Perinatal Management of Haemophilia

Werner Streif¹ Ralf Knöfler²

¹ Medizinische Universität Innsbruck (MUI), Department für Kinder- und Jugendheilkunde, Pädiatrie 1, Innsbruck, Austria

² Universitätsklinikum Dresden Klinik/Poliklinik für Kinder- und Jugendmedizin Bereich Hämatologie, Dresden, Germany

Address for correspondence Ao. Univ.-Prof. Dr. Werner Streif, Medizinische Universität Innsbruck (MUI), Department für Kinder- und Jugendheilkunde, Pädiatrie 1, Anichstrasse 35, A – 6020 Innsbruck, Österreich (e-mail: werner.streif@i-med.ac.at).

Hämostaseologie 2020;40:226–232.

Abstract

The aim of this review is to provide practical guidance for the treatment of carriers of haemophilia and newborns presenting with haemophilia. Both mother and newborn have an increased risk for clinically relevant bleeding. An experienced team should manage genetic counselling, prenatal diagnosis, pregnancy, delivery and the newborn presenting with haemophilia. Published and regularly updated guidelines must guide this team. Vaginal and caesarean deliveries before labour entail a comparable bleeding risk. Haemophilia carriers should receive factor concentrate (FC) at the time of delivery if their factor level is below normal. Evidence remains insufficient to recommend systemic desmopressin and tranexamic acid for the prevention of peripartum haemorrhage. Primary prophylaxis with FC for all newborns with severe haemophilia is not justified. The pattern of bleeding seen in the affected newborns is essentially different from that seen in older children. Estimated frequency of intracranial haemorrhage (ICH) is 2 to 3%. Cranial ultrasound is a good screening method for ICH in newborns. Many neonatal bleeds are iatrogenic in origin. The most prominent concerns regarding neonatal factor replacement are the risk for inhibitor development, followed by local bleeding and issues related to poor vascular access. The preference for plasma-derived FC and recombinant FC differs widely between centres and countries. Replacement therapy should be monitored since newborns may require higher doses of FC. Emicizumab, licensed for all age groups since 2019, should not be used in newborns with severe haemophilia A and acute bleeding, although “non-factor” agents are expected to revolutionise haemophilia therapy.

Keywords

- haemophilia
- pregnancy
- bleeding disorders

Zusammenfassung

Ziel dieser Übersicht ist eine praktische Anleitung zum Umgang mit Überträgerinnen von Hämophilie (Konduktorinnen) und Neugeborenen mit Hämophilie zu geben. Sowohl Konduktorinnen als auch betroffene Nachkommen haben ein relevant erhöhtes Blutungsrisiko. Nur ein erfahrenes Team sollte genetische Beratung, Pränatal diagnostik, Schwangerschaft, Geburt und das betroffene Neugeborene betreuen. Publierte und regelmäßig aktualisierte Leit- und Richtlinien müssen immer die Grundlage des Handelns sein. Die vaginale Entbindung und der elektive Kaiserschnitt haben ein vergleichbares Blutungsrisiko. Für Konduktorinnen, die bei der Geburt einen Faktorspiegel unter dem Normalwert aufweisen, sind Faktorkonzentrate empfohlen. Die Wirksamkeit von Desmopressin und Tranexamsäure zur Behandlung peri- und

received
November 4, 2019
accepted after revision
March 18, 2020

© 2020 Georg Thieme Verlag KG
Stuttgart · New York

DOI <https://doi.org/10.1055/a-1141-1252>.
ISSN 0720-9355.

postpartaler Blutungen ist nicht gesichert. Eine primäre Prophylaxe mit Faktorkonzentraten aller Neugeborenen mit schwerer Hämophilie ist nicht gerechtfertigt. Blutungen des Neugeborenen unterscheiden sich grundsätzlich von denen des älteren Kindes. In 2 bis 3% treten intrakranielle Blutungen auf. Die Ultraschalluntersuchung ist eine gute Suchmethode zum Ausschluss einer intrakraniellen Blutung beim Neugeborenen. Viele Blutungen werden erst durch medizinische Manipulationen verursacht. Die größten Bedenken gegen eine frühe Behandlung mit Faktorkonzentraten von hämophilen Neugeborenen sind die Entwicklung eines Hemmkörpers gegen FVIII/ IX, lokale Blutungskomplikationen und der problematische venöse Zugang. Unterschiedlich nach Land und Zentrum werden bevorzugt aus Plasma hergestellte oder rekombinante Faktorkonzentrate verabreicht. Bei jeder Faktorgabe sollte der Faktorspiegel überwacht werden, da Neugeborene mehr Faktor benötigen können als ältere Kinder. Zurzeit wird von der Verwendung von Emicizumab, das seit 2019 für alle Altersgruppen zugelassen ist, für Neugeborene mit schwerer Hämophilie A und akuter Blutung abgeraten, auch wenn zu erwarten ist, dass "non-factor" Medikamente die Behandlung der Hämophilie revolutionieren werden.

Schlüsselwörter

- ▶ Hämophilie
- ▶ Schwangerschaft
- ▶ Blutungsrisiko

Introduction

Haemophilia A and B are X-linked recessive bleeding disorders that are manifested clinically by excessive bleeding, which eventually leads to clinically relevant blood loss and tissue damage. Of all haemophilia patients, approximately 85% suffer from haemophilia A [factor VIII (FVIII) deficiency] and 15% from haemophilia B [factor IX (FIX) deficiency]. Maternal carriers of haemophilia have a 50% chance of passing on the gene defect. Severity of haemophilia is consistent among family members. The underlying genetic defect also has an effect on inhibitor development, which influences future treatment.

Both mother and newborn have an increased risk for clinically relevant bleeding and blood loss. With the advent of potentially curative strategies for haemophilia, it is imperative that newborns and infants with haemophilia be appropriately diagnosed and managed.

A literature search was conducted in PubMed. This concise review was compiled from published information including guidelines and from personal experience with haemophilia care. The aim of this review is to provide practical guidance for the treatment of carriers of haemophilia and newborns with haemophilia and to highlight important aspects and future developments in haemophilia care in the perinatal period.

Discussion

General Considerations and Aspects

Faced with a positive family history of haemophilia, a team consisting of obstetricians and paediatricians with experience in haemophilia care and 24-hour access to laboratory monitoring and factor replacement therapy should manage all aspects of haemophilia care including genetic counselling, prenatal testing, pregnancy, delivery and the newborn presenting with haemophilia. Written treatment plans that ad-

here to published guidelines and that enjoy a consensus of all involved specialists should be readily available. The diagnosis and its implications should be discussed with the parents before discharge from the hospital. Since bleeding problems can occur at any time, early referral to the local haemophilia treatment centre is highly recommended.

Identification of Carriers of Haemophilia

Although expected to have plasma concentrations of FVIII and FIX corresponding to half the concentration found in healthy individuals, a wide range of FVIII and FIX levels is observed in carriers of haemophilia.¹ This wide range is due to genetic factors including skewed X chromosome inactivation (lyonisation) and ABO blood group. Haemophilia carriership is often not readily considered when unexpected bleeding and blood loss occur in the perinatal period.^{2,3} It is estimated that $\geq 30\%$ of haemophilia cases occur as a consequence of new mutations and affect either the male offspring or a female carrier in whom no personal or family history of bleeding problems is evident. A comprehensive guideline that addresses diagnosis and treatment of unexpected bleeding during and shortly after delivery was published by the AWMF # 015/063 (Peripartale Blutungen, Diagnostik und Therapie).⁴

Genetic Testing and Foetal Sexing

Genetic testing is a powerful and important tool for screening and counselling for haemophilia. The aim of any genetic counselling is to allow future parents to reach a decision that is appropriate for their situation. Families at risk have the option of (1) declining prenatal testing and accepting the risk of having an affected child; (2) conceiving naturally and having a prenatal diagnosis with the option of pregnancy termination if the foetus is found to be affected and; (3) considering advanced assisted conception techniques with pre-implantation genetic diagnosis and embryo selection.^{3,5} § 218a StGB (Germany), §§ 96–98 StGB (Austria) (<https://www.gesundheit.gv.at/leben/eltern/schwangerschaft/info/>

schwangerschaftsabbruch) and §§ 118–120 StGB (Switzerland) regulate the preconditions for intentional termination of pregnancy. Pre-implantation genetic diagnosis is permitted by law in all three German speaking countries (Embryonenschutzgesetz § 3a (G); Fortpflanzungsmedizingesetz § 2a (A); Fortpflanzungsmedizingesetz Art. 5 Abs. 3, Bundesverfassung Art. 119 Abs. 2 Best. c (S)). Based on these regulations, selected ethic committees examine individual circumstances. Decisions are taken on an individual basis.

Chorionic villus sampling is the principal method used for prenatal diagnosis of haemophilia. The procedure is performed at 11 to 14 weeks of gestation and allows diagnosis in the first trimester of pregnancy. Amniocentesis is performed later, namely after 15 weeks of gestation, which must be kept in mind if termination of pregnancy should remain an option.

In a large cohort study, the risk of miscarriage following amniocentesis and chorionic villus sampling was estimated to be as low as -0.36% [95% confidence interval (CI): -1.26 to 0.55%] and 0.29 (95% CI: -0.53 to 1.12%), respectively.⁶ Today, non-invasive testing is limited to foetal sexing that should always be performed as a routine part of antenatal care as it will help in managing pregnancy and delivery. Testing circulating cell-free foetal DNA from maternal blood for Y chromosome-specific sequences from the late first trimester on and ultrasound (US) examination at 18 to 20 weeks of gestation may be applied.³

Delivery

Factor Levels and Bleeding Risk in Carriers of Haemophilia

In a survey of 546 affected women, already only mildly reduced factor levels between 41 and 60% (range: 5 to 219%) were associated with prolonged bleeding.¹ In practical terms, haemophilia carriers should receive prophylactic factor replacement 5 to 219% therapy at the time of delivery if their factor level is not in the normal range and/or they have a history of increased bleeding tendency. As part of normal physiological response, FVIII and von Willebrand factor (VWF), factor antigen levels rise during pregnancy, reaching a plateau around 29 to 35 weeks of gestation, thus protecting haemophilia A carriers at least partly from excessive post-partum bleeding and blood loss. After childbirth, FVIII and VWF levels fall rapidly and usually return to baseline after 7 to 21 days.⁷ The FIX level does not change during pregnancy.^{8,9} Regional anaesthesia and administration of anticoagulants, namely heparin, are reserved for those individuals with factor levels in the normal range ([Table 1](#)).¹⁰

Desmopressin and Tranexamic Acid Use during Pregnancy

Desmopressin (DDAVP), a vasopressin analogue, is a drug used to effectively increase the concentration of FVIII for the following 5 to 6 hours. It has been found to be an effective drug that can reduce the risk of and even stop clinically relevant acute bleeding in inherited bleeding disorders.^{11,12} Hence, although beneficial for achieving haemostasis, severe adverse effects of DDAVP in pregnant women raise concerns. DDAVP may cause placental insufficiency due to arterial vasoconstriction and increase the risk of miscarriage due

to an oxytocic effect and maternal and/or neonatal hyponatraemia. However, pregnant women receiving DDAVP should always be advised to avoid excessive fluid intake. In the absence of high-quality evidence, clinicians should limit the use of DDAVP to the first and second trimesters of pregnancy and decide on its use by applying clinical judgement and personal experience to ensure the safety of both mother and foetus.¹³

The early and systemic use of tranexamic acid (TXA) has been shown to reduce surgical blood loss and mortality due to post-partum haemorrhage (TXA group 1.5% vs. placebo 1.9%).^{14,15} Importantly, adverse events including thromboembolic complications did not differ between the TXA and the placebo group.¹⁵ In a large randomised controlled trial among women with vaginal delivery, in which those with suspected bleeding disorder were excluded, the provider-assessed adjusted clinically significant post-partum bleeding rate was lower in the TXA group than in the placebo group (7.2 vs. 9.7%), albeit the authors concluded that there was no difference between the groups.¹⁶ Frequency of vomiting and nausea was higher in the TXA group. However, the evidence remains insufficient to recommend systemic TXA for the prevention and treatment of post-partum haemorrhage after both vaginal and caesarean deliveries.

Mode of Delivery and Risk of Bleeding for the Newborn

The optimal mode of delivery for a foetus at risk for haemophilia remains the subject of debate. Several publications have addressed the relationship between mode of delivery and risk of bleeding in newborns without haemophilia. The risk for intracranial bleeding in a large cohort of 583,000 live-born singleton infants with birthweight between 2.5 and 4.0 kg was estimated to be 0.035 to 0.12%, depending on the mode of delivery.¹⁷ As compared with the infants delivered spontaneously, those delivered with forceps and by vacuum extraction had a significantly higher rate of subdural or cerebral haemorrhage [odds ratio (OR): 3.4; 95%CI 1.9–5.9 and OR: 2.7; 95%CI: 1.9–3.9, respectively]. The rate of bleeds among infants delivered by caesarean section before labour was not higher than that for newborns delivered spontaneously. As early as 1999, Klinge et al performed a retrospective survey of intracranial haemorrhage (ICH) in haemophiliacs treated at specialised centres of members of the German Thrombosis and Haemostasis Research Group (GTH).¹⁸ In a cohort of spontaneously delivered term haemophilic newborns, the incidence of ICH was significantly higher than that in newborns without haemophilia, namely 1.9 versus 0.11% ($p < 0.0001$).¹⁹ The most important risk factor for ICH was trauma.¹⁸ In keeping with these data and those obtained from other studies, newborns with haemophilia have an increased risk for intra- and extracranial bleeding that secondarily is further increased by instrument delivery and birth trauma.^{19,20} It has been more difficult to define the relative risk for both intra- and extracranial bleeds in uncomplicated spontaneous vaginal delivery than in caesarean delivery. Today the haemophilia carrier status and male sex of the foetus do not prevent spontaneous vaginal

Table 1 Checklist for perinatal haemophilia care (modified from Dunkley et al¹⁰)

Women with known carrier status for haemophilia
<ul style="list-style-type: none"> • Measure factor VIII/IX level • Assess bleeding history • Assess/check genetic test results to assess risk for severe haemophilia in male newborn • Haemostaseologic and genetic counselling
Pregnancy
<ul style="list-style-type: none"> • Discuss/offer prenatal diagnosis • Consider replacement therapy before any invasive procedure <p><i>Third semester</i></p> <ul style="list-style-type: none"> • Measure factor VIII level. FIX level does not change during pregnancy. • Assemble management team • Review peripartal bleeding risk • Prepare for replacement therapy
Delivery
<ul style="list-style-type: none"> • Prepare for/give replacement therapy (factor VIII or IX concentrate) • Administer regional anaesthesia (epidural/spinal) only when the factor level is in normal range (>>50%) • Avoid any foetal trauma including vacuum extraction, forceps and foetal scalp blood sampling • Active management of third-stage labour • Monitor blood loss
Post-delivery care
<p><i>Mother</i></p> <ul style="list-style-type: none"> • Continue factor replacement for 3 to 5 (to 7) days post-partum <ul style="list-style-type: none"> – Administer factor VIII concentrate twice daily – Monitor factor level, strive for normal plasma levels • Monitor for blood loss <p><i>Newborn</i></p> <ul style="list-style-type: none"> • Thorough physical examination for bleeding signs • Measure factor VIII/IX level (physiologically low FIX!) • Avoid i.m. and s.c. injections. No heel prick • Vitamin K p.o. • Transfontanelle/cranial US • Start on replacement therapy only if therapeutic treatment of bleeding is needed • Refer to haemophilia centre

Abbreviations: i.m., intramuscular; p.o., per oral; s.c., subcutaneous; US, ultrasound.

delivery.^{17,21} Elective caesarean section has to be considered on an individual basis.^{21,22}

Haemophilia Care in the Newborn

Diagnosis of Haemophilia in the Newborn

At delivery, a cord blood sample or a carefully taken venous blood sample should be obtained for coagulation screening and FVIII/IX assays and for genetic testing. When using cord blood, precautions must be taken to avoid contamination of the sample with maternal blood.^{23,24} Testing cord blood prevents trauma and bleeding in a newborn with suspected severe haemophilia. Any intramuscular injection or heel prick should be refrained from until the results of coagulation tests are available. Although factor deficiency in haemophilia results in prolonged activated partial thromboplastin time (aPTT), regardless of aPTT values it is imperative to test for FVIII/IX deficiency, respecting age-specific normal ranges. In the term newborn, FVIII levels are indistinguishable from those of adults (day 1: mean 1.00; 95% CI: 0.50–1.78 U/mL), while FIX levels (day 1: mean 0.53; 95% CI: 0.15–0.91 U/mL) are significantly reduced at birth.²⁵ While it is usually possible to diagnose severe and moderate haemo-

philia, mildly affected newborns and those with haemophilia B will require repeated testing. Newborn girls born to haemophilia carriers generally do not require extra attention in the neonatal period, although factor levels may be low enough to cause an increased bleeding tendency later on. Whenever possible, confirmation of girls' carrier status is deferred by most haemophilia centres.

Bleeding of the Newborn with Haemophilia

The pattern of bleeding seen in the newborn with haemophilia is essentially different from that seen in older children. Many neonatal bleeds are iatrogenic in origin; continued oozing and excessive haematoma following heel prick, intramuscular vitamin K administration and venepuncture are common. Prominent post-delivery cephalohaematomas and increased post-surgical bleeding are also well documented. The most frequent ICH site in newborns with haemophilia is subdural.²⁶ The mean age at presentation is 4 to 5 days. Although severe sequelae of ICH occur in at least one-third of survivors, symptoms of ICH can be subtle and non-specific with episodes of apnoea and clinical signs of impaired consciousness. Dramatic cases with haemorrhagic shock, although registered in only few cases, may occur. Preterm

newborns have a further increased risk for ICH.²⁷ Prediction of newborns at highest risk for ICH could facilitate early intervention, either in terms of investigations including cranial US or short-term factor replacement therapy. Of note, again instrument and traumatic delivery bear the highest risk for ICH in newborns with haemophilia.

Bleeding after ritual circumcision is reported in at least one-quarter of healthy newborns.²⁸ In a survey of ritual neonatal circumcision in newborn infants with severe haemophilia, all respondents recommended at least one pre-procedure dose of factor replacement.²⁹

Interestingly, umbilical bleeding is rare in newborns with severe haemophilia; severe umbilical bleeding should trigger further investigations for vitamin K deficiency, factor XIII deficiency and afibrinogenemia.

Muscle and joint bleeds, the hallmark of haemophilia in the child beyond the first year of age, essentially do not occur in the newborn period. Visceral bleeds and other haematoma are typically related to trauma during labour and delivery.

Diagnosis of ICH in the Newborn with Haemophilia

Although not the most sensitive imaging technique, the value of cranial US for diagnosis of ICH in newborns is generally accepted; optimal timing of scanning and the need for sequential scanning are matters of debate. Routine cranial US cannot be relied on to detect all cases of subdural bleeding, but may still be useful for screening investigation.^{30,31} Magnetic resonance imaging (MRI) should be considered in all cases of suspected and manifest ICH. Extent and distribution of lesions are usually demonstrated better with MRI than with US.³² Provided that preparation is adequate, MRI can be performed without general anaesthesia in the neonatal period. Computed tomography (CT) investigations, which are associated with high radiation doses for the newborn, should be limited to selected cases, despite all advantages including short examination time, widespread availability and good sensitivity, for the detection of ICH.

Treatment of the Newborn with Haemophilia

In principle, newborns with haemophilia should receive routine newborn care. The most prominent concerns regarding neonatal factor replacement today are the risk for development of an inhibitor followed by the concern for local bleeding and issues related to poor vascular access. Alloantibodies against FVIII and FIX profoundly complicate treatment following bleeding episodes. The SIPPET study investigating 216 children with severe haemophilia <6 years and having no previous treatment with factor concentrate [FC; previously untreated patients (PUPs)] found a lower rate of high-titre inhibitor development after treatment with plasma-derived FC (pdFC) than with recombinant FC (rFC; 18.6 vs. 28.4%; 95% CI: 11.1–26.9 vs. 95% CI: 19.6–37.2).³³ An earlier study did not detect a difference: PdFC with considerable quantities of VWF carried the same risk for inhibitor development as did rFC [relative risk (RR): 1.0; CI: 0.6–1.6].³⁴ Other factors including the underlying genetic defect, severe bleeding and blood loss (“danger signals”) and exposure to high doses of FC (“peak treatment moments”) are well

known to further increase the risk for development of inhibitors.³³

Short-term prophylaxis with FC in newborns with haemophilia in an attempt to limit the risk of ICH is the subject of debate. However, administration of primary prophylaxis with FC to all newborns with severe haemophilia is not justified. In the same manner, a “single-shot approach” for any significant bleeding in newborns with haemophilia is most likely to be ineffective in controlling severe bleeding. In confirmed cases of bleeding and blood loss, factor replacement therapy must be high-dose and long enough to prevent bleeding in the first few days of life. Reduced *in vivo* recovery and increased clearance of FVIII have been documented in newborns.³ Similar to FVIII, newborns may also require higher doses of FIX concentrate to maintain FIX levels in the target range.³⁵ Therefore, replacement therapy should be monitored by testing for trough factor levels.

Due its dilutional effect fresh frozen plasma is not recommended in newborns, where high haematocrit values are critical.

DDAVP is contraindicated for treatment of mild and moderate haemophilia A in newborns; hyponatraemia and seizures are common in this age group.¹¹ DDAVP is ineffective in all cases of haemophilia B.

TXA is considered useful in newborns and infants undergoing cardiac repair.³⁶ For the use of systemic TXA in newborns and infants presenting with haemophilia for prevention and treatment of bleeding, evidence is insufficient.

Guidelines on the use of FC have been published by various medical associations including the World Federation of Hemophilia (<https://elearning.wfh.org/resource/treatment-guidelines/>) and The Austrian Society of Haemophilia (ÖHG; www.bluter.at).²

New Aspects and Developments

Treatment of haemophilia consists of replacing the missing clotting factor. So far, all commercially available FCs must be administered intravenously. However, biochemically modified FC that can be administered subcutaneously is under phase 2/3 clinical investigation. However, many experts in paediatric haemophilia care consider iatrogenic factor extravasation and leakage of factor into soft tissue a high-risk event for the development of inhibitors against FVIII and FIX.

Just recently, several new FCs have been introduced, which have been modified to extend their clearance from the circulation. Enhanced half-life FIX concentrates demonstrate clinically relevant favourable pharmacodynamics to standard products in children and adults with haemophilia B. For haemophilia A, only a B domain-deleted human recombinant FVIII covalently linked to the Fc domain of human immunoglobulin G 1 that moderately enhances half-life is so far licensed for children <12 years. Second-generation, enhanced half-life FCs for the treatment of haemophilia with more favourable properties are under investigation. Independent of the mechanism by which the enhanced half-life of concentrates is achieved, no data are available for their safe use during pregnancy or for treatment of PUPs and infants.

In 2019 the recombinant, humanised bispecific monoclonal antibody emicizumab that binds FIXa and FX was licensed for patients with severe haemophilia A with and without antibodies to FVIII.³⁷ Emicizumab is the first of several agents under development summarised as “non-factor” therapy. Theoretically, optimal protection from bleeding for a newly diagnosed child with haemophilia would include starting treatment on the day of diagnosis, earliest on the day of birth. Emicizumab is attractive for early intervention due to its weekly or even longer dosing intervals and subcutaneous route of administration. However, emicizumab is ineffective in treating acute bleeding of the newborn presenting with haemophilia A since its haemostatic effect takes days to weeks to develop. Reported episodes of thrombotic microangiopathy and arterial and venous thromboembolic events raise further concerns. The physiologically low FIX levels in newborns may further limit the haemostatic effect of emicizumab. Since we have only very little data and virtually no experience, emicizumab alone or in combination with FC should not be used in newborns or infants presenting with haemophilia A. A guideline for the use of emicizumab has been issued by the “Ständige Kommission Hämophilie” of the GTH.

Conflict of Interest

The authors declare that they have no conflict of interest.

References

- Plug I, Mauser-Bunschoten EP, Bröcker-Vriends AH, et al. Bleeding in carriers of hemophilia. *Blood* 2006;108(01):52–56
- Pabinger I, Heisting M, Muntean W, et al. Treatment of haemophilia in Austria [in German]. *Wien KlinWochenschr* 2015;127 (Suppl 3):S115–S130
- Chalmers E, Williams M, Brennand J, Liesner R, Collins P, Richards M; Paediatric Working Party of United Kingdom Haemophilia Doctors' Organization. Guideline on the management of haemophilia in the fetus and neonate. *Br J Haematol* 2011;154(02):208–215
- Schlembach D, Helmer H, Henrich W, et al. Peripartum haemorrhage, diagnosis and therapy. Guideline of the DGGG, OEGGG and SGGG (S2k Level, AWMF Registry No. 015/063, March 2016). *GeburtshilfeFrauenheilkd* 2018;78(04):382–399
- Harton GL, Magli MC, Lundin K, Montag M, Lemmen J, Harper JC; European Society for Human Reproduction and Embryology (ESHRE) PGD Consortium/Embryology Special Interest Group. ESHRE PGD Consortium/Embryology Special Interest Group—best practice guidelines for polar body and embryo biopsy for preimplantation genetic diagnosis/screening (PGD/PGS). *Hum Reprod* 2011;26(01):41–46
- Beta J, Zhang W, Geris S, Kostiv V, Akolekar R. Procedure-related risk of miscarriage following chorionic villus sampling and amniocentesis. *Ultrasound ObstetGynecol* 2019;54(04):452–457
- James AH, Konkle BA, Kouides P, et al. Postpartum von Willebrand factor levels in women with and without von Willebrand disease and implications for prophylaxis. *Haemophilia* 2015;21(01):81–87
- Yang MY, Ragni MV. Clinical manifestations and management of labor and delivery in women with factor IX deficiency. *Haemophilia* 2004;10(05):483–490
- Chi C, Lee CA, Shiltagh N, Khan A, Pollard D, Kadir RA. Pregnancy in carriers of haemophilia. *Haemophilia* 2008;14(01):56–64
- Dunkley S, Curtin JA, Marren AJ, Heavener RP, McRae S, Curnow JL. Updated Australian consensus statement on management of inherited bleeding disorders in pregnancy. *Med J Aust* 2019;210(07):326–332
- Streif W, Knöfler R, Eberl W, et al; Paediatric Committee of the Society of Thrombosis and Haemostasis Research. Therapy of inherited diseases of platelet function. Interdisciplinary S2K guideline of the Permanent Paediatric Committee of the Society of Thrombosis and Haemostasis Research (GTH e. V.) [in German]. *Hamostaseologie* 2014;34(04):269–275, quiz 276
- Knöfler R, Koscielny J, Tauer JT, et al. Desmopressin testing in haemophilia A patients and carriers: results of a multicentre survey. *Hamostaseologie* 2012;32(04):271–275
- Karanth L, Barua A, Kanagasabai S, Nair NS. Desmopressin acetate (DDAVP) for preventing and treating acute bleeds during pregnancy in women with congenital bleeding disorders. *Cochrane Database Syst Rev* 2019;2:CD009824
- Pabinger I, Fries D, Schöchl H, Streif W, Toller W. Tranexamic acid for treatment and prophylaxis of bleeding and hyperfibrinolysis. *Wien KlinWochenschr* 2017;129(9–10):303–316
- Collaborators WT; WOMAN Trial Collaborators. Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial. *Lancet* 2017;389(10084):2105–2116
- Sentilhes L, Winer N, Azria E, et al; Groupe de Recherche enObstétrique et Gynécologie. Tranexamic acid for the prevention of blood loss after vaginal delivery. *N Engl J Med* 2018;379(08):731–742
- Towner D, Castro MA, Eby-Wilkens E, Gilbert WM. Effect of mode of delivery in nulliparous women on neonatal intracranial injury. *N Engl J Med* 1999;341(23):1709–1714
- Klinge J, Auberger K, Auerswald G, Brackmann HH, Mauz-Körholz C, Kreuz W. Prevalence and outcome of intracranial haemorrhage in haemophiliacs—a survey of the paediatric group of the German Society of Thrombosis and Haemostasis (GTH). *Eur J Pediatr* 1999;158(Suppl 3):S162–S165
- Tarantino MD, Gupta SL, Brusky RM. The incidence and outcome of intracranial haemorrhage in newborns with haemophilia: analysis of the Nationwide Inpatient Sample database. *Haemophilia* 2007;13(04):380–382
- Andersson NG, Auerswald G, Barnes C, et al. Intracranial haemorrhage in children and adolescents with severe haemophilia A or B – the impact of prophylactic treatment. *Br J Haematol* 2017;179 (02):298–307
- Andersson NG, Chalmers EA, Kenet G, Ljung R, Mäkipernaa A, Chambost H; PedNet Haemophilia Research Foundation. Mode of delivery in hemophilia: vaginal delivery and cesarean section carry similar risks for intracranial hemorrhages and other major bleeds. *Haematologica* 2019;104(10):2100–2106
- Karanth L, Kanagasabai S, Abas AB. Maternal and foetal outcomes following natural vaginal versus caesarean section (c-section) delivery in women with bleeding disorders and carriers. *Cochrane Database Syst Rev* 2017;8:CD011059
- Mibashan RS, Rodeck CH, Thumpston JK, et al. Plasma assay of fetal factors VIIIc and IX for prenatal diagnosis of haemophilia. *Lancet* 1979;1(8130):1309–1311
- Mancuso ME, Bidlingmaier C, Mahlangu JN, Carcao M, Tosetto A; Subcommittee on Factor VIII, Factor IX and Rare Coagulation Disorders. The predictive value of factor VIII/factor IX levels to define the severity of hemophilia: communication from the SSC of ISTH. *J ThrombHaemost* 2018;16(10):2106–2110
- Andrew M, Paes B, Milner R, et al. Development of the human coagulation system in the full-term infant. *Blood* 1987;70(01):165–172
- Nagel K, Pai MK, Paes BA, Chan AK. Diagnosis and treatment of intracranial hemorrhage in children with hemophilia. *Blood Coagul Fibrinolysis* 2013;24(01):23–27
- Bidlingmaier C, Bergmann F, Kurnik K. Haemophilia A in two premature infants. *Eur J Pediatr* 2005;164(02):70–72
- Ben Chaim J, Livne PM, Binyamini J, Hardak B, Ben-Meir D, Mor Y. Complications of circumcision in Israel: a one year multicenter survey. *Isr Med Assoc J* 2005;7(06):368–370

- 29 Kearney S, Sharathkumar A, Rodriguez V, et al. Neonatal circumcision in severe haemophilia: a survey of paediatric haematologists at United States hemophilia treatment centers. *Haemophilia* 2015;21(01):52–57
- 30 Wezel-Meijler Gv, de Vries LS. Cranial ultrasound - optimizing utility in the NICU. *CurrPediatr Rev* 2014;10(01):16–27
- 31 Elkhunovich M, Sirody J, McCormick T, Goodarzian F, Claudius I. The utility of cranial ultrasound for detection of intracranial hemorrhage in infants. *PediatrEmerg Care* 2018;34(02):96–101
- 32 Hong HS, Lee JY. Intracranial hemorrhage in term neonates. *Childs NervSyst* 2018;34(06):1135–1143
- 33 Peyvandi F, Mannucci PM, Garagiola I, et al. A randomized trial of factor VIII and neutralizing antibodies in hemophiliaA. *N Engl J Med* 2016;374(21):2054–2064
- 34 Gouw SC, van der Bom JG, Auerswald G, Ettinghausen CE, Tedgård U, van den Berg HM. Recombinant versus plasma-derived factor VIII products and the development of inhibitors in previously untreated patients with severe hemophilia A: the CANAL cohort study. *Blood* 2007;109(11):4693–4697
- 35 Guilcher GM, Scully MF, Harvey M, Hand JP. Treatment of intracranial and extracranial haemorrhages in a neonate with severe haemophilia B with recombinant factor IX infusion. *Haemophilia* 2005;11(04):411–414
- 36 Maeda T, Sasabuchi Y, Matsui H, Ohnishi Y, Miyata S, Yasunaga H. Safety of tranexamic acid in pediatric cardiac surgery: a nationwide database study. *J CardiothoracVascAnesth* 2017;31(02):549–553
- 37 Pierce GF, Hart DP, Kaczmarek R; Committee on Coagulation Products Safety Supply, Access (CPSSA) of the World Federation of Hemophilia (WFH). Safety and efficacy of emicizumab and other novel agents in newborns and infants. *Haemophilia* 2019;25(05):e334–e335