

• 实验研究 •

## 妇科养荣胶囊改善化疗所致小鼠 卵巢功能损伤的效果

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**【摘要】**目的: 观察妇科养荣胶囊(FuKe YangRong capsule, FKYRC)对卵巢损伤小鼠卵巢储备功能和生育力的保护作用。方法: 通过成年雌性小鼠一次性腹腔注射 120 mg/kg 环磷酰胺和 10 mg/kg 白消安建立卵巢损伤小鼠模型, 于造模前 7 d 至造模后 60 d 每日对卵巢损伤小鼠用高、中、低剂量(6 g/kg、4 g/kg 和 2 g/kg)FKYRC(H组、M组、L组)连续灌胃给药; 同时, 于造模前 7 d 一次性皮下注射给予 GnRHa(38 mg/kg)作为阳性对照组(GnRHa组), 用生理盐水(0.2 mL/d)代替 FKYRC 连续灌胃作为卵巢损伤对照组(模型组), 另设正常对照组: 非卵巢损伤正常小鼠腹腔注射给予等体积 DMSO(NC组)。分别于造模后 30 d 和 60 d 取材, 计数卵巢组织中各级卵泡数量, 检测血清 E<sub>2</sub>、FSH、抑制素 B(INHB)和抗苗勒氏管激素(AMH)水平, 检测卵巢组织中翼状螺旋/叉头转录因子 2(FOXL2)和 AMH 蛋白的表达水平。并观察造模 60 d 后各组妊娠率和窝仔数。结果: 各给药组和模型组小鼠血清 E<sub>2</sub> 低于 NC 组( $P < 0.05$ ), 但 FSH 水平组间无统计学差异( $P > 0.05$ )。造模各组卵泡数明显低于 NC 组( $P < 0.05$ ), 且 H 组和 GnRHa 组造模后 60 d 时卵巢组织中窦前卵泡与窦卵泡数较高, 但各干预组与模型组比较无统计学差异( $P > 0.05$ )。模型组小鼠卵巢组织中 FOXL2 和 AMH 蛋白表达水平显著低于各 FKYRC 干预组( $P < 0.05$ ), H 组的妊娠率(80.00%)显著高于模型组(36.36%)( $P < 0.05$ )。结论: 连续 FKYRC(6 g/kg)给药 60 d 后可明显改善烷化剂所致卵巢损伤小鼠的卵巢储备功能和生育能力, 其机制可能与上调颗粒细胞中 FOXL2 和 AMH 的表达水平相关。

**关键词:** 妇科养荣胶囊(FKYRC); 卵巢损伤小鼠; 翼状螺旋/叉头转录因子 2(FOXL2); 抗苗勒氏管激素(AMH); 生育力保护

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## Effects of FuKe YangRong capsule on the fertility preservation of ovarian injured mice

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**【ABSTRACT】 Objective:** To study the protection of the FuKe YangRong capsule (FKYRC) on ovarian reserve function and fertility in ovarian injured mice. **Methods:** Totally 120 mg/kg cyclophosphamide and 10 mg/kg busulfan were administrated to 6–7-week-old C57 mice through intraperitoneal injection to induce ovarian injured model, and the normal control (NC) group were administrated with solvent dimethylsulfoxide (DMSO). Positive group (GnRHa group) was administrated with GnRHa analogue triptorelin 38 mg/kg by using alone hypodermic injection before 7 d cyclophosphamide and busulfan treatment. The group of FKYRC received intragastric administration to mice from 7 d before cyclophosphamide and busulfan treatment to 60 d after cyclophosphamide and busulfan treatment, and the dosages were 6 g/kg (high-dose, H group), 4 g/kg (medium-dose, M group) and 2 g/kg (low-dose, L group), respectively. The ovarian injured control group were intragastric administrated with 0.2 mL saline (model group). The ovaries were collected at 30 d and 60 d after cyclophosphamide and busulfan treatment, and the ovarian follicle was counted, serum E<sub>2</sub>, FSH and anti-Müllerian hormone (AMH) levels were detected by ELISA, the localization and expression of winged helix/forkhead transcription factor 2 (FOXL2) and AMH protein were checked by immunohistochemistry and Western blotting. The pregnant rate and litter size were analyzed at 60 d after cyclophosphamide and busulfan treatment. **Results:** The serum E<sub>2</sub> was lower in all cyclophosphamide and busulfan treatment groups than in NC group ( $P<0.05$ ), but FSH level was not significantly different among all groups. The number of ovarian follicle in all cyclophosphamide and busulfan treatment groups was lower than that in NC group ( $P<0.05$ ), although the preantral follicle and antral follicle in GnRHa group and H group were higher, no significant difference was observed compared with other groups. The expressions of FOXL2 and AMH protein in model group were lower than those in NC group ( $P<0.05$ ), which in H group and M group were higher than those in model group ( $P<0.05$ ). The pregnancy rate in H group (80.00%) was higher than that in model group (36.36%,  $P<0.05$ ). **Conclusion:** The fertility of ovarian injured mice caused by alkylating agent was remarkably improved by administered with 6 g/kg FKYRC, which might be related to the up-regulation of the expression level of FOXL2 and AMH.

# 轴突导向因子及其受体在正常及早期胚胎停止发育绒毛组织中的表达及相互关系

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**【摘要】**目的: 探讨绒毛组织中轴突导向因子(Netrin-1)及其受体结直肠癌缺失基因(deleted in colorectal cancer, DCC)和非协调性分子5同源蛋白B(uncoordinated-5-homolog B, UNC5B)的表达及其与胚胎停止发育的关系。方法: 采用免疫组织化学PV法检测20例正常早期妊娠绒毛(对照组)、25例早期胚胎停止发育绒毛(实验组)组织中Netrin-1及其受体DCC、UNC5B的表达情况。结果: Netrin-1在对照组的阳性表达率为95.00%, 实验组的阳性表达率为76.00%, 组间差异有统计学意义( $P < 0.01$ )。DCC在对照组阳性表达率为95.00%, 实验组阳性表达率为32.00%, 组间差异有统计学意义( $P < 0.01$ )。UNC5B在对照组阳性表达率为55.00%, 实验组阳性表达率为96.00%, 组间差异有统计学意义( $P < 0.01$ )。对照组Netrin-1、DCC和UNC5B三者两两间的表达无显著相关性。实验组DCC和Netrin-1的表达间呈显著负相关( $r = -0.227, P < 0.01$ ), DCC和UNC5B的表达间呈显著正相关( $r = 0.151, P < 0.05$ )。Netrin-1和UNC5B的表达间无显著相关性( $r = -0.065, P = 0.303$ )。结论: Netrin-1及其受体DCC、UNC5B的异常表达可能与早期胚胎停止发育发生有关; 三者可能通过协同作用影响早期胚胎发育过程中胎盘血管的形成, 导致胚胎停止发育。

**关键词:** 早期胚胎停止发育; 轴突导向因子(Netrin-1); 结直肠癌缺失基因(DCC); 非协调性分子5同源蛋白B(UNC5B); 免疫组织化学

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## Expression of Netrin-1 and its receptors deleted in colorectal cancer (DCC) and uncoordinated-5-homolog B (UNC5B) in normal and early miscarriage villi and their relationship

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**【ABSTRACT】 Objective:** To explore the clinical significances of the expression of Netrin-1 and its receptors deleted in colorectal cancer (DCC), uncoordinated-5-homolog B (UNC5B) with the occurrence of early miscarriage. **Methods:** Immunohistochemistry PV-6000 two-step method was used to detect the expression of Netrin-1 and its receptors DCC, UNC5B protein in 20 cases of normal early pregnancy villi (control group), 25 cases of villi from early miscarriage patients (experimental group). **Results:** The positive expression rate of Netrin-1, DCC, UNC5B in control group and experimental group was 95.00% vs 76.00%, 95.00% vs 32.00%, 55.00% vs 96.00%, respectively, with significant differences between the two groups ( $P < 0.01$ ). There were no significant correlations among the three proteins in control group. But there was a significantly negative correlation between DCC and Netrin-1 in experimental group ( $r = -0.227$ ,  $P < 0.01$ ), a significantly positive correlation between DCC and UNC5B in experimental group ( $r = 0.151$ ,  $P < 0.05$ ). No significant correlation was detected between the expression of UNC5B and Netrin-1 ( $r = -0.065$ ,  $P = 0.303$ ). **Conclusion:** The abnormal expression of Netrin-1 and its receptors DCC and UNC5B might be related to early miscarriage. Those proteins might be involved in the placental vasculogenesis in early embryo development.

**Key words:** early pregnancy loss; Netrin-1; deleted in colorectal cancer (DCC); uncoordinated-5-homolog B (UNC5B); immunohistochemistry

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• 临床研究 •

# 多囊卵巢综合征患者在高孕激素超促排卵中 LH与IVF/ICSI临床结局的相关性分析

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**【摘要】**目的: 探讨在高孕激素超促排卵方案中基础血黄体生成素(LH)水平对多囊卵巢综合征(PCOS)患者行体外受精/卵胞质内单精子显微注射(IVF/ICSI)治疗的临床结局的影响。方法: 回顾性分析183例PCOS患者采用从早卵泡期开始使用安宫黄体酮(MPA)联合促性腺激素(Gn)的高孕激素超促排卵方案行IVF/ICSI治疗; 根据基础LH水平分为3组, A组: 0~5 IU/L, B组: 5~10 IU/L, C组: >10 IU/L, 分析3组患者在高孕激素超促排卵过程中不同血LH水平与控制性超促排卵特征及IVF临床结局的相关性。结果: 3组在促排卵过程中LH水平均呈下降趋势, 且在基础LH水平、中期LH水平、诱发排卵当日的LH水平及诱发排卵次日的LH水平3组间比较均有统计学差异( $P < 0.05$ ), 在扳机日LH水平波动于0.08~12.33 IU/L之间, 无一例发生自发性LH峰; 在获卵数、成熟卵数及获卵率A组与C组间有统计学差异( $P < 0.05$ ), 而成熟卵率、正常受精卵数、优质胚胎数及有效胚胎数3组间比较无统计学差异( $P > 0.05$ ); 后续的冻融胚胎移植(frozen-thawed embryo transfer, FET)周期结果表明, 临床妊娠率、早期流产率及继续妊娠率组间比较均无统计学差异( $P > 0.05$ )。结论: 高孕激素促排卵方案可有效预防PCOS患者行IVF/ICSI治疗的自发性LH峰发生, 并且基础高LH水平未损害PCOS患者的卵子及胚胎质量, 对其临床结局也无明显影响, 因此高孕激素超促排卵方案是一种新的简单安全、高效的垂体非降调节超促排卵方案, 但还需大样本多中心的随机对照试验进一步证实。

**关键词:** 安宫黄体酮(MPA); 基础高黄体生成素; 多囊卵巢综合征(PCOS); 体外受精 / 卵胞质内单精子显微注射(IVF/ICSI)

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## Endocrine characteristic and the clinical outcomes of IVF/ICSI treatment in polycystic ovary syndrome patients with serum high LH levels during progestin-primed ovarian stimulation

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**【ABSTRACT】 Objective:** To explore the effects of different basal luteinizing hormone (LH) levels during progestin-primed ovarian stimulation protocol on *in vitro* fertilization/intracytoplasmic sperm injection (IVF/ICSI) outcomes in the patients with polycystic ovary syndrome (PCOS). **Methods:** A total of 183 PCOS patients undergoing progestin-primed ovarian stimulation protocol were analyzed in this retrospective study and were allocated into three groups according to basal LH levels: group A, 0–5 IU/L ( $n=105$ ); group B, 5–10 IU/L ( $n=51$ ); group C, >10 IU/L ( $n=27$ ). Gonadotropins (Gn) and medroxyprogesterone acetate (MPA) were used from the early follicle phase. The hormone profile LH level, embryological characteristics, and the pregnant results after frozen-thawed embryo transfer (FET) were compared among the three groups. **Results:** There was a significant difference in LH levels during the stimulation among the three groups ( $P<0.05$ ), however, no premature LH surges were detected, with a range of 0.08–12.33 IU/L. No differences were found in the number of fertilization, embryo quality, viable embryos and mature oocyte rate among the three groups. The clinical pregnancy rate, the ongoing pregnancy rate and the miscarriage rate were similar in the FET cycles. **Conclusion:** The progestin-primed ovarian stimulation protocol is a novel regimen of ovarian stimulation for the prevention of premature LH surges and to achieve potential embryos. Although the follicular basal LH concentration was high, the embryo quality was not impaired. Furthermore, pregnancy outcome was similar among the three groups. To sum up, the progestin-primed ovarian stimulation protocol is simple, efficient and safe for the PCOS patients. However, further blind randomized controlled trials should be performed to confirm the feasibility of this regimen.

**Key words:** medroxyprogesterone acetate (MPA); basal high luteinizing hormone; polycystic ovary syndrome (PCOS); *in vitro* fertilization/intracytoplasmic sperm injection (IVF/ICSI)

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# 体外受精 / 卵胞质内单精子显微注射 - 胚胎移植技术出生的学龄期儿童内分泌状况的随访研究

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**【摘要】**目的: 探讨通过体外受精 / 卵胞质内单精子显微注射 - 胚胎移植(IVF/ICSI-ET)技术出生的学龄期儿童内分泌状况是否与同年龄段自然受孕出生儿童存在差异。方法: 选择通过 IVF/ICSI-ET 出生的 6~11 岁学龄期儿童(IVF/ICSI 组)87 例, 检测其代谢及内分泌情况, 并随机抽取同年龄段自然受孕出生儿童(NC 组)74 例作为对照。结果: IVF/ICSI 组平均血红蛋白浓度(MCHC)( $334.59 \pm 10.17$  g/L vs  $330.74 \pm 13.58$  g/L)、血糖水平( $4.57 \pm 0.33$  mmol/L vs  $4.45 \pm 0.27$  mmol/L)均高于 NC 组, 差异有统计学意义( $P < 0.05$ )。红细胞数、白细胞数、血小板数、平均红细胞体积(MCV)、红细胞平均血红蛋白量(MCH)、三碘甲状腺原氨酸(T3)、甲状腺素(T4)、促甲状腺素(TSH)、空腹胰岛素(0 h INS)及空腹生长激素(0 h GH)组间差异无统计学意义( $P > 0.05$ )。对影响 MCHC 的因素进行多重线性回归, 是否为双胞胎、儿童身高对 MCHC 有影响; 对影响血糖的因素进行多重线性回归, 结果是否为试管婴儿、儿童性别、身高对血糖有影响。结论: IVF/ICSI-ET 出生儿童内分泌状况与自然妊娠出生儿童无明显差异, 空腹血糖(0 h GLU)水平高于自然妊娠出生儿童, 但均在正常范围内。

**关键词:** 辅助生殖技术(ART); 试管婴儿; 学龄期儿童; 内分泌代谢

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## A follow-up study of endocrine status in Chinese school-age children conceived by *in vitro* fertilization/intracytoplasmic sperm injection

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**【ABSTRACT】 Objective:** To discuss whether there is a difference in endocrine status between the Chinese school-age children conceived by *in vitro* fertilization/intracytoplasmic sperm injection (IVF/ICSI) technology and naturally conceived children. **Methods:** IVF/ICSI born children aged 6–11 years ( $n=87$ ) were selected as IVF/ICSI group, while naturally conceived children at the same age ( $n=74$ ) were randomly collected as normal control (NC) group. The endocrine status between the two groups was compared. **Results:** Twins proportion was higher in IVF/ICSI group, and birth weight, body length of birth, gestational age were lower in IVF/ICSI group than in NC group ( $P<0.05$ ). Red blood hemoglobin concentration (MCHC) level and glucose level in IVF/ICSI group were statistically significantly higher than those in the control ( $334.59 \pm 10.17$  g/L vs  $330.74 \pm 13.58$  g/L,  $4.57 \pm 0.33$  mmol/L vs  $4.45 \pm 0.27$  mmol/L). The factors affecting MCHC were analyzed using multiple linear regression, twin status and height were statistically significant. Similarly, the factors affecting blood sugar were also analyzed, test-tube baby, gender, and height were statistically significant. **Conclusion:** Children born by IVF/ICSI have higher fasting blood glucose levels than the natural pregnancy children, but all in the normal range.

**Key words:** assisted reproductive technology (ART); test-tube baby; school-age children; endocrine metabolism



# 肾损伤分子-1、 $\beta$ 2-微球蛋白、内皮素-1 和肌酐在妊娠期高血压疾病并发 急性肾损伤的临床研究

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**【摘要】**目的: 探讨血清肌酐(SCr)、内皮素-1(ET-1)、肾损伤分子-1(KIM-1)和 $\beta$ 2-微球蛋白( $\beta$ 2-MG)的水平在妊娠期高血压疾病并发早期肾损伤的临床意义。方法: 将妊娠期高血压疾病并发肾损伤的孕产妇40例设为肾病组, 同期正常孕产妇40例设为对照组, 分别在孕龄30周、32周、34周、36周检测孕妇血SCr、ET-1、尿KIM-1和 $\beta$ 2-MG的水平。结果: ①肾病组与对照组比较, 患者的年龄、孕次和流产史均无统计学差异( $P>0.05$ ), 尿量、尿素氮(BUN)、SCr及尿蛋白定量均存在统计学差异( $P<0.001$ ); ②肾病组和对照组整体比较, SCr、ET-1、KIM-1和 $\beta$ 2-MG的组间、时间点间的交互作用均有统计学差异( $P<0.05$ ); ③孕36周SCr、孕32周KIM-1及孕34周ET-1和 $\beta$ 2-MG水平肾病组与对照组组间存在统计学差异( $P<0.05$ ); ④对照组组内不同孕周间SCr、ET-1、KIM-1和 $\beta$ 2-MG水平无统计学差异( $P>0.05$ ); 肾病组组内与孕30周时比, KIM-1水平在孕32周显著升高( $P<0.05$ ), 在孕34周、36周进一步升高( $P<0.01$ ); ET-1和 $\beta$ 2-MG水平在孕34周显著升高( $P<0.05$ ), 而SCr在孕36周显著升高( $P<0.05$ )。结论: 妊娠期高血压疾病孕妇产前监控中, 联合检测SCr、ET-1、KIM-1和 $\beta$ 2-MG能及时发现肾损伤的存在; 妊娠期高血压疾病并发肾损伤时KIM-1、ET-1和 $\beta$ 2-MG的改变早于SCr的改变。

**关键词:** 子痫前期; 肾损伤; 肾损伤分子-1(KIM-1);  $\beta$ 2-微球蛋白( $\beta$ 2-MG); 血清肌酐(SCr); 内皮素-1(ET-1)

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## Clinical research of kidney injury molecules-1, $\beta$ 2-microglobulin, endothelin-1 and creatinine in gestational hypertension complicated with acute kidney injury

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**【ABSTRACT】 Objective:** To explore the clinical significance of the serum creatinine (SCr), kidney injury molecules-1 (KIM-1),  $\beta$ 2-microglobulin ( $\beta$ 2-MG), endothelin-1 (ET-1) gestational hypertension disease complicated with early renal damage. **Methods:** Normal maternal cases ( $n=40$ ) were collected as control group, at the same time gestational hypertension disease complicated with renal injury were collected as maternal group ( $n=40$ ). SCr, ET-1, KIM-1 and  $\beta$ 2-MG levels at gestational age 30 weeks, 32 weeks, 34 weeks and 36 weeks were detected. **Results:** 1) There was no significant difference in history of pregnancy and abortion between nephropathy group and control group ( $P>0.05$ ); while urine output, blood urea nitrogen (BUN), SCr and urinary protein quantitative existed significant differences between the two groups ( $P<0.001$ ). 2) SCr, ET-1, KIM-1 and  $\beta$ 2-MG between nephropathy group and control group, were statistically significant at each time point ( $P<0.05$ ). 3) Compared with control group, the change of SCr appeared a significant difference at gestational age 36 week in nephropathy group. KIM-1 had a significant difference at gestational age 32 weeks ( $P<0.05$ ). ET-1 and  $\beta$ 2-MG concentrations at gestational age 34 weeks nephropathy group was significantly higher than that in control group ( $P<0.05$ ). 4) Contrast in the respective group, SCr, KIM-1, ET-1 and  $\beta$ 2-MG of control group had no significant difference at different gestational age ( $P>0.05$ ). In different gestational ages of the nephropathy group KIM-1 level was significantly increased than gestational age 32 weeks ( $P<0.05$ ), especially at 34 and 36 weeks gestation, this change was more significant ( $P<0.01$ ). ET-1 and  $\beta$ 2-MG in 34 weeks gestation was significantly increased ( $P<0.05$ ), while SCr increased significantly at 36 weeks gestation ( $P<0.05$ ). **Conclusion:** In maternal prenatal monitoring of gestational hypertension disease, jointly detecting SCr, ET-1, KIM-1 and  $\beta$ 2-MG can timely find the existence of kidney damage. In gestational hypertension complicated with kidney injury, KIM-1,  $\beta$ 2-MG and ET-1 are much earlier changing than SCr.

**Key words:** preeclampsia; kidney injury; kidney injury molecules-1 (KIM-1);  $\beta$ 2-microglobulin ( $\beta$ 2-MG); serum creatinine (SCr); endothelin-1 (ET-1)

• 流行病学研究 •

# 1 945 例稽留流产的流行病学及高危因素分析

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**【摘要】**目的: 探讨稽留流产发生的高危因素。方法: 通过病例-对照回顾性研究, 收集稽留流产病例1 945例, 同时与1 874例因非意愿妊娠20周内的单活胎要求终止妊娠者(包括妊娠<12周自愿要求终止妊娠者以及妊娠12~20周内因内外科因素不宜妊娠者)的病例资料进行对比。分析与稽留流产发病相关的高危因素及环境等因素在稽留流产中可能产生的影响。结果: ① Logistic多因素回归分析显示, 与1 945例稽留流产发病正相关的危险因素包括: 室外职业者( $OR=1.777$ ,  $95\%CI=1.538\sim 2.052$ ), 初产妇( $OR=2.305$ ,  $95\%CI=2.013\sim 2.638$ ), 自然流产史( $OR=2.359$ ,  $95\%CI=1.703\sim 3.268$ ), 贫血( $OR=5.498$ ,  $95\%CI=2.243\sim 13.473$ ), 乙肝病毒携带者( $OR=8.126$ ,  $95\%CI=4.688\sim 14.084$ ); 与稽留流产发病负相关的危险因素为人工流产 $\geq 3$ 次( $OR=0.726$ ,  $95\%CI=0.573\sim 0.920$ )。② 稽留流产独立因素构成变化显示, 环境因素及一些未知因素等构成比升高( $P<0.05$ ), 与稽留流产发病数增加有关。结论: 室外职业者、初产妇、自然流产病史、贫血和乙肝病毒携带者是稽留流产发生的独立危险因素, 其中环境因素及一些未知因素的构成比随稽留流产发病数增加而升高。初步推论: 基因、生育史、合并症不能解释稽留流产发病数的升高, 而环境因素和一些未知因素可能是稽留流产病例数升高的重要原因之一。

**关键词:** 稽留流产; 高危因素; 病例对照研究

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## Epidemiology analysis of high risk factors for 1 945 cases of missed abortion

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**【ABSTRACT】 Objective:** To determine the risk factors related to missed abortion. **Methods:** This was a case-control study. We collected data for 1 945 cases of missed abortion in contrast to 1 874 cases of normal pregnancy within 20 weeks of gestation, including those who are pregnant for less than 12 weeks and request voluntarily to terminate and those for from 12 to 20 weeks but inappropriate to be pregnant because of internal or surgical diseases.  $\chi^2$  test and Logistic regressive model were used to evaluate the association of independent risk factors and the uncertain factors, such as environment, with missed abortion so as to explore the reasons for increasing number of patients suffered from missed abortion. **Results:** 1) Logistic regression model indicated that there were 5 independent risk factors were positively correlated with missed abortion, including outdoor working environment ( $OR=1.777$ ,  $95\%CI=1.538-2.052$ ), primipara ( $OR=2.305$ ,  $95\%CI=2.013-2.638$ ), spontaneous abortion history ( $OR=2.359$ ,  $95\%CI=1.703-3.268$ ), anemia ( $OR=5.498$ ,  $95\%CI=2.243-13.473$ ) and hepatitis B virus carrier ( $OR=8.126$ ,  $95\%CI=4.688-14.084$ ). Only one risk factor was negatively correlated with missed abortion, which was induced abortion history of 3 times or greater ( $OR=0.726$ ,  $95\%CI=0.573-0.920$ ). 2) Further research on the changes of components for independent factors of missed abortion showed that, environmental factors and unknown factors were correlated to the increased number of missed abortion ( $P<0.05$ ). **Conclusion:** Outdoor profession, primipara, spontaneous abortion, anemia and hepatitis B virus carrier were independent risk factors of missed abortion. Among all these risk factors, increased constituent of outdoor profession and unknown factors were found to have contribution to the increase of missed abortion. In summary, we primary concluded that genes, reproductive history and complications of pregnancy would not explain the elevated cases of missed abortion, while environmental factors and the other unknown reasons might be the main reasons.

**Key words:** missed abortion; high risk factors; case-control study

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• 循证医学 •

## 复方醋酸环丙孕酮联合二甲双胍对多囊卵巢综合征患者内分泌及代谢影响的 Meta 分析

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**【摘要】**目的: 系统评价二甲双胍与复方醋酸环丙孕酮(CPA)联合应用对多囊卵巢综合征(PCOS)患者内分泌及代谢的影响。方法: 计算机检索 Cochrane Library、PubMed、EMbase、中国生物医学文献数据库、维普数据库、中国知网数据库, 纳入关于二甲双胍与复方CPA联合应用治疗PCOS的对照研究, 检索时限均截止至2015年1月。由2位研究者独立按照纳入与排除标准筛选文献、提取资料 and 评价纳入研究的方法学质量后, 采用 RevMan 5.2 软件进行 Meta 分析。结果: 共纳入9个对照研究, 合计641例患者。Meta分析结果显示: 二甲双胍联合复方CPA组 LH/FSH(MD=-0.42, 95%CI=-0.55~-0.28,  $P<0.000\ 01$ )、睾酮(SMD=-0.42, 95%CI=-0.78~-0.07,  $P=0.02$ )、空腹血糖(MD=-0.91, 95%CI=-1.28~-0.54,  $P<0.000\ 01$ )和空腹胰岛素(MD=-0.63, 95%CI=1.07~0.43,  $P=0.005$ )等方面均优于单纯复方CPA组。结论: 当前证据表明, 二甲双胍联合复方CPA对PCOS患者内分泌激素及代谢的改善效果优于单纯复方CPA。

**关键词:** 二甲双胍; 醋酸环丙孕酮(CPA); 多囊卵巢综合征(PCOS); 系统评价; Meta 分析

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## Compound cyproterone acetate combined metformin for polycystic ovarian syndrome: a systematic review

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**【ABSTRACT】 Objective:** To systematically review the clinical efficacy of metformin combined compound cyproterone acetate (CPA) tablets for polycystic ovary syndrome (PCOS). **Methods:** Such databases as the Cochrane Library, PubMed, EMBASE, CBM, VIP, CNKI and Wanfang Data were searched up to January 2015 for controlled trials about metformin combined compound CPA for PCOS. According to the inclusion and exclusion criteria, two reviewers independently screened literatures, extracted data, and assessed methodological quality of included studies. Then, Meta-analysis was performed using RevMan 5.2 software. **Results:** Nine controlled trials involving 641 patients were included. The results of Meta-analysis showed that, metformin combined compound CPA was superior to compound CPA alone regarding LH/FSH (MD=-0.42, 95%CI=-0.55--0.28,  $P<0.000\ 01$ ), testosterone (SMD=-0.42, 95%CI=-0.78-0.07,  $P=0.02$ ), fasting blood-glucose (MD=-0.91, 95%CI=-1.28--0.54,  $P<0.000\ 01$ ) and fasting insulin (MD=-0.63, 95%CI=-1.07--0.43,  $P=0.005$ ). **Conclusion:** Current evidence shows that metformin combined compound CPA could improve endocrine and metabolism better than CPA alone in PCOS patients.

**Key words:** metformin; cyproterone acetate (CPA); polycystic ovary syndrome (PCOS); systematic review; Meta-analysis

· 综述 ·

## 参与调控始基卵泡激发过程的细胞信号通路

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**【摘要】** 始基卵泡占卵巢所有卵泡的99%以上, 人卵巢组织中最后一批由初级卵母细胞分化形成的始基卵泡的寿命可长达50余年。始基卵泡的有序激活受多种信号通路的调控作用。许多细胞因子可以通过PI3K-AKT信号通路, 激活叉头蛋白转录因子O3a(FoxO3a), 促进始基卵泡的启动, 而该作用可以被抑癌基因PTEN编码的蛋白所抑制; 结节性硬化综合征(TSC)蛋白能够负向调节哺乳动物雷帕霉素靶蛋白复合体1(mTORC1), 在始基卵泡保持静止状态的过程中发挥重要作用; 转化生长因子- $\beta$ (TGF- $\beta$ )家族成员众多, 对始基卵泡的激活作用存在争议, 主要通过蛋白分子Smads控制靶基因的转录; 近期有研究表明, Hippo信号通路在卵泡激活调节过程中有重要作用, 对卵巢组织进行机械切割, 可以抑制Hippo信号通路, 促进卵泡激活。上述不同的信号通路之间存在频繁的交叉对话。对多种信号通路之间进行联系, 能够为整体理解始基卵泡的激活机制提供新的思路。

**关键词:** 卵泡激发; PTEN/PI3K/AKT信号通路; TSC/mTORC1信号通路; 转化生长因子(TGF)- $\beta$ 信号通路; Hippo信号通路

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## Cell signaling pathways involved in the regulation of primordial follicle stimulating processes

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**【ABSTRACT】** Primordial follicle accounts for more than 99% of all ovarian follicles. The last batch of primordial follicles formed by primary oocytes can survive more than 50 years. Multiple signaling pathways regulate the orderly activation of primordial follicles. Many cytokines can activate forkhead box group O3a (FoxO3a) via PI3K-AKT signaling pathway and promote the activation of primordial follicles. This effect can be inhibited by phosphatase and tensin homolog (PTEN). The tumor suppressor tuberous sclerosis complex 1 (Tsc1), which negatively regulates mammalian target of rapamycin complex 1 (mTORC1), functions in oocytes to maintain the quiescence of primordial follicles. Transforming growth factor beta (TGF- $\beta$ ) super family includes many family members, which can control the transcription of target genes through protein Smads. Its role in follicle stimulation is controversial. The recent studies have shown that mechanical cutting of ovarian tissue can inhibit the Hippo signal pathway and promote follicular activation. There are frequent cross talks between the different signal pathways. The link between multiple signaling pathways can provide a new train of thought for us to overall understand the primordial follicle activation mechanism.

**Key words:** follicle activation; PTEN/PI3K/AKT signal pathway; TSC/mTORC1 signal pathway; TGF- $\beta$  signal pathway; Hippo signal pathway

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# 子宫内膜异位症病理机制相关 信号通路的研究进展

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**【摘要】** 子宫内膜异位症(endometriosis, EMS)是常见的良性妇科疾病, 但具有浸润、转移及复发的恶性行为, 其发病机制尚不清楚。近年来研究显示, 子宫内膜细胞的异位浸润及转移是一个多阶段、多因素参与的复杂过程, 其调节涉及多条信号转导通路如 Wnt/ $\beta$ -连环素、MAPK、PI3K、NF- $\kappa$ B、Rho/ROCK、JAK/STAT3、TGF- $\beta$ /Smad。不同的信号转导通路产生了一个复杂的信号网络, 最终影响 EMS 异位内膜黏附、侵袭及血管生成。

**关键词:** 子宫内膜异位症(EMS); 病理机制; 信号转导通路

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## Research progress on the signal transduction pathways involved in pathogenesis of endometriosis

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**【ABSTRACT】** Endometriosis (EMS) is a common benign gynecologic disease, but it has the malignant behavior of infiltration, transfer and recurrence, and its pathogenesis has not been clear. Recent studies have shown that the ectopic invasion and metastasis of endometrial cells was a complex process, and it involved a number of signal transduction pathways (such as Wnt, MAPK, PI3K, NF- $\kappa$ B, Rho/ROCK, JAK/STAT3, TGF- $\beta$ /Smad). Different signaling pathways produce a complex network of signals, which affect the adhesion, invasion and angiogenesis of ectopic endometrium ultimately.

**Key words:** endometriosis (EMS); pathogenesis; signal transduction pathway

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# 辅助生殖技术妊娠丢失的相关因素分析

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**【摘要】** 辅助生殖技术(ART)后妊娠丢失病因复杂, 困扰着大多数不孕患者与临床工作者, 明确其相关因素对改善 ART 妊娠结局至关重要。经过文献综述, 夫妻双方年龄、胚胎染色体异常影响 ART 妊娠结局, 而 ART 方法、多胎妊娠是否影响其妊娠结局, 及 ART 妊娠丢失率是否高于自然妊娠仍需进一步探讨, 这为今后的研究提示了相应的研究方向。

**关键词:** 辅助生殖技术(ART); 妊娠丢失; 年龄; 染色体

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## **Analysis of relative factors for pregnancy loss in assisted reproductive technology**

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**【ABSTRACT】** The etiology of pregnancy loss in assisted reproductive technology (ART) is complicated, which confused most infertile patients and clinicians. Therefore, it is critical to investigate the relative factors for pregnancy loss, which will contribute to improve pregnancy outcome of ART. It's shown that the mainly relative factors are included as follows by the literature review, the couple's age and chromosome abnormality of the embryo. However, methods of ART, multiple pregnancies, the rates of pregnancy loss between natural pregnancy and ART still need further discussion. Thus it provides directions for future research of pregnancy loss in ART.

**Key words:** assisted reproductive technology (ART); pregnancy loss; age; chromosome

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# 生殖器结核对体外受精 - 胚胎移植技术 助孕的影响

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**【摘要】**生殖器结核是输卵管性不孕的重要原因,也是发展中国家寻求体外受精-胚胎移植(IVF-ET)技术助孕治疗的主要病因。如果结核性不孕患者宫腔形态正常、卵巢功能良好,IVF-ET是治疗结核性不孕的有效方法。生殖器结核可以影响IVF-ET治疗结局,首先表现为能够降低卵巢储备功能。其次,影响胚胎着床,如潜伏性子宫内膜结核由于内膜基底层结核菌的存在,影响内膜下血流及激活抗磷脂抗体,诱发微血栓形成,使胚胎的着床失败;内膜结核可引起内膜粘连、瘢痕化及宫腔形态改变,影响胚胎着床。IVF-ET助孕治疗由于超促排卵,高雌孕激素水平可以激活陈旧结核,使潜伏性结核转为活动性结核。另外,结核患者包括生殖器结核患者妊娠后可以通过多种途径感染胎儿,导致新生儿先天性结核。因此,不孕患者在行辅助生殖技术(ART)助孕治疗前,需考虑筛查结核尤其生殖器结核。对于已确诊的结核感染应当规范地进行抗结核治疗;对于潜伏性结核,给予预防性治疗再行IVF-ET助孕会提高成功率,获得较好的妊娠结局。

**关键词:** 生殖器结核; 体外受精 - 胚胎移植(IVF-ET); 妊娠结局

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## Role of genital tuberculosis in IVF-ET outcomes

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**【ABSTRACT】** Genital tuberculosis is a major cause of tubal infertility and seeking for *in vitro* fertilization (IVF) to assist reproduction in developing countries which is an effective method to treat tubercular infertility for a person who has a normal uterine cavity and functional ovaries. Genital tuberculosis can decrease ovarian reserve and affect the embryo implantation. For example, dormant mycobacterium present in the basal endometrial layer may appreciably reduce sub-endometrial blood flow (SEBF) and possibly interfere with implantation. Altered immune response in tuberculosis is known to activate antiphospholipids (aPL), which in turn can lead to activation of aPL antibodies and microthrombosis, a known cause of implantation failure in aPL. What's more, endometrial adhesions, scars and deformation of uterine cavity can have an influence on embryo implantation. Latent genital tuberculosis can be reactivated by the high levels of estrogen and progestin IVF superovulation. Patients who have tuberculosis, including genital tuberculosis, can communicate tuberculosis mycobacterium to infant by any ways, which can lead to congenital tuberculosis. In a word, we should highlight the fact that TB should be considered and excluded in high-risk women before IVF. Women with genital tuberculosis or latent tuberculosis infection (LTBI) require early diagnosis timely and complete short-course anti-tuberculosis therapy (ATT) before initiating them into IVF-ET, so as to optimize their chance of achieving a successful live birth.

**Key words:** genital tuberculosis; *in vitro* fertilization and embryo transfer (IVF-ET)

• 临床报道 •

# 亮丙瑞林在早卵泡期超长方案IVF/ICSI-ET助孕治疗中的应用

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**【摘要】**目的: 探讨亮丙瑞林在早卵泡期超长方案体外受精/卵细胞质内单精子显微注射-胚胎移植(IVF/ICSI-ET)助孕治疗中的垂体降调节效果及临床结局。方法: 回顾性分析本中心行早卵泡期超长方案的974例患者的临床资料, 其中亮丙瑞林组385例, 曲普瑞林组589例, 分析患者的降调节效果及临床妊娠结局。结果: 垂体降调节30 d后亮丙瑞林组患者的FSH及E<sub>2</sub>水平显著高于曲普瑞林组( $P < 0.01$ ), LH水平无统计学差异( $P = 0.38$ ); 亮丙瑞林组的Gn启动时间明显早于曲普瑞林组( $P < 0.01$ ), 因此超促排卵过程中曲普瑞林组内源性早发LH峰形成率显著高于亮丙瑞林组( $P < 0.01$ ); 患者的临床妊娠率、流产率、周期取消率及中重度卵巢过度刺激综合征(OHSS)发生率组间均无统计学差异( $P > 0.05$ ), 但亮丙瑞林组的胚胎种植率明显高于曲普瑞林组(57.61% vs 52.13%,  $P = 0.046$ )。结论: 垂体降调节作用更温和的亮丙瑞林更符合早卵泡期超长方案对内源性性激素水平抑制的要求; 在早卵泡期超长方案中使用亮丙瑞林降调节可获得更佳临床结局。

**关键词:** 亮丙瑞林; 曲普瑞林; 降调节; 临床妊娠率; 胚胎种植率

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## Application of leuprorelin for ovulation induction in long protocol of hormonal suppression in the early follicular phase of IVF/ICSI-ET

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**【ABSTRACT】Objective:** To compare the efficacy of leuprorelin and triptorelin on down regulation of pituitary and clinical outcome of *in vitro* fertilization / intracytoplasmic sperm injection-embryo transfer (IVF/ICSI-ET) with ovulation induction in long protocol of hormonal suppression in the early follicular phase. **Methods:** A retrospective analysis was performed on the clinical data of 974 patients who received long protocol of hormonal suppression in the early follicular phase of IVF/ICSI-ET. Totally 385 patients in leuprorelin group received subcutaneous injection of leuprorelin and 589 patients in triptorelin group received triptorelin for down regulation. The level of hormonal suppression and clinical outcome in two groups were compared. **Results:** The FSH and E<sub>2</sub> levels were much higher in leuprorelin group than in triptorelin group after 30 d of down regulation ( $P<0.01$ ), but the difference of LH level was not significant ( $P=0.38$ ). The duration of down regulation when adding gonadotrophins in leuprorelin group was obviously shorter than that in triptorelin group ( $P<0.01$ ). So more patients had premature LH surge in triptorelin group than in leuprorelin group of ovulation induction ( $P<0.01$ ). The clinical pregnancy rate, the abortion rate, the cancelled cycle rate and the severe ovarian hyperstimulation syndrome (OHSS) rate had no significant difference between the two groups. But the implantation rate was higher in leuprorelin group than in triptorelin group (57.61% vs 52.13%,  $P=0.046$ ). **Conclusion:** Leuprorelin with down-regulating function was more moderate, more appropriate for the requirements of sex hormone level inhibition in long protocol of hormonal suppression in the early follicular phase. Leuprorelin may have a better clinical outcome than triptorelin.

**Key words:** leuprorelin; triptorelin; down regulation; clinical pregnancy rate; embryo implantation rate



# 176例剖宫产疤痕部位妊娠治疗方式选择及预后分析

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**【摘要】**目的: 探讨2种方法治疗剖宫产疤痕部位妊娠(CSP)的预后及治疗方式选择的影响因素。方法: 收集176例确诊CSP患者, 分为药物+清宫组(药物组,  $n=68$ )及介入+药物+清宫组(介入组,  $n=108$ ), 分析清宫时出血量、清宫后hCG下降时间, 并电话随访患者清宫后月经来潮时间、月经量变化及再次妊娠情况。结果: 介入组在住院时间、清宫时出血量、清宫后hCG下降时间上明显优于药物组, 差异有统计学意义( $P<0.05$ )。而在治疗失败率和月经来潮时间上组间均无统计学差异( $P>0.05$ ), 但月经量变化组间比较差异有统计学意义( $P<0.05$ ), 介入组月经量减少者多于药物组, 而再次妊娠者少于药物组。结论: 药物+清宫术治疗与介入+药物+清宫术治疗各有优劣, 故在治疗方式上应结合患者实际情况及再生育要求进行慎重选择。在患者hCG水平不高(如 $<10\ 000$  IU/L)、疤痕较厚( $>0.3$  cm)时可优先考虑药物+清宫术治疗。

**关键词:** 剖宫产疤痕部位妊娠(CSP); 甲氨蝶呤(MTX); 米非司酮; 双侧子宫动脉栓塞术; B超下清宫术

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## Two treatment strategies in 176 cases with cesarean scar pregnancy: efficacy and clinical outcomes

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**【ABSTRACT】 Objective:** To assess medicine administration and uterine arterial embolization with medicine combined with curettage in treating patients with cesarean scar pregnancy (CSP). **Methods:** Pre-, intra- and postoperative conditions of 176 CSP patients were evaluated, of which 68 patients received medicine (methotrexate, mifepristone)+ uterine curettage under ultrasound monitoring (medicine group), while 108 patients were treated with uterine arterial embolization with medicine followed by uterine curettage under ultrasound monitoring (intervention group). The general data, blood loss during curettage, the first menstruation after treatment, the variety of the menstruation and the re-pregnancy outcome of patients were collected and compared. **Results:** Intervention group was superior to medicine group in the hospitalization time, intraoperative blood loss and the recover time of serum  $\beta$ -hCG after surgery, with significant differences ( $P<0.05$ ). There was no significant difference between the two groups with respect to the laparotomy rate and the menstrual resumption time ( $P>0.05$ ), but the ratio of variation of menstrual volume was significantly different between the two groups ( $P<0.05$ ). In intervention group, cases with menstrual volume decrease were more than medicine group, while cases with subsequent intrauterine pregnancies were less than medicine group ( $P<0.05$ ). **Conclusion:** Both medicine and uterine arterial embolization combined with curettage have their own merits in treating CSP. Treatment should be individualized and several conditions including demand for re-pregnancy must be considered. Medicine combined with curettage could be the prior choice in case of serum  $\beta$ -hCG under 10 000 IU/L and scar thickness over 0.3 cm.

**Key words:** cesarean scar pregnancy (CSP); methotrexate; mifepristone; arterial embolization; curettage under ultrasound

· 个案报道 ·

## 长方案降调节后高雌二醇水平获得 双胎妊娠的病例分享

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**【摘要】**目的: 探讨卵胞质内单精子显微注射-胚胎移植(ICSI-ET)长方案降调节后高雌二醇(E<sub>2</sub>)水平的治疗方案。方法: 对1例ICSI-ET长方案降调节后高E<sub>2</sub>水平获得双胎妊娠的病例进行分析并总结经验。结果: 通过适时启动超促排卵, 患者获卵8枚, 形成可用胚胎数3个, 移植胚胎后成功获得双胎妊娠。结论: 对于长方案降调节后E<sub>2</sub>水平仍高的患者应根据其具体情况制定个体化的治疗方案。

**关键词:** 卵胞质内单精子显微注射-胚胎移植(ICSI-ET); 长方案; 降调节; 雌二醇(E<sub>2</sub>)

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## **A patient with high E<sub>2</sub> level after pituitary down-regulation receiving twin pregnancy under intracytoplasmic sperm injection-embryo transfer treatment —— a case report**

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**【ABSTRACT】 Objective:** To report a case of a patient with high E<sub>2</sub> level after pituitary down-regulation receiving twin pregnancy, and to discuss the treatment options for these patients. **Methods:** The patient received intracytoplasmic sperm injection-embryo transfer (ICSI-ET) treatment with long gonadotrophin-releasing hormone agonist (GnRHa) protocol. We reported the case and reviewed the articles. **Results:** With the opportunely start of hyperstimulation, the patient got appropriate number of oocytes and embryos, and received twin pregnancy finally. **Conclusion:** For the patients with high E<sub>2</sub> level after down-regulation, we should have individualized treatments according to their specific conditions.

**Key words:** intracytoplasmic sperm injection-embryo transfer (ICSI-ET); long gonadotrophin-releasing hormone agonist (GnRHa) protocol; down-regulation; estradiol (E<sub>2</sub>)

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