Obstetric Medicine
Obstetric Medicine
2016, Vol. 9(2) 83–89

DOI: 10.1177/1753495X16629300
obm.sagepub.com
SAGE

Pregnancy outcomes of antiphospholipid syndrome: In a low resource South Asian setting

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Abstract

Problem: Antiphospholipid syndrome is associated with recurrent pregnancy loss, and specific treatment improves pregnancy outcome. Laboratory diagnosis is limited in South Asia. We assessed management outcomes of definite/probable antiphospholipid syndrome treated at a tertiary centre in Sri Lanka.

Method: Descriptive cross-sectional study of pregnancy outcomes with heparin and aspirin therapy. Outcome measures: miscarriage, intrauterine death and live birth when compared to previous untreated pregnancies.

Results: Of 646 gestations in 145 women, 146 (22.6%) received specific treatment. In the preceding pregnancies without specific treatment, the rates of miscarriage, late fetal loss, stillbirth and live birth were 60%, 26%, 8% and 7%, respectively. Following specific treatment with low-dose aspirin ± low-molecular weight heparin in 146 pregnancies (145 women), the rates of miscarriage, late fetal loss, stillbirth and live birth were 14%, 10%, 3% and 74%, respectively. Mean birth weight was 2.54 ± 0.62 kg, preterm births complicated 32 (29.6%) with a mean gestational age at delivery 33.7 ± 2.6 weeks, with three neonatal deaths. Maternal complications were: pre-eclampsia 16 (10.9%), gestational diabetes 28 (19.2%), antepartum haemorrhage in 1 patient. Only 73/145 (50.3%) women had laboratory confirmation of antiphospholipid syndrome, while others were treated empirically. Live births in diagnosed vs. empiric treatment – 80.8% vs. 67.1%.

Conclusion: Pregnant women with clinical antiphospholipid syndrome when treated with low-dose aspirin and heparin, the live birth rate of 7% in the previous pregnancy resulted in live births of 74% in a resource limited South Asian setting.

Keywords

Heparin, low-dose aspirin, recurrent pregnancy loss, Sri Lanka

Date received: 12 May 2015; accepted: 5 January 2016

Introduction

Antiphospholipid syndrome (APLS) is characterized by the presence of antiphospholipid antibodies (APAs) and arterial/venous thrombosis and/or pregnancy complications.[1] Lupus anticoagulant (LA), anticardiolipin antibodies (aCL) and anti-beta 2 glycoprotein 1 (anti-β2GP1) antibodies are the key antibodies helpful in confirming APLS.[2,3] In pregnancy, these antibodies can cause miscarriage, intrauterine growth restriction (IUGR) and/or fetal death with an increased incidence of pre-eclampsia.[4] The syndrome can present as primary APLS in the majority (53.1%), but may be associated with other autoimmune diseases, most often systemic lupus erythematous (SLE) (36.2%).[5] APLS occurs mostly in women of reproductive age,[6] is rare among children with 12% occurring after 50 years of age.[7]

To diagnose APLS at least one clinical criterion (vascular thrombosis or pregnancy morbidity) and one of the laboratory criteria should be fulfilled. According to the initial International Consensus guidelines for APLS (Sapporo, 1999),[8] the pregnancy morbidity can be: (1) one or more unexplained deaths of normal fetuses at or beyond the 10th week of gestation, or (2) one or more premature births before the 34th week of gestation because of eclampsia, severe pre-eclampsia, or placental insufficiency, or (3) three or more unexplained consecutive spontaneous miscarriage before the 10th gestational week. Laboratory evidence can be aCL of IgG and/or IgM type or LA. Transient occurrence of APAs may not be associated with APLS. Therefore, it is essential to repeat the tests after at least 12 weeks to confirm diagnosis as per revised in Sapporo in 2006.[6]

The laboratory confirmation of APLS in the state health sector of Sri Lanka that delivers a free service is sub optimal, along with a comprehensive pre-conception package being introduced only very recently in the country. This has greatly hampered the ease and accuracy of confirming APLS and thereby instituting specific therapy. Over the previous decade, the paucity of laboratory confirmation of APLS in Sri Lanka has led clinicians to opt for empiric treatment of ''probable APLS'' as a cause for previous pregnancy loss or as a complication of maternal SLE.

Systematic review of therapeutic trials identified that combination therapy with heparin and aspirin reduces pregnancy failures in women with APLS by 54% and that combination therapy in some studies has a better effect than prescribing aspirin alone.[9] There is paucity of South Asian data on pregnancy outcomes following specific treatment for pregnancies complicated by APLS.

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We present the analysis of pregnancy outcomes in a cohort of Sri Lankan women with confirmed or presumed APLS treated with low-dose aspirin and heparin, in a single unit in a tertiary care center.

Materials and methods

The study was approved by the Ethics Review Committee, Faculty of Medicine, University of Colombo. All women with probable APLS attending the Medical Clinic, University Obstetrics and Gynaecology Unit, De Soysa Hospital for Women (DSHW), Colombo, Sri Lanka, from April 2003 to September 2012 were considered eligible to be recruited. This obstetric medical service is the main referral centre of Sri Lanka in the state health sector for medically complicated pregnancies and has a dedicated service for treating complicated antenatal mothers through multidisciplinary inputs over the past two decades. Antiphospholipid syndrome was diagnosed according to the Sapporo Criteria, 1999[8] until the revised version 2006[6] was applied in 2007.

Data collection

Women with pregnancies complicated by presumed or confirmed 'APLS' were recruited after verbal informed consent to participate in the study. Data collection was done retrospectively initially and prospectively from 2004 by medical graduates not directly involved in patient management through a questionnaire-based interview and study of clinic and patient records. Collected data included socio-demographics, detailed past obstetric and gynaecological histories, medical histories with details of thrombotic events and associated autoimmune disease, drug history and family history. Physical examination focused on resting blood pressure (BP) and cardio vascular system, skin rashes, pallor, alopecia and arthropathy. Immunological investigation results were also recorded and entered into a computerized database.

Outcomes

The clinical presentation and obstetric outcome were measured along with the type of delivery, period of gestation at delivery, weight for gestational age and maternal and neonatal complications following delivery. Maternal co-morbidities together with investigations were also recorded.

Statistical analysis

Statistical Package for Social Sciences (SPSS) version 16 for Windows (SPSS Inc., Chicago, USA) was used for statistical analysis. The outcome measures, live birth, early/late miscarriages, intrauterine deaths and the co-morbidities were compared between the two groups (previously untreated vs. treated with low-dose aspirin and heparin). The live birth rates in the two groups without laboratory evidence and with laboratory evidence for APLS were also compared.

Results

Socio-demography

A total of 145 women were recruited during the study period. The total number of confirmed gestations was 646, of which 146 (22.6%) gestations were treated. The median (IQR) number of gestations was 4 (±2) per person. The mean age of the study sample was 31.6 ± 5.3 years. Ninety-four (64.8%) women had a confirmed intrauterine pregnancy at the time of recruitment (mean period of amenorrhoea (POA) 10 weeks), while 24 (16.6%) were recruited prior to conception and the remaining 27 had biochemical confirmation of pregnancy (mean POA six weeks).

Table 1. Previous medical events reported in the study population.

Diagnosis	Frequency of population affected (percentage)
Deep vein thrombosis (DVT)	10 (6.9)
Stroke	4 (2.8)
Cerebral vein thrombosis (CVT)	3 (2.1)
Transient ischaemic attacks (TIA)	3 (2.1)
Myocardial infarction (MI)	1 (0.9)
Systemic lupus erythematosus (SLE)	8 (5.5)
Type 2 diabetes mellitus (DM)	4 (2.2)
Chronic hypertension	8 (5.5)
Valvular heart disease	9 (6.2)
Migraine	8 (5.5)
History of seizures	5 (3.4)
Hypothyroidism	3 (2.1)

Medical history

Twenty-one (14.5%) of the study population had a recorded history of previous thrombosis. Table 1 displays the previous medical events in 145 women. SLE and hypertension were the commonest associated medical problems. None with chronic hypertension had features of SLE.

Family history

A family history of miscarriage in a first-degree relative was reported by 13 (9%) women, while stroke occurred in 10 (6.9%) and ischaemic heart disease in 9 (6.2%). A total of 51 (35.2%) had type 2 diabetes mellitus (DM) in a first-degree relative and 49 (33.8%) had chronic hypertension. Family history of both DM and hypertension was reported in 24 (16.5%) of the total cohort.

Gynaecological history

Endometriosis was diagnosed in three, while three others had polycystic ovary syndrome. Three had primary subfertility and five had secondary subfertility.

Figure 1 displays the modes of presentation of these 145 women to our unit. The majority, 86 (59.3%), presented with ≥ 3 consecutive miscarriages. There were 31 (21.3%) who had at least one late miscarriage but not ≥ 3 consecutive miscarriages.

Index pregnancy receiving specific treatment

The index pregnancy was considered as the first pregnancy where specific treatment with heparin and/or aspirin was commenced. The majority, 41 (33.3%), of women received specific treatment in their fourth pregnancy. Of the 145 women, among those who received aspirin ($n = 116$), the majority (69.3%) commenced in the first trimester of the index pregnancy at a median POA of 8 weeks (range 6–10 weeks) and in 16.7% from pre-conception.

One hundred and two (70.3%) received heparin with aspirin (75 mg daily) from the time of pregnancy confirmation; when aspirin was commenced in the majority at a median of 8 weeks gestation and heparin at a median of 10 weeks (range 9–12 weeks) following the confirmation of intrauterine pregnancy. Seven (4.8%) received heparin alone in those with a history of aspirin allergy or intolerance and 14 (9.7%) received aspirin alone due to the non-availability of

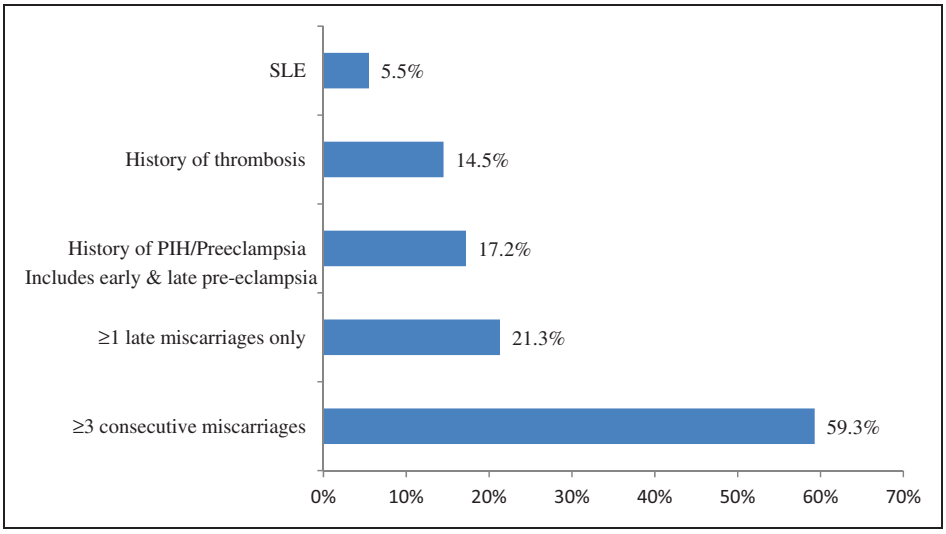

Figure 1. Modes of presentation of pregnant mothers with APLS to University Obstetrics and Gynaecology Unit, Colombo.

low-molecular weight heparin (LMWH) at antenatal clinic at booking. Of the 109 who received heparin (with/without aspirin), four received unfractionated heparin (UFH) and all others received LMWH – Tinzaparin 3500 IU subcutaneously daily.

Investigations

Only 73/145 (50.3%) had clear laboratory evidence to confirm APLS. Due to limited facilities for high cost-specific investigations, the rest were treated empirically with aspirin and heparin as determined by the lead clinician (CNW). Prolonged prothrombin time (PT) was seen in 33/105 (31.4%) and prolonged activated partial thromboplastin time (APTT) in 27/99 (27.2%). Dilute Russell's Viper venom time (DRVVT) was positive in 53/112 (47.3%); Kaolin clotting time (KCT) in 18/64 (28.1%) and aCL positive in 25/78 (32%). Twelve of 74 (16.2%) tested were positive for anti-nuclear factor (ANF), while 8/48 (16.7%) were positive for Anti-dsDNA antibodies. Sera of 15 randomly selected women receiving empiric treatment with no supporting local laboratory testing in Sri Lanka were re-tested in a reference laboratory (UK), the results of which were as follows: all 15 were positive for one or more specific auto-antibody viz. AnnexinV:IgG positive – 2, IgM positive in – 3, anti-β2 glycoprotein 1:IgG in 4, IgM in 2. Phosphatidylinositol positive – 12, phosphatidyl ethanlamine positive – 5, phosphatidyl serine positive – 12. Thrombocytopenia (platelets $< 100 \times 10^9$/L) occurred in 4 (3.4%), and none of them had spontaneous bruising.

Previous pregnancy outcome without specific treatment

At least one miscarriage had occurred in the past in 129 (89%) of the women and 86 (59.3%) had recurrent miscarriages. Early miscarriage (<10 weeks) occurred in 299/500 (59.8%) gestations, while late miscarriage occurred in 129 (25.8%). Intrauterine death occurred in 39 (7.8%) gestations without specific treatment. Pregnancy outcomes immediately preceding the currently reported index pregnancy in the 145 women were: an early first trimester miscarriage in 89 of whom 64 had a first trimester recurrence, late miscarriage (>10 weeks) in 43 of whom 12 had a recurrence, intrauterine deaths complicated by fetal growth restriction in 13 with 8 being complicated by early (<34 weeks) pre-eclampsia and no live birth. Three women had a live birth few gestations before but followed by recurrent pregnancy loss.

Of the 500 untreated previous gestations in 145 women, three had neonatal deaths (two complicated by pre-eclampsia/eclampsia and prematurity and one developed fetal distress at 36 weeks requiring emergency lower segment cesarean section (LSCS). Among the live births, 18 (54.5%) were delivered vaginally and 15 (45.5%) by LSCS, of which 10 were emergency LSCS. Severe pre-eclampsia/eclampsia, fetal distress and obstructed labour were some of the indications for LSCS. There were five elective LSCS, the indications for which were abnormal lie and oligohydramnios. Mean birth weight among those not treated specifically was 2.54 ± 0.70 kg. Figure 2 displays the number of living children among those women before receiving any treatment.

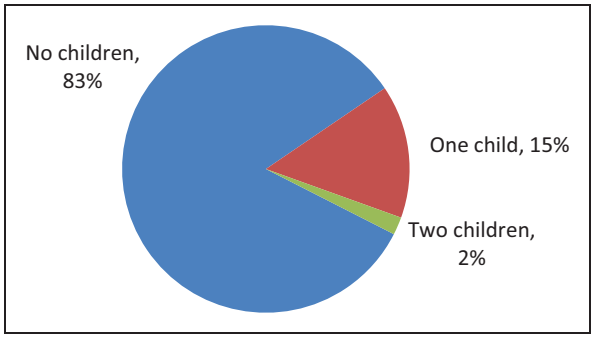

Figure 2. Percentage of number of living children before receiving specific treatment.

Pregnancy outcomes following specific treatment

Of 146 treated gestations, 20 (13.6%) had a recurrence of early miscarriage, 14 (9.6%) had late miscarriage, 4 (2.8%) had intrauterine deaths and 108 (74%) had a live birth. Figure 3 displays the comparison between the two groups. There were 38 (35.2%) live births by vaginal delivery and 64.8% by LSCS, of whom 27.1% were by emergency LSCS due to fetal distress and IUGR, or severe pre-eclampsia. There was one placental abruption. The majority of elective LSCS were due to previous bad obstetric outcome and maternal request at mean gestation of 37.4 ± 0.99 weeks. In the elective LSCS group, 12.9% had undergone a previous LSCS. Gestational diabetes mellitus, fetal macrosomia, breech presentation were other indications for LSCS. The majority (33%) of treated gestations were delivered at 38 weeks. There were 32 (29.6%) preterm deliveries due to severe pre-eclampsia,

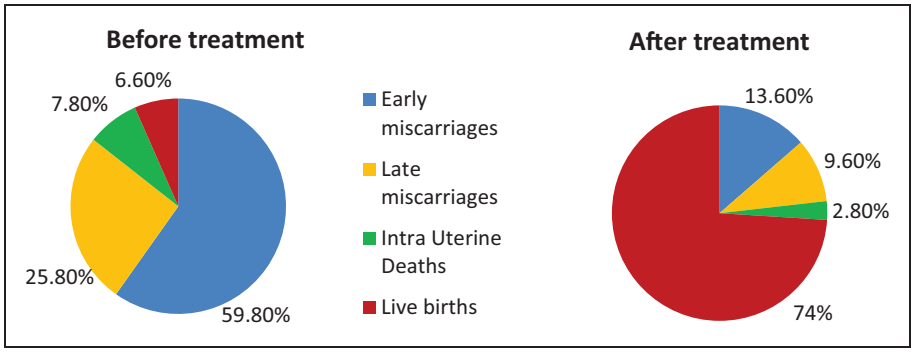

Figure 3. Comparison of pregnancy outcomes before and after treatment.

Table 2. Co-morbidities in previous untreated and current treated gestations.

Co-morbidities	Previous pregnancies without specific treatment (n = 500)	Index pregnancy on specific treatment (n = 146)
PIH/pre-eclampsia (early and late)	19 (3.8%)	16 (10.9%)
Eclampsia	2 (0.4%)	None
GDM	7 (1.4%)	28 (19.2%)
DVT	10 (2.0%)	None
CVA	7 (1.4%)	None
MI	1 (0.2%)	None

PIH: pregnancy induced hypertension; GDM: gestational diabetes mellitus; DVT: deep vein thrombosis; CVA: cerebro vascular accident; MI: myocardial infarction.

Table 3. Pregnancy outcomes in previous untreated and current treated gestations.

Pregnancy outcomes of gestations	Previous pregnancies without specific treatment (n = 500) (%)	Index pregnancy on specific treatment (n = 146)
Early miscarriages	299 (59.8%)	20 (13.6%)
Late miscarriages	129 (25.8%)	14 (9.6%)
Intrauterine deaths (<34 weeks POA)	39 (7.8%)	4 (2.8%)
Live births	33 (6.6%)	108 (74.0%)

POA: Period of Amenorrhoea.

preterm pre-labour, rupture of membranes (PPROM), fetal distress and severe IUGR. The average gestation of preterm delivery was 33.7 ± 2.6 weeks.

There were three neonatal deaths, all being delivered at 28 weeks due to severe pre-eclampsia. One was diagnosed to have a congenital heart defect. Mean birth weight of the treated gestations was 2.54 ± 0.62 kg. There were 39 (36%) who had a birth weight <2.5 kg, but with insufficient data to help explain all contributory causes.

The co-morbidities identified in treated but failed pregnancies (total 38) were GDM (n = 3), SLE (n = 2) and early pre-eclampsia (n = 2), while the others had no clear cause. One patient had a placental abruption. None had bleeding manifestations antepartum nor postpartum. There was no venous thromboembolism, and allergic reactions to heparin occurred in three treated with a generic UFH who thereafter were converted to LMWH (Tinzaparin) with no further problem.

Tables 2 and 3 compare medical co-morbidities and pregnancy outcomes respectively of pregnancies receiving specific therapy for the index pregnancy with those not treated previously.

Table 4 compares live birth outcomes of previous gestations and of the index pregnancy in the two broad categories of women with laboratory confirmation and without laboratory evidence of APLS. Both groups had similar improved pregnancy outcomes. Live birth rates following specific treatment for those with laboratory confirmation vs. without laboratory evidence of APLS, had similar improvement.

Discussion

To the best of our knowledge this is the first report from South Asia that shows treatment with aspirin and/or heparin for women presenting with past pregnancy loss due to confirmed or presumed APLS resulting in a live birth rate of 74% compared to 7% previously when not treated during pregnancy. Our study also illustrates the practical issues encountered with confirming the diagnosis and provides a basis for empiric antenatal treatment of APLS. We also highlight practical problems encountered in a resource limited lower middle-income country.

Within the study population, 14.5% had a previous history of thrombosis which satisfies the diagnostic clinical criteria for APLS.[6] Serrano et al.[10] stated that 35.3% of the population had previous thrombotic events in their study. This difference may be due to our study sample consisting of obstetric patients with APLS with a bias towards recurrent pregnancy loss. Deep vein thrombosis was the commonest thrombotic event reported in our study group. In a similar study on primary antiphospholipid syndrome in Latin America, the commonest thrombotic manifestation was deep vein thrombosis.[11]

It is noteworthy that the majority had specific treatment commenced only in their fourth pregnancy, with significant improvement in pregnancy outcome following the institution of low-dose aspirin and heparin. This observation brings into question the usual approach towards confirming 'recurrent miscarriages' that suggests the diagnosis of APLS must await three consecutive miscarriages, which is the likely cause for most women to be referred to our specialized centre in their fourth or later gestation. However, several studies have failed to demonstrate a reduction in pregnancy loss with the use of antithrombotic treatment for pregnant women with two previous miscarriages, which must caution us.[12,13] Identification of the real reasons for the delay in diagnosis was not adequately approached in our study but should be given due attention in future research. During the treatment for APLS, aspirin and heparin combination was used in the majority of patients. In a randomized control trial of aspirin versus combination therapy, it was found that combination therapy improves the outcome compared with that achieved with monotherapy.[14] This may have contributed to the improved pregnancy outcome in our setting. Since over 95% of Sri Lankan women have biochemical confirmation of pregnancy and

Table 4. Comparison of live birth rates between the two groups; with laboratory evidence and without laboratory evidence for APLS.

Outcomes	Clear diagnosis of APLS with laboratory evidence fulfilling Sapparo criteria	Equivocal diagnosis without complete laboratory evidence
Live births – no previous specific treatment	17 (7.5%) n = 307 gestations	16 (5.9%) n = 339 gestations
Live births – receiving specific treatment	59/73 (80.8%)	49/73 (67%)
Mean birth weight – with specific treatment	2.43 ± 0.63 kg	2.65 ± 0.57 kg
Low birth weight – with specific treatment	46.1%	25%

APLS: antiphospholipid syndrome.

register for maternal care by trained health staff in the first trimester, and these high risk women being able to walk in and report a pregnancy to our weekly high risk clinic, enabled the commencement of low-dose aspirin at 8 weeks in the majority. Those followed up by our clinic were prescribed aspirin from pre-conception (17%). This may have resulted in the early and late miscarriage rates being reduced from 59.8% to 13.6% and 25.8% to 9.6%, respectively. It is noteworthy that we did not encounter an increased risk of haemorrhage among those who miscarried despite specific treatment in the index pregnancy.

However, measuring the outcome of each treatment regime was not possible due to small sample size of each monotherapy arm. LMWH was used in most, with three receiving UFH at the inception of specific treatment in 2003 that led to allergic manifestations. In a study conducted in India comparing UFH and LMWH, it was found that both were effective in recurrent pregnancy loss.[15] However, LMWH has the advantage of not requiring laboratory monitoring and easy once daily administration. Significant bleeding manifestations from LMWH were also not reported.

In our cohort, the specific treatment resulted in an increased live birth rate from 6.6% to 74%. A prospective observational study carried out in a university-based tertiary referral clinic in London, United Kingdom reported a 71% live birth rate with treatment using low-dose aspirin and heparin.[16] In another study of a cohort of Portuguese women attending a recurrent miscarriage clinic, the live birth rate with specific therapy was 85.1%.[10] Thus, it is reasonable to conclude that our own cohort achieved a significant and comparable improvement in pregnancy outcome despite an empiric approach to specific treatment for APLS in those with no supportive laboratory evidence due to resource limitations.

Defective decidual endovascular trophoblast invasion was found to be the most frequent cause of APLS-associated early pregnancy loss in a study which examined products of conception from early pregnancy loss.[17] This explains the highest rate of pregnancy failures occurring in early gestation. It is reasonable to assume that the significant reduction of early miscarriage, late miscarriage and intrauterine death rates in our cohort was due to the specific therapy improving placentation and function. It is noteworthy that the majority presented with three or more consecutive spontaneous miscarriages (59.3%), with a considerable proportion having had one or more late miscarriage (21.3%) in the absence of recurrent miscarriage. Specific treatment was associated with an increase of the operative delivery rate from 45.5% to 64.8%, similar to other reports of a LSCS rate of 59% in those with primary APLS receiving specific treatment.[18] The majority of our cohort who delivered live babies required elective LSCS and were delivered at 38 weeks. This can be explained by the previous pregnancy loss being the most common complication that encouraged the categorization as a high-risk group. Amongst those who required emergency LSCS, the majority was due to fetal distress and pre-eclampsia leading to preterm delivery (29.6%), and comparable to 25% observed among a cohort managed in a resource sufficient setting.[19]

The mean birth weight among the treated pregnancies in our sample was 2.54 ± 0.62 kg, with 36% being low birth weight, with no neonatal deaths among them. In a similar report from the United Kingdom that assessed pregnancy complications of APLS receiving specific treatment, there was a low birth weight rate of 15%.[16] This difference may be explained by inadequate documentation of co-morbidities, ethnic disparities of growth, differences in maternal BMI and hitherto unknown factors. It is interesting that we could not identify any major causative factor in the majority of failed pregnancies despite specific treatment. Hence, a more detailed study is required to identify the cause for such failures by the study of placentae and a search for chromosomal abnormalities, etc. There was one patient in our cohort who developed placental abruption, while on treatment and was delivered prematurely. A study in a developed country reported there was 7% rate of antepartum haemorrhage.[14]

Occurrence of PIH/pre-eclampsia and eclampsia in our treated group of pregnancies was 10.9%. In a similar study in the UK, gestational hypertension complicated 17% of pregnancies,[16] which is higher than our own cohort. When compared to previously untreated gestations more were found to have PIH/pre-eclampsia and gestational diabetes mellitus in the treated group of gestations, which can be explained by the early pregnancy losses in previous pregnancies being too early for gestational diabetes and PIH/pre-eclampsia to manifest, whereas those treated with aspirin and heparin had improved placental growth that possibly facilitated the development of glucose intolerance. Nevertheless, we must bear in mind possible confounders such as higher maternal age and BMI to explain this observation in an ethnic group with a high prevalence of type 2 diabetes in family members (33.4%) as seen in this cohort. Clinical manifestations due to thrombosis have not occurred after treatment when compared with previous gestations, which also supports the improved outcomes of specific treatment. APAs are also associated with thrombocytopenia as well as early pregnancy loss.[20] In our study, thrombocytopenia (platelets $< 100 \times 10^9$/L) was observed in 3.4% with no episodes of spontaneous bruising or bleeding, while in a study conducted in London, thrombocytopenia was observed in many more (23.4%).[21]

The two tests for APLS used in our cohort were LA and aCL. But there are others such as antibodies against β2GP1, prothrombin, annexin, phosphatidyl ethanolamine and phosphatidyl inositol, which are responsible for the pathology of APLS and can aid in the diagnosis.[22] The latter, however, are unavailable routinely and therefore not tested in Sri Lanka due to funding constraints. In our cohort, only half of the population fulfilled the laboratory criteria for the diagnosis of APLS as per revised Sapporo criteria of 2006. Hence, the remainder with equivocal diagnosis due to laboratory constraints was treated empirically after exclusion of other causes of pregnancy loss and taking into account the obstetric history. It is noteworthy that the 15 serum samples of the group receiving empiric treatment when tested in a reference laboratory in the UK proved positive for one or more specific antibodies of APLS. Therefore, it is reasonable to conclude that the entire cohort had APLS. Additionally, both groups of women with confirmed APLS and those empirically treated had a comparable live birth rate with a marked increase from their pre-treatment pregnancy outcomes. This further supports our conclusion that the group treated on an empiric basis also had APLS. This calls for a high degree of clinical suspicion in the patient management in resource-limited settings similar to ours.

In summary, we found the application of sound clinical judgment with cost-effective medications helped markedly improve pregnancy outcomes in our APLS patients.

Acknowledgements

Our sincere thanks and appreciation are extended to the following institutions and individuals for their assistance towards success of the research: Medical officers, Nurses and Staff at Medical clinic, University Obstetrics and Gynaecology Unit, De Soysa Hospital for Women (DSHW), Colombo, Sri Lanka. Director, De Soysa Hospital for Women (DSHW), Colombo, Sri Lanka. Dean of the Faculty of Medicine, Colombo. Head and support staff of Department of Obstetrics and Gynaecology, Faculty of Medicine, University of Colombo. Patients and their families. We confirm the authenticity of this clinical research work and certify that these data have not been published elsewhere nor are currently under consideration for publication elsewhere. With the submission of this manuscript we would like to undertake that all authors of this research paper have directly participated in the planning, execution or analysis of this study; all authors of this paper have read and approved the final version submitted.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethical approval

Ethical approval was obtained by the Ethics Review Committee, Faculty of Medicine, University of Colombo. All women with probable APLS attending the Medical Clinic, University Obstetrics and Gynaecology Unit, De Soysa Hospital for Women (DSHW), Colombo, Sri Lanka from April 2003 to September 2012 were considered eligible to be recruited. Recruitment was done after obtaining verbal informed consent to participate in the study.

Guarantor

CNW

Contributorship

CN Wijeyaratne – clinical lead on medical management who conceptualized the research objective and methodology, supervised data collection and analysis.

SLA Galappaththi – carried out data collection to completion and did most of the data analysis and writing up of this paper.

E Palipane – initiated the data collection and data entry.

DBIA Jayawardane – obstetrician who co-supervised the data analysis and writing.

SH Dodampahala – gave obstetric support and performed serial fetal scanning.

MN Tudawe – initiated the important laboratory support of lupus anticoagulant testing and provided haematology support.

LV Gooneratne – lead clinical haematologist.

R de Silva – lead clinical immunologist and supervised the laboratory testing at MRI.

D Ratnayake – carried out laboratory testing at MRI.

SL Seneviratne – collaborated in testing samples for the immunology panel at Nottingham University Hospitals and helped establish the beta 2 glycoprotein 1(β2GP1) testing at MRI.

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