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Prevalence and pregnancy outcome in antiphospholipid syndrome: an observational study

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Abstract Antiphospholipid syndrome (APS) is an autoimmune disorder characterized by vascular thrombosis, both arterial and venous, and recurrent spontaneous pregnancy loss due to circulating antiphospholipid antibodies (aPL) including anticardiolipin antibodies (aCL) and/or anti-glycoprotein I antibodies (anti-GPI). This observational study was conducted among antenatal women at OBG Department, IMS, and SUM Hospital, Bhubaneswar, over a year from March 2020 to 2021. Of 1260 cases, 25 were diagnosed with ALPA syndrome, with a prevalence rate of 1.98%. The most common age was 26-30 years (40%) with a mean age of 28.83 ± 3.26 years. The primary cause was recurrent 1st-trimester spontaneous miscarriage. Beta 2 glycoprotein antibody was most prevalent (40%). Significant associations were found in hypertensive and FGR APLA patients compared to non-hypertensive and non-FGR APLA patients. Hypertension and FGR occurred in 24% and 20% of APLA patients, respectively. Preterm delivery rate was higher (52%) in APLA syndrome, without significant association. B2GP antibody was linked to the lowest live birth rate, and highest rates of preeclampsia, IUGR, and stillbirth. Screening for B2GP antibodies is recommended for FGR and early onset preeclampsia cases with/without previous spontaneous pregnancy loss.

Keywords: antiphospholipid syndrome, anticardiolipin antibodies, lupus anticoagulant, Beta 2 glycoprotein, vascular endothelial growth factor, fetal growth restriction

1. Introduction

Antiphospholipid syndrome (APS) is an autoimmune prothrombotic condition that is marked by the presence of antibodies that act against phospholipid-binding proteins rather than the phospholipid itself (Hughes 1983). The clinical manifestations of APS include vascular thrombosis, both arterial and venous, and pregnancy complications (Hughes 1993), especially recurrent spontaneous miscarriages and, less frequently, maternal thrombosis (Roubey et al; Hoffman et al 1997). Many other clinical manifestations may occur (Khamashta et al 1990; Mialdea et al 2009). APS occurs as primary in the absence of findings of other autoimmune diseases or as secondary in 36% of cases in the context of another autoimmune disease (SEL, Sjogren's disease, inflammatory bowel disease, etc. The prevalence of aPL is estimated to be 5% of the general population, and APS represents 0.5% (Cervera et al 2002; Derksen et al 2008). However, aPL is commonly found in 15% of women with recurrent pregnancy losses (RPLs), suggesting that APS is one of the most frequent acquired etiologies for RPL (Rai et al 1995). aPL is a heterogeneous family of three autoantibodies, including lupus anticoagulant (LA), anticardiolipin antibodies (aCL), and anti-β2 glycoprotein-1 antibodies (anti-β2GP1 Abs). As β2GP1 seems to be the main antigen for aPL, anti-β2GP1 Abs are now considered among the principal antibodies of the syndrome (de Groot et al 2011; Urbanus et al 2012). During pregnancy, anti-β2GP1 Abs affect trophoblastic cells directly by binding to β2GP1 at the surface of trophoblastic cells (Meroni et al 2004), resulting in the alteration of trophoblastic cells *via* different mechanisms.

1.1. Pathogenesis of Antiphospholipid Antibodies in Pregnancy:

(1) Mechanisms in placental cells
(i) Thrombosis by a specific mechanism (Evain-Brion et al 2009). (ii) Inflammation by complement activation (Mahleret al 2010; Laat et al 2009; van Horn et al 2004; Skrzypczak et al 2011; Shamonki et al 2007). (iii) Immunomodulation by TLR 4 activation by aPL (Satta et al 2008). (iv) Defective placentation. (a) Migration: decrease in IL-6 and STAT3 expression (Mulla et al 2009). (b) Invasion: decrease in integrin expression (Meroni et al 2008). (c) Differentiation: decrease in β-hCG secretion (Meroni et al 2011) and decrease in fusion (Meroni et al 2010).

(2) Mechanisms on endometrial cells (Simone et al 2010; D'Ippolito et al 2012)
(i) Angiogenesis inhibition (ii) Decrease in VEGF secretion (iii) NFκB activation inhibition.

Obstetric complications are the hallmark of antiphospholipid syndrome. Recurrent miscarriage, oligohydramnios, prematurity, intrauterine growth restriction, fetal distress, preeclampsia/eclampsia, HELLP syndrome, arterial or venous

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thrombosis and placental insufficiency are the most severe APS-related complications for pregnant women. Both low-dose aspirin (LDA) and LMWH injections are usually administered and improve both fetal and maternal outcomes (S. M. Bates et al 2012). Thus, without treatment, the chances of successful pregnancy are approximately 30%, 50% with LDA alone, and up to 70% with both molecules (Bramham et al 2010). Nishino et al have shown that aspirin could decrease thromboxane A2 production and prostaglandin I2 formation, (Nishino et al 1990) and aspirin has also been shown to upregulate interleukin-3 (IL-3) production. This molecule seems necessary for trophoblast invasion and placental formation (Fishman et al 1993). Kwak-Kim et al Heparin as LMWH is an anticoagulant molecule that prevents clot formation. LMWH can be safely used during pregnancy due to its antithrombotic, anti-inflammatory and anti-apoptotic properties.

2. Materials and Methods

This is a prospective observational study conducted among antenatal patients registered in the Obstetrics and Gynecology OPD, IMS & SUM Hospital, Bhubaneswar, for a duration of 1 year from March 2020 to March 2021. The study was performed using a convenience sampling method.

Patients with one or more 1st trimester miscarriages, patients with one or more 2nd trimester miscarriages and those with pregnancy loss up to term due to severe preeclampsia, IUGR, oligohydramnios and unexplained intrauterine death. Elevated IgG or IgM anticardiolipin antibody OR elevated IgG or IgM anti b2 glycoprotein antibody OR positive lupus anticoagulant assay must be positive. Those who fulfilled the selection criteria were recruited for the study. They were followed up in the postnatal ward after abortion or preterm delivery. After informed consent was obtained, data were collected by interviews, documents and available laboratory tests.

Patients with congenital malformation of the fetus by ultrasonography, multifetal gestation, anatomical cause and cervical incompetence in the mother detected by US were excluded from our study.

Detailed information regarding previous pregnancy and those cases who have any immunological disorder, such as rhumatoid arthritis, or history of thromboembolism or infectious conditions, such as syphilis, may act as confounding factors. VDRL TEST is routinely performed for all cases in our institute. From the history itself, we ruled out all other immunological cases and selected VDRL-negative cases to minimise confounding factors and losses-their gestational age, documentation of fetal heart, any congenital anomalies, complications during the antenatal period such as severe preeclampsia, IUGR and abruption remote from term, the weight of fetuses and investigation results were collected. Additionally, a detailed history regarding the history of hypertension, gestational diabetes, hypothyroidism, SLE, personal history of thrombosis such as DVT, pulmonary embolism, family history of thrombosis, history of drugs, contraception, addiction, and smoking was taken. Plasma samples were tested for anticardiolipin antibodies and β2GPI antibodies by ELISA quantitative or semiquantitative in vitro assay methods. The lupus anticoagulant test was performed by the nephelometric detection method with a cut off of 23.3-31.3 and a DRVVT test ratio cut off of <1.2. Elevated IgG or IgM anticardiolipin antibody (≥12 PL cut off by EUROIMMUN) and elevated IgG or IgM anti-β2GPI antibody (≥20PL cut off by EUROIMMUN) were considered positive. One or more of these tests must be positive on at least two occasions at least 12 weeks apart to be called APS syndrome. Both Inj LMWH and low- to high-dose aspirin (75-150 mg/day) were added for all pregnant APS women from the positive pregnancy test result to delivery. Statistical analysis was performed using SPSS version 26. Prevalence data were noted as percentages or proportions. The mean and standard deviation were estimated for continuous variables such as age. A chi-square test was used to observe the association between two categorical variables. A p value less than 0.05 was considered statistically significant.

3. Results

There were 1260 screened patients, and 25 were APLA positive. Prevalence 1.9%. The minimum age group with APLA syndrome was 24 years, and the maximum was 36 years, with a mean age of 28.83 ± 2.63 years, as shown in Table 1.

Table 1: Age outcome.

	minimum	Maximum	mean	Standard deviatio
Age outcome	24	36	28.83	3.26

Only one patient had secondary APLA, i.e., h/o SLE with both ACLA and B2GP in our study. Recurrent spontaneous miscarriage occurred mostly in the 1st trimester (52%) in women aged 26-30 years, as shown in Table 2.

Table 2: Miscarriage and Age Group

Age	1st tri	2nd tri	3rd tri	Total
20-25yr	2	1	4	**7**
26-30yr	7	2	1	**10**
≤31	4	3	1	**8**
Total	**13**	**6**	**6**	**25**

Chi-square is 6.77. The p value is 1.48. The result is not significant for the age group of trimesterwise miscarriage.

Most of the pregnancy loss is seen in the 1st trimester, with the main culprit being the B2GP antibody, as shown in Table 3. However, statistically insignificant findings were recorded among miscarriages in different age groups and trimesters. The significant p value is <0.05, but our result is 0.28. Therefore, this is highly insignificant. 2nd- and 3rd-trimester miscarriages associated with ACLA and LA antibodies are shown below in Table 3.

Table 3: Miscarriage and anti-phospholipid antibody.

Pregnancy loss	B2GP	ACLA	LA	TOTAL
1st tri	7	2	1	10
2nd tri	1	1	3	5
3rd tri	3	2	1	6

The chi-square statistic is 5.02. p value is .28. The result is not significant at p< 0.05.

The gain diagram (Figure 1) shows the distribution of different antiphospholipid antibodies among themselves. In this study, beta-2 glycoprotein (B2GP) was positive in 10 cases (40%), anticardiolipin antibodies (ACLA) were positive in 5 cases (20%), and lupus anticoagulant (LA) was positive in 4 cases (16%). The most common antiphospholipid antibody associated with APLA syndrome is B2GP (40%), as shown in Figure 1. Out of 25 APLA cases, 3 cases were found to have both B2GP and ACL Ab (12%), and 1 case was found to have both B2GP and LA (4%). One case had all three antibodies, B2GP, ACLA and LA (4%). Triple antiphospholipid (aPL) antibody positivity is associated with pregnancy complications compared with aPL antibody positivity alone.

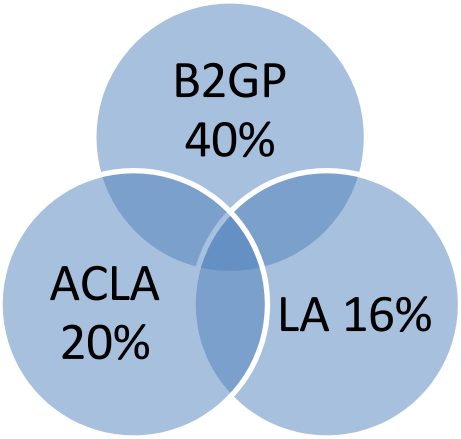

Figure 1: Vain diagram representing the distribution of different antiphospholipid antibodies.

There was a significant association between HTN and non-HTN APLA among different age groups because the chi-square was 17.46 and the p value (0.005-0.002) was highly significant, as shown in Table 4, with a prevalence rate of 24%. Therefore, hypertension is the most common cause of complications in antenatal APLA patients.

Table 4: Age Group and Hypertension.

HDP		20-25yr	26-30yr	≤ 31yr	Total
NO	Count	3	10	6	19
	% within the grp	75%	71.42%	85.72%	
	% of total	12%	40%	24%	76%
YES	Count	1	4	1	6
	% within the grp	25%	28.58%	14.28%	
	% of total	4%	16%	4%	24%
TOTAL	Count	4	14	7	25
	% within the grp	100%	100%	100%	100%
	% of total	16%	56%	28%	100%

Chi-square - 17.46, p=0.005-0.002, statistically significant. There was a statistical significance between Hypertension and No hypertension APLA patients concerning different age groups. Hypertension was there for 24% of APLA patient.

Table 5 shows that there was no association between hypothyroidism and no hypothyroidism APLA in different age groups because the chi-square value was 0.974, the p value was -0.614 and the significant p value was <0.05. However, it shows a high prevalence rate (20.8%).

As shown in Table 6, the highest prevalence rate was found to be preterm birth in APLA-positive patients. There was no significant association between the Preterm and Non-Preterm APLA groups, but they were associated with a high prevalence rate (52%). However, this can cause prematurity and NICU admission.

Table 5: Age Group and Hypothyroidism

Hypothyroidism		20-25yr	26-30yr	≤ 31yr	Total
No	Count	3	13	4	20
	% within group	75%	86.6%	66.6%	79.1%
	% of total	12.5%	50%	16.6%	79.1%
Yes	Count	1	2	2	5
	% within group	25%	13.3%	33.3%	20.8%
	% of total	4.1%	8.3%	8.3%	20.8%
Total	Count	4	15	6	24
	% within the group	100%	100%	100%	100%
	% of the total	16.6%	58.3%	24.9%	100%

Chi-square - 0.974, p value -0.614. So, the result shows a statistically insignificant between hypothyroidism APLA and non-hypothyroidism APLA concerning different age groups. The prevalence of hypothyroidism is 20.8%.

Table 6: Preterm and Age Group.

Preterm		20-25yr	25-30yr	≤ 31yr	Total
NO	Count	2	5	5	12
	%within group	50%	35.72%	71.4%	
	%of total	8%	20%	20%	48%
YES	Count	2	9	2	13
	%within group	50%	64.28%	28.5%	
	%within total	8%	36%	8%	52%
Total	Count	4	14	7	25
	% within group	100%	100%	100%	100%
	% of total	16%	56%	28%	100%

Chi square=2.39, p=0.30, statistically not significant. There does not exist statistical significance between preterm of APLA concerning different age groups. Preterm prevalence among APLA was 52%.

A significant association was observed between FGR APLA and non-FGR APLA in different age groups, as shown in Table 7. FGR was present in 20% of APLA patients. Out of 5 FGR cases, 2 had B2GP, 2 had LA and 1 had ACLA independently, and 1 was stillborn and contained both B2GP and ACLA.

Table 7: FGR and age group.

FGR		20-25yr	26-30yr	=31yr	Total
NO	Count	3	10	7	20
	% within the group	75%	71.4%	100%	
	% of total	12%	40%	28%	80%
YES	Count	1	4	0	5
	% within the group	25%	28.5%	0	
	% of total	4%	16%	0	20%
TOTAL	Count	4	14	7	25
	% within the group	100%	100%	100%	100%
	% of total	16%	56%	28%	100%

Chi square18.5, p=0.005-0.002, statistically significant. There was a statistical significance between FGR and non-FGR APLA patients concerning different age groups. FGR was there for 20% of APLA patients.

Table 8 shows the perinatal outcome, i.e., The most frequent obstetric outcome was hypertensive disorder in pregnancy (24%), and the most common fetal outcome was preterm birth (52%), followed by fetal growth restriction (20%). The maximum number of births occurred through the C-section route, and almost all babies stayed in the NICU due to prematurity.

Table 8: Pregnancy outcome.

Obstetric outcome	Frequency	%
Hypertensive disorder in pregnancy	6	24
GDM	2	8.0
Hypothyroidism	5	20.0
Oligohydramnios	3	12.0
Fetal outcome		
Preterm	13	52.0
FGR	5	20.0
Meconium stained	3	12.0

Out of 25 APLA cases, 24% of mothers develop a hypertensive disorder during pregnancy. Among all APLA cases, 13 were preterm, i.e., 52%. Among preterm, 12 underwent LSCS and 1 vaginal delivery. As most of the babies were preterm, the maximum baby stayed in NICU.

4. Discussion

In the present study of 1260 cases, 25 cases were found to be APLA positive, giving a prevalence of 1.98%. It is estimated that the true incidence of the syndrome can be up to 1–2% or more in the general population (Gómez-Puerta et al 2014). In a retrospective review of a cohort of women without SLE by Oshiro and Branch (1996), the prevalence of APLA was 20% in women with recurrent foetal losses and only 5% in healthy women (Oshiro et al 1996). Out of 10 B2GP antibodies, 6 have IgM (60%) and 3 have IgG (30%) subtypes. Four IgG subtypes of ACLA and 1 IgM ACL antibody, i.e., 80% and 20%, respectively, in my study. Considering the type of immunoglobulin of ACLA cases, 87.5% of cases were of IgG type, and only 12.5% were of IgM type (Gharavi and Haris et al 1887).

For both ACLA and anti-B2 glycoprotein ab, the IgM isotype was more prevalent in APS patients, which correlated with the results of my study. There was a significant difference between hypertensive and nonhypertensive APLA patients in different age groups, with a hypertension prevalence of 24%. Preeclampsia generally affects 2–8% of pregnancies (Costedoat-Chalumeau et al 2012). Out of 25 APLA cases, 2 were preeclampsia (4%), and 4 were HTN (16%), which corroborates the results of my study. A cross-sectional study conducted in Florida on 141 286 women who delivered in 2001 showed that women with high aPL titers (n = 88) had an increased risk of preeclampsia or eclampsia (adjusted odds ratio or AOR 2.93), placenta insufficiency (AOR 4.58), and prolonged length of stay at the hospital (>three days, AOR 3.93) (Nodler et al 2009). In the multicenter PREGNANTS cohort, anti-b2GP1 was associated with the lowest live birth rate and the highest incidence of preeclampsia, IUGR, and stillbirth compared with the presence of CL or LA alone (Saccone et al 2017).

Conversely, in a prospective PROMISSE study, LA was the main predictor of adverse pregnancy outcomes in APL carriers (Yelnik et al 2016). The incidence of FGR was still higher in APS, and aCL positivity was the only risk factor associated with FGR. The value of aCL IgM/IgG was positively correlated with FGR in another study performed by Fangfang Xil et al The risk of FGR varies with the aPL type. ACA and β2GP1 are strongly associated with IUGR. The above study shows similarities with my study. Out of 5 FGR cases, 2 had B2GP, 2 had LA and 1 had ACLA independently, and 1 was stillborn and contained both B2GP and ACLA. No clinical significance exists between nonpreterm APLA and preterm APLA patients concerning different age groups. However, the preterm prevalence among APLA patients is 52%, and the common cause of preterm birth is preeclampsia or placental insufficiency. There was a high preterm prevalence of APLA in women with PREPI in a study by Husain et al There was no statistical significance between hypothyroid of APLA patients concerning different age groups. No clinical difference regarding thrombotic and obstetrical events was observed between APS patients with and without TAI (thyroid autoimmunity) (Mavragani et al 2009).

5. Conclusions

From the above study, it can be concluded that poor obstetric outcomes are seen in APLA-positive pregnant patients. The most common antibody to be involved is B2GP ab. In the PREGNANTS cohort study, anti-b2GP was associated with the lowest live birth rate and the highest incidence of preeclampsia, IUGR, and stillbirth compared with the presence of aCL or LA alone. Obstetric APS is a treatable condition, and this serious condition needs to be recognised. It is our duty to further spread knowledge about the diagnosis and treatment. Hence, screening for B2GP antibody will be a far better rewarding, better result, and cost-effective in comparison to the total APLA antibody panel. Therefore, all cases of FGR and early-onset preeclampsia with or without previous spontaneous pregnancy loss should be screened for APS. We can offer this test to the elderly age group (≥35 yr) with single or multiple early pregnancy losses with usg showing the disappearance of cardiac activity in previously live embryos and IVF (in vitro fertilisation) pregnancy. According to the newer diagnostic criteria (2006) for APLA, in cases with a clinical history of ischemic stroke and transient cerebral ischemia, we should screen for beta2 glycoprotein, as b2gp increases the risk of APS independently. The limitation of our study is the small sample size. However, a well-designed prospective multicentric larger population study is needed to completely understand the optimal diagnosis and treatment of APS patients. Further research will be conducted in APS +ve cases on clinically relevant antibodies and standardisation of their detection and various anticoagulant regimens and durations of thromboprophylaxis.

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Ethical considerations

Ethical approval was not needed, as this was an observational-based study.

Conflict of Interest

The authors declare no conflicts of interest.

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References

Bates SM, Greer IA, Middeldorp S, Veenstra DL, Prabulos A, and Vandvik PO (2012) VTE, thrombophilia, antithrombotic therapy, and pregnancy - antithrombotic therapy and prevention of thrombosis, 9th ed: American college of chest physicians evidence-based clinical practice guidelines Chest 141:e691S–e736S.

Bramham K, Hunt BJ, Germain S et al (2010) Pregnancy outcome in different clinical phenotypes of antiphospholipid syndrome. Lupus 19:58-64.

Cervera R, Piette J, Font J et al (2002) Antiphospholipid syndrome: clinical and immunologic manifestations and patterns of disease expression in a cohort of 1,000 patients. Arthritis and Rheumatism 46:1019–1027.

Costedoat-Chalumeau N, Guettrot-Imbert G, Leguern V et al (2012) Pregnancy and antiphospholipid syndrome. Revue de Medecine Interne 33:209–216.

D'Ippolito S, Marana R, Di Nicuolo F et al (2012) Effect of low molecular weight heparins (LMWHs) on antiphospholipid antibodies (aPL)—mediated inhibition of endometrial angiogenesis. PLoS ONE 7e29660.

de Groot PG, Meijers JCM (2011) β2-Glycoprotein I: evolution, structure and function, Journal of Thrombosis and Haemostasis 9:1275–1284.

de Groot PG, Meijers JCM, Urbanus RT (2012) Recent developments in our understanding of the antiphospholipid syndrome. International Journal of Laboratory Hematology 34:223-231.

de Laat B, Pengo V, Pabinger I et al (2009) The association between circulating antibodies against domain I of beta2-glycoprotein I and thrombosis: an international multicenter study. Journal of Thrombosis and Haemostasis 7:1767-1773.

Derksen RHWM and de Groot P G (2008) The obstetric antiphospholipid syndrome. Journal of Reproductive Immunology 77:41–50.

Di Simone N, DiNicuolo F, D'Ippolito S et al (2010) Antiphospholipid antibodies affect human endometrial angiogenesis. Biology of Reproduction 83:212–219.

Evain-Brion D, Guibourdenche J, Tsatsaris V, and Fournier T (2009) Human trophoblast differentiation. Bulletin de l'Academie Nationale de Medecine 193:1017–1025.

Fangfang Xi, YuliangCai, Min Lv, Ying Jiang, Feifei Zhou, Yuan Chen, Lin Jiang, Qiong Luo (2020) Anticardiolipin Positivity Is Highly Associated With Intrauterine Growth Restriction in Women With Antiphospholipid Syndrome. Clinical and Applied Thrombosis/Hemostasis 26:1-7.

Fishman P, Falach-Vaknine E, Zigelman R et al (1993) Prevention of fetal loss in experimental antiphospholipid syndrome by invivo administration of recombinant interleukin-3. Journal of Clinical Investigation 19:1834–1837.

Gharavi AE, Harris EN, Asherson RA, Hughes GR (1987) Anticardiolipin antibodies: isotype distribution and phospholipid specificity. Ann Rheum Dis 46:1-6.

Gómez-Puerta JA, Cervera R (2014) Diagnosis and classification of the antiphospholipid syndrome. J Autoimmun 48-49:20-5.

Hughes GR (1983) Thrombosis, abortion, cerebral disease and the lupus anticoagulant. BMJ 287:1088–1089.

Hughes GRV (1993) The antiphospholipid syndrome: ten years on. Lancet 342:341-44.

Khamashta MA, Cervera R, Asherson RA, Font J, Gil A, Coltart DJ, Vázquez JJ, Paré C, Ingelmo M, Oliver J (1990) Association of antibodies against pho spholipids with heart valve disease in systemic lupus erythematosus. Lancet 1335:1541–1544.

Kwak-Kim J, Socorro L, Agcaoili M et al (2013) Management of women with recurrent pregnancy losses and antiphospholipid antibody syndrome. The American Journal of Reproductive Immunology 69:569–607.

Mahler M, Norman G L, Meroni P L, Khamashta M (2012) Autoantibodies to domain 1 of beta 2 glycoprotein 1: a promising candidate biomarker for risk management in antiphospholipid syndrome. Autoimmunity Reviews 12:313– 317.

Mavragani CP, Danielides S, Zintzaras E, Vlachoyiannopoulos PG, Moutsopoulos HM. (2009) Antithyroid antibodies in antiphospholipid syndrome: prevalence and clinical associations. Lupus 18:1096–9.

Meroni PL, Simone Di, Testoni C, D'Asta M, Acaia B, Caruso A (2004) Antiphospholipid antibodies as cause of pregnancy loss. Lupus 13:649-652.

Meroni PL, Borghi MO, Raschi E, and Tedesco F (2011) Pathogenesis of antiphospholipid syndrome: understanding the antibodies. Nature Reviews Rheumatology 7:330–339.

Meroni P L, Tedesco F, Locati M et al (2010) Anti-phospholipid mantibody mediated fetal loss: Still an open question from apathogenic point of view. Lupus 19:453–456.

Meroni PL, Gerosa M, Raschi E, Scurati S, Grossi C, and Borghi M O (2008) Updating on the pathogenic mechanisms 5 of the antiphospholipid antibodies-associated pregnancy loss Clinical Reviews in Allergy and Immunology 34:332–337.

Mialdea M, Sangle SR, D'CruzDP (2009) Antiphospholipid (Hughes) syndrome: beyond pregnancy morbidity and thrombosis. Journal of Autoimmune Diseases 19:6.

Mulla MJ, Brosens JJ, Chamley LW et al (2009) Antiphospholipid antibodies induces a pro-inflammatory response in first trimester trophoblast via the TLR4/MyD88 pathway.TheAmerican Journal of Reproductive Immunology 62:96–111.

Nishino E, Takagi T, Mitsuda N et al (1990) Effect of low-dose aspirin therapy on utero-placental blood flow and malondialdehyde (MDA) as an indicator of its therapeutic effect.ActaObstetricaetGynaecologica Japonica 42:1641-1647.

Nodler J, Moolamalla S R, Ledger E M, Nuwayhid B S, and Mulla Z D (2009) Elevated antiphospholipid antibody titers and adverse pregnancy outcomes: analysis of a population-based hospital dataset. BMC Pregnancy and Childbirth 9:11.

Oshiro BT, Silver RM, Scott JR, Yu H, Branch DW (1996) Antiphospholipid antibodies and fetal death. Obstet Gynecol 87:489-93.

Rai RS, Regan L, Clifford K et al (1995) Antiphospholipid antibodies and β2-glycoprotein-I in 500 women with recurrent miscarriage: results of a comprehensive screening approach, Human Reproduction 10:2001–2005.

Roubey RAS, Hoffman M (1997) From antiphospholipid syndrome to antibody-mediated thrombosis. Lancet 350:14913.

Saccone G, Berghella V, Maruotti GM, et al (2007) Antiphospholipid antibody profile based obstetric outcomes of primary antiphospholipid syndrome: the PREGNANTS study. Am J Obstet Gynecol 216:525.

Satta N, Kruithof EKO, Reber G, de Moerloose P (2008) Induction of TLR2 expression by inflammatory stimuli is required for endothelial cell responses to lipopeptides. Molecular Immunology 46:145–157.

Shamonki JM, Salmon JE, Hyjek E, Baergen RN (2007) Excessive complement activation is associated with placental injury in patients with antiphospholipid antibodies. The American Journal of Obstetrics and Gynecology 196:1–167.e5.

Skrzypczak J, Jasi´nski P, Wirstlein P, Go´zdziewicz T, Rajewski M (2011) Histologic changes in placenta and chorion of women with antiphospholipid syndrome and inherited thrombophilia. GinekologiaPolska 82:652–663.

Van Horn JT, Craven CK, Branch DW, Silver RM (2004) Histologic features of placentas and abortion specimens from women with antiphospholipid and antiphospholipis-like syndromes. Placenta 25:642–648.

Yelnik CM, Laskin CA, Porter TF et al (2016) Lupus anticoagulant is the main predictor of adverse pregnancy outcomes in aPL positive patients: validation of PROMISSE study results. Lupus Sci Med 3:e00013.