007; Lecocq et al., 2008). Whether these structural changes and/or possibly exacerbation of these changes due to external factors can lead to reduced biomechanical strength is not yet fully understood. However, in utero hydrostatic forces on the joints by muscular activity may have some influence (Lecocq et al., 2008). The extremely slow turnover of cartilage at mature age makes the pre- and postnatal period, when cartilage metabolism is still high, important in determining the biomechanical characteristics essential for injury resistance (van Weeren and Brama, 2003). This may explain some effects of exercise associated with a reduced occurrence of osteochondral disorders.

In our opinion, an environment should be created in which foals can regularly participate in consistent levels of natural physical activity. This promotes the development of injury-resistant healthy bone and cartilage, reducing the risk of subjecting still-developing joints to biomechanical overload. To create such an environment, foals should be allowed to freely exercise on pasture. Providing foals this free exercise can help in preventing nervosity, agitation, and episodes of intense exercise, which could lead to fatigue and increase susceptibility to biomechanical overload. Additionally, we recommend housing the foal with the mare in a box or small paddock during the first days of life. This period allows the foal's skeleton to gradually acclimate to biomechanical forces, facilitates familiarization with humans, and enhances mother-offspring bonding (Pagan and Jackson, 1996; van Weeren and Brama, 2003; Ytrehus et al., 2007; Counotte et al., 2014).

This management approach is further supported by Vander Heyden et al. (2013), who detected a higher prevalence of OC in foals confined to box rest compared to those kept exclusively on pasture. Conversely, it has been suggested that once an OC lesion is formed, it could be beneficial to restrict exercise, thereby decreasing the risk of fracture through the area of ischemic chondronecrosis and increasing the possibility of healing by secondary intramembranous ossification (Olstad et al., 2013; Santschi et al., 2020). Indeed, exercise could have different effects based on the phase of OC (development versus repair). In terms of the number and severity of OC lesions per foal, no statistically significant effect of different exercise regimes during the first 5 months of life has been detected (van Weeren and Barneveld, 1999).

Lepeule et al. (2009) examined the influence of pasture size on the prevalence of OC and found that foals kept in large pasture areas (>1ha before 2 weeks old and >6ha before 2 months old) had a significantly higher prevalence of OC (35% out of 285 foals affected) compared to foals that were always on a moderate sized pasture (12% out of 32 foals affected), at least in their univariable analysis. Although this association did not remain significant in the final multivariable model, the authors suggested restricting the pasture area granted to foals,

particularly in the period preceding 2 months old to reduce OC prevalence and lesion severity by lowering the risk of traumatic accidents. Additionally, Lepeule et al. (2013b) reported that irregular exercise is a risk factor for higher severity of OC lesions compared to daily free exercise. The need for foals born early in the season in some breeds, due to performance-related benefits, may conflict with this need for free pasture exercise due to unfavourable climatic conditions at that time of the year.

Exercise influences the distribution of lesions in a joint-specific manner. In the stifle joint, horses confined to box rest with sprint training and some free exercise until 5 months developed primarily OC lesions of the lateral trochlear ridge, while the group confined to box rest primarily developed cystic lesions of the femoral condyles (van Weeren and Barneveld, 1999). The same study found no differences in predilection sites in the tibiotarsal joint between these training methods. The high number of lesions at the lateral trochlear ridge of the femur could be explained by considering that this is the site loaded by the patella during exercise (van Weeren and Barneveld, 1999) and where the growth cartilage is thickest, thus vessels must extend the greatest distances from the developing bone to the cartilage (Pool, 1993). Comparably, the group confined to box rest predominantly showed cystic lesions of the femoral condyles, where pressure is highest in the standing animal (van Weeren and Barneveld, 1999). In conclusion, the results of van Weeren and Barneveld (1999) support the hypothesis that biomechanical overload through exercise can lead to vascular channel disruption, resulting in a higher occurrence of OC.

Growth

OC occurs during the period of rapid growth in horses (Carlsten et al., 1993; Jelan et al., 1996; Dik et al., 1999; Donabedian et al., 2006; Robert et al., 2013). Therefore, considerable research has been conducted on the correlation between various growth parameters and the occurrence of OC. In general, this research indicated that the incidence of OC, in a joint dependent manner, increases with higher weight at birth (Sandgren et al., 1993a; Sandgren et al., 1993b), at foal age (Donabedian et al., 2006), and at yearling age (Sandgren et al., 1993b; van Weeren et al., 1999); with a higher withers height at birth (Sandgren et al., 1993a), at foal age (Wittwer et al., 2006), at yearling age (Sandgren et al., 1993a; van Weeren et al., 1999; Wittwer et al., 2006), and at adult age (Stock et al., 2006); with a larger canon width at foal age (Donabedian et al., 2006); with a larger girth circumference (Lepeule et al., 2009); with a higher weight gain rate (Sandgren et al., 1993a; Sandgren et al., 1993b; Pagan and Jackson, 1996; van Weeren et al., 1999; Harris et al., 2004; Vervuert et al., 2004; Fradinho et al., 2019); with a higher canon width gain rate (Donabedian et al., 2006), with a higher growth rate (Sandgren et al., 1993b; Firth et al., 1999; Gee et al., 2005). Furthermore, Donabedian et al. (2006) detected significant correlations between the severity of OC lesions on necropsy and withers height at birth and 2 months old, canon width at 14 weeks and 52 weeks old, and body weight at 2 months old. Fradinho et al. (2019) found a significantly lower instantaneous average daily gain in body mass and withers height before 45 days old and a significantly higher instantaneous average daily gain in body mass, but not in withers height, from 6 months until 18 months old in OC-positive horses compared to OC-negative horses.

The precise mechanisms that link growth parameters to the molecular events that initiate OC are unknown (Staniar, 2010), and are challenging to determine due to the long chain of events between both (Harris et al., 2004). It is plausible that fast-growing foals are more susceptible to overloading their still immature joints, given the body mass that needs to be carried by the skeleton (Cymbaluk et al., 1990; Barneveld and van Weeren, 1999). Others propose that it is rather the increased intramembranous and endochondral ossification rate, as

indicated by higher canon width gain and growth rate, respectively, that are predisposing factors for OC (Donabedian et al., 2006).

Growth is determined by the complex interaction between genetics and the environment (Stromberg, 1979; Staniar, 2010; Kocher and Staniar, 2013). The impact of genetic factors on growth is evident when comparing horses with ponies. Hendrickson et al. (2015) suggested that the higher prevalence of OC in horses than in ponies is due to a higher rate of vascular incorporation into the ossification front of horses, increasing the risk of vascular failure. Additionally, the thicker growth cartilage in horses makes adequate diffusion of nutrients from adjacent patent vessels or synovial fluid, less likely due to the physical distance, further increasing the risk of ischemia and OC.

While the final skeletal height is genetically determined, the time frame in which an individual achieves this height is influenced by the environment and, more in particular, the energy balance (Thompson et al., 1988a; Thompson et al., 1988b; Cymbaluk et al., 1990). Especially, short-term variations in growth patterns are influenced by the environment and are therefore more accessible for management interventions (Kocher and Staniar, 2013) Nonetheless, rapid growth can still solely be due to genetic predisposition, and excessive energy intake does not necessarily lead to rapid growth in every individual. Regardless of the cause, whether genetic or environmental, rapid growth is a risk for the development of OC (Harris et al., 2004; Valette et al., 2004; Donabedian et al., 2006). Investigating differences in short-term growth rate variations during the windows of vulnerability of OC could elucidate some associations with OC occurrence particularly when looking at joint-specific OC lesions (Harris et al., 2004; Vervuert et al., 2005; Kocher and Staniar, 2013). The complex relationship among factors influencing growth parameters, indirectly influencing the prevalence of OC, highlights the need for further research encompassing all interconnected domains.

Numerous horse breeds have undergone extensive selective breeding to increase withers height (Viklund et al., 2011; Ablondi et al., 2019; Salek Ardestani et al., 2019; Almeida et al., 2021). Even today, many studbooks impose a minimum withers size in their breed standard as a prerequisite for allowing animals to be used for breeding purposes. Additionally, selection and feeding regimes are often focused on improving the physical appearance of foals and yearlings, particularly for auction purposes, thereby promoting increased growth rates. However, this form of management and selection may, unintentionally, contribute to a higher occurrence of OC, posing equine welfare concerns.

Anatomical conformation

A correlation exists between joint anatomy and the occurrence and severity of OC, as certain anatomical conformations can create uneven force distribution on joint surfaces. This can generate abnormal stresses (biomechanical overload) on growth cartilage, contributing to OC development (Pool, 1993; Pagan and Jackson, 1996; Ytrehus et al., 2007; Martel et al., 2016a). Additionally, Valette et al. (2004) emphasised the importance of the relation between body mass and bone surface bearing this mass. If this surface becomes smaller relative to the increasing animal's mass, the risk of OC increases. In pigs, selection based on exterior conformation and joint shape has shown a reduction in the incidence of severe stifle lesions (Ytrehus et al., 2007). Considering that there is a range of similarities between animal species (McCoy et al., 2013), it can be hypothesized that anatomical conformation is also important in horses. It has been suggested that horses with straight hocks are more prone to have OC of the intermediate ridge of the tibia and that some inherited conformational abnormalities could predispose to biomechanical trauma leading to POF (Pool, 1993). Outwardly rotated limb axes

may be factors in the development of hock OC (Sandgren et al., 1993b) and POF (Dalin et al., 1993; Sandgren et al., 1993b). However, there remains a noticeable lack of research in this field.

Nutrition

In our experience, interpreting and extrapolating findings of the extensive body of nutritional studies about OC is challenging. Most investigations focus on assessing the quantity and nutrient balance from additional feed such as concentrates and vitamin-mineral supplements, often without evaluating the quantity and composition of roughages. Moreover, these studies often have a low sample size and a lack of information on the type and source of other nutrients, and their metabolic effects, as well as information about how the diet is given and other environmental factors. Some studies only aim to meet the minimum NRC requirements for the "other" nutrients, compared to the nutrient that is targeted in a study. However, these minimum recommendations may not align with the optimum requirements for osteoarticular health, considering factors such as sex and age, leading to potential confounding variables (Kronfeld et al., 1990; Nery et al., 2006; Kocher and Staniar, 2013). As a result, the existing literature presents conflicting findings. Some studies found no significant impact of feeding practices in the pregnant mare, the lactating mare, and the growing foal on the occurrence of OC (Coenen et al., 2004; Lepeule et al., 2009), while other studies could reveal substantial effects, as elaborated upon below.

The maternal diet during gestation has demonstrated notable influences on intrauterine growth and maturation as part of foetal programming (George et al., 2009; Chavatte-Palmer et al., 2015; Peugnet et al., 2015; Robles et al., 2017). The foetus may perceive intrauterine malnutrition as a signal for metabolic and endocrine adaptations that are beneficial for short-term survival once born in the same environmental conditions as the mare, but could be adverse for adult health and longevity (Tauson et al., 2006). In horses, moderately increasing or decreasing the amount and/or changing the type of energy of the maternal diet does not appear to alter the birth weight of the foal but induces metabolic disturbances and influences colostrum and milk quality/yield, impacting passive immunity and foal growth rate (George et al., 2009; Peugnet et al., 2016b). Furthermore, the maternal diet can modulate the onset of endochondral ossification (Sandgren et al., 1993b; Vander Heyden et al., 2013), with possible implications for the osteoarticular health of offspring.

The nutrient supply through the maternal blood going to the placenta plays an important role in the interaction between energy and bone metabolism in the foetus (Confavreux et al., 2009; Chavatte-Palmer et al., 2017). This is shown by the large difference in percentage of OC affected foals from broodmares solely fed with roughage during gestation (4.2%) compared to broodmares fed with concentrates (non-roughage feed) (38.9%), regardless of pasture access (Vander Heyden et al., 2013). Comparably, a decreased incidence of OC was detected in forage-fed energy-deficient broodmares (energy mainly derived from volatile fatty acids) compared to foals of broodmares fed with forage and concentrates with optimal body condition score (energy mainly derived from simple carbohydrates) (Peugnet et al., 2015). The difference in OC incidence of animals examined by Peugnet et al. (2015) at 7 months old diminished at 24 months old (Robles et al., 2017). Nevertheless, foals of energy-deficient broodmares had narrower cannon bones at 19 months of age, suggesting compromised bone strength and mineral content, possibly linked to maternal undernutrition-induced sedentary behaviour (Robles et al., 2017). Maternal obesity during gestation, regardless of nutrition, is significantly linked to a higher prevalence of OC in foals at 12 months. This higher prevalence is accompanied by a low-grade inflammation until 6 months of age and enhanced insulin resistance, both potentially playing a role in OC pathogenesis (Robles et al., 2018).

In foals, excessive energy intake increases the risk of OC development (Stromberg, 1979; Glade and Belling, 1986; Savage et al., 1993a; Valette et al., 2004). Cymbaluk et al. (1990) observed that high energy intake, resulting from ad libitum feeding regime, led to strenuous activity behaviour in young horses when turned out. This can lead to the negative effects discussed in the 'biomechanical trauma and exercise' section. Glade and Belling (1986) attributed the increased risk for OC to hindered capillary penetration by the presence of abnormal cartilage matrix components and high intracellular pH induced by excessive energy intake, although the link between these aspects still requires further elucidation.

Excessive energy intake can result in steeper growth curves (Donabedian et al., 2006), potentially adversely affecting joint development, as discussed in the 'growth section'. Besides the skeletal overload due to higher weight, the high-energy-induced steeper growth curve might also lead to an insufficiency of other nutrients essential for good bone quality (Thompson et al., 1988b; Kronfeld et al., 1990; Valette et al., 2004; Staniar, 2010), This, in turn, may lead to lower resilience of the immature skeleton and joints to physiological biomechanical forces. While high-protein diets may reduce growth rates by requiring energy for amino acid processing and excess ammonia removal, there is currently no evidence supporting a major role of protein intake in influencing the occurrence of OC (Savage et al., 1993a; Harris et al., 2004).

The type of energy intake could also be associated with the risk of OC. OC-positive foals fed without concentrates from weaning (around 6 months old) onwards have a significantly ($P = 0.001$) higher probability of becoming OC-negative at 18 months. There was no significant ($P = 0.06$) higher probability of OC-negative foals at 6 months old to become OC-positive at 18 months old when fed concentrates from weaning onwards (Mendoza et al., 2016). It can be hypothesized that a cereal-rich ration with high concentrations of hydrolysable carbohydrates, resulting in a high glycaemic response, significantly influences hormonal systems important for skeletal development. Moreover, the feeding-fasting cycle in 'modern' management practices may disturb the natural hormonal balance in a, by nature, continuous grazing animal (Staniar, 2010). The hormonal influence on the prevalence of OC is further discussed in the 'hormonal factors' section.

A correct balance of vitamins and minerals is important to support optimal bone growth in horses (Ellis, 2004). Therefore, in terms of nutritional balance, much research has been conducted to investigate the relationship between the development of OC and variations in the concentrations of vitamins and minerals in the feed and blood serum of the pregnant mare, the lactating mare, and the developing foal. An overview of this research is given in Table 2.

Table 2
Overview of research on the relationship between osteochondrosis and micronutrient levels.

Micronutrient	References
Calcium	Knight et al., 1986; Savage et al., 1993b; Hintz, 1996; Van Oldruitenborgh-Oosterbaan et al., 1999; Harris et al., 2004; Valette et al., 2004; Winkelsett et al., 2005
Copper	Carbery, 1978; Bridges et al., 1984; Knight et al., 1986; Bridges and Harris, 1988; Bridges and Moffitt, 1990; Knight et al., 1990; Cymbaluk and Smart, 1993; Hurtig et al., 1993; Davies et al., 1996; Hintz, 1996; Jeffcott and Davies, 1998; Pearce et al., 1998a; Pearce et al., 1998b; Pearce et al., 1998c; Van Weeren et al., 2003; Harris et al., 2004; Valette et al., 2004; Gee et al., 2005; Winkelsett et al., 2005; Gee et al., 2007; Vidal et al., 2009
Magnesium	Counotte et al., 2014
Phosphor	Knight et al., 1986; Savage et al., 1993b; Savage et al., 1993c; Hintz, 1996; Harris et al., 2004; Valette et al., 2004
Vitamin A	Donoghue et al., 1981; Knight et al., 1986; Ellis, 2004
Vitamin D	El Shorafa et al., 1979; Van Oldruitenborgh-Oosterbaan et al., 1999
Zinc	Gunson et al., 1982; Bridges et al., 1984; Eamens et al., 1984; Knight et al., 1986; Coger et al., 1987; Bridges and Moffitt, 1990; Campbell-Beggs et al., 1994; Davies et al., 1996; Hintz, 1996; Harris et al., 2004; Vidal et al., 2009

Research on copper (Cu) revealed a decrease in the prevalence and severity of OC lesions in foals with high Cu storage in their liver due to oral Cu supplementation to pregnant mares (Knight et al., 1990; Pearce et al., 1998a; Pearce et al., 1998b; Pearce et al., 1998c). Notably, the impact of Cu supplementation on foals in these studies is believed to be limited, as foals inefficiently absorb Cu from their digestive tract during the first months of life (Vervuert and Ellis, 2013). Furthermore, supplementing Cu to lactating mares does not yield a higher Cu concentration in the milk (Winkelsett et al., 2005). The decrease in OC prevalence is suggested to be due to the positive effect of Cu supplementation on the repair process of OC lesions in the foal (Knight et al., 1990; Van Weeren et al., 2003). In contrast, parenteral Cu supplementation to gestational mares did not reveal any of the above effects in their offspring (Gee et al., 2005; Gee et al., 2007). Pearce et al. (1998c) observed substantial individual variability in liver Cu concentrations among foals descended from mares that received Cu supplementation. Based on these findings, it is proposed that the diversity in the genetic makeup of the foetus may contribute to differential Cu accumulation in utero. Additionally, Pearce et al. (1998c) identified a correlation between the liver Cu concentration of foals at birth and the age of the mare, suggesting age-related variations in Cu metabolism among pregnant mares.

Foals administered an oral mineral paste, leading to significantly elevated magnesium serum levels at 4 months old, have significantly lower odds of developing fetlock OC (*odds ratio: 2.8, 95% confidence interval: 1.4-5.8*) and hock OC (*odds ratio: 4.2, 95% confidence interval: 1.5-11.6*) at 5 MO compared to the placebo group. However, no statistical difference in the odds of developing stifle OC could be detected between the supplemented and placebo groups (*odds ratio: 0.8, 95% confidence interval: 0.4-1.7*). A second group of foals supplemented with magnesium-rich mineral pellets from an average of 5.5 months old onward, had a statistically significant 14.3% decrease in OC prevalence, with stifle OC prevalence reducing the most, reaching a final prevalence of 41.7% at 12 months old. In contrast, the placebo group showed no reduction in OC prevalence, reaching a final prevalence of 42.9% (Counotte et al., 2014). This suggests a potential beneficial effect of magnesium supplementation on OC occurrence. Despite numerous research efforts to identify other links between minerals/vitamins and the prevalence of OC, robust evidence could not be provided, except in cases of extreme under- or over-supplementation. However, these extreme cases cannot be directly compared to real-world field conditions and, in most instances, lead to generalised lesions rather than OC lesions at typical predilection sites (Pool, 1993). In conclusion, OC prevalence and severity seem to be more influenced by the quantity and type of energy consumed than by differences in nutrient balance.

An important principle is to adjust the foal's diet based on its needs and genetic predisposition, ensuring that its growth follows an optimal curve to minimize the prevalence of osteochondral disorders (Kronfeld et al., 1990). While limited information is available on how an optimal growth curve should look like (Jelan et al., 1996; Vervuert et al., 2004; Kocher and Staniar, 2013), it seems best to avoid rapid changes in growth and to strive for the smoothest and most continuous growth curve possible, reducing the risk of biomechanical overload, as discussed in the ‘growth’ and ‘biomechanical trauma and exercise’ sections. This can be monitored with direct measures such as withers height, girth circumference and body mass, with any sudden change signalling the need for closer monitoring (Kocher and Staniar, 2013; Lepeule et al., 2013a; Fradinho et al., 2019). Conversely, the optimal growth pattern for osteoarticular health may conflict with economic goals, such as foal and yearling auction, due to decreased maturity (Kronfeld et al., 1990).

Weaning

Weaning is a highly stressful period for foals nutritionally, physically and psychologically. This stress is particularly high in domestic settings where separation from the dam often occurs abruptly at the age of 4-6 months, in contrast to the gradual process in nature, which starts around 8 months old (Waran et al., 2008; Dubcová et al., 2015). Different weaning management approaches and associated stress levels can have, often temporary, effects on factors associated with OC occurrence. These effects include alterations in growth rates (Reichmann et al., 2004; Brown-Douglas et al., 2005; Kocher and Staniar, 2013), weight gain rates (Cymbaluk and Laarveld, 1996; Warren et al., 1998; Coleman et al., 1999; Rogers et al., 2004; Waran et al., 2008; Dubcová et al., 2015), immunity (Waran et al., 2008), blood and saliva cortisol concentrations (Dubcová et al., 2015), locomotor patterns (McCall et al., 1985; Waran et al., 2008), serum insulin-like growth factor 1 (IGF-I) levels (Cymbaluk and Laarveld, 1996), serum osteocalcin levels (Fletcher et al., 2000), cannon bone circumference growth (Warren et al., 1998) and bone mineral content (Reichmann et al., 2004).

Between foals, there is large individual variability in the ability to cope with weaning suggesting that, besides management, also individual differences in maturity, reactivity, maternal bond and maternal parity may influence the coping ability and associated physical effects (Cymbaluk and Laarveld, 1996; Rogers et al., 2004; Waran et al., 2008). The amount (Waran et al., 2008), content (Nicol et al., 2005), and processing method (Flores et al., 2011) of solid feed provided before weaning can influence stress levels, with creep feed and fibre diets being more beneficial than high sugar and starch diets (Nicol et al., 2005). Growth curve deviations and other stress-related effects due to weaning management could increase the occurrence of OC, DOF and POF, particularly in commercial conditions where early weaning for auctions may increase stress levels (Harris et al., 2004). Unfortunately, longitudinal studies examining the impact of different pre-weaning, weaning, and post-weaning management practices on the occurrence of OC, DOF, and POF are currently lacking.

Hormonal factors

The relationship between hormones and OC has been extensively studied. Some of the hormones investigated are IGF-I and IGF-II, which play an important role in mediating the functions of growth hormones. They can act as mitogens for equine chondrocytes, promoting their growth and differentiation (Henson et al., 1997a; Ellis, 2004; Staniar, 2010). IGF-I can influence cartilage repair by stimulating cartilage matrix synthesis and inhibiting cartilage matrix degradation (Verwilghen et al., 2009; Staniar, 2010). Because IGF-I levels are initially high in colostrum and then plateau to low levels in mare's milk (Cymbaluk and Laarveld, 1996; Palm et al., 2013), the increase in plasma IGF-I of foals from 2 days old onwards is due to endogenous synthesis (Palm et al., 2013). Foals under 12 months old with OC showed significantly lower plasma levels of IGF-I (Van Oldruitenborgh-Oosterbaan et al., 1999). This is interesting as foals of primiparous 3-year-old mares have lower serum IGF-I (Cymbaluk and Laarveld, 1996), and foals born to mares under 10 years old have significantly higher odds of developing OC (*odds ratio of 2.3, 95% confidence interval: 1.0-4.72*) compared to foals born to mares between 10 and 15 years old (Lepeule et al., 2009).

High glycaemic peaks, high insulin peaks and persisting elevated plasma insulin levels due to reduced insulin sensitivity resulting from diets high in sugar and starch may predispose foals to develop OC (Glade et al., 1984; Ralston, 1996; Jeffcott and Henson, 1998; Pagan et al., 2001; Harris et al., 2004; Treiber et al., 2005; Staniar, 2010). The study of Henson et al. (1997a) suggested that insulin levels and the associated IGF-I and IGF-II levels are important for the survival and differentiation of foetal and, to a lesser extent, post-natal chondrocytes. Disruption

in insulin/glucose balance can disturb this interaction, potentially leading to increased OC occurrence. However, this idea is contradicted by the findings of Ott et al. (2005) who showed no difference in the incidence of OC between groups fed with low-, medium- and high-starch concentrate.

The relationship between thyroid hormones and OC has been under investigation, given that increased insulin can decrease thyroid hormone production which is important in blood vessel invasion, collagen and proteoglycan synthesis, and chondrocyte differentiation in growth cartilage (Glade and Belling, 1984; Glade et al., 1984; Savage et al., 1993a; Ellis, 2004; Ahmadi et al., 2021). Due to the inhibitory effect of cortisol on IGF-I, some studies measured serum cortisol concentrations, revealing lower levels in foals affected by OC (Van Oldruitenborgh-Oosterbaan et al., 1999) and an increase in fasting serum cortisol concentrations in horses consuming high-energy diets (Glade et al., 1984; Savage et al., 1993a). Despite these investigations, conclusive findings regarding the precise relationship between these hormones and OC remain elusive.

In conclusion, hormones and factors influencing them could be important in the development and/or healing process of OC due to their role in cartilage metabolism, chondrocyte maturation and bone formation. Hormonal abnormalities could directly disrupt the process of endochondral ossification, leading to OC, or may act permissively for other factors to trigger OC development. Additionally, they might result in a diminished healing response when OC lesions are present. Despite the identified links between bone development and the different hormones mentioned above, the exact reason for an association with OC occurrence still requires further elucidation.

Bacterial infection

Bacteraemia and the ensuing inflammatory response can compromise endothelial integrity, providing bacteria with the potential to colonize, impair, and obstruct cartilage canal vessels. This bacterial-induced destruction of cartilage canal blood supply can result in ischemic chondronecrosis, with or without osteomyelitis, depending on the age-related location of the affected vessels. Ischaemic chondronecrosis forms an initial step towards the development of (septic) OC (Wormstrand et al., 2018). Hendrickson et al. (2018) observed significantly increased OC prevalence in standardbred horses that underwent a bacterial infection from 1-150 days old. Additionally, they detected a significantly higher number of affected joints and number of lesions per affected horse. Bacterial-induced osteochondral lesions appear to exhibit differences in symmetry and severity of lesions. For POF specifically, there also appears to be variation in the location of lesions, with a higher proportion of them being located laterally. The relative contributions to OC prevalence of direct bacterial impairment and obstruction of cartilage canal vessels, as compared to systemic effects of illness on factors such as nutrition, growth, and physical activity, remain to be clarified. Nonetheless, both the maternal immunity of the foal and the microbial load should be regarded as important environmental factors.

Sex

The influence of sex on the occurrence of OC is not clear. Sex differences in the prevalence of OC appear to depend on the breed and OC location under investigation (Hilla and Distl, 2014). Several studies report significant differences in prevalence between males and females. Some report a higher prevalence in males (Stromberg, 1979; Philipsson et al., 1993; Sandgren et al., 1993a), while for the South German Coldblood horse, a higher prevalence has been reported in females (Wittwer et al., 2006). Conversely, multiple studies could not identify significant sex differences in disease prevalence (Hoppe, 1984; GrØndahl, 1991; Philipsson et

al., 1993; van Weeren et al., 1999; Vervuert et al., 2004; Stock et al., 2006; Lepeule et al., 2009). Similarly, no significant sex differences in disease prevalence of POF could be detected (Philipsson et al., 1993; Sandgren et al., 1993a). If genuine differences exist, it is theorized that these variations arise due to hormonal effects (Cymbaluk and Laarveld, 1996; Stock et al., 2005; Robert et al., 2013), sex-dependent growth rates (Goyal et al., 1981; Stock et al., 2005) and/or differences in the rate of ossification (Wittwer et al., 2006).

Date of birth

Numerous authors have reported an association between the month of birth and the prevalence of OC (Philipsson et al., 1993; Sandgren et al., 1993a; Pagan and Jackson, 1996; Wilke et al., 2003; Wittwer et al., 2006; Lepeule et al., 2009; Hilla and Distl, 2014) and POF (Philipsson et al., 1993), while others could not identify a relationship (Vervuert et al., 2004). van Weeren et al. (1999) also did not identify this relationship, possibly because most foals (30/43) were born in the same 2 months. Given distinct weather conditions between months, the month of birth determines whether a foal is primarily housed indoors or outdoors, thereby significantly influencing exercise, feed quantity and quality, associated growth rates and the timing of management changes. Therefore, it is not surprising that differences in the development of body mass and withers height, depending on the month of birth, are noticed (Harris et al., 2004; Brown-Douglas et al., 2005; Kocher and Staniar, 2013). Consequently, it is believed that the difference in prevalence of OC is primarily due to variation in rearing conditions during the windows of vulnerability, rather than directly by the month of birth itself. Supporting this perspective, the effects on plasma concentrations of bone turnover markers due to the rearing conditions associated with the month of birth have been described (Price et al., 2001; Fradinho et al., 2006; Vervuert et al., 2007).

Other environmental factors

Multiple other environmental factors have been investigated for an association with the risk of developing OC, DOF and POF. However, the outcomes have yielded only limited evidence for favourable, adverse, or neutral effects. Among these factors are group size (Lepeule et al., 2009), age at which grass is first made available to foals (Lepeule et al., 2009), changes in the makeup of the broodmare group (Lepeule et al., 2009), metacarpal and carpal circumference (Sandgren et al., 1993a; Sandgren et al., 1993b), administration of polysulfated glycosaminoglycans (White et al., 2007) and standing-up behaviour (van Grevenhof et al., 2017). More details on these factors are presented in Table 3.

Table 3
Other factors associated with OC, DOF and/or POF prevalence and severity.

Factor	Findings	References
Group size*	20% of 25 foals that were kept in a group <3 brood mares at less than 2 months old were affected with OC. 33% of 135 foals that were kept in a group ≥ 3 brood mares at less than 2 months old and <8 brood mares afterwards were affected with OC. 34% of 167 foals that were kept in a group ≥ 3 brood mares at less than 2 months old and >8 brood mares afterwards were affected with OC.	Lepeule et al., 2009
Age of first grass intake*	41% of 64 foals, 28% of 129 foals, 31% of 89 foals, 39% of 46 foals and 56% of 16 foals where OC-positive if age at which grass is first made available is 1 week old, 2 weeks old, 3-4 weeks old, 2 months old and ≥3 months old, respectively.	Lepeule et al., 2009
Changes within broodmare groups*	22% of 90 foals and 36% of 226 foals were OC-positive if there was no or at least one change of broodmares within a broodmare group, respectively.	Lepeule et al., 2009
Metacarpal circumference	Significantly larger circumference at the midpoint of left metacarpus in foals that developed hock OC	Sandgren et al., 1993b
Carpal circumference	Significantly larger circumference of the carpus in foals that developed POF or hock OC	Sandgren et al., 1993a; Sandgren et al., 1993b
Polysulfated glycosaminoglycans	Intramuscular injection of polysulfated glycosaminoglycans to foals from 8 weeks old until November of the foal's yearling year reduced the severity of DOF and OC lesions indicated by a reduced number of clinically significant DOF lesions and reduced number of required surgeries for both DOF and OC lesions.	White et al., 2007
Standing-up behaviour	Foals that stand up more often with the hindlimbs first or are prone to sliding during standing up do not present a significant increase in hock OC at 6 and 12 months old.	van Grevenhof et al., 2017

DOF, Dorsal osteochondral fragments of the proximal phalanx; OC, Osteochondrosis; POF, Palmar- and plantarproximal osteochondral fragments of the proximal phalanx.
*, These factors led to a significant correlation with OC prevalence in univariate analysis but not in the final multivariable mixed effects logistic regression model.

Conclusion

This scoping review presents the current evidence regarding the environmental factors that are associated with the occurrence of OC, DOF, and POF in horses. While research on DOF and POF remains scarce, understanding the environmental impact on OC prevalence remains challenging due to the dynamic nature and varying phenotypes of the disease, as well as the methodological differences across studies. Various factors such as prenatal environment, biomechanical loading, exercise, growth, anatomical conformation, nutrition, weaning, hormonal factors, bacterial infection are discussed in relation to the development, and, if applicable, healing of these disorders. Additionally, the interplay amongst the environmental factors and between the environmental and the genetic factors are addressed. Future research should engage in a multidisciplinary approach, with an emphasis on longitudinal studies and precise phenotype definitions to better understand the complex interactions and determine causal or correlational relationships between environmental factors and OC, DOF, and POF. This enhanced understanding will inform the development of comprehensive management strategies aimed at improving equine orthopaedic health.

Conflict of interest statement

None of the authors of this paper has a financial or personal relationship with other people or organisations that could inappropriately influence or bias the content of the paper.

Acknowledgement

Bram Van Mol received a PhD fellowship in fundamental research from The Research Foundation – Flanders (FWO-FR 11B3921N).

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version.

References

Ablondi, M., Viklund, Å., Lindgren, G., Eriksson, S., Mikko, S., 2019. Signatures of selection in the genome of swedish warmblood horses selected for sport performance. BMC Genomics 20.

Adams, O.R., 1966. Chip fractures of the first phalanx in the metacarpophalangeal (fetlock)joint. Journal of the American Veterinary Medical Association 148, 360-363.

Adams, R., Poulos, P., 1988. A skeletal ossification index for neonatal foals. Veterinary Radiology 29, 217-222.

Ahmadi, F., Mirshahi, A., Mohri, M., Sardari, K., Sharif, K., 2021. Osteochondrosis dissecans (ocd) in horses: Hormonal and biochemical study (19 cases). Veterinary Research Forum 12, 325-331.

Allen, W.R., Wilsher, S., Tiplady, C., Butterfield, R.M., 2004. The influence of maternal size on pre- and postnatal growth in the horse: Iii postnatal growth. Reproduction 127, 67-77.

Almeida, J.A.T.d., Lucena, J.E.C., Santiago, J.M., Gonzaga, I.V.F., Nascimento, C.A.d.M.S., Miranda, M.B.R.d., Pinto, A.P.G., 2021. Temporal analysis of demographic and biometric parameters of the mangalarga breed. Ciencia Rural 51.

Ammann, L., Ohlerth, S., Furst, A.E., Jackson, M.A., 2022. Differences of morphological attributes between 62 proximal and distal subchondral cystic lesions of the proximal phalanx as determined by radiography and computed tomography. American journal of veterinary research 83.

Baccarin, R.Y.A., Pereira, M.A., Roncati, N.V., Bergamaschi, R.R.C., Hagen, S.C.F., 2012. Development of osteochondrosis in lusitano foals: A radiographic study. Canadian Veterinary Journal-Revue Veterinaire Canadienne 53, 1079-1084.

Barneveld, A., van Weeren, P.R., 1999. Conclusions regarding the influence of exercise on the development of the equine musculoskeletal system with special reference to osteochondrosis. Equine Veterinary Journal Supplement 31, 112-119.

Brama, P.A.J., Tekoppele, J.M., Bank, R.A., Barneveld, A., Van Weeren, P.R., 2000. Functional adaptation of equine articular cartilage: The formation of regional biochemical characteristics up to age one year. Equine Veterinary Journal 32, 217-221.

Brama, P.A.J., Tekoppele, J.M., Bank, R.A., Van Weeren, P.R., Barneveld, A., 1999. Influence of different exercise levels and age on the biochemical characteristics of immature equine articular cartilage. Equine Veterinary Journal 31, 55-61.

Bridges, C., Harris, E., 1988. Experimentally induced cartilaginous fractures (osteochondritis dissecans) in foals fed low-copper diets. Journal of the American Veterinary Medical Association 193, 215-221.

Bridges, C., Moffitt, P., 1990. Influence of variable content of dietary zinc on copper metabolism of weanling foals. American journal of veterinary research 51, 275-280.

Bridges, C., Womack, J., Harris, E., Scrutchfield, W., 1984. Considerations of copper metabolism in osteochondrosis of suckling foals. Journal of the American Veterinary Medical Association 185, 173-178.

Brown-Douglas, C.G., Parkinson, T.J., Firth, E.C., Fennessy, P.F., 2005. Bodyweights and growth rates of spring- and autumn-born thoroughbred horses raised on pasture. New Zealand Veterinary Journal 53, 326-331.

Campbell-Beggs, C.L., Johnson, P.J., Messer, N.T., Lattimer, J.C., Johnson, G., Casteel, S.W., 1994. Osteochondritis dissecans in an appaloosa foal associated with zinc toxlcosis. Journal of Equine Veterinary Science 14, 546-550.

Carbery, J.T., 1978. Osteodysgenesis in a foal associated with copper deficiency. New Zealand Veterinary Journal 26, 279-279.

Carlson, C.S., Cullins, L.D., Meuten, D.J., 1995. Osteochondrosis of the articular-epiphyseal cartilage complex in young horses: Evidence for a defect in cartilage canal blood supply. Veterinary pathology 32, 641-647.

Carlsten, J., Sandgren, B., Dalin, G., 1993. Development of osteochondrosis in the tarsocrural joint and osteochondral fragments in the fetlock joints of standardbred trotters. I. A radiological survey. Equine Veterinary Journal 25, 42-47.

Chavatte-Palmer, P., Peugnet, P., Robles, M., 2017. Developmental programming in equine species: Relevance for the horse industry. Animal Frontiers 7, 48-54.

Chavatte-Palmer, P., Richard, C., Peugnet, P., Robles, M., Rousseau-Ralliard, D., Tarrade, A., 2015. The developmental origins of health and disease: Importance for animal production. Animal reproduction 12, 505-520.

Clothier, J., Small, A., Hinch, G., Brown, W.Y., 2020. Prematurity and dysmaturity are associated with reduced height and shorter distal limb length in horses. Journal of Equine Veterinary Science 91, 103129.

Coenen, M., Vervuert, I., Granel, M., Winkelsett, S., Borchers, A., Christmann, L., Bruns, E., Distl, O., Hertsch, B., 2004. Feeding practice in hanoverian warmblood mares and foals with regard to the incidence of osteochondrose, In: 2nd European Workshop on Equine Nutrition, ENESAD, Dijon, France, pp. 239-240.

Coger, L., Hintz, H., Schryver, H., Lowe, J., 1987. The effect of high zinc intake on copper metabolism and bone development in growing horses, In: Proceeding 10th Equine Nutrition & Physiology Symposium, p. 173.

Coleman, R.J., Mathison, G.W., Burwash, L., 1999. Growth and condition at weaning of extensively managed creep-fed foals. Journal of Equine Veterinary Science 19, 45-50.

Confavreux, C.B., Levine, R.L., Karsenty, G., 2009. A paradigm of integrative physiology, the crosstalk between bone and energy metabolisms. Molecular and Cellular Endocrinology 310, 21-29.

Cornelissen, B.P.M., Van Weeren, P.R., Ederveen, A.G.H., Barneveld, A., 1999. Influence of exercise on bone mineral density of immature cortical and trabecular bone of the equine metacarpus and proximal sesamoid bone. Equine Veterinary Journal 31, 79-85.

Counotte, G., Kampman, G., Ir, V.H., 2014. Feeding magnesium supplement to foals reduces osteochondrosis prevalence. Journal of Equine Veterinary Science 34, 668-674.

Cymbaluk, N.F., Christison, G.I., Leach, D.H., 1990. Longitudinal growth analysis of horses following limited and ad libitum feeding. Equine Veterinary Journal 22, 198-204.

Cymbaluk, N.F., Laarveld, B., 1996. The ontogeny of serum insulin-like growth factor-i concentration in foals: Effects of dam parity, diet, and age at weaning. Domestic Animal Endocrinology 13, 197-209.

Cymbaluk, N.F., Smart, M.E., 1993. A review of possible metabolic relationships of copper to equine bone disease. Equine Veterinary Journal 25, 19-26.

Dalin, G., Sandgren, B., Carlsten, J., 1993. Plantar osteochondral fragments in the metatarsophalangeal joints in standardbred trotters; result of osteochondrosis or trauma? Equine Veterinary Journal 25, 62-65.

Davies, M., Pasqualicchio, M., Henson, F., Hernandez-Vidal, G., 1996. Effects of copper and zinc on chondrocyte behaviour and matrix turnover. Pferdeheilkunde 12, 367-370.

Declercq, J., Martens, A., Maes, D., Boussauw, B., Forsyth, R., Boening, K.J., 2009. Dorsoproximal proximal phalanx osteochondral fragmentation in 117 warmblood horses. Veterinary and comparative orthopaedics and traumatology : V.C.O.T 22, 1-6.

Denoix, J.M., Jeffcott, L.B., McIlwraith, C.W., van Weeren, P.R., 2013. A review of terminology for equine juvenile osteochondral conditions (jocc) based on anatomical and functional considerations. The Veterinary Journal 197, 29-35.

Dik, K.J., Enzerink, E., van Weeren, P.R., 1999. Radiographic development of osteochondral abnormalities, in the hock and stifle of dutch warmblood foals, from age 1 to 11 months. Equine Veterinary Journal Supplement 31, 9-15.

Donabedian, M., Fleurance, G., Perona, G., Robert, C., Lepage, O., Trillaud-Geyl, C., Leger, S., Ricard, A., Bergero, D., Martin-Rosset, W., 2006. Effect of fast vs. Moderate growth rate related to nutrient intake on developmental orthopaedic disease in the horse. Animal Research 55, 471-486.

Donoghue, S., Kronfeld, D.S., Berkowitz, S.J., Copp, R.L., 1981. Vitamin a nutrition of the equine: Growth, serum biochemistry and hematology. The Journal of Nutrition 111, 365-374.

Dubcová, J., Bartošová, J., Komárková, M., 2015. Effects of prompt versus stepwise relocation to a novel environment on foals' responses to weaning in domestic horses (equus caballus). Journal of Veterinary Behavior 10, 346-352.

Eamens, G., Macadam, J., Laing, E., 1984. Skeletal abnormalities in young horses associated with zinc toxicity and hypocuprosis. Australian Veterinary Journal 61, 205-207.

El Shorafa, W.M., Feaster, J.P., Ott, E.A., Asquith, R.L., 1979. Effect of vitamin d and sunlight on growth and bone development of young ponies. Journal of Animal Science 48, 882-886.

Ellerbrock, R.E., Canisso, I.F., Larsen, R.J., Garrett, K.S., Stewart, M.C., Herzog, K.K., Kersh, M.E., Moshage, S.G., Podico, G., Lima, F.S., et al., 2021. Fluoroquinolone

exposure in utero did not affect articular cartilage of resulting foals. Equine Veterinary Journal 53, 385-396.

Ellerbrock, R.E., Canisso, I.F., Roady, P.J., Litsky, A., Durgam, S., Podico, G., Li, Z., Lima, F.S., 2020. Administration of enrofloxacin during late pregnancy failed to induce lesions in the resulting newborn foals. Equine Veterinary Journal 52, 136-143.

Ellis, A.D., 2004. The potential impact of nutrition on bone growth in horses, In: 2nd European Workshop on Equine Nutrition, ENESAD, Dijon, France, pp. 257-271.

Firth, E.C., van Weeren, P.R., Pfeiffer, D.U., Delahunt, J., Barneveld, A., 1999. Effect of age, exercise and growth rate on bone mineral density (bmd) in third carpal bone and distal radius of dutch warmblood foals with osteochondrosis. Equine Veterinary Journal Supplement 31, 74-78.

Fletcher, K.L., Topliff, D.R., Cooper, S.R., Freeman, D.W., Geisert, R.D., 2000. Influence of age and sex on serum osteocalcin concentrations in horses at weaning and during physical conditioning. Journal of Equine Veterinary Science 20, 124-126.

Flores, R.S., Byron, C.R., Kline, K.H., 2011. Effect of feed processing method on average daily gain and gastric ulcer development in weanling horses. Journal of Equine Veterinary Science 31, 124-128.

Fontaine, P., Blond, L., Alexander, K., Beauchamp, G., Richard, H., Laverty, S., 2013. Computed tomography and magnetic resonance imaging in the study of joint development in the equine pelvic limb. The Veterinary journal 197, 103-111.

Fradinho, M.J., Ferreira-Dias, G., Mateus, L., Santos-Silva, M.F., Agrícola, R., Barbosa, M., Abreu, J.M., 2006. The influence of mineral supplementation on skeleton formation and growth in lusitano foals. Livestock Science 104, 173-181.

Fradinho, M.J., Mateus, L., Bernardes, N., Bessa, R.J.B., Caldeira, R.M., Ferreira-Dias, G., 2019. Growth patterns, metabolic indicators and osteoarticular status in the lusitano horse: A longitudinal study. PLoS One 14.

Gee, E., Davies, M., Firth, E., Jeffcott, L., Fennessy, P., Mogg, T., 2007. Osteochondrosis and copper: Histology of articular cartilage from foals out of copper supplemented and non-supplemented dams. Veterinary Journal 173, 109-117.

Gee, E.K., Firth, E.C., Morel, P.C.H., Fennessy, P.F., Grace, N.D., Mogg, T.D., 2005. Articular/epiphyseal osteochondrosis in thoroughbred foals at 5 months of age: Influences of growth of the foal and prenatal copper supplementation of the dam. New Zealand Veterinary Journal 53, 448-456.

George, L.A., Staniar, W.B., Treiber, K.H., Harris, P.A., Geor, R.J., 2009. Insulin sensitivity and glucose dynamics during pre-weaning foal development and in response to maternal diet composition. Domestic Animal Endocrinology 37, 23-29.

Glade, M.J., Belling, T.H., 1986. A dietary etiology for osteochondrotic cartilage. Journal of Equine Veterinary Science 6, 151-155.

Glade, M.J., Belling, T.H., Jr., 1984. Growth plate cartilage metabolism, morphology and biochemical composition in over- and underfed horses. Growth 48, 473-482.

Glade, M.J., Gupta, S., Reimers, T.J., 1984. Hormonal responses to high and low planes of nutrition in weanling thoroughbreds. Journal of Animal Science 59, 658-665.

Goyal, H.O., MacCallum, F.J., Brown, M.P., Delack, J.B., 1981. Growth rates at the extremities of limb bones in young horses. Canadian Veterinary Journal 22, 31-33.

GrØndahl, A.M., 1991. The incidence of osteochondrosis in the tibiotarsal joint of norwegian standardbred trotters. Journal of Equine Veterinary Science 11, 272-274.

Gunson, D., Kowalczyk, D., Shoop, C., Ramberg Jr, C., 1982. Environmental zinc and cadmium pollution associated with generalized osteochondrosis, osteoporosis, and nephrocalcinosis in horses. Journal of the American Veterinary Medical Association 180, 295-299.

Harris, P., Staniar, W., Ellis, A.D., 2004. Effect of exercise and diet on the incidence of dod, In: The Growing Horse: Nutrition and Prevention of Growth Disorders. Wageningen Academic Publishers, Wageningen, The Netherlands. 2nd European Conference on Equine Nutrition. Dijon, France, pp. 273-290.

Hellings, I.R., Dolvik, N.I., Ekman, S., Olstad, K., 2017. Cartilage canals in the distal intermediate ridge of the tibia of fetuses and foals are surrounded by different types of collagen. Journal of Anatomy 231, 615-625.

Hendrickson, E.H.S., Lykkjen, S., Dolvik, N.I., Olstad, K., 2018. Prevalence of osteochondral lesions in the fetlock and hock joints of standardbred horses that survived bacterial infection before 6months of age. BMC Veterinary Research 14.

Hendrickson, E.H.S., Olstad, K., Nodtvedt, A., Pauwels, E., van Hoorebeke, L., Dolvik, N.I., 2015. Comparison of the blood supply to the articular-epiphyseal growth complex in horse vs. Pony foals. Equine Veterinary Journal 47, 326-332.

Henson, F.M.D., Davenport, C., Butler, L., Moran, I., Shingleton, W.D., Jeffcott, L.B., Schofield, P.N., 1997a. Effects of insulin and insulin-like growth factors i and ii on the growth of equine fetal and neonatal chondrocytes. Equine Veterinary Journal 29, 441-447.

Henson, F.M.D., Davies, M.E., Jeffcott, L.B., 1997b. Equine dyschondroplasia (osteochondrosis)—histological findings and type vi collagen localization. The Veterinary Journal 154, 53-62.

Hilla, D., Distl, O., 2014. Heritabilities and genetic correlations between fetlock, hock and stifle osteochondrosis and fetlock osteochondral fragments in hanoverian warmblood horses. Journal of Animal Breeding and Genetics 131, 71-81.

Hintz, H., 1996. Mineral requirements of growing horses. Pferdeheilkunde 12, 303-306.

Hoppe, F., 1984. Radiological investigations of osteochondrosis dissecans in standardbred trotters and swedish warmblood horses. Equine Veterinary Journal 16, 425-429.

Howald, H., 1942. Zur kenntnis der osteochondrosis dissecans (osteochondritis dissecans). Archiv für orthopädische und Unfall-Chirurgie, mit besonderer Berücksichtigung der Frakturenlehre und der orthopädisch-chirurgischen Technik 41, 730-788.

Hurtig, M., Green, S.L., Dobson, H., Mikuni-Takagaki, Y., Choi, J., 1993. Correlative study of defective cartilage and bone growth in foals fed a low-copper diet. Equine Veterinary Journal 25, 66-73.

Jacquet, S., Robert, C., Valette, J.P., Denoix, J.M., 2013. Evolution of radiological findings detected in the limbs of 321 young horses between the ages of 6 and 18 months. The Veterinary Journal 197, 58-64.

Jeffcott, L.B., 1993. Problems and pointers in equine osteochondrosis. Equine Veterinary Journal 25, 1-3.

Jeffcott, L.B., 2004. Developmental diseases affecting growing horses, In: 2nd European Workshop on Equine Nutrition, ENESAD, Dijon, France, pp. 243-255.

Jeffcott, L.B., Henson, F., 1998. Studies on growth cartilage in the horse and their application to aetiopathogenesis of dyschondroplasia (osteochondrosis). The Veterinary Journal 156, 177-192.

Jeffcott, L.B., Davies, M.E., 1998. Copper status and skeletal development in horses: Still a long way to go. Equine Veterinary Journal 30, 183-185.

Jelan, Z.A., Jeffcott, L., Lundeheim, N., Osborne, M., 1996. Growth rates in thoroughbred foals. Pferdeheilkunde 12, 291-295.

Kawcak, C.E., Mcllwraith, C.W., 1994. Proximodorsal first phalanx osteochondral chip fragmentation in 336 horses. Equine Veterinary Journal 26, 392-396.

Knight, D.A., Gabel, A.A., Reed, S.M., Embertson, R.M., Tyznik, W.J., Bramlage, L.R., 1986. Correlation of dietary mineral to incidence and severity of metabolic bone disease in ohio and kentucky. Proceedings of the Annual Convention of the American Association of Equine Practitioners 31, 445-461.

Knight, D.A., Weisbrode, S.E., Schmall, L.M., Reed, S.M., Gabel, A.A., Bramlage, L.R., Tyznik, W.I., 1990. The effects of copper supplementation on the prevalence of cartilage lesions in foals. Equine Veterinary Journal 22, 426-432.

Kocher, A., Staniar, W.B., 2013. The pattern of thoroughbred growth is affected by a foal's birthdate. Livestock Science 154, 204-214.

König, 1888. Ueber freie körper in den gelenken. Deutsche Zeitschrift für Chirurgie 27, 90-109.

Kronfeld, D.S., Meacham, T.N., Donoghue, S., 1990. Dietary aspects of developmental orthopedic disease in young horses. Veterinary Clinics of North America: Equine Practice 6, 451-465.

Lecocq, M., Girard, C.A., Fogarty, U., Beauchamp, G., Richard, H., Laverty, S., 2008. Cartilage matrix changes in the developing epiphysis: Early events on the pathway to equine osteochondrosis? Equine Veterinary Journal 40, 442-454.

Lemirre, T., Santschi, E.M., Girard, C.A., Fogarty, U., Janes, J.G., Richard, H., Laverty, S., 2022. Microstructural features of subchondral radiolucent lesions in the medial femoral condyle of juvenile thoroughbreds: A microcomputed tomography and histological analysis. Equine Veterinary Journal 54, 601-613.

Lepeule, J., Bareille, N., Robert, C., Ezanno, P., Valette, J.P., Jacquet, S., Blanchard, G., Denoix, J.M., Seegers, H., 2009. Association of growth, feeding practices and exercise conditions with the prevalence of developmental orthopaedic disease in limbs of french foals at weaning. Preventive Veterinary Medicine 89, 167-177.

Lepeule, J., Bareille, N., Robert, C., Valette, J.-P., Jacquet, S., Blanchard, G., Denoix, J.-M., Seegers, H., 2013a. Association of growth, feeding practices and exercise conditions with the severity of the osteoarticular status of limbs in french foals. The Veterinary Journal 197, 65-71.

Lepeule, J., Bareille, N., Robert, C., Valette, J.P., Jacquet, S., Blanchard, G., Denoix, J.M., Seegers, H., 2013b. Association of growth, feeding practices and exercise conditions with the severity of the osteoarticular status of limbs in french foals. Veterinary Journal 197, 65-71.

Martel, G., Couture, C.A., Gilbert, G., Bancelin, S., Richard, H., Moser, T., Kiss, S., Legare, F., Laverty, S., 2016a. Femoral epiphyseal cartilage matrix changes at predilection sites of equine osteochondrosis: Quantitative mri, second-harmonic microscopy, and histological findings. Journal of Orthopaedic Research 34, 1743-1752.

Martel, G., Kiss, S., Gilbert, G., Anne-Archard, N., Richard, H., Moser, T., Laverty, S., 2016b. Differences in the vascular tree of the femoral trochlear growth cartilage at osteochondrosis-susceptible sites in foals revealed by swi 3t mri. Journal of Orthopaedic Research 34, 1539-1546.

McCall, C.A., Potter, G.D., Kreider, J.L., 1985. Locomotor, vocal and other behavioral responses to varying methods of weaning foals. Applied Animal Behaviour Science 14, 27-35.

McCoy, A.M., Toth, F., Dolvik, N.I., Ekman, S., Ellermann, J., Olstad, K., Ytrehus, B., Carlson, C.S., 2013. Articular osteochondrosis: A comparison of naturally-occurring human and animal disease. Osteoarthritis and Cartilage 21, 1638-1647.

McIlwraith, C.W., 1993. Inferences from referred clinical cases of osteochondritis dissecans. Equine Veterinary Journal 25, 27-30.

McIlwraith, C.W., 2013. Surgical versus conservative management of osteochondrosis. The Veterinary Journal 197, 19-28

Mcllwraith, C.W., Foerner, J.J., Davis, D.M., 1991. Osteochondritis dissecans of the tarsocrural joint: Results of treatment with arthroscopic surgery. Equine Veterinary Journal 23, 155-162.

Mendoza, L., Lejeune, J.P., Caudron, I., Detilleux, J., Sandersen, C., Deliege, B., Serteyn, D., 2016. Impact of feeding and housing on the development of osteochondrosis in foals-a longitudinal study. Preventive Veterinary Medicine 127, 10-14.

Nery, J., Schelino, G., O'Sullivan, J.A., Perona, G., Bergero, D., 2006. Dod incidence in thoroughbred foals between 23 and 45 weeks of age - growth, nutrition and genetic factors. Animal Research 55, 591-601.

Nicol, C.J., Badnell-Waters, A.J., Bice, R., Kelland, A., Wilson, A.D., Harris, P.A., 2005. The effects of diet and weaning method on the behaviour of young horses. Applied Animal Behaviour Science 95, 205-221.

Nixon, A.J., Pool, R.R., 1995. Histologic appearance of axial osteochondral fragments from the proximoplantar/proximopalmar aspect of the proximal phalanx in horses. Journal of the American Veterinary Medical Association 207, 1076-1080.

Olstad, K., Cnudde, V., Masschaele, B., Thomassen, R., Dolvik, N.I., 2008. Micro-computed tomography of early lesions of osteochondrosis in the tarsus of foals. Bone 43, 574-583.

Olstad, K., Ekman, S., Carlson, C.S., 2015a. An update on the pathogenesis of osteochondrosis. Veterinary pathology 52, 785-802.

Olstad, K., Hendrickson, E.H.S., Carlson, C.S., Ekman, S., Dolvik, N.I., 2013. Transection of vessels in epiphyseal cartilage canals leads to osteochondrosis and osteochondrosis dissecans in the femoro-patellar joint of foals; a potential model of juvenile osteochondritis dissecans. Osteoarthritis and Cartilage 21, 730-738.

Olstad, K., Ostevik, L., Carlson, C.S., Ekman, S., 2015b. Osteochondrosis can lead to formation of pseudocysts and true cysts in the subchondral bone of horses. Veterinary pathology 52, 862-872.

Olstad, K., Ytrehus, B., Ekman, S., Carlson, C.S., Dolvik, N.I., 2007. Early lesions of osteochondrosis in the distal tibia of foals. Journal of Orthopaedic Research 25, 1094-1105.

Olstad, K., Ytrehus, B., Ekman, S., Carlson, C.S., Dolvik, N.I., 2008a. Epiphyseal cartilage canal blood supply to the distal femur of foals. Equine Veterinary Journal 40, 433-439.

Olstad, K., Ytrehus, B., Ekman, S., Carlson, C.S., Dolvik, N.I., 2008b. Epiphyseal cartilage canal blood supply to the tarsus of foals and relationship to osteochondrosis. Equine Veterinary Journal 40, 30-39.

Olstad, K., Ytrehus, B., Ekman, S., Carlson, C.S., Dolvik, N.I., 2009. Epiphyseal cartilage canal blood supply to the metatarsophalangeal joint of foals. Equine Veterinary Journal 41, 865-871.

Ott, E.A., Brown, M.P., Roberts, G.D., Kivipelto, J., 2005. Influence of starch intake on growth and skeletal development of weanling horses. Journal of Animal Science 83, 1033-1043.

Pagan, J., Geor, R., Caddel, S., Pryor, P., Hoekstra, K., 2001. The relationship between glycemic response and the incidence of ocd in thoroughbred weanlings: A field study. Proceedings of the American Association of Equine Practitioners 47.

Pagan, J., Jackson, S.G., 1996. The incidence of developmental orthopedic disease on a kentucky thoroughbred farm. Pferdeheilkunde 12, 351-354.

Palm, F., Nagel, C., Bruckmaier, R.M., Aurich, J.E., Aurich, C., 2013. Clinical parameters, intestinal function, and igf1 concentrations in colostrum-deprived and colostrum-fed newborn pony foals. Theriogenology 80, 1045-1051.

Pearce, S.G., Firth, E.C., Grace, N.D., Fennessy, P.F., 1998a. Effect of copper supplementation on the evidence of developmental orthopaedic disease in pasture-fed new zealand thoroughbreds. Equine Veterinary Journal 30, 211-218.

Pearce, S.G., Grace, N.D., Firth, E.C., Wichtel, J.J., Holle, S.A., Fennessy, P.F., 1998b. Effect of copper supplementation on the copper status of pasture-fed young thoroughbreds. Equine Veterinary Journal 30, 204-210.

Pearce, S.G., Grace, N.D., Wichtel, J.J., Firth, E.C., Fennessy, P.F., 1998c. Effect of copper supplementation on copper status of pregnant mares and foals. Equine Veterinary Journal 30, 200-203.

Peugnet, P., Mendoza, L., Wimel, L., Duchamp, G., Dubois, C., Reigner, F., Caudron, I., Deliege, B., Toquet, M.P., Richard, E., et al., 2016a. Longitudinal study of growth and osteoarticular status in foals born to between-breed embryo transfers. Journal of Equine Veterinary Science 37, 24-38.

Peugnet, P., Robles, M., Mendoza, L., Wimel, L., Dubois, C., Dahirel, M., Guillaume, D., Camous, S., Berthelot, V., Toquet, M.P., et al., 2015. Effects of moderate amounts of barley in late pregnancy on growth, glucose metabolism and osteoarticular status of pre-weaning horses. PLoS One 10.

Peugnet, P., Robles, M., Wimel, L., Tarrade, A., Chavatte-Palmer, P., 2016b. Management of the pregnant mare and long-term consequences on the offspring. Theriogenology 86, 99-109.

Peugnet, P., Wimel, L., Duchamp, G., Sandersen, C., Camous, S., Guillaume, D., Dahirel, M., Dubois, C., Jouneau, L., Reigner, F., et al., 2014. Enhanced or reduced fetal growth induced by embryo transfer into smaller or larger breeds alters post-natal growth and metabolism in pre-weaning horses. PLoS One 9, e102044.

Philipsson, J., Andréasson, E., Sandgren, B., Dalin, G., Carlsten, J., 1993. Osteochondrosis in the tarsocrural joint and osteochondral fragments in the fetlock joints in standardbred trotters. Ii. Heritability. Equine Veterinary Journal 25, 38-41.

Pool, R., 1993. Difficulties in definition of equine osteochondrosis; differentiation of developmental and acquired lesions. Equine Veterinary Journal 25, 5-12.

Price, J.S., Jackson, B.F., Gray, J.A., Harris, P.A., Wright, I.M., Pfeiffer, D.U., Robins, S.P., Eastell, R., Ricketts, S.W., 2001. Biochemical markers of bone metabolism in growing thoroughbreds: A longitudinal study. Research in Veterinary Science 71, 37-44.

Ralston, S.L., 1996. Hyperglycemia/hyperinsulinemia after feeding a meal of grain to young horses with osteochondritis dissecans (ocd) lesions. Pferdeheilkunde Equine Medicine 12, 320-322.

Raub, R.H., Jackson, S.G., Baker, J.P., 1989. The effect of exercise on bone growth and development in weanling horses. Journal of Animal Science 67, 2508-2514.

Reichmann, P., Moure, A., Gamba, H.R., 2004. Bone mineral content of the third metacarpal bone in quarter horse foals from birth to one year of age. Journal of Equine Veterinary Science 24, 391-396.

Rejnö, S., Strömberg, B., 1978. Osteochondrosis in the horse. Ii. Pathology. Acta Radiol Suppl 358, 153-178.

Robert, C., Valette, J.P., Jacquet, S., Lepeule, J., Denoix, J.M., 2013. Study design for the investigation of likely aetiological factors of juvenile osteochondral conditions (jocc) in foals and yearlings. The Veterinary Journal 197, 36-43.

Robles, M., Gautier, C., Mendoza, L., Peugnet, P., Dubois, C., Dahirel, M., Lejeune, J.P., Caudron, I., Guenon, I., Camous, S., et al., 2017. Maternal nutrition during pregnancy affects testicular and bone development, glucose metabolism and response to overnutrition in weaned horses up to two years. PLoS One 12.

Robles, M., Nouveau, E., Gautier, C., Mendoza, L., Dubois, C., Dahirel, M., Lagofun, B., Aubriere, M.C., Lejeune, J.P., Caudron, I., et al., 2018. Maternal obesity increases insulin resistance, low-grade inflammation and osteochondrosis lesions in foals and yearlings until 18 months of age. PLoS One 13.

Rogers, C.W., Gee, E.K., Faram, T.L., 2004. The effect of two different weaning procedures on the growth of pasture-reared thoroughbred foals in new zealand. New Zealand Veterinary Journal 52, 401-403.

Rossdale, P.D., Ousey, J.C., 2002. Fetal programming for athletic performance in the horse: Potential effects of iugr. Equine Veterinary Education 14, 98-112.

Rovel, T., Zimmerman, M., Duchateau, L., Delesalle, C., Adriaensen, E., Marien, T., Saunders, J.H., Vanderperren, K., 2021. Computed tomographic examination of the articular process joints of the cervical spine in warmblood horses: 86 cases (2015-2017). Javma-Journal of the American Veterinary Medical Association 259, 1178-1187.

Salek Ardestani, S., Aminafshar, M., Zandi Baghche Maryam, M.B., Banabazi, M.H., Sargolzaei, M., Miar, Y., 2019. Whole-genome signatures of selection in sport horses revealed selection footprints related to musculoskeletal system development processes. Animals (Basel) 10.

Sandgren, B., Dalin, G., Carlsten, J., 1993a. Osteochondrosis in the tarsocrural joint and osteochondral fragments in the fetlock joints in standardbred trotters. I. Epidemiology. Equine Veterinary Journal 25, 31-37.

Sandgren, B., Dalin, G., Carlsten, J., Lundeheim, N., 1993b. Development of osteochondrosis in the tarsocrural joint and osteochondral fragments in the fetlock joints of standardbred trotters. Ii. Body measurements and clinical findings. Equine Veterinary Journal 25, 48-53.

Santschi, E.M., Prichard, M.A., Whitman, J.L., Batten, C.A., Strathman, T.A., Canada, N.C., Morehead, J.P., 2020. Stifle radiography in thoroughbreds from 6 to 18 months of age. Equine Veterinary Education 32, 78-84.

Savage, C.J., McCarthy, R.N., Jeffcott, L.B., 1993a. Effects of dietary energy and protein on induction of dyschondroplasia in foals. Equine Veterinary Journal 25, 74-79.

Savage, C.J., McCarthy, R.N., Jeffcott, L.B., 1993b. Effects of dietary phosphorus and calcium on induction of dyschondroplasia in foals. Equine Veterinary Journal 25, 80-83.

Savage, C.J., McCarthy, R.N., Jeffcott, L.B., 1993c. Histomorphometric assessment of bone biopsies from foals fed diets high in phosphorus and digestible energy. Equine Veterinary Journal 25, 89-93.

Shingleton, W.D., Mackie, E.J., Cawston, T.E., Jeffcott, L.B., 1997. Cartilage canals in equine articular/epiphyseal growth cartilage and a possible association with dyschondroplasia. Equine Veterinary Journal 29, 360-364.

Skarbek, A., Ramseyer, A., Koch, C., Van der Vekens, E., 2020. Radiography and standing computed tomography of an osteochondritis dissecans lesion found at the dorsodistolateral aspect of the calcaneus in a 3-year-old horse. Journal of Equine Veterinary Science 94.

Staniar, W.B., 2010. Linking dietary energy and skeletal development in the horse. Revista Brasileira de Zootecnia 39, 138-144.

Stock, K.F., Hamann, H., Distl, O., 2005. Prevalence of osseous fragments in distal and proximal interphalangeal, metacarpo- and metatarsophalangeal and tarsocrural joints of hanoverian warmblood horses. Journal of Veterinary Medicine Series A: Physiology, Pathology, and Clinical Medicine 52, 388-394.

Stock, K.F., Hamann, H., Distl, O., 2006. Factors associated with the prevalence of osseous fragments in the limb joints of hanoverian warmblood horses. Veterinary Journal 171, 147-156.

Stromberg, B., 1979. A review of the salient features of osteochondrosis in the horse. Equine Veterinary Journal 11, 211-214.

Tauson, A., Harris, P., Coenen, M., 2006. Intrauterine nutrition: Effect on subsequent health. In: Nutrition and feeding of the broodmare, Wageningen Academic, Leiden, The Netherlands, pp. 367-386.

Theiss, F., Hilbe, M., Fürst, A., Klein, K., von Rechenberg, B., 2010. Histologic evaluation of intraarticular osteochondral fragments. Pferdeheilkunde 26, 541-552.

Thompson, K.N., Baker, J.P., Jackson, S.G., 1988a. The influence of supplemental feed on growth and bone development of nursing foals. Journal of Animal Science, 1692-1696.

Thompson, K.N., Jackson, S.G., Baker, J.P., 1988b. The influence of high planes of nutrition on skeletal growth and development of weanling horses. Journal of Animal Science 66, 2459-2467.

Thorp, B.H., Farquharson, C., Kwan, A.P.L., Loveridge, N., 1993. Osteochondrosis/dyschondroplasia: A failure of chondrocyte differentiation. Equine Veterinary Journal 25, 13-18.

Treiber, K.H., Boston, R.C., Kronfeld, D.S., Staniar, W.B., Harris, P.A., 2005. Insulin resistance and compensation in thoroughbred weanlings adapted to high-glycemic meals. Journal of Animal Science 83, 2357-2364.

Tricco, A.C., Lillie, E., Zarin, W., O'Brien, K.K., Colquhoun, H., Levac, D., Moher, D., Peters, M.D.J., Horsley, T., Weeks, L., et al., 2018. Prisma extension for scoping

reviews (prisma-scr): Checklist and explanation. Annals of Internal Medicine 169, 467-473.

Valette, J.P., Paragon, B.M., Blanchard, G., Robert, C., Denoix, J.M., 2004. Feeding practices and prevention of developmental diseases, In: 2nd European Workshop on Equine Nutrition, ENESAD, Dijon, France, pp. 291-301.

van de Lest, C.H., Brama, P.A., Van Weeren, P.R., 2002. The influence of exercise on the composition of developing equine joints. Biorheology 39, 183-191.

van de Lest, C.H.A., Brama, P.A.J., van El, B., DeGroot, J., van Weeren, P.R., 2004. Extracellular matrix changes in early osteochondrotic defects in foals: A key role for collagen? Biochimica Et Biophysica Acta-Molecular Basis of Disease 1690, 54-62.

van den Hoogen, B.M., van den Lest, C.H., van Weeren, P.R., van Golde, L.M., Barneveld, A., 1999. Effect of exercise on the proteoglycan metabolism of articular cartilage in growing foals. Equine Veterinary Journal Supplement 31, 62-66.

van Grevenhof, E.M., Meerburg, A., van Dierendonck, M.C., van den Belt, A.J.M., van Schaik, B., Meeus, P., Back, W., 2017. Quantitative and qualitative aspects of standing-up behavior and the prevalence of osteochondrosis in warmblood foals on different farms: Could there be a link? BMC Veterinary Research 13.

Van Oldruitenborgh-Oosterbaan, M.M.S., Mol, J.A., Barneveld, A., 1999. Hormones, growth factors and other plasma variables in relation to osteochondrosis. Equine Veterinary Journal 31, 45-54.

van Weeren, P.R., Barneveld, A., 1999. The effect of exercise on the distribution and manifestation of osteochondrotic lesions in the warmblood foal. Equine Veterinary Journal Supplement 31, 16-25.

van Weeren, P.R., Brama, P.A.J., 2003. Equine joint disease in the light of new developments in articular cartilage research. Pferdeheilkunde 19, 336-+.

van Weeren, P.R., Knaap, J., Firth, E.C., 2003. Influence of liver copper status of mare and newborn foal on the development of osteochondrotic lesions. Equine Veterinary Journal 35, 67-71.

van Weeren, P.R., Van Oldruitenborgh-Oosterbaan, M.M.S., Barneveld, A., 1999. The influence of birth weight, rate of weight gain and final achieved height and sex on the development of osteochondrotic lesions in a population of genetically predisposed warmblood foals. Equine Veterinary Journal 31, 26-30.

Vander Heyden, L., Lejeune, J.-P., Caudron, I., Detilleux, J., Sandersen, C., Chavatte, P., Paris, J., Deliège, B., Serteyn, D., 2013. Association of breeding conditions with prevalence of osteochondrosis in foals. Veterinary Record 172, 68-68

Vervuert, I., Borchers, A., Granel, M., Winkelsett, S., Christmann, L., Distl, O., Bruns, E., Hertsch, B., Coenen, M., 2005. Estimation of growth rates in warmblood foals and the incidence of osteochondrosis. Pferdeheilkunde 21, 129-130.

Vervuert, I., Coenen, M., Borchers, A., Granel, M., Winkelsett, S., Christmann, L., Distl, O., Bruns, E., Hertsch, B., 2004. Growth rates in hanoverian warmblood foals and the

development of osteochondrosis, In: 2nd European Workshop on Equine Nutrition, ENESAD, Dijon, France, pp. 85-87.

Vervuert, I., Ellis, A.D., 2013. 32 - developmental orthopedic disease, In: Equine applied and clinical nutrition. W.B. Saunders, pp. 536-548.

Vervuert, I., Winkelsett, S., Christmann, L., Bruns, E., Hoppen, H.O., Distl, O., Hertsch, B., Coenen, M., 2007. Evaluation of the influences of exercise, birth date, and osteochondrosis on plasma bone marker concentrations in hanoverian warmblood foals. American journal of veterinary research 68, 1319-1323.

Verwilghen, D.R., Vanderheyden, L., Franck, T., Busoni, V., Enzerink, E., Gangl, M., Lejeune, J.P., van Galen, G., Grulke, S., Serteyn, D., 2009. Variations of plasmatic concentrations of insulin-like growth factor-i in post-pubescent horses affected with developmental osteochondral lesions. Veterinary Research Communications 33, 701-709.

Vidal, G.H., Garza, J.R.K., Romero, R.R., Tovar, L.E.R., Garza, A.M.N., Valdez, F.A.M., Hernandez, J.J., Davis, E., Jeffcott, L.B., 2009. Effects of copper and zinc on cathepsin b activity in equine articular chondrocytes. Journal of Animal and Veterinary Advances 8, 935-945.

Viklund, Å., Näsholm, A., Strandberg, E., Philipsson, J., 2011. Genetic trends for performance of swedish warmblood horses. Livestock Science 141, 113-122.

Waran, N.K., Clarke, N., Farnworth, M., 2008. The effects of weaning on the domestic horse (equus caballus). Applied Animal Behaviour Science 110, 42-57.

Warren, L.K., Lawrence, L.M., Parker, A.L., Barnes, T., Griffin, A.S., 1998. The effect of weaning age on foal growth and radiographic bone density. Journal of Equine Veterinary Science 18, 335-342.

White, G.W., Fregin, G.F., Selden, J.R., 2007. Effect of prophylactic intramuscular administration of polysulfated glycosaminoglycan on developmental and traumatic joint injuries in thoroughbred foals. Journal of Equine Veterinary Science 27, 107-111.

Wilke, A., Coenen, M., Distl, O., Hertsch, B., Christmann L., Bruns, E., 2003. Effect of locomotion on the development of osteochondrosis (oc) in hannovarian warmblood foals, In: Book of abstracts of the 54th annual eaap meeting. Wageningen Academic Publishers, Rome, Italy, p. 392.

Winkelsett, S., Vervuert, I., Granel, M., Borchers, A., Coenen, M., 2005. Feeding practice in warmblood mares and foals and the incidence to osteochondrosis. Pferdeheilkunde 21, pp. 124-126.

Wittwer, C., Hamann, H., Rosenberger, E., Distl, O., 2006. Prevalence of osteochondrosis in the limb joints of south german coldblood horses. Journal of Veterinary Medicine Series a-Physiology Pathology Clinical Medicine 53, 531-539.

Wormstrand, B., Ostevik, L., Ekman, S., Olstad, K., 2018. Septic arthritis/osteomyelitis may lead to osteochondrosis-like lesions in foals. Veterinary pathology 55, 693-702.

Wormstrand, B.H., Fjordbakk, C.T., Griffiths, D.J., Lykkjen, S., Olstad, K., 2021. Development of the blood supply to the growth cartilage of the medial femoral condyle of foals. Equine Veterinary Journal 53, 134-142.

Ytrehus, B., Carlson, C.S., Ekman, S., 2007. Etiology and pathogenesis of osteochondrosis. Veterinary pathology 44, 429-448.