Women’s values and preferences on low-molecular-weight heparin and pregnancy: a mixed-methods systematic review

MONTSERRAT LEÓN-GARCÍA (mleong@santpau.cat)
Biomedical Research Institute Sant Pau (IIB Sant Pau). Barcelona

BRITTANY HUMPHRIES
Cytel Inc, Toronto, Ontario

ANDREA MARABOTO
Knowledge and Evaluation Research Unit, Department of Medicine, Mayo Clinic, Rochester, MN

MONTSERRAT RABASSA
Biomedical Research Institute Sant Pau (IIB Sant Pau). Barcelona

KASEY R. BOEHMER
Knowledge and Evaluation Research Unit, Department of Medicine, Mayo Clinic, Rochester, MN

LILISBETH PERESTELO-PEREZ
Evaluation Unit (SESCS), Canary Islands Health Service (SCS), Tenerife

FENG XIE
Centre for Health Economics and Policy Analysis, McMaster University, Hamilton, Ontario

IRENE PELAYO
Department of Obstetrics and Gynecology, PhD. Ramón y Cajal Hospital. Madrid

MARK ECKMAN
Division of General Internal Medicine and Center for Clinical Effectiveness, University of Cincinnati School of Medicine, Cincinnati, OH

SHANNON BATES
Department of Medicine, McMaster University, Hamilton, Ontario

ANNA SELVA
Clinical Epidemiology and Cancer Screening, Corporació Sanitaria Parc Taulí, Sabadell, Barcelona

PABLO ALONSO-COELLO
Biomedical Research Institute Sant Pau (IIB Sant Pau). Barcelona

Research Article

Keywords: Venous thromboembolism, low-molecular-weight-heparin, pregnancy, values and preferences

Posted Date: July 19th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1835329/v1
Abstract

**Background:** Venous thromboembolism (VTE) in pregnancy is an important cause of maternal morbidity and mortality. Low-molecular-weight heparin (LMWH) is the cornerstone of prophylaxis and treatment of thrombotic events during pregnancy. LMWH has fewer adverse effects than other anticoagulants, does not cross the placenta, and is safe for the fetus. However, the use of LMWH during pregnancy is sensitive to women's underlying preferences. The objective of this review is to systematically assess women's values and preferences research evidence on this topic.

**Methods:** We searched four electronic databases from inception to March 2022, and included studies examining values and preferences of using LMWH among pregnant women at risk of VTE. We followed a convergent integrated mixed-methods design to compare and contrast quantitative (utility and non-utility measures) and qualitative findings. We assessed the certainty of the values and preferences evidence with the GRADE approach for quantitative findings, and with GRADE-CERqual for qualitative evidence. Results were presented in a conjoint display.

**Results:** We screened 3,393 references and identified seven eligible studies. The mixed methods analysis resulted in four themes. Datasets confirmed each other in that: 1) the majority of women consider that benefits of treatment outweigh the inconveniences of daily injections; and 2) main concerns around medication are safety and injections administration. Quantitative outcomes expanded on the qualitative findings in that: 3) participants who perceived a higher risk of VTE were more willing to take LMWH. Finally, we found a discrepancy between the datasets around: 4) the amount of information preferred to make the decision; however, qualitative data expanded to clarify that women prefer making informed decisions and receive support from their clinician in their decision-making process.

**Conclusions:** We are moderately confident that in the context of pregnancy, using LMWH is preferred by women given its net beneficial balance. Integrating data from different sources of evidence, and representing them in a jointly manner helps to identify patient’s values and preferences. Our results may inform clinical practice guidelines and support shared decision-making process in the clinical encounter for the management of VTE in the context of pregnancy.

1. **Background**

Venous thromboembolism (VTE) in pregnancy is an important cause of maternal morbidity and mortality in developed countries(1), responsible for approximately 1.5 to 2% of maternal deaths during pregnancy and the postpartum period(2, 3). The normal hypercoagulable state during pregnancy increases the risk of developing VTE by 5- to 10-fold compared with non-pregnant women(2, 3). Other medical conditions in pregnancy, such as inherited or acquired risk factors for thrombosis (thrombophilia), can also increase risk of VTE and poor pregnancy outcomes, including placental abruption, preeclampsia, fetal growth restriction, stillbirth, and recurrent miscarriage(4). Low-molecular-weight heparin (LMWH) is the cornerstone of prophylaxis and treatment of thrombotic events during pregnancy and the postpartum period(5). LMWH has fewer adverse effects than other anticoagulants, does not cross the
placenta, and is safe for the fetus\(^6\),\(^7\). However, the use of LMWH during pregnancy is challenging, as it is expensive, uncomfortable to administer, may be associated with an increased risk of major obstetrical bleeding, and may jeopardize the use epidural analgesia\(^7\)–\(^9\).

Like many other decisions in health care, the prevention of VTE during pregnancy does not have a single best option. Many factors influence the decision-making process, and, therefore, it is considered a preference-sensitive decision\(^10\). This is probably one of the reasons why in a recent critical appraisal of guidelines for the prevention and treatment of pregnancy-associated VTE, recommendations were inconsistent\(^5\). Similarly, one “strongly recommended for use in practice” guideline included in the critical appraisal, the American Society of Hematology 2018, concluded that healthcare professionals should make decisions through a shared decision-making (SDM) process, incorporating patients’ values and preferences \(^11\).

Two previous reviews have addressed the topic of values and preferences in thrombosis \(^10\),\(^12\). These reviews show that patients’ values and preferences appear to be highly variable. However, to date, there is not a specific review addressing women’s values and preferences for antithrombotic therapy during pregnancy. Furthermore, one of these reviews\(^10\) only included quantitative measures while the other\(^12\) collected information from both quantitative and qualitative measures, but synthesized the information independently and did not integrate findings. Good Reporting of A Mixed Methods Study (GRAMMS) criteria have highlighted this limitation, in which judgements about integration could rarely be made due to the lack of integration of data and findings \(^13\). Therefore, this review contributes to the field of mixed methods research by using an integrative-convergent designs \(^14\) that are optimal to conduct the study of this phenomena \(^15\)–\(^17\).

Our aim was to conduct a systematic review on values and preferences for LMWH therapy during pregnancy using a mixed-methods integrative design. We conducted this review as part of the DASH-TOP study \(^18\) that aims to improve the quality of thromboprophylaxis decisions in this population.

2. Methods

We registered the protocol in PROSPERO (CRD42020193925), and adhered to the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) 2020 statement\(^19\).

2.1 Design

We followed a mixed-methods approach\(^20\)–\(^23\) to synthesize and integrate different types of evidence, either quantitative and qualitative \(^24\)–\(^26\). We followed a convergent integrated design that comprises three-steps (Fig. 1. Mixed-method analysis and synthesis): i) Segregated data extraction and analyses of the evidence, maintaining a clear distinction between quantitative and qualitative datasets with individual
synthesis prior to the mixed-methods synthesis(23, 27); ii) Integration of data following a QUANT + qual integration procedure (24); and, iii) Mixed-methods synthesis.

2.2 Data sources and searches

We used a validated search strategy to identify studies on patients’ values and preferences (28). The search strategy used terms related to LMWH and pregnancy. Searches were conducted from inception to September 2020 in the following databases: in MEDLINE (accessed via PubMed), PsycINFO (accessed via EBSCO host), CINAHL (accessed via EBSCO host), and The Cochrane Central Register of Controlled Trials (search strategies are available in the Additional file 1. and preserve search strings on searchRxiv https://searchrxiv.org/). We conducted literature surveillance via MEDLINE (accessed via PubMed alerts) until the review was submitted for publication (July 7th, 2022). We did not restrict our search by publication status, language, or date of publication. We also reviewed reference lists of the included articles, and relevant systematic reviews.

2.3 Eligibility criteria

We included studies that enrolled pregnant women, or women who were planning pregnancy, for whom anticoagulation with LMWH was considered and:

- Examined women’s values and preferences for LMWH vs. watchful waiting or alternative anticoagulant therapy.
- Examined choices patients make when presented with management options regarding antithrombotic therapy.
- Examined women’s experiences and beliefs of LMWH therapy in pregnancy.

We considered studies to be eligible using preference-elicitation methods detailed in Fig. 2. Preference-elicitation methods. Selva.et.al. 2017 (12, 28).

We excluded studies that rated health states related to VTE in pregnancy, but did not involve the decision of whether to use LMWH. We also excluded studies addressing the use of other antithrombotic medicines such as aspirin. Finally, we excluded study protocols, conference abstracts, reviews, and non-peer reviewed publications such as letters or editorials.

2.4 Selection of Studies and Data Extraction

All steps were conducted independently by pairs of calibrated reviewers, using standardized and piloted forms. Disagreements were resolved with the help of a third reviewer.

We extracted information on - study design; objectives; population characteristics (mean age, level of education and income level); reasons for VTE risk in pregnancy (for example: history of VTE, thrombophilia, mechanical heart valves, antiphospholipid syndrome); if LMWH was used for prevention or treatment during antepartum, postpartum or both periods; and, a description of the methods used to obtain preferences (including instruments and techniques for preference elicitation). Outcomes included quantitative utility values and non-utility preferences (collected as means with standard deviations, interquartile ranges or percentages, as available), and qualitative preferences (collected as themes and illustrative quotes).
2.5 Data synthesis and analysis

We conducted a descriptive analysis for quantitative data(29). For utility outcomes, we reported the mean value for the scores of the health state ‘Pregnancy with LMWH’ (participants rate how close the health state ‘pregnancy with LMWH’ is to good health on a 0-100 scale)(12, 30). For non-utility outcomes, we reported overall means, frequencies or proportions.

For qualitative findings, we conducted open coding thematic analyses to collect and analyze the data (27, 31, 32). We extracted interpretative findings reported by authors and supporting quotes. We categorized these findings in themes using an interactive process that involved a careful and repetitive reading of all pieces of extracted text.

For the mixed-method synthesis we integrated the data following a QUANT + qual design(24): themes from the quantitative data were prioritized and supplemented with qualitative findings (the rationale for having the quantitative dataset leading the integration is that there is a larger body of evidence(28)). We presented this integration process using a conjoint display (21, 25, 26); specifically, we used a side-by-side comparison (20, 21, 26) to assess whether datasets were in discordance, confirmation, or expansion(26). Discordance was defined as quantitative and qualitative results that were inconsistent or contradictory. Confirmation occurred when findings from both types of data reinforced each other. When findings from one type of data expanded upon insights from the other type of data, this was classified as expansion. Findings were synthesized and reported narratively and tabulated.

2.6 Appraisal of the evidence

For quantitative studies, we applied the GRADE approach to assess the risk of bias and certainty of evidence(33, 34). For qualitative studies, we used the CASP Qualitative Checklist tool(35, 36) to appraise the methodological quality, and the CERQual (Confidence in the Evidence from Reviews of Qualitative Research) approach to assess the certainty of evidence(37).

To assess the certainty of the evidence of the mixed-methods findings, we selected the dataset with the highest certainty of evidence(38).

3. Results

3.1 Study and population characteristics

We identified 3,393 references, of which eight publications (39–46) reporting on seven studies met our eligibility criteria (Fig. 3. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA Statement 2020) flow chart).

Included studies are summarized in Table 1.
From the studies, we included information on 427 women, with a mean age of 33.8 years (SD = 5.53). Two studies were focused on the antepartum period (40, 42, 46) in women where the risk of VTE was exclusive due to history of VTE: one compared their choices regarding thromboprophylaxis (40, 46); the other (42) studied the use of unfractionated heparin (UFH) for both prevention and treatment purposes; although UFH was not part of our inclusion criteria we included this study as they reported on the preference regarding injectable administration of heparin, and in this regard we found it relevant to inform the context of this decision-making process. Two studies (39, 41) focused on the postpartum period for women with multiple risk factors for VTE. In both cases, authors explored women's views, experiences and adherence to LMWH for VTE prevention alone. The other three studies (43–45) assessed preferences, both during the antepartum and postpartum period: two (44, 45) included women with antiphospholipid syndrome which is associated with recurrent pregnancy loss. The other study (43), included women with multiple risk factors such as history of VTE, antiphospholipid syndrome, stillbirth in previous pregnancy and placental complications. They collected views and beliefs about enoxaparin prescribed for both prevention and treatment.

### 3.2 Women’s values and preferences

One of the included studies reported utility measures (40, 46), five reported non-utility measures (39–43, 46), and three studies informed qualitative findings (43–45).

Women’s preferences reported from quantitative studies are outlined in Table 1 and from qualitative studies in Table 2 (available in the Additional file 2).

#### A. Quantitative findings

##### A.1 Utility measures

**Pregnancy with LMWH prophylaxis**

The utility value for the health state ‘pregnancy with LMWH prophylaxis’ was measured using a feeling thermometer (a visual analogue scale (VAS)) (40, 46). The overall mean and standard deviation (SD) was 81 (15) meaning that women placed receiving LMWH injections during pregnancy at around 80 on a scale of 0 to 100, hence, taking LMWH during pregnancy as something relatively close to good health.

##### A.2 Non-Utility measures

**Willingness to take LMWH**

One study (40, 46) assessed the willingness for thromboprophylaxis with LMWH in the antepartum population using two different instruments:

1. A direct choice exercise in which authors presented women with a decision board that described different risks of developing VTE during pregnancy based on characteristics of their prior VTE. The results showed that the majority of women were willing to take LMWH, regardless of their VTE risk, and that the higher their risk, the greater was their willingness to take it.
2. A probability trade-off exercise in which authors used this instrument to determine women's thresholds for accepting LMWH prophylaxis(40). The median threshold reduction in VTE risk at which women were willing to accept use of LMWH was 3%. Furthermore, women with less previous (under 2 weeks) experience with LMWH during pregnancy compared to those with more experience, required a greater VTE risk reduction; it also showed that there were no significant differences between pregnant women and women planning pregnancy.

Another study(41) assessed compliance with thromboprophylaxis, and reported that if thromboprophylaxis was indicated in a future pregnancy, most women (94.5%) would accept it.

Beliefs towards the harms, overuse, necessity, and concerns of taking LMWH

Two studies(39, 43) used the Beliefs about Medicines Questionnaire (BMQ) (47). The BMQ questionnaire includes 18-items and four subscales assessing beliefs associated with the medication (in this case use of enoxaparin). Subscales for general harm and overuse (based on four items each) could have a minimum score of four and a maximum score of 20. Subscales for specific necessity and concerns (based on five items each) have a minimum score of five and a maximum score of 25.

The Necessity-Concerns Differential (NCD)(47), is used to report on the balance between necessity and concerns of medications. The Necessity-Concerns Differential (NCD) was found to be 1.18(39) and 2.20(43), both with a positive differential, suggesting that women felt that the necessity of the enoxaparin was greater than any concerns they may have held regarding its use.

Reason for not being adherent when using LMWH

One study(41), reported reasons for not completing treatment that included bruising or wound complications; forgetting; fear or dislike of needles, and emotional reasons for stopping.

Preference for route of administration

One study(42) assessed the preferred mode of administration for UFH. The majority preferred injecting heparin through a Teflon catheter over standard subcutaneous injections. This was due mainly because it caused less pain and less bruising than injections.

Preferred amount of information regarding LMWH

One study(41) assessed preferences regarding the amount of the information given about the decision to use LMWH during pregnancy: the majority of women reported that they had received enough information about treatment, however 16.6% reported that they would have liked more information or training on injections before leaving the hospital.

B. Qualitative findings

We synthesized qualitative findings using five main themes.

Attitude towards LMWH during pregnancy
The majority of women were willing to receive LMWH injections (43–45). They felt that responding to their situation by taking action with daily LMWH injections comforted them and decreased anxiety. Women understood that the desired outcome of a successful pregnancy could not be predicted and they accepted uncertainty and maintained the perspective that a positive outcome far outweighed any temporary discomfort. Miscarriage was considered a very traumatic situation and was perceived as leading to a high risk of complications during pregnancy, thus they felt motivated to use LMWH; in the study (43) that included women at low risk for VTE, participants still reported anxiety relief by using LMWH.

**Experience of using LMWH during pregnancy**

Three studies (43–45) reported challenges with injections, such as bruising, pain, and bleeding; one study (43) stated that easier routes of administration would be desirable. However, complications of the medication did not influence the decision to take LMWH, and it became part of their pregnancy experience.

**Concerns about medication**

The main concern surrounding LMWH was safety (43–45). The majority of women placed a higher priority on their baby’s safety. However, in one study first-time mothers placed a higher priority on the baby’s safety, while mothers with other children prioritized their own health. Other concerns included fear of forgetting a dose; fear of needles; fear of bleeding during labor; and needing a scheduled labor (off LMWH) to be able to get an epidural.

**Information needs to inform the decision**

Two studies (43, 44) found that the majority of women felt they had not received enough information to address their concerns. Most frequently, women felt uninformed about how LMWH worked, injection technique and side effects. The information was not always prompted by the physician and, in many cases, there were limited available resources for women. Information was gathered from different sources including the internet, books on pregnancy, health professionals, or word of mouth. Sharing stories with other women proved to have a compelling influence on decision making, and was also reassuring and encouraging.

**Patient involvement in the decision-making**

Seeking information proved a powerful means by which women were able to take control and actively address their needs. In addition, patients described how physicians influenced their decision-making process, highlighting the importance of the physician-patient relationship (43–45). Patients felt empowered by their healthcare professionals and did not feel pressured to take LMWH. Several women (44) expressed anxiety regarding the weight of responsibility involved in making medical decisions that could affect the pregnancy outcome.

### 3.3 Mixed-methods results

Three quantitative outcomes (Beliefs about harms, overuse, necessity, and other concerns about taking LMWH; reasons for reason for not being adherent when using LMWH; preference for route of administration)
were merged into a single outcome to inform the corresponding mixed-methods theme (“Beliefs towards medication”). Four mixed-methods themes were identified. Results are detailed in Table 2.

Pregnancy with LMWH prophylaxis
This theme was informed by four studies (40, 43–46). Both datasets confirm findings on considering this health state as close to ‘perfect health’ and having LMWH as an option far outweighed any temporary discomfort caused by the injections. Prior experience using LMWH was important and very informative on how women considered daily injections.

Willingness to take heparin
Five studies informed this theme (40, 41, 43–46). Both data sets confirmed that the majority of women would be willing to take LMWH; that they understood that the desired outcome of a successful pregnancy could not be predicted, and uncertainty was well tolerated. The quantitative data expands on this by showing a direct relationship between high perceived risk and increased willingness to take the medication.

Beliefs towards medication
This mixed-method theme was reported by six studies (39, 41–45). There was confirmation that women viewed LMWH more as a necessity than a concern; the main consideration being safety, especially for their unborn baby. Women preferred to use devices that facilitated the administration of the injections. Qualitative data expanded upon quantitative data, by reporting other concerns associated with antepartum use of LMWH (e.g. withholding injections before a scheduled labor and delivery).

Preferred amount of information regarding LMWH
This mixed method theme was the least informed. Three studies reported discordances (41, 43, 44) and four included expansion (41, 43–45). Discrepancies occurred when women were asked about their preferences for the amount of information they received. Quantitative results reported that women felt well-informed, while the opposite was the case in qualitative findings.

In qualitative reports women understood that benefits outweighed risks, but they didn’t feel they had sufficient information, especially about the effect of LMWH on their condition, injection techniques, side effects, or what to do if a difficult situation arose. Qualitative data also expanded findings, showing that this decision needs adequate support from the healthcare professional.

3.4 Quality appraisal

Assessments of the quality of the evidence are available Additional file 3.

The certainty of the evidence for all the quantitative outcomes was rated as very low, mainly due to risk of bias (unclear sampling strategies (40, 42, 43, 46) and high attrition rates (39, 41)); indirectness (due to methodological elements (39–43, 46)); and imprecision (small sample sizes (39–43, 46)). Regarding qualitative research, both studies (44, 45) presented methodological concerns regarding selection bias, and lack of consideration of the relationship between researchers and women. The confidence for all qualitative
findings was moderate (due to concerns about rigor (unclear recruitment and sampling strategy)) except for
the finding Information needs to inform the decision(43, 44), which was rated as low, due to concerns
regarding adequacy and relevance of the data. The certainty of the evidence for all the mixed-methods
themes was rated as moderate, except for ‘Adequacy of the information regarding LMWH’ which was low.

4. Discussion

Main findings

Our mixed methods systematic review is the first to assess preferences of women towards using LMWH
during pregnancy. We included seven studies: five studies(39–43, 46) were conducted among women who
had a history of VTE, in which heparin was used for VTE prevention and/or treatment in the ante- and/or
post-partum period. The other two qualitative studies(44, 45) were conducted in women with thrombophilia,
where LMWH was used to reduce risk of miscarriage.

After quantitative and qualitative datasets were merged, four mixed- methods findings were identified
reporting on women’s preferences towards using LMWH during pregnancy.

Datasets confirmed each other in that: 1) the majority of women considered that benefits of treatment
outweighed the inconvenience of daily injections; and 2) main concerns were about medication safety and
the need to give injections. Quantitative outcomes expanded on the qualitative findings in that: 3) women
who perceived a higher risk of VTE were more willing to take LMWH. Finally, we found a discrepancy between
the datasets regarding: 4) the amount of information preferred to make the decision; however, qualitative
data expanded to clarify this discrepancy. Women expressed feeling confused about how VTE could affect
their baby, how it could compromise their own health, and why it was particularly relevant during pregnancy.
Therefore, informed decisions are preferred and the role of clinicians to support their decision-making
process was highlighted. The overall quality of the evidence was moderate.

Limitations, strengths and previous research

Our review has several limitations. There are still very few studies, including very few women, in this field. As
a result of this limitation in the body of evidence, we only captured preferences for women at risk for VTE or
pregnancy loss during pregnancy. We were not able to identify preferences in other conditions such as
women with heart valve prostheses(8, 9, 48, 49). In addition to the limited number of published studies,
another reason to downgrade the quality of the evidence in our review is inconsistency across studies. For
example, for outcomes such as “willingness to take LMWH” the patient populations included women using
LMWH to prevent miscarriage (women with thrombophilia) and women using it as thromboprophylaxis to
prevent recurrent VTE. Risk perceptions differ according to the condition for which LMWH was going to be
used for. This was evident in one of the studies that included both populations; those with thrombophilia had
higher risk perception vs those with a prior VTE (43). Despite these limitations, by leveraging both qualitative
and quantitative data, our review was able to demonstrate a relationship between level of VTE risk and
willingness to take LMWH.
As noted in other reviews of values and preferences (12, 50), we were able to collect and analyze quantitative data more easily than qualitative data. As measures are inconsistent and we lack a specific framework to guide the analysis of qualitative data, we opted to use an open coding approach for extracted data, which is the gold standard methodology to study phenomena in qualitative methods (27, 32). In addition, we used a validated search strategy that was designed to include qualitative studies containing preferences (28) to ensure the identification of the full body of qualitative evidence. Therefore, a strength of this systematic review was our demonstration that qualitative methods are useful to inform on the context, the grounds by which the decision is made; and address issues like level of information is needed to inform the decision, what is the preferred level of patient involvement, and the role of the healthcare professional in supporting the decision (45).

Assessing the certainty of the evidence is critical in understanding how our findings support suggestions to use shared decision-making in clinical practice and guideline development. Although, there are specific quality of evidence appraisal tools for mixed-methods systematic reviews, these methods still face the challenge of assessing integrated findings (51); hence, we assessed independently the certainty of the evidence for both datasets using the GRADE approach, which has specific guidance for the topic. We used specific guidelines to assess the evidence about values and preferences described in quantitative findings (33, 34), and used GRADE-CERqual to judge qualitative evidence. (33, 34, 52). Finally, we selected findings with the highest certainty to inform the quality of our mixed-methods findings (38).

An important strength of this review is the mixed-methods integrative approach, which expanded our findings, by increasing the ability of data analyzed and subsequently used to inform policy and practice (24). The design of this review leverages qualitative and quantitative data to help us confirm and expand on findings, as well identify discordances between the types of data. Other mixed-methods systematic reviews (12, 50, 53) assessing preferences using different methods to analyze outcomes, rarely integrated data from quantitative and qualitative datasets to improve understanding of the phenomena (24). The conduction of an integrative analysis contributes to the field of mixed methods research (14) and specifically in the field of systematic reviews (27, 54). Also, attempting to integrate data and findings from the individual components is considered adequate criteria in Good Reporting of A Mixed Methods Study (GRAMMS) (13).

**Implications for practice and research**

While more research is needed on women's preferences for VTE prophylaxis during pregnancy and pregnancy loss, our findings can support recommendations (11) regarding the types of information pregnant women at risk of VTE need to participate in a SDM process. These factors have been shown to influence the decision-making process (45), and their clarification is especially important in low risk settings (i.e., women with a prior history of VTE associated with a non-hormonal temporary provoking risk factor), in which we showed lower levels of willingness to take antithrombotic treatment (40, 46). This is particularly relevant when using systematic reviews to inform the development of tools used to support SDM (18).

More research is needed on specific qualitative frameworks to assess preferences delivered through qualitative instruments, such as interviews or clinical observations (55). For example, one study (45) included in this review reported that the husband of a pregnant women was very concerned about the safety of LMWH.
and its effect on his wife's health. 'What other people think I should do' is an aspect that can affect the decision. Burke’s motives pentad framework was used to deductively categorize patient reflections by their reasons, as to why their care plans made sense in the context of thromboprophylaxis in atrial fibrillation decision-making(56).

In addition, further guidance from the GRADE-CERQUAL group is also needed to assess certainty of the evidence in mixed methods reviews that integrates findings coming from different methodologies. The CERQUAL methodology to assess the relevance and adequacy domains(57, 58) may help clarify when findings coming from different study designs are complementary or discordant among studies. (37).

5. Conclusion

This mixed-method systematic review showed among women at risk for recurrent VTE during pregnancy and pregnancy loss, LMWH prophylaxis was preferred to watchful waiting due to its perceived net clinical benefit. However, more evidence is needed in women at lower risk of VTE in pregnancy as the certainty of this evidence was only moderate. Integrating data from different sources of evidence, and representing them in a joint manner helps us better understand women’s preferences and contributes to the field of mixed-methods research. Our results may inform clinical practice guidelines and support a shared decision-making process in the clinical encounter for the management of VTE in the context of pregnancy.

Declarations

1. Ethics approval and consent to participate
   Not applicable

2. Consent for publication
   Not applicable

3. Availability of data and materials
   All data generated or analysed during this study are included in this published article [and its supplementary information files]. Preserve search strings are available in searchRxiv https://searchrxiv.org/)

4. Competing interests
   Nothing to declare

5. Funding
   ML received a doctoral award from Health Institute Carlos III (Grant number: F18/00014). This study has been funded by Instituto de Salud Carlos III (Grant number: PI17/01874), and Co-funded by the European Regional Development Fund "A way to make Europe".

6. Authors’ contributions
CRediT authorship contribution statement

ML-G: Conceptualization, Methodology, Formal analysis, Data curation, Investigation, Writing – original draft, Visualization, Project administration. BH: Conceptualization, Methodology, Formal analysis, Writing – review & editing. AM: Formal analysis, Writing – review & editing. MR: Methodology, Writing – review & editing. KB: Methodology, Visualization, Writing – review & editing. LP-P: Conceptualization, Methodology, Writing – review & editing, Project administration. FX: Methodology, Writing – review & editing, Project administration. IP: Methodology, Writing – review & editing. ME: Methodology, Writing – review & editing. SB: Methodology, Writing – review & editing. AS: Conceptualization, Methodology, Formal analysis, Data curation, Visualization, Writing – review & editing, Supervision. PA-C: Conceptualization, Methodology, Data curation, Writing – review & editing, Supervision, Project administration, Funding acquisition.

7. Acknowledgements

Montserrat León- García is a doctoral candidate for the Ph.D. in Methodology of Biomedical Research and Public Health, Universitat Autònoma de Barcelona, Barcelona, Spain; and this review will be part of her thesis dissertation. The authors wish to acknowledge and thank Yang Song, Ena Pery Niño de Guzmán Quis, Claudia Valli, Claudio Rocha for their contributions on abstract screening and guidance on approaching mixed-methods methods. We thank Ivan Solá for his help on conducting and executing the search strategy.

8. Authors' information (optional)

Montserrat León- García is a doctoral candidate for the Ph.D. in Methodology of Biomedical Research and Public Health, Universitat Autònoma de Barcelona, Barcelona, Spain

References

1. Heit JA, Kobbervig CE, James AH, Petterson TM, Bailey KR, Melton LJ. Trends in the incidence of venous thromboembolism during pregnancy or postpartum: A 30-year population-based study. Annals of Internal Medicine. 2005;143(10).

2. Bailly J, Jacobson BF, Louw S. Safety and efficacy of adjusted-dose enoxaparin in pregnant patients with increased risk for venous thromboembolic disease. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics. 2019;145(1):70–5.

3. MBRRACE-UK. Saving lives, improving mother's care report. MBRRACE-UK. Vol. 31, Midwifery. 2019.

4. Nahas R, Saliba W, Elias A, Elias M. The Prevalence of Thrombophilia in Women With Recurrent Fetal Loss and Outcome of Anticoagulation Therapy for the Prevention of Miscarriages. Clinical and applied thrombosis/hemostasis: official journal of the International Academy of Clinical and Applied Thrombosis/Hemostasis. 2018;24(1):122–8.

5. Zheng J, Chen Q, Fu J, Lu Y, Han T, He P. Critical appraisal of international guidelines for the prevention and treatment of pregnancy-associated venous thromboembolism: A systematic review. BMC Cardiovascular Disorders. 2019;19(1):1–10.
6. Romualdi E, Dentali F, Rancan E, Squizzato A, Steidl L, Middeldorp S, et al. Anticoagulant therapy for venous thromboembolism during pregnancy: a systematic review and a meta-analysis of the literature. J Thromb Haemost. 2013;11(2):270–81.

7. Sucker C. Prophylaxis and Therapy of Venous Thrombotic Events (VTE) in Pregnancy and the Postpartum Period. GebFra Science. 2020;80:48–59.

8. Rodger MA, Carrier M, le Gal G, Martinelli I, Perna A, Rey E, et al. Meta-analysis of low-molecular-weight heparin to prevent recurrent placenta-mediated pregnancy complications. Blood. 2014;123(6):822–8.

9. Skeith L, Rodger M. Anticoagulants to prevent recurrent placenta-mediated pregnancy complications: Is it time to put the needles away? Thrombosis Research. 2017;151:S38–42.

10. MacLean S, Mulla S, Akl EA, Jankowski M, Vandvik PO, Ebrahim S, et al. Patient values and preferences in decision making for antithrombotic therapy: A systematic review - Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2012;141(2 SUPPL.):e1S-e23S.

11. Bates SM, Rajasekhar A, Middeldorp S, McLintock C, Rodger MA, James AH, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: Venous thromboembolism in the context of pregnancy. Blood Advances. 2018 Nov 27;2(22):3317–59.

12. Etxeandia-Ikobaltzeta I, Zhang Y, Brundisini F, Florez ID, Wiercioch W, Nieuwlaat R, et al. Patient values and preferences regarding VTE disease: A systematic review to inform American Society of Hematology guidelines. Blood Advances. 2020;4(5):953–68.

13. O’Cathain A, Murphy E, Nicholl J. The quality of mixed methods studies in health services research. Journal of Health Services Research and Policy. 2008 Apr;13(2):92–8.

14. Fetters MD, Molina-Azorin JF. New Requirements to Include the Methodological Contribution in Articles Published in the Journal of Mixed Methods Research. Vol. 13, Journal of Mixed Methods Research. 2019. p. 138–42.

15. Sale JEM, Marwah A, Naeem F, Yu W, Meadows L. Evidence of patient beliefs, values, and preferences is not provided in osteoporosis clinical practice guidelines. Osteoporosis International. 2019;30(7):1325–37.

16. Chong CAY, Chen IJ, Naglie G, Krahn MD. How well do guidelines incorporate evidence on patient preferences? Journal of General Internal Medicine. 2009;24(8):977–82.

17. Selva A, Sanabria AJ, Niño de Guzman E, Ballesteros M, Selva C, Valli C, et al. Colorectal cancer guidelines seldom include the patient perspective. Journal of Clinical Epidemiology. 2019;116:84–97.

18. Humphries B, León-Garcia M, Bates S, Guyatt G, Eckman M, Souza RD, et al. Decision Analysis in SHared decision making for Thromboprophylaxis during Pregnancy (DASH-TOP): a sequential explanatory mixed methods pilot study protocol. BMJ Open. 2021;11:1–12.

19. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. British Medical Journal. 2021;372(n71).

20. Creswell JW, Plano Clark VL. Designing and Conducting Mixed Methods Research [Internet]. Third Edit. SAGE Publications, Inc; 2017. 520 p. Available from: https://us.sagepub.com/en-us/nam/designing-and-
21. Guetterman TC, Fetters MD, Creswell JW. Integrating quantitative and qualitative results in health science mixed methods research through joint displays. Annals of Family Medicine. 2015;13(6):554–61.

22. Sandelowski M, Voils CI, Barroso J. Defining and Designing Mixed Research Synthesis Studies. Res sch [Internet]. 2006;13(1):29. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3624763/pdf/nihms412728.pdf

23. Tashakkori A, Teddie C. Sage Handbook of Mixed Methods in Social & Behavioral Research, 2nd ed. Sage Publications, Thousand Oaks, CA. 2010.

24. Pearson A, White H, Bath-Hextall F, Salmond S, Apostolo J, Kirkpatrick P. A mixed-methods approach to systematic reviews. International Journal of Evidence-Based Healthcare. 2015;13(3):121–31.

25. Fetters MD, Curry LA, Creswell JW. Achieving integration in mixed methods designs - Principles and practices. Health Services Research. 2013;48(6 PART2):2134–56.

26. Moseholm E, Rydahl-Hansen S, Lindhardt B, Fetters MD. Health-related quality of life in patients with serious non-specific symptoms undergoing evaluation for possible cancer and their experience during the process: a mixed methods study. Quality of Life Research. 2017;26(4):993–1006.

27. Sandelowski M, Barroso J. Focus on research methods toward a metasynthesis of qualitative findings on motherhood in HIV-positive women. Research in Nursing and Health. 2003;26(2):153–70.

28. Selva A, Solà I, Zhang Y, Pardo-hernandez H, Haynes RB, García LM, et al. Development and use of a content search strategy for retrieving studies on patients’ views and preferences. Health and Quality of Life Outcomes. 2017;15(126):1–9.

29. Campbell M, McKenzie JE, Sowden A, Katikireddi SV, Brennan SE, Ellis S, et al. Synthesis without meta-analysis (SWiM) in systematic reviews: Reporting guideline. The BMJ. 2020;368.

30. Zhang Y, Morgan RL, Alonso-Coello P, Wiercioch W, Bala MM, Jaeschke RR, et al. A systematic review of how patients value COPD outcomes. European Respiratory Journal. 2018;52(1).

31. Aromataris E, Munn Z. JBI Manual for Evidence Synthesis. JBI, 2020. [Internet]. 2020. Available from: https://wiki.jbi.global/display/MANUAL/8.3+The+JBI+approach+to+mixed+method+systematic+reviews

32. Pearson A, Robertson-malt S, Rittenmeyer L. Synthesizing Qualitative Evidence Evidence. 2011.

33. Zhang Y, Coello PA, Guyatt GH, Yepes-Nuñez JJ, Akl EA, Hazlewood G, et al. GRADE guidelines: 20. Assessing the certainty of evidence in the importance of outcomes or values and preferences— inconsistency, imprecision, and other domains. Journal of Clinical Epidemiology. 2019;111:83–93.

34. Zhang Y, Alonso-Coello P, Guyatt GH, Yepes-Nuñez JJ, Akl EA, Hazlewood G, et al. GRADE Guidelines: 19. Assessing the certainty of evidence in the importance of outcomes or values and preferences—Risk of bias and indirectness. Journal of Clinical Epidemiology. 2019;111:94–104.

35. CASP Qualitative Checklist. Critical Appraisal Skills Programme (CASP) part of Better Value Healthcare Ltd [Internet]. 2018. Available from: www.casp-uk.net

36. Noyes J, Booth A, Moore G, Flemming K, Tunçalp Ö, Shakibazadeh E. Synthesising quantitative and qualitative evidence to inform guidelines on complex interventions: Clarifying the purposes, designs and outlining some methods. BMJ Global Health. 2019;4(Supplement1).
37. Lewin S, Bohren M, Rashidian A, Munthe-Kaas H, Glenton C, Colvin CJ, et al. Applying GRADE-CERQual to qualitative evidence synthesis findings-paper 2: How to make an overall CERQual assessment of confidence and create a Summary of Qualitative Findings table. Implementation Science. 2018;13(Suppl 1).

38. Cuello-Garcia CA, Santesso N, Morgan RL, Verbeek J, Thayer K, Ansari MT, et al. GRADE guidance 24 optimizing the integration of randomized and non-randomized studies of interventions in evidence syntheses and health guidelines. Journal of Clinical Epidemiology. 2022;142:200–8.

39. Guimicheva B, Patel JP, Roberts LN, Subramanian D, Arya R. Women’s views, adherence and experience with postnatal thromboprophylaxis. Thromb Res. 2019;173:85–90.

40. Bates SM, Alonso-Coello P, Tikkinen KAO, Ebrahim S, Lopes LC, McDonald SD, et al. Women’s values and preferences and health state valuations for thromboprophylaxis during pregnancy: A cross-sectional interview study. Thrombosis Research. 2016;140:22–9.

41. Hordern CE, Bircher CW, Prosser-Snelling EC, Fraser FK, Smith RP. Patient compliance with postnatal thromboprophylaxis: An observational study. Journal of Obstetrics and Gynaecology. 2015;35(8):793–6.

42. Anderson DR, Ginsberg JS, Brill-Edwards P, Demers C, Burrows RF, Hirsh J. The Use of an Indwelling Teflon Catheter for Subcutaneous Heparin Administration During Pregnancy. Arch Intern Med [Internet]. 1993;153:841–4. Available from: http://dx.doi.org/10.1038/nrcardio.2015.172

43. Patel JP, Auyeung V, Patel RK, Marsh MS, Green B, Arya R, et al. Women’s views on and adherence to low-molecular-weight heparin therapy during pregnancy and the puerperium. Journal of Thrombosis and Haemostasis. 2012;10(12):2526–34.

44. Martens TZ, Emed JD. The experiences and challenges of pregnant women coping with thrombophilia. J Obstet Gynecol Neonatal Nurs. 2007;36(1):55–62.

45. Skeith L, Rodger MA, Bates SM, Gonsalves C, Karovitch A, Taylor TS. Part of the Ritual: Exploring Patient and Physician Decision Making Regarding Anticoagulation Use in Obstetric Antiphospholipid Syndrome. Thrombosis and Haemostasis. 2021;

46. Eckman MH, Alonso-Coello P, Guyatt GH, Ebrahim S, Tikkinen KAO, Lopes LC, et al. Women’s values and preferences for thromboprophylaxis during pregnancy: A comparison of direct-choice and decision analysis using patient specific utilities. Thrombosis Research. 2015;136(2):341–7.

47. Horne R, Weinman J, Hankins M. The beliefs about medicines questionnaire: The development and evaluation of a new method for assessing the cognitive representation of medication. Psychology and Health. 1999;14(1):1–24.

48. Kai S, Fujita Y, Sato Y, Kido S, Hidaka N, Sakamoto I, et al. Pregnancy managed by unfractionated heparin after mechanical aortic valve replacement. Journal of Maternal-Fetal and Neonatal Medicine. 2020;33(6):1030–2.

49. McLintock C. Anticoagulant therapy in pregnant women with mechanical prosthetic heart valves: No easy option. Thrombosis Research. 2011;127(SUPPL. 3).

50. Hiligsmann M, Bours SPG, Boonen A. A Review of Patient Preferences for Osteoporosis Drug Treatment. Current Rheumatology Reports. 2015;17(9).
51. Hong QN, Gonzalez-Reyes A, Pluye P. Improving the usefulness of a tool for appraising the quality of qualitative, quantitative and mixed methods studies, the Mixed Methods Appraisal Tool (MMAT). Journal of Evaluation in Clinical Practice. 2018;24(3):459–67.

52. Lewin S, Booth A, Glenton C, Munthe-Kaas H, Rashidian A, Wainwright M, et al. Applying GRADE-CERQual to qualitative evidence synthesis findings: Introduction to the series. Implementation Science. 2018;13.

53. Valli C, Rabassa M, Johnston BC, Kuijpers R, Prokop-Dorner A, Zajac J, et al. Health-related values and preferences regarding meat consumption a mixed-methods systematic review. Annals of Internal Medicine. 2019;171(10):742–55.

54. Gough D. Qualitative and mixed methods in systematic reviews. Vol. 4, Systematic Reviews. 2015.

55. Booth A. Searching for qualitative research for inclusion in systematic reviews: A structured methodological review. Systematic Reviews. 2016;5(1).

56. Kunneman M, Hargraves IG, Sivly AL, Branda ME, LaVecchia CM, Labrie NHM, et al. Co-creating sensible care plans using shared decision making: patients’ reflections and observations of encounters. Patient Education and Counseling. 2021;

57. Noyes J, Booth A, Lewin S, Carlsen B, Glenton C, Colvin CJ, et al. Applying GRADE-CERQual to qualitative evidence synthesis findings-paper 6: How to assess relevance of the data. Implementation Science. 2018;13.

58. Glenton C, Carlsen B, Lewin S, Munthe-Kaas H, Colvin CJ, Tunçalp Ö, et al. Applying GRADE-CERQual to qualitative evidence synthesis findings-paper 5: How to assess adequacy of data. Implementation Science. 2018;13.

Tables

Tables 1 and 2 are available in the Supplementary Files section.

Figures

Figure 1

Mixed-method analysis and synthesis

Figure 2

Preference-elicitation methods. Selva.et.al. 2017

Figure 3
Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table1.Studyandpopulationcharacteristics.docx
- Table2.ConjointdisplaySUBMISSION.docx
- AdditionalFile1.docx
- Additionalfile2.docx
- Additionalfile3.docx