Low Molecular Weight Heparin and Aspirin for Recurrent Pregnancy Loss: Results from the Randomized, Controlled HepASA Trial

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ABSTRACT. ***Objective.*** To compare live birth rates in women with recurrent pregnancy loss (RPL) and either autoantibodies or a coagulation abnormality, treated with low molecular weight heparin plus aspirin (LMWH/ASA) or ASA alone, and to place our results in context with other randomized clinical trials (RCT) with similar cohorts.

Methods. The HepASA Trial was an RCT including patients with a history of RPL and at least 1 of the following: antiphospholipid antibody (aPL), an inherited thrombophilia, or antinuclear antibody. Treatment groups were stratified by aPL status and history of early versus late pregnancy losses. Patients received either LMWH/ASA or ASA alone. The primary outcome was live birth; secondary outcomes included adverse events and bone loss at the spine and femoral neck. Literature over the past 20 years was reviewed to identify comparable RCT.

Results. Over 4 years, 859 women with RPL were screened: 88 (10.2%) fulfilled inclusion criteria, became pregnant and were randomized to receive either LMWH/ASA or ASA alone. aPL were present in 42 (47.7%) patients in each group. The trial was stopped after 4 years when an interim analysis showed no difference in live birth rates in the 2 groups, and a lower rate of pregnancy loss in the ASA only group than expected. In the LMWH/ASA group, 35/45 (77.8%) had a live birth versus 34/43 (79.1%) in the ASA only group (p = 0.71). Neither number of prior losses nor aPL status was correlated with pregnancy outcome. There were no cases of pregnancy related thrombosis in either group. Mean change in BMD did not differ by treatment group at either the lumbar spine (p = 0.57) or femoral neck (p = 0.15). RCT since 2000 for aPL positive women with RPL and similar inclusion criteria report a mean live birth rate of 75% with either LMWH or ASA.

Conclusion. LMWH/ASA did not confer incremental benefit compared to ASA alone for this population. Regardless of treatment regimen, number of prior losses, or aPL positivity, almost 80% of women in our RPL cohort had a successful pregnancy outcome. These findings contribute to a growing body of literature that contests the emerging standard of care comprising LMWH/ASA for this population. (J Rheumatol First Release Feb 1 2009; doi:10.3899/jrheum.080763)

Approximately 15% of all clinically recognizable pregnancies end in pregnancy loss[1,2], and it has been estimated that recurrent pregnancy loss (RPL) affects up to 5% of couples trying to conceive[3]. A patient who has had 2 or more consecutive losses can be classified with RPL[4]. Possible causes to consider in evaluating RPL include anatomical, genetic, and hormonal factors, but in over 50% of cases no etiology is found[5]. Pregnancy loss in patients with antiphospholipid antibodies (aPL) including anticardiolipin (aCL) and the lupus anticoagulant (LAC) has been attributed to placental infarcts and vascular thrombosis leading to placental insufficiency[6,7]. Others have observed an inhibition of trophoblast invasion and differentiation as a possible mechanism for early pregnancy loss[8,9]. The role of an immune-mediated mechanism to explain RPL has been examined based on observations initially made in women with systemic lupus erythematosus (SLE), an autoimmune disease that can be accompanied by higher than normal rates of fetal loss[10]. Certainly, the deposition of immunoglobulins, com-

plement, anti-DNA antibodies, and antinuclear antibodies (ANA) in the lupus placenta suggest that coagulopathy is not the only mechanism of placental (and therefore fetal) ischemia, and that immune-mediated inflammatory mechanisms may also contribute to intrauterine growth restriction (IUGR) and fetal loss[11].

The present standard of care for women with aPL and RPL is treatment with heparin and aspirin (ASA)[12]. Early data supporting the use of ASA and unfractionated heparin to improve live birth rate in women with RPL and aPL appeared in 2 small studies in the 1990s[13,14]. Rai and colleagues[14], in determining the required sample size for their randomized trial, predicted rates of loss with ASA alone that were significantly higher than observed by others both before and since[15-17]. They included women with very low levels of aPL, and found a decrease in early fetal loss with the use of unfractionated heparin and ASA compared to ASA only. They also reported no treatment benefit for pregnancies that survived beyond 13 weeks' gestation, a finding not supported by others[18]. In a more recent randomized clinical trial (RCT), Farquharson, et al found no improvement in pregnancy outcomes of aPL positive women with a history of RPL when comparing treatment with low molecular weight heparin (LMWH)/ASA vs ASA alone[17] and Carmona, et al found that preconceptual ASA treatment was an independent predictor of live birth[19]. Subsequent to the design and initiation of our HepASA trial, Empson, et al[20], in a Cochrane database review, concluded that treatment with unfractionated heparin and ASA may reduce pregnancy loss by 54% but that large randomized controlled trials are still needed to explore potential differences between unfractionated heparin and LMWH.

A relationship between inherited and acquired thrombophilias and RPL has been examined, with small uncontrolled studies favoring treatment with LMWH to improve pregnancy outcome[21-23], but evidence supporting this treatment remains inadequate[24]. A recent systematic review concluded that owing to limited evidence of efficacy, treatment with LMWH/ASA remains empiric in women with inherited thrombophilias[25].

As previous studies of these therapeutic regimens have not proven conclusive due to small sample sizes and/or weak study design, we undertook a randomized controlled trial of LMWH and ASA versus ASA alone for women with prior adverse obstetric outcomes, autoantibodies including aPL, and inherited thrombophilias, commencing randomization early in the first trimester. The primary objective of the HepASA Trial was to investigate whether treatment with LMWH plus ASA results in an increased rate of live births compared to treatment with ASA alone. The secondary objective was to compare adverse events and the incidence of bone loss in the 2 groups. In addition, we wanted to place our findings in the context of other comparable trials and determine why, in the apparent absence of consistent findings, a standard of care has emerged for this population.

MATERIALS AND METHODS

Objectives. In this open label RCT, we investigated whether treatment with LMWH/ASA results in increased live births in women with a history of consecutive RPL and autoantibodies compared to treatment with ASA alone.

Participants. Inclusion criteria: Women considered for participation in this trial fulfilled the following criteria: aged 18–44 years at the time of randomization; a history of ≥ 2 unexplained consecutive pregnancy losses prior to 32 weeks gestation; presence of at least 1 of the following: ANA, aPL, or an inherited thrombophilia; and confirmed pregnancy by either 2 appropriately rising quantitative beta human chorionic gonadotropin (ßhCG) tests performed 48 h apart or by ultrasound confirming fetal heart activity.

Exclusion criteria: Exclusion criteria included SLE (fulfilling American College of Rheumatology classification criteria[26]), known peptic ulcer disease (within the last 5 yrs), sensitivity to ASA or heparin obtained by self report, bone mineral density z score < –2.5, known platelet function abnormality, or a previous thromboembolic event (TE) requiring ongoing anticoagulant therapy including heparin, ASA, or warfarin, verified in medical records. Patients were also excluded if any genetic, anatomic, or hormonal etiology for pregnancy loss was identified by (respectively) karyotype analysis of both partners, hysterosalpingogram/sonohystogram, and a hormonal evaluation (which included either an endometrial biopsy or loss while taking progesterone or clomiphene therapy or mid luteal phase serum progesterone levels timed appropriately). Any such patient was referred for appropriate counseling or treatment. Geographic distance from the clinic and hospitals in Toronto/Hamilton, Ontario, as well as failure to consent to participate were additional exclusion criteria.

Laboratory evaluation: Positive serology was defined as at least one of the following tests found to be positive on 2 occasions at least 8 weeks apart: anticardiolipin IgG [> 15 IgG phospholipid units (GPL)] or IgM [> 25 IgM phospholipid units (MPL)]; LAC measured by Russell's viper venom time (RVVT), kaolin-cephalin clotting time (KCCT), dilute prothrombin time (DilPT), or lupus sensitive activated partial thromboplastin time (aPTT-LA)[27]; or the presence of 1 positive test on a thrombophilia screen [which included protein C (functional), protein S (free) antigen functional, activated protein C resistance (APCR) assay, factor V Leiden, prothrombin 20210 AG, and methylenetetrahydrofolate reductase (MTHFR)]; or ANA ≥ 1/80. All eligible patients signed consent to participate at the pretrial visit and again at randomization once confirmed pregnant.

Clinical assessments: A study physician evaluated all randomized women every 6 weeks during their pregnancy. The assessment included a general examination preceded by a detailed history including a functional inquiry assessing for the presence of a systemic autoimmune disorder. Platelets were measured 6 to 12 days after beginning LMWH and every 6 weeks thereafter. Partial thromboplastin time (PTT) was measured at each visit. Obstetrical evaluations were performed according to accepted standard of practice. Data were collected at the obstetrical visits to document fetal development and well-being as well as maternal complications. Delivery information was obtained from the obstetrician or from medical records. Patients were seen 6 weeks post partum and had a bone mineral density (BMD) performed 6-12 weeks' post partum. Spine (L2–L4) and hip (femoral neck) BMD were measured in g/cm² by dual energy x-ray absorptiometry using a Lunar DPX-L bone densitometer (Lunar Corporation, Madison, WI, USA). Measurements throughout the trial were performed by a single, certified densitometry technician. The coefficient of variation determined by test-retest with repositioning was 1.18% at the spine and 1.56% at the femoral neck.

Adverse events: Side effects were recorded at each visit by the study physician using a standard questionnaire. BMD was assessed prepregnancy

and 6–12 weeks at a single laboratory by a single technician to allow quantification of the effect of LMWH on BMD as well as to determine the effect of pregnancy on BMD in the ASA only group.

Interventions/trial products. The trial drug, LMWH (Fragmin, dalteparin sodium), was provided by Pfizer (formerly Pharmacia and Upjohn) as a solution for injection with potency described in international anti-Xa units (IU) and supplied in multidose vials (25,000 anti-Xa IU/ml). All patients randomized to receive LMWH were taught to self-inject the medication subcutaneously once daily until 35 weeks' gestation or delivery, at a dose of 5000 IU/day. ASA (81 mg enteric coated) was used in combination with LMWH in the investigational group, and ASA alone was administered in the reference group. Medication compliance was measured at each clinical visit by patient self-report and return of used LMWH vials.

Sample size. The sample size estimate was based upon an expected live birth rate of 50% in the ASA-treated patients derived from the live birth rate in the placebo arm of the ASA/P study[15]. A 25% absolute improvement in live birth rate with LMWH/ASA treatment was hypothesized[14]. The sample size was based on the number needed to show a significant difference in proportions, with a 2-sided alpha of 0.05 and a beta of 0.10, and was calculated to be 90 patients per group (180 patients in total). We assumed a 10% dropout rate, resulting in a planned sample size of 200 with an accrual rate of 50 per year for the 4-year funding period. An interim analysis was built into the study design to occur once 90 patients were randomized.

Randomization. The randomization schedule was created by the Coordinating and Methods Centre (CMC) of McMaster University in Hamilton. Randomization was performed at the CMC, with communication by telephone, when an eligible patient was confirmed pregnant. Patients were randomized to receive prophylactic doses of LMWH and ASA or ASA only. The CMC assigned a study number to the patient and provided treatment allocation data to the study coordinator. Patients were stratified by presence or absence of aPL, and early (≤ 14 wks) versus late (15–32 wks) losses. The rationale for stratification was to enable subgroup analysis of aPL positive women, who may have a different risk or poorer outcomes than the other women included in this study. Women with a history of both early and late losses were assigned to the late stratum.

Blinding. The trial was an open label design, as the investigators did not consider daily subcutaneous placebo injections to pregnant women ethical; further, ascertainment of the primary endpoint (live birth) should not be subject to bias as a result of knowledge of treatment strategies. We also examined safety variables including adverse events and changes in BMD.

Statistical analysis. The primary analysis was "intent to treat" based on stratified logistic regression with an adjustment for age and timing of losses as well as the treatment variable. The trial design planned for a multivariate analysis, permitting subgroup analysis paying attention to antibody profiles, early and late losses, maternal age, and side effect profiles. Mean change in BMD from baseline to followup was compared by treatment group using a Student's t test. Participants were classified as having experienced bone loss at the spine and femoral neck separately based on the estimated least significant change. Logistic regression was used to examine the effect of treatment group on BMD loss for the spine and femoral neck separately. Statistical analysis was performed using SAS (Version 9.1).

Ethics approval. Our study was approved by the University of Toronto Ethics Review Board, Toronto, and by the Ethics Review Board at McMaster University (ClinicalTrials.gov registration number NCT00564174).

RESULTS

A total of 859 women were screened for inclusion in the HepASA trial between 2000 and 2004 (Figure 1). From the panel of laboratory markers tested, 266 women (31%) had at least 1 positive result. One hundred eighty-three of the positive patients completed the required gynecologic tests, and 112 of these patients consented to participate once they became pregnant. Twenty-four failed to conceive during the study period and 88 patients were randomized (10.2% of the total screened): 43 patients to receive ASA only and 45 to receive LMWH/ASA.

Figure 1 summarizes study recruitment. Baseline patient characteristics are summarized in Table 1. There were no significant differences between the 2 groups in demographic characteristics, obstetric history, mean age at randomization (33.8 vs 34.6 yrs), or laboratory profile. Forty-two patients (47.7%) of those randomized were aPL positive (25 for IgG; 6 for IgM; 15 for LAC; and some patients for more than 1 aPL) and 22% had one of the panel of thrombophilia markers tested, all heterozygous.

Our study was designed to have a sample size of 200 patients and we had anticipated completion within the 4-year funding period. However, after 4 years of recruitment and screening 859 women, only 88 patients had been randomized (Figure 1). The steering committee decided to end the trial upon completion of the 4-year funding period when it was revealed that an interim analysis showed no significant difference in pregnancy outcome between the groups. In addition, the pregnancy loss event rate in the ASA only group was much lower than originally hypothesized.

There were 35 (77.8%) live births in the LMWH/ASA group and 34 (79.1%) live births in the ASA only group (p = 0.75 by Fisher's exact test, Table 2). There was no association between number of previous pregnancy losses (2 vs ≥ 3) and pregnancy outcome: relative risk (RR) 0.70; 95% confidence interval (CI) of RR: 0.40–1.22 (p = 0.20). Mode of delivery was similar in the 2 groups: RR 1.04; 95% CI 0.77–1.41 (p = 0.80). One patient in the ASA only group had a twin pregnancy that resulted in 1 live birth and 1 stillbirth. Thus the total number of outcomes in the ASA only group was 44. A neonatal death occurred in the ASA group, attributed to cervical incompetence, preterm premature rupture of membranes, and delivery at 22 weeks' gestation (with the neonate living for less than 1 h). Spontaneous abortions ≤ 14 weeks' gestation occurred in 7 (15.5%) of the LMWH/ASA pregnancies and in 8 (18.6%) of the ASA only pregnancies with the mean (range) gestational age at the time of loss being 9.8 (7.7–10.7) weeks versus 8.9 (5.9–13.0) weeks, respectively. There were no pregnancy losses between 15 and 20 weeks' gestation.

The median birth weight in the LMWH/ASA group was 3404.5 grams (g) and 3250 g in the ASA only group (p = 0.627). Birth weights were below the 10th percentile based on Canadian census data[28] in 9 patients (including 1 twin stillbirth), with 3 in LMWH/ASA group and 6 in the ASA only group. Placental maturation was noted in one of these patients and increasing blood pressure in another, both resulting in the decision to induce labor. Obstetric histories of early versus late loss were not associated with any difference in the live birth rate in the 2 groups (Figure 2). Of the 11 patients with a history of stillbirth, none had a late preg-
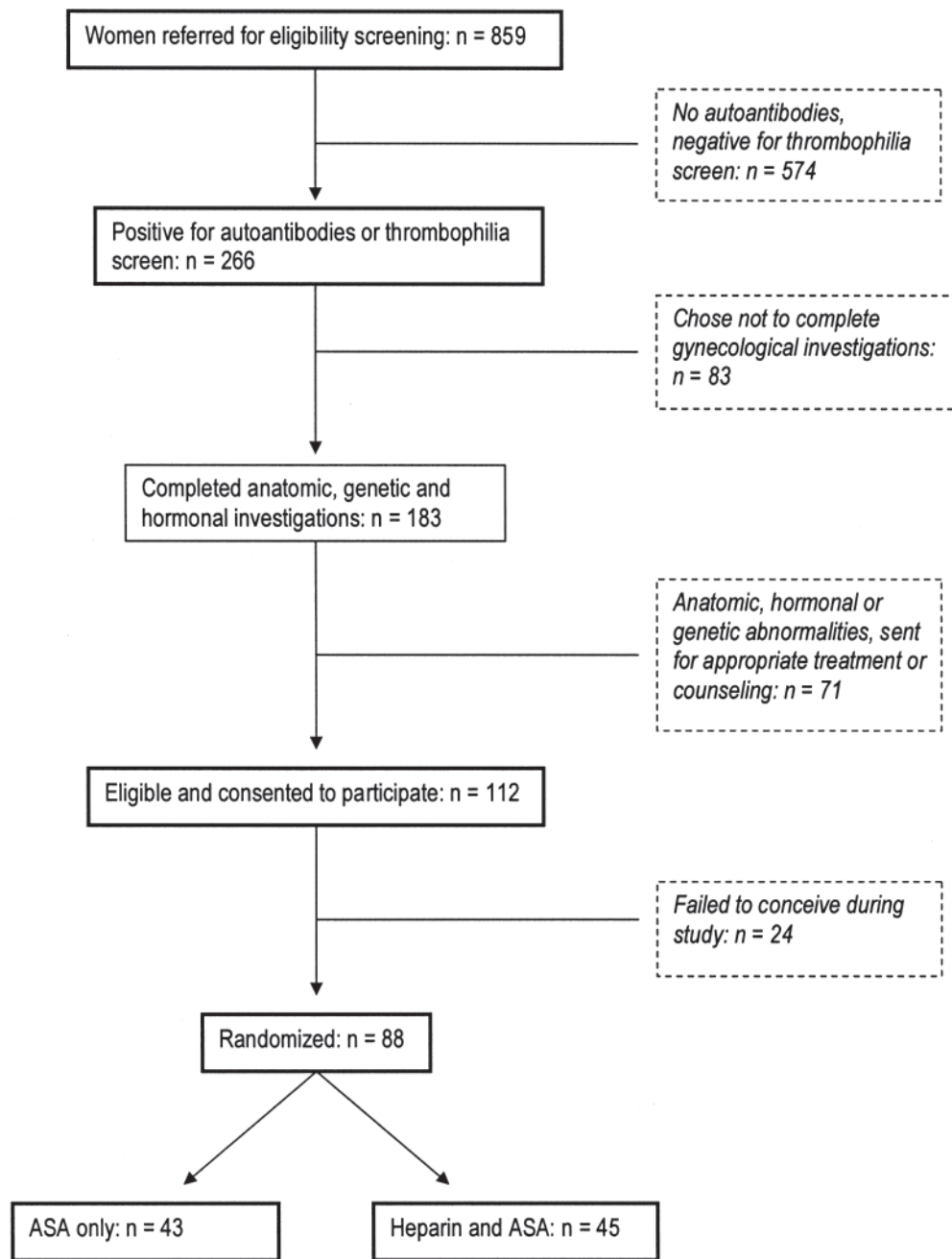
Figure 1. CONSORT flow chart for recruitment to the HepASA trial.

nancy loss or stillbirth in the study pregnancy: 7 had a live birth; 4 had early pregnancy losses. Three of the 7 live births occurred among the 9 patients with a birthweight less than the 10th percentile.

Stratification by presence or absence of aPL at randomization resulted in 22 aPL positive patients randomized to LMWH/ASA (48.9%) and 20 randomized to ASA (46.5%) (Table 1). Table 3 summarizes pregnancy outcome based on aPL presence and treatment group. No significant difference was detected with respect to pregnancy outcome. Live births

were evenly distributed across GPL and MPL titers in both treatment groups, but the sample sizes were too small to enable any conclusions regarding the significance of that observation. There were no cases of a maternal thromboembolic event either during pregnancy or in the postpartum period in either group.

Of the 88 trial participants, 23/45 randomized to LMWH/ASA and 15/43 randomized to ASA alone completed both baseline and followup BMD assessments. For these 38 women, the mean duration of time between assessments

Table 1. Baseline patient characteristics of the 2 treatment groups.

Variable, n	ASA Only (n = 43)	LMWH/ASA (n = 45)
History of early losses (≤ 14 wks)	34	32
History of late losses (> 14 wks)	9	13
Still birth ever (20–32 wks)	7	4
Live birth ever	15	15
Maternal age at randomization, yrs, mean (SD)	33.8 (4.1)	34.6 (3.9)
Gestational age at randomization, wks, mean (SD)	5.6 (1.5)	5.8 (1.5)
Current smoker	3	5
aPL (aCL and/or LAC)	20	22
Inherited thrombophilia	10*	9**
ANA	15	15
≥ 2 Laboratory abnormalities	4	7

ASA: aspirin; LMWH: low molecular weight heparin; aPL: antiphospholipid antibody; aCL: anticardiolipin antibody; LAC: lupus anticoagulant; ANA: antinuclear antibody; SD: standard deviation. * 7 heterozygous for Factor V Leiden, 3 heterozygous for prothrombin 20210 AG. ** 7 heterozygous for Factor V Leiden, 1 heterozygous for prothrombin 20210 AG, and 1 heterozygous for both prothrombin 20210 AG and methylenetetrahydrofolate reductase (MTHFR).

Table 2. Pregnancy outcome stratified by treatment group. Data are presented as n (%). There were no statistically significant differences between the 2 treatment groups with regard to obstetrical outcomes. There was 1 twin pregnancy in the ASA only group, resulting in 44 pregnancy outcomes from 43 pregnancies.

Pregnancy Outcome, n	LMWH/ASA, n = 45	ASA Only, n = 43
Loss, ≤ 14 wks gestation	7 (15.6)	8 (18.6)
Loss, 14 to 20 wks gestation	0 (0)	0 (0)
Ectopic pregnancy	2 (4.4)	0 (0)
Still birth (20–32 wks)	1 (2.2)	1* (2.3)
Live birth	35 (77.8)	34* (79.1)
Induced delivery	9 (20.0)	8 (18.2)
Caesarian section	11 (24.4)	14 (31.8)
Neonatal death	0 (0)	1
Total	45	44*

* One patient had a twin birth with 1 still birth and 1 live birth. LMWH: low molecular weight heparin; ASA: aspirin.

was 1.35 years (0.84–2.82 yrs) and was similar for the 2 groups (p = 0.18). Mean change in BMD for the 38 women was –0.05 g/cm^2 at the spine (range –0.30 to 0.07) and –0.01 g/cm^2 at the femoral neck (range –0.16 to 0.115). Mean change in BMD did not differ by treatment group at either the lumbar spine (p = 0.57) or femoral neck (p = 0.15). Twenty-eight of the 38 women with complete BMD data experienced significant loss of bone mass over the intervening period at 1 or both of the lumbar spine or femoral neck; 27 of the 28 experienced loss at the spine, and 13 of the 28 experienced loss of bone mass at the femoral neck. The odds of loss of bone mass were not significantly different for those in the LMWH/ASA group compared with those in the

ASA alone group [odds ratio, OR (any loss) = 0.97, 95% CI 0.22 – 4.24, p = 0.97; OR (spine loss) = 0.71, 95% CI 0.17–2.92, p = 0.63; and OR (hip loss) = 2.33, 95% CI 0.57–9.29].

DISCUSSION

The HepASA trial, comparing LMWH/ASA and ASA alone in women with RPL, did not show any demonstrable difference in the rate of live births in the 2 groups. Our results add to the body of literature[16,17] suggesting that use of heparin plus ASA in women with RPL may not be as beneficial as originally suggested[13,14]. There were no major adverse events associated with either treatment. One stillbirth did occur in each treatment arm and the only neonatal death occurred in the ASA only group, associated with cervical incompetence and preterm premature rupture of membranes at 22 weeks' gestation.

Two subgroups included in HepASA have been the subject of much discussion. The study was stratified by presence of aPL, as this population has been included in many previous studies. Although our final sample size resulted in lower than the desired statistical power, the subgroup of women with aPL did not appear to benefit from the use of LMWH plus ASA (Table 3). Unfortunately, although aCL titers and live births in our aPL positive women were evenly distributed between the 2 treatment groups, the sample size was not sufficient to enable any conclusions to be drawn with regard to titer-based treatment efficacy. Of patients screened for this trial, the number positive for aPL was 31% (256/859), which was lower than our previous experience[15], and as not all of these women satisfied our inclusion/exclusion criteria, we concur with the findings that approximately 20% of women with RPL have aPL[29].

The data collected in this study did not show evidence that LMWH use was associated with increased bone loss versus the ASA group. The safety of LMWH in pregnancy has been described by others[30,31] and bone loss appears to be similar for women on LMWH or on unfractionated heparin[32]. Both pre- and post-BMD measurements were obtained in 54% (38/70) of the patients with live births. We surmise that as our patients come from a wide radius around Toronto, the followup BMD appointment at the reference laboratory, located downtown, may have been difficult to attend despite our efforts to accommodate schedules. Additionally, since a number of our patients became pregnant very quickly after their successful pregnancy in this trial, they may not have undergone postpartum BMD if they were already pregnant.

We included women with a history of 2 or more consecutive first trimester pregnancy losses, as we and others have noted that the causes of RPL are similar in women with 2 or 3 losses[33]. We support investigation and, if appropriate, treatment of women with RPL after 2 consecutive losses rather than after a third loss[4]. Indeed, our analysis of women
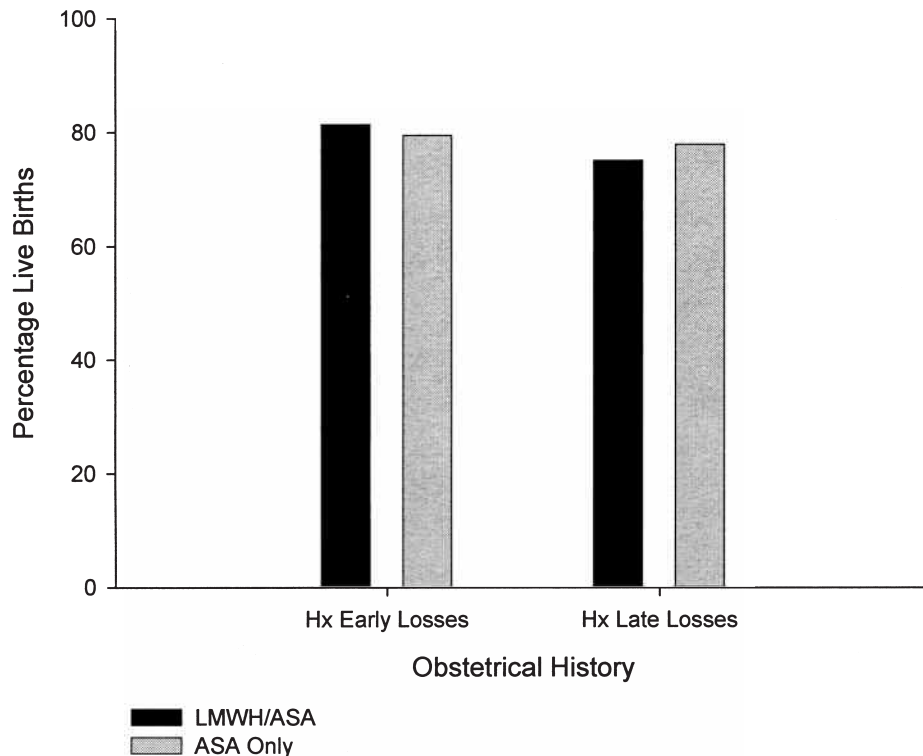
Figure 2. Comparison of pregnancy outcomes for treatment groups with history of early versus late losses.

Table 3. Pregnancy outcome stratified by presence or absence of antiphospholipid antibody (aPL) and treatment group.

| Pregnancy Outcome (n) | LMWH/ASA (n = 45) | | ASA Only (n = 43) | |
	aPL + (n = 22)	aPL - (n = 23)	aPL + (n = 20)	aPL - (n = 23)
Spontaneous abortion (15)	3	4	5	3
Still birth (2)	1	0	0	1*
Ectopic pregnancy (2)	1	1	0	0
Neonatal death (1)	0	0	0	1**
Live birth (69)	17	18	15	19*
Birthweight < 10th percentile (9)	1	2	0	6

* One patient had a twin birth with 1 still birth and 1 live birth. ** Patient had cervical incompetence, premature rupture of membranes; baby died < 1 h after delivery. LMWH: low molecular weight heparin; ASA: aspirin.

randomized in this trial showed that pregnancy outcome in those with a history of 2 versus 3 or more previous pregnancy losses did not differ. It is also interesting to note that a history of early versus late loss did not affect the live birth rate in either of the 2 groups (Figure 2).

Our study has a number of weaknesses that must be noted. This was an open label RCT. Patients were blindly randomized through a centralized methods center upon pregnancy confirmation, but they were then made aware of the group to which they were assigned. When designing the study, it was decided that the objective outcome of our study, live birth rate, combined with the ethical concern of subjecting pregnant women to daily placebo injections, warranted an open label design.

Our inclusion of women positive for a broader panel of

autoantibodies and not exclusively aPL may also be controversial. However, since RPL is a feature of SLE regardless of aPL positivity[34], we consider it appropriate to test for a broader spectrum of autoantibodies in women who are presenting with RPL in the absence of a connective tissue disease. Moreover, it is emerging that in patients with primary antiphospholipid syndrome, there may be an inflammatory component to the RPL[35], with an etiology that has yet to be elucidated.

An interim analysis built into the original design was to occur after 90 patients were randomized. However, accrual was much slower than anticipated, and at the end of 4 years, despite screening over 800 patients, only 88 patients had been randomized. The study steering committee, based on results of an interim analysis on the first 88 patients, decid-

ed to end the trial at the end of the 4-year funding period. The pregnancy loss event rate was much lower in the ASA only group than originally hypothesized and there was no difference in live birth rate in the 2 treatment groups. It was clear that a much expanded sample size would be necessary to detect a difference between the 2 arms and would require screening thousands more patients.

Our experience highlights the difficulty in recruiting RPL patients with autoantibodies and inherited thrombophilias into clinical trials and suggests that investigators studying this population need to carefully consider feasibility and multicenter collaboration. Despite the high referral rate to our center (> 200 patients/yr), it was not feasible to fulfill enrollment in an appropriately-powered decisive trial in 4 years. We recognized the need for collaborators early on but it proved difficult to find centers willing to participate. Some potential collaborators who treat women with RPL were uncomfortable with the trial inclusion of an ASA only treatment arm, as they felt it inappropriate to withhold heparin from aPL- or inherited thrombophilia-positive patients. Literature available at the time of trial design suggested a much higher incidence of inherited and acquired throm-

bophilias in women with RPL[19] than we have subsequently reported[36]. Although the association of thrombophilias with RPL has been confirmed in 2 metaanalyses[37,38] data supporting recommendations to treat with anticoagulants remain limited[24], and the small sample size of patients with thrombophilias in each of our study groups did not permit statistically valid comparison of treatment efficacy.

There have been a number of RCT for patients with RPL with aPL evaluating either unfractionated (UFH) or LMWH (Table 4) over the past 15 years. Each trial determined its own aPL inclusion criteria; for example, cutoffs for aCL IgG levels varied from a low of 5[14] to a high of 30[39] GPL, and each center measured LAC by different methodologies, and intuitively, these design inconsistencies might be expected to result in differential outcomes. However, regardless of differences in aPL status among the various trials, the live birth rates, whether in the UFH or LMWH treatment groups, are similar, ranging from 71.1% to 84%, with a weighted mean of 77.0% (standard deviation: 4.1). The only significant differences among trial outcomes are in the ASA-only treatment arms (Table 5): the live birth rates in those vary from a low of 42.2%[14] to a high of 80.0%[16]. Interestingly,

Table 4. Comparison of live birth rates for women with recurrent pregnancy loss and aPL. Results from 8 randomized clinical trials from 1996 to 2008 evaluating either unfractionated heparin or low molecular weight heparin in combination with aspirin.

Author, year	n	Determination of aPL Positivity	Intervention	Live Births (%)
Kutteh, 1996[13]	25	aCL IgG ≥ 27 or IgM ≥ 27 (Pos LAC excluded)	ASA 81 mg/day + sc UFH 5000 U bid	20/25 (80.0)
Rai, 1997[14]	45	aCL IgG > 5 or IgM > 3 or LAC (RVVT)	ASA 75 mg/day + sc UFH 5000 U bid	32/45 (71.1)
Cowchock, 1992[39]	26	aCL IgG > 30 or IgM > 11 or LAC (DRVVT or APPT)	ASA 80 mg/day + sc UFH 10,000 U bid	19/26 (73.1)
Noble, 2005[40]	25	aCL IgG > 20 or IgM > 20 or aPS > 3 MOM or LAC (DRVVT)	ASA 80 mg/day + sc UFH 5000 U bid	20/25 (80.0)
Franklin, 2002[41]	25	aCL IgG > 20 or IgM > 20 and/or aPS > 3 MOM and/or LAC (DRVVT)	ASA 81 mg/day + sc LMWH 5000 IU bid	19/25 (76.0)
Farquarson, 2002[17]	51	aCL IgG > 9 and/or IgM > 5 or LAC (DRVVT)	ASA 75 mg/day + sc LMWH 5000 IU/day	40/51 (78.4)
Noble, 2005[40]	25	aCL IgG > 20 and/or IgM > 20 and/or aPS > 3 MOM and/or LAC (DRVVT)	ASA 81 mg/day + sc LMWH 40 mg/day	21/25 (84.0)
Laskin, 2008	22	aCL IgG > 15 and/or IgM > 25 and/or LAC (DRVVT, PTTLA, DilPT, KCT)	ASA 81 mg/day + sc LMWH 5000 IU/day	17/22 (77.3)

RPL: recurrent pregnancy loss; UFH: unfractionated heparin; LMWH: low molecular weight heparin; ASA: aspirin; aPL: antiphospholipid antibody; aCL: anticardiolipin; LAC: lupus anticoagulant; DRVVT: dilute Russell's viper venom time; MOM: multiples of the mean; PTTLA: lupus anticoagulant sensitive partial thromboplastin time; DilPT: dilute prothrombin time.

Table 5. Comparison of studies with ASA only treatment arms for aPL positive patients with recurrent pregnancy loss.

Study, Year	n	aPL Positivity	% Live Births
Cowchock, 1992[39]	19	aCL IgG > 30 or IgM > 11 and/or LAC (DRVVT or APPT)	68.4
Kutteh, 1996[13]	25	aCL IgG ≥ 27 or IgM ≥ 27 (Pos LAC excluded)	44.0
Rai, 1997[14]	45	aCL IgG > 5 or IgM > 3 and/or LAC (RVVT)	42.2
Pattison, 2000[16]	20	aCL IgG ≥ 5 or IgM ≥ 5 and/or LAC (aPTT, DRVVT, KCT)	80.0
Farquarson, 2002[17]	47	aCL IgG > 9 or IgM > 5 and/or LAC (DRVVT)	72.3
Laskin, 2008	21	aCL IgG > 15 or IgM > 25 and/or LAC (DRVVT, PTTLA, DilPT, KCT)	71.4

ASA: aspirin; aPL: antiphospholipid antibody; aCL: anticardiolipin; LAC: lupus anticoagulant; DRVVT: dilute Russell's viper venom time; PTTLA: lupus anticoagulant sensitive partial thromboplastin time; DilPT: dilute prothrombin time.

both the lowest and the highest birth rates with ASA only treatment occurred in the trials with the lowest cutoff for aCL positivity, and the second lowest birth rate occurred in a trial that excluded LAC positive patients altogether[13]. The 2 trials with the lowest birth rates with ASA only treatment[13,14] were among the earliest completed with this population, and were also among those few that have reported a significant benefit for heparin and ASA over ASA alone. Their findings helped to establish the current standard of care that continues to recommend the use of LMWH/ASA for women with RPL and aPL.

However, the results from our HepASA trial add to a growing body of evidence reported since 2000[16,17,40,41] that does not support the use of LMWH plus ASA over ASA alone in this population. We agree with Gates, et al[42], who concluded after a thorough literature review, that for women with aPL, RPL, and no prior history of thrombosis, there is insufficient evidence to base recommendations for thromboprophylaxis in pregnancy.

ACKNOWLEDGMENT

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