四川大学学报（医学版） 2024，55（3）：513－520
J Sichuan Univ（Med Sci） doi: 10.12182/20240560104

在线全文

• 生育力下降现状的生殖医学对策 •

‖ 热点述评 ‖

产科抗磷脂综合征的诊治原则与热点问题述评*

高 睿[1,2]，秦 朗[1,2△]

1. 四川大学华西第二医院 妇产科 生殖医学中心（成都 610041）；
2. 出生缺陷与相关妇儿疾病教育部重点实验室（四川大学）（成都 610041）

【摘要】 产科抗磷脂综合征（obstetric antiphospholipid syndrome, OAPS）是一种与多种病理妊娠事件相关的自身免疫疾病，严重威胁我国育龄期女性生育健康。OAPS的具体发病机制尚不明确，可能与局部微血栓形成及炎症反应有关，全孕期低分子肝素联合阿司匹林治疗是OAPS的标准治疗方案。及时、准确地诊断OAPS是规范化治疗的基础，然而，全世界对OAPS的诊断标准尚未形成共识，这导致诊治不规范的现象普遍存在。本文旨在总结OAPS的诊治原则，并对非标准OAPS的概念、抗磷脂抗体（antiphospholipid antibody, aPL）的检测方法选择、非标准aPL解读与应用、基于aPL的风险分层等热点问题进行述评，为该病的临床管理提供借鉴与参考。

【关键词】 抗磷脂综合征 抗磷脂抗体 产科 诊断 治疗 综述

Obstetric Antiphospholipid Syndrome: Insights on the Diagnosis, Treatment, and Hot Issues *GAO Rui*[1,2], *QIN Lang*[1,2△].
1. *The Reproductive Medical Center, Department of Obstetrics and Gynecology, West China Second University Hospital, Sichuan University*, Chengdu 610041, China; 2. *Key Laboratory of Birth Defects and Related Diseases of Women and Children of the Ministry of Education, Sichuan University*, Chengdu 610041, China
△ Corresponding author, E-mail: cacier@163.com

【**Abstract**】 Obstetric antiphospholipid syndrome (OAPS) is an autoimmune disorder associated with various pathological pregnancies, such as recurrent miscarriage, stillbirth, severe pre-eclampsia and severe placental insufficiency. The persistent presence of antiphospholipid antibodies (aPLs) is the most important laboratory characteristic of OAPS. OAPS severely affects the reproductive health of women of childbearing age in China. Reports indicate that approximately 9.6% stillbirths, 11.5% severe pre-eclampsia, and 54% recurrent miscarriages are associated with OAPS or aPLs. However, the pathogenesis of OAPS remains unclear. Previously, thrombosis at the maternal-fetal interface (MFI) was considered the main mechanism of OAPS-related pathological pregnancies. Consequently, the use of low molecular weight heparin and aspirin throughout pregnancy was recommended to improve outcomes in OAPS patient. In recent years, many studies have found that thrombosis in MFI is uncommon, but various inflammatory factors are significantly increased in the MFI of OAPS patients. Based on these findings, some clinicians have started using anti-inflammatory treatments for OAPS, which have preliminarily improved the pregnancy outcomes. Nevertheless, there is no consensus on these second-line treatments of OAPS. Another troubling issue is the clinical diagnosis of OAPS. Similar to other autoimmune diseases, there are only classification criteria for OAPS, and clinical diagnosis of OAPS depends on the clinicians' experience. The present classification criteria of OAPS were established for clinical and basic research purposes, not for patient clinical management. In clinical practice, many patients with both positive aPLs and pathological pregnancy histories do not meet the strict OAPS criteria. This has led to widespread issues of incorrect diagnosis and treatment. Timely and accurate diagnosis of OAPS is crucial for effective treatment. In this article, we reviewed the epidemiological research progress on OAPS and summarized its classification principles, including: 1) the persistent presence of aPLs in circulation; 2) manifestations of OAPS, excluding other possible causes. For the first point, accurate assessment of aPLs is crucial; for the latter, previous studies regarded only placenta-related pregnancy complications as characteristic manifestations of OAPS. However, recent studies have indicated that adverse pregnancy outcomes related to trophoblast damage, such as recurrent miscarriage and stillbirth, also need to be considered in OAPS. We also discussed several key issues in the diagnosis and treatment of OAPS. First, we addressed the definition of non-standard OAPS and offered our opinion on

* 四川省科技厅项目（No. 2022ZYD0067、No. MZGC20230024）资助
△ 通信作者，E-mail: cacier@163.com
出版日期：2024-05-20

defining non-standard OAPS within the framework of the 2023 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) APS criteria. Then, we discussed the advantages and disadvantages of different aPL testing methods, emphasizing that harmonizing results across platforms and establishing specific reference values are keys to resolving controversies in aPL testing results. We also introduced the application of non-criteria aPLs, especially anti-phosphatidylserine/prothrombin antibody (aPS/PT) and anti-β2 glycoprotein Ⅰ domain Ⅰ antibody (aβ2GPⅠDⅠ). Additionally, we discussed aPL-based OAPS risk classification strategies. Finally, we proposed potential treatment methods for refractory OAPS. The goal is to provide a reference for the clinical management of OAPS.

【Key words】 Antiphospholipid syndrome Antiphospholipid antibodies Obstetrics Diagnosis Treatment Review

抗磷脂综合征(antiphospholipid syndrome, APS)是一种以循环中抗磷脂抗体(antiphospholipid antibody, aPL)持续存在为核心特征的自身免疫疾病,临床表现复杂,主要包括动/静脉血栓形成、病理妊娠事件及微血管病变等[1]。产科APS(obstetric antiphospholipid syndrome, OAPS)指临床表现为病理妊娠事件的APS[2],是APS的一部分,包括单纯性OAPS以及合并血栓事件的OAPS。OAPS对妊娠的影响贯穿全孕期,在早孕期可引起复发性流产,在中晚孕期可诱发死胎、子痫/子痫前期、胎盘功能不全、早产等不良妊娠结局或妊娠并发症[3-4]。

及时诊断和治疗是改善OAPS患者妊娠结局的关键。然而,由于目前尚无公认的诊断标准,临床实践中对OAPS的诊断多参考APS的分类标准,后者依赖完整的病史和辅助检查结果,主要为了规范临床和基础研究而制订,难以应用于复杂的临床情景。OAPS的治疗也存在一定争议,低分子肝素(low molecular weight heparin, LMWH)联合阿司匹林的经典治疗方案对晚期妊娠并发症的防治效果有限,羟氯喹、糖皮质激素等辅助方案尚缺乏证据支持。基于上述争议,OAPS的临床管理始终是生殖医学及产科领域的难题。本文旨在对OAPS的临床诊治原则进行述评,并对OAPS诊治过程中的热点问题进行解析,以期为OAPS的规范化管理提供参考。

1 OAPS的流行病学研究进展

目前尚无针对OAPS的大样本流行病学调查,对OAPS流行病学特征的认识多基于全部APS人群的研究。APS的预估患病率为40~50/100 000人,年发病率为1~2/100 000人年[5]。一项针对1 000例APS患者的研究发现,该病男女患病比约为1∶5,且高达87.3%的患者年龄小于50岁,这提示育龄期女性可能是APS的易感人群[6]。值得关注的是,这些研究只纳入了最典型的APS患者,许多患者处于疾病早期或病史特征不够典型,在调查中被忽略,因而真实的APS患病率和发病率可能高于上述数据。研究显示,分别有9.6%的死胎[7]、11.5%的重度子痫前期或胎盘功能不全[8]、54%的早孕期复发性流产患者外周血中aPL持续阳性[9],而OAPS患者出现死胎、子痫前期、胎儿生长受限的风险分别为健康孕妇的3~5倍、1.5~2.3倍和4.65倍[7, 10],提示OAPS对妊娠的影响意义重大、不容忽视,在病理妊娠的病因筛查中应充分考虑OAPS的可能性。

2 OAPS的分类与临床诊断原则

OAPS是由多种临床和实验室表现组成的综合征,分类标准只能识别最典型的患者,并不适用于所有临床情景,其临床诊断需要由医生结合患者的症状、体征、辅助检查结果等信息综合判断[11-12]。根据APS是否继发于其他自身免疫疾病,可将其分为原发性APS和继发性APS,二者比例大概相等[6],而小样本研究数据显示原发性OAPS比例可能更高[13],这与本团队对中国人群的观察结果一致。目前较为公认的APS分类标准主要包括2006年发布的Sydney标准[14]及2023年美国风湿病学会(American College of Rheumatology, ACR)/欧洲抗风湿病联盟(the European League Against Rheumatism, EULAR)分类标准[15],具体内容分别如表1和表2所示,二者均遵循以下两点原则:①存在相同的致病机制,即循环中持续检出aPL阳性;②具有aPL相关的临床表现,排除其他可能的病因。

2.1 循环中aPL持续存在

aPL是一类以磷脂或磷脂结合蛋白作为靶抗原的自身抗体总称,其中狼疮抗凝物(lupus anticoagulant, LAC)、IgG/IgM型抗心磷脂抗体(anticardiolipin antibody, aCL)和IgG/IgM型抗β2糖蛋白Ⅰ抗体(anti-β2 glycoprotein Ⅰ, aβ2GPⅠ)与病理妊娠事件的关系密切[16],是公认的OAPS实验室指标。LAC指循环中可以和凝血酶原激活物复合体结合的物质,在体外导致凝血时间延长,LAC试验可检出所有与带负电荷磷脂结合的aPL,表现为凝血时间延长,但可被磷脂中和[17]。aCL和aβ2GPⅠ则是针对特定靶抗原的抗体。Sydney标准与ACR/EULAR标准均将间隔12周以上检测2次LAC、aCL或aβ2GPⅠ阳性作为APS的实验室标准。在Sydney标准中,3种指标任意一种

表 1　Sydney标准中OAPS分类依据

Table 1　The classification of OAPS in Sydney criteria

Clinical/laboratory criteria	Classification
Clinical criteria	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;
	One or more premature births of a morphologically normal neonate before the 34th week of gestation because of: 1) eclampsia or severe pre-eclampsia, or 2) recognized features of placental insufficiency*;
	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.
Laboratory criteria	LA present in plasma, on two or more occasions at least 12 weeks apart;
	aCL-IgG/IgM 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;
	aβ2GPⅠ-IgG/IgM 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.

* The features of placental insufficiency include: 1) abnormal or non-reassuring fetal surveillance test(s), e.g. a non-reactive non-stress test, suggestive of fetal hypoxemia, 2) abnormal Doppler flow velocimetry waveform analysis suggestive of fetal hypoxemia, e.g. absent end-diastolic flow in the umbilical artery, 3) oligohydramnios, e.g. an amniotic fluid index of 5 cm or less, or 4) a postnatal birth weight less than the 10th percentile for the gestational age. LA: lupus anticoagulant; aCL: anti-cardiolipin antibody; aβ2GPⅠ: anti-β2 glycoprotein Ⅰ. Obstetric antiphospholipid syndrome requires the combination of at least one clinical and one laboratory criterion.

表 2　2023年ACR/EULAR标准中OAPS的临床和实验室标准评分

Table 2　The clinical and laboratory scores of OAPS in 2023 ACR/EULAR criteria

Criteria	Weight
Obstetric clinical domains and criteria	
⩾3 consecutive pre-fetal (<10 weeks) and/or early (10-16 weeks) fetal deaths, or⩾1 fetal death (16-34 weeks) alone;	1
Fetal death (16-33 weeks) in the absence of pre-eclampsia with severe features or placental insufficiency with severe features;	1
Preeclampsia with severe features or placental insufficiency with severe features (<34 weeks) with or without fetal death;	3
Preeclampsia with severe features and placental insufficiency with severe features (<34 weeks) with or without fetal death.	4
Laboratory domains and criteria	
Antiphospholipid antibody (aPL) testing by coagulation-based functional assays: lupus anticoagulant test	
Positive LA (single – one time)	1
Positive LA (persistent*)	5
aPL testing by solid-phase assays: IgG/IgM aCL and IgG/IgM aβ2GPⅠ enzyme-linked immunosorbent assay (persistent*)	
Moderate or high positive (IgM alone) (aCL and/or aβ2GPⅠ)	1
Moderate positive (IgG) (aCL and/or aβ2GPⅠ)	4
High positive (IgG) (aCL or aβ2GPⅠ)	5
High positive (IgG) (aCL and aβ2GPⅠ)	7

* "Persistent" is defined as a positive result on at least 2 occasions, at least 12 weeks apart. Moderate-level (40-79 units) and high-level (⩾80 units) aCL/aβ2GPⅠ are based on enzyme-linked immunosorbent assays. LA: lupus anticoagulant; aCL: anti-cardiolipin antibody; aβ2GPⅠ: anti-β2 glycoprotein Ⅰ. Classify as obstetric antiphospholipid syndrome for research purposes if there are at least 3 points from clinical domains and at least 3 points from laboratory domains.

持续阳性即满足分类要求[14], 而在ACR/EULAR标准中, LAC、aCL-IgG及aβ2GPⅠ-IgG阳性具有更高比重, 满足APS的实验室标准, 而单独的aCL-IgM及aβ2GPⅠ-IgM阳性不满足APS的实验室标准[15]。

2.2　存在aPL相关的临床表现，排除其他可能的病因

既往研究认为, aPL主要作用于血管内皮细胞、单核细胞等, 造成母胎界面血栓形成, 引起胎盘源性妊娠并发症[18], 主要包括子痫/重度子痫前期及胎盘功能不全, 后者可表现为: ①胎儿监护异常, 如NST无反应型等胎儿宫内缺氧征象; ②异常脐动脉血流多普勒分析结果, 如舒张末期血流反向; ③羊水过少, 如羊水指数≤5 cm; ④胎儿生长受限或小于胎龄儿[15]。aPL与胎盘源性妊娠并发症的相关性得到了较多研究证实[8]。而死胎作为胎盘功能不全的早期表现, 也被发现与aPL密切相关[7, 19]。相较于晚期并发症, 早孕期复发性流产(recurrent miscarriage, RM)与aPL的关系存在一定争议, 部分回顾性研究发现aPL与早孕期RM关系密切[9, 20-22], 也有一部分研究发现早孕期RM患者中aPL的阳性率与对照人群无明显差异[10, 23]。各个研究采用的aPL的检测方法和阈值不同, 早孕期RM的病因复杂, 研究对象的纳入标准不同对结果的影响巨大,

均可导致研究结果的异质性。Sydney标准将≥1次孕10周以上形态学正常的胎死宫内、≥1次因子痫/重度子痫前期/胎盘功能不全引起的34周前的早产纳入OAPS的临床标准,而早孕期RM要求至少≥3次,且排除内分泌、遗传和解剖因素的影响[14]。ACR/EULAR分类标准在此基础上进行了优化,不再强调早产这一结果,更重视早发型子痫/重度子痫前期/胎盘功能不全的表型,但同时下调了早孕期RM和死胎的权重,即单纯表现为早孕期RM和死胎的患者无法分类为OAPS[15]。早孕期RM病因复杂,开展高水平的循证医学研究较为困难,但最新的基础研究表明,aPL对妊娠的影响不完全依赖于胎盘,aPL也可直接作用于滋养细胞或蜕膜组织,造成妊娠丢失[18, 24]。此外,流行病学研究提示早孕期RM是OAPS最常见的表现[13],如在分类标准中排除,或导致临床治疗不及,不符合我国实际情况。

2.3 分类标准与临床诊断的区别

Sydney标准与ACR/EULAR标准均为分类标准,与诊断标准不同,其作用在于减少疾病的异质性,促进临床和基础研究纳入研究对象的同质性,但并不完全适用于疾病的临床诊治。例如,ACR/EULAR标准发布的同时提供了两个APS外部验证队列,明确说明使用的诊断金标准为专家意见[15],提示APS的临床诊断不能完全照搬分类标准。由于针对中国人群的APS研究较少,质量普遍较低,尚无法形成适合我国国情的APS分类或诊断标准。在OAPS的临床诊断过程中,要结合我国国情与患者的实际情况,适当放宽对既往病史的要求,对于表现为早孕期RM、死胎、晚孕期胎盘源性并发症及早产的患者,在排除其他可能因素及获得实验室证据支持下,应及时作出OAPS的临床诊断。

3 OAPS诊断中的热点问题述评

3.1 非标准OAPS的概念

Sydney标准对临床表现的要求较为严苛,因而有研究提出了非标准OAPS的概念。非标准临床表现包括:①连续≥2次孕10周前不能解释的自发性流产;②不连续≥3次孕10周前不能解释的自发性流产;③>34周因子痫/重度子痫前期/胎盘功能不全引起的早产;④>34周因子痫/重度子痫前期/胎盘功能不全引起的胎盘血肿或胎盘早剥。非典型实验室标准包括:①间隔<12周的aPL阳性;②aCL-IgG/IgM或aβ2GPⅠ-IgG/IgM中滴度阳性。满足1条“典型临床标准”+1条“非典型实验室标准”或1条“非典型临床标准”+1条“典型实验室标准”即可分类为非标准OAPS[25-26]。随着ACR/EULAR分类标准的发布,传统非标准OAPS的分类方法不再适用,目前尚无新的方法提出。严苛的分类标准无疑限制了基础和临床研究的开展,本团队基于ACR/EULAR标准提出了新的非标准OAPS分类方法:临床标准≥1分+实验室标准≥1分,并排除其他可疑的病因即可分类为非标准OAPS。值得关注的是,上述分类方法为专家意见,需要进一步开展循证医学研究验证。

3.2 aPL的检测方法选择

aPL检测的争议主要包括检测方法和参考值两方面。国际血栓与止血联盟(International Society on Thrombosis and Haemostasis, ISTH)对LAC的检测方法进行了明确的规定[27],推荐的检测方法包括稀释蝰蛇毒时间和活化部分凝血活酶时间试验法,须进行初筛实验、混合实验和确证实验,并规定了相应的参考值。aCL和aβ2GPⅠ的检测争议较大,现有分类标准推荐的首选检测方法均为酶联免疫吸附测定(enzyme-linked immunosorbent assay, ELISA),所提供的参考值也均基于ELISA。Sydney标准推荐的aCL中高滴度参考值为>40 GPL/MPL或正常人的99分位数,aβ2GPⅠ中高滴度参考值为>正常人的99分位数[14]。ACR/EULAR标准推荐的aCL和aβ2GPⅠ中滴度参考值均为40 units,高滴度参考值均为80 units[15]。然而,ELISA操作复杂、误差较大,不适用于大规模临床应用。化学发光法(chemiluminescent immunoassay, CLIA)等自动化定量检测方法是未来应用的趋势[28-29],但各个平台的检测结果差异较大,结果难以解读。建议各个单位分别依据自己的检测平台建立aCL和aβ2GPⅠ的参考值,并通过ELISA和APS分类标准中推荐的参考值对检测结果进行校准,有条件者还应建立妊娠期特异性参考值[30],通过这种方式,可在最大限度减少因aPL检测带来的误诊和漏诊。

3.3 非标准aPL解读与应用

除经典的aPL外,近年来,研究发现抗磷脂酰丝氨酸/凝血酶原抗体(anti-phosphatidylserine/prothrombin antibody, aPS/PT)-IgG/IgM和抗β2糖蛋白Ⅰ结构域Ⅰ抗体(anti-β2 glycoprotein Ⅰ domain Ⅰ antibody, aβ2GPⅠDⅠ)-IgG也与不良妊娠结局密切相关[31]。凝血酶原又称Ⅱ因子,是凝血途径中至关重要的物质。既往研究探讨了抗凝血酶原抗体(anti-prothrombin antibody, aPT)对血栓事件和病理妊娠事件的影响,但未得出一致的结论。ATSUMI等[32]发现凝血酶原与磷脂酰丝氨酸形成复合物后,可放大其生理功能,而针对这一复合物的自身抗体,即aPS/PT,在APS辅助诊断中的效能更稳定。aβ2GPⅠDⅠ是针对β2GPⅠ结构域Ⅰ的特异性自身抗体,

比经典的aβ2GPⅠ靶点更具有特异性, 可能具有更强的致病效能。一项研究纯化了APS患者体内的aPS/PT和aβ2GPⅠDⅠ, 发现二者在体外条件下可促进脂多糖诱导的单核细胞、血管内皮细胞损伤, 增加组织因子和一氧化氮的表达[33]。另一项研究通过为大鼠静脉注射单克隆大鼠抗大鼠PS/PT IgM抗体成功诱导了大鼠血栓模型, 进一步印证了aPS/PT对血栓事件的影响[34]。

尽管目前对于aPS/PT和aβ2GPⅠDⅠ产生和致病的机制理解尚不深入, 但临床研究均提示aPS/PT和aβ2GPⅠDⅠ对于OAPS具有较好的诊断效能[35-36], 且提示血栓形成的高风险[37-39]、或与经典的aPL高风险谱显著相关[40]。一项回顾性病例对照研究纳入了186例APS患者、48例血清学阴性APS患者和176例阳性对照, 结果显示86.0%的APS患者至少检出1种亚型的aPS/PT阳性, IgG型aPS/PT阳性患者发生静脉血栓事件的风险是对照人群的6.72倍, IgG或IgM型aPS/PT阳性患者发生妊娠丢失的风险是对照人群的9.44倍[31]。晚期妊娠并发症患者aPS/PT-IgG/IgM阳性率也远高于对照组[41]。另一项回顾性病例对照研究纳入了192例APS患者、193例阳性对照和120例健康对照, 发现aβ2GPⅠDⅠ与3种经典的aPLs阳性相关, 显著增加了妊娠期并发症和血栓事件的风险[38]。由于缺乏循证医学证据, 目前aPS/PT和aβ2GPⅠDⅠ尚未纳入OAPS的分类标准, 在临床实践中, 对于临床表现高度疑似OAPS而经典aPL阴性的患者, 可以考虑进一步排查aPS/PT和aβ2GPⅠDⅠ[42], 如发现aPS/PT和aβ2GPⅠDⅠ阳性, 可视为OAPS进行管理。

3.4　基于aPL的风险分层

风险分层是APS临床管理中的重要环节。SCIASCIA等[43]提出的GAPSS评分中纳入了aCL-IgG/IgM、aβ2GPⅠ-IgG/IgM、aPS/PT-IgG/IgM和LAC四种aPL, 分别赋5分、4分、3分和4分, 总分的高低可反映不良妊娠结局或血栓事件的风险程度, 对于OAPS患者治疗的反应性和妊娠成功率也具有一定预测价值[44]。EULAR发布的APS成人管理共识及我国的OAPS诊治专家共识将aPL分为高风险谱(LAC阳性、≥2种经典aPL高滴度阳性)、中风险谱(至少1种经典aPL高滴度阳性)和低风险谱(aPL低滴度阳性或一过性阳性)[25-26]。在ACR/EULAR分类标准中, 持续性的IgG型aCL和/或aβ2GPⅠ中高滴度阳性(ELISA法> 40 units)及LAC阳性均被赋予较高分值, 可视为高风险谱, 而持续性的中高滴度IgM型aCL和/或aβ2GPⅠ阳性(ELISA法> 40 units)及一过性LAC阳性可视为低风险谱[15]。现有风险分层的方法较多, 可根据实际情况使用, 但对临床治疗的指导价值理解尚不够具体, 还需要进一步验证。

4　OAPS治疗中的热点问题解析

OAPS的治疗包括妊娠前、妊娠期和产褥期。对于临床诊断为OAPS的患者, 再次计划妊娠时建议使用75 ~ 100 mg/d小剂量阿司匹林(low dosage of aspirin, LDA), 如OAPS患者常规治疗失败、合并其他自身免疫疾病、高风险谱、合并血栓事件等, 建议备孕期予以200 ~ 400 mg/d羟氯喹治疗。OAPS的产褥期治疗也相对明确, 由于这类患者产后出现血栓事件的风险较高, 建议使用预防剂量LMWH至少至产后6周; 对于既往有血栓史的OAPS患者, 建议使用治疗剂量LMWH至产后6 ~ 12周, 减少产后血栓事件风险。对于非标准OAPS或aPL携带者, 产褥期预防性抗凝治疗的方案应根据患者的情况制定。妊娠期OAPS治疗是临床关注的重点, 全孕期LMWH联合LDA是OAPS患者的标准治疗方案, 可显著降低患者血栓发生风险, 提高患者的活产率[25-26, 45-46]。对于仅有aPL阳性、既往没有APS相关临床表现的患者, 我们推荐预防性给予LDA, 如患者出现疾病进展, 可考虑加用LMWH[47-48]。然而, 近年发表的回顾性队列显示, LMWH联合LDA对OAPS患者妊娠并发症的防治作用有限, 在接受标准治疗后, 仍有约10% ~ 20%的OAPS患者再次发生妊娠丢失、9% ~ 10%的患者再次发生子痫前期[49-50]; 接受标准治疗的OAPS患者早孕期自然流产率、死胎率与健康人群差异无统计学意义, 但早产、重度子痫前期、早发性子痫前期、小于胎龄儿的发生率仍显著高于健康孕妇[50]。临床上将标准治疗失败的OAPS患者称为难治性OAPS, 这类患者的治疗方案尚未达成共识。

经验性的难治性OAPS治疗方案包括羟氯喹、静脉注射免疫球蛋白(intravenous immunoglobulin, IVIG)、小剂量糖皮质激素、治疗剂量LMWH等。羟氯喹是常用的抗疟药, 具有抗炎和免疫调节活性, 且妊娠期安全, 广泛用于妊娠合并自身免疫性疾病的治疗[46]。研究发现, 在标准治疗的基础上添加羟氯喹可显著提高难治性OAPS患者的活产率[51], 降低妊娠并发症发生率[52]。一项系统评价与Meta分析发现, 小剂量IVIG(每月剂量< 2 g/kg)也可改善难治性OAPS患者的妊娠结局, 但原始研究数量较少、质量较低, 需要未来研究进一步探讨[53], 而小剂量糖皮质激素和治疗剂量LMWH对难治性OAPS患者妊娠结局的改善作用有限[53]。基于有限的证据, 我们建议对于难治性OAPS患者或高风险的OAPS患者尽早进行羟氯喹治疗, 如妊娠期出现疾病快速进展或出现其他脏器的受累, 可以考虑IVIG治疗, 但仍需高级别的循证医学证据支持。

5 总结

OAPS是一种复杂的自身免疫疾病,目前学界对其认知尚浅,对OAPS发病机制的研究尚不够深入,其临床诊断、治疗尚未达成共识,因而临床管理过程中普遍存在过度治疗或治疗不及的问题。除本文探讨的热点问题外,OAPS在临床实践过程中还存在很多争议,比如aPL是否有必要在孕期重复监测、aPL检测的时机以及新型检测平台的应用价值、现有的免疫学指标能否监测OAPS患者孕期疾病的进展、非标准OAPS是否应视为OAPS进行治疗、OAPS患者产后是否需要进行长期管理等。需要生殖医学、产科学、风湿免疫学、检验医学等领域的专家共同探讨,制定科学可行的应对策略。总之,OAPS的诊治困难,需要临床医生结合最佳的研究证据、患者的实际情况进行综合决策,针对这些临床实践中的争议,未来还需要开展高质量的科学研究,以期为OAPS的诊治带来新的突破。

* * *

作者贡献声明 高睿负责论文构思和初稿写作,秦朗负责论文构思、经费获取和审读与编辑写作。所有作者已经同意将文章提交给本刊,且对将要发表的版本进行最终定稿,并同意对工作的所有方面负责。

Author Contribution GAO Rui is responsible for conceptualization and writing--original draft. QIN Lang is responsible for conceptualization, funding acquisition, and writing--review and editing. All authors consented to the submission of the article to the Journal. All authors approved the final version to be published and agreed to take responsibility for all aspects of the work.

利益冲突 所有作者均声明不存在利益冲突

Declaration of Conflicting Interests All authors declare no competing interests.

参 考 文 献

[1] RUIZ-IRASTORZA G, CROWTHER M, BRANCH W, *et al*. Antiphospholipid syndrome. Lancet, 2010, 376(9751): 1498–1509. doi: 10.1016/s0140-6736(10)60709-x.

[2] SCHREIBER K, SCIASCIA S, De GROOT P G, *et al*. Antiphospholipid syndrome. Nat Rev Dis Primers, 2018, 4: 17103. doi: 10.1038/nrdp.2017.103.

[3] SCHREIBER K, HUNT B J. Managing antiphospholipid syndrome in pregnancy. Thromb Res, 2019, 181: S41–S46. doi: 10.1016/s0049-3848(19)30366-4.

[4] MERONI P L, BORGHI M O, GROSSI C, *et al*. Obstetric and vascular antiphospholipid syndrome: same antibodies but different diseases? Nat Rev Rheumatol, 2018, 14(7): 433-440. doi: 10.1038/s41584-018-0032-6.

[5] DABIT J Y, VALENZUELA-ALMADA M O, VALLEJO-RAMOS S, *et al*. Epidemiology of antiphospholipid syndrome in the general population. Curr Rheumatol Rep, 2022, 23(12): 85. doi: 10.1007/s11926-021-01038-2.

[6] CERVERA R, PIETTE J C, FONT J, *et al*. Antiphospholipid syndrome: clinical and immunologic manifestations and patterns of disease expression in a cohort of 1, 000 patients. Arthritis Rheum, 2002, 46(4): 1019–1027. doi: 10.1002/art.10187.

[7] SILVER R M, PARKER C B, REDDY U M, *et al*. Antiphospholipid antibodies in stillbirth. Obstet Gynecol, 2013, 122(3): 641–657. doi: 10.1097/AOG.0b013e3182a1060e.

[8] GIBBINS K J, TEBO A E, NIELSEN S K, *et al*. Antiphospholipid antibodies in women with severe preeclampsia and placental insufficiency: a case-control study. Lupus, 2018, 27(12): 1903–1910. doi: 10.1177/0961203318787035.

[9] SANTOS T D S, IEQUE A L, De CARVALHO H C, *et al*. Antiphospholipid syndrome and recurrent miscarriage: a systematic review and meta-analysis. J Reprod Immunol, 2017, 123: 78–87. doi: 10.1016/j.jri.2017.09.007.

[10] SHEHATA H, ALI A, SILVA-EDGE M, *et al*. Thrombophilia screening in women with recurrent first trimester miscarriage: is it time to stop testing? --a cohort study and systematic review of the literature. BMJ Open, 2022, 12(7): e059519. doi: 10.1136/bmjopen-2021-059519.

[11] ARINGER M, COSTENBADER K, DAIKH D, *et al*. 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus. Ann Rheum Dis, 2019, 78(9): 1151–1159. doi: 10.1136/annrheumdis-2018-214819.

[12] RAMOS-CASALS M, BRITO-ZERÓN P, BOMBARDIERI S, *et al*. EULAR recommendations for the management of Sjögren's syndrome with topical and systemic therapies. Ann Rheum Dis, 2020, 79(1): 3–18. doi: 10.1136/annrheumdis-2019-216114.

[13] ALIJOTAS-REIG J, FERRER-OLIVERAS R, RUFFATTI A, *et al*. The European Registry on Obstetric Antiphospholipid Syndrome (EUROAPS): a survey of 247 consecutive cases. Autoimmun Rev, 2015, 14(5): 387–395. doi: 10.1016/j.autrev.2014.12.010.

[14] MIYAKIS S, LOCKSHIN M D, ATSUMI T, *et al*. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost, 2006, 4(2): 295–306. doi: 10.1111/j.1538-7836.2006.01753.x.

[15] BARBHAIYA M, ZUILY S, NADEN R, *et al*. 2023 ACR/EULAR antiphospholipid syndrome classification criteria. Ann Rheum Dis, 2023, 82(10): 1258–1270. doi: 10.1136/ard-2023-224609.

[16] PANTHAM P, ABRAHAMS V M, CHAMLEY L W. The role of anti-phospholipid antibodies in autoimmune reproductive failure. Reproduction, 2016, 151(5): R79–R90. doi: 10.1530/rep-15-0545.

[17] CHATURVEDI S, McCRAE K R. Diagnosis and management of the antiphospholipid syndrome. Blood Rev, 2017, 31(6): 406–417. doi: 10.1016/j.blre.2017.07.006.

[18] MERONI P L, BORGHI M O, RASCHI E, *et al*. Pathogenesis of antiphospholipid syndrome: understanding the antibodies. Nat Rev Rheumatol, 2011, 7(6): 330–339. doi: 10.1038/nrrheum.2011.52.

[19] PAGE J M, CHRISTIANSEN-LINDQUIST L, THORSTEN V, *et al*. Diagnostic tests for evaluation of stillbirth: results from the stillbirth collaborative research network. Obstet Gynecol, 2017, 129(4): 699–706. doi: 10.1097/aog.0000000000001937.

[20] XU J, CHEN D, DUAN X, *et al*. The association between

antiphospholipid antibodies and late fetal loss: a systematic review and meta-analysis. Acta Obstet Gynecol Scand, 2019, 98(12): 1523–1533. doi: 10.1111/aogs.13665.

[21] STERN C, CHAMLEY L, HALE L, *et al*. Antibodies to beta2 glycoprotein Ⅰ are associated with *in vitro* fertilization implantation failure as well as recurrent miscarriage: results of a prevalence study. Fertil Steril, 1998, 70(5): 938–944. doi: 10.1016/s0015-0282(98)00312-4.

[22] SUGI T, KATSUNUMA J, IZUMI S, *et al*. Prevalence and heterogeneity of antiphosphatidylethanolamine antibodies in patients with recurrent early pregnancy losses. Fertil Steril, 1999, 71(6): 1060–1065. doi: 10.1016/s0015-0282(99)00119-3.

[23] ANDREOLI L, CHIGHIZOLA C B, BANZATO A, *et al*. Estimated frequency of antiphospholipid antibodies in patients with pregnancy morbidity, stroke, myocardial infarction, and deep vein thrombosis: a critical review of the literature. Arthritis Care Res (Hoboken), 2013, 65(11): 1869–1873. doi: 10.1002/acr.22066.

[24] TONG M, VIALL C A, CHAMLEY L W. Antiphospholipid antibodies and the placenta: a systematic review of their *in vitro* effects and modulation by treatment. Hum Reprod Update, 2015, 21(1): 97–118. doi: 10.1093/humupd/dmu049.

[25] TEKTONIDOU M G, ANDREOLI L, LIMPER M, *et al*. EULAR recommendations for the management of antiphospholipid syndrome in adults. Ann Rheum Dis, 2019, 78(10): 1296–1304. doi: 10.1136/annrheumdis-2019-215213.

[26] 中华医学会围产医学分会. 产科抗磷脂综合征诊断与处理专家共识. 中华围产医学杂志, 2020, 23(8): 517–522. doi: 10.3760/cma.j.cn113903-20200402-00299.
Society of Perinatal Medicine, Chinese Medical Association. Expert consensus on diagnosis and management of obstetric antiphospholipid syndrome. Chin J Perinat Med, 2020, 23(8): 517–522. doi: 10.3760/cma.j.cn113903-20200402-00299.

[27] PENGO V, TRIPODI A, REBER G, *et al*. Update of the guidelines for lupus anticoagulant detection. Subcommittee on Lupus Anticoagulant/Antiphospholipid Antibody of the Scientific and Standardisation Committee of the International Society on Thrombosis and Haemostasis. J Thromb Haemost, 2009, 7(10): 1737–1740. doi: 10.1111/j.1538-7836.2009.03555.x.

[28] MAHLER M, BENTOW C, SERRA J, *et al*. Detection of autoantibodies using chemiluminescence technologies. Immunopharmacol Immunotoxicol, 2016, 38(1): 14–20. doi: 10.3109/08923973.2015.1077461.

[29] CINQUANTA L, FONTANA D E, BIZZARO N. Chemiluminescent immunoassay technology: what does it change in autoantibody detection? Auto Immun Highlights, 2017, 8(1): 9. doi: 10.1007/s13317-017-0097-2.

[30] GAO R, YUE X, HUANG W, *et al*. Trimester-specific reference values for the anticardiolipin antibody by chemiluminescence immunoassay in healthy pregnancy. Clin Chem Lab Med, 2022, 60(6): e146–e149. doi: 10.1515/cclm-2022-0044.

[31] SHI H, ZHENG H, YIN Y F, *et al*. Antiphosphatidylserine/prothrombin antibodies (aPS/PT) as potential diagnostic markers and risk predictors of venous thrombosis and obstetric complications in antiphospholipid syndrome. Clin Chem Lab Med, 2018, 56(4): 614–624. doi: 10.1515/cclm-2017-0502.

[32] ATSUMI T, IEKO M, BERTOLACCINI M L, *et al*. Association of autoantibodies against the phosphatidylserine-prothrombin complex with manifestations of the antiphospholipid syndrome and with the presence of lupus anticoagulant. Arthritis Rheum, 2000, 43(9): 1982–1993. doi: 10.1002/1529-0131(200009)43:9<1982::Aid-anr9>3.0.Co;2-2.

[33] CIFU A, DOMENIS R, PISTIS C, *et al*. Anti-beta2-glycoprotein I and anti-phosphatidylserine/prothrombin antibodies exert similar pro-thrombotic effects in peripheral blood monocytes and endothelial cells. Auto Immun Highlights, 2019, 10(1): 3. doi: 10.1186/s13317-019-0113-9.

[34] YAMADA M, KAWAKAMI T, TAKASHIMA K, *et al*. Establishment of a rat model of thrombosis induced by intravenous injection of anti-phosphatidylserine-prothrombin complex antibody. Rheumatology (Oxford), 2017, 56(6): 1013–1018. doi: 10.1093/rheumatology/kew477.

[35] ZHANG S, WU Z, ZHANG W, *et al*. Antibodies to phosphatidylserine/prothrombin (aPS/PT) enhanced the diagnostic performance in Chinese patients with antiphospholipid syndrome. Clin Chem Lab Med, 2018, 56(6): 939–946. doi: 10.1515/cclm-2017-0811.

[36] HU C, LI S, XIE Z, *et al*. Evaluation of the diagnostic value of non-criteria antibodies for antiphospholipid syndrome patients in a Chinese cohort. Front Immunol, 2021, 12: 741369. doi: 10.3389/fimmu.2021.741369.

[37] LEE J S, GU J, PARK H S, *et al*. Coexistence of anti-beta2-glycoprotein Ⅰ domain Ⅰ and anti-phosphatidylserine/prothrombin antibodies suggests strong thrombotic risk. Clin Chem Lab Med, 2017, 55(6): 882–889. doi: 10.1515/cclm-2016-0676.

[38] LIU T, GU J, WAN L, *et al*. Anti-β2GP Ⅰ domain 1 antibodies stratify high risk of thrombosis and late pregnancy morbidity in a large cohort of Chinese patients with antiphospholipid syndrome. Thromb Res, 2020, 185: 142–149. doi: 10.1016/j.thromres.2019.11.029.

[39] KIM H, KIM J E, HWANG S M, *et al*. Synergistic thrombotic risk of antibodies against phosphatidylserine and prothrombin and beta-2-glycoprotein Ⅰ. Clin Appl Thromb Hemost, 2014, 20(4): 442–447. doi: 10.1177/1076029613497424.

[40] HOXHA A, RUFFATTI A, MATTIA E, *et al*. Relationship between antiphosphatidylserine/prothrombin and conventional antiphospholipid antibodies in primary antiphospholipid syndrome. Clin Chem Lab Med, 2015, 53(8): 1265–1270. doi: 10.1515/cclm-2014-1129.

[41] FODDAI S G, RADIN M, CECCHI I, *et al*. The prevalence of antiphospholipid antibodies in women with late pregnancy complications and low-risk for chromosomal abnormalities. J Thromb Haemost, 2020, 18(11): 2921–2928. doi: 10.1111/jth.15053.

[42] PIGNATELLI P, ETTORRE E, MENICHELLI D, *et al*. Seronegative antiphospholipid syndrome: refining the value of "non-criteria" antibodies for diagnosis and clinical management. Haematologica, 2020, 105(3): 562–572. doi: 10.3324/haematol.2019.221945.

[43] SCIASCIA S, SANNA G, MURRU V, *et al*. GAPSS: the Global Anti-Phospholipid Syndrome Score. Rheumatology (Oxford), 2013, 52(8): 1397–1403. doi: 10.1093/rheumatology/kes388.

[44] RADIN M, CECCHI I, SCHREIBER K, *et al*. Pregnancy success rate and response to heparins and/or aspirin differ in women with antiphospholipid antibodies according to their Global Antiphos Pholipid Syndrome Score. Semin Arthritis Rheum, 2020, 50(3): 553–556. doi: 10.1016/j.semarthrit.2020.01.007.

[45] HAMULYAK E N, SCHERES L J, MARIJNEN M C, *et al*. Aspirin or heparin or both for improving pregnancy outcomes in women with persistent antiphospholipid antibodies and recurrent pregnancy loss. Cochrane Database Syst Rev, 2020, 5: CD012852. doi: 10.1002/14651858.CD012852.pub2.

[46] ANDREOLI L, BERTSIAS G K, AGMON-LEVIN N, *et al*. EULAR recommendations for women's health and the management of family planning, assisted reproduction, pregnancy and menopause in patients with systemic lupus erythematosus and/or antiphospholipid syndrome. Ann Rheum Dis, 2017, 76(3): 476–485. doi: 10.1136/annrheumdis-2016-209770.

[47] GAO R, ZENG X, QIN L. Systemic autoimmune diseases and recurrent pregnancy loss: research progress in diagnosis and treatment. Chin Med J (Engl), 2021, 134(17): 2140–2142. doi: 10.1097/cm9.0000000000001691.

[48] GAO R, QIN L. Correspondence on 'EULAR recommendations for the management of antiphospholipid syndrome in adults'. Ann Rheum Dis, 2023, 82(5): e106. doi: 10.1136/annrheumdis-2021-220092.

[49] LOCKSHIN M D, KIM M, LASKIN C A, *et al*. Prediction of adverse pregnancy outcome by the presence of lupus anticoagulant, but not anticardiolipin antibody, in patients with antiphospholipid antibodies. Arthritis Rheum, 2012, 64(7): 2311–2318. doi: 10.1002/art.34402.

[50] BOUVIER S, COCHERY-NOUVELLON E, LAVIGNE-LISSALDE G, *et al*. Comparative incidence of pregnancy outcomes in treated obstetric antiphospholipid syndrome: the NOH-APS observational study. Blood, 2014, 123(3): 404–413. doi: 10.1182/blood-2013-08-522623.

[51] MEKINIAN A, LAZZARONI M G, KUZENKO A, *et al*. The efficacy of hydroxychloroquine for obstetrical outcome in anti-phospholipid syndrome: data from a European multicenter retrospective study. Autoimmun Rev, 2015, 14(6): 498–502. doi: 10.1016/j.autrev.2015.01.012.

[52] GERDE M, IBARRA E, MAC KENZIE R, *et al*. The impact of hydroxychloroquine on obstetric outcomes in refractory obstetric antiphospholipid syndrome. Thromb Res, 2021, 206: 104–110. doi: 10.1016/j.thromres.2021.08.004.

[53] RUFFATTI A, TONELLO M, FAVARO M, *et al*. The efficacy and safety of second-line treatments of refractory and/or high risk pregnant antiphospholipid syndrome patients. A systematic literature review analyzing 313 pregnancies. Semin Arthritis Rheum, 2021, 51(1): 28–35. doi: 10.1016/j.semarthrit.2020.10.001.

（2024－01－16收稿，2024－04－15修回）

编辑 余 琳

本 刊 征 稿 启 事

《四川大学学报(医学版)》(原《华西医科大学学报》)是由教育部主管、四川大学主办的综合性医药类学术刊物，以报道医学相关学科的科研成果为主。主要阅读对象为从事医药卫生工作的科研人员及高等医药院校的师生。2021年起，本刊设有专家笔谈、专家共识、指南解读、医学教育、中医药·中西医结合、论著、临床研究及新技术新方法等栏目。

创刊以来，本刊曾荣获各级部门颁发的数次荣誉称号，如全国优秀科技期刊一等奖、国家期刊奖提名奖、国家期刊奖百种重点期刊奖、教育部中国高校精品科技期刊、中国国际影响力优秀学术期刊、中国高校编辑出版质量优秀科技期刊、中国高校百佳科技期刊等。现已被中国科技论文与引文数据库(CSTPCD)、中国科学引文数据库(CSCD)(核心版)、北京大学图书馆《中文核心期刊要目总览》、中国学术期刊网全文数据库(CNKI)、美国《医学索引》(IM/Medline)、美国生物医学全文数据库PubMed Central(PMC)、美国EBSCO学术数据库、美国《生物学文摘》(BA)、美国《化学文摘》(CA)、荷兰《文摘与引文数据库》(Scopus)、日本科学技术振兴机构数据库(JST)等检索系统收录。

凡属于国家重点研发计划、国家自然科学基金及其他部省级以上科研基金资助的来稿或具有创新性、实用性等的来稿，编辑部将优先发表。欢迎积极投稿！

本刊在线投稿网址：https://ykxb.scu.edu.cn

地址：四川省成都市人民南路三段17号《四川大学学报(医学版)》编辑部

邮政编码：610041

联系电话：(028)85501320，(028)85500106

E-mail：scuxbyxb@scu.edu.cn

《四川大学学报(医学版)》编辑部