孕妇血清FA，MCP-1，PIBF水平检测与早期妊娠胚胎停止发育的相关性研究

王　峥，胡人芳，陈　哲，张先华，潘凤莲（荆州市第二人民医院妇产科，湖北荆州 434000）

摘　要：目的　研究孕妇血清叶酸(FA)、单核细胞趋化蛋白-1(MCP-1)和孕酮诱导的阻断因子(PIBF)水平与早期妊娠胚胎停止发育的相关性。**方法**　选取2021年12月～2023年12月荆州市第二人民医院收治的早期妊娠胚胎停止发育孕妇98例为胎停组，另选同期进行孕检的正常早期妊娠孕妇50例为对照组，收集一般临床资料，酶联免疫吸附试验(ELISA)检测血清FA，MCP-1和PIBF水平。多因素Logistic回归分析早期妊娠胚胎停止发育的影响因素；绘制受试者工作特征(ROC)曲线分析血清FA，MCP-1和PIBF对早期妊娠胚胎停止发育的预测价值；Pearson法分析血清FA，MCP-1，PIBF与孕酮(PROG)、雌二醇(E2)以及β-人绒毛膜促性腺激素(β-HCG)的相关性。**结果**　与对照组相比，胎停组的血清FA(9.51±1.21nmol/L vs 11.32±1.56nmol/L)，PIBF(295.46±30.22 ng/ml vs 342.14±36.97ng/ml)水平降低，血清MCP-1(1.02±0.15 mg/ml vs 0.82±0.11 mg/ml)水平升高，差异具有统计学意义(t=7.785，8.347，8.229，均$P<0.001$)。两组孕妇的胎停史(75.64% vs 25.36%)，PROG(13.32±1.81 ng/ml vs 23.65±2.74 ng/ml)，E2(221.34±25.69 pmol/L vs 298.65±31.64 pmol/L)以及β-HCG(5 323.62±536.85 U/L vs 8 562.31±924.55 U/L)水平比较，差异具有统计学意义(t/χ^2=6.548～27.428，均$P<0.05$)。孕妇胎停史、MCP-1水平升高为影响早期妊娠胎停的危险因素(Wald χ^2=4.239，4.613，均$P<0.05$)，β-HCG，FA以及PIBF水平升高为影响早期妊娠胎停的保护因素(Wald χ^2=4.476，4.423，5.974，均$P<0.05$)；FA，MCP-1，PIBF以及联合预测早期妊娠胚胎停止发育的AUC分别为0.811，0.805，0.816和0.908，联合预测显著优于FA，MCP-1，PIBF单独预测(Z=2.749，2.381，1.993，均$P<0.05$)。FA，PIBF与PROG，E2，β-HCG呈正相关(r=0.433~0.512，均$P<0.05$)，MCP-1与PROG，E2，β-HCG呈负相关(r=−0.432，−0.487，−0.458，均$P<0.05$)。**结论**　早期妊娠胚胎停止发育孕妇血清FA，PIBF水平降低，MCP-1水平升高，三者均为影响孕妇胚胎停止发育的影响因素，对早期妊娠胚胎停止发育具有一定辅助预测价值。

关键词：叶酸；单核细胞趋化蛋白-1；孕酮诱导的阻断因子；早期妊娠；胚胎停止发育
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Study on the Correlation between Maternal Serum Levels of FA, MCP-1, PIBF and Embryo Stop Development in Early Pregnancy

WANG Zheng, HU Renfang, CHEN Zhe, ZHANG Xianhua, PAN Fenglian (*Department of Obstetrics and Gynecology, the Second Hospital of Jingzhou, Hubei Jingzhou* 434000, *China*)

Abstract: Objective To investigate the correlation between maternal serum folic acid (FA), monocyte chemoattractant protein-1 (MCP-1), progesterone-induced blocking factor (PIBF) levels and embryonic development cessation in early pregnancy. **Methods** From December 2021 to December 2023, 98 pregnant women with embryonic development cessation in early pregnancy admitted to the Second Hospital of Jingzhou were regarded as the cessation group, and 50 normal early pregnancy pregnant women who underwent pregnancy examinations during the same period were as the control group. General clinical data was collected and analyzed. Enzyme-linked immunosorbent assay (ELISA) was applied to detect serum levels of FA, MCP-1 and PIBF. Multivariate logistic regression was applied to analyze the influencing factors of early pregnancy embryo cessation of development. Receiver operating characteristic (ROC) curve was plotted to analyze the predictive value of serum FA, MCP-1, and PIBF for early embryonic development cessation in pregnancy. Pearson method was applied to analyze the correlation between serum FA, MCP-1, PIBF, progesterone(PROG), estradiol(E2) and β-human chorionic gonadotropin (β-HCG). **Results** Compared with the control group, the serum FA (9.51 ± 1.21 nmol/L vs 11.32 ± 1.56 nmol/L) and PIBF (295.46 ± 30.22 ng/ml vs 342.14 ± 36.97 ng/ml) levels in the cessation group were greatly reduced, while the serum MCP-1 (1.02 ± 0.15 mg/ml vs 0.82 ± 0.11 mg/ml) level was greatly increased, and the differences were statistically significant (t=7.785, 8.347, 8.229, all $P<0.001$). There were great statistical differences in the history of embryonic development cessation (75.64% vs 25.36%), PROG(13.32 ± 1.81 ng/ml vs 23.65 ± 2.74 ng/ml), E2 (221.34 ± 25.69 pmol/L vs 298.65 ± 31.64 pmol/L), and β-HCG levels

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作者简介：王峥(1986−)，女，本科，主治医师，研究方向：妇产科相关疾病研究，E-mail：hzgl2vj@163.com。

(5 323.62 ± 536.85U/L vs 8 562.31 ± 924.55 U/L) between the two groups (t/χ^2=6.548~27.428, all P<0.05). Pregnant women's history of embryonic development cessation and elevated level of MCP-1 were risk factors for embryonic development cessation in early pregnancy (Wald χ^2=4.239, 4.613, all P<0.05), while elevated levels of β-HCG, FA and PIBF were protective factors for embryonic development cessation in early pregnancy (Wald χ^2=4.476, 4.423, 5.974, all P<0.05). The AUC of FA, MCP-1, PIBF, and their combination in predicting early embryonic development cessation in pregnancy was 0.811, 0.805, 0.816 and 0.908, respectively. The combined prediction was greatly better than that of individual diagnosis of FA MCP-1, and PIBF (Z=2.749, 2.381, 1.993, all P<0.05). FA and PIBF were positively correlated with PROG, E2 and β-HCG (r=0.433~0.512, all P<0.05), while MCP-1 was negatively correlated with PROG, E2 and β-HCG (r=−0.432, −0.487, −0.458, all P<0.05). **Conclusion** The serum levels of FA and PIBF in pregnant women with embryonic development cessation in early pregnancy decrease, while the level of MCP-1 increases. These three factors are all influencing factors for embryonic development cessation in pregnant women, and have certain auxiliary predictive value for embryonic development cessation in early pregnancy.

Keywords: folic acid; monocyte chemotactic protein-1; progesterone-induced blocking factor; early pregnancy; embryo stop development

全球育龄夫妇的不孕患病率为8%～12%，不育人口的增加加速了人口老龄化的进程，这已成为一个严重的社会问题[1]。早期胚胎停止发育是导致女性不孕的常见现象[2-3]。早期胚胎停育是早期自然流产的因素之一，也是妊娠早期常见的并发症，可导致不良妊娠结局。近年来，育龄妇女胚胎停育的风险不断增加，引起了广泛关注[4]。因此寻找相关高效生物标志在预测早期胚胎停止发育具有必要性。

叶酸(folate，FA)是核苷酸和氨基酸生物合成的必需营养素[5]，在缺乏足够FA的情况下，同型半胱氨酸水平会升高，导致血压升高[6]。FA是怀孕早期的关键营养物质，孕早期母体红细胞FA水平较高与妊娠期高血压风险显著相关[7]。单核细胞趋化蛋白-1(monocyte chemotactic protein-1，MCP-1)调节黏附分子和促炎细胞因子[8]，影响多个器官的纤维化[9]，MCP-1受妊娠相关因素的调控，其浓度的差异可导致正常妊娠进展和病理妊娠[10]。孕酮(progesterone，PROG)诱导的阻断因子(Progesterone-induced blocking factors，PIBF)在维持人类妊娠和母亲的PROG依赖性免疫调节中起着重要作用[11]。PIBF可以预测怀孕6～10周的先兆流产风险，PIBF在复发性流产的预防和治疗中发挥着重要作用[12]。目前，有关FA，MCP-1，PIBF在早期胚胎停止发育中的相关研究较少，因此通过酶联免疫吸附试验(ELISA)检测早期胚胎停止发育孕妇中FA，MCP-1，PIBF水平，进一步分析三者与早期胚胎停止发育的相关性，以期为临床提供参考依据。

1 材料与方法

1.1 研究对象 选取2021年12月～2023年12月荆州市第二人民医院收治的早期妊娠胚胎停止发育孕妇98例为胎停组，纳入标准：①符合胚胎停止发育的相关诊断标准[13]；②心管搏动停止且经复查未变化；③孕周＜13周；④单胎妊娠；⑤年龄＞18岁。排除标准：①异位妊娠；②并发肿瘤疾病；③肝肾功能障碍；④生殖道疾病；⑤子宫发育畸形；⑥服用激素类药物；⑦免疫系统疾病或严重感染。另选同期进行孕检的正常早期妊娠孕妇50例为对照组。该研究经医院医学伦理委员会批准(伦理学批号：2021-09031)，所有研究对象及家属均知情同意。

1.2 仪器与试剂 Tecan InfiniteF50酶标仪(上海桑晒生物科技有限公司，货号：Tecan InfiniteF50)；无菌磷酸盐缓冲溶液(上海谱析生物科技有限公司，货号：XY-S0354-250ML)；FA，MCP-1，ELISA检测试剂盒(深圳子科生物科技有限公司，货号：ZK-H061，ZK-H1145)；PIBF ELISA检测试剂盒(武汉益普生物科技有限公司，货号：CSB-E12872h)。

1.3 方法

1.3.1 一般资料收集：收集孕妇年龄、是否初次妊娠、经产史、自然流产史、胎停史，并采用全自动生化分析仪检测孕妇PROG，雌二醇(estradiol，E2)以及β-人绒毛膜促性腺激素(β-human chorionic gonadotropin，β-HCG)水平。

1.3.2 ELISA检测FA，MCP-1，PIBF水平：于孕妇入组次日采集空腹肘静脉血5ml，正常早期妊娠孕妇于孕检当天采血，采用高速离心机离心后，收集上清液，立即送检，采用ELISA试剂盒检测血清FA，MCP-1，PIBF水平。

1.4 统计学分析 采用SPSS 25.00进行数据统计分析，计数资料(年龄、是否初次妊娠、经产史、妊娠史、自然流产史、胎停史)以n(%)表示，采用χ^2检验，经正态分布检验后，计量资料(PROG，E2，β-HCG，FA，MCP-1，PIBF水平)以均数±标准差($\bar{x}\pm s$)表示，采用独立样本t检验，采用多因素Logistic回归分析早期妊娠胚胎停止发育的影响因素；绘制受试者工作特征(receiver operating characteristic，ROC)曲线分析血清FA，MCP-1，PIBF对早期妊娠胚胎停止发育的预测价值；Pearson法分析血清FA，MCP-1，PIBF与PROG，E2以及β-HCG的相关性，P＜0.05

为差异具有统计学意义。

2 结果

2.1 胎停组与对照组血清FA，MCP-1，PIBF水平比较 与对照组相比，胎停组的血清FA(9.51 ± 1.21 nmol/L vs 11.32 ± 1.56 nmol/L)，PIBF(295.45 ± 30.22 ng/ml vs 342.14 ± 36.97 ng/ml) 水平降低，血清MCP-1(1.02 ± 0.15 mg/ml vs 0.82 ± 0.11 mg/ml)水平升高，差异具有统计学意义(t=7.785，8.229，8.347，均$P<0.001$)。

2.2 早期妊娠胚胎停止发育的单因素分析 见表1。结果显示，胎停组与对照组孕妇的年龄、是否初次妊娠、经产史、自然流产史之间差异无统计学意义(均$P>0.05$)，但两组孕妇的胎停史、PROG，E2，β-HCG水平之间差异具有统计学意义(均$P<0.05$)。

表 1 影响早期妊娠胚胎停止发育的单因素分析 [n(%)，$\bar{x}\pm s$]

因 素		n	胎停组(n=98)	对照组(n=50)	t/χ^2	P
年龄(岁)	＞30	72	52(72.22)	20(27.78)	2.261	0.133
	≤30	76	46(60.53)	30(39.47)		
初次妊娠	是	65	39(60.00)	26(40.00)	2.002	0.157
	否	83	59(71.08)	24(28.92)		
经产史	是	75	48(64.00)	27(36.00)	0.334	0.563
	否	73	50(68.49)	23(31.51)		
自然流产史	是	77	56(72.73)	21(27.27)	3.042	0.081
	否	71	42(59.15)	29(40.85)		
胎停史	是	78	59(75.64)	19(24.36)	6.548	0.010
	否	70	39(55.74)	31(44.26)		
PROG(ng/ml)			13.32 ± 1.81	23.65 ± 2.74	27.428	＜0.001
E2(pmol/L)			221.34 ± 25.69	298.65 ± 31.64	15.985	＜0.001
β-HCG(U/L)			5 323.62 ± 536.85	8 562.31 ± 924.55	26.944	＜0.001

2.3 影响早期妊娠胚胎停止发育的多因素Logistic回归分析 见表2。以早期妊娠孕妇是否发生胎停为因变量(否=0，是=1)，以上述单因素分析差异具有统计学意义的孕妇是否有胎停史(否=0，是=1)，β-HCG，FA，MCP-1，PIBF水平(均为实测值)为自变量进行Logistic回归分析，结果显示，孕妇胎停史、MCP-1水平升高为影响孕妇胎停的危险因素(均$P<0.05$)，β-HCG，FA以及PIBF水平升高为影响孕妇胎停的保护因素(均$P<0.05$)。

表 2 影响早期妊娠胚胎停止发育的 Logistic 回归分析

因素	β	SE	Wald χ^2	P	OR	95%CI
胎停史	0.523	0.254	4.239	0.040	1.687	1.025~2.775
β-HCG	−0.144	0.068	4.476	0.034	0.866	0.758~0.989
FA	−0.269	0.128	4.423	0.035	0.764	0.594~0.982
MCP-1	0.335	0.156	4.613	0.032	1.398	1.030~1.898
PIBF	−0.374	0.153	5.974	0.015	0.688	0.510~0.929

2.4 血清FA，MCP-1，PIBF对早期妊娠胚胎停止发育的预测价值 见表3，图1。以早期妊娠孕妇是否发生胎停为因变量(否=0，是=1)，以孕妇FA，MCP-1，PIBF(均为实测值)为自变量绘制ROC曲线，结果显示，FA，MCP-1，PIBF以及联合预测早期妊娠胚胎停止发育的AUC分别为0.811，0.805，0.816和0.908，联合预测显著优于FA，MCP-1，PIBF单独检测(Z=2.749，2.381，1.993，均$P<0.05$)。

表 3 血清 FA，MCP-1，PIBF 对早期妊娠胚胎停止发育的预测价值

类别	AUC	灵敏度(%)	特异度(%)	截断值	约登指数	95%CI
FA	0.811	84.69	62.00	10.84 nmol/L	0.467	0.738~0.870
MCP-1	0.805	83.67	66.00	0.87 mg/ml	0.497	0.732~0.866
PIBF	0.816	85.71	66.00	317.73 ng/ml	0.517	0.744~0.875
联合检测	0.908	81.63	94.00	—	0.756	0.850~0.950

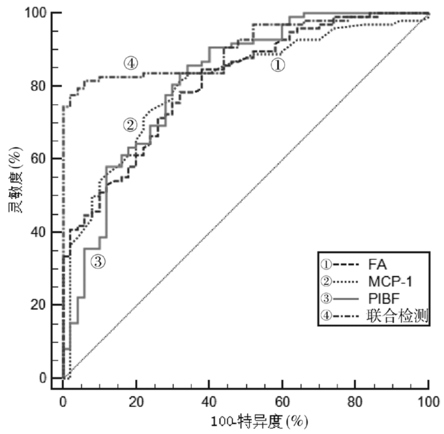

图1 血清FA，MCP-1，PIBF预测早期妊娠胚胎停止发育的ROC曲线

2.5 血清FA，MCP-1，PIBF与PROG，E2，β-HCG的相关性 见表4。结果显示，FA，PIBF与PROG，E2，β-HCG呈正相关，MCP-1与PROG，E2，β-HCG呈负相关(均$P<0.05$)。

表4 血清FA，MCP-1，PIBF与PROG，E2，β-HGG的相关性

项目	FA		MCP-1		PIBF	
	r	P	r	P	r	P
PROG	0.477	<0.05	−0.432	<0.05	0.481	<0.05
E2	0.433	<0.05	−0.487	<0.05	0.457	<0.05
β-HCG	0.512	<0.05	−0.458	<0.05	0.506	<0.05

3 讨论

胚胎停育是指妊娠早期胚胎死亡，发生率为10%～15%，80%的流产发生在妊娠的前12周内。近年来，早期胚胎停育的发生率呈上升趋势，胚胎停育的高发给很多女性和家庭带来了严重的伤害[14]。不利的环境和遗传因素可能导致胚胎停育，如染色体异常、免疫、感染、内分泌功能失调、基因突变或缺失、环境理化因素、母体肥胖等，20%～40%的病例原因不明[15-16]。胚胎停育也会导致育龄夫妻心情低落，焦虑障碍，因此寻找相关预测的生物标志物迫在眉睫。

FA是由蝶啶环，对氨基苯甲酸和谷氨酸盐组成的分子家族，在单碳代谢中起着重要作用，这种代谢是多种生物过程所必需的，包括DNA合成、DNA修复和通过高半胱氨酸甲基化产生蛋氨酸[17-18]。FA在怀孕期间发挥着重要的生理作用，可支持子宫和胎盘的生长和发育，维持胎儿生长所需的细胞分裂，预防神经管缺陷。怀孕期间，FA水平增加以适应胎儿-胎盘不断增长的需求，以及母体代谢需求的增加[19]。研究发现，FA可通过保护卵泡颗粒细胞免受凋亡和衰老，从而改善体内和体外的卵母细胞功能和胚胎发育[20]。本研究结果显示，早期胚胎停止发育孕妇的FA水平降低，为影响孕妇早期胚胎停止发育的保护因素，且与PROG，E2以及β-HCG呈正相关，经分析FA参与胎儿生长发育、机体代谢、FA水平降低、胎儿营养缺乏、生长发育受损或FA水平降低可导致卵泡颗粒细胞凋亡衰老，卵母细胞功能降低，胚胎发育停止。此外，FA还为细胞分裂过程中DNA复制的核苷酸生成和DNA甲基化(DNAm)提供甲基基团，FA减低也会导致滋养层的生存力和侵袭能力下降，胎盘形态改变和胎盘早剥，影响胎盘发育。FA预测孕妇早期发生胚胎停止发育的AUC为0.811，提示FA水平与孕妇早期胎停具有密切联系，对其具有一定辅助预测价值。王松伟等[21]研究也表明补充FA是胚胎停止发育的保护因素。

MCP-1在许多病理状况中起着至关重要的作用，例如心血管疾病、脑部病变、骨关节疾病、呼吸道感染、癌症和内皮功能障碍[22]。MCP-1与其受体结合后，可诱导淋巴细胞和自然杀伤细胞的归巢、迁移、活化、分化和发育，促进单核细胞和巨噬细胞的浸润，促进炎症发生[23]。MCP-1还导致异位子宫内膜细胞的增殖和维持，因此，它可能与子宫内膜异位症的发病机制有关[24]。本研究结果显示，早期胚胎停止发育孕妇的MCP-1水平显著升高，为影响孕妇早期胚胎停止发育的危险因素，且与PROG，E2以及β-HCG呈负相关，分析原因为相关细胞因子诱导MCP-1水平升高，促进炎症发生、子宫微环境受损和孕妇发生早期胎停，并且MCP-1水平升高还可能与DNAm有关，导致不良妊娠，并且可能对孕妇发生早期胎停具有一定辅助预测价值。经分析MCP-1在母体-胎儿界面非常重要，其表达和分泌可受多种内源性因素调节，以确保良好的子宫微环境，但趋化因子水平异常则被认为是自然流产额外的危害，且复发性妊娠失败的受访者比正常孕妇表达更高水平的MCP-1[25]。

PIBF基因包含孕酮反应元件，PIBF是正常人类妊娠的特征，但在妊娠并发症如早产和有流产风险的妇女中其浓度降低[26]。本研究结果显示，早期胚胎停止发育孕妇的PIBF水平显著降低，为影响孕妇早期胚胎停止发育的保护因素，且与PROG，E2以及β-HCG呈正相关，推测PIBF作为具有抗流产特性的免疫调节因子，PIBF水平降低，淋巴细胞增殖，NK细胞活化，炎症发生，破坏子宫免疫平衡，导致

胎儿停止发育，造成流产，其可能作为早期胚胎停育的研究靶点。PIBF介导PROG的免疫效应，是一种具有抗流产特性的免疫调节因子，抑制淋巴细胞增殖，NK细胞活化和炎症，为发育中的胎儿建立良好的免疫环境起着重要作用。研究证明PIBF的局部存在可能是蜕膜NK活性低的一个因素，与先兆流产孕妇的妊娠结局具有密切联系[27-28]。但FA，MCP-1，PIBF单独预测的特异度较低，联合预测特异度升高，提示联合预测显著优于FA，MCP-1，PIBF单独预测，可提高临床预测准确度。

综上所述，早期妊娠胚胎停止发育孕妇血清FA，PIBF水平降低，MCP-1水平升高，三者均为影响孕妇胚胎停止发育的影响因素，对早期妊娠胚胎停止发育具有一定辅助预测价值。但本研究所选样本量较少，且FA，MCP-1，PIBF在早期妊娠胚胎停止发育中的作用机制尚不清晰，需进一步深入研究。

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