ORIGINAL RESEARCH

Assessing Pregnancy Outcome Predictors: Utilizing Uterine Artery Pulsatility Index and Antiphospholipid Antibody Profile in Early Pregnancy

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ABSTRACT

Background:The study's primary objective is to investigate the relationship between uterine artery pulsatility index (P.I.) values and antiphospholipid antibodies (APLA) values. This analysis seeks to discern potential correlations or interactions between these two parameters, shedding light on their interplay in the context of pregnancy complications. Additionally, the study aims to observe pregnancy outcomes in distinct scenarios: first, where uterine artery P.I. values are elevated while the APLA profile remains normal, and second, when both uterine artery P.I. and APLA profiles show abnormalities.**Methods**: A prospective study included 340 pregnant women with a history of recurrent miscarriage linked to antiphospholipid antibodies. These individuals received a combination of low-dose aspirin and heparin. Doppler assessments of uterine arteries were conducted at 16–18 and 22–24 weeks to identify notches and measure the pulsatility index. **Results**:Out of 234 pregnancies, 228 resulted in live births, and six experienced midtrimester losses. Preeclampsia and small-for-gestational-age (SGA) prevalence was both 10%. Uterine artery pulsatility index at 16–18 and 22–24 weeks was not predictive for preeclampsia or SGA. Doppler accuracy was limited, except for bilateral uterine artery notches at 22–24 weeks in the lupus anticoagulant-positive subgroup. It showed high predictive value with 76% sensitivity, 93% specificity, and 76% positive and 93% negative predictive values. These findings highlight Doppler's nuanced role in specific subgroups for predicting adverse pregnancy outcomes with antiphospholipid antibodies.**Conclusion**:In pregnancies linked to lupus anticoagulant, uterine artery Doppler at 22–24 weeks proves to be a valuable screening test for predicting both preeclampsia and small-for-gestational-age (SGA) infants.

Keywords:preeclampsia,antiphospholipid,anticoagulant.

INTRODUCTION

Antiphospholipid antibodies, encompassing lupus anticoagulant as well as IgG and IgM anticardiolipin antibodies, have been consistently linked to a spectrum of adverse pregnancy outcomes. These outcomes include recurrent fetal loss, preeclampsia, fetal growth restriction, placental abruption, and preterm delivery.[1] The multifaceted impact of these antibodies on pregnancy is thought to involve several mechanisms.One key mechanism revolves around the direct damage inflicted upon trophoblast cells by antiphospholipid antibodies. This interference with trophoblast function can disrupt the delicate balance required for successful implantation and fetal development, contributing to recurrent fetal loss and impaired pregnancy progression.Additionally, the generation of thrombi in the intervillous space is considered a significant factor in the pathophysiology associated with antiphospholipid antibodies.[2] Thrombotic events within the placental vasculature can compromise blood flow to the developing fetus, leading to complications such as fetal growth restriction and placental abruption.Another critical aspect involves the impairment of maternal spiral arterial blood flow. Antiphospholipid antibodies have been implicated in disrupting the normal remodeling of maternal arteries that is essential for establishing proper blood flow to the placenta. This vascular impairment can contribute to the development of preeclampsia and preterm delivery, both of which are characterized by inadequate maternal-fetal blood supply.[3,4,5]In summary, the association between

antiphospholipid antibodies and adverse pregnancy outcomes underscores the intricate interplay of various mechanisms. From direct trophoblast damage to thrombus formation and vascular impairment, understanding these processes is pivotal for developing targeted interventions aimed at mitigating the impact of antiphospholipid antibodies on maternal and fetal health during pregnancy.

Antiphospholipid Antibody Syndrome (APS) is a complex disorder characterized by the presence of elevated levels of specific antibodies, namely lupus anticoagulant antibodies (LAC) and anticardiolipin antibodies (aCL), collectively referred to as antiphospholipid antibodies (aPL).[6] Initially recognized in the early 1980s, APS was initially observed in individuals with systemic lupus erythematosus, and when it occurs in otherwise healthy individuals, it is termed primary APS.A distinctive hallmark of APS is its association with both arterial and venous thrombosis, resulting in an increased propensity for blood clot formation. This heightened thrombotic risk extends beyond the vascular system, impacting pregnancy outcomes. APS is notably linked to adverse events in pregnancy, including early pregnancy loss and fetal death in advanced stages of gestation. The presence of placental thrombosis and infarction often characterizes intrauterine fetal deaths related to aPL. However, it is important to recognize that thrombosis is not uniformly observed in all cases, prompting ongoing investigations into alternative mechanisms contributing to pregnancy loss in APS.[7]The intricate interplay of antiphospholipid antibodies and their impact on both vascular and reproductive health underscores the complexity of APS. Understanding the diverse manifestations of this syndrome is essential for comprehensive patient care, particularly in the context of pregnancy, where APS poses unique challenges and considerations. Ongoing research endeavors aim to delve deeper into the mechanisms underlying pregnancy complications in APS, offering opportunities for improved diagnostics, management strategies, and interventions tailored to enhance both maternal and fetal outcomes. The evolving landscape of APS research holds promise for refining our understanding and approach to this syndrome, ultimately benefiting individuals affected by its diverse clinical manifestations.

The failure of normal trophoblastic implantation leading to abnormal uteroplacental blood flow is associated with subsequent complications, including preeclampsia, fetal growth restriction, and placental abruption. Despite this association, the utility of uterine artery Doppler screening in clinical studies remains a subject of contradiction.Recent meta-analyses have underscored the limitations of uterine artery Doppler in predicting adverse pregnancy outcomes. The flow velocity waveform ratio, a parameter commonly assessed in these screenings, has been found to have limited diagnostic accuracy for predicting preeclampsia, intrauterine growth retardation, and perinatal death.While existing literature on uterine artery Doppler screenings has been sparse, some reports have hinted at its potential in predicting adverse outcomes in specific populations.[8] Notably, in women with primary antiphospholipid syndrome, there have been suggestions that uterine artery Doppler screening may hold promise in predicting the development of preeclampsia or the likelihood of delivering small-for-gestational-age (SGA) infants.The complexity of predicting these pregnancy complications underscores the need for continued research and a nuanced approach to uterine artery Doppler screening. The contradictions in clinical studies emphasize the importance of considering specific risk factors, such as primary antiphospholipid syndrome, in tailoring screening strategies. As our understanding evolves, further investigations may shed light on the specific scenarios where uterine artery Doppler screening can provide valuable insights into the risk assessment and management of adverse pregnancy outcomes.In a prospective study, our aim was to evaluate the predictive utility of midtrimester uterine artery Doppler in women with a history of recurrent miscarriage associated with antiphospholipid antibodies. These women were undergoing treatment with a regimen comprising low-dose aspirin and low-dose heparin. The focus of the study was to assess the ability of uterine artery Doppler measurements during the midtrimester to predict the occurrence of preeclampsia and the likelihood of delivering infants classified as small-for-gestational-age (SGA).

The rationale behind this investigation lies in the unique challenges faced by individuals with recurrent miscarriage and antiphospholipid antibodies, for whom the risk of adverse pregnancy outcomes is heightened.[9] By employing midtrimester uterine artery Doppler, which provides insights into blood flow dynamics, we sought to identify potential markers that could serve as predictors for the development of preeclampsia and the delivery of SGA infants in this specific population.The utilization of a prospective design allows for the real-time collection of data, enhancing the reliability of the study findings. This research contributes to the broader understanding of risk assessment and management strategies in pregnancies complicated by recurrent miscarriage and antiphospholipid antibodies. The results obtained from this study have the potential to inform clinical practices, offering valuable insights for the tailored care of individuals facing these specific challenges during pregnancy.

MATERIALS AND METHODS

Over a span of three years, our study enrolled a cohort of 340 pregnant women, with a median age of 30 years (ranging from 20 to 40 years), all of whom had a history of recurrent miscarriage. Notably, each participant consistently tested positive for

antiphospholipid antibodies on at least two occasions separated by more than 6 weeks before the onset of pregnancy. It is pertinent to highlight that none of the participants had a diagnosis of systemic lupus erythematosus or a history of previous thromboembolic disease.This meticulous inclusion criteria aimed to create a homogeneous study population, ensuring that the observed outcomes and findings could be attributed specifically to the presence of antiphospholipid antibodies in the context of recurrent miscarriage. The absence of systemic lupus erythematosus and prior thromboembolic disease in the study participants adds a layer of specificity, allowing us to focus on the unique challenges associated with antiphospholipid antibodies in isolation.The three-year duration of the study facilitated the collection of comprehensive data over an extended period, enhancing the robustness and reliability of our findings. This research initiative holds promise in contributing valuable insights into risk assessment, management, and outcomes in pregnancies marked by recurrent miscarriage and the presence of antiphospholipid antibodies.

In the realm of high-risk obstetric care, our approach encompasses comprehensive early pregnancy complications management and specialized investigations, which notably include access to state-of-the-art Doppler ultrasound facilities within the fetomaternal unit. This integrative care model is designed to address the unique challenges and complexities associated with high-risk pregnancies.Our dedicated nursing staff plays a pivotal role in this holistic care paradigm. They not only facilitate regular antenatal sessions to monitor and assess the well-being of expectant mothers but also provide essential patient education. Moreover, our nursing team offers hands-on training for self-administered injections when required, empowering patients to actively participate in their care.This multifaceted approach aims to optimize maternal and fetal health outcomes by combining advanced diagnostic tools, specialized medical interventions, and ongoing patient education and support. By integrating these components, we strive to provide a comprehensive and patient-centric framework that caters to the distinctive needs of individuals navigating high-risk pregnancies.

The screening for antiphospholipid antibodies followed a previously established protocol. In summary, the dilute Russell's viper venom time, coupled with a platelet neutralization procedure, was employed to detect lupus anticoagulant. For patient samples exhibiting dilute Russell's viper venom time ratios of at least 1.1, a retesting process with the platelet neutralization procedure was conducted. A positive diagnosis for lupus anticoagulant was assigned when there was a decrease of 10% or more in the ratio.In the case of anticardiolipin antibodies, identification was carried out utilizing a standardized enzyme-linked immunosorbent assay (ELISA). A positive result for anticardiolipin antibodies was defined by an IgG level equal to or greater than 5 GPL (G phospholipid) units and an IgM level equal to or greater than 3 MPL (M phospholipid) units.This meticulous and standardized approach to antibody screening ensures accuracy and consistency in the identification of lupus anticoagulant and anticardiolipin antibodies, providing a solid foundation for the assessment and management of patients with antiphospholipid syndrome and related complications.

After completing 12 weeks of gestation, women attending the recurrent miscarriage clinic were extended invitations to participate in the Doppler study. Prior to inclusion, informed consent was diligently obtained from all participants, and the study received formal approval from the local ethics committee, ensuring adherence to ethical standards. Throughout the designated study period, a total of 576 consecutive women with a singleton pregnancy attending the clinic were initially considered eligible.However, within this pool, 224 women were either not recruited or opted not to participate in the Doppler study. Additionally, four women necessitated termination of pregnancy due to fetal chromosomal abnormalities and were consequently excluded from the study. A further four women were lost to follow-up, leading to their exclusion from the final analysis. As a result, the study cohort ultimately comprised 340 women, constituting the total participants included in our comprehensive analysis.This rigorous recruitment and exclusion process aimed to establish a well-defined and representative cohort for the Doppler study, ensuring the reliability and relevance of the findings to the specific population under investigation.

RESULTS

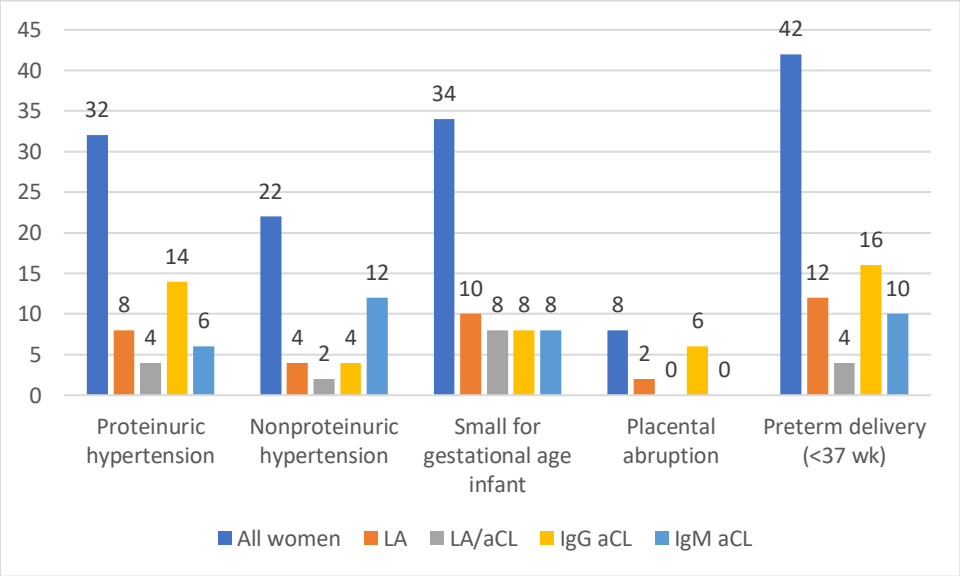
Among the participants, there were a total of 328 live births and 12 midtrimesterfetal losses. The midtrimester losses included 8 fetal deaths occurring between 17 and 23 weeks' gestation, as well as 4 miscarriages at 17 and 19 weeks, which were preceded by spontaneous rupture of membranes.The study delved into pregnancy complications in relation to different antiphospholipid antibody subtypes. The findings, as outlined in Table 1, revealed that pregnancies associated with lupus anticoagulant and IgG anticardiolipin antibodies exhibited the highest prevalence of complications. Conversely, pregnancies linked to IgM anticardiolipin antibodies in isolation demonstrated the lowest rate of complications.This nuanced exploration of pregnancy outcomes based on specific antiphospholipid antibody subtypes adds granularity to our understanding of the varied impact of these antibodies on maternal and fetal health. The identification of differing complication rates among the antibody subtypes contributes valuable insights for risk assessment and tailored management approaches in the context of recurrent miscarriage and antiphospholipid antibodies.

Table 1: Complications in Pregnancies Beyond 24 Weeks' Gestation

	All women	LA	LA/aCL	IgG aCL	IgM aCL
Proteinuric hypertension	32 (10%)	8 (13%)	4(17%)	14 (13%)	6 (4%)
Nonproteinuric hypertension	22 (7%)	4 (6%)	2 (8%)	4 (4%)	12 (8%)
Small for gestational age infant	34 (10%)	10 (16%)	8 (33%)	8 (9%)	8 (5%)
Placental abruption	8 (2.4%)	2 (3%)	0	6 (7%)	0
Preterm delivery (<37 wk)	42 (13%)	12 (19%)	4 (17%)	16 (18%)	10 (7%)

LA = lupus anticoagulant; aCL = anticardiolipin.

Figure1: Complications in Pregnancies Beyond 24 Weeks' Gestation



In the study, proteinuric hypertension was observed in 32 women, constituting 10% of the total participants, while nonproteinuric hypertension was noted in 22 women, representing 7% of the cohort. Among the subset of women experiencing hypertension during pregnancy, the majority, specifically 40 out of 54, delivered at term (between 37 and 41 weeks' gestation). However, severe preeclampsia, necessitating early delivery before 37 weeks' gestation, was noted in seven women.Furthermore, placental abruption, a potentially serious complication, occurred in four pregnancies. Notably, three of these cases were associated with normal maternal blood pressure, while one case was linked to severe preeclampsia. This complex interplay of hypertension and associated complications underscores the multifaceted nature of maternal health during pregnancy, necessitating comprehensive monitoring and management strategies to mitigate adverse outcomes.

In the entire study population, the assessment at 16 weeks' gestation revealed that 20% of women exhibited bilateral uterine artery notches, while 27% had unilateral notches (18% on the left side and 8% on the right side). By 24 weeks' gestation, these values decreased to 9% for bilateral notches and 13% for unilateral notches (8% on the left side and 4% on the right side). Additionally, 11% of women had a high pulsatility index (PI) greater than the 95th centile on the right, and 8% on the left at 16 weeks. These proportions decreased to 5% on the right and 4% on the left at 24 weeks in the overall study population.However, in the subgroup of women with lupus anticoagulant, a higher prevalence of uterine artery notches and high PI was noted. Among women with lupus anticoagulant, 26% had bilateral notches, and 31% had unilateral notches (17% on the left side and 14% on the right side) at 16 weeks' gestation. These values changed to 26% for bilateral notches and 6% for unilateral notches (6% on the left side) at 24 weeks' gestation. In this subgroup, 13% of women had a high uterine artery PI greater than the 95th centile on the left side, and 15% on the right side at 16 weeks' gestation. At 24 weeks, the corresponding values were 15% on the left side and 10% on the right side.These findings highlight the dynamic changes in uterine artery notches and PI throughout pregnancy and emphasize the heightened prevalence of these indicators in women with lupus anticoagulant, underscoring the importance of tailored monitoring and management in this specific population.

DISCUSSION

Antiphospholipid antibodies are linked to a diverse range of obstetric complications, encompassing recurrent miscarriage, preeclampsia, fetal growth restriction, and placental abruption. While thromboprophylaxis has demonstrated a significant improvement in the live birth rate, successful pregnancies in individuals with antiphospholipid

antibodies remain at a heightened risk of complications, particularly preeclampsia and small-for-gestational-age (SGA) infants. Despite the prevalent belief that the presence of antiphospholipid antibodies contributes to abnormal placentation, only a few small-scale studies have endeavored to explore uterine artery Doppler screening in primary antiphospholipid syndrome.Existing reports from these studies suggest that uterine Doppler screening holds promise in predicting the onset of preeclampsia and/or SGA in women diagnosed with primary antiphospholipid syndrome. The limited but valuable insights gleaned from these studies underscore the potential utility of Doppler screening as a prognostic tool in managing pregnancies complicated by antiphospholipid antibodies, shedding light on the intricate relationship between these antibodies and adverse pregnancy outcomes.

Antiphospholipid Syndrome (APS) is widely acknowledged as a pivotal risk factor contributing to a spectrum of obstetric complications, notably including recurrent miscarriage, intrauterine growth restriction (IUGR), pre-eclampsia, fetal death, and preterm labor.[10] Since its original description, APS has emerged as the most significant treatable cause of recurrent miscarriage, presenting a substantial challenge in the realm of reproductive health.The prevalence of antiphospholipid antibodies (aPL), a hallmark feature of APS, in cases of recurrent miscarriage is estimated to be approximately 15.5%. These antibodies, which target phospholipid molecules, have been implicated in disrupting normal placental function and vascular homeostasis, thereby contributing to adverse pregnancy outcomes.For women with aPL and a history of previous pregnancy loss, the risk of subsequent pregnancy loss is a matter of concern. While the precise numerical estimate is not well-defined, it is generally presumed to exceed 60%. This underscores the considerable impact of APS on reproductive health and emphasizes the need for comprehensive management strategies.Recognizing APS early in the course of reproductive care is essential for implementing targeted interventions, close monitoring, and timely therapeutic measures.[11] The intricate interplay between antiphospholipid antibodies and pregnancy complications necessitates a multidisciplinary approach involving obstetricians, hematologists, and other healthcare professionals. Advancements in understanding and managing APS in the context of recurrent miscarriage are crucial for improving overall pregnancy outcomes and enhancing the quality of care for individuals affected by this complex and multifaceted condition.

Various interventions, including both single agents and combinations thereof, have been employed to enhance the suboptimal live birth rates observed among women with antiphospholipid antibodies (aPL), with reported live birth rates ranging from 30% to 100% of pregnancies. However, the treatment of pregnant women positive for aPL to improve pregnancy outcomes remains largely empirical.The challenge lies in the limited availability of data from large, well-designed trials that compare different management options in similar groups of pregnant women grappling with this complex disease. This scarcity of robust evidence complicates the formulation of clear-cut recommendations for the management of pregnancies in women with aPL.[12] Consequently, the approach to managing these pregnancies is often guided by insights gleaned from observational studies, personal experiences, and the opinions of seasoned practitioners familiar with the intricacies of managing women with aPL during pregnancy.Given the inherent complexity and variability in individual cases, a personalized and multidisciplinary approach becomes imperative in navigating the management of pregnancies in women with aPL. The quest for more comprehensive and evidence-based guidelines remains an ongoing challenge in improving the care and outcomes for this particular patient population.

In this expansive prospective study, the primary objective was to assess the effectiveness of midtrimester uterine artery Doppler, specifically examining pulsatility index (PI) and/or diastolic notch, in predicting the occurrence of preeclampsia and/or small-for-gestational-age (SGA) infants among women with a history of recurrent miscarriage associated with antiphospholipid antibodies. These women were undergoing a treatment regimen involving aspirin and heparin.[13] The prevalence of both preeclampsia and SGA was found to be similar, standing at 10%.Surprisingly, the study revealed that uterine artery PI measured at either 16 or 24 weeks and uterine artery notching at 16 weeks did not exhibit significant predictive value for the development of preeclampsia and/or SGA. However, a notable exception was the persistence of bilateral uterine artery notching at 24 weeks, which demonstrated a statistically significant association with the subsequent occurrence of SGA infants and preeclampsia.Despite this specific association, the overall performance of Doppler in predicting these adverse outcomes across the entire study population was deemed suboptimal. The study sheds light on the challenges of relying on midtrimester uterine artery Doppler as a reliable predictor for preeclampsia and SGA in the specific cohort of women with antiphospholipid antibodies and recurrent miscarriage.[14] The noted limitations underscore the complexities of predicting these outcomes, particularly in populations where the prevalence of the conditions is relatively low.The high negative predictive values, though noteworthy, are contextualized within the broader challenge of dealing with diseases of lower prevalence. The findings align with other studies that emphasize the specificity and negative predictive value of midtrimester uterine artery Doppler but highlight its limitations in terms of

sensitivity and positive predictive value, particularly in populations with lower disease prevalence. As such, the study underscores the ongoing need for refined approaches and additional research to enhance the precision of predictive tools in managing pregnancies in this unique and challenging patientpopulation.

In a recent meta-analysis conducted by Chien et al, it was concluded that the utilization of uterine artery flow velocity waveform with or without diastolic notch has limited diagnostic accuracy for predicting conditions such as preeclampsia, intrauterine growth retardation, and perinatal death, applicable to both low- and high-risk populations.[15] However, the specific role of uterine artery diastolic notch alone in predicting preeclampsia within a high-risk population remains a topic requiring further exploration.In alignment with these observations, the present study corroborates and extends these findings. The research reveals that pregnancies associated with lupus anticoagulant or IgG anticardiolipin antibodies carry a heightened risk of developing preeclampsia and small-for-gestational-age (SGA) compared to those associated with IgM anticardiolipin antibodies alone. Notably, uterine artery notching at 22–24 weeks emerged as a predictor for preeclampsia and SGA specifically in pregnancies linked with lupus anticoagulant, whereas it did not demonstrate the same predictive capability in those associated with IgG anticardiolipin antibodies or IgM anticardiolipin antibodies.This nuanced insight underscores the complex interplay of various antiphospholipid antibodies in influencing pregnancy outcomes and highlights the need for tailored approaches in risk assessment and prediction, particularly in high-risk populations. Further exploration and validation of these findings will contribute to refining predictive models and enhancing clinical decision-making for pregnant individuals with antiphospholipid antibodies.

CONCLUSION

In pregnancies where lupus anticoagulant is present, the study underscores the significance of uterine artery Doppler assessment conducted at 22–24 weeks as a valuable screening tool. This screening test proves to be instrumental in predicting the occurrence of two crucial complications: preeclampsia and the birth of small-for-gestational-age (SGA) infants. The implication of this finding is profound, as it provides healthcare practitioners with a practical and timely method for risk assessment and the early identification of potential complications in pregnancies affected by lupus anticoagulant.The incorporation of uterine artery Doppler measurements into the clinical toolkit is highlighted as a proactive strategy for anticipating and managing complications that may arise during pregnancy. This screening approach not only aids in the identification of pregnancies at an elevated risk of preeclampsia but also offers insights into the potential for fetal growth restriction, as indicated by the risk of SGA infants. By leveraging the predictive capabilities of uterine artery Doppler in the context of lupus anticoagulant-associated pregnancies, healthcare professionals can tailor their monitoring and intervention strategies, ultimately contributing to improved outcomes for both mothers and infants.As part of a comprehensive prenatal care strategy, the use of uterine artery Doppler assessments at the specified gestational age becomes a pivotal component in the early identification of risks, allowing for timely interventions and personalized care plans. The study's findings underscore the practical utility of this screening tool in enhancing the precision of risk assessment and management strategies in the complex landscape of pregnancies affected by lupus anticoagulant. Further research and validation of these findings may contribute to the ongoing refinement of clinical protocols and guidelines for managing high-risk pregnancies.

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