

doi: 10.13241/j.cnki.pmb.2019.14.037

妊娠梅毒患者外周血中 Th17 和 Treg 细胞水平及其临床意义分析 *

彭 莉¹ 蒋传好² 焦 巍¹ 程杨艳¹ 梁 惠¹

(1 长沙市妇幼保健院 检验科 湖南 长沙 410006; 2 中南大学湘雅附二医院 检验科 湖南 长沙 410011)

摘要 目的:探讨妊娠梅毒患者外周血中 Th17 和 Treg 细胞水平及其临床意义。**方法:**选择 2015 年 4 月至 2016 年 5 月我院收治的 35 例妊娠梅毒患者作为观察组,并选择同期进行孕检的健康孕妇 30 例作为对照组。分析和比较其外周血 Th17 和 Treg 细胞水平及其诊断妊娠梅毒的临床价值。**结果:**观察组患者外周血 Th17 水平显著高于对照组,而外周血 Treg 水平显著低于对照组 ($P<0.05$)。多因素 logistic 回归分析结果显示外周血 Th17 和 Treg 水平与妊娠梅毒发病具有明显相关性。外周血 Th17 诊断妊娠梅毒的 AUC 为 0.776,95%CI 为 0.656~0.896,外周血 Treg 诊断妊娠梅毒的 ROC 曲线下的面积(area under curve,AUC)为 0.947,95%CI 为 0.897~0.997,Th17+Treg 诊断妊娠梅毒的 AUC 为 0.960,95%CI 为 0.913~1.000;Th17 和 Treg 单独检测分别和联合检测曲线下面积比较均具有显著差异($Z=-2.807$ 、 -0.375 , $P<0.05$);Th17+Treg 联合检测的特异度、准确度分别为 91.73%、93.28%,显著高于各指标单独检测($P<0.05$)。**结论:**妊娠梅毒患者外周血 Th17 细胞增多,Treg 细胞减少,联合检测外周血 Th17 和 Treg 细胞水平诊断妊娠梅毒具有较高的准确度,可作为诊断妊娠梅毒的重要参考指标。

关键词:妊娠梅毒;Th17 细胞;Treg 细胞

中图分类号:R714.259 **文献标识码:**A **文章编号:**1673-6273(2019)14-2771-04

Analysis of the Expression and Clinical Significance of Th17 and Treg Cells in the Peripheral Blood for the Pregnant Syphilis Patients*

PENG Li¹, JIANG Chuan-hao², JIAO Wei¹, CHENG Yang-yan¹, LIANG Hui¹

(1 Changsha maternal and child health care laboratory, Changsha, Hunan, 410006, China;

2 Department of clinical laboratory; Second Affiliated Hospital of Central South University, Changsha, Hunan, 410011, China)

ABSTRACT Objective: To study the expression and clinical significance of Th17 and Treg cells in the peripheral blood for the pregnant syphilis patients. **Methods:** 35 pregnant syphilis patients admitted to our hospital from April 2015 to May 2016 were selected as the observation group, and 30 healthy pregnant women were selected as the control group. The levels of Th17 and Treg cells in the peripheral blood and their clinical value for the diagnosis of pregnancy syphilis were analyzed. **Results:** The peripheral blood Th17 level in the observation group was significantly higher than that in the control group, while the peripheral blood Treg level was significantly lower than that in the control group ($P<0.05$). Multivariate logistic regression analysis showed that the levels of Th17 and Treg in the peripheral blood were significantly correlated with the incidence of pregnancy syphilis. The area under the ROC Curve (AUC) of peripheral blood Th17 for the diagnosis of pregnancy syphilis was 0.776, and the 95%ci was 0.656~0.896. The AUC of peripheral blood Treg for the diagnosis of pregnancy syphilis was 0.947, and the 95%ci was 0.897~0.997. The AUC of Th17+Treg for the diagnosis of pregnancy syphilis was 0.960, and the 95%ci was 0.913~1.000. The AUC of single detection of Th17 or Treg were lower than that of combination of Th17 and Treg ($Z=-2.807$, -0.375 , $P<0.05$). The specificity and accuracy of combined detection of Th17+Treg were 91.73% and 93.28%, respectively, which were significantly higher than those of single detection of Th17 or Treg ($P<0.05$). **Conclusion:** Peripheral blood Th17 cells were increased and Treg cells were decreased in the patients with pregnancy syphilis. Combined detection of peripheral blood Th17 and Treg cells showed higher accuracy in the diagnosis of pregnancy syphilis, which can be used as important reference index for the diagnosis of pregnancy syphilis.

Key words: Syphilis in pregnancy; Th17 cells; Treg cells

Chinese Library Classification (CLC): R714.259 **Document code:** A

Article ID: 1673-6273(2019)14-2771-04

前言

梅毒的传播方式主要是性交和血液,其可以侵入机体内存

何器官,是一种全身感染^[1,2]。妊娠梅毒是指发生在妊娠期的梅毒,是患者怀孕或者孕妇在怀孕期间由于感染,通过胎盘向胎儿传播病原体导致流产、早产、死胎,给孕妇健康带来严重影响^[3,4]。

* 基金项目:湖南省卫生计生委科研基金项目(132013-083)

作者简介:彭莉(1983-),女,硕士,主管技师,研究方向:梅毒螺旋体免疫预防,电话:13327310872, E-mail:lijingys517@163.com

(收稿日期:2018-12-15 接受日期:2019-01-11)

但是,目前妊娠梅毒的发病机制仍不完全明确。

Th17是由TH0细胞在IL6和白介素23(IL23)的刺激下分化而成的辅助性T细胞,在自身免疫中起重要的作用^[5,6]。Treg是一类特异性表达转录因子,控制体内自身免疫反应性的T细胞亚群,这些细胞的数量和功能障碍可以降低其对效应T细胞的抑制作用,导致免疫失衡^[7,8]。外周血Th17和Treg水平都与妊娠梅毒的发生有着密切的关系,但其具体意义还需进一步探究。本研究主要探讨了妊娠梅毒患者外周血Th17、Treg水平,并分析了其对妊娠梅毒的诊断价值,现将结果报道如下。

1 资料与方法

1.1 一般资料

分别选择2015年4月至2016年5月我院收治的妊娠梅毒患者35例(观察组)和同期进行孕检的健康孕妇30例(对照组)作为本次研究对象,研究已获得伦理委员会批准。观察组患者年龄21~36岁,平均(27.64±4.22)岁;对照组患者年龄23~37岁,平均(28.03±3.61)岁。两组一般临床资料比较差异无统计学意义($P>0.05$),具有可比性。

纳入标准:①患者本人或配偶有梅毒感染史;②具有各期梅毒临床症状;③梅毒血清学检测阳性。排除标准:①原有梅毒

史;②确诊后各种原因中断妊娠者。

1.2 检测方法

采集所有患者5 mL清晨空腹静脉血,抗凝后以3000 r·min⁻¹的速度进行离心,时间10 min,提取上层血清后,置于零下20℃的冷冻箱内存储以备检测,所有患者静脉血加入标记抗体5 μL,暗处室温孵育15 min,以细胞裂解液溶解红细胞,等溶血后洗涤,使用Beckman Coulter FC500全自动流式细胞仪检测外周血Th17和Treg水平。

1.3 统计学分析

以SPSS18.0软件包处理实验数据,计量资料均为正态分布,以均数±标准差($\bar{x} \pm s$)表示,组间比较采用t检验,外周血Th17和Treg与妊娠梅毒之间的相关性分析使用多元线性逐步回归分析,并使用受试者工作特征曲线(ROC)分析外周血Th17和Treg的诊断效能, $P<0.05$ 表示差异具有统计学意义。

2 结果

2.1 两组患者外周血Th17和Treg水平的比较

观察组患者外周血Th17水平显著高于对照组,Treg水平显著低于对照组($P<0.05$),见表1。

表1 两组外周血Th17和Treg水平比较($\bar{x} \pm s$,%)

Table 1 Comparison of the Th17 and Treg levels in the peripheral blood between the two groups($\bar{x} \pm s$,%)

Groups	n	Th17	Treg
Observation group	35	1.39±0.61	3.08±1.53
Control group	30	0.79±0.32	6.03±1.48
t value		4.843	7.867
P value		0.000	0.000

2.2 外周血Th17和Treg水平与妊娠梅毒患者相关性分析

在多因素logistic回归分析结果显示外周血Th17和Treg

水平与妊娠梅毒发病具有明显相关性,见表2。

表2 外周血Th17和Treg水平与妊娠梅毒患者相关性分析

Table 2 Correlation analysis of peripheral blood Th17 and Treg levels with pregnancy syphilis patients

Factors affecting the	B	SE	Wald	OR值	95%CI	P value
Th17	-0.238	0.113	4.498	0.617	0.603~0.984	0.002
Treg	2.701	0.617	16.352	0.371	0.166~0.937	0.000

2.3 外周血Th17和Treg水平诊断妊娠梅毒的价值

将上述2个变量代入回归模型,外周血Th17诊断妊娠梅毒的AUC为0.776,95%CI为0.656~0.896,Treg诊断妊娠梅毒的AUC为0.947,95%CI为0.897~0.997,Th17+Treg诊断妊娠梅毒的AUC为0.960,95%CI为0.913~1.000;Th17和Treg单独检测分别和联合检测曲线下面积比较均具有显著差异($Z=2.807$ 、 -0.375 , $P<0.05$);Th17+Treg联合检测的特异度、准确度分别为91.73%、93.28%,显著高于各指标单独检测。具体见图5、表2、表3。

3 讨论

妊娠梅毒患者唾液、乳汁、精液、尿液及皮肤损害表面均含有大量的梅毒螺旋体^[9,10]。梅毒螺旋体通常在怀孕后进入血液循环,对胎盘的损害导致患者流产、早产、胎儿畸形或先天性梅毒,几乎涉及全身各器官,给母婴带来巨大的损害^[11,12]。进一步探讨妊娠梅毒的病因对其临床治疗具有重要作用^[13,14]。

Th17细胞与Treg细胞是密切相关的,其在功能上相互拮抗,但在分化过程中又相互联系^[15,16],其数量和功能异常会导致疾病的发生和发展^[17,18]。Th17细胞是近来发现的一种免疫细胞,分泌的主要细胞因子是IL-17,能增强免疫应答,与Th1和Th2免疫细胞不同,CD+T亚群具有很强的促炎作用^[19,20]。在正常人体内,Th17细胞保持一定比例,Th17细胞失衡会导致免

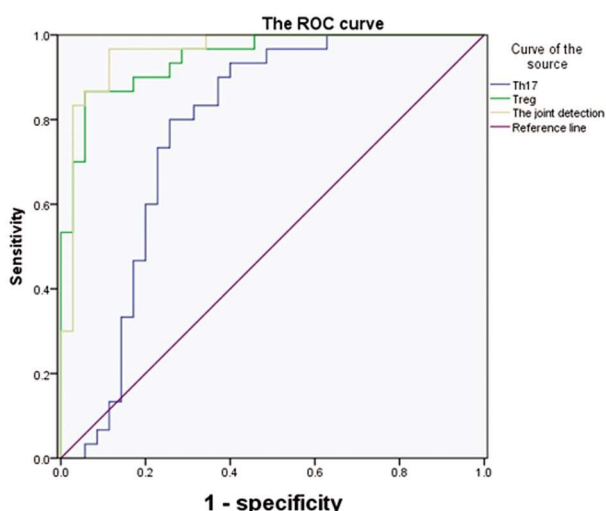


图1 外周血 Th17、Treg 和联合检测妊娠梅毒的 ROC 曲线

Fig.1 ROC curve of Treg combined with Th17 levels in the peripheral blood for the diagnosis of pregnancy syphilis

表3 外周血 Th17、Treg 和联合检测妊娠梅毒的 ROC 曲线下面积(AUC)

Table 3 Area under the ROC curve of Treg combined with Th17 levels in the peripheral blood for the diagnosis of pregnancy syphilis

Test variables	AUC	Standard errora	P	95%CI
Th17	0.776	0.061	0.000	0.656~0.896
Treg	0.947	0.025	0.000	0.897~0.997
Th17+Treg	0.960	0.024	0.000	0.913~1.000

表4 外周血 Th17、Treg 单独检测和联合检测妊娠梅毒的诊断效能

Table 4 Diagnostic value of detection of Th17 and Treg in the Peripheral blood for the pregnancy syphilis

Test variables	Sensitivity	Specific degrees	The accuracy of	About an index
Th17	80.93	73.05	80.27	1.53
Treg	81.18	75.17	76.36	1.57
Th17+Treg	82.06	91.73	93.28	1.73

Treg 细胞低于正常孕妇,可作为妊娠期梅毒的标志性参考指标^[28]。本研究结果显示妊娠梅毒患者外周血 Treg 水平低于正常妊娠的患者,且与妊娠梅毒的发病具有明显的相关性,提示不同程度病情患者外周血 Treg 也大有不同,可作为诊断妊娠梅毒的标准指标,这与 Matthias J M^[29]等研究结果相似。分析原因是因为 Treg 是在免疫抑制行细胞因子诱导下发育而成的,能够通过分泌白介素-10(IL-10)抑制记忆型 T 细胞增殖反应。

此外,本次研究结果还显示联合诊断妊娠梅毒诊断效能的 AUC 为 0.960,95%CI 为 0.913~1.000,Th17 诊断妊娠梅毒的 AUC 为 0.776,95%CI 为 0.656~0.896,Treg 诊断妊娠梅毒的 AUC 为 0.947,95%CI 为 0.897~997,且特异度、准确度分别为 91.73%、93.28%,明显高于各指标单独检测,Matthias J M^[30]等研究证明 Th17 和 Treg 细胞功能上相互拮抗,诱导免疫耐受,过强的免疫反应可能导致了结核病的免疫病理损害,但更详细的免疫损害机理须进一步研究。在病毒性感染性疾病中 Th17 细胞/Treg 细胞比例失衡在免疫病理损害中起了重要的作用。本研究结果支持 Th17 细胞、Treg 细胞的共同作用可能对妊娠梅毒患者的病理损害也起到了重要作用,提示出联合检测在诊

断妊娠梅毒上具有更高的价值。当妊娠妇女发生梅毒时,Th17 水平也随之变化。因此,检测外周血 Th17 水平高低可作为诊断妊娠梅毒的参考指标段,其水平越高,提示病情程度越重^[23,24]。Ochoa-Manjarrés MT^[25]等研究报道 Th17 在肺癌中的表达水平随肿瘤分期而上升,提示 Th17 可能促进肺癌的进展。本研究结果显示妊娠梅毒患者外周血 Th17 水平高于正常妊娠的患者,且与妊娠梅毒的发病具有明显的相关性。这提示外周血 Th17 可作为诊断妊娠梅毒的重要参考指标。患者感染梅毒螺旋体后,刺激机体的天然免疫应答,从而分泌细胞因子,细胞因子刺激 Th17 细胞增殖,将在某些免疫细胞中细菌抗原的存在会引发一系列的免疫反应,导致 Th17 细胞上升。

Treg 细胞是维持机体自身免疫耐受的重要组成部分,参与抑制抗肿瘤免疫,导肿瘤局部免疫耐受,其活化后能抑制自身反应性 T 细胞的活化、增殖、分化,通过分泌抑制细胞因子来抑制身体的免疫反应^[26,27]。有研究显示妊娠期梅毒患者外周血

断妊娠梅毒上具有更高的价值。

综上所述,妊娠梅毒患者外周血 Th17 细胞增多,Treg 细胞减少,联合检测外周血 Th17 和 Treg 细胞水平诊断妊娠梅毒具有较高的准确度,可作为诊断妊娠梅毒的重要参考指标。

参考文献(References)

- [1] Kale PL, Jorge MHPM, Fonseca SC, et al. Deaths of women hospitalized for childbirth and abortion, and of their concept, in maternity wards of Brazilian public hospitals[J]. Cien Saude Colet, 2018, 23(5): 1577-1590
- [2] Woodring J, Ishikawa N, Nagai M, et al. Integrating HIV, hepatitis B and syphilis screening and treatment through the Maternal, Newborn and Child Health platform to reach global elimination targets [J]. Western Pac Surveill Response J, 2017, 8(4): 1-5
- [3] Biswas HH, Chew Ng RA, Murray EL et al. Characteristics Associated With Delivery of an Infant With Congenital Syphilis and Missed Opportunities for Prevention-California, 2012 to 2014 [J]. Sex Transm Dis, 2018, 45(7): 435-441
- [4] Howe B, Foster K, Waldram A, et al. Challenges in the management of syphilis in pregnancy: completing a multicentre audit cycle with

- mixed outcomes[J]. *Int J STD AIDS*, 2018, 29(4): 418-420
- [5] Villalon-Gomez JM. Pityriasis Rosea: Diagnosis and Treatment [J]. *Am Fam Physician*, 2018, 97(1): 38-44
- [6] Dou LX, Wang Q, Wang XY, et al. Serologic surveillance indicators analysis among syphilis-infected pregnant women in East China [J]. *Zhonghua Yu Fang Yi Xue Za Zhi*, 2018, 52(1): 68-72
- [7] Taylor M, Gliddon H, Nurse-Findlay S, et al. Revisiting strategies to eliminate mother-to-child transmission of syphilis [J]. *Lancet Glob Health*, 2018, 6(1): e26-e28
- [8] Maddox BLP, Wright SS, Namadingo H, et al. Assessing stakeholder perceptions of the acceptability and feasibility of national scale-up for a dual HIV/syphilis rapid diagnostic test in Malawi [J]. *Sex Transm Infect*, 2017, 93(S4): S59-S64
- [9] Pala S, Conti C, Goldoni P, et al. A five year retrospective study on Syphilis in the Sexual Transmitted Disease Centre (STDC) of the teaching Hospital Umberto I in Rome [J]. *Ann Ig*, 2018, 20(1): 66-70
- [10] Verghese VP, Henderson L, Singh A, et al. Early Childhood Neurodevelopmental Outcomes in Infants Exposed to Infectious Syphilis In Utero [J]. *Pediatr Infect Dis J*, 2018, 37(6): 576-579
- [11] De Carolis S, Tabacco S, Rizzo F, et al. Association between false-positive TORCH and antiphospholipid antibodies in healthy pregnant women [J]. *Lupus*, 2018, 27(5): 841-846
- [12] Kingston M, French P, Fifer H, et al. Congenital syphilis in England and amendments to the BASHH guideline for management of affected infants [J]. *Int J STD AIDS*, 2017, 28(13): 1361-1362
- [13] Bopage RI, Vollmer-Conna U, Shand AW, et al. Sex differences in the significance of isolated reactive treponemal chemiluminescence immunoassay results [J]. *Sex Transm Infect*, 2018, 94(3): 187-191
- [14] Rodrigues DC, Domingues RMSM. Management of syphilis in pregnancy: Knowledge and practices of health care providers and barriers to the control of disease in Teresina, Brazil [J]. *Int J Health Plann Manage*, 2018, 33(2): 329-344
- [15] Ebenezer ED, Benjamin SJ, Sahni RD, et al. A retrospective study of the prevalence and outcomes of syphilis in pregnancy in a 5-year period [J]. *Int J Gynaecol Obstet*, 2018, 140(1): 42-46
- [16] Patel CG, Huppert JS, Tao G. Provider Adherence to Syphilis Testing Recommendations for Women Delivering a Stillbirth [J]. *Sex Transm Dis*, 2017, 44(11): 685-690
- [17] Zhang W, Luo H, Ma Y, et al. Monetary incentives for provision of syphilis screening, Yunnan, China [J]. *Bull World Health Organ*, 2017, 95(9): 657-662
- [18] Lee T, Bell S, Scimeme J, et al. Congenital Syphilis Masquerading as Leukemia [J]. *AJP Rep*, 2017, 7(3): e167-e170
- [19] Patel NU, Oussedik E, Landis ET, et al. Early Congenital Syphilis: Recognising Symptoms of an Increasingly Prevalent Disease [J]. *J Cutan Med Surg*, 2018, 22(1): 97-99
- [20] Correa ME, Croda J, Coimbra Motta de Castro AR, et al. High Prevalence of *Treponema pallidum* Infection in Brazilian Prisoners [J]. *Am J Trop Med Hyg*, 2017, 97(4): 1078-1084
- [21] Mark J, Kinuthia J, Roxby AC, et al. Uptake of Home-Based Syphilis and Human Immunodeficiency Virus Testing Among Male Partners of Pregnant Women in Western Kenya [J]. *Sex Transm Dis*, 2017, 44(9): 533-538
- [22] Taylor MM, Peeling RW, Toskin I, et al. Role of dual HIV/syphilis test kits in expanding syphilis screening [J]. *Sex Transm Infect*, 2017, 93(7): 458-459
- [23] Gliddon HD, Peeling RW, Kamb ML, et al. A systematic review and meta-analysis of studies evaluating the performance and operational characteristics of dual point-of-care tests for HIV and syphilis [J]. *Sex Transm Infect*, 2017, 93(S4): S3-S15
- [24] Chotun N, Preiser W, van Rensburg CJ, et al. Point-of-care screening for hepatitis B virus infection in pregnant women at an antenatal clinic: A South African experience [J]. *PLoS One*, 2017, 12(7): e0181267
- [25] Ochoa-Manjarrés MT, Gaitán-Duarte HG, Caicedo S, et al. Introduction of rapid syphilis and HIV testing in prenatal care in Colombia: qualitative analysis [J]. *Rev Panam Salud Publica*, 2016, 40(6): 462-467
- [26] Rogozińska E, Kara-Newton L, Zamora J R, et al. On-site test to detect syphilis in pregnancy: a systematic review of test accuracy studies [J]. *Bjog*, 2017, 124(5): 734-741
- [27] Magalhães M, Basto L, Areia A L, et al. Syphilis in Pregnancy and Congenital Syphilis: Reality in a Portuguese Central University Hospital [J]. *Rev Bras Ginecol Obstet*, 2017, 39(06): 265-272
- [28] Dhanaselvi H, Kalaivani S. Untreated Late Latent Syphilis of Both Spouses with Observation of Kassowitz Law: Adverse Pregnancy Outcomes in the Postpenicillin Era [J]. *Indian Journal of Dermatology*, 2017, 62(2): 221-222
- [29] Dalle J, Ramos M C, Jimenez M F, et al. Oral Desensitization to Penicillin for the Treatment of Pregnant Women with Syphilis: A Successful Program [J]. *Rev Bras Ginecol Obstet*, 2017, 40(01): 043-046
- [30] Matthias J M, Rahman M M, Newman D R, et al. Effectiveness of Prenatal Screening and Treatment to Prevent Congenital Syphilis, Louisiana and Florida, 2013-2014 [J]. *Sexually Transmitted Diseases*, 2017, 44(8): 498-502