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早、晚发型重度子痫前期胎盘组织内质网应激及滋养细胞凋亡相关标志物的表达水平分析

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摘要 **目的** 探讨早、晚发型重度子痫前期(SPE)和正常妊娠孕妇胎盘组织中内质网应激(ERS)和滋养细胞凋亡相关标志物的表达水平与SPE的相关性。**方法** 收集医院就诊的早、晚发型SPE单胎孕妇的胎盘组织各20例(早发组、晚发组),选择同期在该院分娩的血压正常无其它妊娠并发症的孕妇20例作为正常组。透射电镜观察胎盘组织中滋养细胞内质网的超微结构,蛋白质印迹实验检测胎盘组织中ERS相关蛋白的表达水平[葡萄糖调节蛋白78(GRP78)、C/EBP同源蛋白(CHOP)、磷酸化真核翻译起始因子2α(p-eIF2α)和磷酸化肌醇需求酶1(p-IRE1)α],免疫组化法检测胎盘组织中增殖标志物增殖细胞核抗原(Ki67)的表达,TUNEL染色检测胎盘组织滋养细胞凋亡情况。**结果** 正常孕妇组胎盘组织中滋养细胞内质网体积正常,无扩张和肿胀。而SPE组胎盘组织内质网出现明显水肿,呈现显著扩张的状态,且早发组比晚发组扩张明显;与正常组相比,早发组和晚发组胎盘组织中ERS相关蛋白GRP78($P<0.001$,$P<0.05$)和CHOP($P<0.01$,$P<0.001$)的表达水平及eIF2α($P<0.000\ 1$,$P<0.01$)、IRE1α($P<0.000\ 1$,$P<0.001$)磷酸化水平增加,p-eIF2α/eIF2α($P<0.001$)和p-IRE1α/IRE1α($P<0.05$)比值及GRP78蛋白($P<0.01$)表达水平在早发组中均高于晚发组;与正常组相比,早发组和晚发组每个视野下Ki67阳性细胞数减少($P<0.000\ 1$,$P<0.05$),早发组胎盘Ki67阳性细胞数少于晚发组($P<0.01$);早发组胎盘组织中每个视野阳性凋亡细胞多,滋养细胞凋亡率高于其他两组($P<0.001$,$P<0.01$)。**结论** SPE患者胎盘组织滋养细胞凋亡增加和增殖受抑制可能与ERS过度激活相关,其在早发型SPE患者胎盘组织中激活水平高于晚发组。

关键词 子痫前期;胎盘;内质网应激;增殖;凋亡;孕周

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子痫前期(preeclampsia,PE)是妊娠期特有的累及多系统的进展性疾病,伴有严重临床表现的PE诊断为重度子痫前期(severe preeclampsia,SPE)。PE的发病机制包括胎盘功能障碍、氧化应激和内质网应激(endoplasmic reticulum stress,ERS)和内皮功能障碍等因素。胎盘在PE的发展中起着至关重要的作用。PE患者滋养细胞浅侵袭和螺旋动脉重构不足导致胎盘缺血 - 再灌注损伤,引起内质网(endoplasmic reticulum,ER)中未折叠或错误折叠蛋白的积累,触发ERS的发生并激活未折叠蛋白反应(unfolded protein reaction,UPR)[1]。UPR是一种细胞自我防御机制,旨在缓解ERS,重建体内平衡。UPR的3个关键的跨膜传感器通过各自的信号级联调节UPR[2]。已有临床研究表明ERS介导的胎盘滋养细胞凋亡可能参与PE的发病[3]。

目前有关ERS与SPE的发病关系的研究较少,为探讨ERS介导的滋养细胞凋亡与SPE不同亚型组之间的关系,该研究通过透射电镜观察早、晚发SPE和正常妊娠孕妇胎盘组织内质网超微结构,并采用蛋白印迹实验检测ERS相关蛋白的表达,免疫组化法检测滋养细胞增殖标志物Ki67表达水平和TUNEL染色检测滋养细胞的凋亡情况,为进一步了解早、晚发SPE发病机制的不同提供实验基础。

1 材料与方法

1.1 病例资料 选取2022年9月—2023年4月间在安徽医科大学第一附属医院产科分娩的单胎孕妇60例,正常组、早发组与晚发组每组各20例,所有参与患者均为剖宫产方式终止妊娠并签署知情同意

2024 - 11 - 10 接收

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书。SPE 组纳入标准:符合 SPE 的诊断标准的单胎孕妇。SPE 诊断标准参照第 9 版《妇产科学》[4]。排除标准:妊娠合并慢性高血压,既往有心肺疾病、肝肾功能不全,病历资料不完全及诊断不明的患者。正常组纳入标准:无妊娠期高血压疾病的正常妊娠孕妇。本课题经安徽医科大学第一附属医院伦理委员会审查通过(批号:PJ 2023-04-33)。

1.2 收集标本和临床资料 剖宫产术中胎盘娩出后,在胎盘母体面靠近脐带的位置,同时避开出血、坏死及钙化区,切割出大小约 1 cm×1 cm×1 cm 的胎盘组织若干块。将收集好的胎盘组织随机分为 3 部分,一部分放置在 4% 多聚甲醛溶液中固定 24 h,随后进行脱水处理,石蜡包埋并切成薄片;一部分保存于 -80 ℃冰箱,用于蛋白的提取;另一部分放于 3% 戊二醛中,用于透射电镜实验。同时收集孕妇的人口学资料和妊娠结局。

1.3 试剂 TUNEL 细胞凋亡检测试剂盒、抗荧光淬灭封片剂、RIPA 裂解液、磷酸酶抑制剂、苯甲基磺酰氟(phenylmethanesulfonyl fluoride,PMSF)、5×蛋白上样缓冲液和 SDS-PAGE 电泳相关试剂购于北京碧云天生物技术公司;抗体真核翻译起始因子 2α(eukaryotic translation initiation factor 2α,eIF2α)(货号:5324T)、磷酸化 eIF2α(phosphorylated eIF 2α,p-eIF2α)(货号:3398T)、肌醇需求酶 1(inositol-requiring enzyme 1,IRE1)α(货号:3294T)和 Ki67(货号:9449T)购于美国 CST 公司;抗体磷酸化肌醇需求酶 1(phosphatidylinositol-requiring enzyme 1,p-IRE1)α(货号:ab124945)购于英国 Abcam 公司;抗体葡萄糖调节蛋白 78(glucose-regulated protein 78,GRP78)(货号:11587-I-AP)和 C/EBP 同源蛋白(C/EBP homologous protein,CHOP)(货号:15204-I-AP)购于武汉三鹰生物技术有限公司;鼠多克隆 β-肌动蛋白(beta-actin,β-actin)抗体(货号:TA-09)、山羊抗鼠(货号:TA-08)和抗兔(货号:ZB-2306)通用型二抗购自北京中杉金桥公司。

1.4 透射电镜观察内质网结构变化 收集胎盘组织,放入 3% 戊二醛中,4 ℃避光过夜进行固定;随后漂洗、后固定、再漂洗、块染和梯度脱水,最后用环氧树脂包埋,包埋块修理后切片(70 nm);用枸橼酸铅染色,样本晾干后上机观察。透射电镜对切片进行观察并随机选取 10 个非连续性视野进行拍照。

1.5 蛋白质印迹实验检测蛋白表达 从 -80 ℃冰箱取出人胎盘组织,剪取适当大小,按照 1 mg/10 μl 的比例加入裂解液。提取蛋白和蛋白质印迹实验具体实验步骤参照先前研究[5],一抗包括 GRP78、CHOP、eIF2α、p-eIF2α、IRE1α 和 p-IRE1α(稀释比例均为1∶1 000)和 β-actin(1∶2 000);二抗(兔二抗1∶10 000,鼠二抗1∶10 000)常温孵育 2 h,洗膜后用 ECL 发光显影液进行显色。

1.6 免疫组化检测增殖标志物 Ki67 表达 各组人胎盘组织切片厚度为 5 μm,采用免疫组化法以 Ki67 为增殖标志物检测胎盘组织增殖水平,具体检测方法参照先前研究[5]。每组至少检测来自 3 个不同患者的胎盘组织。每张切片随机选取 5 个不连续的视野进行观察。在每个视野中,计算 Ki67 阳性细胞占细胞总数百分比的平均值并将该值作为评估指标,分别进行定量分析。

1.7 TUNEL 染色检测滋养细胞凋亡 取制备好的各组人胎盘组织切片,采用 TUNEL 试剂盒检测滋养细胞凋亡,加入 TUNEL 工作液染色,PBS 清洗后加入 DAPI 染细胞核,滴加抗荧光淬灭封片剂封固,室温晾干,置于荧光显微镜下观察滋养细胞凋亡情况并拍照,镜下绿色荧光标记的细胞为 TUNEL 阳性,代表细胞凋亡,每组随机选择 9 个视野计数,以 TUNEL 阳性细胞数目与总细胞数目之比记为 TUNEL 阳性细胞比例。

1.8 统计学处理 使用 SPSS 23.0 和 GraphPad-Prism 7.0 软件进行数据分析和作图,对于蛋白质印迹实验条带的分析采用 Image J 软件进行处理,所有数据均用均值±标准误($\bar{x} \pm SEM$)表示。符合正态分布的计量资料采用单因素方差分析来比较多组间的差异。计数资料以率或构成比(%)的形式表示,通过 χ^2 检验或 Fisher 确切概率法进行组间的对比。$P<0.05$ 为差异有统计学意义。

2 结果

2.1 早、晚发型 SPE 与正常妊娠孕妇一般临床资料及妊娠结局的比较 正常组、早发组与晚发组在入院孕周、收缩压、舒张压、分娩孕周、新生儿出生体质量和低蛋白血症上存在显著差异($P<0.05$)。早发组和晚发组的入院孕周和分娩孕周小,两组的新生儿出生体质量均低于正常组($P<0.001$),收缩压和舒张压高于正常组($P<0.001$),早发组中低蛋白血症的发生率高于其他两组($P=0.029$)。见表 1。

表 1 早、晚发型 SPE 与正常妊娠孕妇一般临床资料及妊娠结局比较($\bar{x} \pm s$)

Tab. 1 Comparison of general clinical data and pregnancy outcomes between early and late-onset severe preeclampsia and normal pregnancies ($\bar{x} \pm s$)

Item	Normal group (n = 20)	Early-onset group (n = 20)	Late-onset group (n = 20)	χ^2 / F value	P value
Age (years)	29.30 ± 3.05	32.65 ± 5.29	32.10 ± 5.56	2.838	0.067
Gestation age of admission (weeks)	38.79 ± 1.72	31.63 ± 2.33	37.66 ± 1.67	79.695	<0.001
BMI before pregnancy (kg/m^2)	22.44 ± 3.59	24.33 ± 5.03	24.62 ± 4.77	1.388	0.258
BMI at delivery (kg/m^2)	27.83 ± 4.06	29.45 ± 5.09	31.08 ± 5.21	2.275	0.112
Systolic blood pressure (kPa)	15.36 ± 1.41	21.60 ± 2.43	21.90 ± 2.92	49.656	<0.001
Diastolic blood pressure (kPa)	9.72 ± 0.81	14.30 ± 1.53	13.43 ± 1.39	71.850	<0.001
Gestation age at delivery (weeks)	38.95 ± 1.77	32.26 ± 2.29	37.83 ± 1.55	71.171	<0.001
Birth weight (g)	3 222.50 ± 421.75	1 436.75 ± 364.50	2 928.00 ± 645.88	75.552	<0.001
Assisted reproductive technology [n(%)]				1.586	0.589
Yes	2 (10.0)	4 (20.0)	5 (25.0)		
No	18 (90.0)	16 (80.0)	15 (75.0)		
HELLP syndrome [n(%)]				2.765	0.329
Yes	0 (0)	2 (10.0)	0 (0)		
No	20 (100.0)	18 (90.0)	20 (100.0)		
Hypoproteinemia [n(%)]				6.209	0.029
Yes	0(0)	4 (20.0)	0(0)		
No	20 (100.0)	16 (80.0)	20 (100.0)		
Placental abruption [n(%)]				1.851	>0.05
Yes	0 (0)	1 (5.0)	0 (0)		
No	20 (100.0)	19 (95.0)	20 (100.0)		
Intensive care unit admission [n(%)]				1.851	>0.05
Yes	0 (0)	1 (5.0)	0 (0)		
No	20 (100.0)	19 (95.0)	20 (100.0)		

2.2 早、晚发型 SPE 孕妇与正常妊娠孕妇胎盘组织中滋养细胞内质网超微结构观察 早发组和晚发组胎盘组织滋养细胞的超微结构相较正常组均存在不同程度的异常形态变化。可见早发组和晚发组滋养细胞内细胞核形态不规则,线粒体嵴模糊或排列紊乱。且两组内质网明显水肿,体积显著增大,内质网扩张,早发组比晚发组扩张明显,内质网脱颗粒改变明显。而正常组胎盘组织滋养细胞内内质网形态规整,体积正常,无肿胀及扩张。见图 1。

2.3 早、晚发型 SPE 孕妇与正常妊娠孕妇胎盘中 ERS 相关蛋白的表达 蛋白质印迹实验结果显示,与正常组相比,早、晚发型 SPE 患者胎盘中 p-eIF2α/eIF2α($P < 0.000\ 1$, $P < 0.01$)和 p-IRE1α/IRE1α($P < 0.000\ 1$, $P < 0.001$)比值及 GRP78($P < 0.001$, $P < 0.05$)和 CHOP($P < 0.01$, $P < 0.001$)蛋白表达水平均升高,且在早发组中,p-eIF2α/eIF2α($P < 0.001$)和 p-IRE1α/IRE1α($P < 0.5$)比值和 GRP78($P < 0.01$)蛋白表达水平均高于晚发组。见图 2,定量分析结果见表 2。

2.4 早、晚发型 SPE 孕妇与正常妊娠孕妇胎盘组织中增殖标志物 Ki67 的表达 对各组的胎盘切片进行 Ki67 增殖标志物的免疫组织化学染色。Ki67 阳性表达主要定位在细胞滋养细胞,与正常组相比,早发组和晚发组胎盘组织中各视野 Ki67 阳性细胞数量减少,且在早发组中的数量低于晚发组($P < 0.01$)。见图 3 和表 2。

2.5 早、晚发型 SPE 孕妇与正常妊娠孕妇胎盘组织中滋养细胞凋亡的表达情况 通过对各胎盘切片进行 TUNEL 染色检查各组滋养细胞凋亡率的情况,凋亡细胞呈绿色,早发组胎盘组织中各视野阳性凋亡细胞多($P < 0.001$, $P < 0.05$),滋养细胞凋亡率显著高于正常组和晚发组($P < 0.001$, $P < 0.01$)。见图 4 和表 2。

3 讨论

PE 作为一种严重的妊娠并发症,目前唯一有效的治疗方法是终止妊娠并娩出胎盘,这提示胎盘是 PE 发病的核心,胎盘的形成和发育是一个复杂的多步骤过程,探索胎盘上相关的发病机制,对提升人们对该病的了解和改善其妊娠结局具有至关重要的意义。UPR 信号通路作为应对 ERS 的主要通路[6-7],通过多种方式来维护内质网的稳态,然而当 ERS 的持续时间和强度超过 UPR 处理能力时,UPR 将无法继续维持内质网的稳态,GRP78 表达增加与未折叠

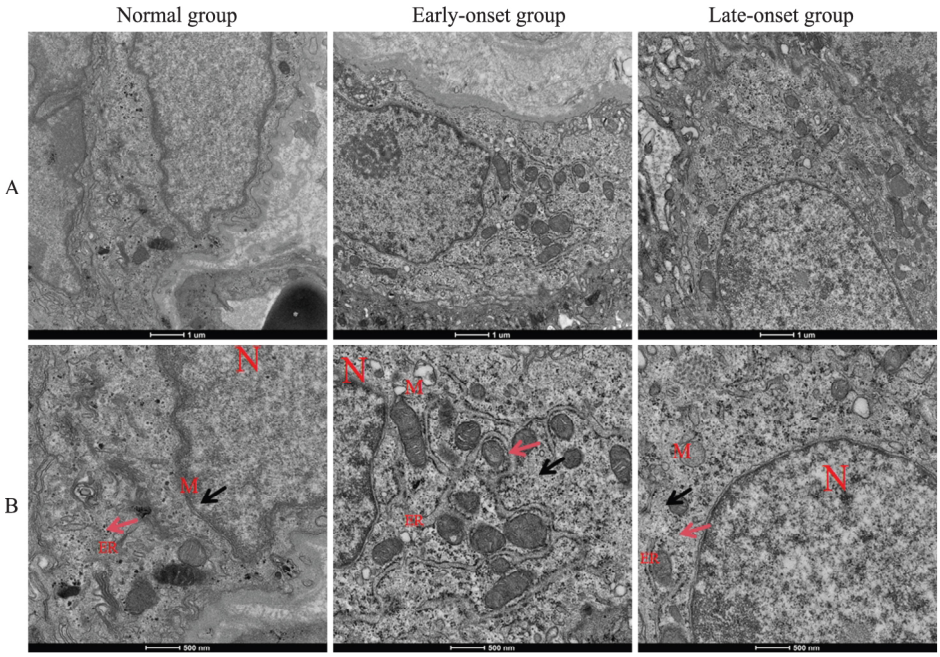

图 1 透射电镜下三组孕妇胎盘组织滋养细胞内质网形态的观察

Fig. 1 Transmission electron microscopy of endoplasmic reticulum morphology of trophoblast cells in placental tissues of three groups of pregnant women

A: Transmission electron microscopy images of endoplasmic reticulum of three groups of human placental tissues ×6 700; B: Transmission electron microscopy images ofendoplasmic reticulum of three groups of human placental tissues × 13 500; N: trophoblast nucleus; M: mitochondrion; ER: endoplasmic reticulum. Black arrows indicate that the mitochondrial cristae were blurred or disorganized in the early-onset and late-onset SPE groups compared with the normal group, and red arrows indicate that the endoplasmic reticulum was obviously edematous and significantly enlarged in size in the early-onset and late-onset groups compared with the normal, and the early-onset group had significantly expanded the endoplasmic reticulum compared with the late-onset group.

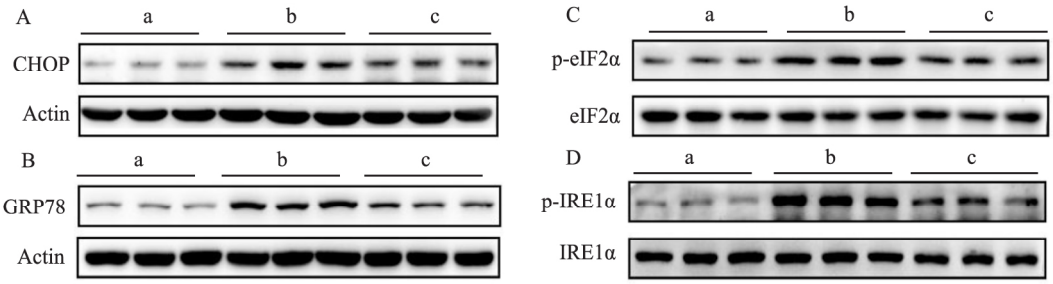

图 2 蛋白质印迹法检测正常组、早发组、晚发组胎盘组织 ERS 相关蛋白的表达情况

Fig. 2 Expression of endoplasmic reticulum stress-related proteins in placental tissues of normal, early-onset, and late-onset groups

A: CHOP; B: GRP78; C: p-eIF2α; D: p-IRE1α; a: Normal group; b: Early-onset group; c: Late-onset group.

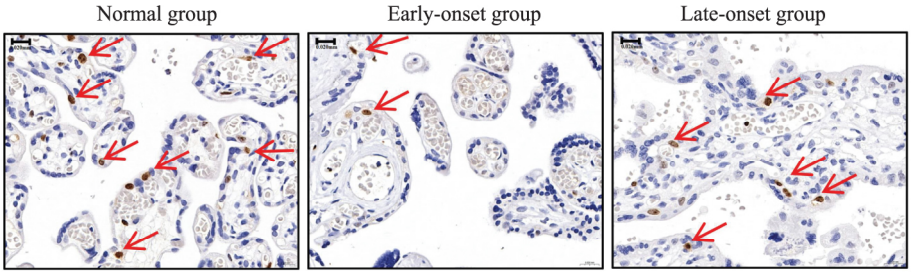

图 3 正常组、早发组、晚发组胎盘组织滋养细胞 Ki67 染色情况 ×400

Fig. 3 Proliferation of trophoblast cells in placental tissues of normal, early-onset and late-onset groups ×400

Cells with brownish-yellow nuclear staining were positive cells, and positive cells were indicated by red arrows.

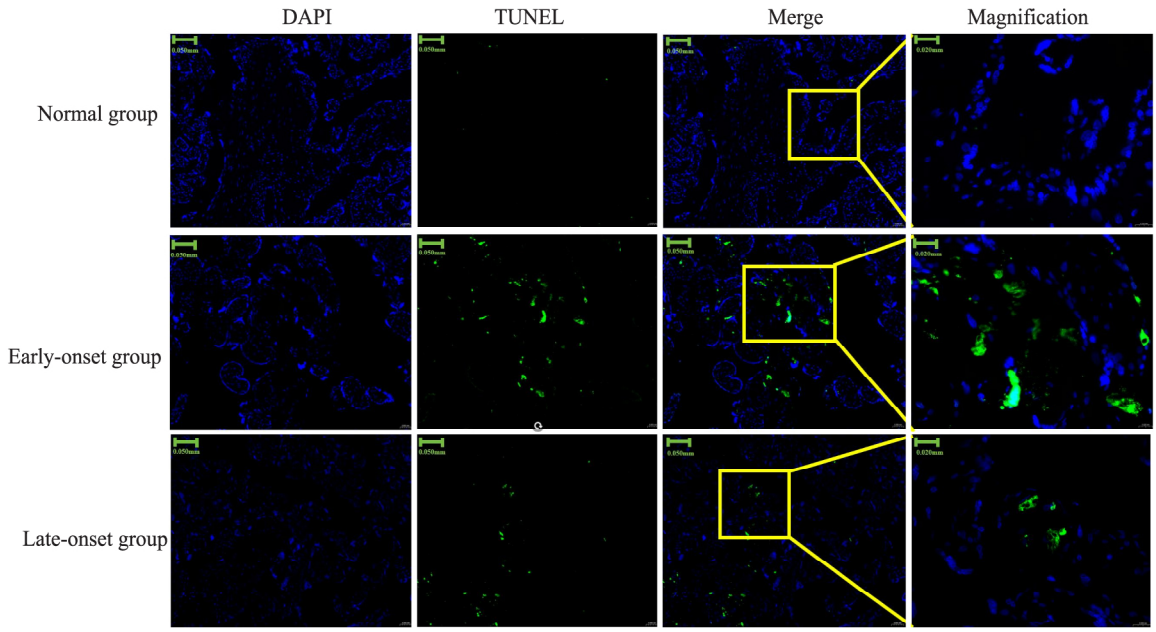

图 4 正常组、早发组、晚发组胎盘组织滋养细胞凋亡情况

Fig. 4 Apoptosis of trophoblast cells in placental tissues of normal, early-onset and late-onset groups

DAPI: cell nucleus ×50; TUNEL: TUNEL positive cells ×50; Merged: synthetic picture ×50; scale bar is 50 μm; magnification: magnified picture, scale bar is 20 μm; Apoptotic cells are in green color.

表 2 早、晚发型 SPE 组与正常组实验结果定量分析表($\bar{x} \pm s$)

Tab. 2 Quantitative analysis of the experimental results of the early and late-onset severe preeclampsia groups and the normal group ($\bar{x} \pm s$)

Variable	Normal group($n=20$)	Early-onset group($n=20$)	Late-onset group($n=20$)	F value	P value
CHOP (μg/μl)	1.00 ± 0.21	2.21 ± 0.32**	2.34 ± 0.09***	31.30	<0.001
GRP78 (μg/μl)	1.00 ± 0.11	2.43 ± 0.26***##	1.64 ± 0.16*	43.35	<0.001
p-eIF2α/eIF2α (μg/μl)	1.00 ± 0.13	2.23 ± 0.13****###	1.54 ± 0.06**	93.44	<0.001
p-IRE1α/IRE1α (μg/μl)	1.00 ± 0.26	2.74 ± 0.80****#	2.29 ± 0.08***	92.87	<0.001
Ki67 (positivity rate)	27.31 ± 2.51	6.57 ± 2.66****##	19.11 ± 1.64*	61.07	<0.001
TUNEL staining (positivity rate)	0.25 ± 0.22	3.95 ± 0.85***##	1.20 ± 0.47	33.24	<0.001

* $P<0.05$, ** $P<0.01$, *** $P<0.001$, **** $P<0.0001$ *vs* Normal group; # $P<0.05$, ## $P<0.01$, ### $P<0.001$ *vs* Late-onset group.

蛋白结合,通过下游 CHOP 和 Caspase-12 介导的生物学效应促进细胞凋亡[8]。研究[9]表明,SPE 与人胎盘中几种应激信号通路的激活有关,如 UPR、丝裂原活化蛋白激酶(MAPK)应激、热休克蛋白和腺苷酸活化蛋白激酶(AMPKa)。SPE 患者胎盘滋养细胞的凋亡涉及多种途径,包括线粒体凋亡途径和 ERS 凋亡途径。ERS 激活的水平和平衡的状态对胎盘的正确形成至关重要。轻度的 ERS 应激水平可诱导适应性反应,ERS 过度激活将抑制细胞增殖,导致妊娠障碍。ERS 在 PE 患者胎盘增殖中有报道[10]。有研究[11]在 PE 胎盘中观察到 ERS 标记物 GRP78 和 CHOP 表达显著升高,导致凋亡增加和 UPR 激活。GRP78 和 CHOP 均是 ERS 反应蛋白,其表达是 ERS 活化的典型标志。先前的一项研究[12]证实 CHOP 是通过不同机制介导内质网相关凋亡的最重要介质之一。CHOP 表达的急性升高可激活线粒体介导的凋亡途径。在本研究中早、晚发型 SPE 患者胎盘组织中 Ki67 表达水平均显著低于正常组,早发组中滋养细胞凋亡数显著高于正常组,GRP78、CHOP 和 UPR 通路中相关蛋白表达增加,提示过度激活的 ERS 可能通过抑制细胞的增殖和促进滋养细胞凋亡参与 SPE 的发病。

一项荟萃分析[13]表明,胎盘病理谱在早发型比晚发型疾病更严重。PE 胎盘代谢组学研究指出早发型和晚发型 SPE 的发病机制存在显著差异。早发型由胎盘缺陷引起,被认为是一种更严重的 SPE,具有更高的围产期和孕产妇死亡风险[14],与更严重的胎盘病变相关。研究[15]显示,胎盘 ERS 存在于妊娠 34 周的早期 PE 中。晚发型可能是正常衰老的胎盘和母体与心血管和代谢疾病的遗传易感性之

间的相互作用。Burton et al[16] 发现氧化应激和 UPR 的激活在早期比晚期更显著。在本研究中，早发型患者中 UPR 相关蛋白表达水平高于晚发型患者，细胞增殖受抑制较晚发型严重，滋养细胞凋亡率高于晚发型，这与既往研究一致。此外，本研究通过透射电镜观察了内质网的超微结构，与正常妊娠孕妇的胎盘相比，SPE 患者胎盘组织中滋养细胞内质网出现了显著的病理改变，内质网体积明显增大，呈现扩张及液泡化的现象，且内质网的脱颗粒改变显著，提示 ER 在 SPE 患者中扮演了重要的角色。

综上所述，该研究表明，SPE 胎盘组织滋养细胞凋亡增加和细胞增殖受抑制与 ERS 过度激活相关，并且在早、晚发型 SPE 患者中 ERS 相关蛋白表达水平存在差异，早发型患者胎盘组织滋养细胞凋亡率更高，增殖受抑制明显，胎盘病变更严重，进一步揭示了早发型和晚发型 SPE 在内质网应激及滋养细胞凋亡病理生理机制上存在显著差异。

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Analysis of expression levels of endoplasmic reticulum stress and trophoblast apoptosis-related markers in placental tissues of early and late-onset severe preeclampsia

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Abstract ***Objective*** To explore the correlation between the expression levels of endoplasmic reticulum stress (ERS) and trophoblast apoptosis-related markers and severe preeclampsia (SPE) in placental tissues of pregnant women with early- and late-onset SPE and normal pregnancy. ***Methods*** Placental tissues from 20 early and late haired severe preeclamptic singleton pregnant women who attended the Hospital were collected (early-onset group, late-onset group), and 20 cases pregnant women of normal blood pressure and no other pregnancy complications who delivered in our hospital during the same period were selected as the normal group. Transmission electron microscopy was used to observe the ultrastructure of the endoplasmic reticulum of trophoblast cells in placental tissues. Protein blotting assay was used to detect the expression levels of endoplasmic reticulum stress-related proteins, including Glucose-regulated protein 78 (GRP78), C/EBP homologous protein(CHOP), Phosphorylated eukaryotic translation initiation factor 2α (p-eIF2α) and Phosphatidylinositol-requiring enzyme 1 (p-IRE1)α. Immunohistochemistry assay was used to detect the expression of proliferating cell nuclear antigen (Ki67), a proliferation marker, in placental tissues, and TUNEL staining was used to detect placental tissue trophoblast apoptosis. ***Results*** The endoplasmic reticulum of trophoblast cells in the placental tissues of the normal pregnant women group was normal in volume, with no dilatation or swelling. In contrast, the endoplasmic reticulum of placental tissues in the severe preeclampsia group showed obvious edema and significant dilatation, and the dilatation was more obvious in the early-onset group than in the late-onset group. The expression level of endoplasmic reticulum stress-related proteins GRP78 ($P<0.001$, $P<0.05$) and CHOP ($P<0.01$, $P<0.001$), the phosphorylation levels of eIF2α ($P<0.000\ 1$, $P<0.01$) and IRE1α ($P<0.000\ 1$, $P<0.001$) increased in placental tissues of both early-onset and late-onset groups compared to those of the normal group. The p-eIF2α/eIF2α ($P<0.001$) to p-IRE1α/IRE1α ratio ($P<0.05$) and GRP78 ($P<0.01$) protein expression levels were significantly higher in the early-onset group than in the late-onset group. Compared with the normal group, the number of Ki67-positive cells per field of view was significantly reduced in the early-onset and late-onset groups ($P<0.000\ 1$, $P<0.05$), and the number of Ki67-positive cells was significantly lower in the early-onset group than in the late-onset group ($P<0.01$). There were more positive apoptotic cells per field of view in the placental tissues of the early-onset group, and the apoptosis rate of trophoblast cells was significantly higher than that in the other two groups ($P<0.001$, $P<0.01$). ***Conclusion*** Increased trophoblast apoptosis and suppressed proliferation in placental tissues of patients with severe preeclampsia may be associated with endoplasmic reticulum stress overactivation, and the activation level is higher in placental tissues of early-onset severe preeclampsia than that of late-onset group.

Key words preeclampsia; placenta; endoplasmic reticulum stress; proliferation; apoptosis; gestation weeks

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