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CASE STUDY

"I didn't know women could have haemophilia": A qualitative case study

Simon Fletcher

Introduction: There is a historic but persistent belief in haemophilia care that women do not suffer with the condition, they merely carry and transmit it. However, around 250 women worldwide are known to have factor levels within the severe to moderate haemophilia range (<1 IU/dL to 5 IU/dL), and the true figure may be greater than this. The experience of these women may be the same as or similar to those of men with similar factor levels, but there may be significant differences. What these differences are and what they mean to the women affected are not well understood as their voices are not heard. This case study highlights the issues and experiences of one woman living severe haemophilia. **Methods:** A single semi-structured qualitative interview was undertaken to explore the experiences of a young woman who has factor VIII levels of <1 IU/dL. The interview was recorded, transcribed and thematically analysed. **Results:** Four interlinked themes were identified: recognition, self-advocacy, identity and access to treatment. **Conclusion:** This case study indicates that, despite recent attempts to improve the diagnostic nomenclature, women and girls with haemophilia continue to find it difficult to access similar levels of care to men and boys. As such, they may fail to achieve parity in terms of safety, integrity and wellbeing, and have a reduced quality of life. If women and girls affected by haemophilia are to receive levels of treatment comparable to men, diagnostic criteria need to change further. Focusing on genotype, levels of factor expressed and phenotypical presentation rather than biological sex will acknowledge and validate their experiences, and improve treatment for all people with haemophilia in the future.

Keywords: *Haemophilia, Identity, Clinical trials, Women, Case study*

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Based on the lived experience of a woman with severe haemophilia, this case study contends that diagnostic criteria and opportunities to participate in clinical research need to be improved if women and girls affected by haemophilia are to achieve equitable access to treatment.

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Haemophilia is an X-linked condition characterised by a reduction or absence of clotting factor VIII (FVIII) in haemophilia A or factor IX (FIX) in haemophilia B [1,2]. Resulting in an impaired or incomplete clotting pathway and attendant bleeding risk in affected persons, it is categorised according to the amount of factor

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expressed (mild >5–45 IU/dL; moderate 1–5 IU/dL; severe <1 IU/dL) [3]. Bleeding tendency correlates with the severity of the condition, those with severe haemophilia bleeding more frequently than those with milder forms.

Affecting approximately 1:3,500 births worldwide [4], there are approximately 1.25 million men in the world with haemophilia, 420,000 of whom have severe haemophilia [5]. Current treatments consist of factor replacement, coagulation pathway rebalancing or, in the near future, gene therapy [6-8]. Haemophilia and its treatment come with significant individual, family and organisational burdens [9,10].

As haemophilia is an X-linked recessive condition, it has been accepted historically that women are largely unaffected and merely carry and transmit the condition [11]. However, this is far from the truth. Some women who carry the genetic mutation may, because of compound heterozygosity, incomplete X chromosomal inactivation or skewed lyonization, have factor levels commensurate with men with a diagnosis of haemophilia [12]. Miller and Bean [10] report that there are thought to be 250 women worldwide with factor levels in the severe to moderate range, though the true figure may be even higher, with many cases going unreported. The number of women who carry the haemophilia gene and are symptomatic to any degree is not known, but Kasper and Lin [13] suggest there may be nearly 2 million women worldwide who carry a mutation of haemophilia.

Similar to men with haemophilia, treatment for women with low factor levels depends on the severity of the presentation but can include factor replacement. Unlike men with haemophilia, however, the care of women with low factor levels can be complicated by the presence of additional haemostatic challenges throughout their lives [14], as well as a perceived inherent sexism in bleeding disorders care [15]. Treatment for women, therefore, depends upon adequate testing, accurate diagnosis and comprehensive follow-up.

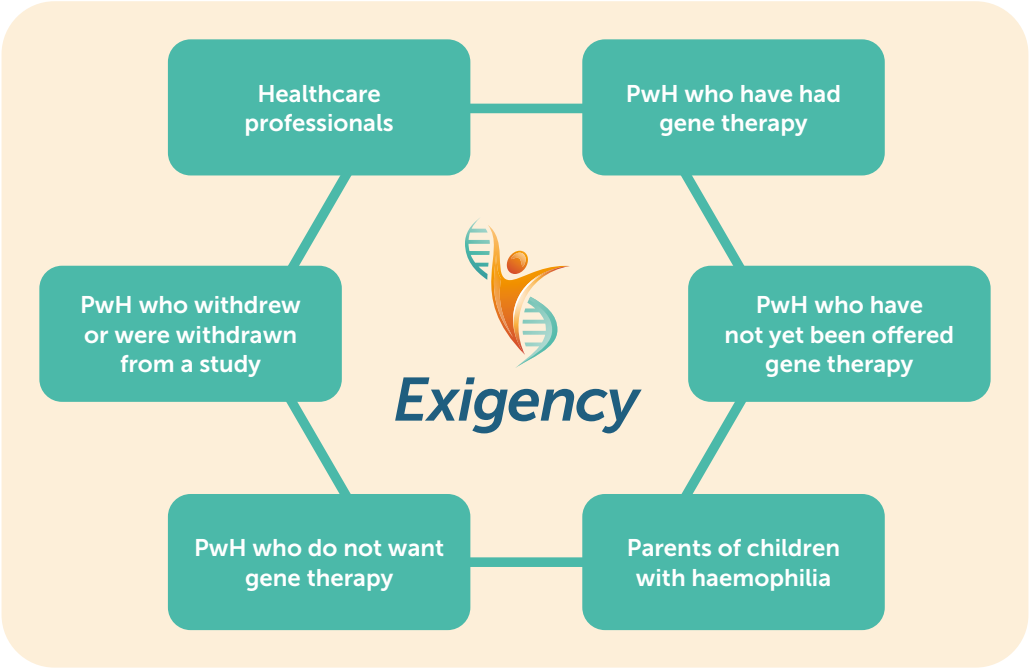
This case study presents the experience of a woman with severe haemophilia A and explores what implications these experiences might have for all healthcare professionals involved in the care of people with haemophilia (PwH) now and in the future.

METHODOLOGY

Case selection

This case study emerged from the ongoing Exigency programme [16-18], a nested group of studies looking into the views and experiences of gene therapy among six stakeholder groups: parents of children with haemophilia, PwH who have undergone gene therapy, PwH who have either withdrawn or were withdrawn from a gene therapy study, PwH who do not want

Figure 1. Diagrammatic representation of the Exigency study



gene therapy, PwH who have not yet been offered gene therapy, and healthcare professionals (Figure 1).

Other than parents of children with haemophilia and partners of men with haemophilia, women were excluded from the Exigency programme. This was a pragmatic decision based on the exclusion of women from haemophilia gene therapy studies. Despite this, Jayne (a pseudonym), a woman with haemophilia, contacted the study team asking to participate. Her approach prompted the study team to acknowledge that, rather than canvassing the views of PwH about gene therapy, they were only canvassing those of men with haemophilia, potentially giving an unintended skewed view. Jayne was therefore invited to participate in a separate intrinsic descriptive case study [19], in which her experiences – those of an individual from an excluded and potentially disadvantaged group [20] – could be heard.

Data collection and analysis

A single semi-structured qualitative interview was carried out by the author using the video-conferencing platform Zoom® in January 2022. The interview guide was adapted from that used in the Exigency study and addressed issues including Jayne's personal haemophilia story, her treatment history and ongoing care, and her thoughts on the future of haemophilia care (see Table 1 of the Appendix for the interview guide). Zoom® was used because of ongoing social distancing guidelines in the UK and because the travel requirements involved in meeting face to face would have been prohibitive. Zoom® has been found to be a useful and positive tool in qualitative research. [21,22].

The interview lasted 60 minutes, and was recorded, transcribed verbatim, and thematically coded using an inductive coding methodology [23].

Ethics

The Health Research Authority (HRA) decision-making tool was used to decide whether a formal application to the HRA and NHS Research Ethics Committee (REC) would be required for the interview [24]. As the interview would not generate any transferable or generalisable data and would not necessitate any change to Jayne's normal treatment regimen, it was deemed by the tool that no requirement for REC review and approval would be needed. The participant was asked to sign a consent form to confirm that she was happy to be interviewed and for pseudonymised quotes from the interview be used in any publications generated. It was stressed, however, that complete anonymisation may not be possible because, as a member of a rare subgroup of a rare condition, she may still be recognisable. A copy of this publication was sent to her prior to its submission to further confirm consent and correct any factual errors.

RESULTS

Biographical information

Jayne (pseudonym) is in her 20s and was born into a family with a known history of haemophilia A. Her maternal grandfather had severe haemophilia and her mother is therefore an obligate carrier. Her mother has a history of easy bruising and heavy menstrual bleeding; her factor levels were never formally tested, and although she was informed that she was a symptomatic carrier of haemophilia, no specific management options were made available to her.

When her mother became pregnant with Jayne, she informed her care team that she was a carrier of haemophilia. She was told by them that she had nothing to worry about as her child was a girl; it would not be a problem as *"only boys can get haemophilia"*. Jayne's birth was uneventful but it was soon noticed that, like her mother, she was prone to easy unexplained bruising. This was not picked up on by her health visitor, but at the age of six months Jayne developed a significant bleed at which point her GP suggested she should have her factor levels checked. When the results revealed a factor level of <1 IU/dL, further blood was taken and tested as it was thought there had been a mix-up and an incorrect result had been reported. The second sample confirmed a level of <1 IU/dL, her diagnosis was established and she was started on factor replacement therapy.

Jayne describes her childhood as one with few constraints: *"I can't say that I ever felt I was restricted in any way."* Her mother would ensure that she always sought advice if there was anything Jayne wished to do, but *"she found a way to do it"*. Despite ongoing factor replacement therapy, Jayne had regular breakthrough bleeds, most noticeably in her ankles, and felt like she was taking factor so frequently that she might as well have been taking it daily. At this time, she went through a period of rebellion and admits to having taken her factor less frequently than advised. She felt that she needed to have some control over her life and to be allowed *"to make the decisions for myself"*.

Jayne now uses an extended half-life factor prophylactically but states that she continues to have *"frequent bleeds"*, particularly into her ankles. She is hoping to be able to start emicuzumab in the near future, though has had difficulty convincing

her treatment centre to consider it as an option. The paucity of data on the use of emicizumab in women of childbearing age has meant that Jayne's treatment team were reticent to prescribe it until she decided to have no further children.

Jayne is married and has two children, neither of whom are affected by haemophilia.

Thematic analysis

Four major themes emerged during the interview: recognition, self-advocacy, identity, and access to treatment.

Recognition

Jayne spoke throughout her interview of the difficulty she has had in her condition and its severity being recognised. As described in the biographical sketch, this began at the point of diagnosis when her results came back: *"Their first thought was 'no, that can't be right'."*

This attitude of disbelief has continued to be a common occurrence. Jayne reports still being told by non-specialist healthcare staff when she informs them of her condition, *"Oh right, ok, yes [...] that's fine,"* and yet appropriate advice or the assistance of her haemophilia care team is rarely sought by them. She feels that, because of the relative rarity of haemophilia and it typically being understood as a condition that women *"can't actually have"*, there appears to be a disconnect between her reality and the understanding of haemophilia, even within a healthcare setting. This disconnect means that, at times, she has been left feeling unsafe in the care she has received.

> *"That's really upsetting, to think I don't feel safe [...] I don't feel like they're taking me seriously, I don't feel like they're getting the right advice. That's scary."*

Self-advocacy

Because of lack of recognition of the importance of her condition, Jayne feels she must constantly advocate for herself to ensure she receives appropriate care. This often means having to contact her treatment centre to inform them that she is about to have a procedure when the relevant care team have not done so. She feels that this is not something she should always have to think about and do.

> *"I shouldn't be having to think, 'Right, what do I need to tell them to do? Who do I need to tell them to contact?'"*

She accepts that, as a woman with severe haemophilia, her condition is rare within an already rare condition and that it's *"just one of those thing[s] where they just don't see it enough"*, but that equally it does not *"really excuse the fact that it's happening"*.

Jayne wonders whether an increase in training, not just in the bleeding disorders community but *"in women's services and things that are only really affecting women"*, is what is needed to improve both her own experience and that of all women with bleeding disorders.

Identity

Jayne spoke about the differences that exist for her as a result of her haemophilia. This manifested most clearly in adolescence, around the time of her menarche.

> *"I found that quite embarrassing, because it's something that every woman has to go through but you don't usually have to talk with doctors and nurses about it at such a young age in detail [...] Other girls didn't have to speak to a doctor about it unless... unless they had to go to the doctors about it for some reason. Even before I'd started they [the doctors and nurses] were talking about it."*

She also spoke about being seen as different from men with severe haemophilia:

> *"If it's a man and he says, 'I've got a bleeding disorder,' it is like, 'Oh right, ok, 100% we understand that,' but if it's a woman it will be like, 'Oh, right, ok... So, are you a carrier?'"*

Jayne sees herself as more a member of a community of women with bleeding disorders than a member of the haemophilia community.

> *"I understand that in my situation, yes, it is quite rare [...] but are they not taught about bleeding disorders and women with bleeding disorders and how to deal with it?"*

It is not that she feels deliberately excluded from the haemophilia community, but that being seen as 'only' a carrier lessens and demeans her experiences.

Access to treatment

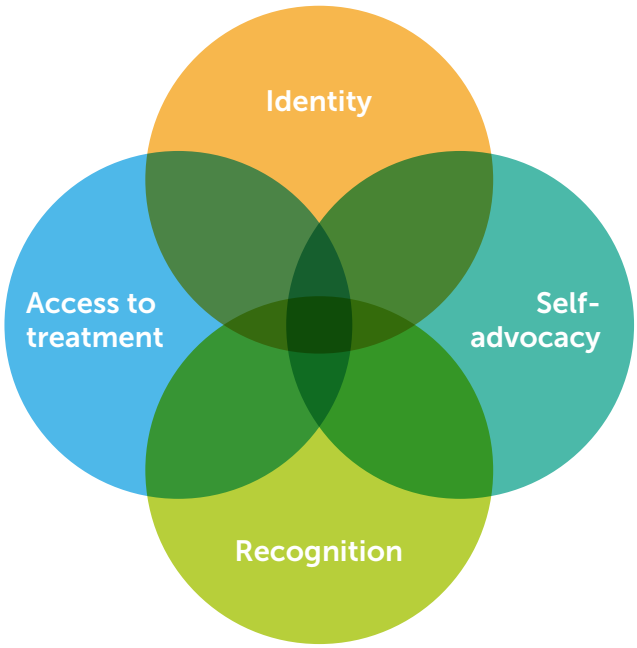
A major issue for Jayne is access to new treatments and the disparity that exists because she is a woman rather than a man.

Discussing new treatments and those currently in development, including gene therapy, Jayne is concerned that few, if any, women affected by haemophliia will be able to access them. Citing her own experience, she reports that it has taken a lot of negotiation with her care team for them to consider emicizumab as a treatment option: *"They're too scared [...] because what if it affects fertility or what if it affects periods, things like that."*

Much of the problem, she believes, stems from the fact that women are not included in many, if any, clinical trials of new therapies for haemophilia. She wonders whether this is due to a combination of women with haemophilia being rarer or not recognised, or that pharmaceutical companies are too cautious. Jayne says she has applied to take part in studies and believes there are other women who might be similarly willing but have been told that, as women, they are not able to participate. She says the exclusion of women in this way has to change because it feels like they are being *"punished for having children or wanting to have children or having periods"*. The right to choose to have a treatment or not, as some men with haemophilia are choosing not to with gene therapy [17], should be fundamental. To have those decisions enforced because of a lack of available safety data resulting from exclusion from clinical trials would appear to be unjust.

Further quotes supporting the themes arising from Jayne's interview can be found in Table 2 of the Appendix.

Figure 2. Thematic interactions observed in the case study



DISCUSSION

Though four major themes emerged in the interview – identity, recognition, self-advocacy and access to treatment – it became apparent that they were not completely distinct and that there was a great deal of interaction between them. It was impossible, for example, to think about identity without recognising how that impacted upon and in turn was impacted by recognition, access to treatment and self-advocacy (Figure 2). The themes' overlapping nature means that it is difficult to discuss one single element of Jayne's condition without reference to another.

One of the major issues Jayne discussed is difficulty accessing treatment because of the reluctance of her medical team to prescribe treatments that have not been tested on women. The problem, as she noted, is that women have generally been underrepresented in clinical trials and almost entirely excluded from haemophilia clinical trials.

Seen as vulnerable group, women have traditionally been excluded from clinical research [14,25,26]. This led to the rise of the male norm bias [27], where women's participation in clinical research was seen as unimportant due to the belief that data from studies which included only men could also be applied to women. More recently, sex-related differences, including differences between the progression and physiological characteristics of diseases, have been noted [28-30]. As such, the importance of including women in clinical research has again come to the fore.

The underrepresentation of women in haemophilia care is, in some senses, understandable for two reasons. The first, as highlighted above, is that historically only men have been thought to be affected, and as such the inclusion of women in clinical trials for haemophilia treatments was not seen to be necessary. The second is that, even though some women may benefit from a particular treatment, there are too few to make their inclusion in a trial practical or even possible. While both of these issues perhaps make the recruitment of women into haemophilia clinical trials complex, neither should necessarily have excluded them. Ineligibility purely on the basis of sex when other inclusion criteria are met – including the presence of the genetic mutation, a severe bleeding phenotype, factor usage, bleed data and willingness to participate – would seem to be wrong. A second X chromosome should not preclude women from taking part in clinical studies [15]. The advent of improved testing and new treatments, some of which may have applications in other (non-haemophilia) bleeding disorders, also

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highlights a growing need to redress this balance and ensure that women are recruited to any future studies so that there is an adequate body of evidence to allow parity of treatment with men.

More recently, sex-related diagnostic criteria have been called into question with the recognition of gender dysphoria and transgenderism [31,32]. Valk's 2018 case study [33], in particular, of a person with mild haemophilia (10 IU/dL) transitioning from female to male, and therefore from a carrier with low factor levels to person with haemophilia, shows that any diagnosis for haemophilia based purely on sex may no longer be valid or morally and legally defensible.

Identity as a woman with haemophilia has always been difficult for Jayne but it has also been an issue for many other women with haemophilia and other bleeding disorders. Sanigorska et al. [34] have shown that for many women the term 'carrier' has negative connotations, dismissing and devaluing their experiences, and resulting in feelings of insecurity and the avoidance of healthcare settings.

In an attempt to mitigate some of these concerns, the Scientific and Standardization Committee (SSC) of the International Society on Thrombosis and Haemostasis (ISTH) has proposed a number of changes to the nomenclature for affected women and girls [35]. However, these changes, while seeking to improve both diagnosis and clinical care for women and girls with haemophilia, may achieve less than hoped as they continue to perpetuate the sex-based discrimination that exists. Rather than streamlining and simplifying the definition of haemophilia for women, the guideline has created five new definitions, maintaining the distinction that while women may be symptomatic they fundamentally remain carriers rather than people with haemophilia.

Limitations

As with all case studies, the focus on a single individual whose concerns and issues may not be the same as other women with haemophilia means this case study has limited generalisability [36]. However, while Jayne's case may be the voice of an individual, it is the voice of an individual from an excluded and disadvantaged group [14]. There are obviously fewer women with severe haemophilia than there are women affected by haemophilia – but if a woman with a diagnosis of severe haemophilia is not recognised and cannot access care and treatments at parity with men, what hope do women less severely affected have?

The rarity of this case and other women with severe haemophilia makes the generation of any data important. This can add greatly to our knowledge of the aetiology, natural history and treatment [37,38], as well as our understanding of women with bleeding disorders' experience through narrative analysis [39].

CONCLUSION

Women with severe haemophilia form a rare group within an already rare disease. As such, their condition and/or specific needs are poorly understood. This case study shows how one woman with a phenotypically severe form of haemophilia feels about her condition and treatment. She feels that she and other women in the bleeding disorders community, including those with milder forms of haemophilia, are being disadvantaged in the treatment options available to them both now and in the future.

If there is to be equitable availability of treatment for women and girls affected by haemophilia, then two issues need to be addressed. The first is that the diagnostic criteria, based predominantly on an individual's sex, need to be reviewed and formally amended. Women should not be penalised for having a second X chromosome but should be treated according to their level of expressed factor and the severity of their symptoms. Secondly, women with haemophilia should have equal opportunity to be involved in clinical research and contribute to the safety and efficacy data of any new treatment in the same way as men with similar factor levels can.

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Informed consent has been obtained from the individual reported in this case study.

The author has advised no interests that might be perceived as posing a conflict or bias.

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Table 1. Interview guide

Thank you for agreeing to take part in this interview. Everything you tell us in this interview will be treated with complete confidence but some comments may be used in a publication, subject to your prior review – your identity will never be revealed.

In this interview we want to know, as a woman, what your experience of haemophilia is, what it has been like growing up with it, and how it impacts on your day-to-day life.

Are you OK to proceed and are you happy that we record the interview?

QUESTIONS	PROMPTS
Can you begin by telling me how old you are and a little bit about what hobbies you have?	
Can you tell me about your haemophilia?	• When were you diagnosed? • Do you have a history of haemophilia in your family? • How did your parents cope with the diagnosis?
Can you tell me about what it was like growing up with haemophilia?	• What was school like? • Did you feel excluded because of your haemophilia? • When did your periods start and how was that for you?
Can you recall how many bleeds you have on average?	
How are your joints?	• Do you have any joints that bleed more than others? • How do/did you manage those bleeds?

What about pain? Do you have any pain now?
 	
Imagine a scale of 1 to 6, where 1 is very little pain and 6 is the worst pain. How bad is that pain?
	• How has it been over the past month?
	  • Do you get pain every day?
	  • Is it joint-related/arthritic, or is it haemophilia-related?
	• How does arthritic pain differ from the pain of a bleed (if applicable)?

What impact has having haemophiila had on you and your family?	• Have there been any negative impacts? • Do you think there are any positive impacts? • How worried are you about an injury? • Was it difficult talking about your haemophilia to boyfriends/your spouse?
Do you feel that because you are a woman your care is different from that of men with haemophilia.	• In what ways?
	• How long have you been on it? • Have you been on any other treatments?
What treatment are you on?	
Have you ever had an operation in hospital? What was it for?	
Do you have any children of your own?	
Have you heard about any other treatments that might be available in the future?	• What do you know about them? • Do you think any of them are an option for you? • If not, why not?
Is there anything else you would like to say or ask of me?	

Thank you for taking part in this interview.

It is my intention to publish the interview as a case study in a haemophilia journal. As mentioned at the start of the interview, I will endeavour to keep protect your identity by removing any identifying data and using a pseudonym for you. Once it is written I will send you copy for you to comment on.

If you have any questions between then and now, please don't hesitate to contact me.

Table 2. Supporting quotes

Recognition	She [mother] took me to the GP, and it was the GP that said, "I think we should test her for haemophilia."
	I don't know how the GP... I don't know if it happened that my mum said, "Oh, I do have haemophilia in my family but they said it couldn't be that," and whether they just thought we've got to rule it out. I don't know how it happened, really. But I just know that the GP was the one who sent my mum and me to the hospital to get the blood tests done.
	I don't know what the things were like [all those years ago], but perhaps they could have thought at the very least that maybe I was a carrier and would still have... just maybe have low levels but not enough to make me a haemophiliac.
	I've found they've been like, "Oh – really?" and "I've never had a woman with haemophilia." The attitude has been not necessarily that they don't believe me, but the attitude has been, "Well, I don't know anything about haemophilia, never had a woman with haemophilia, so I don't know."
	Well, I mean, haemophilia isn't the only bleeding disorder, so you can't say that the next day they wouldn't see someone, see a woman, with a different bleeding disorder. I understand that in my situation, yes, it is quite rare. But why aren't they... I don't know, obviously, what goes on in their medical training and how much time they spend on different areas, but are they not taught about bleeding disorders and women with bleeding disorders and how to deal with it?
Self-advocacy	It was like, ok, so they diagnosed me with that, they said what they wanted to do – they wanted to do surgery. And it was like, "Ok, but I have haemophilia A."
	And he said, "Probably going to be surgery." I said, "Right, ok. I have haemophilia A, severe," and they were like, "Oh, right, ok." I said, "You need to contact my centre. Or you need to speak to an on-call haematologist here. But you need to speak to someone. I'm not happy to have surgery without you having spoken to someone and have a plan in place."
	When they took us aside to speak to the midwife about what to expect and everything, I said, "What about my haemophilia? Is that going to have an effect? Should I do anything different?" And she went, "Oh. I don't know because I've never had a woman with haemophilia," and it was just left at that. And it was kind of like... well, ok, it's good that you're admitting that you don't know, but could you find out, could you speak to someone? And instead I went home and I actually contacted my haemophilia centre myself, and obviously had to explain to them what had happened and ask them for advice or what I should do. And I just feel like I probably shouldn't have had to do that. Something that was so upsetting at the time, why did I need to go and seek out my own medical care, my own advice and things like that?
	I'd say all my life me or my mum have had to advocate for me.
Identity	I mean, I think one of the big things is that so many people still think that women don't get these certain bleeding disorders, and that's probably the biggest thing.
	I've spoken to people when I've been doing interviews or surveys and things like that, and they've sort of been like, "We're really excited to speak to you because we didn't know that women... we didn't know there'd be a woman with haemophilia." So, they don't even sort of wonder if it's out there. They don't wonder if there's women out there with haemophilia or certain bleeding disorders. They've been told that there's not, so they don't include them, I'm guessing.
	I've spoken to a lot of mums whose daughters might have haemophilia mildly or they've been told that they're a carrier and they're experiencing some symptoms, and I talk to them and they seem to have a lot of the experiences that I have in terms of heavy periods, bleeding in joints and things like that, which I can say, "Oh, well, yes. Because it's actually documented that I have haemophilia, this is what I... this is the medication that I can use, or this is what the doctor prescribed me, or this is what I do." And they still find that helpful.

Identity	**Interviewer:** Do you think there should be a move now... You talked earlier about women who are symptomatic carriers, they have low levels of factor VIII, whatever it may be, whether it corresponds with a mild or a moderate or a severe. Do you think we should stop calling symptomatic carriers symptomatic carriers, we should call them women with haemophilia? **Jayne:** Yes. **Interviewer:** Because it's the same thing? **Jayne:** Because, yes, because I think if we started calling them or diagnosing them with haemophilia, all of a sudden there would be all these women with haemophilia who people could talk to and could be included in clinical studies
	And on the Friday when I'd been up to have blood tests I'd said to them I've got haemophilia A, severe. They were like, "Oh right, ok, yes." And I was like, "Yes. Ok?" and they were like, "Yes, yes, that's fine. Never met a woman with haemophilia A."
Access to treatment	I do want to go to Hemlibra, but [...] it's been delayed and delayed. And that's what's prompted me to be like, "Why is there never any data on women?" I know that it's probably a lot harder to find women with haemophilia, but I don't know... I kind of feel like is there not another way to find some data around women and these different drugs?
	I don't have a lot of understanding on it [gene therapy] because it's not something that I've ever been approached about. I didn't really even know anything about Hemlibra until I read that it was... it had been approved on the NHS for severe and people with inhibitors. I sort of... I think I'd sort of seen that maybe something like that was in the works, but I didn't know that it was here, that it was an option, until it sort of was.
	Interviewer: So the information you're getting you're having to get yourself. **Jayne:** Yes. **Interviewer:** It sounds like it's not being offered because nobody's really sure whether it's appropriate or not at the moment. **Jayne:** Yes.
	Why are they never... When they put the feelers out for, you know, "We want to speak to men of this age, this background," or whatever they're looking for to include in their study, why isn't it... why are there never feelers out for women? I know that it might be harder to find them, but can they not reach out to centres and say, "Do you have any patients with any of these conditions – or anything like that – and would they be interested in taking part?" I mean, some people wouldn't be and that's just personal preference. They might not be suitable, whatever they've got as the criteria. But there must be ways to find women. But when I see studies it is like... it's asking for men. And most of the time, if I apply – when it starts involving medical treatments and things like that, it's like they're too scared to ask.

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