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地屈孕酮治疗早期先兆流产效果的影响因素及妊娠结局随访研究*

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摘要 目的:探讨地屈孕酮治疗早期先兆流产效果的影响因素,并随访继续妊娠患者的妊娠结局。**方法:**于2017年1月至2019年1月期间选取我院收治的300例早期先兆流产患者,均给予地屈孕酮首次剂量40 mg/次口服,之后改为30 mg/次,2次/d。按照治疗是否有效分为有效组和无效组,收集两组基本临床资料,采用多因素 Logistic 回归分析地屈孕酮治疗早期先兆流产效果的影响因素,并随访妊娠结局。**结果:**300例患者治疗有效245例(81.67%),治疗无效55例(18.33%);单因素分析显示:与无效组比较,有效组的年龄、孕次、流产次数、产次、抗子宫内膜抗体(EMAb)阳性率较小,血清 β -人绒毛膜促性腺激素(β -HCG)、孕酮(P)、雌二醇(E_2)水平较高,差异有统计学意义($P<0.05$),多因素 Logistic 回归分析显示:年龄(较大)、孕次(较多)、产次(较多)、流产次数(较多)、EMAb 阳性是影响地屈孕酮治疗效果的危险因素($P<0.05$),血清 β -HCG(较高)、P(较高)、 E_2 (较高)是影响地屈孕酮治疗效果的保护因素($P<0.05$)。随访结果显示:继续妊娠的245例患者平均分娩孕周(39.43 ± 1.06)周,产妇结局:出现产后出血6例,产后胎盘粘连17例;新生儿结局:Apgar 评分为(9.43 ± 0.20)分,出现早产2例,畸形1例,永存右脐静脉1例。**结论:**年龄、孕产次数、流产次数、EMAb 阳性、血清 β -HCG、P、 E_2 是地屈孕酮治疗早期先兆流产效果的影响因素,地屈孕酮治疗早期先兆流产是否会增加产妇及新生儿不良结局的发生风险仍需进一步研究。

关键词:地屈孕酮;先兆流产;疗效;影响因素;产妇结局;新生儿结局

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Follow up Study on Influencing Factors and Pregnancy Outcomes of Early Threatened Abortion Treated with Dydrogesterone*

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ABSTRACT Objective: To investigate the influencing factors of the effect of dydrogesterone in the treatment of early threatened abortion, and follow up the pregnancy outcome of patients with continued pregnancy. **Methods:** 300 patients with early threatened abortion who were admitted to our hospital from January 2017 to January 2019 were selected. All patients were given the first dose of dydrogesterone 40 mg/time orally, then changed to 30 mg/time, twice a day. They were divided into effective group and ineffective group according to whether the treatment was effective or not, basic clinical data of the two groups were collected. Multivariate Logistic regression was used to analyze the influencing factors of the effect of dydrogesterone on early threatened abortion, and the pregnancy outcome was followed up. **Results:** Among the 300 patients, 245 cases (81.67%) were effective, and 55 cases (18.33%) were ineffective. Univariate analysis showed that compared with the ineffective group, the age, gestational times, abortion times, birth times and anti-endometrial antibody(EMAb) positive rate in the effective group were lower, and the serum levels of β -human chorionic gonadotropin (β -HCG), progesterone (P) and estradiol (E_2) were higher, and the differences were statistically significant ($P<0.05$). Multivariate Logistic regression analysis showed that: Age (older), gestational times (more), birth times (more), abortion times (more) and EMAB positive were the risk factors affecting the effect of dydrogesterone treatment ($P<0.05$). Serum β -HCG (higher), P (higher) and E_2 (higher) were the protective factors affecting the effect of dydrogesterone treatment ($P<0.05$). Follow-up results showed that the average gestational age of the 245 patients with continued pregnancy was (39.43 ± 1.06) weeks. The maternal outcomes were as follows: 6 cases had postpartum hemorrhage, and 17 cases had postpartum placental adhesion. Neonatal outcome: Apgar score was (9.43 ± 0.20) score, preterm delivery occurred in 2 cases, malformation occurred in 1 case, and right umbilical vein was permanent in 1 case. **Conclusion:** Age, pregnancies times, abortion times, EMAB positive, serum β -HCG, P and E_2 are the influencing factors for the efficacy of dydrogesterone in the treatment of early threatened abortion, whether the treatment of Early Threatened Abortion with didroxyprogesterone can increase the risk of

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adverse maternal and neonatal outcomes remains to be further studied.

Key words: Dydrogesterone; Threatened abortion; Curative effect; Influencing factors; Maternal outcomes; Neonatal outcome

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前言

先兆流产为常见的产科疾病,是指孕 28 周前出现阴道出血症状,不伴或伴腰背痛、腹痛,但胎膜未破,宫颈口未开,胎儿依然存活于宫腔内^[1,2]。其中,发生在妊娠 12 周以内的先兆流产称为早期先兆流产,占 80%以上,发生在妊娠 12~28 周之间的称为晚期先兆流产^[3,4]。先兆流产发生率约占全部妊娠的 10%~15%,若不及时治疗因妊娠物排出而流产的风险达 57%^[5]。地屈孕酮是治疗早期先兆流产的常用药物,属于一种天然孕激素,在维持妊娠中起到重要的作用^[6-8],但有些患者经地屈孕酮治疗后仍出现流产,最终保胎失败。本研究分析了地屈孕酮治疗早期先兆流产效果的影响因素,并随访继续妊娠患者的妊娠结局,现报道如下。

1 对象与方法

1.1 研究对象

选取我院自 2017 年 1 月至 2019 年 1 月收治的 300 例早期先兆流产患者为观察对象,纳入标准:① 单活胎妊娠;② 符合《妇产科学》^[9]中早期先兆流产的诊断标准:产科检查胎膜未破,宫颈口未开;影像学检查:孕囊大小、胎儿大小、子宫体积及发育均与孕周相符;有停经史,停经 12 周前出现阴道少量流血,无妊娠组织排出,伴或不伴腰背痛、下腹坠痛;黄体期孕酮(P) < 48 nmol/L;③ 无沟通障碍。排除标准:① 合并造血系统疾病及心、肝、肺等脏器功能障碍;② 因遗传、生殖器及畸形或肿瘤等原因的流产;③ 合并精神疾病;④ 彩超诊断为异位妊娠;⑤ 合并妊娠糖尿病、妊娠高血压等妊娠并发症;⑥ 合并急慢性感染。

1.2 方法

1.2.1 治疗方法 指导孕妇加强营养支持、卧床休息、戒烟戒酒、禁止性生活,常规给予补充叶酸、维生素 E 等治疗。进行 B 超检查,孕囊内无明显异常或变化时,给予地屈孕酮首次剂量 40 mg/次口服,之后改为 30 mg/次,2 次/d。

1.2.2 基本资料收集 收集患者的体重、身高、年龄、职业、受教育程度、孕次、孕周、产次、流产次数、初潮年龄、月经期、月经周期、抗子宫内膜抗体(EMAb)阳性、甲状腺功能减退情况。

1.2.3 实验室指标检测 于孕 4~9 周抽取静脉血 3 mL,使用化学发光法检测血清 β -人绒毛膜促性腺激素(β -HCG)、P、雌二醇(E2)水平。

1.3 疗效评定

治疗有效:治疗后,阴道出血停止,血清 β -HCG 正常升高,P、E₂正常,B 超显示胎心搏动正常,正常妊娠 ≥ 12 周。治疗无效:阴道出血症状加重,妊娠组织排出,清宫;发展成为过期流产、难免流产、不全流产或完全流产^[10]。

1.4 妊娠结局

跟踪随访产妇分娩孕周、产后出血、产后胎盘粘连等发生情况。随访新生儿 Apgar 评分,以及早产(妊娠满 28 周至不足 37 周)、畸形、永存右脐静脉等发生情况。

1.5 统计学分析

使用 SPSS25.0 统计学软件分析。计数资料用%表示,行 χ^2 检验。计量资料用" $\bar{x} \pm s$ "表示,行 t 检验。采用多因素 Logistic 回归分析地屈孕酮治疗早期先兆流产效果的影响因素。 $P < 0.05$ 表示差异有统计学意义。

2 结果

2.1 地屈孕酮治疗早期先兆流产的效果

300 例患者治疗有效 245 例 (81.67%), 治疗无效 55 例 (18.33%)。治疗有效者作为有效组,治疗无效者作为无效组。

2.2 治疗效果影响因素的单因素分析

有效组与无效组的身高、体重、受教育程度、职业、孕周、初潮年龄、月经期、月经周期、甲状腺功能减退比较差异无统计学意义($P > 0.05$)。与无效组比,有效组的年龄、孕次、流产次数、产次、EMAb 阳性率较小,血清 β -HCG、P、E₂ 水平较高,差异有统计学意义($P < 0.05$)。见表 1。

2.3 治疗效果影响因素的多因素 Logistic 回归分析

多因素 Logistic 回归分析显示,年龄、孕次、产次、流产次数、EMAb 阳性、血清 β -HCG、P、E₂ 均可影响地屈孕酮治疗早期先兆流产的效果($P < 0.05$),其中年龄(较大)、孕次(较多)、产次(较多)、流产次数(较多)、EMAb 阳性是影响地屈孕酮治疗效果的危险因素,血清 β -HCG(较高)、P(较高)、E₂(较高)是影响地屈孕酮治疗效果的保护因素。见表 2。

2.4 妊娠结局随访

随访结果显示,继续妊娠的 245 例中,平均分娩孕周(39.43 $\pm$ 1.06)周,产后出血 6 例(2.45%),产后胎盘粘连 17 例(6.94%);新生儿无死亡案例,新生儿平均 Apgar 评分为(9.43 $\pm$ 0.20)分,早产 2 例(0.82%),畸形 1 例(0.41%),永存右脐静脉 1 例(0.41%)。

3 讨论

近年来,孕妇受到环境污染的加重、作息规律的改变、生活压力的增大等影响,早期先兆流产的发病率呈上升趋势^[11,12],而未及时有效治疗的早期先兆流产患者,可进展为不完全流产、完全流产、难免流产等,对孕妇的身心健康及家庭的稳定幸福带来严重威胁^[13,14]。目前,早期先兆流产的病因多样,病理机制复杂,并受到胎儿、母体、免疫及外界因素等影响,与母体生殖内分泌系统紊乱引起的生殖内分泌功能失调的关系最为紧密^[15-17]。因此明确早期先兆流产的影响因素,并及时的采取保胎治疗等措施,具有重要的临床意义。地屈孕酮是常用的保胎治疗方法,能够抑制母体对胚胎的排异反应,维持正常妊娠,且可通过调节机体孕酮水平,降低流产发生率^[18,19]。本研究早期先兆流产患者经地屈孕酮治疗后,治疗有效率为 81.67%,与张艳^[20]等人报道的 89.6%结果相当,但仍有 55 例患者为治疗无效,因而需进一步分析治疗效果的影响因素。

表 1 治疗效果影响因素的单因素分析
Table 1 Univariate analysis of influencing factors of treatment effect

General data	Effective group(n=245)	Ineffective group(n=55)	χ^2/t	P
Age(years)	27.25± 2.63	34.45± 3.22	17.571	0.000
Height(m)	1.53± 0.62	1.56± 0.86	0.300	0.765
Weight(kg)	59.15± 6.25	58.18± 6.67	1.040	0.303
Education level (n,%)			2.926	0.232
Primary school or below	15(5.91)	7(12.73)		
Junior high school to junior college	56(22.05)	11(20.00)		
Bachelor degree or above	174(68.50)	37(67.27)		
Occupation (n,%)			3.998	0.135
Civil servants/institutions	65(25.59)	10(18.18)		
Enterprise staff	146(57.48)	32(58.18)		
Other	34(13.39)	13(23.64)		
Menarche age(years)	10.25± 2.21	10.37± 2.31	0.361	0.720
Menstrual period(d)	5.66± 1.39	5.78± 1.28	0.587	0.560
Menstrual cycle(d)	26.35± 4.39	26.98± 4.85	0.943	0.350
Hypothyroidism(n,%)	5(2.04)	2(3.64)	0.502	0.479
Gestational week (weeks)	9.16± 0.76	9.27± 0.92	0.931	0.356
Pregnancies times(times)	1.82± 0.78	2.91± 0.95	8.981	0.000
Birth times(times)	1.22± 0.34	2.04± 0.45	15.164	0.000
Abortion times(times)	0.61± 0.12	1.57± 0.33	36.237	0.000
EMAb positive (n,%)	26(10.61)	30(54.55)	57.103	0.000
β -HCG(mIU/mL)	59634.28± 16201.95	24596.46± 7913.13	15.610	0.000
P(nmol/L)	34.25± 11.21	26.79± 11.07	4.470	0.000
E ₂ (mIU/mL)	918.53± 313.971	394.62± 145.03	1.236	0.000

表 2 地屈孕酮治疗早期先兆流产效果的影响因素多因素 Logistic 回归分析

Table 2 Multivariate Logistic regression analysis of the influencing factors of the effect of early threatened abortion treated with dydrogesterone

Factors	β	Standard error	Wald(χ^2)	P	OR	95%CI	
						Upper limit	Lower limit
Age	1.913	0.625	18.972	0.000	6.773	2.215	21.224
Gestational times	1.685	0.502	15.516	0.000	5.392	3.017	17.912
Birth times	1.703	0.566	16.135	0.000	5.490	3.659	16.973
Abortion times	1.603	0.491	14.473	0.000	4.968	2.264	12.005
EMAb positive	1.419	0.433	12.269	0.000	4.133	2.063	9.971
β -HCG	-1.125	0.396	6.751	0.001	0.325	0.098	0.869
P	-0.835	0.352	4.963	0.011	0.434	0.078	0.889
E ₂	-0.961	0.379	5.724	0.003	0.383	0.094	0.924

经单因素及多因素 Logistic 回归分析显示, 年龄越大, 孕产次数越多, 流产次数越多, EMAb 阳性, 的患者经地屈孕酮治疗后无效的可能性较大, 血清 β -HCG、P、E₂ 较高是影响地屈孕酮治疗效果的保护因素, 孙红芳等人^[21]的研究指出早期先兆流

产产妇产安胎失败与产妇产年龄、既往流产次数、阴道大量出血等因素存在密切关联。程胜花等^[22]研究发现年龄、孕次、产次、流产史等均与早期先兆流产存在密切关联。究其原因因为:(1)年龄及孕产因素:随着年龄增长, 孕妇卵巢功能下降, 影响卵母细胞

功能、黄体功能,加之高龄孕妇的坐骨、耻骨及髌骨均存在不同程度地固化,胎盘摄取营养相对不足及妊娠时出现的并发症均可增加保胎失败的风险,因此美国妇产科学会及遗传医学会明确规定,对于 ≥ 35 岁的孕妇需接受侵入性产前诊断,以减少不良妊娠发生;多次孕产可对生殖系统产生影响,导致生殖系统功能衰退,增加保胎失败的几率^[23,24];(2)流产因素:多次自然流产可导致习惯性流产,且人工流产操作过程中,宫腔钳刮会损伤子宫内膜,破坏子宫内膜受容性,且会增加宫腔感染的发生风险,引起宫颈粘连,进而影响宫内环境,影响排卵、输卵管拾卵、受精卵正常着床过程等,增加保胎失败的几率^[25];(3)EMAb因素:EMAb与特异性靶抗原结合后可引起抗原免疫反应,使子宫内膜腺体功能受损,影响受精卵着床及胚胎发育,增加保胎失败的风险^[26,27];(4) β -HCG、P和 E_2 因素:在正常妊娠早期,排卵后8~10d即可检出 β -HCG,其浓度随孕周的增加而递增,如若 β -HCG在孕早期分泌不足时,可造成卵巢妊娠黄体功能不良,出现流产^[28]。P激素是子宫的"安慰剂",可促进子宫合成肌蛋白,松弛子宫肌纤维,促进子宫肌细胞肥大,在前列腺素影响子宫肌层而升高应激性反应时,镇静作用明显,并可使妊娠子宫对缩宫素的敏感性降低,子宫收缩减少,从而利于受精卵在子宫内生长发育,因此具有维持妊娠的作用,而其水平的高低,与先兆流产密切相关^[29]。妊娠初期 E_2 可反映卵巢黄体的功能、优势卵泡的质量,当其超过排卵阈值时,表明卵巢黄体功能由胎盘接替,妊娠可继续维持,其水平的上升表明胎儿胎盘单位功能良好并存活,利于胎儿生产,因此其具有维持妊娠、保持黄体期限等作用,故而血清高水平的 β -HCG、P、 E_2 是先兆流产患者的保胎因素^[30]。

随访结果显示,继续妊娠的245例患者平均分娩孕周(39.43 ± 1.06)周,新生儿平均Apgar评分为(9.43 ± 0.20)分,提示在给予地屈孕酮补充外源性激素后,有利于预防流产,维持正常妊娠,改善妊娠结局。但产妇出现产后出血6例,产后胎盘粘连17例,新生儿出现早产2例,畸形1例,永存右脐静脉1例。地屈孕酮治疗早期先兆流产是否会增加产妇及新生儿不良结局的发生风险仍需进一步研究。

综上所述,年龄、孕产次数、流产次数、EMAb阳性、血清 β -HCG、P、 E_2 是地屈孕酮治疗早期先兆流产效果的影响因素。社会健康管理中心和优生优育的有关部门做好优生优育宣传,尤其针对各孕期或育龄期的高龄、孕产流产次数较多的女性,可通过多种宣传模式普及生殖健康教育知识;对于已妊娠的女性,医院方面应加强对孕妇的健康教育和孕期管理,严格按期及时进行孕检,在孕早期应积极进行血清 β -HCG、P、 E_2 监测,以判断早期先兆流产保胎结局并给予指导治疗。

参考文献(References)

- [1] Ata N, Kulhan M, Kulhan NG, et al. Can neutrophil-lymphocyte and platelet-lymphocyte ratios predict threatened abortion and early pregnancy loss? [J]. Ginekol Pol, 2020, 91(4): 210-215
- [2] Bhoil R, Kaushal S, Sharma R, et al. Color Doppler ultrasound of spiral artery blood flow in mid first trimester (4-8 weeks) in cases of threatened abortion and in normal pregnancies [J]. J Ultrason, 2019, 19(79): 255-260
- [3] Feng QT, Chen C, Yu QY, et al. The benefits of higher LMR for early threatened abortion: A retrospective cohort study [J]. PLoS One, 2020, 15(4): e0231642
- [4] 刘华, 马海健, 龚弘超. 硫酸镁治疗晚期先兆流产孕妇的风险预警管理[J]. 实用临床医药杂志, 2020, 24(17): 118-121
- [5] 纪诚, 刘莹钰, 李硕, 等. 产妇产期先兆流产的发生情况及影响因素分析[J]. 中国实验诊断学, 2017, 21(4): 617-619
- [6] Chan DM, Cheung KW, Yung SS, et al. A randomized double-blind controlled trial of the use of dydrogesterone in women with threatened miscarriage in the first trimester: study protocol for a randomized controlled trial [J]. Trials, 2016, 17(1): 408
- [7] Carp H. A systematic review of dydrogesterone for the treatment of threatened miscarriage [J]. Gynecol Endocrinol, 2012, 28(12): 983-990
- [8] 林洁娜, 廖秀玲, 郭惠娟. 滋肾育胎丸联合地屈孕酮片治疗早期先兆流产的疗效观察 [J]. 中国医院用药评价与分析, 2017, 17(4): 459-461
- [9] 谢幸, 孔北华, 段涛. 妇产科学[M]. 第9版. 北京:人民卫生出版社, 2018: 195-198
- [10] 王蔚文. 临床疾病诊断与疗效判断标准 [M]. 北京: 科学技术文献出版社, 2010: 794
- [11] Liu LP, Gong YB. LncRNA-TCL6 promotes early abortion and inhibits placenta implantation via the EGFR pathway [J]. Eur Rev Med Pharmacol Sci, 2018, 22(21): 7105-7112
- [12] 宋敬, 李越, 韩世愈, 等. 血清P、 β -HCG联合检测预测和治疗先兆流产的临床研究[J]. 现代生物医学进展, 2011, 11(19): 3771-3773
- [13] 凌爱华, 赵维英. 黄体酮联合加味寿胎丸治疗肾虚型早期先兆流产及对炎症因子影响[J]. 中国计划生育学杂志, 2020, 28(1): 98-101
- [14] Feng QT, Chen C, Yu QY, et al. The benefits of higher LMR for early threatened abortion: A retrospective cohort study [J]. PLoS One, 2020, 15(4): e0231642
- [15] Zhou J, Huang Z, Pan X, et al. New thoughts in exploring the pathogenesis, diagnosis, and treatment of threatened abortion [J]. Biosci Trends, 2019, 13(3): 284-285
- [16] 沈丽梦, 李娜, 陆子红, 等. 固肾安胎丸联合黄体酮对先兆流产者的保胎效果及作用机制[J]. 西北药学杂志, 2020, 35(1): 109-112
- [17] 胡萍芳, 杨爱平, 陈玉洁, 等. 先兆流产的常见病因及相关实验室指标[J]. 中国卫生检验杂志, 2015, 25(21): 3789-3792
- [18] 曾薇薇, 周华, 陆齐天, 等. 补肾活血方联合地屈孕酮片治疗先兆流产合并宫腔积血的临床观察[J]. 上海中医药大学学报, 2020, 34(3): 26-30
- [19] Wang S, Wang XT, Liu RH, et al. Dydrogesterone has no effect on uterine fibroids when used to prevent miscarriage in pregnant women with uterine fibroids [J]. Ginekol Pol, 2017, 88(12): 679-685
- [20] 张艳, 周晓媚, 何佩, 等. 达芙通在早期先兆流产中的应用分析[J]. 中华内分泌外科杂志, 2017, 11(2): 140-142
- [21] 孙红芳. 早期先兆流产安胎结局的影响因素分析 [J]. 中国妇幼保健, 2020, 35(4): 706-709
- [22] 程胜花, 陈云翔. 早期先兆流产母体相关因素对保胎疗效影响的分析[J]. 中国现代药物应用, 2014, 7(20): 222-223
- [23] Ozdemirci S, Karahanoglu E, Esinler D, et al. Influence of threatened miscarriage on pregnancy and early postpartum period: a case-control report [J]. J Matern Fetal Neonatal Med, 2015, 28(10): 1186-1189
- [24] Biesiada L, Krekora M, Krasomski G. Subchorionic hematoma as a risk factor of pregnancy and delivery in women with threatening abortion [J]. Ginekol Pol, 2010, 81(12): 902-906

- patients with renal anemia: a prospective, observational, multicenter study[J]. *Renal Replacement Therapy*, 2019, 5(1): 3
- [19] Sanghani N S, Haase V H. Hypoxia-Inducible Factor Activators in Renal Anemia: Current Clinical Experience [J]. *Advances in Chronic Kidney Disease*, 2019, 26(4): 253-266
- [20] Feng H L, Chen Y H, Jeng S S. Effect of Zinc Supplementation on Renal Anemia in 5/6-Nephrectomized Rats and a Comparison with Treatment with Recombinant Human Erythropoietin[J]. *International Journal of Molecular Sciences*, 2019, 20(20): 4985
- [21] K Yahata, K Seta, Kikuchi Y, et al. Treatment for renal anemia and outcomes in non-dialysis patients with chronic kidney disease: the current status of regional medicine according to the Kyoto Fushimi Renal Anemia (KFRA) study[J]. *Clinical and Experimental Nephrology*, 2019, 23(10): 1211-1220
- [22] Laura H E, Eugenia I, Ana A, et al. Root Infection of Canker Pathogens, *Fusarium circinatum* and *Diplodia sapinea*, in Asymptomatic Trees in *Pinus radiata* and *Pinus pinaster* Plantations [J]. *Forests*, 2018, 9(3): 128
- [23] Tsai S T, Lin C Y, Dong Y X, et al. Analyses of Growth Parameters of TiO₂ Nanotube Arrays and Their Effect on C₁₄H₁₄N₃NaO₃S Methyl Orange Degradation [J]. *Sensors and materials*, 2019, 31(2(2)): 457-467
- [24] Honjoh H, Takeguchi F, Kato M, et al. Refusal of blood transfusion by a hemodialysis patient with renal anemia for religious reasons[J]. *Nihon Toseki Igakkai Zasshi*, 2018, 51(6): 409-413
- [25] Ali A, Salih R. Renal anemia syndromes in iraqi hemodialysis patients according to iron status[J]. *Saudi journal of kidney diseases and transplantation: an official publication of the Saudi Center for Organ Transplantation, Saudi Arabia*, 2018, 29(1): 127
- [26] Jing-Yuan, Cao, Bi-Cheng, et al. Current insights into the role of HIF-PHD axis in renal anemia[J]. *Sheng li xue bao : [Acta physiologica Sinica]*, 2018, 70(6): 623-629
- [27] B H M S A, D C J W B, G S L L A E F. Physiology and pathophysiology of renal erythropoietin-producing cells [J]. *Journal of the Formosan Medical Association*, 2018, 117(11): 955-963
- [28] Karsten V W, Van C, Wim V B, et al. The effects of aerobic exercise on eGFR, blood pressure and VO₂peak in patients with chronic kidney disease stages 3-4: A systematic review and meta-analysis [J]. *PLOS ONE*, 2018, 13(9): e0203662
- [29] Heo J S, Lee J M. The Long-Term Effect of Preterm Birth on Renal Function: A Meta-Analysis[J]. *International Journal of Environmental Research and Public Health*, 2021, 18(6): 2951
- [30] Mizuno K, Tsujimoto K, Tsuji T. Effect of Prism Adaptation Therapy on the Activities of Daily Living and Awareness for Spatial Neglect: A Secondary Analysis of the Randomized, Controlled Trial [J]. *Brain Sciences*, 2021, 11(3): 347
- [31] Vo-Thi-Kim A, Tan V Q, Nguyen-Thanh B, et al. The effect of medical treatment on nasal exhaled nitric oxide (NO) in patients with persistent allergic rhinitis: A randomized control study [J]. *Advances in Medical Sciences*, 2020, 65(1): 182-188
- [32] Ru Zhentsova T A, Khavkina D A, Chukhlaev P V, et al. Effect of anticoagulant therapy on the course of COVID-19 in comorbid patients[J]. *Voprosy Virusologii*, 2021, 66(1): 40-46
- [33] Tion M A, Orga M T, Adeka I A. The effect of calorie to protein ratio of practical diets on performance and carcass quality of broiler chickens[J]. *Nigerian Journal of Animal Production*, 2021, 32(2): 253-260
- [34] Elamin Z M, Badi S, Yousef B A. Assessment of Erythropoiesis-Stimulating Agents for Anemia Treatment among Chronic Kidney Disease Patients: A Descriptive, Retrospective Study [J]. *Matrix Science Medica*, 2021, 5(1): 21
- [35] Asadur R, Daisuke Y, Abu S, et al. A novel approach to adenine-induced chronic kidney disease associated anemia in rodents [J]. *Plos One*, 2018, 13(2): e0192531

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- [25] Li L, Zhang Y, Fang F. Authors' reply re: Effect of progestogen for women with threatened miscarriage: a systematic review and meta-analysis[J]. *BJOG*, 2020, 127(10): 1304
- [26] 刁晓珍, 吴红莲, 闫贵贞. 习惯性流产患者血清 TGF- β 1、EmAb、TNF- α 及红细胞免疫、细胞免疫的变化研究 [J]. *实用预防医学*, 2014, 21(12): 1500-1501
- [27] 杨艳, 蔺雪晴, 黄楠, 等. EMAB、血清 β -HCG 及黄体酮联合预测早孕先兆流产结局[J]. *检验医学与临床*, 2012, 9(15): 1844-1845
- [28] Li X, Zhang C, Li Y, et al. Predictive values of the ratio of beta-human chorionic gonadotropin for failure of salpingostomy in ectopic pregnancy[J]. *Int J Clin Exp Pathol*, 2019, 12(3): 901-908
- [29] 夏小艳, 李耀军. 血清 β 人绒毛膜促性腺激素、孕激素、可溶性人类白细胞抗原 G 动态变化在早期先兆流产结局预测中应用研究 [J]. *中国医药导报*, 2017, 14(12): 101-104
- [30] Huang Q, Niu Y, Xu L, et al. Relationship between a low ratio of serum estradiol to follicle number and fertility treatment outcomes: A retrospective cohort study of 516 cases [J]. *Medicine (Baltimore)*, 2018, 97(34): e12017