doi: 10.3978/j.issn.1000-4432.2020.10.04
View this article at: http://dx.doi.org/10.3978/j.issn.1000-4432.2020.10.04

早产儿视网膜病变危险因素研究新进展

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[摘 要] 早产儿视网膜病变(retinopathy of prematurity，ROP)是一种血管增殖性视网膜疾病，出生胎龄及体重、出生后氧疗是其发病主要危险因素。作为全球儿童可预防性失明的主要疾病，受到越来越多的关注，相关基础和临床研究也逐渐深入。

[关键词] 早产儿；早产儿视网膜病变；危险因素

Research progress on the risk factors of retinopathy of prematurity

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Abstract Retinopathy of prematurity (ROP) is a category of retinal vascular proliferative disease, of which gestational age, birth weight and postnatal oxygen therapy are the main risk factors. As a major preventable blindness disease in children worldwide, ROP has attracted more and more attention, and in-depth basic and clinical researches have been gradually conducted.

Keywords prematurity; retinopathy of prematurity; risk factors

早产儿视网膜病变(retinopathy of prematurity，ROP)主要表现为视网膜缺血、新生血管形成、纤维组织增生，最终牵拉视网膜，造成视网膜脱离。随着新生儿监护室的发展和普及，早产儿存活率逐渐提升[1]，新生儿病死率下降导致ROP高危儿数量不断增加，包括我国在内的许多亚洲中等收入国家正处于“第三次ROP流行”时期[2]。本文主要阐述近年来有关ROP发病相关危险因素的研究新发现，以期为ROP筛查和预防提供帮助。

1 ROP 发病的主要危险因素

早产、低出生体重和吸氧是ROP公认的三大危险因素。对于早产儿，尤其是极低出生体重儿，增加出生体重和胎龄可明显降低ROP的发生率。CRYO-ROP多中心试验研究[3]结果显示：出生体重每增加100 g，ROP发生率下降27%；出生胎龄每周增加1周，ROP发生率下降19%。这些结果在后续大量研究[4-7]中得到了证实，目

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前各国筛查标准的制定也主要基于出生胎龄和体重这两大因素。早产儿未成熟的视网膜血管对高氧环境十分敏感，吸氧时间及浓度都会影响视网膜血管的发育。机械通气时间越长、吸氧浓度越高，越易发生严重ROP[8-11]。严格控制早产儿血氧饱和度，可降低极低出生体重儿发生重度ROP的概率[12]。Lundgren等[13]研究发现将氧饱和度从88%~92%提升到91%~95%可降低体重增加不良带来的负面影响。

此外，随着ROP研究的不断深入，一些与ROP密切相关的因素也逐渐为人所熟知。患有妊娠期高血压或糖尿病可引起糖代谢及血管内皮生长因子(vascular endothelial growth factor，VEGF)分泌异常；高龄产妇、多胎妊娠、胎膜早破会增加早产风险；妊娠期药物使用，例如妊娠晚期使用β受体阻滞剂和抗组胺药物与ROP发生有关；Apgar评分低、新生儿呼吸窘迫综合征、支气管肺发育不良等新生儿并发症也是ROP的危险因素。还有研究表明，种族和胎儿性别也与ROP有关。黑人ROP发生率低于白人，而男婴发病率高于女婴[8]。

2 ROP 发病危险因素新进展

2.1 妊娠期吸烟

美国一项调查[14]显示：约7.2%的孕妇在妊娠期间吸烟。Hudalla等[15]研究发现：吸烟是早产儿发生严重ROP的独立危险因素。一种模仿卷烟的电子产品，俗称“电子烟”，是通过雾化器将烟草中的尼古丁变成蒸汽，和普通香烟相比，其造成的不良结果都是一样的[16]。烟草中的有害成分尼古丁等可能引起死产、早产等不良围产期结局，与低出生体重、胎儿宫内生长受限、先天性异常等疾病发生有关[17-19]。妊娠期母体吸烟还可能引起早产儿严重的神经损伤和支气管肺发育不良[20]，一项Meta分析[21]结果也证实了这一点。吸烟也是胎膜早破、宫颈功能不全和绒毛膜炎的危险因素[22]，以上均是自发性早产的主要原因。但是既往研究中并没有纳入吸烟数量对ROP的影响，这也是未来研究需要考虑的重要因素。

吸烟对ROP的作用机制可能包括：1)烟草的主要成分尼古丁可引起血管收缩，降低子宫血流量，导致胎儿宫内生长受限和早产[23-24]。2)吸烟会增加血液中一氧化碳的含量，使其容易通过胎盘，取代血红蛋白中的氧气，降低血红蛋白向组织释放氧气的能力，引起胎儿缺氧。3)吸烟可使母体氧化应激和抗氧化能力降低，孕酮水平下降，催产素敏感性增加和前列腺素合成紊乱，促进子宫收缩，诱发早产[24]。这些原因导致早产或多种新生儿并发症，间接引发ROP。体外试验[25]已证实，烟草中的去甲基烟碱和尼古丁可上调VEGF信号通路，促进内皮细胞增殖迁移和管腔形成。

即使对经常吸烟的人来说，戒烟或在怀孕早期戒烟，也能有效降低早产的风险[26]。欧洲国家通过戒烟立法政策，有效地降低了早产和低出生体重儿的发病率[27]。因此我们应加强对孕产妇的健康教育，及时戒烟，预防早产及ROP的发生。

2.2 辅助生殖

目前通过辅助生殖技术(assisted reproductive technology，ART)受孕的婴儿数量逐年增加。一项Meta分析[28]结果显示：ART的使用与后代ROP的发生有显著的关联，尤其是采用体外人工授精(in vitro fertilization，IVF)受孕的婴儿。Wu等[29]对中国极低出生体重儿的研究结果中，IVF是ROP发生的独立危险因素。通过IVT受孕的28周以前出生的单胎婴儿比自然受孕出生的婴儿更容易出现严重的ROP[30]。

与自然受孕的妇女相比，采用ART的孕妇发生围产期并发症的风险更高，例如妊娠期糖尿病、妊娠高血压、胎盘早剥、胎膜早破等[31]，尤其是IVF可大大增加先兆子痫的风险[32]。据报道[33]，接受ART的患者中，约24%的女性超过40岁，多胎妊娠发生率为28.0%~31.3%。多种不孕因素、年龄、多次流产、多胎妊娠等多种原因也可引起ART患者早产概率的增加[34]。其次，采用ART受孕的婴儿患心血管、肌肉骨骼、泌尿生殖系统、胃肠道和呼吸系统缺陷等新生儿并发症的风险也显著增加[35]。有研究[36]认为，通过IVF技术受孕成功的母亲血清胰岛素样生长因子I(insulin like growth factor-1，IGF-1)水平偏高，这可能也会影响到胎儿视网膜血管发育。不孕症或父母潜在的遗传因素也可能与ROP的发生有关。然而这些研究结果都存在争议。Barker等[37]承认ART会增加ROP患儿数量且加重筛查负担，但不认为ART是ROP发生的危险因素。Trifonova等[38]也认为有关ART作为ROP的危险因素的数据尚不明确。

总之，辅助生殖技术有增加早产风险的可

能，可将采用ART的新生儿视为ROP的危险人群，在筛查时予以更多关注，适当放宽筛查标准，必要时对非早产的ART新生儿也可进行筛查。

2.3 IGF-1 和新生儿体重增加

ROP的发病过程可能涉及到VEGF、红细胞生成素(erythropoietin，EPO)，IGF-1和ω-长链多不饱和脂肪酸等多个因子[39]。VEGF可刺激血管内皮细胞有丝分裂、迁移和血管管腔形成，刺激产生新的视网膜血管。IGF-1是一种细胞生长因子，可增加VEGF活性，可调控视网膜血管发育[40]。

新生儿出生时血清IGF-1水平依赖于母体。早产儿出生时血清IGF-1水平低，抑制了VEGF活性和视网膜血管发育，导致视网膜局部VEGF积累。随着内源性IGF-1产生达到VEGF激活的阈值，开始出现大量视网膜新生血管。多个研究[41-42]已证实出生后低水平血清IGF-1与严重ROP发生有关。此外，低水平IGF-1还与其他疾病发生有关，例如坏死性小肠结肠炎、支气管肺发育不良和新生儿脑室出血[43]，同时这些新生儿并发症的出现又增加了ROP发生的概率。

新生儿体重增加缓慢也是ROP发生的危险因素。在泰国的一项研究[44]中，新生儿出生2周内，体重增加不良和低热量摄入，即体重相对增重率<2.9 g/kg/d和总热量摄入<98.5 kcal/kg/day，与需要激光治疗的严重ROP的发生直接相关。Leng等[45]也发现，出生后每日体重增加是ROP发病的独立危险因素。Binenbaum等[46]认为应将出生后的生长情况纳入ROP筛查标准中，以此减少需要筛查的婴儿数量。

血清IGF-1水平与新生儿出生后的生长情况相关，一些研究将出生后体重增加作为血清IGF-1水平的替代指标，预测ROP的发生。但是IGF-1并不是新生儿体重增加的唯一影响因素，营养摄入不足、感染或患有其他疾病等均可影响新生儿生长。将体重增加不良和低水平IGF-1都纳入ROP筛查危险因素可更全面地评估早产儿发生ROP的风险，更有利于防治ROP。

2.4 新生儿贫血与输血

出生后血红蛋白浓度下降在早产儿中尤其明显，特别是在妊娠28周之前出生的极早产儿，这是由于EPO分泌不足导致红细胞生成受损，被称为早产贫血。EPO受肾和视网膜中氧气的调节，是一种重要的促血管生成因子，与血-视网膜屏障稳定性、视网膜血管生成有关[47]。Lundgren等[48]研究发现，患有严重ROP的患儿与不需要治疗的ROP患儿相比，平均EPO水平在出生后第7天显著升高；但在多元回归分析中发现，出生1周内的贫血是ROP的一个独立危险因素。这些结果表明，EPO水平升高与严重ROP风险增加之间的关联可能是贫血刺激EPO合成增加的结果，而早期贫血才是ROP发生真正的危险因素，减少早产儿早期贫血可能降低ROP发展的风险。贫血对ROP的影响仍是一个有争议的话题，贫血的严重程度、持续时间和治疗策略可能会对ROP产生不一样的影响结果。

输血是早产儿就治的常用手段，但也是ROP发生的危险因素。Del等[49]研究发现，控制早产儿输血率，可明显降低ROP的发生。一项Meta分析[50]结果显示，对于出生胎龄<32周的早产儿，输血是ROP发生的独立危险因素。输血对ROP的作用机制主要有以下两种假说：其一，视网膜氧含量增加。新生儿早期的血红蛋白主要为胎儿型血红蛋白(HbF)，当输入成人血时，胎儿型与成人型血红蛋白(HbA)的比例突然发生改变[51]。由于它们对氧的亲和力不同，HbA比HbF会释放更多的氧到视网膜中，促使氧化应激反应[52]。基于这一假说，Podraza建议使用“新生儿输血”，即从健康新生儿的胎盘中收集脐带血(几乎含有100%的HbF)，然后将其用于早产儿的贫血治疗。其二，铁过载。早产儿血浆铜蓝蛋白和转铁蛋白浓度很低，输血后转铁蛋白迅速饱和，血浆中过多的游离铁催化活性氧反应，形成氧自由基，增加视网膜损伤风险[53]。

3 结语

ROP是儿童盲的主要原因，世界卫生组织视觉2020行动将ROP定义为“可避免性疾病”，通过适当的筛查和及时干预治疗是降低ROP致盲的有效措施。ROP相关研究逐年深化，无论从发病机制、筛查标准到治疗方法，我们对ROP的认识正在改变，同时也提出了许多有待解决的新问题。ROP是多因素共同作用引起的疾病，涉及母亲、新生儿、治疗、护理等多方面因素。在关注已知危险因素的同时，不要忽略其他因素对ROP的影响。本文综述了ROP发病危险因素最新研究

进展及可能的发病机制，以期为后续ROP预防和治疗提供理论支持。

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本文引用： 杜淼, 陈婷婷, 苏毅华, 黄静文, 余芬芬, 朱文珲, 万鹏霞. 早产儿视网膜病变危险因素研究新进展[J]. 眼科学报, 2020, 35(4): 249-254. doi: 10.3978/j.issn.1000-4432.2020.10.04

Cite this article as: DU Miao, CHEN Tingting, SU Yihua, HUANG Jingwen, YU Fenfen, ZHU Wenhui, WAN Pengxia. Research progress on the risk factors of retinopathy of prematurity[J]. Yan Ke Xue Bao, 2020, 35(4): 249-254. doi: 10.3978/j.issn.1000-4432.2020.10.04