Postpartum Management of Women at Increased Risk of Thrombosis — Results of a Canadian Pilot Survey

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ABSTRACT. ***Objective.*** To determine current practice patterns in the postpartum management of women at increased risk of thrombosis.

Methods. Physicians affiliated with the University of Toronto departments of Obstetrics and Gynecology, Rheumatology, Hematology, and Obstetric Medicine who provide care to pregnant women were mailed a questionnaire that presented 6 clinical scenarios involving postpartum management of a woman at risk for thrombosis, with (1) recurrent pregnancy loss and antiphospholipid antibody syndrome (APS) treated with aspirin (ASA) in the pregnancy; (2) 2 pregnancy losses and a low titer antiphospholipid antibody (aPL) treated with ASA and low molecular weight (LMW) heparin with placental insufficiency; (3) known APS and pregnancy loss treated with LMW heparin and delivered by cesarean section; (4) a previous 17 week fetal death and aPL; (5) a previous deep vein thrombosis while on oral contraception; and (6) systemic lupus erythematosus and secondary APS with a history of a stillbirth. Physicians were asked whether they would recommend postpartum coagulation, and if so to choose from a list of treatment options.

Results. Of the 71 questionnaires mailed, 44 were returned (62%). Three physicians replied that their practices do not include patients similar to those presented in the cases and chose not to respond to the clinical scenarios. Percentages of responders recommending treatment in each scenario were 29% for Case 1, 49% for Case 2, 63% for Case 3, 41% for Case 4, 51% for Case 5, and 58% for Case 6. Recommendation for treatment differed among medical specialties, with rheumatologists being less likely to treat in all cases. Prophylactic heparin was selected as the treatment of choice most frequently by those recommending anticoagulation 70% (84/120).

Conclusion. Postpartum treatment recommendations for women at increased risk of thrombosis are variable across different practitioner specializations demonstrating clinical equipoise regarding therapy. More definitive research is needed and broader study of physicians involved in the care of these patients is planned to more accurately describe and understand the decision to treat these patients. (First Release Sept 15 2006; J Rheumatol 2006;33:2222–6)

Key Indexing Terms:
POSTPARTUM THROMBOSIS RISK ANTIPHOSPHOLIPID ANTIBODIES

Women with antiphospholipid antibodies (aPL) are considered at increased risk for recurrent pregnancy loss (RPL), intrauterine growth restriction, stillbirth, and thrombotic events (TE)[1-3]. The first 6 weeks after pregnancy has been shown to be a period of increased risk of TE in women with a history of prior TE and aPL[4]. These women are classified as having antiphospholipid antibody syndrome (APS). This syndrome involves both clinical features, including a history of thrombosis, recurrent pregnancy loss before 10 weeks' gestation, fetal death after 10 weeks, or premature birth due to preeclampsia or intrauterine growth restriction, and laboratory criteria including moderate to high titers of anticardiolipin antibodies (aCL) and/or the circulating/lupus anticoagulant (LAC)[5]. Primary APS includes patients with no underlying autoimmune disorder, while secondary APS describes patients with an autoimmune disease such as systemic lupus erythematosus (SLE) in addition to APS.

In patients who do not have aPL the reported rates of postpartum deep vein thrombosis (DVT) range from 0.06 to 3.0%[6-8], while the rate of pulmonary embolism at any point in pregnancy is estimated to be between 0.04% and 0.13%[9-11]. Retrospective data suggest that a high proportion of initial thrombotic events in women with aPL occur in proximity to pregnancy or oral contraceptive use[12]. The overall risk of first thrombosis in patients with asymptomatic aPL is unknown, while the risk of recurrent thrombosis in APS has been shown to be as high as 70%[13]. The rate is far higher than that reported in women with non-aPL associated prior thrombosis, where the reported rates range from 0 to 13%[14]. Given the perception

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of a high risk of recurrent TE, postpartum antithrombotic prophylaxis in women with APS and prior TE is generally accepted[15].

Women with APS manifest exclusively with obstetrical complications have an unknown risk of thrombosis and lack clear evidence-based recommendations for postpartum management. The observation that aPL are associated with thrombosis, coupled with the observed increased risk of thrombosis during and after pregnancy in women without aPL, logically allows the inference that women with aPL are at increased risk of TE. However, the magnitude of that risk is unknown[16]. The Royal College of Obstetrics and Gynaecology Guidelines[17] suggest using low molecular weight (LMW) heparin for 3–5 days after delivery in women with APS based only on obstetrical features. The American College of Obstetricians and Gynecologists (ACOG) states that the postpartum management of this population is uncertain and suggests that optimal management includes no treatment, treatment with low-dose aspirin (ASA), or treatment with ASA in combination with prophylactic-dose heparin, but also states that if prophylaxis is used during pregnancy, it should be continued for 6–8 weeks postpartum[18]. Neither guideline presents data to support the recommendations.

Many studies investigating obstetric manifestations of APS have been directed at the management of pregnancy with the aim of increasing the live birth rate[19]. To our knowledge, the prior research has not been directed at reducing TE in pregnancy or postpartum[20-22]. Considering the dearth of methodologically rigorous evidence to guide practice[19], we investigated how clinicians currently manage patients with various manifestations of APL in the peripartum period. We designed a pilot survey with a series of hypothetical cases focusing on subtle clinical and laboratory variables that clinicians encounter when managing patients with APS and with aPL. The survey was sent to a pilot group of obstetricians, rheumatologists, general internists, and hematologists, as these specialties have been identified as managing such patients in the postpartum period.

MATERIALS AND METHODS

Questionnaire. A self-administered survey was mailed to 71 physicians affiliated with the University of Toronto Departments of Obstetrics and Gynecology, Rheumatology, and Hematology (Appendix 1).

The questionnaire, covering letter, and postage-paid addressed return envelope were mailed in June 2005. Each questionnaire was assigned a unique identifier to enable tracking of responses. Completed questionnaires were coded and entered into a database not linked to names or addresses of the respondents, thus rendering the responses confidential. A followup reminder/thank you card was sent 5–6 weeks later that included a telephone number and e-mail address for anyone to request another copy of the questionnaire.

The closed-ended questionnaire contained 6 different clinical scenarios focusing on postpartum management of women at increased risk of thrombosis. The scenarios included (1) a woman with RPL and a moderately positive IgM aCL treated with ASA in her pregnancy who delivered at 40 weeks; (2) a woman with 2 early pregnancy losses between 10 and 12 weeks with a low positive IgG aCL, treated with ASA and prophylactic LMW heparin, induced at 36 weeks due to placental thrombosis; (3) a woman with APS, a history of thrombocytopenia, 3 pregnancy losses, a known LAC but no history of TE, treated with prophylactic LMW heparin delivered at term by cesarean section; (4) a woman with one second trimester fetal death with a strongly positive aCL IgG and LAC, but no history of TE, who delivered vaginally at term; (5) a woman with a history of a DVT while taking oral contraception 6 years ago, negative for aPL and thrombophilia, who delivered vaginally at 41 weeks; and (6) a woman with SLE well controlled with azathioprine and APS with a history of a stillbirth at 28 weeks showing intrauterine growth restriction, strongly positive for aCL IgG, and no prior TE, who was treated with LMW heparin and ASA and delivered at 34 weeks due to premature rupture of membranes.

Respondents were asked whether they would anticoagulate postpartum and, if so, to choose from a list of treatment options: 81 mg of ASA; prophylactic heparin; prophylactic heparin + 81 mg of ASA; therapeutic heparin; therapeutic heparin + 81 mg of ASA; or other (specify). Respondents were also asked to select the duration of the therapy chosen: short course (up to 14 days); long course (up to 8 weeks); or other (specify).

Respondents. Demographic information regarding the respondents was collected including medical specialty, sex, and year of completion of residency. Additionally, 3 questions were asked to determine how many patients similar to those presented in the scenarios they see, treat, and/or refer to other specialists. We also requested that respondents record the start and completion times for the survey, and included a section for comments.

Statistical analysis. Within and between-specialty responses were compared using Sigma Stat Version 3.1 (Systat Software, Point Richmond, CA, USA).

RESULTS

Seventy-one surveys were mailed and 44 physicians replied (62%). Three physicians chose not to complete the questionnaire because they do not see this patient population in their practice. Table 1 lists the demographics and specialty of the respondents. Of the 41 physicians completing surveys, 15 were rheumatologists, 7 were internists (including hematologists and obstetric medicine), and 19 were obstetricians (including one gynecologist). The majority (76%) of respondents reported seeing patients similar to the survey patients in their practices, 71% reported treating such patients, and 61% said they would refer similar patients to rheumatologists, hematologists, and obstetric medicine and maternal fetal medicine subspecialists with particular interests in this area.

Table 2 presents the distribution of management scenarios selected, including both the preferred treatment and its duration. In all cases prophylactic heparin alone was most commonly selected (70%). The questionnaire did not specify type of heparin (unfractionated vs LMW), although some respon-

Table 1. Characteristics of respondents (n = 41).

	N (%)
Female	16 (39)
Specialty	
Rheumatology	15 (37)
Hematology/Ob medicine/internist	7 (17)
Obstetrics & gynecology	19 (44)
See similar patients	31 (76)
Treat similar patients	29 (71)
Refer to other	25 (61)

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Table 2. Postpartum treatment recommendations by case. Case summaries: (1) Recurrent pregnancy loss and antiphospholipid syndrome (APS) treated with aspirin (ASA) in the pregnancy. (2) Two pregnancy losses and low-titer antiphospholipid antibodies (aPL) treated with ASA and low molecular weight (LMW) heparin with placental insufficiency. (3) Known APS and pregnancy loss treated with LMW heparin and delivered by cesarean section. (4) Previous 17-week fetal death and aPL, delivered vaginally. (5) A previous deep vein thrombosis while taking oral contraception, delivered vaginally. (6) SLE and secondary APS (with a history of one stillbirth) delivered vaginally. Results are expressed as number (%) of physicians recommending each treatment option.

Case	No Treatment	ASA Only	Prophylactic Heparin	Prophylactic Heparin + ASA	Therapeutic Heparin	Therapeutic Heparin + ASA
1	29 (70.7)	2 (4.9)	8 (19.5)	2 (4.9)	0	0
2	21 (51.2)	0	14 (34.1)	3 (7.3)	3 (7.3)	0
3	15 (36.6)	1 (2.4)	20 (48.8)	3 (7.3)	2 (4.9)	0
4	24 (58.5)	4 (9.8)	11 (26.8)	0	2 (4.9)	0
5	20 (48.8)	3 (7.3)	16 (39.0)	1 (2.4)	1 (2.4)	0
6	17 (41.5)	2 (4.9)	15 (36.6)	5 (12.2)	0	2 (4.9)

dents did specify that they would use LMW heparin. Long course prophylaxis, defined as up to 8 weeks of postpartum therapy, was selected most frequently regardless of the anticoagulant chosen. Cases 3 and 6 had the most responses to treat, with Case 6 being the only case in which therapeutic heparin + ASA was selected.

The percentage of respondents who chose to treat in each clinical case grouped by specialty is shown in Figure 1. Rheumatologists were less likely to treat than other respondents in all cases ($p = 0.002$). Case 3, which specified delivery by cesarean section, was the only scenario where the percentage recommending treatment was higher among obstetricians than hematologists/internists.

DISCUSSION

The results of this survey highlight the lack of consensus in the treatment of women at increased risk of postpartum thrombosis. Cases were designed with subtle differences in clinical histories to detect trends in practice patterns. No single case received unanimous agreement with respect to postpartum anticoagulation.

Our survey identified differences in management choices among specialists involved in the care of these patients. Rheumatologists were consistently less likely to treat regardless of the patient scenario, while hematologists/internists were most likely to treat most often. The only exception to this was Case 3, where delivery was by cesarean section and obstetricians were most likely to treat. Cases 1 and 2 did not specify delivery mode and one obstetrician respondent noted that if delivery was by cesarean section they would recommend anticoagulation until discharge. Mode of delivery appeared to be a factor for obstetricians favoring thrombopro-

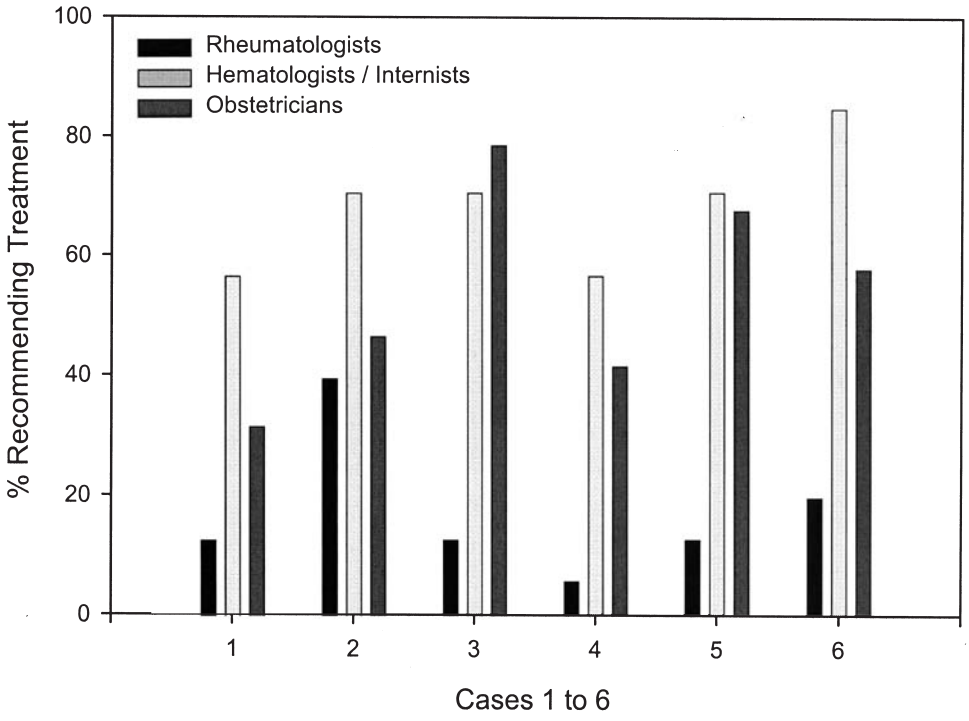

Figure 1. Treatment decision rates by specialty.

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APPENDIX. Physician survey of clinical practice management of postpartum women at risk of thrombosis.

I. Postpartum Management Cases

Please complete the questions relating to the following 6 cases.

Case 1
A 37 year old, with a history of 3 early pregnancy losses (<8 weeks gestation) has a moderately positive IgM anticardiolipin antibody (35 MPL – upper limit of normal 25MPL) and thus meets criteria for antiphospholipid antibody syndrome. In her current pregnancy she was treated with 81 mg of ASA/day until 35 weeks gestation. She delivered at 40 weeks and her placenta appeared normal.

Post Partum do you treat her with anticoagulants? ☐ Yes ☐ No

If **No**, please proceed to Case 2.

If **Yes**, please choose one of the following and answer the question that follows:
- ☐ 81 mg ASA
- ☐ Prophylactic heparin
- ☐ Prophylactic heparin and 81 mg of ASA
- ☐ Therapeutic heparin
- ☐ Therapeutic heparin and 81 mg of ASA
- ☐ Other (please specify) _____

How long would you continue the therapy selected above?
- ☐ Short course – up to 14 days
- ☐ Long course – up to 8 weeks
- ☐ Other (please specify) _____

Case 2
A 32 year old woman with a history of 2 fetal losses between 10-12 weeks gestation has a repeatedly low positive anticardiolipin IgG (18.6 GPL – upper limit of normal 15 GPL). She was on ASA 81 mg and prophylactic low molecular weight heparin during the pregnancy. Fetal and placental assessment at 36 weeks suggested extensive placental thrombosis prompting induction at 36 weeks.

Post Partum do you treat her with anticoagulants? ☐ Yes ☐ No

If **No**, please proceed to Case 3.

If **Yes**, please choose one of the following and answer the question that follows :
- ☐ 81 mg ASA
- ☐ Prophylactic heparin
- ☐ Prophylactic heparin and 81 mg of ASA
- ☐ Therapeutic heparin
- ☐ Therapeutic heparin and 81 mg of ASA
- ☐ Other (please specify) _____

How long would you continue the therapy selected above?
- ☐ Short course – up to 14 days
- ☐ Long course – up to 8 weeks
- ☐ Other (please specify) _____

Case 3
A 40 year old woman with known primary antiphospholipid antibody syndrome has a history of thrombocytopenia, a known circulating anticoagulant (LAC) and 3 previous pregnancy losses. She has never had a thrombotic event. She was treated with prophylactic doses of low molecular weight heparin in this pregnancy. She delivered this pregnancy at term by Cesarean section due to breech presentation.

Post Partum do you treat her with anticoagulants? ☐ Yes ☐ No

If **No**, please proceed to Case 4.

If **Yes**, please choose one of the following and answer the question that follows :
- ☐ 81 mg ASA
- ☐ Prophylactic heparin
- ☐ Prophylactic heparin and 81 mg of ASA
- ☐ Therapeutic heparin
- ☐ Therapeutic heparin and 81 mg of ASA
- ☐ Other (please specify) _____

How long would you continue the therapy selected above?
- ☐ Short course – up to 14 days
- ☐ Long course – up to 8 weeks
- ☐ Other (please specify) _____

Case 4
A 28 year old woman with a history of a 17 week fetal death has a positive circulating anticoagulant (LAC) and a high titre IgG anticardiolipin antibody (>150 GPL). She has never had a thrombotic event. Her current pregnancy went to term and she delivered vaginally.

Post Partum do you treat her with anticoagulants? ☐ Yes ☐ No

If **No**, please proceed to Case 5.

If **Yes**, please choose one of the following and answer the question that follows :
- ☐ 81 mg ASA
- ☐ Prophylactic heparin
- ☐ Prophylactic heparin and 81 mg of ASA
- ☐ Therapeutic heparin
- ☐ Therapeutic heparin and 81 mg of ASA
- ☐ Other (please specify) _____

How long would you continue the therapy selected above?
- ☐ Short course – up to 14 days
- ☐ Long course – up to 8 weeks
- ☐ Other (please specify) _____

Case 5
A 34 year old women with a history of a deep vein thrombosis (DVT) while taking oral contraceptives 6 years ago. She has tested negative for antiphospholipid antibodies and thrombophilia. During this, her first pregnancy, she was on no medication and delivered vaginally at 41 weeks.

Post Partum do you treat her with anticoagulants? ☐ Yes ☐ No

If **No**, please proceed to Case 6.

If **Yes**, please choose one of the following and answer the question that follows :
- ☐ 81 mg ASA
- ☐ Prophylactic heparin
- ☐ Prophylactic heparin and 81 mg of ASA
- ☐ Therapeutic heparin
- ☐ Therapeutic heparin and 81 mg of ASA
- ☐ Other (please specify) _____

How long would you continue the therapy selected above?
- ☐ Short course – up to 14 days
- ☐ Long course – up to 8 weeks
- ☐ Other (please specify) _____

Case 6
A 34 year old woman with secondary phospholipid antibody syndrome with underlying systemic lupus erythematosus, a history of a stillbirth at 28 weeks with IUGR and a high titre IgG anticardiolipin antibody (76 GPL) whose lupus is well controlled and is on Imuran. She has no history of thrombotic events. In this pregnancy, she is treated with low molecular weight heparin and ASA. She delivered vaginally at 34 weeks secondary to premature rupture of membranes (PROM).

Post Partum do you treat her with anticoagulants? ☐ Yes ☐ No

If **No**, please proceed the final section of the survey.

If **Yes**, please choose one of the following :
- ☐ 81 mg ASA
- ☐ Prophylactic heparin
- ☐ Prophylactic heparin and 81 mg of ASA
- ☐ Therapeutic heparin
- ☐ Therapeutic heparin and 81 mg of ASA
- ☐ Other (please specify) _____

How long would you continue the therapy selected above?
- ☐ Short course – up to 14 days
- ☐ Long course – up to 8 weeks
- ☐ Other (please specify) _____

II. Demographic Information

1. Date completed 2005/___/___.
   mm dd

2. Which of the following specialties describes your practice?
   - ☐ obstetrics
   - ☐ gynecology only
   - ☐ hematology
   - ☐ rheumatology
   - ☐ other _____

3. Gender ☐ Female ☐ Male

4. In what year did you complete your residency in the above-specified specialty? _____

5) Over the last 12 months have you **seen** patients similar to those described?
   - ☐ Yes
     If yes, please estimate the number _____/year
   - ☐ No

6) Over the last 12 months have you **treated** patients similar to those described?
   - ☐ Yes
     If yes, please estimate the number _____/year
   - ☐ No

7) Over the last 12 months, have you **referred** patients similar to those described to a specialist?
   - ☐ Yes
     If yes, please specify type of specialist _____
   - ☐ No

III. Comments on Questionnaire

Please indicate any comments you have on this questionnaire.

Time completed questionnaire_____am or pm

phylaxis and may have affected responses towards treatment even in those patients viewed as "low risk."

With the exception of Case 5, all cases fulfilled clinical and laboratory criteria for APS, yet not all respondents proposed postpartum anticoagulation. Case 5 had a history of TE while taking oral contraceptives, but was aPL-negative. In all the other cases the patients had either an elevated aCL IgG (low in Case 2, high in Cases 4, 6), an elevated aCL IgM (Case 1),

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or LAC (Case 3). Although the clinical significance of aCL IgM is controversial[23,24], it is included in the Sapporo Criteria[5] for the classification of APS. Interestingly, the ACOG guidelines defining APS include IgG aCL and LAC but not the IgM aCL. This could account for the very low treatment response among obstetricians in Case 1. As the Sapporo criteria are perhaps more familiar to rheumatologists and hematologists, subtle but distinct differences in classification criteria might affect how specialties evaluate treatment strategies.

Our results are likely to be generalizable for several reasons. The surveyed physicians have prior experience in the treatment of such patients, as over 70% reported seeing and treating similar patients in their practices. Our response rate of 62% is slightly higher than the mean response rate of published physician surveys of 54%[25]. Finally, our results mirror our anecdotal experience, which suggests that women receive a wide variety of treatments in this setting.

Our study has a number of limitations. It was a small pilot study intended to survey the instrument and the importance of the question. It was not set up to definitively evaluate the treatment options. Secondly, the numbers of physicians responding in each specialty were dissimilar and the reliability of the cumulative responses could be lower, particularly among the hematologists, of whom only 7 replied compared to 15 rheumatologists and 19 obstetricians. Finally, only physicians working in highly specialized tertiary care settings were included in this study, and these responses may not reflect responses among a broader sample of physicians. By the same token, one could argue that few community-based practitioners have any substantial experience managing these types of patients and therefore tertiary-care-based practitioners may be the most appropriate sample of respondents. We will address these concerns when administering a nationwide survey of specialists.

The findings of our survey support the lack of consensus among physicians treating this group, despite the women's potential serious morbidity, and suggest that there is room for improvement in the postpartum care of women with aPL. Further research, including a national survey to confirm these results and a clinical trial, are planned to try to obtain evidence to assist in the peripartum management of these patients.

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