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Women’s values and preferences and health state valuations for thromboprophylaxis during pregnancy: A cross-sectional interview study

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A B S T R A C T
Background: Pregnant women with prior venous thromboembolism (VTE) are at risk of recurrence. Prophylaxis with low molecular weight heparin (LMWH) reduces that risk but is inconvenient, costly, and may be associated with increased risks of obstetrical bleeding. The views of pregnant women, crucial when making prophylaxis recommendations, are currently unknown.

Methods: Cross-sectional international multicenter study. We included women with a history of VTE who were either pregnant or planning pregnancy. We provided information regarding risk of VTE recurrence with and without LMWH and determined participant’s willingness to receive LMWH prophylaxis through direct choice exercises, preference-elicitation (utilities) for health states (e.g. burden of LMWH prophylaxis), and a probability trade-off exercise.

Results: Of 123 women, more women at high risk than those at low risk of recurrence (86.4% vs. 60.0%; p = 0.003) chose to use LMWH. The median threshold reduction in VTE at which women were willing to accept use of LMWH, given a 16% risk of VTE without prophylaxis, was 3% (interquartile range: 1 to 6). Participants’ evaluation of the relevant health states varied widely and was unrelated to their direct choices to use or not use LMWH.

Conclusions: Although the majority of women with a previous VTE, pregnant or planning pregnancy choose to take LMWH during pregnancy, a minority – and in low risk women, a large minority– do not. Our results highlight the need for individualized shared decision-making (SDM) in the clinical encounter, and for guideline panels to make weak recommendations in favor of LMWH that make clear the need for SDM.

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1. Introduction

Pregnancy-associated venous thromboembolism (VTE), which may manifest as pulmonary embolism (PE) or deep vein thrombosis (DVT), is an important cause of maternal morbidity and mortality [1,2]. Women with prior VTE are at increased risk of thrombosis during subsequent pregnancies, although the absolute magnitude of that risk remains controversial [1,3–5]. Two randomized trials compared heparin prophylaxis to placebo or no prophylaxis in pregnant women with prior VTE but suffered from major limitations, including very small sample sizes [6,7]. Best estimates of the impact of prophylaxis to prevent recurrent pregnancy-related VTE, therefore, are based primarily on risk estimates from observational studies and indirect evidence from other settings suggesting that low molecular weight heparin (LMWH) decreases the risk of VTE by approximately 70% [1,8]. LMWH, which is recommended in this setting, does not cross the placenta, increase the risk of serious adverse fetal outcomes or significantly increase the risk of thrombocytopenia (~0.1%) or osteoporosis (~1%) [1]. It is, however, expensive, inconvenient, uncomfortable to administer, may be associated with an increased risk of major obstetrical bleeding [1,9], and generally necessitates a planned delivery to permit epidural analgesia [1]. Additionally, women may perceive that LMWH creates an undesirable medicalization of their pregnancy.

Given the competing drawbacks and benefits of prophylaxis, as well as the limitations of the available evidence, the decision to use or not use LMWH is likely to be preference sensitive. In addition to holding different attitudes toward the risk of recurrent thrombosis and the burdens associated with the use of prophylaxis, women are also likely to place varying importance on seeing pregnancy as a normal part of a healthy woman’s life, rather than as a medical condition. Although investigators have evaluated patients’ values and preferences with respect to anticoagulant therapy in atrial fibrillation [10,11], and to a lesser extent in VTE [12]; a recent systematic review of patient preferences for antithrombotic treatment did not identify any studies addressing pregnant women [13]. We, therefore, addressed this gap in knowledge by determining the values and preferences, and the choices, of women with prior VTE who were currently pregnant or might in the future become pregnant.

2. Materials and methods

We summarize here the methods of our multi-center international cross-sectional interview study. Readers will find further details in a previously published protocol [14].

2.1. Study population and eligibility criteria

We included pregnant women with a history of lower extremity DVT or PE who were considering thromboprophylaxis to prevent recurrent antepartum VTE; women with a history of lower extremity DVT or PE who were planning pregnancy; and women 18 to 45 years of age with a history of lower extremity DVT or PE who were considering thromboprophylaxis to prevent recurrent pregnancy-related VTE. Women with prior VTE who were currently pregnant or might in the future become pregnant.

We excluded women who were currently receiving thromboprophylaxis or full-dose anticoagulation, had undergone surgical sterilization (tubal ligation or hysterectomy), had a partner who had undergone a vasectomy, and those unwilling or unable to provide informed consent. The study was approved by the Ethics Committees at all participating institutions and all patients provided written informed consent.

2.2. Recruitment strategy

We prospectively identified women who were currently pregnant or planning a pregnancy as they were referred for counseling and identified women with a history of VTE with the potential to become pregnant by reviewing patient files. We approached women referred for consideration of thromboprophylaxis prior to their consultation and made initial contact with women who were not currently pregnant or planning a pregnancy by letter and then by telephone.

2.3. Study maneuvers

We used standardized scripts developed by the research team. Expert and non-expert clinicians and allied health professionals reviewed and revised the scripts to ensure clinical verisimilitude, as well as understandability and readability by a lay person with a grade 9 reading level. Scripts were translated, where necessary, using professional translators.

2.4. The participant interview

We collected information about the participants’ age, highest educational level achieved and current pregnancy status; as well as details regarding their thromboembolic events (including occurrence of PE or DVT, number of events, date of the last event, presence or absence of precipitating factors prior to their event, known hypercoagulable states, family history of VTE, type and duration of treatment for their event(s), completeness of their recovery [presence or absence of residual chest pain or shortness of breath, and/or residual leg swelling, pain or discoloration], and presence or absence of prior experience with injection of prophylactic doses of LMWH during pregnancy. Patients were classified as being at low or high risk for recurrent VTE during pregnancy based on precipitating factors associated with their initial event. Women were considered lower risk for antepartum recurrence if their previous event was associated with a major transient risk factor (leg casting, major surgery [spinal or general anesthetic for at least 30 min], significant medical illness with hospitalization for at least three days, immobilization for at least three days, active malignancy) and they had no known thrombophilia. Women were considered higher risk if their event had been unprovoked, estrogen-related, or they were known to have a thrombophilia.

2.5. Direct choice exercises

We determined participants’ willingness to receive LMWH prophylaxis through direct choice exercises using decision boards. Women initially completed what we refer to as the real-life scenario (representing the best estimate of their personal risk of recurrence), followed in order by hypothetical scenarios, the visual analog scale, the probability trade-off exercise, a review of their answers, and finally questions to examine their understanding of the scenarios.

2.5.1. Real-life scenario

We initially presented women with a decision board that included the probabilities of developing VTE during pregnancy given the characteristics of their prior event. We constructed two boards, one for lower and one for higher risk of recurrence. Women at low risk were presented with a potential baseline risk of antepartum recurrence of 0 to 5% and high risk women with a baseline antepartum risk of 5 to 10%. To ensure optimal understanding, the risk of recurrence with and without LMWH prophylaxis was presented in three different ways: table, bar chart and pictograph (Fig. 1).

For the VTE health state, we instructed women to consider their previous venous thromboembolic event. We instructed women with previous experience in the use of prophylactic LMWH for 2 weeks or longer during pregnancy to consider their previous experience when making a decision. We prepared a description of the experience of LMWH use throughout pregnancy for women without prior experience with LMWH prophylaxis during pregnancy (Appendix 1).

After they reviewed this information, participants decided whether or not they were willing to use LMWH during their current or future pregnancy. Following the interview, women referred for consideration of prophylaxis met with their health care provider and, if desired,
discussed the information provided with family members, friends, or others.

2.5.2. Hypothetical scenarios
We provided study participants with three scenarios in which the baseline risk of recurrent VTE was varied (4%, 10%, and 16%). After interviewers showed each woman a decision board with pictograms, tables, and pictographs representing the three baseline risk levels and predicted risks with LMWH prophylaxis, participants expressed their willingness to use LMWH for each scenario.

2.5.3. Probability trade-off
Interviewers undertook probability trade-off exercises to determine participant thresholds for accepting LMWH prophylaxis. The interviewer systematically varied the risk of VTE with LMWH prophylaxis (alternating between high and low risks) to determine the minimum acceptable reduction in the risk of VTE with prophylaxis at which the participant would agree to initiate LMWH. We set this risk fixed at 16% (based on the upper bound of the 95% confidence interval around the risk of antepartum recurrence in the largest published prospective cohort [3]) on one side of the flipchart and offered probabilities ranging from 16 fewer VTE events per 100 pregnancies (maximum absolute risk reduction) to 0 less VTE events (same VTE risk as no prophylaxis) on the other side of the chart.

2.6. Visual Analog Scale (feeling thermometer)
We determined the value patients place on relevant health states (pregnancy with LMWH prophylaxis, pregnancy with their own most recent VTE experience, pregnancy-related DVT, pregnancy-related PE, and obstetrical bleed) using a visual analog scale called the Feeling Thermometer (FT) [14] (Appendix 2). When making ratings using the FT, women choose the score on the thermometer that represents the value they place on the health state they are evaluating. The FT is anchored at death (0) and full health (100).

2.7. Check for consistency and understanding
After presenting the descriptions and recording patient responses, interviewers reviewed participant responses to the various exercises to check for consistency in participants’ choice. When interviewers identified inconsistencies, they offered participants a chance to review and change their responses, avoiding any suggestion that responses should be changed. The reasons for any apparent inconsistencies were determined and recorded. Following this consistency check, interviewers asked participants two standardized questions to evaluate their understanding of the information provided during the interview. Interviewers also provided a rating of the extent to which they believed the respondents had a clear understanding of the questions and their confidence in this assessment.

2.7.1. Sample size
Previous research from our group in patients with atrial fibrillation [10], and from other groups studying non-pregnant women with prior VTE [13], suggested that moderately precise estimates of patient preference can be obtained with sample sizes of approximately 100 participants. In the most relevant recent experience, co-investigators on the current project enrolled 96 patients with risk factors of atrial fibrillation [10]. This sample size provided an acceptable confidence interval around the primary outcome. Given the range of VTE prevented (0 to 16) in our study is smaller than the range for the primary outcome used in the atrial fibrillation study (0 to 100), we reasoned that we would find smaller variability and greater precision (smaller confidence intervals). We used the available resources to maximize the number actually recruited, which was 123.

2.7.2. Analysis
We calculated the median threshold reduction in VTE at which women were willing to accept use of LMWH and the interquartile range. We calculated the proportion of women who were willing to take prophylactic LMWH, in both real and hypothetical scenarios, and the associated 95% confidence intervals (CI) in each of the low and high risk groups. For the different scenarios, we compared these proportions using a Chi-square test or Fisher’s Exact test, depending on the event size. We calculated median and interquartile ranges of women’s ratings for each health state due to the abnormal distribution of the data.

We developed multivariable linear regression models to explore determinants of the VTE threshold. In this analysis, the VTE threshold was the dependent variable. Independent variables included: i) previous experience of VTE categorized as severe (PE or previous DVT with residual symptoms) or non-severe (DVT without residual symptoms); ii) previous experience with prophylactic LMWH (yes, problematic; yes, no problems; no prior experience); iii) highest level of education completed (some postsecondary versus no post-secondary); iv) study site (North America, Northern Europe, Spain and Brazil); and vi) pregnancy status (currently pregnant or planning a pregnancy versus neither).

A planned analysis comparing results and the pattern of responses based on participant understanding of the study scenarios and questions was not undertaken as only 4 women were categorized as not understanding by the study interviewers.

3. Results

3.1. Recruitment and characteristics of participants
Between June 2011 and March 2013, we recruited 123 women (we approached 187 women, main reason [47 women] for not participating being women taking thromboprophylaxis or full dose anticoagulation) from seven centers in six countries (Canada, USA, Brazil, Finland, Norway and Spain), all of whom completed the interview. Table 1 presents women’s characteristics, including location, education, and pregnancy status, previous VTE and LMWH experience, date of last event and risk of recurrence. Appendix 3 presents the proportion of VTE risk factors of recurrent VTE by strata (lower and higher risk women). Of note, 3 women were misclassified. Their results were analyzed as per their original study classification. The women were subsequently informed of the misclassification error and their true risk status.

3.2. Probability trade-off
The median threshold reduction in VTE risk at which women were willing to accept use of LMWH, given a fixed 16% risk of VTE without prophylaxis, was 3% (interquartile range: 1% to 6%). In our regression analysis, women with less than 2 weeks of previous experience with LMWH during pregnancy, compared to those with 2 weeks or more of previous experience required a greater VTE risk reduction (2.0%; 95% CI: 0.3% to 3.8%) (Table 2). Pregnant women and women planning pregnancy required a greater VTE risk reduction (1.6%; 95% CI: -0.0% to 3.3%), compared to those neither pregnant nor planning a pregnancy, though the results did not reach conventional statistical significance (p = 0.07). No other factors were significantly associated with the VTE threshold.

3.3. Real-life and hypothetical scenarios
The majority of women were willing to use prophylactic LMWH in the real-life scenario (21 of 35 or 60.0% of low risk women and 76 of 88 or 86.4% of high risk women) (p-value for difference between low
and high risk, 0.003). This proportion was smaller in the women pregnant or planning a pregnancy (26 of 36 or 76.2% at higher risk of recurrence and 11 of 20 or 55.0% of those at lower risk). The preference for prophylaxis was consistent in all three hypothetical (low, medium and high risk of VTE) scenarios (67.0%, 84.0%, 89.7% respectively) (Table 3).
The inclination to use LMWH at particular levels of benefit was greater in those without prior experience of LMWH compared to those with such experience. Participants’ evaluations of the relevant health states varied widely and were unrelated to the direct choices to use or not use LMWH.

### 4.2. Strengths and limitations

Strengths of our study include the diversity of populations that included six countries in Europe and the Americas, and the rigorous study design documented in a previously published protocol [14]. That design included a structured interview with a predesigned script that was first pilot tested. Interviewers were trained and calibrated. The interview included the presentation of results in multiple ways to maximize understanding and the conduct of tests for understanding confirmed that almost all women understood our questions.

Our study has limitations. It may have been preferable to include only those women who were pregnant or planning pregnancy and to exclude those who might become pregnant in the future; the latter group constituted 50% of our sample. Results suggested that those who were referred for counseling due to pregnancy or planned pregnancy required a greater VTE reduction to use LMWH, although the results did not reach statistical significance; our overall results may therefore, represent an overestimate of women’s inclination to use LMWH.

A second limitation relates to the number of variables that could be explored in our linear regression model that was limited by the number of variables that could be explored in our linear regression model.
of events. We chose to explore those we felt most likely to impact on women’s choices. It is possible, however, that factors we failed to measure, including time elapsed from the last VTE event, and family history of VTE, may have also influenced decisions. In particular attitudes toward taking risks, might have been even more strongly associated with choice than those we measured and included in our analysis.

Thirdly, we chose to focus on the antepartum period. We could also have addressed another related, but fundamentally different choice: the choice regarding postpartum prophylaxis. Differences regarding that choice include different risks of thrombosis and bleeding, different duration of thromboprophylaxis, and the ability to use oral anticoagulants (vitamin K dependent antagonists) in those averse to subcutaneous injections and the shorter required timeframe for prophylaxis. A separate study would be required to delineate values and preferences around postpartum prophylaxis.

4.3. Our study in relation to previous research

Ours is the first study addressing values and preferences regarding VTE prophylaxis in pregnant women. As in previous studies [10,11,13], we have observed that there is wide variability in patients’ values and preferences and that, as a result, patients presented with identical probabilities of the same desirable and undesirable consequences will make different choices.

4.4. Implications for practice and research

Our results have implications for guideline panels, clinicians and patients. The most recent American College of Chest Physicians (ACCP) guidelines make weak recommendations in favor of antepartum LMWH for pregnant women at higher risk of recurrent VTE and against antepartum prophylaxis in those at low risk [1]. However, as the majority of well-informed women in both low and high risk groups in our study chose to use LMWH, guideline panel recommendations should probably favor LMWH prophylaxis in all women with prior VTE. That said, over 10% of women at high risk and close to half of those at low risk declined LMWH. Thus, for clinicians, our results demonstrate that ensuring each patient receives optimal management for her particular values and preferences will require individualized shared decision making. Guideline panel recommendations should be weak, reflecting this need for shared decision making.

Our results demonstrate the power of inquiry regarding values and preferences to determine both optimal approaches to individual decision-making and for informing guideline panel recommendations. There remains a paucity of information available informing patient values and preferences; much remains to be done. Researchers may find that our methods provide a helpful model for similar future studies.

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Competing interests

SMB has support from Physicians Services Incorporated Foundation and ME has support from NIH/NCATS Grant Number 8U1TR000077–05, the Pfizer Education Group, and Informed Medical Decision Foundation for the submitted work. KT was supported by the Academy of Finland (#276046), Competitive Research Funding of the Helsinki and Uusimaa Hospital District, Finnish Medical Foundation, Finnish Cultural Foundation, Jane and Aatos Erkko Foundation, and Sigrid Juselius Foundation. SMB, PAC, KAOT, SE, LCL, SDM, QZ, EAA, IN, AFJ, YZ, AS, JMA-B, PMS, WB, MHE, GHG have no relations with companies that might have an interest in the submitted work in the previous 3 years. SMB, PAC, KAOT, SE, LCL, SDM, QZ, EAA, IN, AFJ, YZ, AS, JMA-B, PMS, WB, MHE, GHG have no non-financial interests that may be relevant to the submitted work.

Contributors

SMB, PAC, KAOT, SE, LCL, SDM, IN, QZ, ME, GHG designed the study. SMB, PAC, KAOT, LCL, EA, AFJ, AS, JMA-A, PMS, and WB enrolled patients. SMB, PAC, QZ, ME, and GHG analyzed the data. All of the authors participated in writing and reviewing the manuscript and agreed to submit this article for publication. All of the authors had full access to all of the data and can take full responsibility for the integrity of the data and the accuracy of the data analysis.

Data sharing

No additional data available.

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Appendix A

Appendix 1

Description of low molecular weight heparin use during pregnancy provided to study participants.

| Things to know about taking low molecular weight heparin to prevent blood clots during pregnancy |
| Preventive blood thinning |
| You use low molecular weight heparin needles beneath the skin for the rest of your pregnancy. |
| You or a family member learn to give these needles. |
| You continue blood thinners for at least 6 weeks after your baby is born, either with needles or with a tablet. If you |

(continued on next page)
Appendix 2

Standardized health states.

Pregnancy-associated deep vein thrombosis

<table>
<thead>
<tr>
<th>Symptoms &amp; signs</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Your leg is painful and swollen and hurts when you walk for more than short distances.</td>
<td>Your doctor performs an ultrasound and confirms that you have a blood clot in your leg vein. You are admitted to the Emergency Department overnight.</td>
</tr>
<tr>
<td>You worry about the health effects this blood clot might have on your unborn baby.</td>
<td>You are worried about your baby’s health.</td>
</tr>
<tr>
<td>Skin reactions (e.g., itching or an itchy raised rash) can occur which may require switching to a different heparin preparation.</td>
<td>Your blood thinners are stopped.</td>
</tr>
<tr>
<td>Despite reassurance you are concerned that these medications may not be safe for your baby.</td>
<td>You require blood tests.</td>
</tr>
<tr>
<td>You are told that there may be a small increase in the risk of major bleeding, osteoporosis (thinning of the bones), and having an allergic reaction to heparin called heparin-induced thrombocytopenia.</td>
<td>An ultrasound is performed to assess your baby.</td>
</tr>
<tr>
<td>Your delivery plans will need to be modified to allow you to receive an epidural, to minimize your risk of bleeding and to minimize the risk of additional blood clots.</td>
<td>Your baby’s heart rate will be monitored.</td>
</tr>
<tr>
<td>Your delivery plans will need to be modified to allow you to receive an epidural, to minimize your risk of bleeding and to minimize the risk of additional blood clots.</td>
<td>You remain in hospital for several days until your doctors are sure that your bleeding has slowed or stopped.</td>
</tr>
<tr>
<td>Your baby is not affected by your blood clot or blood thinning medicine.</td>
<td>You and your baby will be closely monitored after discharge.</td>
</tr>
<tr>
<td>Your leg returns to normal. After anticoagulants are stopped, you feel worried sometimes if you have aches or pains in your leg.</td>
<td>Your baby is okay.</td>
</tr>
<tr>
<td>You are asked if you would like testing for a clotting disorder.</td>
<td>You feel worried with future pregnancies.</td>
</tr>
<tr>
<td>You are told you may be required to take blood thinning injections during future pregnancies.</td>
<td>You are at risk of placental abruption with future pregnancies.</td>
</tr>
<tr>
<td>Major antepartum obstetrical bleed</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Symptoms &amp; signs</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>You develop abdominal pain, contractions and vaginal bleeding in the later part of your pregnancy.</td>
<td>You are admitted to hospital.</td>
</tr>
<tr>
<td>Intravenous lines are placed and you are given fluids.</td>
<td>Your blood thinners are stopped.</td>
</tr>
<tr>
<td>Your blood thinners are stopped.</td>
<td>You require blood tests.</td>
</tr>
<tr>
<td>An ultrasound is performed to assess your baby.</td>
<td>Your baby’s heart rate will be monitored.</td>
</tr>
<tr>
<td>Your baby’s heart rate will be monitored.</td>
<td>You remain in hospital for several days until your doctors are sure that your bleeding has slowed or stopped.</td>
</tr>
<tr>
<td>You and your baby will be closely monitored after discharge.</td>
<td>Your baby is okay.</td>
</tr>
<tr>
<td>You feel worried with future pregnancies.</td>
<td>You are at risk of placental abruption with future pregnancies.</td>
</tr>
<tr>
<td>Management of future pregnancies will be modified – you will need to be more closely monitored than with a routine pregnancy.</td>
<td>You are at risk of placental abruption with future pregnancies.</td>
</tr>
</tbody>
</table>
Appendix 3

Presence or absence of precipitating risk factors.*

<table>
<thead>
<tr>
<th>Risk factors occurring in the eight weeks prior to the VTE diagnosis</th>
<th>High risk women (n = 88)</th>
<th>Low risk women (n = 35)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leg casting</td>
<td>1 (1.14%)</td>
<td>10 (28.6%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Major surgery</td>
<td>3 (3.4%)</td>
<td>10 (28.6%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Acute medical illness with hospital admission for ≥3 days (Admission)</td>
<td>3 (3.4%)</td>
<td>10 (28.6%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Immobilization ≥3 days</td>
<td>4 (4.6%)</td>
<td>18 (51.4%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Active cancer</td>
<td>0</td>
<td>1 (2.9%)</td>
<td>0.28</td>
</tr>
<tr>
<td>Minor risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy</td>
<td>18 (20.5%)</td>
<td>3 (8.6%)</td>
<td>0.18</td>
</tr>
<tr>
<td>Postpartum</td>
<td>10 (11.4%)</td>
<td>5 (14.3%)</td>
<td>0.66</td>
</tr>
<tr>
<td>Hormonal contraception</td>
<td>53 (60.2%)</td>
<td>17 (48.6%)</td>
<td>0.31</td>
</tr>
<tr>
<td>Airplane travel &gt;6 h</td>
<td>5 (5.7%)</td>
<td>0</td>
<td>0.32</td>
</tr>
<tr>
<td>Known thrombophilia</td>
<td>33 (37.5%)</td>
<td>1 (2.9%)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

* Results add up to more than 100 because women could have more than one risk factor; patients with both major and minor risk factors at the time of the diagnosis were considered lower risk for recurrence. As noted in the text, 3 women were misclassified.

References


