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· 论 著 ·

## 血清β-人绒毛膜促性腺激素对甲氨蝶呤单次注射治疗异位妊娠结局的预测作用

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**[摘要]** **目的** 评估血清β-人绒毛膜促性腺激素(β-hCG)对甲氨蝶呤(MTX)单次肌内注射治疗异位妊娠疗效的预测价值。**方法** 回顾性分析2010年1月1日至2018年12月31日在海军军医大学(第二军医大学)长海医院接受MTX单次肌内注射治疗的96例异位妊娠患者的临床资料。患者均接受MTX 50 mg/m<sup>2</sup>单次肌内注射方案, 定期检测血清β-hCG水平。接受MTX单次注射治疗后随访血清β-hCG降至正常2次并且未再接受第2次MTX治疗或手术治疗者视为治疗成功。根据治疗结局将患者分为治疗成功组和治疗失败组, 比较两组治疗前血清β-hCG水平。根据治疗前血清β-hCG水平将患者分为<1 000、1 000~1 999、2 000~2 999、≥3 000 mIU/mL组, 比较各组间MTX单次注射治疗成功率。分析治疗后不同时间点血清β-hCG对预后的预测价值。**结果** 96例异位妊娠患者中, 57例(59.4%)患者MTX单次注射治疗成功, 39例(40.6%)失败。治疗成功组和治疗失败组治疗前血清β-hCG水平分别为343.00(212.50, 720.00)和716.00(341.00, 1 619.00) mIU/mL, 差异有统计学意义( $P=0.007$ )。随着治疗前血清β-hCG水平的升高, MTX单次注射治疗成功率逐步降低, 但当治疗前β-hCG的水平<3 000 mIU/mL时, 不同β-hCG水平亚组之间的成功率差异无统计学意义( $P>0.05$ )。治疗后4 d血清β-hCG预测MTX单次注射治疗成功的AUC为0.80(95% CI 0.70~0.88,  $P<0.001$ ), 阈值为650 mIU/mL, 灵敏度为91.2%, 特异度为66.7%; 治疗后7 d血清β-hCG预测MTX单次注射治疗成功的AUC为0.71(95% CI 0.58~0.82,  $P<0.001$ ), 阈值为103 mIU/mL, 灵敏度为42.9%, 特异度为100.0%。治疗后4 d血清β-hCG≤650 mIU/mL组的治疗成功率较>650 mIU/mL组高, 差异有统计学意义( $P<0.001$ ); 治疗后7 d血清β-hCG≤103 mIU/mL组与>103 mIU/mL组治疗成功率差异无统计学意义( $P=0.146$ )。**结论** 对于接受MTX单次注射治疗的异位妊娠患者, 治疗成功者初始血清β-hCG水平较低, 治疗后4 d血清β-hCG≤650 mIU/mL可作为预测治疗成功的指标。

**[关键词]** 人绒毛膜促性腺激素β亚单位; 异位妊娠; 甲氨蝶呤; 单次注射**[中图分类号]** R 714.22**[文献标志码]** A**[文章编号]** 0258-879X(2021)03-0270-05

## Role of serum β-human chorionic gonadotropin in predicting the outcome of ectopic pregnancy treated with single-dose injection of methotrexate

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**[Abstract]** **Objective** To evaluate the value of serum β-human chorionic gonadotropin (β-hCG) for predicting the outcome of ectopic pregnancy treated with single-dose intramuscular injection of methotrexate (MTX). **Methods** The clinical data of 96 ectopic pregnancy patients treated with MTX intramuscular injection in Changhai Hospital of Naval Medical University (Second Military Medical University) from Jan. 1, 2010 to Dec. 31, 2018 were retrospectively analyzed. All patients received MTX single-dose (50 mg/m<sup>2</sup>) intramuscular injection, and the serum β-hCG level was detected regularly. After receiving MTX single-dose intramuscular injection, the patients whose serum β-hCG levels were reduced to the normal twice, and who did not receive the second MTX treatment or surgical treatment were considered as successful. According to the treatment outcome, the patients were divided into treatment success group and failure group. The serum β-hCG levels of

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the two groups were compared before treatment. According to the pre-treatment serum  $\beta$ -hCG levels, they were divided into  $<1\ 000$ ,  $1\ 000$ - $1\ 999$ ,  $2\ 000$ - $2\ 999$  and  $\geq 3\ 000$  mIU/mL groups, and the success rates of MTX single-dose injection were compared among the groups. The prognostic value of serum  $\beta$ -hCG was analyzed at different time points after treatment. **Results** Of the 96 ectopic pregnancy patients, 57 (59.4%) cases were treated successfully with MTX single-dose injection, and 39 (40.6%) cases were failed. The pre-treatment serum  $\beta$ -hCG levels were 343.00 (212.50, 720.00) and 716.00 (341.00, 1 619.00) mIU/mL in the treatment success group and failure group, respectively, with significant difference ( $P=0.007$ ). With the increase of pre-treatment serum  $\beta$ -hCG level, the success rate of MTX single-dose injection decreased gradually; however, there were no significant differences in the success rates among the subgroups with different levels of  $\beta$ -hCG when the pre-treatment  $\beta$ -hCG level was lower than 3 000 mIU/mL ( $P>0.05$ ). The area under curve (AUC) of serum  $\beta$ -hCG 4 days after treatment in predicting the success of MTX single-dose injection was 0.80 (95% confidence interval [CI] 0.70-0.88,  $P<0.001$ ), the cut-off value was 650 mIU/mL, the sensitivity was 91.2%, and the specificity was 66.7%; the AUC of serum  $\beta$ -hCG 7 days after treatment in predicting the success of MTX single-dose injection was 0.71 (95% CI 0.58-0.82,  $P<0.001$ ), the cut-off value was 103 mIU/mL, the sensitivity was 42.9%, and the specificity was 100.0%. The success rate in the group with serum  $\beta$ -hCG  $\leq 650$  mIU/mL 4 days after treatment was significantly higher than that in the group with serum  $\beta$ -hCG  $>650$  mIU/mL ( $P<0.001$ ), while the success rates were similar in the groups with serum  $\beta$ -hCG  $\leq 103$  mIU/mL and  $>103$  mIU/mL 7 days after treatment ( $P=0.146$ ). **Conclusion** For ectopic pregnancy patients receiving a single-dose injection of MTX, the initial  $\beta$ -hCG levels are lower in patients with successful treatment. Serum  $\beta$ -hCG  $\leq 650$  mIU/mL on day 4 after treatment could be a predictor of treatment success.

[Key words] human chorionic gonadotropin  $\beta$  unit; ectopic pregnancy; methotrexate; single-dose injection

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异位妊娠的治疗分为保守治疗（观察及药物治疗）和手术治疗。随着超声技术的发展及血清人绒毛膜促性腺激素（human chorionic gonadotropin, hCG）检查的普及，近年来异位妊娠在妊娠较早期即可诊断，提高了保守治疗成功率，减少了手术及麻醉的风险。甲氨蝶呤（methotrexate, MTX）是保守治疗异位妊娠的首选药物，单次肌内注射效果较好，且不良反应发生率低。一项meta分析显示，MTX单次注射治疗异位妊娠的成功率可达88.1%<sup>[1]</sup>。治疗前的初始血清 $\beta$ -hCG水平是临床医师选择治疗方案的重要依据，有研究发现治疗前hCG水平在2 000~5 000 mIU/mL范围内者MTX单次注射治疗的成功率高<sup>[2-4]</sup>。然而，药物保守治疗随访周期较长，血清hCG预测保守治疗疗效的阈值尚无统一标准。本研究回顾性分析了2010年1月1日至2018年12月31日于我院接受MTX单次注射治疗的96例异位妊娠患者资料，评估治疗后血清 $\beta$ -hCG水平变化对疗效的预测价值，现报告如下。

## 1 资料和方法

1.1 病例资料 回顾性纳入2010年1月1日至2018年12月31日于我院接受MTX单次注射治疗的96例异位妊娠患者资料。异位妊娠诊断标准：（1）超声下见附件区包块；（2）血清 $\beta$ -hCG $>2\ 000$  mIU/mL时阴道超声未发

现宫内妊娠囊。纳入研究的96例异位妊娠女性年龄为20~45岁，平均（30.0 $\pm$ 6.7）岁。治疗前血清 $\beta$ -hCG水平为47~5 052 mIU/mL，中位数（下四分位数，上四分位数）为452（229，904）mIU/mL。其中84例（87.5%）患者入院前阴道超声可见附件区包块，长径为6~63 mm，平均（22.0 $\pm$ 11.0）mm；其余12例（12.5%）患者入院前阴道超声下未见明确附件区包块，但有明显的腹痛及血清 $\beta$ -hCG进行性上升，入院后复查超声可见附件区包块。

1.2 MTX治疗指征 （1）无腹腔活动性出血；（2）血清 $\beta$ -hCG $<5\ 000$  mIU/mL；（3）超声下未见宫外心管搏动；（4）宫外包块长径 $<40$  mm；（5）肝功能正常；（6）无MTX过敏史；（7）血流动力学稳定；（8）充分知情同意。92例患者符合保守治疗指征，4例附件区包块长径 $>40$  mm及1例治疗前血清 $\beta$ -hCG $>5\ 000$  mIU/mL者被充分告知病情及治疗风险后签字要求先行药物保守治疗。

1.3 治疗方法 患者均采用MTX 50 mg/m<sup>2</sup>单次肌内注射方案，治疗期间减少活动，保持大便通畅，禁止性生活。保守治疗过程中观察并记录患者的血压、脉搏，观察腹痛及阴道流血情况，定期检测血清 $\beta$ -hCG水平。

1.4 MTX单次注射治疗成功标准及分组 患者诊断为异位妊娠后即接受MTX单次注射治疗，接受MTX单次注射治疗后随访 $\beta$ -hCG降至正常2次

且未再接受第2次MTX治疗或手术治疗者判断为治疗成功。根据治疗结局分为治疗成功组和治疗失败组,比较2组治疗前血清β-hCG水平。根据治疗前血清β-hCG水平分为<1 000、1 000~1 999、2 000~2 999、≥3 000 mIU/mL组,比较各组间MTX单次注射治疗成功率。

1.5 统计学处理 采用SPSS 12.0软件进行统计学分析。呈正态分布的计量资料以 $\bar{x} \pm s$ 表示,两组间比较采用独立样本t检验;不满足正态分布的计量资料以中位数(下四分位数,上四分位数)表示,组间比较采用Mann-Whitney U检验。计数资料以例数和百分数表示,组间比较采用 $\chi^2$ 检验或Fisher确切概率法。通过ROC曲线评估β-hCG水平对MTX单次注射治疗结局的预测价值。检验水准( $\alpha$ )为0.05。

## 2 结果

2.1 治疗成功组与失败组一般资料及治疗前血清β-hCG水平比较 96例异位妊娠患者中,57例(59.4%)经MTX单次注射治疗成功,39例(40.6%)失败。由表1可见,治疗成功组及失败组年龄、停经时间、治疗前附件区包块长径差异均无统计学意义( $P$ 均>0.05),但治疗成功组治疗前血清β-hCG水平低于失败组,差异有统计学意义( $P=0.007$ )。96例患者中,32例(33.3%)治疗后4 d血清β-hCG水平较治疗前上升,其中10例(10.4%)血清β-hCG水平上升>50%。57例治疗成功组患者中,9例(15.8%)治疗后4 d血清β-hCG较治疗前上升,其中1例(1.8%)血清β-hCG上升>50%;29例(50.9%)治疗后4 d血清β-hCG水平较治疗前下降≥20%。39例治疗失败组患者中,3例患者在接受MTX单次注射治疗后4 d内出现手术指征并接受手术治疗;余36例患者MTX单次注射治疗后复查超声提示包块增大且β-hCG下降不明显或上升,告知病情后患者要求手术。此36例患者中,23例(63.9%)治疗后4 d血清β-hCG较治疗前上升,其中9例(25.0%)血清β-hCG上升>50%;6例(16.7%)治疗后4 d血清β-hCG水平较治疗前下降≥20%。

2.2 按治疗前血清β-hCG水平分组的患者治疗结局 根据治疗前血清β-hCG水平进行分组,β-hCG<1 000 mIU/mL组治疗成功率最高(66.2%,49/74),随着治疗前β-hCG水平上升,治疗成功率下降,β-hCG≥3 000 mIU/mL组治疗均失败(表2)。统计学分析表明,当治疗前血清β-hCG<3 000 mIU/mL时(β-hCG≥3 000 mIU/mL组仅2例,未纳入分析),各亚组的治疗成功率差异并无统计学意义( $P>0.05$ )。

表1 MTX单次注射治疗成功组及失败组异位妊娠患者一般资料及治疗前血清β-hCG水平比较

Tab 1 Comparison of general information and serum β-hCG levels before treatment between treatment success and failure groups of ectopic pregnancy patients

Group	<i>n</i>	Age/year, $\bar{x} \pm s$	Menopause time/d, $\bar{x} \pm s$	Adnexal mass diameter/mm, <i>M</i> ( <i>Q<sub>L</sub></i> , <i>Q<sub>U</sub></i> )	β-hCG/(mIU·mL <sup>-1</sup> ), <i>M</i> ( <i>Q<sub>L</sub></i> , <i>Q<sub>U</sub></i> )
Failure	39	30.10±5.20	47.87±7.93	16.0 (12.0, 24.5)	716.00 (341.00, 1 619.00)
Success	57	29.54±5.86	51.16±9.48	19.0 (15.0, 25.5)	343.00 (212.50, 720.00)
Statistic		<i>t</i> =0.480	<i>t</i> =-1.779	<i>Z</i> =-1.480	<i>Z</i> =-2.686
<i>P</i> value		0.632	0.078	0.140	0.007

MTX: Methotrexate; β-hCG: β-human chorionic gonadotropin; *M* (*Q<sub>L</sub>*, *Q<sub>U</sub>*): Median (lower quartile, upper quartile).

表2 按治疗前血清β-hCG水平分组的患者MTX单次注射治疗结局

Tab 2 Outcome of MTX single-dose injection in subgroups with different serum β-hCG levels before treatment

β-hCG/(mIU·mL <sup>-1</sup> )	<i>N</i>	<i>n</i> (%)	
		Success	Failure
<1 000	74	49 (66.2)	25 (33.8)
1 000-1 999	14	6 (42.9)	8 (57.1)
2 000-2 999	6	2 (33.3)	4 (66.7)
≥3 000	2	0	2 (100.0)

β-hCG: β-human chorionic gonadotropin; MTX: Methotrexate.

2.3 血清β-hCG预测MTX单次注射治疗结局的价值 ROC曲线分析结果(图1)显示,治疗后4 d血清β-hCG预测MTX单次注射治疗结局的AUC为0.80(95%CI 0.70~0.88,  $P<0.001$ ),阈值为650 mIU/mL,灵敏度为91.2%,特异度为66.7%,阳性预测值为81.2%,阴性预测值为82.8%;治疗后7 d血清β-hCG预测MTX单次注射治疗结局的AUC为0.71(95%CI 0.58~0.82,  $P<0.001$ ),阈值为103 mIU/mL,灵敏度为42.9%,特异度为100.0%,阳性预测值为100.0%,阴性预测值为16.7%。

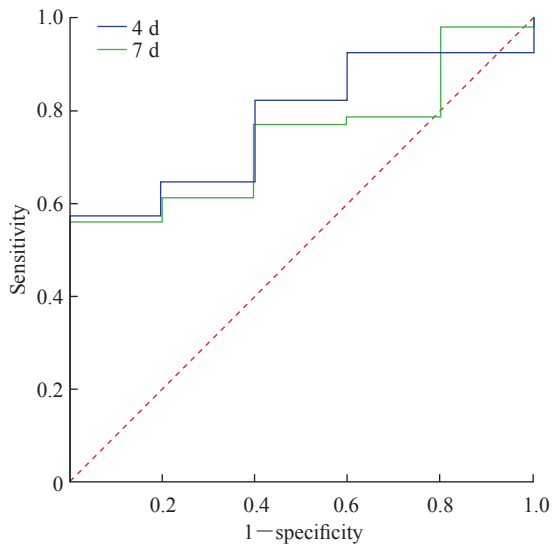


图1 治疗后4、7 d血清β-hCG预测MTX单次注射治疗结局的ROC曲线

Fig 1 ROC curves of serum β-hCG 4 d and 7 d after treatment in predicting outcome of single-dose injection of MTX

β-hCG: β-human chorionic gonadotropin; MTX: Methotrexate; ROC: Receiver operating characteristic.

以ROC曲线得出的治疗后4 d和7 d血清β-hCG阈值作为依据分组后进行预后比较, 结果(表3)显示治疗后4 d血清β-hCG ≤ 650 mIU/mL组的治疗成功率较 > 650 mIU/mL组高, 差异有统计学意义 ( $\chi^2 = 34.464$ ,  $P < 0.001$ ); 治疗后7 d血清β-hCG ≤ 103 mIU/mL组与 > 103 mIU/mL组治疗成功率差异无统计学意义 ( $P = 0.146$ )。

表3 根据治疗后4 d和7 d血清β-hCG阈值分组后MTX单次注射治疗结局比较

Tab 3 Comparison of outcome of MTX single-dose injection between groups divided by cut-off value of serum β-hCG 4 d and 7 d after treatment

Outcome	4 d β-hCG/(mIU·mL <sup>-1</sup> )		7 d β-hCG/(mIU·mL <sup>-1</sup> )	
	≤650 N=64	>650 N=29	≤103 N=15	>103 N=24
Success	52 (81.2)	5 (17.2)	15 (100.0)	20 (83.3)
Failure	12 (18.8)	24 (82.8)	0	4 (16.7)
Statistic	$\chi^2 = 34.464$		Fisher exact test	
P value	<0.001		0.146	

β-hCG: β-human chorionic gonadotropin; MTX: Methotrexate.

### 3 讨论

MTX治疗异位妊娠由Tanaka等<sup>[5]</sup>首次报道, 随后因不良反应发生率低、对卵巢功能影响较小

而被广泛应用于临床。既往研究显示血清β-hCG > 5 000 mIU/mL、宫外有心血管搏动、病灶直径 > 40 mm者易出现MTX治疗失败<sup>[6]</sup>。MTX治疗过程中, 临床上通过监测治疗后4、7、14 d的血清β-hCG水平评估治疗效果, 之后可每周1次直至降至正常。但目前为止, 对于预测MTX单次注射治疗失败的治疗后4 d血清hCG阈值没有统一的标准。

既往已有文献报道预测MTX治疗失败的初始hCG阈值为2 000~5 000 mIU/mL<sup>[4,7-8]</sup>, 最新美国异位妊娠治疗指南推荐MTX的治疗适用于β-hCG水平较低的患者及β-hCG水平处于不再进行性上升的平台期患者<sup>[9]</sup>。因此, 本研究纳入的病例中仅有2例患者治疗前β-hCG ≥ 3 000 mIU/mL, 且用药前已充分告知患者保守治疗相关风险。本研究中MTX单次注射治疗成功率为59.4% (57/96), 低于既往文献报道成功率(65%~100%)<sup>[10-12]</sup>。治疗失败组39例患者中9例(23.1%)治疗后4 d血清β-hCG较治疗前上升 > 50%, 低于Mashiach等<sup>[13]</sup>的研究结果(69%)。由于治疗过程中出现的腹痛症状和腹腔镜手术的普及, 部分患者在治疗期间出现腹痛加重或β-hCG下降不明显时会要求行手术治疗, 这可能是本研究MTX单次注射治疗成功率和治疗失败组治疗后4 d β-hCG较治疗前上升 > 50%的患者比例较低的原因。

Brady等<sup>[14]</sup>在体外受精人群中的研究结果发现, MTX单次注射治疗成功组与失败组阴道超声提示的附件区包块长径存在差异。但本研究中两组附件区包块长径差异无统计学意义, 与Helmy等<sup>[15]</sup>的研究结果一致。这可能与研究样本量较小有关。另外, 接受体外受精的受孕人群经历促排卵、取卵过程, 可能因卵巢组织受损、修复而存在炎症及非炎症增大, 造成超声测量误差。

2007年, Agostini等<sup>[16]</sup>提出hCG指数的概念, hCG指数计算公式为(治疗后4 d hCG水平 - 治疗前hCG水平) / 治疗前hCG水平, hCG指数的阈值为0.2时可较好地预测MTX单次注射治疗结局。Levin等<sup>[17]</sup>的回顾性研究中建议将治疗后4 d血清hCG较治疗后1 d下降 ≥ 22%作为预测MTX单次注射治疗成功的阈值。本研究MTX单次注射治疗成功组中有29例(50.9%)患者治疗后4 d血清β-hCG水平较治疗前下降 ≥ 20%, 失败组中(剔除3例于治疗后4 d内接受手术的患者)仅有6例(16.7%)治疗后4 d血清β-hCG水平较治疗前下降 ≥ 20%。因此, 本研究结果也支持0.2可作为

hCG 指数阈值预测 MTX 单次注射治疗结局。

有学者认为随访过程中可以不监测治疗后 4 d hCG 水平,而是将治疗后 7 d hCG 下降 >50% 单独作为 MTX 单次注射治疗成功的预测指标<sup>[18]</sup>。但由于异位妊娠病灶破裂出血易危及生命,且考虑经济成本效益,我们依然建议监测治疗后 4 d 和 7 d hCG 水平。本研究中经 ROC 曲线得出预测 MTX 单次注射治疗结局的治疗后 4 d 和 7 d 血清  $\beta$ -hCG 阈值分别为 650 mIU/mL 和 103 mIU/mL,且以治疗后 4 d 血清  $\beta$ -hCG 阈值分组后两组的治疗成功率差异有统计学意义,而以治疗后 7 d 血清  $\beta$ -hCG 阈值分组后两组的治疗成功率差异并无统计学意义,因此,我们认为治疗后 4 d 血清  $\beta$ -hCG  $\leq$  650 mIU/mL 作为预测 MTX 单次注射治疗成功的临床意义更大。

综上所述,MTX 单次注射治疗后 4 d 及 7 d 的血清  $\beta$ -hCG 变化及 hCG 指数有助于预测治疗效果,为后续治疗随访方案的选择提供参考,并且治疗后 4 d 的血清  $\beta$ -hCG 较 7 d  $\beta$ -hCG 可能在临床实际工作中更有指导意义。但本研究样本量较小,个别患者的治疗方案受患者意愿等因素影响,存在一定的选择性偏倚,今后仍需要开展大样本的研究进一步证实。

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