

“Part of the Ritual”: Exploring Patient and Physician Decision Making Regarding Anticoagulation Use in Obstetric Antiphospholipid Syndrome

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Abstract

Background Antiphospholipid syndrome is associated with recurrent pregnancy loss. Low-molecular-weight heparin (LMWH) and/or aspirin (ASA) prophylaxis during pregnancy to prevent future loss is based on limited trial data with mixed results.

Objectives Given the clinical equipoise, we sought to understand how patients and physicians navigate the decision-making process for use of LMWH and/or ASA in pregnancy.

Methods We interviewed 10 patients and 10 thrombosis physicians in Ottawa, Canada from January 2017 to March 2018. Patients who had ≥ 1 late pregnancy loss or ≥ 2 early losses and persistently positive antiphospholipid antibodies based on the revised Sapporo/Sydney criteria were identified in the a Thrombosis Clinic. Patients were also identified by the TIPPS Study screening logs of excluded patients. Data collection and analysis occurred iteratively, in keeping with constructivist grounded theory methodology.

Results Our analysis generated three themes, present across both patient and physician interviews, which captured a patient-led decision-making experience: (1) managing high stakes, (2) accepting uncertainty, and (3) focusing on safety. Patients and physicians acknowledged the high emotional burden and what was at stake: avoiding further pregnancy loss. Patients responded to their situation by taking action (i.e., using LMWH injections became a “ritual”), whereas physicians reacted by removing themselves from the final decision by “[leaving] it up to the patient.”

Keywords

- antiphospholipid syndrome
- pregnancy complications
- low-molecular-weight heparin
- aspirin
- qualitative

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Conclusion Our findings should be considered when designing future research on studying the role for LMWH/ASA in this population, as it suggests that the perceived benefits of treatment go beyond improving pregnancy rates. Rather, patients described potential benefit from the process of taking action, even in the absence of a guaranteed good outcome.

Introduction

Antiphospholipid syndrome (APS) is a rare systemic autoimmune disease categorized by persistently positive antiphospholipid antibodies (APLAs) and clinical manifestations of venous, arterial, or small vessel thrombosis or obstetrical complications, including pregnancy loss.^{1,2} In women with positive APLAs and prior recurrent early or a late (≥ 10 weeks' gestation) pregnancy loss, clinical practice guidelines recommend use of daily low-molecular-weight heparin (LMWH) prophylaxis and/or aspirin (ASA) during pregnancy.^{3–5} However, the use of LMWH and/or ASA during pregnancy to prevent future pregnancy loss is based on limited randomized controlled trial (RCT) data that have generated mixed results.^{6–9} Use of LMWH prophylaxis in pregnancy is associated with side effects of antepartum bleeding (minor, as well as uncommon but serious antepartum bleeding), allergic reactions, and rarely heparin-induced thrombocytopenia.^{10–12}

Without high-quality evidence to guide decisions regarding anticoagulant use during pregnancy, it is unclear how these decisions are made by patients and physicians. In a related study, researchers evaluated different decision-making methods for the use of LMWH prophylaxis in pregnant patients with past venous thromboembolism (VTE) and found that there was a high level of discordance between what was predicted using decision modeling and what women chose to do.¹³ Two different methods (health state utility and probability trade-off exercises) could not predict or account for the nuanced decision making around thromboprophylaxis that happens during pregnancy. Thus, our collective understanding of this decision-making process remains incomplete.

We recently conducted the pilot APPLE (AntiPhospholipid Syndrome Low-molecular-weight Heparin Pregnancy Loss Evaluation) trial, which was a pilot open-label RCT of tinzaparin/ASA versus ASA prophylaxis alone during pregnancy in women with prior pregnancy losses (≥ 2 losses < 10 weeks' gestation and/or ≥ 1 loss > 10 weeks' gestation) and positive APLAs based on the revised Sapporo/Sydney criteria.¹⁴ The primary outcome of the pilot APPLE trial was mean recruitment rate, to determine if recruitment to a larger multinational trial was possible given the generally accepted use of LMWH/ASA for this indication. The pilot APPLE trial closed early due to low recruitment rate and was not feasible—in part because this is a rare disorder with a low number of eligible patients (4 eligible patients were identified among 25 screened patients from November 2017 to March 2019 in

Ottawa, Canada), but also because women wanted a choice to use LMWH/ASA (1 eligible patient who declined participation) or ASA alone (2 eligible patients who declined participation) during pregnancy.¹⁴ Better understanding of decision making and the individual choices that patients make in this clinical scenario is needed.

Given the relative clinical equipoise that exists and the challenge of conducting RCTs in this area, we sought to understand how women with APS and physicians navigate the decision-making process for initiation of LMWH and/or ASA prophylaxis during pregnancy. By approaching this research question in a qualitative way, we can build on existing clinical research to better inform the feasibility of future research and the impact of individualized decision making in this area.

Methods

We conducted a qualitative study using thematic analysis informed by the key tenets of constructivist grounded theory, to better understand this socially situated research question.¹⁵ We conducted semistructured interviews with 10 patients (L.S. and T.S.T.) and 10 thrombosis physicians (L.S.) in Ottawa, Canada from January 2017 to March 2018. Consecutive patients with positive APLAs based on the revised Sapporo/Sydney criteria and who had at least one prior late pregnancy loss (≥ 10 weeks' gestation) or two early pregnancy losses (< 10 weeks' gestation) were identified and approached in a specialty Thrombosis Clinic to participate. Potential participants were also identified from a screening log from the TIPPS study (Thrombophilia in Pregnancy Prophylaxis Study) and contacted by mail.¹² The potential participants we identified from the screening log were excluded from the TIPPS study. Because we were pragmatically limited by our inclusion criteria, sampling was both purposeful and convenient. For broader sampling, patients who were pregnant and not pregnant were included. Semistructured interviews with patients were conducted in person or over the phone. The interview guide is in ► **Supplementary Appendix A** (available in the online version) with interview questions. Some of the interview guide questions are about further research planning and is reported in a separate manuscript.

Ten physicians with expertise in thrombosis medicine were approached and interviewed in person as part of a larger study about practice variation. The interview included

a clinical vignette of a 30-year-old pregnant patient with positive β -2 glycoprotein antibodies on two occasions >12 weeks apart, and a history of two consecutive early pregnancy losses (<10 weeks' gestation). In follow-up questions, the type and level of APLA and pregnancy loss history was varied to better understand decision making among physicians (► **Supplementary Appendix A**, available in the online version).

The audio recordings and iterative analysis meetings were transcribed verbatim; field notes about each interview were used to supplement the data analysis. L.S. and T.S.T. conducted the interviews and brought different perspectives to data analysis as a thrombosis medicine researcher and an obstetrician/gynecologist, respectively. We conducted theoretical sampling by revising the interview guide based on our ongoing analysis. Data were analyzed iteratively using NVivo 12 software to code the data and assist in organizing the codes, as we conducted constant comparative analysis leading to more conceptual categories and the relationships between those categories (QSR International, Version 12, 2018). We generated codes through our line-by-line review of the transcripts independently. As part of an iterative process, we had analytic meetings that compared the similarities and differences between our generated codes, and then we collapsed codes into larger categories. We then used Mind Node software to reorganize and explore the relationships between categories before arriving to the final themes identified. This study was approved by the Ottawa Health Science Network Research Ethics Board (20160323-01H).

Results

Among the 10 patients who were interviewed, two were pregnant at the time of the interview, and the remaining eight participants' responses were related to decision making during their previous pregnancies. Ten out of the 11 thrombosis physicians in Ottawa, Canada were interviewed (one excluded: C.G. helped to develop the physician interview guide as part of a larger research project about practice variation in thrombosis medicine). Among the 10 physicians interviewed, there were six men and four women, and six hematologists and four general internal medicine specialists.

Our analysis generated three primary themes that included the concept of (1) *managing high stakes*, (2) *accepting uncertainty*, and (3) *focusing on safety* in pregnancy. (1) Managing high stakes captured how both patients and physicians reacted to and managed the high-stakes decision making in future pregnancy. In the first theme of *managing high stakes*, we identified a subtheme: *physician-patient relationship matters*. When deciding to use LMWH prophylaxis and/or ASA in pregnancy, physicians and patients (2) *accepted uncertainty* and (3) *focused on safety* in the decision-making process. Physicians focused on the uncertainty of the diagnosis and management of APS during pregnancy, while patients grappled with the uncertainty about future pregnancy outcomes even with treatment. Both patients and physicians identified safety of the medications as important

to the decision-making process of using LMWH/ASA or ASA alone in pregnancy.

Contextual factors about a patient's situation provided more nuanced decision making and helped to identify a patient-led decision-making experience. These themes are described further and illustrated using salient quotations from interviews with (##) indicating anonymous patient participant codes and (MD##) indicating physician participant codes.

Managing High Stakes

The theme of *managing high stakes* describes how patients and physicians acknowledged and reacted to the perceived high stakes of a pregnancy with the goal of avoiding a future pregnancy loss. Patients described trying to do "everything you can to mitigate any factors in your control" (06) because "this is going to be my life story if I don't do something differently" (02). Patients responded to their situation by taking action with daily LMWH injections, and acknowledged that by doing *something*, this helped them regain hope and decrease anxiety:

"Although it wasn't fun injecting myself it was part of the ritual. ...It felt like I was doing something instead of just waiting there to see if I would miscarry. ...It felt like I at least had a very, very, very small hand in helping." (11)

For many patients, they described the decision to use LMWH injections as "automatic" (10) and the only way forward once they were presented with the option, because they described feeling that they were "definitively coming to the narrowing of the pass" (02) and were at the "end of the road" (08) of their journey. The use of LMWH injections also became part of their pregnancy experience:

"I did get my pregnancy photos done, but literally a week before he was born and only because my friend said, we'll just photoshop the bruises. We actually did take pictures with the bruises, obviously, and left them as is, because that's part of the experience I had during the pregnancy. It's a terrible sight, but it is what it is. [07]"

However, not all patients felt that they needed or wanted to use LMWH injections. Some patients were relieved that they were not considered or were not classified as a high-risk pregnancy:

"So, I felt comfortable enough going on the aspirin and seeing how it would go. And I honestly didn't feel like I needed anything more. ...I was hoping in the long run I wouldn't be considered high risk because I like going with my midwife." (06)

In contrast, physicians acknowledged and managed the high stakes of the pregnancy by leaving the final treatment "decision up to the patient" (MD02; MD04). Physicians described their role in the clinical interaction to provide patients with information, "an opinion" (MD03) or to "just

help explain [the situation]" (MD09), so the patient can then make a decision:

"I'm a consultant and the patient is the decision-maker. Present the data, try and anchor things for them by giving them a sense of how we would make these decisions." (MD06)

When describing a theoretical example of a patient with a prior late fetal loss at 35 weeks' gestation, one physician echoed the psychological need for action that patients had also described:

"...there's no way she's not leaving without LMWH because I guarantee she's come in with so much emotion, that she couldn't psychologically get through another pregnancy unless she was doing something... And it's hard to argue against that. I mean what a devastating life event, right?" (MD02)

As this example also illustrates, physicians pointed to many contextual factors that influenced how the tone of the conversation would go and what they expected about a patients' decision to use LMWH injections. These included late fetal loss, multiple pregnancy losses, and older patient age because it is "higher stakes from a patient perspective" (MD06). However, physicians also acknowledged that there was a "whole spectrum" (MD10) of patients who had "different psychological outcomes" (MD02) from a past pregnancy loss, and that this was a "value judgment" (MD06) that physicians could not always predict. Physicians also described other external factors, including other physicians involved, that shaped the discussion:

"It depends what wording the obstetrician has used; [patients] come with preconceived ideas. And if they've been told by their obstetrician, I'm going to send you to see these thrombosis doctors and they're going to put you on an anticoagulant so your baby doesn't die, I can't get out of that conversation." (MD02)

Subtheme within Managing High Stakes: The Physician–Patient Relationship Matters

A subtheme within *managing high stakes* was the concept that the physician–patient relationship mattered to patients. Patients described how physicians influence the decision that they made based on the information presented and physicians' openness to accept different management options.

"You place your faith in that doctor...that's what makes you make that decision to go for it or not [to use LMWH injections], it depends on the kind of information you're being given." (07)

Physicians often had a preference of using LMWH/ASA or ASA alone for a given case, and either described shaping the

conversation with these preferences, or more implicitly "hoping that she would be happy with" (MD06) a specific treatment. However, the patient–physician interaction was more than just about the information presented. Physicians were supporting patients to help them make a decision during a highly stressful time:

"I felt pretty involved. I didn't feel like pressured into taking [LMWH] if I did get pregnant. It was really up to me to say I want to take the injections or not... I felt involved in the decision." (01)

In summary, when managing high stakes of a pregnancy, patients often took action by using LMWH injections and/or ASA. Physicians provided patients with information and support to help guide, while at the same time leaving the final decision in the patient's control.

Accepting Uncertainty

Both patients and physicians described grappling with the uncertainty of the situation in different ways. Patients acknowledged and accepted uncertainty about their future pregnancy outcomes, while physicians focused on the uncertainty of the diagnosis and management of APS.

Patients' past pregnancy losses influenced and inevitably informed many aspects of their future pregnancy experience. Women with past pregnancy loss described feeling more guarded about a successful outcome of a live birth in a future pregnancy because "after having a loss, the safety bubble in your head is gone" (06). Patients recounted how they did not allow themselves to enjoy or make plans in pregnancy, or connect with the baby:

"I never allowed myself to plan for him, throughout my pregnancy I don't think I ever talked about when he gets here, you know how most women are planning the nursery and everything is based on that plan and having that baby. And I never went there with him, I never allowed myself to go there, ever." (04)

While patients focused on uncertainty of the pregnancy outcome itself, physicians emphasized the uncertainty of the diagnosis of APS and whether LMWH/ASA could improve pregnancy outcomes when counseling patients on their options.

"It's sort of a longer conversation. My approach is that studies are conflicting. There are studies that show it has a good benefit, and there are studies that show it doesn't have a benefit." (MD09)

"I think a lot of patients like this are treated and we're not sure if that's the right thing or not." (MD07)

Despite the uncertainty that physicians described with the diagnosis and management of APS, patients felt hopeful and relieved to have the diagnosis of APS:

So, I was a little luckier that I was only two [pregnancy losses]... It's still hard. I know a lot of women go through a lot worse than I did, so I actually feel quite lucky, and I don't know how I could have known any earlier than I did. And I just feel lucky that I do know, because it's for my own health going forward that I know that I'm positive [for antiphospholipid antibodies]." (10)

Many patients accepted the uncertainty of their situation; they acknowledged that there are no guarantees while at the same time seeing LMWH/ASA as a cause for cautious optimism. They felt hopeful but were also reluctant to expect a better pregnancy outcome with LMWH and/or ASA:

"We were upset, and I can't remember which doctor I was talking to, they said it may help, it may not, so don't ... he wasn't saying don't get excited, but it was like this is something we're going to try and we'll just see what happens. So, we were kind of prepared for either way ...

But it did give me the hope to think maybe this would solve the problem. So, it was a bit of excitement plus a bit of nervousness, just because you don't know what to expect. [08]"

In summary, while physicians focused on the uncertainty of the diagnosis and management of APS in pregnancy, patients looked to APS for answers, while still being guarded in their pregnancy outcome expectations and in acknowledging the ongoing uncertainty regardless of treatment options.

Focusing on Safety

When making the decision about the use of LMWH and/or ASA, both groups weighed the risks and benefits of treatment and largely focused on the low-risk nature and safety of these medications. Both physicians and patients described the LMWH injections as "low risk" (12) with "minimal side effects (MD04), and that, compared to the "emotional pain with loss, a little bit of physical pain from a needle is small potatoes" (12).

Patients focused on the safety to the fetus, with little concern for maternal risk. Women acknowledged that it would have to be a large or serious risk not to consider taking the LMWH injections:

"... It would have to be a pretty large risk for me not to do it. But if a drug or an injection increased my chances of carrying a baby full term, I can't think of anything that I wouldn't be at least open to talking about and finding out all about information about it first before I made a decision." (11)

"I wanted another baby really badly but not enough to harm my health to take care of my first child. So, I think that would have been my no go point. If it had been something that would have permanently altered my health or my longevity, I probably wouldn't have risked that just to have another baby." (10)

This was echoed in the physician interviews on how they counsel patients about the risk and decision for use of LMWH and ASA prophylaxis during pregnancy:

"In my experience, most people do accept anticoagulation, and I probably have a bias myself [because] the risks are low, and obviously, you're coming to me because you're trying to do something differently, so I think it's a reasonable thing to try." (MD09)

Some patients acknowledged that the level of risk differed between them and the partner who was involved in the decision making:

"I wanted a baby so bad, I was like I don't care, I'll do it ... the chance of it harming me, I think my husband was a little more concerned, like it was going to do me harm, then he was like no, we're not doing that. But we were pretty desperate at the time. [08]"

However, not all patients agreed that the LMWH injections were low risk. Some patients did choose to go on ASA alone, because LMWH injections seemed "too invasive" based on the available evidence:

"I think if I had more research of a greater possibility of it helping would probably sway me [to use LMWH], but I think it would have to be pretty high to make you want to go through all that." (06)

"It was less invasive to take baby aspirin. If you have a choice, I think most people would choose the easier, less painful route so I just didn't feel I had that big motivation. I didn't have the high levels [of antiphospholipid antibodies] or the clear link to research that was motivating me to go with the harder option." (03)

In summary, both physicians and patients focused on the safety and risk of the prophylactic-dose LMWH; however, how patients processed the risks and benefits of LMWH injections remained individualized.

Discussion

In this setting of clinical equipoise and in the absence of serious safety concerns with LMWH/ASA use, decision making around LMWH/ASA during pregnancy to prevent future pregnancy loss was largely directed by patient's choice. These findings require serious consideration when designing future research on the role for LMWH/ASA in this population, as it suggests that the perceived benefits of treatment may go beyond improving pregnancy rates. Rather, many patients in our study described psychological benefit from the process of taking action, even in the absence of a guaranteed good outcome. However, not all patients chose to use LMWH and some preferred to use ASA alone during pregnancy, reflecting the deeply individualized nature of this decision-making process.

Living with uncertainty after pregnancy loss in future pregnancies has been well described.^{16,17} Improving a patient's control when uncertainty exists has been described in other perinatal scenarios, such as developing birth plans including around a trial of labor after caesarean delivery.¹⁸ The patients in our study described managing expectations and uncertainty of a successful future pregnancy and looked to the diagnosis and management of APS with cautious optimism.

Competing interests between the mother and the fetus can complicate decision making during pregnancy, although the health of the fetus remains inextricably linked to the health of the mother.¹⁹ During decision making in pregnancy, internal conflict can exist. With an extreme example of breast cancer treatment during pregnancy, chemotherapy may potentially negatively affect fetal outcomes while improving maternal outcomes and chance of survival. Among women who have been diagnosed with breast cancer in pregnancy, women described anxiety and stress associated with this decision-making conflict.^{20,21} In contrast, we did not uncover any major decision-making conflicts or associated anxiety or stress about the treatment decision in our study. Because physicians and patients often accepted the LMWH injections as being relatively low risk and safe for the fetus, coupled with the high stakes of preventing recurrent fetal loss, there was no major conflict present and for many participants the decision to use LMWH injections was straightforward. The safety of the fetus helped to justify a decision, which has been described in other areas including initiating human immunodeficiency virus treatment during pregnancy,²² violence and pregnancy,²³ and pregnancy in chronic disease.²⁴ In a study exploring adherence to LMWH prophylaxis during pregnancy, most women were adherent during pregnancy but this adherence went down in the postpartum period when protecting their unborn baby's health was not a consideration.²⁵ However, the decision was still individualized as not all patients (or physicians) felt that LMWH injections were needed and that the side effects and burden of LMWH use throughout pregnancy outweighed their uncertain benefit.

While many interview participants described patients making the final treatment decision to use LMWH and/or ASA, patients often relied on their physicians for accurate information and the support to choose different treatment options. We found that the quality of the physician–patient relationship was important to decision making in our study. In another study about decision making around the choice of induction of labor, patients often looked to their obstetrician's knowledge about perceived risk and described that their obstetricians' personality (relaxed or anxious) and the trusting relationship impacted the decision they made.²⁶ As some of the participants in our study acknowledged that it would have to be a large or serious risk to not take the LMWH injections and many had a very low threshold for LMWH/ASA in the absence of evidence, we believe this points to the added responsibility that physicians bear in providing accurate information and recommendations for informed shared decision making.

As with any study, our chosen methodology comes with inherent limitations. Our results reflect the experiences and perceptions of our participants and are thus influenced by the nuances of their particular story. Patients with APS have heterogeneous presentations and so have unique experiences. Participants may have answered differently if they were currently pregnant or not, or had a previous successful pregnancy. We primarily focused on the patient and physicians in this study, but also acknowledge that this decision is not made in isolation including obtaining information from other sources and decision making with their partner and other people in their social network. The physicians used a standardized scenario that was designed to reflect the ambiguity evident in practice but did have different variables presented (type and level of antibodies, type and number of losses) and was meant to act as a starting place for a discussion. The discussions centered around LMWH/ASA to prevent pregnancy loss, rather than VTE or other pregnancy complications. How physicians made diagnostic and management decisions or discussed these concepts with patients in real life could only be extrapolated based on the interview conversations we had. How the approach and decision making may differ among physicians at different institutions is unknown. It is possible that physicians may have answered these questions differently if they were at institutions that had a different medicolegal landscape. Additionally, we did not interview obstetricians/gynecologists, which may have provided different viewpoints. These are important areas of future study.

The results of our study may impact future plans and the ability to conduct RCTs evaluating LMWH and ASA therapy. Patients valued the option of having LMWH/ASA available and being able to do something in their pregnancy, so patients may be unwilling to risk randomization to a nontreatment arm. A patient's decision was also highly individualized for their situation; some patients described choosing LMWH/ASA, whereas others preferred to use ASA alone. This remains one of the biggest challenges in APS research—many patients described wanting more answers about the utility of LMWH injections, but also valued the ability to make their own decisions and the chance to have access to a treatment that could possibly improve their pregnancy outcome. The accepted use of a treatment in clinical practice despite mixed and limited evidence hinders continued research. This was evident with the TIPPS trial, which studied the use of LMWH prophylaxis versus no LMWH to prevent recurrent placenta-mediated pregnancy complications in women with inherited thrombophilia and took over 12 years to complete because of the generalized acceptance of LMWH prophylaxis into practice.¹²

In summary, the decision to use LMWH and/or ASA during pregnancy to prevent recurrent pregnancy loss was largely driven by patients and was highly individualized. Better understanding of how to incorporate patient decision making into clinical decision models or clinical research deserves further study.^{27,28}

What is known about this topic?

- In women with antiphospholipid syndrome (APS), low-molecular-weight heparin (LMWH) and/or aspirin (ASA) prophylaxis given during pregnancy to prevent future loss is based on limited trial data with mixed results.
- Guidelines differ and suggest LMWH and/or ASA prophylaxis in pregnant women with APS based on the clinical scenario and individual risk profile.

What does this paper add?

- This article describes how patients and physicians navigate the decision-making process for initiation of LMWH and/or ASA prophylaxis during pregnancy in APS.
- The decision to use LMWH and/or ASA prophylaxis is largely individualized.
- Patients describe benefit from the processing of taking action by using LMWH and/or ASA prophylaxis, even in the absence of a guaranteed good outcome.

Author Contributions

L.S. developed the study, developed both interview guides, conducted the patient and physician interviews, analyzed the interview transcripts, and wrote the first and subsequent drafts of the manuscript. T.S.T. developed the study, developed the patient interview guide, conducted the patient interviews, analyzed the interview transcripts, and provided feedback on subsequent drafts of the manuscript. C.G. developed the study, developed the physician interview guide, contributed to the analysis of the physician study, and provided feedback on subsequent drafts of the manuscript. M.A.R., S.M.B., and A.K. helped to develop the study, provided feedback throughout, and contributed to drafts of the manuscript.

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Conflict of Interest

L.S.: honoraria from LEO Pharma; Research funding from CSL Behring. M.A.R.: no conflicts of interest to report. S.M.B.: honoraria from LEO Pharma. C.G.: no conflicts of interest to report. A.K.: no conflicts of interest to report. T.S.T.: no conflicts of interest to report. S.M.B. holds the Eli Lilly Canada/May Cohen Chair in Women's Health. M.R. is the McGill Harry Webster Thorp Professor of Medicine.

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THIEME