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ORIGINAL ARTICLE

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Neonatal Outcomes of Women with Recurrent Pregnancy Loss from Immunologic Causes in the Philippine General Hospital from 2010-2015

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ABSTRACT

Background: Recurrent pregnancy loss (RPL) has been classically defined as three consecutive pregnancy losses, which may be associated with several immunologic and non-immunologic etiologies. There are two immunologic mechanisms, autoimmune or alloimmune, of RPL that have drawn much interest in recent years. The direct effects of these immunologic dysregulations on the clinical outcomes of children born from mothers afflicted with Antiphospholipid Antibody Syndrome (APS) or alloimmune causes still need further investigation.

Objective: To determine the neonatal outcome of infants born from mothers with RPL from immunologic causes at the Philippine General Hospital (PGH) from 2010-2015. Pregnant women with RPL from immunologic causes are classified as high-risk pregnancies. The results of this study hope to guide physicians in close monitoring and early intervention of mothers with RPL and their neonates.

Methodology: This was a retrospective study of neonates born from mothers diagnosed to have immunologic causes of RPL from 2010-2015 at the PGH. All patients born from mothers diagnosed to have an immunologic cause of RPL from 2010-2015 based on the patient database of the section of Allergy and Immunology of the PGH.

Results: The prevalence of neonates born from mothers with RPL from identified immunologic causes and unexplained causes among all infants born at the PGH from 2010 to 2015 is 0.18%. There were 5.1% of the neonates that were classified as Classical APS, 63.8% as Obstetric Morbidity associated with Antiphospholipid Antibody Syndrome (OMAPS), and 31% had an unexplained cause. There were no cases classified under other immunologic causes. Most neonates under Classical APS were born live, full-term, via cesarean delivery with a mean birth weight of 2206 ± 539.48 grams with APGAR Score (AS) of 9 and 9. The majority of the neonates under OMAPS were born live, full-term, via cesarean delivery with a mean birth weight of 2537 ± 737.46 grams and AS of 9 and 9. Most of the neonates under the unclassified cause of RPL were born live, full-term via cesarean delivery with a mean birth weight of 2228.75 ± 887.05 grams and an AS of 9 and 9.

Conclusion: The majority of these infants born from mothers with RPL from immunologic or unexplained causes had a good birth outcome. Hence, the immunologic cause of RPL has minimal effects on the neonate.

Keywords: recurrent pregnancy loss, antiphospholipid syndrome, obstetric morbidity APS

INTRODUCTION

Rationale

Recurrent pregnancy loss (RPL) has been classically defined as three consecutive pregnancy losses prior to 20 weeks from the last menstrual period.[1] Recently, however, there have been studies that suggest a role for evaluating the cause of RPL in patients with no prior live births but only two consecutive pregnancy losses. This is supported by data showing a similar risk of subsequent miscarriages after two and three losses of 30% and 33%, respectively.[1] The American Society for Reproductive Medicine, thus, has defined RPL as two or more failed pregnancies.[2]

There are several etiologic factors associated with RPL, such as (a) endocrine factors (i.e., untreated hypothyroidism, uncontrolled diabetes mellitus); (b) anatomic factors (i.e., certain uterine anatomic abnormalities); (c) genetic factors (i.e., parental chromosomal abnormalities); (d) infections (i.e., cytomegalovirus, rubella, and herpes simplex virus infections); and (e) immunologic causes (i.e., antiphospholipid syndrome or APS). Despite a thorough evaluation of these cases, 40-50% of cases would remain unexplained.[1]

During pregnancy, several immunologic events occur which protect the fetus from rejection. There are several immunologic mechanisms for fetal tolerance that have been documented and proposed, such as a predominance of humoral response, which counteracts the rejection reaction towards the fetus via prevention of complement cell-mediated lysis, the predominance of Th2 response preventing anti-trophoblast cytotoxic reactions and decidual NK cells which are involved in cytokine-mediated immune regulation of maternal immune response resulting to local immunosuppression.[3] Carp et al., characterized immune-mediated abortions as either autoimmune or alloimmune.[3]

Autoimmune abortions involve maternal autoantibodies and autoreactive cells that target decidual and trophoblastic molecules, affecting the embryo's development. One of the most commonly associated autoimmune causes of RPL is APS. It is an autoimmune disorder characterized by the presence of antiphospholipid autoantibodies (aPL) directed against decidual and trophoblastic molecules. The presence of such autoantibodies has been associated with a wide range of diseases, including venous and arterial thromboembolic diseases, rheumatic and connective tissue disorders, some infections, lymphoproliferative diseases, and other autoimmune diseases. A major feature of APS is recurrent miscarriages and its prevalence has been reported to be between 7% and 42% among women with RPL.[1] The presence of other autoantibodies such as ANA and antibodies against single- and double-stranded DNA, histones or non-DNA nuclear components, and anti-thyroid antibodies (thyroglobulin and thyroid peroxidase) have also been observed in some women with RPL.

Alloimmune abortions involve allogenic rejection-type reactions between the maternal immune system and the embryo causing damage to the trophoblasts. In alloimmune abortions, the embryo is described to be "rejected" by the mother as it is noted to be infiltrated with lymphocytes. The lesions found in the placenta are similar to allogenic reactions seen in transplanted grafts. The mechanisms behind these pregnancy losses are due to a predominant T-helper 1-type (TH_1) response secreting proinflammatory cytokines such as IL-2, Interferon-Υ, and tumor necrosis factor-α, which adversely affects embryo development. Rejections occur due to immune-induced inflammation, tissue degradation, and coagulation. Furthermore, decidual NK cells are stimulated by TH_1 cytokines and cause direct damage to the trophoblast by releasing cytolytic substances.

Alloimmune and autoimmune mechanisms of RPL have drawn much interest in recent years. The autoimmune causes of RPL, particularly APS, have been well-studied with several therapeutic approaches developed. On the other hand, knowledge of the pathophysiology, diagnostics, and therapeutics of alloimmune causes of RPL is still lacking. Furthermore, the direct effects of these immunologic dysregulations on the clinical outcomes of children born from mothers afflicted with APS or alloimmune causes still need further investigation. Locally, there is no published study on the neonatal outcomes of mothers with RPL secondary to immunologic causes.

OBJECTIVES

General Objective

To determine the neonatal outcome of infants born from mothers with RPL from immunologic causes at the Philippine General Hospital (PGH) from 2010-2015.

Specific Objectives

1. To determine the prevalence of neonates born from mothers with RPL from immunologic causes among all infants born in the PGH from 2010-2015.
2. To determine the prevalence of neonates born from mothers with antiphospholipid antibody syndrome, obstetric morbidity associated with antiphospholipid antibody syndrome (OMAPS), and other immunologic causes among all infants born from mothers with RPL from immunologic causes in PGH from 2010-2015.
3. To describe the following outcomes of infants born from mothers with RPL:
    - perinatal outcome (live or stillbirth)
    - neonatal outcome (preterm, full-term or post-term; manner of delivery; pediatric age upon delivery; APGAR score upon delivery)

- birth anthropometrics (birthweight, appropriateness of weight for gestational age, head circumference)
- morbidity (neonatal pneumonia, neonatal sepsis, others)
- necessitated neonatal intensive care unit admission

Significance of the Study

RPL from immunologic causes such as APS has been associated with serious morbidity in both the mother and the fetus, such as preeclampsia, eclampsia, abruptio placentae, abortions, fetal deaths, intrauterine growth restriction, and prematurity. As such, pregnant women diagnosed to have RPL from immunologic causes are classified as high-risk pregnancies. Hence, close monitoring of both the mother and the fetus is of importance. The information gathered in this study will hopefully guide physicians in close monitoring and early intervention of mothers with RPL. Furthermore, this study also aims to provide information that will be essential to pediatricians in closely monitoring of babies born from mothers with RPL due to immunologic rejection. Close monitoring of the outcomes of babies born from these mothers will aid in the early detection of medical problems and thereby also aid in providing early intervention.

Review of Related Literature

The Practice Committee of the American Society for Reproductive Medicine has recognized the rate of recurrence of RPL at 15-25%.[4] Furthermore, the same committee has 'estimated that fewer than 5% of women will experience two consecutive miscarriages, and only 1% experience three or more.[4]

A study on the reproductive outcome in pregnant women with RPL compared the pregnancy success rate of women with RPL to a control group.[5] They found that in women with RPL treated with aspirin and low-molecular-weight heparin, the success rate was 91.2%, comparable to the control group's success rate (96.7%). In another study in the UK, they also found similar obstetric and neonatal outcomes between women with RPL and healthy women.[6] This study also showed that the rates of preterm delivery, small-for-gestational-age, and cesarean deliveries were significantly higher than those for the control group.

The prognosis for RPL depends on the underlying cause of pregnancy loss and the number of previous losses.[1] As mentioned earlier, there are several etiologies for RPL which may be broadly classified as immunologic and non-immunologic (Table 1). Among the different autoimmune causes of RPL, aPL was the predominant autoantibody detected.[3] In autoimmune causes of RPL, several foreign studies describing the neonatal outcome of women with

Table 1. Immunologic Versus Non-immunologic Causes of RPL

Non-immunologic Causes	Immunologic Causes
Genetic	Autoimmune
Anatomic	Alloimmune
Endocrinologic	
Environmental	
Unclassified	

APS have been published.[1,6-11] APS may be diagnosed when arterial or venous thrombosis or recurrent miscarriage occurs in a subject whose laboratory tests for aPL are positive'.[7] These aPL need to be persistently positive, as they may be transiently present in the aforementioned disease states. Antiphospholipid antibodies may appear in different scenarios such as (1) asymptomatic "carrier"; (2) "classical" APS with RPL; (3) patients with RPL; (4) patients with non-thrombotic manifestations; and (5) catastrophic APS.

In 2006, Miyakis et al., revised the classification criteria for APS, otherwise known as the Sydney Criteria (Table 2).

In a study done by Cervera et al., an analysis of the prevalence and characteristics of the clinical and immunologic manifestations of APS in 1000 patients was done.[9] This study has shown the diversity of the clinical and laboratory findings of patients with APS, making it difficult to make a precise diagnosis. The findings of this study were consistent with other studies in terms of the prevalence of the major clinical manifestations, which are as follows: deep venous thrombosis (38.9%), stroke (19.8%), pulmonary embolism (14.1%), superficial thrombophlebitis in the legs (11.7%), transient ischemic attacks (11.1%) and obstetric, both fetal and maternal, morbidity. This study also identified that the most common fetal complications are early fetal loss, late fetal loss, and premature birth.

In recent years, the focus has been on the obstetric manifestations of APS. In the preliminary first-year report of the European Registry on Obstetric APS, women were classified as either obstetric antiphospholipid antibody syndrome (OAPS) or obstetric morbidity associated with antiphospholipid antibody syndrome (OMAPS).[10] Women with inflammation and/or thrombotic events occurring in the placenta without systemic thrombosis are classified as OAPS, while women who do not fulfill criteria for APS but present with antiphospholipid antibody-related obstetric complications, such as late preeclampsia, placental abruption, late premature birth, etc., are classified as OMAPS. The European Registry on Obstetric Antiphospholipid Antibody Syndrome (EUROAPS) in 2014 found evidence that the laboratory markers, treatment response, maternal complications, and long-term follow-up of patients with purely obstetric APS may differ from those observed in classical APS.[10] It was also suggested that

Table 2. Revised Classification Criteria for Antiphospholipid Syndrome

Antiphospholipid Antibody Syndrome (APS) is present if at least one of the clinical criteria and one of the laboratory criteria that follow are met:*

Clinical Criteria

1) Vascular Thrombosis†
   One or more clinical episodes‡ of arterial, venous, or small vessel thrombosis§, in any tissue or organ. Thrombosis must be confirmed by objective validated criteria (i.e., unequivocal findings of appropriate imaging studies or histopathology). For histopathologic confirmation, thrombosis should be present without significant evidence of inflammation in the vessel wall
2) Pregnancy Morbidity
   a) One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation, with normal fetal morphology documented by ultrasound or by direct examination of the fetus, or
   b) One or more premature births of a morphologically normal neonate before the 34th week of gestation because of (i) eclampsia or severe pre-eclampsia defined according to standard definitions, or (ii) recognized features of placental insufficiency¶, or
   c) Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded. In studies of populations of patients who have more than one type of pregnancy morbidity, investigators are strongly encouraged to stratify groups of subjects according to a, b, or c above.

Laboratory Criteria**

1) Lupus anticoagulant (LA) present in plasma on two or more occasions at least 12 weeks apart, detected according to the guidelines of the International Society on Thrombosis and Haemostasis (Scientific Subcommittee on LAs/phospholipid-dependent antibodies)
2) Anticardiolipin (aCL) antibody of IgG and/or IgM isotype in serum or plasma, present in medium or high titer (i.e., >40 GPL or MPL, or >the 99th percentile), on two or more occasions, at least 12 weeks apart, measured by a standardized ELISA
3) Anti-β2 glycoprotein-I antibody of IgG and/or IgM isotype in serum or plasma (in titer >the 99th percentile), present on two or more occasions, at least 12 weeks apart, measured by a standardized ELISA, according to recommended procedures

* *Classification of APS should be avoided if less than 12 weeks or more than five years separate the positive aPL test and the clinical manifestation.*

† *Coexisting inherited or acquired factors for thrombosis are not reasons for excluding patients from APS trials. However, two subgroups of APS patients should be recognized according to (a) the presence, and (b) the absence of additional risk factors for thrombosis. Indicative (but not exhaustive) such cases include: age (>55 years in men and >65 years in women), and the presence of any of the established risk factors for cardiovascular disease (hypertension, diabetes mellitus, elevated LDL or low HDL cholesterol, cigarette smoking, family history of premature cardiovascular disease, body mass index ‡30 kg/m²), microalbuminuria, estimated GFR <60 mL/min), inherited thrombophilias, oral contraceptives, nephrotic syndrome, malignancy, immobilization, and surgery. Thus, patients who fulfill the criteria should be stratified according to contributing causes of thrombosis.*

‡ *A thrombotic episode in the past could be considered as a clinical criterion, provided that thrombosis is proved by appropriate diagnostic means and that no alternative diagnosis or cause of thrombosis is found.* §*Superficial venous thrombosis is not included in the clinical criteria.*

¶ *Generally accepted features of placental insufficiency include: (i) abnormal or non-reassuring fetal surveillance test(s), e.g., a non-reactive non-stress test, suggestive of fetal hypoxemia, (ii) abnormal Doppler flow velocimetry waveform analysis suggestive of fetal hypoxemia, e.g., absent end-diastolic flow in the umbilical artery, (iii) oligohydramnios, e.g., an amniotic fluid index of 5 cm or less, or (iv) a postnatal birth weight less than the 10th percentile for the gestational age.*

** *Investigators are strongly advised to classify APS patients in studies into one of the following categories: I, more than one laboratory criteria present (any combination); IIa, LA present alone; IIb, aCL antibody present alone; IIc, anti-b2 glycoprotein-I antibody present alone.*

Adapted from Miyakis S, Lockshin, Atsumi T, Branch DW, Brey RL, Cervera R, Derksen RHWM, De Groot PG, Koike T, Meroni PL, Reber G, Shoenfeld, Y, Tincani A., Vlachoyiannopoulos PG. and Krilis SA. International Consensus Statement on an Update of the Classification Criteria for Definite Antiphospholipid Syndrome (APS). Journal of Thrombosis and Haemostasis. 2006; Vol 4: pp 295-306.

there is a difference in the characteristics of classical APS and OAPS.[10]

In addition to the obstetric complications of APS, the presence of fetal morbidity has also been well-documented. Tincani et al., summarized the mechanisms of anti-phospholipid-mediated fetal injury into 3 points: (1) fetal injury secondary to impaired fetal blood supply caused by placental thrombosis and infarction; (2) antiphospholipid antibodies target the surface of trophoblasts thereby impairing the formation of syncytiotrophoblasts and the synthesis of human chorionic gonadotropin; and (3) activation of inflammatory molecules causing damage. In mice models, the local activation of the complement pathway, through C3 and C5, has been shown to cause damage in the vascular endothelium and trophoblasts. In the few studies done on humans, these results were noted to be conflicting.[10]

Several studies have looked into the fetal outcomes of mothers diagnosed with APS.[9–11] Motta et al., made a preliminary report on the babies of mothers with APS.[12] This prospective study on 141 babies of a mother with APS showed a preterm rate of 16% and a low birth weight of 17%. In addition, there were also documented cases of placental transfer of antiphospholipid antibodies (20% for lupus anticoagulant, 25% for anticardiolipin, and 43% for anti-β2 glycoprotein I) and behavior abnormalities in four children at 24 months of age. Neurodevelopmental abnormalities were evident in infants of mothers with autoimmune disease, especially in those with systemic lupus erythematosus. Experimental mice models have shown that

prolonged exposure to aPL caused hyperactive behavior and neurological dysfunctions.[13] In a study done by Mayer-Pickel K., neonatal complications included the following: 2 cases of dystonia, 2 cases of developmental delay, 1 case of ataxia and dyspraxia, 2 cases of mild respiratory distress syndrome, and 2 children who developed neonatal lupus.[14] Peixoto et al., reviewed literature reports on neonatal thrombosis and APS and retrieved 21 cases from 1987-2013.[15] Seventeen of the 21 cases showed arterial thrombosis in the neonate, while the remaining showed venous thrombosis. The most common manifestation reported was stroke, followed by involvement of the aorta, mesenteric, femoral, and renal arteries.

In a study by Ruffatti et al., they reported the following neonatal outcome parameters in pregnant women diagnosed with APS: mean gestational age of 36 ± 3 weeks, mean ± SD birth weight of 49.15 ± 23.15 percentiles, and mean ± SD 5 minute APGAR score of 9.3 ± 1.0 (range 5-10).[16] In this same study, 16.2% of infants underwent cardiopulmonary resuscitation, and 28.8% were admitted to the neonatal intensive care unit. Other complications noted in the infants included in this study were neonatal sepsis (8.1%) and respiratory distress syndrome (26.1%). Brewster et al., did a chart review of 62 infants born from mothers with APS and found that the median birth weight was 3.237 kg.[17] Cetkovic et al. did a prospective study and found that in mothers with APS, 80% resulted in live birth, 12% ended in spontaneous abortions, and 8% in stillbirths.[18] Of the 80% of live births, the mean gestational age upon delivery was 37 ± 1 week, with a mean neonatal birth weight of 2930.4 ± 428.0 g. Finally, in a study done by Jemeric et al. in 2015, the outcomes of 55 women with APS were described to be as follows: the average gestational age upon delivery was 35.45 ± 4.18 weeks with a mean birth weight of 2762.25 ± 756.86 g.[19]

METHODOLOGY

Design and Setting

This was a retrospective study of neonates born from mothers diagnosed to have immunologic causes of RPL from 2010-2015 at the PGH.

Study Participants

Sample Size Computation

This study included all patients born from mothers diagnosed to have an immunologic cause of RPL from 2010-2015 based on the patient database of the section of Allergy and Immunology of the PGH.

Inclusion Criteria

All neonates born from mothers with RPL with immunologic work-up from 2010 until 2015 at the PGH based on information from the database of the section of Allergy and Immunology of the PGH.

Exclusion Criteria

Neonates born from mothers with other non-immunologic causes of RPL, such as infectious, anatomic, or hormonal, will be excluded. Neonates born from mothers without any single immunologic test done for RPL will also be excluded from the study.

Operational Definition

- *Antiphospholipid Antibody Syndrome (Classical* APS): Women fulfilling the Sydney criteria (see Table 2).
- *Obstetric Morbidity associated with Antiphospholipid Antibody Syndrome* (OMAPS): Women with pregnancy complications possibly related to aPL (such as late preeclampsia, placental abruption, late premature birth, etc.) with any of the following laboratory criteria in Table 3.
- *Other Immunologic Causes:* Women with RPL and positive immunologic work-up not part of the above-mentioned laboratory work-up (e.g. NK Cell Determination, Leukocyte Antibody Detection, etc.)
- *Unexplained Cause:* Women with RPL suspected to be secondary to immunologic causes, have negative work-up for APAS but had no other further immunologic work-up by the time of the study.

Procedure

A review of the patient database from the Section of Allergy and Immunology from 2010-2015 on RPL of immunologic cause was done. The clinical profile and laboratory results of mothers with RPL were extracted from the database. The following data on these patients were gathered:

- obstetric history, which included:
  - the number of full-term births
  - the number of preterm births and the age of gestation upon delivery
  - the number of abortions and their identified reasons
  - the number of living children

Table 3. Laboratory Criteria in Diagnosing OMAPS

Standard Laboratory Criteria according to Sydney Criteria
Non-standard aPL: anti-annexin A5, anti-phosphatidylserine (aPS), anti-PS/prothrombin (aPS/PT), or other aPL
Standard or non-standard antibodies just described above, detected less than 12 weeks apart on two or more occasions
Standard or Non-standard antibodies just described above, detected only on one occasion, especially in gestational time
Low levels of anticardiolipin antibodies (aCL) (IgG/IgM) and/or anti-β_2GPI antibodies (levels <99 percentile)

Adapted from: Alijotas-Reig, J., Ferrer-Oliveras, R., on behalf of the EUROAPS Study Group. The European Registry on Obstetric Antiphospholipid Antibody Syndrome (EUROAPS): A Preliminary First Year Report. Lupus. 2012, Vol 21, pp 766-768.

- results of laboratory tests done for RPL, which included
  - lupus anticoagulants
  - anticardiolipin antibodies
  - anti-β2 glycoprotein-I antibody of IgG and or IgM isotype
  - other non-standard aPL: anti-annexin A5, anti-phosphatidylserine (aPS), anti-PS/prothrombin (aPS/PT) or other aPL
  - other immunologic work-ups for RPL

The mothers were classified according to the immunologic cause of RPL- APS, OMAPS, other immunologic causes, and unexplained immunologic causes. The records of the offspring of these mothers were then retrieved from the PGH Record Section. The following information were gathered:

- perinatal outcome (live or stillbirth)
- neonatal outcome (preterm, full-term or post-term; manner of delivery; pediatric age upon delivery; APGAR score upon delivery)
- birth anthropometrics (birthweight, appropriateness of weight for gestational age, head circumference)
- morbidity (neonatal pneumonia, neonatal sepsis, others)
- necessitated neonatal intensive care unit admission

Statistical Analysis

For categorical data, values were expressed as numbers and percentages. For continuous variables, values were expressed as mean and standard deviation.

Ethical Considerations

This study was conducted upon approval of the University of the Philippines Manila Research Ethics Board (UPMREB). All patient information was anonymized and kept confidential. All data were encoded in a private desktop computer that is password encrypted. Hard copies of data collection forms are kept in a locked storage container in the Section of Allergy and Immunology office.

The authors declare that there is no conflict of interest regarding this study.

RESULTS

The total live births delivered in the PGH from 2010-2015 was 31,678. There were 58 births from mothers with RPL who were all were enrolled in this study. The prevalence of neonates born from mothers with RPL from identified and unexplained immunologic causes among all infants born at the PGH from 2010 to 2015 is 0.18%.

Among the 58 births from mothers with RPL from an immunologic cause, 5.1% were classified as Classical APS, 63.8% as OMAPS, and 31% as unexplained immunologic cause. There were no cases classified under other immunologic causes. Table 4 summarizes the perinatal and neonatal outcomes of infants born from mothers with RPL from immunologic causes.

All the neonates classified under classical APS were born live. The majority of them were born full-term via cesarean Delivery. The pediatric aging of these neonates was between 33 and 39 weeks upon delivery. Most of these patients had their birth weight appropriate for the gestational age, with a mean birth weight of 2,206 grams ± 539.48. Only one patient had a documented head circumference recorded at 28 cm. The APGAR score of these patients were all normal, 9 and 9 at the 1st and 5th minute, respectively. Only one patient necessitated admission to the nursery intensive care unit (NICU) due to prematurity and other associated morbidities. The patient was diagnosed with hyaline membrane disease, neonatal neumonia, and early onset sepsis during the course of the admission but was discharged well thereafter.

The neonates classified as OMAPS mainly were born live, term via cesarean Delivery. The pediatric aging of these neonates ranged from 27 weeks to 40 weeks upon delivery. The average birth weight of these neonates was noted at 2537 ± 737.46 grams, mostly born appropriate for gestational age. The average head circumference of the neonates belonging to this group was 33.6 ± 1.7 cm. Only 1/3 of the subjects had a record of their head circumference. Most of the neonates in this group had a normal APGAR Score of 9 and 9 on the 1st and 5th minute, respectively. There were only two neonates with low APGAR Scores, 3 and 5, in the first minute, and this was noted to improve in the 5th minute to APGAR Scores of 9 and 9. Most of the neonates in this group were directly roomed in and only one subject had associated morbidity which was physiologic jaundice. Those that required admission at the NICU had associated morbidities such as prematurity, neonatal pneumonia, intraventricular hemorrhage, early-onset sepsis, transient tachypnea of the newborn, and hyaline membrane disease. Of the eight neonates admitted to the NICU, one neonate died during admission. The rest of the neonates were discharged well.

Finally, the neonates that had unexplained causes were mostly born live via cesarean delivery. Most of these patients were born term with pediatric aging ranging from 29-39 weeks. The average birth weight of these neonates was 2228.75 ± 887.05 grams and the majority of them were born appropriately for gestational age. Only 1/3 of the neonates had records of their head circumference and the average measurement was noted at 32.2 cm. The majority of the APGAR Score of these patients at the 1st and 5th minute was noted at 9 and 9, respectively. Two patients were noted to have low APGAR scores during the 1st minute (AS=4-6). The APGAR score of one of the two patients improved in the 5th minute (AS=8) while the other remained

Table 4. Neonatal Outcome of Infants born from Mothers with RPL from Immunologic Causes, 2010-2015

	Classical APS N= 3 (n,%)	OMAPS N= 37 (n,%)	Unclassified N=18 (n,%)
Perinatal outcome			
Live	3 (100)	35 (94.6)	16 (88.9)
Still Birth	0 (0)	2 (5.4)	2 (11.1)
Neonatal outcome (n,%)			
Preterm	1 (33.3)	11 (29.7)	4 (22.2)
Term	2 (66.7)	24 (64.9)	12 (66.7)
Post Term	0 (0)	0 (0)	0 (0)
Manner of Delivery			
NSD n=(%)	1 (33.3)	10 (27)	4 (22.2)
CS n=(%)	2 (66.7)	25 (67.5)	12 (66.7)
Birth Weight mean (SD)	2206.67 (539.48)	2537 (737.46)	2228.75 (887.05)
<2000 grams	1 (33.3)	6 (16.2)	7 (38.9)
2000-2500 grams	1 (33.3)	6 (16.2)	3 (16.7)
2500-3000 grams	1 (33.3)	16 (43.2)	3 (16.7)
>3000 grams	0 (0)	7 (18.9)	3 (16.7)
Appropriateness of Age for Gestational Age			
SGA	1 (33.3)	5 (13.5)	5 (27.7)
AGA	2 (66.7)	30 (81.1)	10 (55.6)
LGA	0 (0)	0 (0)	1 (5.6)
Head Circumference mean (SD)	28 (0)	33.6 (1.7)	32.1 (1.9)
APGAR Score			
1st minute			
1-3	0 (0)	1 (2.7)	0 (0)
4-6	0 (0)	1 (2.7)	2 (11.1)
7-9	3 (100)	33 (89.1)	14 (77.8)
5th minute			
1-3	0 (0)	0 (0)	0 (0)
4-6	0 (0)	0 (0)	1 (5.6)
7-9	3 (100)	35 (94.5)	15 (83.3)
Morbidities			
Neonatal Pneumonia	1 (33.3)	2 (5.4)	1 (5.6)
Sepsis	0 (0)	1 (2.7)	1 (5.6)
Intraventricular Hemorrhage	0 (0)	1 (2.7)	0 (0)
Transient Tachypnea of the Newborn	0 (0)	1 (2.7)	1 (5.6)
Neonatal Pneumonia, Hyaline Membrane Disease, Sepsis	1 (33.3)	0 (0)	0 (0)
Hyaline Membrane Disease	0 (0)	1 (2.7)	0 (0)
Physiologic Jaundice	0 (0)	1 (2.7)	0 (0)
Necessitated NICU Admission			
Yes	1 (33.3)	8 (21.6)	5 (27.8)
No	2 (66.7)	27 (73)	11 (61.1)

low (AS=6). The majority of the patients did not need NICU admission. However, of the five admitted patients, two had documented morbidities, specifically neonatal pneumonia and early onset sepsis and transient tachypnea of the newborn. The rest of the admitted patients at the NICU was because of prematurity. One neonate was directly roomed-in and was noted to have transient tachypnea of the newborn. All the patients admitted to the NICU were discharged well after treatment. All the patients who were directly roomed in were also sent home well.

In all three groups, neonates were mostly born via cesarean delivery. Table 5 shows the cesarean delivery indications identified in some neonates.

The majority of the neonates had no data gathered regarding their indications for the cesarean section. However, based on the information available, pre-eclampsia is the only identified reason for cesarean delivery for the Classical APS group. In the OMAPS group, the more common indications for the cesarean section include pre-eclampsia, malpresentation, and dystocia. The most

Table 5. Indications for Cesarean Delivery

Indication	Classical APS N=2 (n,%)	OMAPS N=25 (n, %)	Unexplained N=12 (n,%)
Preeclampsia	1 (50)	2 (8)	
Minimal Variability		1 (4)	1 (8.3)
Malpresentation		2 (8)	1 (8.3)
CPD		1 (4)	
Dystocia		2 (8)	
Repeat		1 (4)	2 (16.6)
Fetal Bradycardia		1 (4)	
No Data	1 (50)	15 (60)	8 (66.7)

common indication for cesarean delivery for neonates under the unexplained group based on available data is repeat cesarean section.

DISCUSSION

This study aimed to determine the neonatal outcome of infants born from mothers with RPL from immunologic causes. Several immunologic factors have been identified that have been associated with RPL: autoantibodies (like aPL, anti-nuclear antibodies, and anti-thyroid antibodies) and NK cells. Numerous journals have already published the association of these factors in RPL, but only a few have shown reports on its effect on neonatal outcomes.[9,11–19]

Most of the neonates in this study were classified under Classical APS and OMAPS. As mentioned earlier, the mechanisms of antiphospholipid-mediated fetal injury include impaired fetal blood supply secondary to placental thrombosis and infarction, impairment of formation of syncytiotrophoblasts and synthesis of human chorionic gonadotropin secondary to aPL, and activation of inflammatory molecules causing damage to the fetus.[10] Tincani et al. also mentioned that fetal and neonatal complications of maternal aPL may occur because of placental transfers of the antiphospholipid antibodies or may be secondary to the prematurity, which often complicates the pregnancies of women with APS.[10] Although aPL is detected in the cord blood and the neonate, its presence does not necessarily indicate clinical findings of APS.[10] In the European Registry of babies born to mothers with APS, lupus anticoagulant, anticardiolipin antibodies IgG, and anti-β_2 glycoprotein-I IgG and IgM were detected in the serum of some of the neonates included in the study.[12] However, none of the subjects enrolled in the said study showed signs of thrombosis or systemic lupus erythematosus. The results of our study revealed that the majority of the neonates were born live, full term, via cesarean delivery with birth weights appropriate for gestational age and normal APGAR scores despite these immunologic abnormalities.

APGAR score is an accepted, standardized scoring system comprising five components: infant's (1) color, (2) heart rate, (3) reflexes, (4) muscle tone, and (5) respiration. It defines the physiologic condition of an infant at a particular point in time and its response to resuscitation. An APGAR score of 7-10 in the 5th minute is defined as reassuring, 4-6 as moderately abnormal, and 0-3 as low in the term and post-term infant.[20] This scoring method may be influenced by subjective components like interobserver variability and other factors such as maternal sedation, trauma, congenital abnormalities, and gestational age. The 1st minute APGAR score does not predict anything but changes in the score between the 1st and 5th minute provide an index of response to resuscitation.[20]

Low APGAR scores may be influenced by the physiologic maturity of an infant and other variations in normal transition, such as low initial oxygen saturation.[10] Two neonates in the OMAPS group had a low APGAR score in the 1st minute but improved to a normal APGAR score in the 5th minute. These neonates were preterm at 28 and 23 weeks age of gestation, respectively, and their general condition improved after newborn resuscitation. Another neonate belonging to the unexplained group, with a low APGAR score on the 1st minute improving to a normal score on the 5th minute, was also preterm at 29 weeks. Hence, these results may be attributed to the conditions of the infants after birth rather than a direct effect of the immunologic cause of their mother's RPL. The last neonate with a low APGAR score on the 1st and 5th minute (4 and 6 respectively) was born term at 39 weeks. However, difficulty in transitioning intrautero to extrautero cannot completely be ruled out. This neonate had an acceptable APGAR score of 7 at the 10th minute.

There are several neonates across all groups that were delivered via cesarean section. This result was consistent with the study conducted by Jivraj et al. on the outcomes of women with RPL.[6] Since 30% of the neonates delivered via cesarean section had an unexplained cause of RPL, it is difficult to explain the reason for such occurrence. In the limited data for both Classical APS and OMAPS, preeclampsia was a dominant indication for a cesarean delivery. In previous studies, preeclampsia has been noted to be one of the most common obstetric complications of pregnant women with APS and one of the more common reasons for preterm delivery in these cases.[9,10] The presence of APS in pregnant women leads to a hypercoagulable state. During pregnancy, a physiologic adaptation occurs to prevent postpartum bleeding, such as an impairment in fibrinolysis, an increase in clotting factors and thrombin, and a decrease in some anti-coagulants. These same factors, fibrinolysis, and the coagulation cascade together with platelet abnormalities, are also the mechanisms behind the hypercoagulable state in APS.[3] Pre-eclampsia occurs

because of placental underperfusion leading to chronic ischemia and oxidative stress. Oxidative stress causes the release of substances, such as free radicals, oxidized lipids, and cytokines, that causes systemic endothelial dysfunction causing the symptoms of preeclampsia.[21] Therefore, the combination of these conditions – APS and pregnancy – causing hypercoagulability and chronic ischemia of the placenta may be strong contributory factors for preeclampsia. It is worth mentioning that APS is just one of the many risk factors for pre-eclampsia. Other risk factors include: renal disease, prior pre-eclampsia, systemic lupus erythematosus, multiparity, chronic hypertension, diabetes mellitus, multiple gestations, etc.[21]

In this study, there was one preterm subject, 31 weeks of pediatric aging upon delivery, classified under OMAPS, with reported Intraventricular hemorrhage (IVH). According to an article written by Ballabh, there are three main causes of IVH in the preterm: inherent fragility of the germinal matrix vasculature, disturbance in the cerebral blood flow, and platelet and coagulation disorders.[22] As mentioned earlier, platelet abnormalities and the coagulation cascade are significant components of thrombosis in APS. Several risk factors may predispose a preterm infant to develop IVH by affecting cerebral blood flow. These include a low APGAR score, severe respiratory distress syndrome, seizures, hypoxia, patent ductus arteriosus, thrombocytopenia, and infection. Hence, due to the multifactorial causes of this condition, it is difficult to ascertain whether the IVH can be attributed solely to APS or any other immunologic causes related to maternal RPL. The rest of the 57 subjects did not show any signs of thrombosis.

There were 27.5% of the neonates born preterm regardless of the classification of the immunologic cause of RPL. This result was consistent with the study done by Jivaraj which also showed an increased rate of preterm deliveries in women with RPL regardless of the cause.[7] However, prematurity has numerous underlying causes, including infection, pre-eclampsia, eclampsia, intrauterine growth restriction, and other maternal illnesses (ie, gestational diabetes mellitus, hypertension). Some of these neonates were born prematurely because of pre-eclampsia, which may be secondary to maternal APS. Any of these mechanisms, including immunologic causes such as APS, may contribute to the preterm delivery of these subjects.

Most of the neonates that were delivered prematurely necessitated NICU admissions. The above-mentioned identified morbidities were also mostly noted in preterm neonates. Neonatal pneumonia and sepsis have the same causes and risk factors in the neonate. This includes maternal factors like fever, chorioamnionitis, prolonged rupture of membrane, and neonatal risk factors such as prematurity and low birth weight.[23] Both neonatal pneumonia and sepsis may also be associated with prolonged stay in the neonatal intensive care unit due to the infant's prematurity.

Hyaline membrane disease (HMD) is a consequence of inadequate production of pulmonary surfactants due to prematurity. Identified risk factors for this condition includes prematurity, maternal diabetes, genetic factors, perinatal asphyxia, and delivery via cesarean section without labor.[23] The subject with HMD in this study was born preterm at 27 weeks and the mother has been diagnosed with diabetes mellitus.

Among the neonates who were directly roomed in, one morbidity noted in a full-term infant delivered via cesarean section belonging to the group with unclassified cause and another morbidity in a full-term infant born via normal spontaneous delivery belonging to the OMAPS group. These subjects were diagnosed with transient tachypnea of the newborn (TTN) and physiologic jaundice, respectively. Transient tachypnea of the newborn is a self-limiting disease characterized by tachypnea and other signs of respiratory distress due to delayed clearance of fetal lung fluid.[23] This condition has been associated with operative births, prematurity, and precipitous births, possibly due to the absence of the "thoracic squeeze" that normally occurs after vaginal delivery.[23] Physiologic jaundice is defined in some literature as an expected increase in bilirubins in term and premature infants due to increased bilirubin production, increased enterohepatic circulation, defective bilirubin uptake from plasma, defective conjugation, and decreased hepatic excretion of bilirubin expected in the first few days of life. The two neonates with TTN and physiologic jaundice were discharged well after 3 and 7 days, respectively.

In Tincani's review of 6 studies on outcomes of neonates of mothers with APS, no clinical manifestations of APS were noted in the 277 infants studied. The only complications mentioned were due to prematurity. Likewise, this study has identified several morbidities that may be attributed to prematurity rather than a direct effect of the placental transfer of antiphospholipid antibodies to the neonate.

Numerous causes of RPL have already been identified. Immunologic causes, to which APS belong, are just one of them. In the majority of the cases of RPL, the etiology is still left unexplained. In this study, 30% of the subjects included in the Section of Allergy and Immunology RPL database have unexplained losses. The outcomes of these patients' neonates are comparable to those of the neonates belonging to both Classical APS and OMAPS groups. These results indicate a normal pregnancy except for the higher rate of cesarean delivery. Ideally, these results should be analyzed according to identified causes of RPL. However,

since this is not possible, it is sufficient to know that patients with recurrent miscarriage represent a population at high risk for obstetric problems and close surveillance during the antenatal period.[8]

CONCLUSION AND RECOMMENDATIONS

In conclusion, the majority of these infants born from mothers with RPL had a good birth outcome. Most neonates born from mothers with RPL from immunologic cause are born live, full term, via cesarean section, with an average birth weight between 2461.7 ± 768.5 grams, appropriate for gestational age with an APGAR score of 7-9 on the 1st and 5th minute. The same general outcomes were noted across all classifications of immunologic cause (Classical APS, OMAPS, and those with unexplained losses). Hence, the immunologic cause of RPL has minimal effects on the neonate.

This study was limited to patients identified in one institution. As such, cases identified were limited to Classical APS, OMAPS, and unexplained losses. A multi-center study design may improve the pool of neonates and contribute to the diversity of immunologic causes of RPL. A follow-up birth cohort study on the growth and development of these patients is also recommended since some studies show preliminary observations of abnormal development of behavior. Studies to identify other factors, such as treatment received and other maternal co-morbidities, that may be correlated to prematurity, or other morbidities in the outcomes of these patients are also suggested.

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