NICOLAUS COPERNICUS UNIVERSITY IN TORUŃ

Quality in Sport. eISSN 2450-3118.

Journal Home Page
https://apcz.umk.pl/QS/index

HABA Sylwia, DAPKIEWICZ Ewa, HABA Natalia, TARKA Jan, GĄSOWSKI Dawid. Hemophilia in Women: Beyond the Carrier State - Clinical, Genetic, and Diagnostic Challenges. Quality in Sport. 2026;54:70793. eISSN 2450-3118. https://doi.org/10.12775/QS.2026.54.70793

The journal has been awarded 20 points in the parametric evaluation by the Ministry of Higher Education and Science of Poland. This is according to the Annex to the announcement of the Minister of Higher Education and Science dated 05.01.2024, No. 32553. The journal has a Unique Identifier: 201398. Scientific disciplines assigned: Economics and Finance (Field of Social Sciences); Management and Quality Sciences (Field of Social Sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398. Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).
The authors declare that there is no conflict of interest regarding the publication of this paper.
Received: 12.04.2026. Revised: 12.04.2026. Accepted: 18.04.2026. Published: 21.04.2026.

Hemophilia in Women: Beyond the Carrier State - Clinical, Genetic, and Diagnostic Challenges

Sylwia Haba[1]
ORCID: https://orcid.org/0000-0001-8396-5948
E-mail: habasylwia@wp.pl
[1]University Clinical Hospital of Bialystok: Białystok, Podlasie, PL

Ewa Dapkiewicz[2]
ORCID: https://orcid.org/0009-0000-2148-3484
E-mail: ewa.dapkiewicz@gmail.com
[2]Independent Public Health Care Institution of the Ministry of the Interior and Administration in Białystok: Białystok, Podlasie, PL

Natalia Haba[3]
ORCID: https://orcid.org/0009-0008-2485-1922
E-mail natalia.haba@op.pl
[3]Medical University of Bialystok: Bialystok, Podlasie, PL

Jan Tarka[4]
ORCID: https://orcid.org/0009-0005-8235-1174
E-mail: lek.jan.tarka@gmail.com
[4]Medical University of Bialystok: Bialystok, Podlasie, PL

Dawid Gąsowski[5]
ORCID: https://orcid.org/0009-0006-9574-584X
E-mail: gasowski.dawid@wp.pl
[5]Independent Public Health Care Institution in Łapy, Podlasie, PL

Corresponding author:
Sylwia Haba, habasylwia@wp.pl

ABSTRACT

Background: Hemophilia is a genetic bleeding disorder resulting from a deficiency of specific coagulation factors. The most common forms, hemophilia A and B, are X-linked and mainly affect males, with females usually being asymptomatic carriers. Some females may experience clinically significant bleeding due to reduced clotting factor activity or other genetic or biological aspects.
Aim: The aim of this study was to address hemophilia in women, including its clinical manifestations, associated challenges, and the genetic mechanisms underlying symptomatic individuals, such as Turner Syndrome, X-chromosome abnormalities, or a 46, XY karyotype.
Materials and methods: A comprehensive literature review was conducted using major databases, including PubMed, Google Scholar, ResearchGate, and ScienceDirect, covering publications from 1975 to March 2026, as well as educational materials and reports from hemophilia-related platforms and organizations.
Results: Symptomatic hemophilia in women may be caused by a variety of factors, such as Turner syndrome, mutations on the X chromosome, or a 46, XY karyotype. In most cases, further genetic diagnostics reveal the alterations responsible for this phenotype.

Conclusions: Regardless of the phenotypic presentation, in cases of fully symptomatic hemophilia in women, extended diagnostic evaluation for genetic disorders should be considered.

Keywords: Female hemophilia, hemophilia carriers, Turner syndrome, disorders of sex development, X-chromosome inactivation, bleeding disorders

1. Introduction

Hemophilia is a hereditary bleeding disorder caused by a deficiency of specific coagulation factors. The two most prevalent forms, hemophilia A and hemophilia B, are inherited in an X-linked recessive pattern and are characterized by deficiencies of factor VIII and factor IX, respectively. Consequently, the clinical manifestation of these disorders occurs predominantly in males, whereas females are typically asymptomatic carriers. In contrast, hemophilia C, which is characterized by factor XI deficiency, follows an autosomal pattern of inheritance and therefore affects both males and females. [1] Hemophilia may also develop later in life as acquired hemophilia which represents an autoimmune condition rather than an inherited bleeding disorder. The majority of the cases occur in middle-aged or elderly individuals and women in late pregnancy or the postpartum period. [2] Based on residual factor activity, hemophilia is classified as mild, moderate, or severe. The severity of hemophilia is determined based on the residual activity of the deficient clotting factor measured in the patient's plasma. Factor levels are expressed as a percentage of normal activity or in international units per milliliter (IU/mL), with the normal range defined by the World Federation of Hemophilia as 50-150% (0.50-1.5 IU/mL). [3] According to data from national patient registries and reports from the World Federation of Hemophilia, approximately 1,125,000 men worldwide are estimated to have hemophilia, with a substantial proportion remaining undiagnosed. The condition affects about 1 in 10,000 live births. Hemophilia A accounts for the majority of cases (approximately 80-85%), whereas hemophilia B constitutes the remaining 15-20%. In Poland, 30-50% of cases are attributed to de novo mutations, occurring in the absence of a positive family history. The prevalence of hemophilia A and B in Poland has been estimated at approximately 1 in 12,300 inhabitants. [4] Although the precise prevalence of hemophilia carriers remains unknown, current estimates suggest that there may be up to five potential female carriers for every male diagnosed with hemophilia. [5]

Despite growing clinical awareness, hemophilia A and B continue to be viewed primarily as male disorders, with women often characterized merely as asymptomatic or mildly affected carriers, an assumption that does not fully reflect the spectrum of clinical manifestations observed in females. Women carrying pathogenic variants in the F8 (factor VIII) or F9 (factor IX) genes may have reduced factor levels and clinically significant bleeding symptoms. It should also be emphasized that a fully symptomatic clotting factor deficiency may occur in women with skewed X-chromosome inactivation, in individuals with Turner syndrome (monosomy X), and in daughters born to an affected father and a carrier mother. The diagnosis of hemophilia is established through the assessment of FVIII activity and confirmed by molecular analysis of the F8 gene. Determining mutation status is important for identifying carriers and guiding clinical management. [6] In addition, karyotype evaluation may be necessary, as in rare cases, hemophilia in females can be associated with chromosomal

abnormalities or disorders of sex development. [6, 7] Although awareness of the underdiagnosis and undertreatment of bleeding symptoms in women with hemophilia has increased in recent years, substantial gaps remain in the understanding of their clinical presentation, diagnostic approaches, and epidemiological data. This review aims to underline that hemophilia among women cannot be viewed solely as a carrier condition.

2. Materials and Methods

A comprehensive literature review in Polish and English was conducted, through a search of major electronic databases, including PubMed, Google Scholar, ResearchGate, and ScienceDirect, using keywords related to hemophilia among women and its genetic background, covering the period from 1975 to March 2026. Additionally, educational materials, annual reports, and clinical resources from professional medical platforms and hemophilia-related organizations were also analyzed. Various types of publications were included in the analysis, such as case reports, systematic reviews, narrative reviews, qualitative studies, survey-based studies, and observational cohort studies.

3. Research results

3.1. Hemophilia in Female Carriers

Hemophilia in women has traditionally been addressed primarily in terms of carrier status, due to its X-linked pattern of inheritance. While much attention has focused on the genetic background of hemophilia carriers, significant gaps remain in understanding the full spectrum of clinical and psychosocial challenges they face. Many of these issues have not been fully recognized and addressed yet. [8] Increasing evidence suggests that focusing solely on carrier status may underestimate the clinically relevant bleeding manifestations experienced by this population. In 2019 a new nomenclature for hemophilia in women and girls was proposed. The updated classification is based on factor levels and bleeding phenotype, differentiating five categories: mild, moderate, and severe hemophilia (according to residual factor activity), as well as symptomatic and asymptomatic carriers, depending on the presence or absence of bleeding symptoms, despite factor levels above 40%. It is important to underline that the term “asymptomatic carrier” does not fully reflect the true psychological and clinical impact of carrier status. The introduction of this new nomenclature supports a shift toward more inclusive and gender-equitable hemophilia care, ensuring that women and girls are no longer marginalized within comprehensive care models. [9] Bleeding manifestations in female carriers include an increased tendency to bruise, prolonged bleeding after surgery or dental procedures, prolonged nosebleeds, bleeding from minor wounds, gum bleeding, joint and muscle hemorrhages, and, more frequently, heavy and prolonged menstrual bleeding, which can lead to iron deficiency and an increased likelihood of hysterectomy. [10-14] Current data also highlight the need for further research on musculoskeletal complications, including joint and muscle bleeding, and the potential effects on bone density. [13,15] Awareness of carrier status may have a meaningful impact on women’s physical and psychological health, career choices, and social functioning. It may also have a significant influence on reproductive planning and related decision-making. [10, 16-21] A considerable proportion of women, even from heavily affected families, remain unaware of their condition, and girls are generally diagnosed at an older age than boys. Delayed diagnosis may result from insufficient awareness among both

affected individuals and health professionals. [10] Furthermore, carriers with clotting factor deficiency differ from male patients in having higher average factor levels, and in the factors that prompt their diagnosis. [22] Consequently, all confirmed and potential carriers should undergo measurement of their FVIII or FIX levels. Individuals with factor levels below 60% should be regarded and managed as patients with mild hemophilia. Carriers exhibiting clotting factor activity below 30% require regular follow-up at a dedicated hemophilia treatment center. [10] Symptomatic hemophilia carriers should undergo extended genetic evaluation, as additional X-linked mutations may underlie their clinical symptoms. [23]. In addition, factors beyond baseline clotting levels should be identified to better guide treatment decisions. Continued improvements in diagnosis and care, and conducting large cohort studies, are essential to optimize care and understand the diversity of bleeding manifestations in women and girls with hemophilia. [24] The study by Renault et al. suggests that hemophilia carriers are at risk of receiving inadequate care, often due to healthcare professionals minimizing their symptoms and concerns. Such experiences may arise both during the diagnostic process and in decisions regarding treatment and preventive plans. Systemic medical errors, insufficient communication, and limited awareness of bleeding disorders in women may compromise the quality of care and adversely affect patients' psychological and overall well-being. [25] Moreover, women's perceptions and emotional reactions regarding their health may change over time, shaped by familial experiences, the information they acquire, and individual life circumstances. [18] A well-organized programme is essential to provide women with bleeding disorders with timely access to specialist care, facilitate multidisciplinary collaboration, and ensure that treatment remains current and of the highest quality. [26] Specialized hemophilia centres and peer support networks may significantly improve counselling, empowerment, and psychosocial outcomes in women and girls with bleeding disorders. [10] Expanding the inclusion of women and girls with hemophilia in clinical trials and patient registries is essential to guide clinical decision-making. At the same time, reducing disparities in healthcare access and promoting gender equity in bleeding disorder care remain crucial for improving outcomes. Recognizing women as more than carriers and developing gender-specific diagnostic and therapeutic strategies may ultimately improve the quality of life of women living with hemophilia and other bleeding disorders. [27]

3.2. X-Linked Mutations Associated with Hemophilia in Females

Other, rarer genetic variants may also predispose women to the development of hemophilia. These include extreme lyonization (i.e., skewed X-chromosome inactivation), deletions, translocations, large chromosomal rearrangements affecting the F8 or F9 genes, and germline or somatic mosaicism. Di Paola et al. reported the case of a 4 months old girl diagnosed with severe F9 deficiency. Genetic testing identified the underlying cause of this condition as a balanced translocation between one of the X-chromosomes and chromosome 14, with breakpoints at bands Xq27.1 and 14q32.3. No chromosomal abnormalities were detected in either parent and there was no family history of the bleeding disorders. She had a history of multiple hemarthrosis. [28] The other report shows a history of a girl with balanced de novo translocation t(X;1). Genetic studies revealed that the translocated X was preferentially active and according to methylation analysis of the DXS255 locus, skewed X-chromosome inactivation was present, with the paternal allele remaining functional. This chromosomal

alteration led to partial deletion of the factor IX gene. [29] Schröder et al. described a female patient with a de novo translocation 46,X,t(X;15)(q27.1;p11.2), which is consistent with a probable break near the factor IX gene. High-resolution R-banding demonstrated that the structurally normal X chromosome was late replicating and inactivated in all metaphases. The breakpoint region on the X chromosome and the involvement of the factor IX gene were further characterized by fluorescence in situ hybridization (FISH) using YAC and cosmid probes. [30] In another study, Windson et al. described a 2-year-old girl with severe hemophilia. Family history of bleeding disorders was negative. Cytogenetic evaluation showed an interstitial deletion of the X chromosome involving the Xq26–q28 region. It was also revealed that the patient's F8 gene was inherited from the father, so the deletion of X chromosome had occurred de novo in the maternal germ line. Additional investigation of the paternally inherited factor VIII gene in the proband identified a de novo inversion mutation (type 1, distal pattern). Therefore, the blood clotting disorder presented in this girl is a result of two de novo mutations, both affecting the F8 gene. [31]

Another article describes various genetic mechanisms leading to hemophilia based on seven female cases. In two of the women, homozygous missense mutations (Arg593Cys and Tyr1680Phe), resulting from consanguineous marriages, were identified. The third patient was a compound heterozygote, carrying a missense mutation (Leu412Phe) inherited from her carrier mother together with a de novo deletion spanning exons 9-22, most likely of paternal origin. In the subsequent three cases, heterozygous mutations in the F8 gene (Arg1781His, Arg327His, small deletion in exon 10) were observed in combination with non-random X-chromosome inactivation. The final case involved the coexistence of hemophilia A and Coffin-Lowry syndrome within the same family. In this case, hemophilia resulted from a heterozygous deletion in the F8 gene (c.6872 del CT leading to Thr2272fs) together with inactivation of the maternal X chromosome. [32] Coleman et al. reported a female infant whose mother had incontinentia pigmenti and father had haemophilia A. She inherited both diseases. Analysis of peripheral blood DNA showed a highly skewed pattern of X inactivation. The child's sisters were healthy. Selective inactivation of the X chromosome harboring the IP mutation, presumably as a result of negative selection, appears to have revealed the factor VIII mutation present on the infant's alternate X chromosome. [33] Several other articles presented cases of fully symptomatic hemophilia in women resulting from the phenomenon of lyonization. It is a process that involves the inactivation of one of the two X chromosomes in female cells. It serves to equalize the level of expression of genes located on the X chromosome between males and females. The process occurs at an early stage of embryogenesis, and the inactivated chromosome is subsequently transmitted to the daughter cells. Acquila et al. described two women with a positive family history of hemophilia A. The first one, with a 46, XX karyotype, had a hemophilia carrier mother and a healthy father. Diagnostic analysis showed that the paternal X chromosome was inactive, which explains the occurrence of symptoms in the patient. The second reported case represents a different situation. The described patient was the child of consanguineous parents. Her father and brother were affected by hemophilia A, as was most likely her maternal grandfather. Further analysis of the patient's DNA demonstrated balanced lyonization. [34] The occurrence of hemophilia may also result from skewed X-chromosome inactivation, as illustrated in the study by Reunault et al. In this case, the cause of the disease was investigated in three heterozygous women from the same family. A positive

linear relationship was found between factor VIII activity and the proportion of the activated normal X chromosome. Each of the affected women had an XCIR skewed toward activation of the mutant X-chromosome. These findings demonstrated that fully symptomatic hemophilia may also occur in women who are heterozygous for a hemophilia-causing mutation if skewed X-chromosome inactivation takes place. [35] Another rare genetic condition which leads to the manifestation of a bleeding disorder in women is SHAM (Severe Hemophilia A and Moyamoya syndrome), which is resulting from microdeletions at the Xq28 locus. These deletions affect a specific region of the X chromosome that includes the F8 and BRCC3 genes. [36] In the case reported by Janczar et al. a patient with that syndrome presented phenotypically hemophilia A, moyamoya angiopathy, hypertension, and dysmorphic features. Genetic testing revealed that both her mother and sister were carriers of the mutation. The mother was asymptomatic, whereas the sister exhibited mild hemophilia A, coarctation of the aorta, hypertension, and ventricular arrhythmia. Further evaluation of the women in this family demonstrated a skewed pattern of X-chromosome inactivation, resulting in preferential inactivation of the X chromosome without the Xq28 deletion in the patient's sister. Among the described family members, differential expression of genes from the deleted region was observed, which was reflected in the phenotypic variability. [37]

3.3. Hemophilia in women with Turner Syndrome

Another condition in which hemophilia may be clinically expressed in women is Turner Syndrome. It is a genetic disorder characterized by partial or complete monosomy of the X chromosome affecting all of the body's cells or occurring in a mosaic form. Given that hemophilia A and B is inherited as an X-linked recessive disorder, a patient with Turner syndrome requires only one mutant allele to develop clinical symptoms. The coexistence of these two conditions is extremely rare, but several cases have been reported in the literature. In the study by Al Khudari et al., authors described a case of a girl with Turner syndrome and the deficiency of factors V and VIII, the combination of which has been never reported in the literature. In this case, a 5-year-old girl was diagnosed because of the hematologic symptoms such as epistaxis and hemorrhage of gum and associated with short stature, spaced nipples and winged neck, which led to clinical suspicion of Turner syndrome. There was no family history of blood clotting disorders. This highlights the importance of karyotyping in females with hemophilia, even when there are no obvious manifestations of Turner syndrome or other genetic disease. Another important conclusion is that when factor VIII deficiency is detected, evaluation of the other coagulation factors should be performed. [38] Berendt et al. described a case of a preterm girl diagnosed due to prolonged bleeding from injection sites. Due to negative paternal family history, the female sex and dysmorphic features, the diagnostic evaluation was expanded to include genetic testing, which confirmed the diagnosis of Turner syndrome. [39] This case highlights that hemophilia should be included in the differential diagnosis even in the absence of a family history of bleeding disorders, especially when the clinical presentation is unusual. Williams et al. described the diagnostic pathway that may separate the recognition of excessive bleeding after trauma from the diagnosis of a genetic syndrome. In the reported situation, hemarthrosis following minor trauma in a two-year-old girl raised suspicion of a coagulation disorder. Subsequent diagnostic evaluation suggested that the girl was homozygous for a missense mutation in exon 14 of the F8 gene, which led to the

development of symptomatic hemophilia A. In order to determine the cause of this apparent homozygosity, the patient was referred for genetic evaluation, where Turner syndrome was ultimately diagnosed. [40] In a case report by Panarello et al., a woman with Turner syndrome and moderate hemophilia A was described. The patient's karyotype was 46,X,idic(X)(p11). The idic(X) chromosome contained alleles from both maternal X chromosomes; however, it was inactivated. Therefore, the patient's hemophilia was most likely caused by a de novo mutation arising on the normal paternal X chromosome. [41] Weinspach et al. described a 3-month-old girl with severe hemophilia A who developed an intracranial hemorrhage three weeks after a fall from an infant carrier. Recurrent bleeding following neurosurgery prompted physicians to investigate possible bleeding disorders, which ultimately led to the diagnosis of hemophilia A. This case demonstrates that establishing a final diagnosis requires correlation of the patient's clinical presentation with laboratory and genetic findings. Furthermore, when a patient presents with concerning symptoms, less likely diagnoses should also be considered and excluded, such as hemophilia in a female patient in this instance. [42]

3.4. Hemophilia Associated with Disorders of Sex Development

Hemophilia can appear in individuals with a female phenotype and karyotype 46, XY, which can occur in some cases of disorders of sex differentiation. There are reported cases in which hemophilia coexist with complete androgen insensitivity syndrome (Morris syndrome; CAIS; testicular feminization syndrome), which is a disorder of sex differentiation caused by a mutation in the androgen receptor gene on the X chromosome, leading to complete tissue insensitivity to androgens. [43]. A case of hemophilia A coexisting with testicular feminization syndrome was described by Andrejev et al. in an 18-year-old phenotypically-female individual, with both conditions showing a familial pattern and transmission through the female line. The patient presented with a very low factor-VIII level (1.66%) and a history of recurrent joint bleeding, requiring major surgery for a haemophilic thigh pseudotumor at the age of 18. Despite severe factor VIII deficiency, the clinical manifestation of haemophilia was milder than that observed in affected males in her family and in the general population. [44] In the study by Janczar et al., which aimed to analyze genetic variants in female patients with hemophilia, a 55-year-old patient with a 46, XY karyotype was also reported. [45] Huisse et al. reported a case of mild hemophilia A in a 40-year-old phenotypically female patient with a 46, XY karyotype and clinical features consistent with complete androgen insensitivity syndrome. The diagnosis was established prior to thoracic surgery, and laboratory findings showed reduced factor VIII activity (4%) with normal von Willebrand factor parameters, and no personal or family history of bleeding. [46] Martín-Salces et al. presented two sisters with Morris syndrome (46, XY), who were hemizygous for a novel F8 mutation (p.Phe2127Ser) and exhibited mild to moderate hemophilia A. [47] In a report by Sánchez Lucero et al., a 2-year-old phenotypically female patient presented with spontaneous hematomas and severe bleeding was described. Laboratory testing revealed FVIII deficiency (<1%), and genetic analysis identified a type I intron 22 inversion, also present in her mother. Karyotype analysis showed 46, XY, and the patient was referred for further investigation of her sexual development. [6] Sitalakshmi et al. reported a case of hemophilia in a phenotypically female patient who was found to have a male sex chromosome pattern. [48] In addition to complete androgen insensitivity syndrome, Swyer syndrome (46, XY; pure gonadal dysgenesis), characterized by female external and

internal genitalia and hypergonadotropic hypogonadism [49], has also been associated with hemophilia. Loreth et al. described a 33-year-old phenotypically female patient diagnosed with Swyer syndrome and mild hemophilia A, with no personal or family history of abnormal bleedings. This rare coexistence demonstrates that chromosomal abnormalities may contribute to the expression of hemophilia in individuals with a female phenotype. [50]**.** Such cases highlight the importance of considering sex development disorders in the diagnostic and genetic evaluation of affected women. An accurate identification of underlying genetic and hematologic abnormalities enables tailored treatment, genetic counseling, and multidisciplinary care that integrates medical management, psychological support, and consideration of potential chromosomal or developmental issues, ensuring comprehensive care for both physical and mental health.

4. Limitations

This review is limited by the heterogeneity of the included studies (e.g., case reports, systematic and narrative reviews), with a predominance of case reports that typically describe rare and more complex presentations. Moreover, available data on hemophilia in women remain limited due to variability in the interpretation of carrier status, as well as underdiagnosis and underreporting, partly related to low awareness among both patients and healthcare professionals. As a result, the findings may not fully reflect the true scale of the problem.

5. Conclusions

Hemophilia in women is not only applicable to being only a carrier for the faulty gene. Under this statement there are many different clinical symptoms of varying intensity, problems with self-esteem, doubts about one's future, career, and being a burden on the family. Although rare, hemophilia in women could be phenotypically present. Some cases are associated with de-novo mutation, however if symptoms of hemophilia occur there needs to be a watch for other comorbidities. Women presenting with symptoms of hemophilia should undergo diagnostic evaluation, including laboratory and molecular testing. Karyotyping is also crucial in the diagnostic process, as it allows for the determination of whether the symptoms are related to co-occurring genetic syndromes resulting from the possession of a single X chromosome, even if there is no phenotypic evidence of their presence. It is important to emphasize that diagnostics should be of high quality, with the experience and continuous training of the medical personnel responsible for ordering and interpreting test results being crucial. Accurate diagnosis and thorough genetic analysis are crucial for appropriate counseling, personalized clinical management, and offer multidisciplinary support, including access to specialized care and relevant medical or psychosocial interventions. There is a need for comprehensive research to explore the medical, psychological, and social consequences of hemophilia in female patients. Promoting societal awareness, ensuring gender-equitable healthcare access, and providing specialized support and educational programs are essential for improving care and quality of life for women with hemophilia.

Disclosure

Author's contribution:

Conceptualization: Sylwia Haba, Ewa Dapkiewicz
Methodology: Ewa Dapkiewicz, Jan Tarka
Software: Natalia Haba, Dawid Gąsowski
Check: Natalia Haba, Jan Tarka
Formal analysis: Sylwia Haba, Natalia Haba
Investigation: Jan Tarka, Dawid Gąsowski
Resources: Natalia Haba, Dawid Gąsowski
Data curation: Sylwia Haba, Ewa Dapkiewicz
Writing-rough preparation: Sylwia Haba, Ewa Dapkiewicz
Writing-review and editing: Sylwia Haba, Ewa Dapkiewicz, Natalia Haba, Jan Tarka, Dawid Gąsowski
Visualization: Natalia Haba, Dawid Gąsowski
Supervision: Ewa Dapkiewicz, Jan Tarka
Project administration: Sylwia Haba
Receiving funding: Not applicable

All authors have read and agreed with the published version of the manuscript.

Funding Statement:

The study did not receive special funding.

Institutional Review Board Statement:

Not applicable.

Informed Consent Statement:

Not applicable.

Data Availability Statement:

Not applicable.

Acknowledgments:

Not applicable.

Conflict Of Interest:

The authors declare no conflict of interest.

AI Declaration

During the preparation of this manuscript, the authors used ChatGPT (OpenAI) for language editing and improvement of text clarity. All content was subsequently reviewed and revised by the authors, who take full responsibility for the final version of the manuscript.

References

1. Wróblewska, K., Bieszczad, D., Popławska, M., Ziętara, K. J., Zajączkowska, M., & Filip, A. (2025). Gene therapy as an innovative approach to the treatment of hemophilia B-a review. Journal of applied genetics, 66(3), 569–577. https://doi.org/10.1007/s13353-025-00952-w
2. Windyga, J. (2010). Acquired hemophilia. (Article in Polish) Journal of Transfusion Medicine and Hemostasis, 3(4), 131–132. https://doi.org/10.5603/jtm.28410
3. Hemophilia News Today. Severity levels of hemophilia https://hemophilianewstoday.com/severity-levels-of-hemophilia/
4. Gałązka-Sobotka M, Gierczyński J, Sobol A,Sejbuk-Rozbicka K, Windyga J, Woźnica-Karczmarz I. (2025) Hemophilia: Current status and future directions (Report in Polish) https://izwoz.lazarski.pl/fileadmin/user_upload/instytut_izwoz/Raport_Hemofilia_raport_stan_obecny_i_kierunki_rozwoju_0.9.pdf
5. Street, A. M., Ljung, R., & Lavery, S. A. (2008). Management of carriers and babies with haemophilia. Haemophilia : the official journal of the World Federation of Hemophilia, 14 Suppl 3, 181–187. https://doi.org/10.1111/j.1365-2516.2008.01721.x
6. Sánchez Lucero, A., Veber, S. E., Casanovas, A., Martinez, G., D'Aloi, K., Elena, G. O., Radic, C. P., Abelleyro, M. M., & Bruno, S. (2017). Severe hemophilia A in a patient with sexual differentiation disorder: A case report. Blood, 130(Suppl 1), 4884.
7. Miller, C. H., & Bean, C. J. (2021). Genetic causes of haemophilia in women and girls. Haemophilia : the official journal of the World Federation of Hemophilia, 27(2), e164–e179. https://doi.org/10.1111/hae.14186
8. Chaigneau, M., Botros, M., Grabell, J., Hopman, W., & James, P. (2022). Challenges and knowledge gaps facing hemophilia carriers today: Perspectives from patients and health care providers. Research and practice in thrombosis and haemostasis, 6(6), e12783. https://doi.org/10.1002/rth2.12783
9. van Galen, K. P. M., d'Oiron, R., James, P., Abdul-Kadir, R., Kouides, P. A., Kulkarni, R., Mahlangu, J. N., Othman, M., Peyvandi, F., Rotellini, D., Winikoff, R., & Sidonio, R. F. (2021). A new hemophilia carrier nomenclature to define hemophilia in women and girls: Communication from the SSC of the ISTH. Journal of thrombosis and haemostasis : JTH, 19(8), 1883–1887. https://doi.org/10.1111/jth.15397
10. Women and Girls with Hemophilia. World Federation of Hemophilia. https://www1.wfh.org/publications/files/pdf-2342.pdf
11. Plug, I., Mauser-Bunschoten, E. P., Bröcker-Vriends, A. H., van Amstel, H. K., van der Bom, J. G., van Diemen-Homan, J. E., Willemse, J., & Rosendaal, F. R. (2006). Bleeding in carriers of hemophilia. Blood, 108(1), 52–56. https://doi.org/10.1182/blood-2005-09-3879
12. Mauser-Bunschoten EP. Symptomatic carriers of hemophilia. (2008). Van Creveldkliniek and Haematology, University Medical Centre, Utrecht, The Netherlands. https://www1.wfh.org/publication/files/pdf-1202.pdf
13. Weyand, A. C., Sidonio, R. F., Jr, & Sholzberg, M. (2022). Health issues in women and girls affected by haemophilia with a focus on nomenclature, heavy menstrual bleeding, and musculoskeletal issues. Haemophilia : the official journal of the World Federation of Hemophilia, 28 Suppl 4(Suppl 4), 18–25. https://doi.org/10.1111/hae.14535

14. Paroskie, A., Oso, O., Almassi, B., DeBaun, M. R., & Sidonio, R. F., Jr (2014). Both hemophilia health care providers and hemophilia a carriers report that carriers have excessive bleeding. Journal of pediatric hematology/oncology, 36(4), e224–e230. https://doi.org/10.1097/MPH.0000000000000022
15. Citla-Sridhar, D., Sidonio, R. F., Jr, & Ahuja, S. P. (2022). Bone health in haemophilia carriers and persons with von Willebrand disease: A large database analysis. Haemophilia : the official journal of the World Federation of Hemophilia, 28(4), 671–678. https://doi.org/10.1111/hae.14565
16. Tedgård, U., Ljung, R., & McNeil, T. F. (1999). Reproductive choices of haemophilia carriers. British journal of haematology, 106(2), 421–426. https://doi.org/10.1046/j.1365-2141.1999.01566.x
17. Cutica, I., Mortarino, M., Garagiola, I., Pravettoni, G., & Peyvandi, F. (2023). Psychological and cognitive factors involved in decision-making process of haemophilia carriers in reproductive choices. Haemophilia : the official journal of the World Federation of Hemophilia, 29(5), 1313–1319. https://doi.org/10.1111/hae.14836
18. von der Lippe, C., Frich, J. C., Harris, A., & Solbrække, K. N. (2017). "It was a lot Tougher than I Thought It would be". A Qualitative Study on the Changing Nature of Being a Hemophilia Carrier. Journal of genetic counseling, 26(6), 1324–1332. https://doi.org/10.1007/s10897-017-0112-9
19. Punt, M. C., Aalders, T. H., Bloemenkamp, K. W. M., Driessens, M. H. E., Fischer, K., Schrijvers, M. H., & van Galen, K. P. M. (2020). The experiences and attitudes of hemophilia carriers around pregnancy: A qualitative systematic review. Journal of thrombosis and haemostasis: JTH, 18(7), 1626–1636. https://doi.org/10.1111/jth.14825
20. Chi, C., Lee, C. A., Shiltagh, N., Khan, A., Pollard, D., & Kadir, R. A. (2008). Pregnancy in carriers of haemophilia. Haemophilia : the official journal of the World Federation of Hemophilia, 14(1), 56–64. https://doi.org/10.1111/j.1365-2516.2007.01561.x
21. Cassis, F. R., Querol, F., Forsyth, A., Iorio, A., & HERO International Advisory Board (2012). Psychosocial aspects of haemophilia: a systematic review of methodologies and findings. Haemophilia : the official journal of the World Federation of Hemophilia, 18(3), e101–e114. https://doi.org/10.1111/j.1365-2516.2011.02683.x
22. Raso, S., Lambert, C., Boban, A., Napolitano, M., Siragusa, S., & Hermans, C. (2020). Can we compare haemophilia carriers with clotting factor deficiency to male patients with mild haemophilia?. Haemophilia : the official journal of the World Federation of Hemophilia, 26(1), 117–121. https://doi.org/10.1111/hae.13891
23. Dardik, R., Janczar, S., Lalezari, S., Avishai, E., Levy-Mendelovich, S., Barg, A. A., Martinowitz, U., Babol-Pokora, K., Mlynarski, W., & Kenet, G. (2023). Four Decades of Carrier Detection and Prenatal Diagnosis in Hemophilia A: Historical Overview, State of the Art and Future Directions. International journal of molecular sciences, 24(14), 11846. https://doi.org/10.3390/ijms241411846
24. d'Oiron, R., O'Brien, S., & James, A. H. (2021). Women and girls with haemophilia: Lessons learned. Haemophilia : the official journal of the World Federation of Hemophilia, 27 Suppl 3, 75–81. https://doi.org/10.1111/hae.14094

25. Renault, N. K., Howell, R. E., Robinson, K. S., & Greer, W. L. (2011). Qualitative assessment of the emotional and behavioural responses of haemophilia A carriers to negative experiences in their medical care. Haemophilia : the official journal of the World Federation of Hemophilia, 17(2), 237–245. https://doi.org/10.1111/j.1365-2516.2010.02424.x
26. Winikoff, R., Amesse, C., James, A., Lee, C., & Pollard, D. (2004). The role of haemophilia treatment centres in providing services to women with bleeding disorders. Haemophilia : the official journal of the World Federation of Hemophilia, 10 Suppl 4, 196–204. https://doi.org/10.1111/j.1365-2516.2004.01001.x
27. Gualtierotti, R., Garagiola, I., Mortarino, M., Spena, S., Romero-Lux, O., & Peyvandi, F. (2024). Gender equity in hemophilia: need for healthcare, familial, and societal advocacy. Frontiers in medicine, 11, 1345496. https://doi.org/10.3389/fmed.2024.1345496
28. Di Paola, J., Goldman, T., Qian, Q., Patil, S. R., & Schutte, B. C. (2004). Breakpoint of a balanced translocation (X:14) (q27.1;q32.3) in a girl with severe hemophilia B maps proximal to the factor IX gene. Journal of thrombosis and haemostasis : JTH, 2(3), 437–440. https://doi.org/10.1111/j.1538-7933.2004.00626.x
29. Krepischi-Santos, A. C., Carneiro, J. D., Svartman, M., Bendit, I., Odone-Filho, V., & Vianna-Morgante, A. M. (2001). Deletion of the factor IX gene as a result of translocation t(X;1) in a girl affected by haemophilia B. British journal of haematology, 113(3), 616–620. https://doi.org/10.1046/j.1365-2141.2001.02786.x
30. Schröder, W., Poetsch, M., Gazda, H., Werner, W., Reichelt, T., Knoll, W., Rokicka-Milewska, R., Zieleniewska, B., & Herrmann, F. H. (1998). A de novo translocation 46,X,t(X;15) causing haemophilia B in a girl: a case report. British journal of haematology, 100(4), 750–757. https://doi.org/10.1046/j.1365-2141.1998.00621.x
31. Windsor, S., Lyng, A., Taylor, S. A., Ewenstein, B. M., Neufeld, E. J., & Lillicrap, D. (1995). Severe haemophilia A in a female resulting from two de novo factor VIII mutations. British journal of haematology, 90(4), 906–909. https://doi.org/10.1111/j.1365-2141.1995.tb05213.x
32. Pavlova, A., Brondke, H., Müsebeck, J., Pollmann, H., Srivastava, A., & Oldenburg, J. (2009). Molecular mechanisms underlying hemophilia A phenotype in seven females. Journal of thrombosis and haemostasis: JTH, 7(6), 976–982. https://doi.org/10.1111/j.1538-7836.2009.03346.x
33. Coleman, R., Genet, S. A., Harper, J. I., & Wilkie, A. O. (1993). Interaction of incontinentia pigmenti and factor VIII mutations in a female with biased X inactivation, resulting in haemophilia. Journal of medical genetics, 30(6), 497–500. https://doi.org/10.1136/jmg.30.6.497
34. Acquila, M., Caprino, D., Bicocchi, P., Mori, P. G., & Tagliaferri, A. R. (1995). A skewed lyonization phenomenon as cause of hemophilia A in a female patient. Blood, 85(2), 599–600.
35. Renault, N. K., Dyack, S., Dobson, M. J., Costa, T., Lam, W. L., & Greer, W. L. (2007). Heritable skewed X-chromosome inactivation leads to haemophilia A expression in heterozygous females. European journal of human genetics : EJHG, 15(6), 628–637. https://doi.org/10.1038/sj.ejhg.5201799

36. Kashari, O. F., Maimani, Y. T., Alhareeri, A., Jastaniah, W., Baothman, E. A., Elimam, N., Alqaisi, A. M., Alam, M. M., Alqattan, J., & Khoshhal, O. (2024). Severe hemophilia A and Moyamoya (SHAM) syndrome caused by Xq28 microdeletion without risk of thrombosis: A case report. Blood, 144(Supplement 1), 5493. https://doi.org/10.1182/blood-2024-193104
37. Janczar, S., Kosinska, J., Ploski, R., Pastorczak, A., Wegner, O., Zalewska-Szewczyk, B., Paige, A. J., Borowiec, M., & Mlynarski, W. (2016). Haemophilia A and cardiovascular morbidity in a female SHAM syndrome carrier due to skewed X chromosome inactivation. European journal of medical genetics, 59(1), 43–47. https://doi.org/10.1016/j.ejmg.2015.12.004
38. Al Khudari, R., Batesh, D., Habash, R., & Hamdn, O. (2023). Hemophilia A and factor V deficiency in a girl with Turner syndrome: a case report. Journal of medical case reports, 17(1), 480. https://doi.org/10.1186/s13256-023-04215-2
39. Berendt, A., Wójtowicz-Marzec, M., Wysokińska, B., & Kwaśniewska, A. (2020). Severe haemophilia a in a preterm girl with turner syndrome - a case report from the prenatal period to early infancy (part I). Italian journal of pediatrics, 46(1), 125. https://doi.org/10.1186/s13052-020-00892-7
40. Williams, V. K., Suppiah, R., Coppin, B., Nicholls, C. M., Simsek, A., & McGregor, L. K. (2012). Investigation of inflicted injury in a young girl reveals mild haemophilia A and Turner's syndrome. International journal of laboratory hematology, 34(1), 98–101. https://doi.org/10.1111/j.1751-553X.2011.01347.x
41. Panarello, C., Acquila, M., Caprino, D., Gimelli, G., Pecorara, M., & Mori, P. G. (1992). Concomitant Turner syndrome and hemophilia A in a female with an idic(X)(p11) heterozygous at locus DXS52. Cytogenetics and cell genetics, 59(4), 241–242. https://doi.org/10.1159/000133259
42. Weinspach, S., Siepermann, M., Schaper, J., Sarikaya-Seiwert, S., Rieder, H., Gerigk, M., Höhn, T., & Laws, H. J. (2009). Intracranial hemorrhage in a female leading to the diagnosis of severe hemophilia A and Turner syndrome. Klinische Padiatrie, 221(3), 167–171. https://doi.org/10.1055/s-0029-1220701
43. Kowalczyk, K., Przyborowska, M., Rybka, A., Udongwo, M., Pluta, D., Urban, A., … & Madej, P. (2019). Am I a woman? A case report of complete androgen insensitivity syndrome and a literature review. (Article in Polish). Ginekologia i Perinatologia Praktyczna, 4(3), 129–132. https://doi.org/10.5603/gipp.64673.
44. Andrejev, N. J., Korenevskaya, M. I., Rutberg, R. A., Dukarevitch, M. Z., Pokrovskiy, P. I., & Tokarev, N. Y. (1975). Haemophilia A in a patient with testicular feminization. Thrombosis et diathesis haemorrhagica, 33(2), 208–216.
45. Janczar, S., Babol-Pokora, K., Jatczak-Pawlik, I., Taha, J., Klukowska, A., Laguna, P., Windyga, J., Odnoczko, E., Zdziarska, J., Iwaniec, T., Koltan, A., Jamrozik, M., Rurańska, I., Janczar, K., Szczepański, T., Pietrys, D., Balwierz, W., Treliński, J., & Mlynarski, W. (2020). Six molecular patterns leading to hemophilia A phenotype in 18 females from Poland. Thrombosis Research, 193, 9–14. https://doi.org/10.1016/j.thromres.2020.05.041

46. Huisse, M. G., de Grouchy, J., Menaché, D., de Crépy, B., Andreassian, B., & Baumann, J. (1980). Hemophilia A in a phenotypic female with normal male karyotype associated with a low factor XII level. Annales de genetique, 23(1), 31–34.
47. Martín-Salces, M., Venceslá, A., Alvárez-Román, M. T., Rivas, I., Fernandez, I., Butta, N., Baena, M., Fuentes-Prior, P., Tizzano, E. F., & Jiménez-Yuste, V. (2010). Clinical and genetic findings in five female patients with haemophilia A: Identification of a novel missense mutation, p.Phe2127Ser. Thrombosis and haemostasis, 104(4), 718–723. https://doi.org/10.1160/TH10-02-0085.
48. Sitalakshmi, S., Tilak, P., Srikrishna, A., Damodar, P., & Thomas, I. M. (2001). An unusual case of haemophilia--a case report. Indian journal of pathology & microbiology, 44(3), 367–368.
49. Errahali, Y., Malad, M., Lakssir, I., Issouani, J., & Guerboub, A. A. (2026). Clinical Presentation and Management of Swyer Syndrome: A Case Report. Cureus, 18(1), e100735. https://doi.org/10.7759/cureus.100735
50. Loreth, R. M., El-Maarri, O., Schröder, J., Budde, U., Herrmann, F. H., & Oldenburg, J. (2006). Haemophilia A in a female caused by coincidence of a Swyer syndrome and a missense mutation in factor VIII gene. Thrombosis and haemostasis, 95(4), 747–748.