RESEARCH PAPER

Placental Pathology and Neutrophil Extracellular Traps in Antiphospholipid Syndrome: A Comparative Study with Antiphospholipid Syndrome-Like Conditions

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ABSTRACT

Background: Antiphospholipid syndrome (APS) is an acquired autoimmune disorder associated with recurrent thrombosis and adverse pregnancy outcomes. Placental injury resulting from thrombosis and vascular dysfunction is believed to play a major role in fetal morbidity and mortality. In recent years, neutrophil extracellular traps (NETs) have emerged as important mediators of inflammation and immunothrombosis in APS. However, information regarding placental pathology and NET formation in APS-like conditions remains limited.

Methods: We conducted a prospective comparative study on placentas obtained from women diagnosed with APS and APS-like conditions over a two-year period. Twenty placentas from women fulfilling the criteria for APS and twenty placentas from women with APS-like clinical manifestations but negative lupus anticoagulant testing were included. Gross and microscopic placental features were assessed using a standardized scoring system. Immunohistochemistry for myeloperoxidase was performed to quantify polymorphonuclear neutrophils and neutrophil extracellular traps. Clinical, obstetric and pathological parameters were compared between the two groups.

Results: Women in both groups had comparable obstetric outcomes and gestational ages at delivery. We found significantly higher gross infarction scores, microscopic infarction scores and decidual thrombosis in the APS group. Syncytial knots, intervillous fibrin deposition and decidual vasculopathy were also observed more frequently in APS, although statistical significance was not reached. NET formation was markedly increased in APS compared with APS-like conditions. A significant positive correlation was noted between placental infarction and NET ratio in both groups.

Conclusion: Our study demonstrates that placental thrombosis and infarction are more pronounced in APS than in APS-like conditions. Increased NET formation appears to contribute to placental injury and may represent an important mechanism linking inflammation and thrombosis in APS. Further studies involving larger cohorts are needed to clarify the pathogenic pathways operating in APS-like conditions.

Keywords: Antiphospholipid syndrome; Placenta; Neutrophil extracellular traps; Immunothrombosis; Pregnancy loss; Placental infarction

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INTRODUCTION

Antiphospholipid syndrome (APS) is one of the most important acquired thrombophilic disorders encountered in women of reproductive age. It is characterized by recurrent arterial or venous thrombosis and pregnancy-related complications occurring in association with persistent antiphospholipid antibodies [1]. Obstetric manifestations include recurrent pregnancy loss, fetal growth restriction, placental insufficiency, preterm delivery and intrauterine fetal death. Despite improvements in diagnosis and treatment, APS continues to contribute substantially to maternal and fetal morbidity worldwide [2].

The placenta plays a central role in the pathogenesis of obstetric APS. Antiphospholipid antibodies interact with trophoblasts, endothelial cells and coagulation pathways, leading to placental vascular injury and impaired uteroplacental circulation [3]. Histopathological examination of placentas from affected pregnancies has demonstrated several characteristic abnormalities including infarction, decidual vasculopathy, thrombosis,

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increased fibrin deposition and accelerated villous maturation [4,5]. These pathological changes reduce placental perfusion and contribute to adverse fetal outcomes.

In routine practice, we occasionally encounter women who present with clinical manifestations strongly suggestive of APS but do not satisfy the laboratory criteria required for a definite diagnosis. These patients are often categorized as having APS-like or seronegative APS conditions. Although their clinical presentation resembles APS, the underlying mechanisms responsible for placental injury remain poorly understood [6]. Studying placental pathology in these patients may provide useful insights into alternative pathogenic pathways contributing to adverse pregnancy outcomes.

Recent research has highlighted the role of neutrophil extracellular traps (NETs) in autoimmune diseases and thrombotic disorders. NETs are extracellular networks composed of decondensed chromatin, histones and antimicrobial proteins released by activated neutrophils [7]. While NET formation serves as a defence mechanism against infection, excessive NET release may promote endothelial injury, inflammation and thrombosis [8]. Experimental studies have demonstrated that antiphospholipid antibodies can directly stimulate neutrophils to release NETs, thereby enhancing immunothrombotic responses [9,10].

Several investigators have shown increased NET formation in patients with APS and have proposed NET-mediated vascular injury as an important contributor to disease pathogenesis [11,12]. NETs have also been implicated in placental dysfunction through endothelial activation, microvascular thrombosis and impaired maternal-fetal exchange [13,14]. However, comparative studies evaluating NET formation in APS and APS-like conditions remain scarce.

In our study, we examined placentas from women with APS and APS-like conditions to identify differences in gross morphology, histopathological features and NET formation. We also explored the relationship between placental infarction and NET burden. By comparing these two clinically similar groups, we aimed to better understand the pathological mechanisms contributing to adverse pregnancy outcomes and to identify potential targets for future therapeutic intervention.

MATERIALS AND METHODS

Study Design and Setting

We conducted a prospective comparative study over a period of two years in the Department of Pathology at our tertiary care teaching hospital. The study was approved by the Institutional Ethics Committee, and written informed consent was obtained from all participants prior to inclusion.

Study Population

The study included women who underwent testing for lupus anticoagulant (LAC) during pregnancy and whose placentas were subsequently submitted for histopathological examination following delivery.

Based on clinical and laboratory findings, participants were classified into two groups:

APS Group

The APS group consisted of women who fulfilled the revised Sydney classification criteria for antiphospholipid syndrome. These patients had clinical manifestations suggestive of APS along with persistent positivity for lupus anticoagulant on two occasions at least 12 weeks apart.

APS-like Group

The APS-like group consisted of women with clinical manifestations suggestive of obstetric APS, including recurrent pregnancy loss, fetal demise, placental insufficiency or thrombotic events, but who did not fulfil the laboratory criteria for definite APS. These patients were negative for lupus anticoagulant on repeated testing and were therefore classified as APS-like conditions.

A total of 40 placentas were included in the study, comprising 20 placentas from women with APS and 20 placentas from women with APS-like conditions.

Exclusion Criteria

Women with the following conditions were excluded:

- Systemic lupus erythematosus
- Sepsis
- Urinary tract infection
- Hypothyroidism
- Known hereditary thrombophilia
- Chronic systemic illnesses affecting placental morphology

Clinical Data Collection

Demographic information and obstetric details were collected from hospital records. Information regarding maternal age, previous pregnancy losses, thromboembolic events, gestational age at delivery, treatment received during pregnancy and pregnancy outcome was documented.

Placental Examination

All placentas were received fresh in the Department of Pathology and examined according to standard placental pathology protocols.

During gross examination, the following parameters were assessed:

- Placental weight
- Presence and extent of infarction
- Calcification
- Umbilical cord abnormalities

- Membrane abnormalities

Placental weight was compared with the expected 50th percentile weight for the corresponding gestational age.

Representative tissue sections were sampled from the placental disc, membranes, umbilical cord and grossly abnormal areas. Sections were processed routinely and stained with hematoxylin and eosin.

Special stains including Periodic Acid–Schiff (PAS) and Verhoeff–Van Gieson (VVG) were performed wherever indicated.

Histopathological Assessment

Microscopic examination focused on the following placental lesions:

- Infarction
- Syncytial knots
- Intervillous fibrin deposition
- Perivillous fibrinoid change
- Chronic villitis
- Decidual vasculopathy
- Decidual thrombosis

A semi-quantitative scoring system adapted from the method described by Van Horn et al. was used to grade placental lesions.

All slides were independently reviewed by the principal investigator and a perinatal pathologist who was blinded to the clinical diagnosis and laboratory findings.

Immunohistochemistry

Immunohistochemical staining for myeloperoxidase (MPO) was performed on paraffin-embedded placental tissue sections.

Neutrophils showing cytoplasmic MPO positivity with preserved multilobated nuclei were counted as intact polymorphonuclear neutrophils (PMNs).

Neutrophil extracellular traps (NETs) were identified as extracellular MPO-positive material associated with disrupted and decondensed nuclear material within intervillous spaces.

Quantification was performed by counting PMNs and NETs in ten high-power fields (40× magnification). The NET ratio was subsequently calculated for each case.

Outcome Measures

The primary outcome of the study was comparison of placental pathological changes between APS and APS-like groups.

Secondary outcomes included:

- Quantification of NET formation
- Correlation between NET burden and placental infarction
- Evaluation of pregnancy outcomes

Statistical Analysis

Data analysis was performed using R statistical software (version 3.4.2).

Continuous variables were expressed as mean ± standard deviation, while categorical variables were expressed as frequencies and percentages.

Comparisons between groups were performed using:

- Student's t-test for continuous variables
- Chi-square test for categorical variables

Receiver operating characteristic (ROC) analysis was performed to evaluate the diagnostic utility of the NET ratio.

Pearson correlation analysis was used to assess the relationship between placental infarction score and NET ratio.

A p-value of less than 0.05 was considered statistically significant.

RESULTS

Baseline Characteristics and Pregnancy Outcomes

During the study period, 495 women of reproductive age were investigated for lupus anticoagulant. Among them, placental specimens from 40 pregnancies fulfilled the study criteria and were included for analysis. Twenty placentas belonged to women with confirmed APS and twenty belonged to women with APS-like conditions.

The women in both groups were predominantly between 21 and 35 years of age. The mean gestational age at delivery was comparable between APS and APS-like groups (27.45 ± 7.44 weeks versus 26.15 ± 8.53 weeks). Adverse pregnancy outcomes were common in both groups. Intrauterine fetal demise was the most frequent outcome, accounting for 11 cases in the APS group and 10 cases in the APS-like group. Preterm deliveries occurred in 5 women with APS and 8 women with APS-like conditions, while term deliveries were observed in 4 and 2 cases respectively. We did not observe any significant difference in pregnancy outcome between the two groups.

Table 1. Baseline Clinical Characteristics and Pregnancy Outcomes of Women with APS and APS-like Conditions

Variable	APS (n=20)	APS-like (n=20)	P value
Mean gestational age (weeks)	27.45 ± 7.44	26.15 ± 8.53	NS
Intrauterine fetal demise	11	10	NS
Preterm delivery	5	8	NS
Term delivery	4	2	NS

Mean duration of treatment (months)	6 ± XX	6 ± XX	NS

Gross Placental Findings

On gross examination, most placentas from both groups weighed below the expected 50th percentile for gestational age. Reduced placental weight was observed in 85% of APS placentas and 90% of APS-like placentas. However, the difference in mean placental weight between the two groups was not statistically significant.

Placental infarction was identified in both groups, but the extent of infarction was considerably greater in the APS group. Large infarcts involving more than 20% of the placental parenchyma were frequently encountered in APS, whereas extensive infarction was uncommon in APS-like conditions. The difference in gross infarction score was statistically significant (p=0.010).

Table 2. Gross Placental Findings in APS and APS-like Conditions

Parameter	APS (n=20)	APS-like (n=20)	P value
Placental weight (g)	264.1 ± 126.3	213.3 ± 126.6	0.222
Gross infarction score	1.20 ± 0.77	0.65 ± 0.49	0.010
Calcification (n)	7 (35%)	17 (85%)	0.083

Calcification was observed more frequently in APS-like placentas. Grossly appreciable calcification was present in 17 cases (85%) in the APS-like group compared with 7 cases (35%) in the APS group. Although this difference did not reach statistical significance, we noticed a clear tendency towards increased placental calcification among APS-like cases.

Histopathological Findings

Microscopic examination revealed a spectrum of placental lesions in both groups. The most consistent findings included placental infarction, syncytial knot formation, intervillous fibrin deposition and decidual vascular changes.

Microscopic infarction was significantly more extensive in APS placentas. The mean infarction score was 1.4 ± 0.82 in APS compared with 0.75 ± 0.91 in APS-like conditions (p=0.022). Areas of infarction often corresponded to regions showing marked vascular compromise and fibrin deposition.

Table 3. Histopathological Findings in APS and APS-like Conditions.

Histological Feature	APS Mean ± SD	APS-like Mean ± SD	P value
Infarction score	1.40 ± 0.82	0.75 ± 0.91	0.022
Syncytial knots	1.95 ± 0.76	1.41 ± 1.18	0.121
Intervillous fibrin deposition	1.20 ± 0.52	1.15 ± 0.81	0.752
Perivillous fibrinoid change	0.50 ± 0.51	0.55 ± 0.51	0.759
Decidual vasculopathy	0.10 ± 0.31	0.05 ± 0.22	0.548
Decidual thrombosis	0.30 ± 0.48	0	0.008
Chronic villitis	0	0	-

Syncytial knots were observed in both groups but were more frequent in APS. The mean syncytial knot score was 1.95 ± 0.76 in APS and 1.41 ± 1.18 in APS-like conditions. Although the difference was not statistically significant, we consistently observed more prominent villous maturation changes in APS placentas.

Intervillous fibrin deposition was also encountered in both groups. The distribution and extent of fibrin deposition were broadly similar, with mean scores of 1.20 ± 0.52 and 1.15 ± 0.81 respectively. Likewise, perivillous fibrinoid deposition showed no significant difference between groups.

Decidual vasculopathy was identified more often in APS placentas, although statistical significance was not achieved. In contrast, decidual thrombosis showed a striking difference. Six APS placentas demonstrated decidual thrombosis, whereas none of the APS-like placentas showed this feature. This difference was statistically significant (p=0.008).

Chronic villitis was not identified in any placenta included in the study.

IMMUNOHISTOCHEMICAL FINDINGS

Immunohistochemical staining for myeloperoxidase clearly demonstrated neutrophils and neutrophil extracellular traps within the intervillous spaces.

The APS group showed significantly increased NET formation when compared with APS-like conditions. The mean NETratio was 2.5 ± 1.6 in APS and 1.1 ± 0.74 in APS-like placentas (p=0.001). We frequently observed extracellular MPO-positive material associated with disrupted neutrophilic nuclear remnants in APS placentas, indicating active NET formation.

Receiver operating characteristic analysis demonstrated that a NET ratio of 1.25 could predict placental pathology associated with APS with a sensitivity of 85% and specificity of 65%. The area under the curve was 0.797.

Correlation Between NET Formation and Placental Infarction

To determine whether NET formation was associated with placental injury, we assessed the relationship between microscopic infarction scores and NET ratios.

A strong positive correlation was identified in both groups. In the APS group, the correlation coefficient was 0.76 (p=0.0001), whereas the APS-like group demonstrated an even stronger correlation coefficient of 0.90 (p=0.00001).

We found that placentas with higher NET burdens consistently showed more extensive infarction. This observation supports a possible association between NET-mediated immunothrombosis and placental vascular injury.

Table 4. Summary of Significant Placental Findings in APS

Finding	APS	APS-like	Significance
Gross infarction	Increased	Lower	Significant
Microscopic infarction	Increased	Lower	Significant
Decidual thrombosis	Present	Absent	Significant
NET formation	Increased	Lower	Significant
Calcification	Less frequent	More frequent	Trend observed
Chronic villitis	Absent	Absent	Not significant

DISCUSSION

In our study, we compared placental pathology and neutrophil extracellular trap formation in women with APS and APS-like conditions. Both groups had poor obstetric outcomes, but we found more definite thrombotic placental pathology in the APS group. The important findings in our study were significantly higher gross infarction score, microscopic infarction score, decidual thrombosis and NET ratio in APS placentas.

The mean gestational age in our study was comparable between APS and APS-like groups, with 27.45 ± 7.44 weeks in APS and 26.15 ± 8.53 weeks in APS-like conditions. Intrauterine fetal demise was seen in 11 cases in APS and 10 cases in APS-like group. Preterm delivery was seen in 5 cases in APS and 8 cases in APS-like group. This shows that the clinical burden was almost similar in both groups, even though the laboratory profile was different. Van Horn et al. also observed that women with APS-like conditions can show adverse pregnancy outcomes similar to definite APS, supporting the idea that antibody-negative patients may still have significant placental disease [2].

Placental weight was reduced in both groups in our study. We found that 85% of APS placentas and 90.25% of APS-like placentas were below the expected 50th percentile for gestational age. However, there was no statistically significant difference in mean placental weight between APS and APS-like groups. Ogishima et al. also reported no major difference in placental weight between APS and APS-like/SLE-associated groups, although they observed lower placental weight in patients with combined lupus anticoagulant and anticardiolipin antibody positivity [7]. In our study, anticardiolipin antibody and anti-β2 glycoprotein I antibody were not assessed, so this comparison could not be made.

Gross placental infarction was more prominent in APS. The mean gross infarction score was 1.2 ± 0.767 in APS and 0.65 ± 0.489 in APS-like conditions, and this difference was statistically significant (p=0.010). Microscopically also, infarction was significantly higher in APS, with a mean score of 1.4 ± 0.820 compared with 0.75 ± 0.910 in APS-like placentas (p=0.022). Magid et al. reported reduced placental weight and extensive infarction in placentas from patients with SLE and APS [9]. In contrast, Ogishima et al. did not observe extensive infarction in all APS placentas, possibly due to differences in antibody profile, sample size and treatment status [7]. Our findings suggest that infarction remains one of the most important placental lesions in APS, especially when thrombosis is active.

Calcification showed a different pattern. In our study, gross calcification was noted in 7 cases (35%) in APS, while 17 cases (85%) in APS-like group showed calcification. Although this difference did not reach statistical significance, we noticed that calcification was more frequent in APS-like placentas. This finding is interesting because it suggests that APS-like conditions may not be driven purely by the same thrombotic pathway seen in APS. There may be other placental ageing, metabolic, inflammatory or unidentified antibody-mediated mechanisms contributing to calcification in this group.

On histology, syncytial knots were more frequent in APS placentas. The mean score was 1.95 ± 0.76 in APS and 1.41 ± 1.18 in APS-like conditions, but the difference was not statistically significant. Intervillous fibrin deposition was also slightly higher in APS, with a mean score of 1.2 ± 0.52 compared with 1.15 ± 0.81 in APS-like group. Van Horn et al. described increased syncytial knots, infarction and decidual vasculopathy in APS and APS-like placentas, but many of these differences were not statistically significant [2]. Our findings are similar, as many microscopic features were more frequent in APS, but only infarction and decidual thrombosis reached statistical significance.

Decidual thrombosis was one of the strongest histological differences in our study. It was present in 6 APS placentas and absent in all APS-like placentas, and this difference was statistically significant (p=0.008). This supports the classical concept that APS is primarily a thrombotic placental disorder. Van Horn et al. reported thrombosis in a smaller number of APS placentas [2], while Ogishima et al. did not find prominent decidual thrombosis in their APS cases [7]. The higher decidual thrombosis in our study may be related to the selection of clinically severe cases and the presence of persistent lupus anticoagulant positivity.

Chronic villitis was absent in both groups. This is useful because it suggests that the placental damage in our series was more vascular and thrombotic rather than chronic inflammatory villitis pattern. The absence of chronic

villitis also helps to separate APS-related placental injury from infective or chronic inflammatory placental lesions.

The most important observation in our study was the increased NET formation in APS. The mean NET ratio was 2.5 ± 1.6 in APS and 1.1 ± 0.74 in APS-like conditions, and this difference was highly significant (p=0.001). Marder et al. demonstrated NETs in placentas from lupus and preeclampsia pregnancies and showed that NETs may contribute to placental inflammation and vascular injury [3]. Yalavarthi et al. also showed that antiphospholipid antibodies can stimulate neutrophils to release NETs, providing a direct link between aPL antibodies and immunothrombosis [12].

Meng et al. demonstrated in experimental models that NETs play an active role in antiphospholipid antibody-mediated venous thrombosis [11]. This supports our observation that NET burden was higher in APS placentas where decidual thrombosis and infarction were also more prominent. In our study, the NET ratio showed a strong positive correlation with microscopic infarction score in APS (r=0.76, p=0.0001). This suggests that increased NET formation may not be a passive finding, but may contribute to placental vascular occlusion and infarction.

Interestingly, the APS-like group also showed a strong correlation between NET ratio and infarction score (r=0.90, p=0.00001), although the absolute NET burden was lower than APS. This finding suggests that NET-mediated injury may also operate in APS-like conditions, but probably with lesser intensity. It is possible that unidentified antibodies, complement activation, endothelial dysfunction or non-criteria antiphospholipid antibodies may be involved in these patients. This needs further evaluation in larger studies.

ROC analysis in our study showed that a NET ratio cut-off of 1.25 had 85% sensitivity and 65% specificity for predicting APS-associated placental pathology, with an AUC of 0.797. This indicates moderate diagnostic utility. While this cannot be used as a stand-alone diagnostic marker, it may help in understanding the burden of immunothrombotic injury in placental tissue. Further validation is needed before using NET quantification in routine placental pathology reporting.

Overall, our study supports the concept that APS placental pathology is mainly driven by thrombosis, infarction and NET-mediated immunothrombosis. APS-like placentas showed similar poor pregnancy outcomes but lesser decidual thrombosis and lower NET burden. The increased calcification seen in APS-like placentas suggests that additional pathogenic mechanisms may be operating in this group.

STRENGTHS

The main strength of our study is that we compared definite APS with APS-like conditions using both routine histopathology and immunohistochemistry. We also quantified NETs using MPO staining and correlated NET burden with infarction score. The slides were reviewed with perinatal pathology input, and the observer was blinded to clinical and laboratory details.

LIMITATIONS

Our study has a few limitations. The sample size was small, with only 20 placentas in each group. This may explain why some histological findings did not reach statistical significance. The study was done in a single centre. Only lupus anticoagulant testing was used for grouping, while anticardiolipin and anti-β2 glycoprotein I antibodies were not evaluated. Non-criteria antiphospholipid antibodies were also not studied. Long-term neonatal follow-up was not available. The histological scoring system was modified from previous literature but was not externally validated.

CLINICAL IMPLICATIONS

Our findings highlight the importance of detailed placental examination in pregnancies complicated by APS and APS-like conditions. Placental infarction and decidual thrombosis were significantly more common in APS and were associated with increased NET formation. Recognition of these lesions may provide valuable information regarding disease activity and mechanisms of fetal compromise.

The significantly increased NET burden observed in APS suggests that NET-mediated immunothrombosis may represent an important therapeutic target. Strategies aimed at reducing neutrophil activation, NET formation and thrombo-inflammatory pathways may improve placental function and pregnancy outcome in women with APS.

The findings also suggest that APS-like conditions may represent a biologically distinct group. Despite adverse pregnancy outcomes similar to APS, these patients demonstrated less thrombosis and lower NET burden but more extensive calcification. Further studies are required to identify the factors responsible for these differences.

FUTURE DIRECTIONS

Future studies should include larger multicentric cohorts with complete antiphospholipid antibody profiling, including anticardiolipin antibodies, anti-β2 glycoprotein I antibodies and non-criteria antiphospholipid antibodies. Evaluation of complement activation pathways, endothelial injury markers and inflammatory mediators may further improve understanding of placental injury in APS and APS-like conditions.

Long-term neonatal follow-up studies are also required to determine the impact of specific placental lesions on neonatal outcome. In addition, further research evaluating NET-targeted therapies and immunomodulatory approaches may help develop newer treatment strategies for obstetric APS.

CONCLUSION

In conclusion, our study demonstrated that placentas from women with APS show significantly greater infarction, decidual thrombosis and neutrophil extracellular trap formation compared with APS-like conditions. We found

that NET burden correlated strongly with placental infarction, supporting the role of NET-mediated immunothrombosis in placental injury associated with APS.

Although women with APS and APS-like conditions experienced similar adverse pregnancy outcomes, the underlying placental pathology differed. APS was characterized predominantly by thrombotic and infarctive lesions, whereas APS-like placentas showed comparatively less thrombosis but more frequent calcification. These findings suggest that additional pathogenic mechanisms may be involved in APS-like conditions.

Our study adds to the growing evidence that NETs contribute to placental vascular injury in APS and may represent a potential biomarker as well as a therapeutic target. Larger prospective studies are needed to validate these observations and further define the biological differences between APS and APS-like disorders.

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FIGURES

Figure 1A
Distribution of placental infarction scores in antiphospholipid syndrome (APS) and APS-like groups. Extensive infarction (score 2, >20% placental involvement) was observed only in the APS group.

Figure 1B
Gross photograph of placental cut sections showing extensive pale, firm, wedge-shaped infarcted areas (arrow)

in a placenta from a patient with antiphospholipid syndrome.

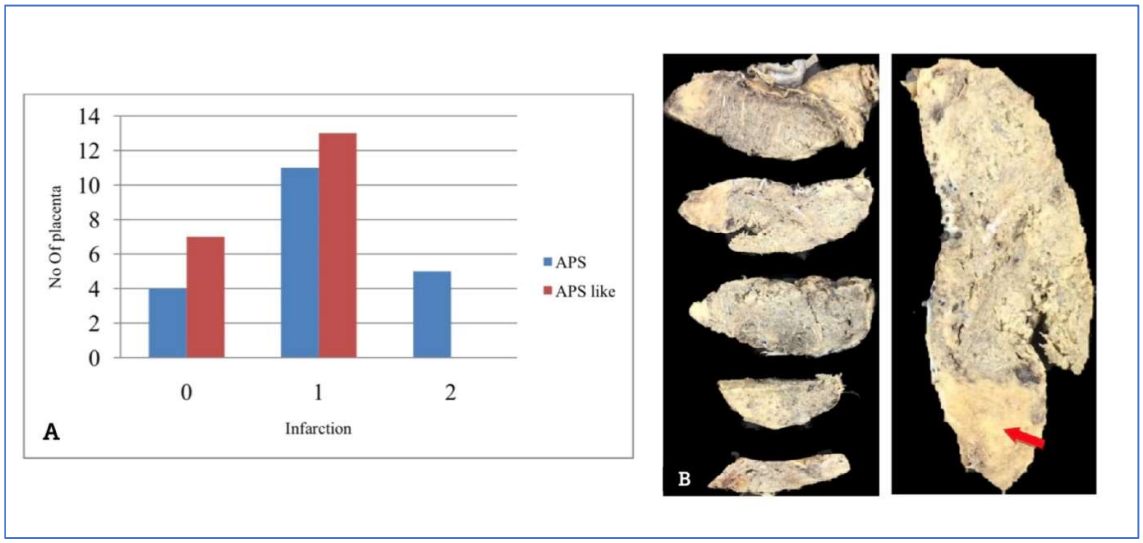

Figure 2

Figure 2A
Placental infarction showing eosinophilic ghost villi with loss of normal villous architecture (H&E, ×40).

Figure 2B
Placental calcification demonstrating coarse dystrophic calcific deposits within placental tissue (H&E, ×40).

Figure 2C
Increased syncytial knot formation indicating accelerated villous maturation (H&E, ×40).

Figure 2D
Perivillous fibrinoid deposition surrounding chorionic villi (H&E, ×40).

Figure 2E
Intervillous fibrin deposition within intervillous spaces (H&E, ×40).

Figure 2F
Decidual vasculopathy showing vascular wall thickening and luminal narrowing (H&E, ×40).

Figure 2G
Periodic Acid–Schiff (PAS) stain highlighting fibrinoid material within placental tissue (PAS, ×40).

Figure 2H
Verhoeff–Van Gieson stain demonstrating elastic fibres within decidual blood vessels (VVG, ×40).

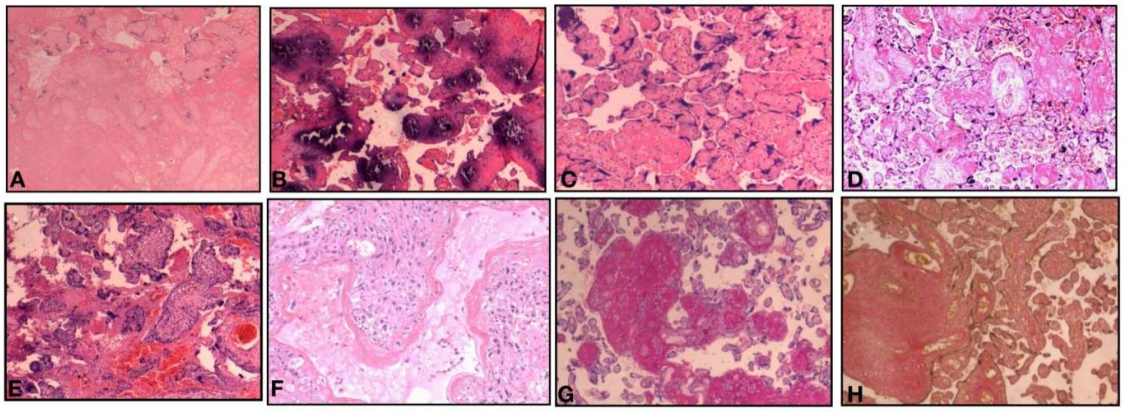

Figure 3

Figure 3A
MPO immunohistochemistry demonstrating intervillous accumulation of neutrophils within placental tissue (MPO IHC, ×10).

Figure 3B
High-power photomicrograph showing extracellular MPO-positive material associated with disrupted neutrophilic nuclei, consistent with neutrophil extracellular trap (NET) formation (MPO IHC, ×40).

Figure 3C

High-power photomicrograph showing intact MPO-positive polymorphonuclear neutrophils within intervillous spaces (MPO IHC, ×40).

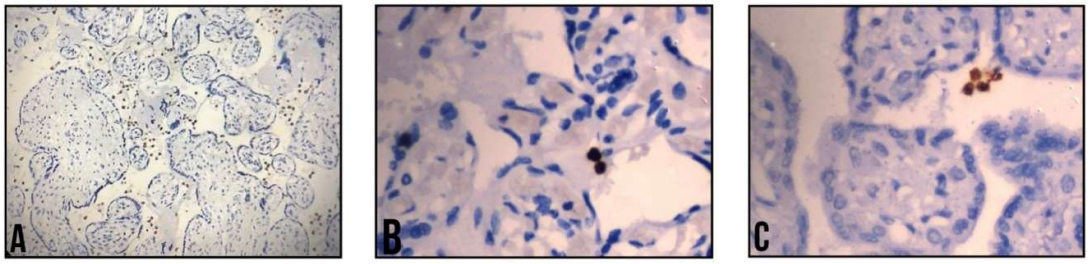

Figure 4

Figure 4A
Box-and-whisker plot comparing NET ratio between APS and APS-like groups. APS placentas demonstrated significantly higher NET burden than APS-like placentas (p=0.001).

Figure 4B
Receiver operating characteristic (ROC) curve demonstrating the diagnostic performance of NET ratio in identifying APS-associated placental pathology. The area under the curve (AUC) was 0.797.