

极低出生体质量儿人乳喂养与早产儿视网膜病变发病率关系的 Meta 分析

门光国 王丽丽 姜燕丽 吕勤

【摘要】目的 系统评价人乳喂养对极低出生体质量儿(VLBWI)早产儿视网膜病变(ROP)发病率的影响。**方法** 利用万方、中国知网、PubMed、MEDLINE、EMBASE、CINAHL、Cochrane Central Register of Clinical Trials 等数据库,检索 1990 年后发表的关于出生时胎龄 ≤ 28 周和/或出生体质量 ≤ 1500 g 的 VLBWI 人乳喂养与 ROP 发病率关系的文献,研究设计包括纯人乳(EHM)与早产儿配方奶(EPTF)、部分人乳与 EPTF、高剂量人乳与低剂量人乳喂养婴儿的 ROP 发病率比较,共有 29 篇文献纳入研究。**结果** 2 项随机试验、5 项观察性研究分别报道了 EHM 与 EPTF 喂养 ROP 发病率比较的结果,差异均无统计学意义(均 $P > 0.05$);其中 3 项研究报道了 EHM 与 EPTF 喂养严重 ROP 发病率比较的结果,显示 EHM 喂养能降低严重 ROP 发病率($RR=0.22, RD=-0.08, OR=0.20, P<0.05$)。6 项观察性研究报道了部分人乳与 EPTF 喂养 ROP 发病率比较的结果,显示差异无统计学意义($P > 0.05$),其中 3 项研究报道了部分人乳与 EPTF 喂养严重 ROP 发病率比较的结果,差异亦无统计学意义($P > 0.05$)。4 项随机试验报道了高剂量与低剂量人乳喂养 ROP 发病率比较的结果,显示差异无统计学意义($P > 0.05$);19 项观察性研究报道了高剂量与低剂量人乳喂养 ROP 发病率比较的结果,显示高剂量人乳喂养能降低 ROP 发病率($RR=0.82, RD=-0.03, OR=0.75, P<0.05$);其中 13 项研究报道了高剂量与低剂量人乳喂养严重 ROP 发病率比较的结果,显示高剂量人乳喂养能降低严重 ROP 发病率($RR=0.66, RD=-0.02, OR=0.64, P<0.05$)。**结论** EHM 或高剂量人乳喂养可能降低 VLBWI 发生 ROP 的风险。

【关键词】 早产儿 人乳 早产儿配方奶 早产儿视网膜病变

Meta-analysis on relationship between human milk feeding and retinopathy of prematurity in very low birth weight infants MEN Guangguo, WANG Lili, JIANG Yanli, et al. Department of NICU, Ningbo Women and Children's Hospital, Ningbo 315012, China

【Abstract】Objective To evaluate systematically the effects of human milk feeding on the incidence of retinopathy of prematurity (ROP) in very low birth weight infants (VLBWI). **Methods** The literature published after 1990 was searched from Wanfang, CNKI, PubMed, MEDLINE, EMBASE, CINAHL, Cochrane Central Register of Clinical Trials and other databases. The incidence of ROP in between VLBWIs with exclusive human milk (EHM) and exclusive preterm formula (EPTF) feeding, any human milk and EPTF feeding, high-dose human milk and low-dose human milk feeding was compared. A total of 29 studies were included for analysis. **Results** Two randomized trials and five observation studies reported that by comparison of incidence of ROP between EHM and EPTF, the differences were not statistically significant ($P > 0.05$); 3 of these studies reported that EHM feeding reduced the incidence of severe ROP ($RR=0.22, RD=-0.08, OR=0.20, P<0.05$). Six observation studies reported the incidence of ROP between any human milk and EPTF feeding was not significantly different ($P > 0.05$); 3 of which reported that the incidence of severe ROP was also not significantly different between any human milk and EPTF feeding ($P > 0.05$). Four randomized trials reported that there was no significant difference in the incidence of ROP between high-dose human milk feeding and low-dose human milk feeding ($P > 0.05$). Nineteen observation studies reported that high-dose human milk feeding reduced the incidence of ROP ($RR=0.82, RD=-0.03, OR=0.75, P<0.05$). Thirteen studies reported that compared with low-dose human milk feeding, high-dose human milk feeding reduced the incidence of severe ROP ($RR=0.66, RD=-0.02, OR=0.64, P<0.05$). **Conclusion** EHM or high-dose human milk feeding may reduce the risk of ROP in VLBWI.

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作者单位:315012 宁波市妇女儿童医院 NICU(门光国、吕勤);山东省东阿县人民医院儿科(王丽丽);宁波市第七医院儿科(姜燕丽)

通信作者:吕勤, E-mail: qingpingguo911@163.com

【Key words】 Preterm infant Human milk Preterm formula milk Retinopathy of prematurity

随着全球早产儿的增加以及早期新生儿管理的进展,最小和最弱新生儿存活率明显升高^[1-2],某些慢性疾病发病率也相应增加^[3-4]。如近年来中国^[5]、土耳其^[6]、美国^[2]和瑞典^[7]等国家早产儿视网膜病变(ROP)发病率有所增加。ROP是导致儿童失明的主要原因^[8],主要发生在胎龄<32周的新生儿,且胎龄越小则发生ROP的风险和严重程度越高。相关研究表明,极低出生体质量儿(VLBWI)的ROP发病率为20%~50%,其中严重ROP占4%~19%^[8-9]。人乳是早产儿的首选食物。但并非所有母亲都可以提供足够的母乳,因此可适当补充早产儿配方奶(PTF)或捐赠人乳(DHM)。目前建议首选母亲自己的人乳(MOM)。如果MOM不足,经适当筛选和巴氏灭菌的DHM为仅次于MOM的最佳选择^[10]。有研究表明,早产儿人乳喂养与ROP发病率降低有关^[11-13],且对早产儿包括ROP在内的主要疾病具有明显的剂量效应,特别在出生后前14d^[14]。但也有研究表明,未见这种保护作用存在^[15-16]。本文就VLBWI人乳喂养与ROP发病率的关系作一Meta分析,以探讨人乳喂养是否对ROP有保护作用以及人乳剂量与ROP发病的关系,现将结果报道如下。

1 资料和方法

1.1 文献检索 利用万方、中国知网、PubMed、MEDLINE、EMBASE、CINAHL、Cochrane Central Register of Clinical Trials等数据库,检索时限为1990年1月1日至2018年6月30日。中文检索词包括极低出生体质量儿、人乳、早产儿视网膜病变;英文检索词包括very low birth weight infants, human milk, retinopathy of prematurity。研究类型包括观察性(队列或病例对照)和实验性研究。纳入标准:(1)研究对象为胎龄≤28周的早产儿和/或平均出生体质量≤1500g;(2)研究设计包括纯人乳(EHM)与EPTF、部分人乳(EHM或人乳+PTF)与EPTF、高剂量人乳(EHM或高剂量人乳+PTF)与低剂量人乳(低剂量人乳+PTF)的比较;(3)结局指标包括ROP和严重ROP。

1.2 文献筛选 由2位研究者按标题及摘要独立筛选文献,如遇分歧则通过讨论解决,若结果未达成一致,由第3位研究者决定。最终有29篇文献纳入研究。

1.3 资料提取 由2位研究者提取资料,包括纳入文献的发表年份、作者、国家、研究设计、ROP诊断标准以及研究对象胎龄、体质量、喂养类型、OR值、危险差(RD)、

相对危险度(RR)及95%CI。

1.4 质量评价 研究者对每项研究的选择或剔除标准、报告偏倚进行评估。同时采用GRADE系统评估证据质量和建议强度。无限制的随机试验被认为是高质量的证据,观察性研究被认为是较低质量的证据。基于风险偏倚,不一致性、间接性、不严密和发表偏倚的研究可被降级为一类(严重的问题)或二类(非常严重的问题)。具有较大效应的观察性研究由于具有强有力的协同效应可以被升级,定义为 $RR \leq 0.5$ 。最终根据研究设计、报告结果的确定性分别4个级别,即非常低、低、中、高。

1.5 统计学处理 应用RevMan 5.3统计软件。采用 P 评估各项研究的异质性, $P > 75\%$ 表示异质性明显,采用随机效应模型分析。 $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 纳入文献特征 纳入研究共有29项,包括随机试验6项^[17-22]、时间不连续的序列4项^[23-26]、病例对照研究2项^[27-28]和队列研究17项^[13, 15-16, 29-42]。29项研究均报道了ROP,其中16项报道了严重ROP。除了4项研究没有提供ROP定义^[18-19, 25, 31]外,其他25项研究均采用了ROP的国际分类标准^[43];而严重ROP的定义各不相同。

2.2 EHM与EPTF喂养ROP发病率的比较 共有2项随机试验报道了EHM与EPTF喂养ROP发病率比较的结果^[19, 21],显示差异无统计学意义($RR=1.49$, 95%CI: 0.72~3.10; $RD=0.08$, 95%CI: -0.06~0.22; $OR=1.67$, 95%CI: 0.67~4.16, $P > 0.05$),见图1-3。共有5项观察性研究报道了EHM与EPTF喂养ROP发病率比较的结果^[13, 25, 29, 36-37],显示差异无统计学意义($RR=0.66$, 95%CI: 0.38~1.12; $RD=-0.08$, 95%CI: -0.17~0.02; $OR=0.55$, 95%CI: 0.26~1.14, $P > 0.05$),见图1-3。共有3项研究报道了EHM与EPTF喂养严重ROP发病率比较的结果^[13, 29, 37],显示EHM喂养能降低严重ROP发病率,差异有统计学意义($RR=0.22$, 95%CI: 0.08~0.64; $RD=-0.08$, 95%CI: -0.15~-0.01; $OR=0.20$, 95%CI: 0.07~0.63, $P < 0.05$),见图4-6。

2.3 部分人乳与EPTF喂养ROP发病率的比较 共有6项观察性研究报道了部分人乳与EPTF喂养ROP发病率比较的结果^[15-16, 25, 29, 37-38],显示差异无统计学意义($RR=1.08$, 95%CI: 0.79~1.48; $RD=0.02$, 95%CI: -0.07~0.10; $OR=1.11$, 95%CI: 0.69~1.79, $P > 0.05$),见图1-3。

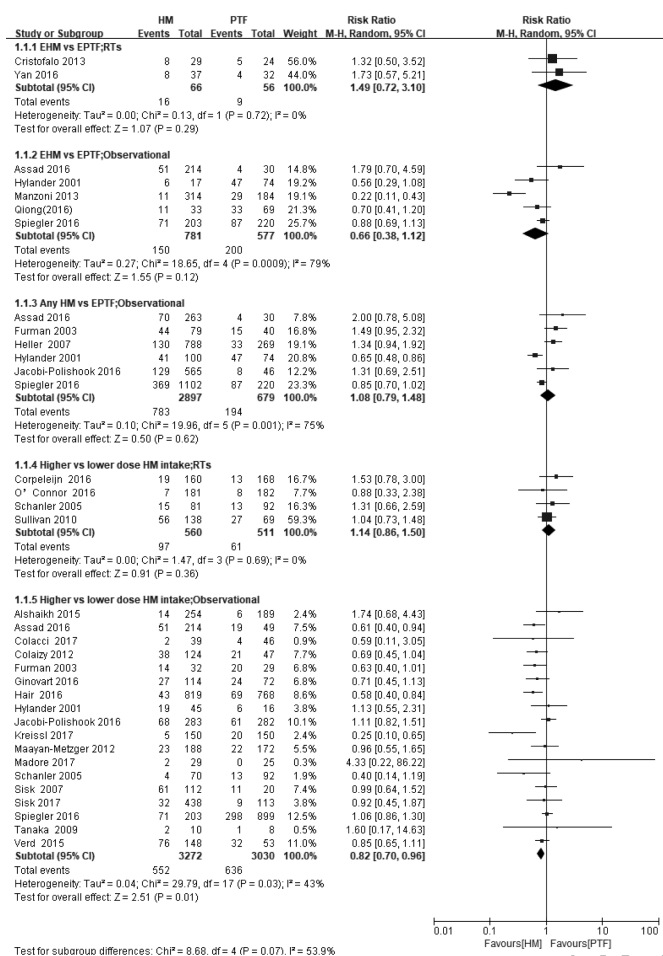


图 1 EHM 与 EPTF 喂养 ROP 发病率的 RR 值森林图

共有 3 项研究报道了部分人乳与 EPTF 喂养严重 ROP 发病率比较的结果^[16,29,37],显示差异无统计学意义($RR=0.91$, $95\%CI:0.51\sim1.62$; $RD=-0.00$, $95\%CI:-0.05\sim0.05$; $OR=0.91$, $95\%CI:0.48\sim1.71$, $P>0.05$),见图 4-6。

2.4 高剂量与低剂量人乳喂养 ROP 发病率的比较 共有 4 项随机试验报道了高剂量与低剂量人乳喂养 ROP 发病率比较的结果^[17-18,20,22],显示差异无统计学意义($RR=1.14$, $95\%CI:0.86\sim1.50$; $RD=0.01$, $95\%CI:-0.02\sim0.04$; $OR=1.22$, $95\%CI:0.84\sim1.77$, $P>0.05$),见图 1-3。共有 19 项观察性研究报道了高剂量与低剂量人乳喂养 ROP 发病率比较的结果^[15,17,23-26,28-33,35,37-42],显示高剂量人乳喂养能降低 ROP 发病率,差异有统计学意义($RR=0.82$, $95\%CI:0.70\sim0.96$; $RD=-0.03$, $95\%CI:-0.06\sim-0.00$; $OR=0.75$, $95\%CI:0.59\sim0.94$, $P<0.05$),见图 1-3。共有 13 项研究报道了高剂量与低剂量人乳喂养严重 ROP 发病率比较的结果^[17,23-24,26,29-30,33,35,37,39-42],显示高剂量人乳喂养能降低严重 ROP 发病率,差异有统计学意义($RR=0.66$, $95\%CI:0.47\sim0.94$; $RD=-0.02$, $95\%CI:-0.05\sim-0.00$; $OR=0.64$, $95\%CI:0.44\sim0.93$, $P<0.05$),见图 4-6。

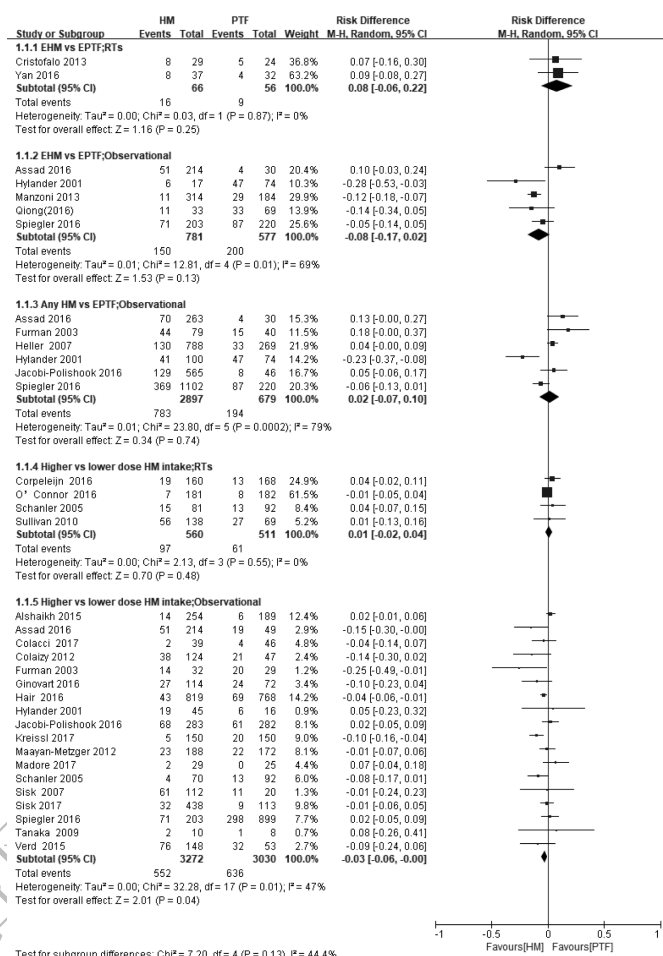


图 2 EHM 与 EPTF 喂养 ROP 发病率的 RD 值森林图

3 讨论

研究表明,体质量 $<1250g$ 的极低早产儿发生严重 ROP 的概率高达 37%^[44]。关于 ROP 的发病原因,主要包括早产、低出生体质量、高浓度氧疗、营养欠佳等。笔者通过检索儿科和眼科学相关期刊最新研究成果,就 VLBWI 人乳喂养与 ROP 发病率的关系进行 Meta 分析,从而探讨人乳喂养是否为 ROP 提供保护。

本项 Meta 分析包括 29 项研究,文献多来自发达国家,反映了现代新生儿重症监护室的做法,使得这些结果可以被推广。本研究结果显示,与 EPTF 相比,无证据证明 EHM 喂养对 ROP 有影响,但可能降低严重 ROP 发病率;与 EPTF 相比,无证据证明部分人乳喂养对 ROP 或严重 ROP 有影响;与低剂量人乳相比,高剂量人乳喂养能降低 ROP 或严重 ROP 发病率。因此,建议在母亲无法满足其婴儿喂养要求时,也要尽量使用 100% 人乳,以免婴儿发生严重 ROP。

此外,笔者还检索了其他 Meta 分析的研究结果。Zhou 等^[45]对有限的研究证据进行系统评价,结果显示在

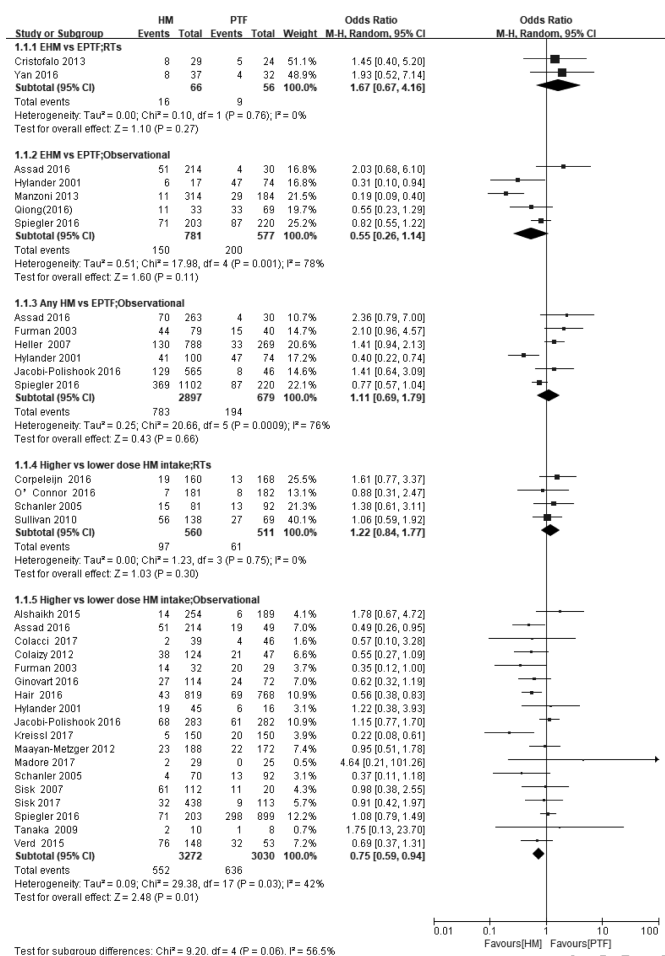


图3 EHM与EPTF喂养ROP发病率的OR值森林图

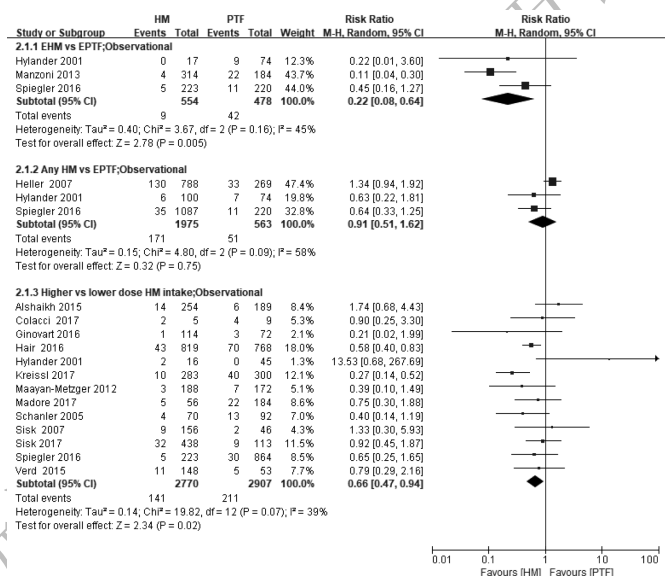


图4 EHM与EPTF喂养严重ROP发病率的RR值森林图

早产儿中,人乳喂养可能对任何阶段的ROP或严重ROP起到预防作用。Miller等^[46]对EHM或部分人乳与EPTF喂养婴儿的ROP发病率进行了系统比较,结果显

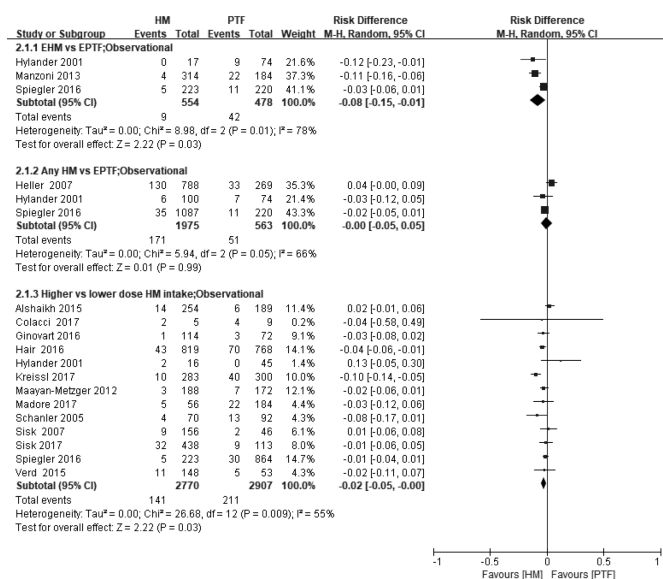
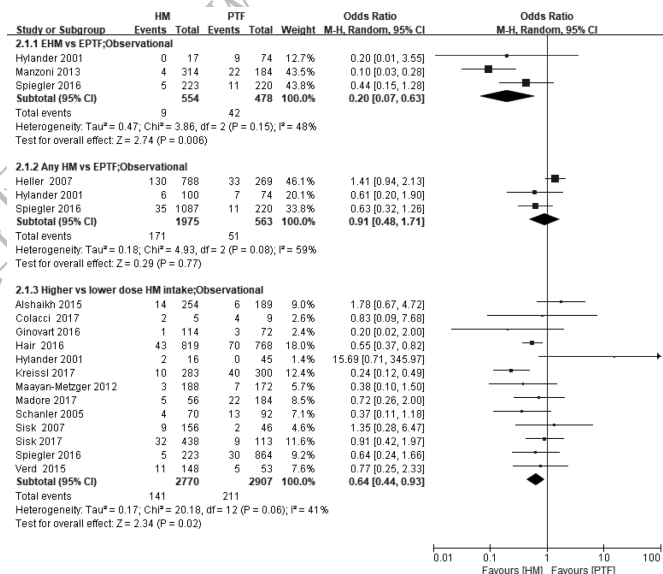


图5 EHM与EPTF喂养严重ROP发病率的RD值森林图



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