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Ageing and women with bleeding disorders

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As life expectancy increases, women with bleeding disorders can expect to live for decades after their menopause – potentially with a range of comorbidities including cardiovascular (CV) disease, cancer and osteoporosis. Menstrual bleeding around the menopause may be heavy and unpredictable for women with bleeding disorders (WBD). Hormone replacement therapy (HRT) remains the gold standard for those with debilitating menopausal symptoms and for osteoporosis prevention. Levels of endogenous von Willebrand factor (VWF) increase with age in the general population without bleeding disorders, with an associated rise in levels of Factor VIII (FVIII). Evidence also suggests age-related increases in VWF in people with von Willebrand disease (VWD), with limited but potentially associated evidence for increases in FVIII in those with mild or moderate haemophilia A. However, it appears that age-related changes in factor levels do not correlate completely with bleeding episodes, and more data are needed to fully understand the picture. New models of comprehensive care are needed that take account of age-related comorbidities in both women and men with bleeding disorders, including the impact of polypharmacy and its potential for causing adverse effects and impaired treatment adherence. Consideration will also be needed for bleeding cover during interventions such as surgery, radiotherapy and chemotherapy that become more likely with age. Protocols and care pathways need to be updated as the implications of ageing in women and men with bleeding disorders become better understood.

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REPORTS FROM THE SECOND EUROPEAN CONFERENCE ON WOMEN AND BLEEDING DISORDERS

Keywords: *Women with bleeding disorders, Ageing, Menopause, Hormone replacement therapy, Factor levels, Comorbidity, Comprehensive health care*

THE MENOPAUSE – DO WE KNOW ENOUGH ABOUT IT?

A girl born in 2000 can expect to live almost half of her life after her menopause. It is therefore important to optimise the quality of life of all women as they age, including women with bleeding disorders (WBD). Over 10 years ago the British Menopause Society recommended that primary care teams should invite women to register on or around their 50th birthday for a health and lifestyle consultation to discuss a personal health plan for the menopause and beyond [1]. This rarely happens in the UK – or in many countries – but recent publicity about menopausal issues is resulting in growing demand for effective care and support at menopause clinics and other related services.

The menopause is said to have occurred one year after a woman's last menstrual period and happens

J Haem Pract 2022; 9(1). doi: 10.2478/jhp-2022-0016

at an average age of 51 [2]. Women generally start to experience symptoms about four years before the menopause (the climacteric); early menopause is defined as happening before the age of 45 and premature ovarian insufficiency (POI) before the age of 40.

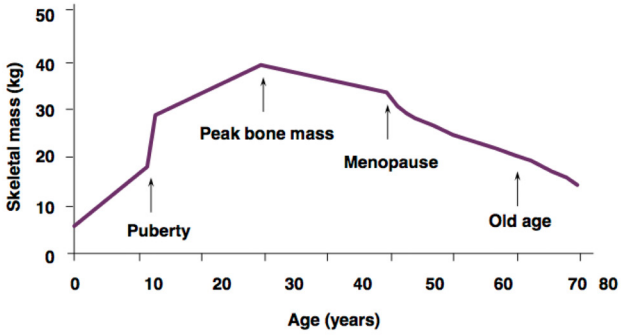
The menopause occurs when all the eggs with which a girl was born are exhausted. Ovarian failure can be diagnosed by measuring the amount of follicle stimulating hormone (FSH) in the blood (two tests around six weeks apart). FSH is the hormone which stimulates oestrogen production, which in turn stimulates development of ovarian follicles and egg release. Ovarian failure can also be diagnosed with an antral follicular count scan to show reduced follicle count, or by a blood test for anti-Müllerian hormone (AMH). Estimating AMH may help to predict the menopause and the transition from the time around the menopause (perimenopause) to the menopause itself.

POI remains an under-researched area and there is a need for high quality observational data as the diagnosis can be devastating for women trying to conceive. POI also has implications for increased risk of osteoporosis and heart disease owing to the prolonged time that women with this condition have reduced oestrogen levels. These women need hormone replacement therapy (HRT) irrespective of whether they have menopausal symptoms.

Other investigations that may be carried out include thyroid function testing for slow metabolism, DEXA scan for reduced bone density and risk of osteoporosis, a test for autoantibodies that may destroy ovarian tissue, and genetic tests (e.g. for fragile X chromosome which increases the risk of POI).

Many women experience heavy, unpredictable bleeding during the perimenopause, irrespective of whether they have a bleeding disorder [3]. This is likely to be due to the reduction in levels of the hormone progesterone, which occurs when eggs stop being released, leading to thickening of the lining of the womb. Shedding of this thickened lining results in heavier bleeding than usual and needs to be monitored as very heavy bleeding and thickening of the womb lining (hyperplasia) can lead to cancerous changes. Scans are needed to check for this serious potential outcome. Other symptoms occurring during the perimenopause and for some time after the menopause include hot flushes, night sweats, insomnia and fatigue, memory loss and mood changes, vaginal dryness, and increased urinary symptoms. Loss of oestrogen also leads to increased cardiovascular risk, with narrowing of blood vessels, increased platelet aggregation, worsening lipid profile, increased insulin resistance, and reduced blood flow; reduced oestrogen also leads to bone loss and increased risk of osteoporosis (Figure 1) [4].

Figure 1. Relation of age to skeletal mass. Reduced oestrogen following menopause leads to bone loss and increased risk of osteoporosis. Adapted from Birdwood, 1996 [4]



In addition to peri- and menopausal reductions in oestrogen and progesterone, there is also a decline in androgens (e.g. testosterone). Testosterone – usually thought of as a male hormone – is very important for young women, whose testosterone levels may be three to four times higher than their oestrogen levels [5]. Menopausal reduction in testosterone leads to reduced libido, energy and mood, as well as changes in bone and muscle mass.

HRT is the gold standard treatment for women with significant menopausal symptoms and/or risk of osteoporosis. Not every woman needs HRT, and lifestyle measures are also important, as are cognitive behaviour therapy (CBT) and non-hormonal treatment, such as venlafaxine and gabapentin, for managing mood changes.

CHANGES IN BLEEDING PHENOTYPES WITH AGE

New models of care are needed for women with bleeding disorders that take account of the complexity of managing these conditions, particularly in older people. Three quarters of people with haemophilia aged over 65 have two or more comorbidities [6]. However, there is little experience- or evidence-based information about the treatment of the emerging population of middle-aged and elderly women and men with bleeding disorders who have comorbidities, such as cancer, cardiovascular disease, renal diseases, osteopenia/osteoporosis and cognitive decline.

Levels of endogenous von Willebrand factor (VWF) increase with age in the general population without bleeding disorders, with an associated rise in levels of Factor VIII (FVIII). Evidence also suggests age-related increases in VWF in people with von Willebrand

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disease (VWD), with limited but potentially associated evidence for increases in FVIII in those with mild or moderate forms of haemophilia A [7,8,9,10]. It also appears that the age-related changes in factor levels do not correlate completely with bleeding episodes, and more data are needed to fully understand the picture [11,12,13].

Standardised bleeding assessment tools (BAT), such as ISTH-BAT, are often used at the time of diagnosing a bleeding disorder to help establish the bleeding phenotype. In the context of age-related changes in factor levels, there may be a need to re-evaluate these – for example, to develop a new BAT focused on the previous five to ten years. The evaluation of any changes in bleeding phenotype with age needs to evolve in a standardised way to enable comparison of the data collected.

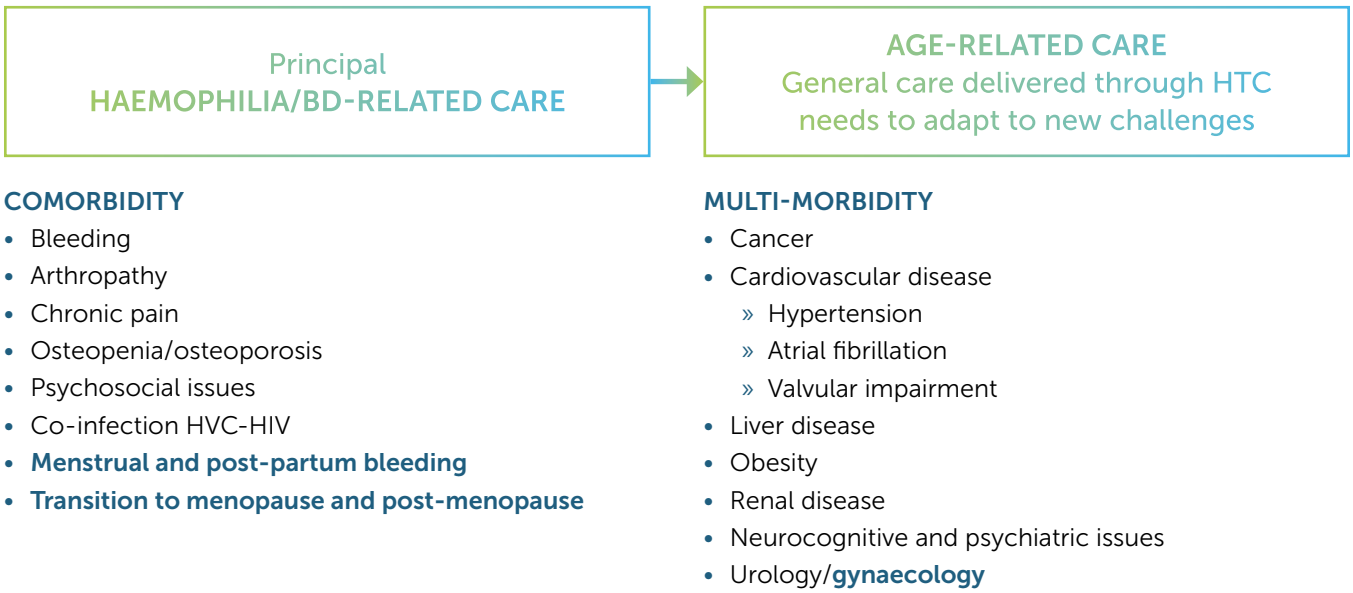
In a cohort of 39 patients, 32 of them women, aged around 40, with VWD type 1, mean VWF antigen was within the normal range (0.83 + 0.37 IU/ml) and mean bleeding score measured by MCMDM-1 VWD was 2.51+ 2.90 [12]. In this study, bleeding score was shown to be inversely proportional to age. However, this trend has not always been found in other studies and raises the question of whether some older patients with VWD and normal VWF can tolerate invasive procedures without the need for VWD-specific therapy [13].

Type, location and severity of bleeding evolve with age and vary between bleeding disorders. For example, from childhood into adulthood, platelet disorders (e.g. Glanzmann's thrombasthenia) tend to be characterised by nose and mouth bleeds, and in girls and women, heavy menstrual bleeding; in adulthood, challenges associated with surgery are more common and severe bleeding episodes can include gastrointestinal bleeds [14,15]. In afibrinogenemia, bleeding symptoms such as muscle and joint bleeds are present from childhood, but some may go on to develop thrombotic events, usually in adulthood – making management more complicated [16].

Although cardiovascular disease can occur in people with haemophilia, it appears they are at lower risk of the final thrombotic changes in the artery that lead to heart attacks and strokes. However, hypertension appears to be more common in those with haemophilia [17]. Research in women who carry the haemophilia gene – who can have reduced factor levels and may have haemophilia clinically – has shown reduced overall and ischaemic heart disease mortality but increased mortality due to coagulation disorders and intracranial haemorrhages, with no clear effect on stroke incidence [18].

Further research is needed to monitor and fully understand age-related changes in bleeding disorders and their implications for all aspects of patient care. The ADVANCE Working Groups have collected data from haemophilia treatment centres in 15 European countries, Canada and Japan, with the aim of raising awareness of issues related to ageing, identifying effective management strategies and generating recommendations. Data from an initial ADVANCE cohort showed fewer strokes and heart disease in people with haemophilia and more hypertension [19], but research to date has largely focused on men. ADVANCE is now extending its research to women with bleeding disorders, including a comparison of comorbidities in women and men and the risk factors that are involved.

Figure 2. Shifts in models of bleeding disorders care in an ageing population



As new models of care are developed that take account of age-related comorbidities in both women and men (Figure 2), there will also be a need to consider the impact of polypharmacy issues that are likely to accompany other diagnoses, e.g. cancer, cardiovascular (CV) disease, renal diseases, cognitive and other disorders. This will include effects on bleeding and mortality, with potential for adverse events and inappropriate prescribing, as well as treatment adherence. For example, some analgesics used by people with bleeding disorders have adverse effects that may be increasingly relevant in an ageing population, including gastrointestinal toxicity and higher bleeding risk with non-steroidal anti-inflammatory drugs (NSAIDs). These agents also have a potential contributory effect to hypertension. Other painkillers also have potential to cause harm if used inappropriately, including liver damage with paracetamol and addiction with opiates.

Bleed cover needs to be considered if biopsies are required for cancer diagnosis and treatment. Additionally, cancer chemotherapies that reduce platelet count may have important implications for people with bleeding disorders, with the need for increased prophylactic measures. In some cases, however, a bleeding disorder may have advantages – for example, when a bleeding episode leads to a referral and earlier diagnosis of cancer than would usually occur.

Comprehensive care is needed for women and men with bleeding disorders as they get older. Protocols and pathways should be updated to take account of the need to effectively diagnose, register and manage comorbidities alongside bleeding disorders, with a good understanding of the implications for multidisciplinary clinics.

DISCUSSION

If WBD have a good understanding of menopausal changes, they are more likely to seek help for symptoms and impaired quality of life. Multiple appropriate specialties need to be involved in care, with detailed records of symptoms in notes – simply recording that a woman is menopausal is not enough. Increased awareness of the menopause from an early age, e.g. through the school curriculum, should aim to encourage a more positive approach with greater understanding of how symptoms can be effectively addressed.

Natural oestrogen in women of reproductive age has a protective effect against CV risk. This is not affected by the progesterone component of hormonal contraception, with the possible exception of depot medroxyprogesterone acetate which may be associated with a slightly increased CV risk [20]. The type of oestrogen used in HRT is comparable to natural oestrogen but in a lower amount than is present in women of reproductive age. In post-menopausal women, HRT reduces CV risk. When women stop taking HRT, their CV risk rises to that of other women not using HRT.

WBD may be at increased risk of osteoporosis but other factors, such as family history of osteoporosis and natural bone density, may play a part. In addition to HRT, calcium/vitamin D supplements and weight bearing exercise can help to preserve bone health but

anyone with bone pain should have it investigated by their doctor. Depending on the result of bone density tests, women may be advised to take HRT or other drugs that preserve bone and/or relieve symptoms.

Gastrointestinal bleeding may occur in women with severe von Willebrand disease (predominantly type 2a or type 3) as they get older, but it is unclear why some women are affected, while others are not – despite having similarly low factor levels. It is one of the greatest unmet needs for WBD. When it first occurs, it needs to be addressed and followed up by multidisciplinary teams as it is likely to become a chronic condition. Initial treatment is with prophylactic von Willebrand factor (VWF) and/or hormone therapy including somatostatin, but success is generally for a limited time, and recurrent severe bleeding leads to anaemia and hospitalisation. Combined clinics are needed with gastroenterologists who can treat recurrent bleeds with endoscopic procedures. Research is underway to find out whether recombinant VWF concentrates may be more effective for prophylaxis than standard products.

TOP THREE TAKE-AWAYS

- WBD should be aware of the potential impact of menopausal changes, including unpredictable perimenopausal bleeding and increased osteoporosis risk, and should have access to effective care and support for all menopausal symptoms
- Factor levels may increase with age but this does not necessarily correspond with a change in bleeding phenotype; types of bleeding may also change with age
- New models of care are needed for both women and men with bleeding disorders to take account of age-related multi-morbidity, protect against adverse events and ensure appropriate prescribing

ACKNOWLEDGEMENTS

The authors have advised no interests that might be perceived as posing a conflict or bias.

This paper does not contain any studies involving human participants or animals performed by any of the authors.

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HOW TO CITE THIS ARTICLE:
Radhakrishnan S, d'Oiron R. Ageing and women with bleeding disorders. *J Haem Pract* 2022; 9(1): 126-131. *https://doi.org/10.2478/jhp-2022-0016*