

吸烟对妊娠结局及子代健康的影响研究进展

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摘要

烟草燃烧会产生多种有毒、有害物质, 如尼古丁、焦油等, 但烟草燃烧的副产物比尼古丁本身对胎儿造成的损害更大。研究表明, 吸烟(包括被动吸烟)可导致多种妊娠不良结局, 如: 早产、胎盘早剥、死胎、胎儿生长受限等, 并为子代出生后罹患各种疾病埋下伏笔。这些吸烟导致的胎源性疾病均有一个共同点: 它们是永久性的, 对于许多疾病, 目前只能采用对症治疗。本文将重点探讨吸烟导致的不良妊娠结局和对子代健康的不良影响的研究进展, 以期引起人们的重视, 减少吸烟带来的不良影响。

关键词

吸烟, 不良妊娠结局, 二手烟, 子代健康

Research Progress on the Effect of Smoking on Pregnancy Outcome and Offspring Health

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Abstract

Tobacco combustion produces many toxic and harmful substances such as nicotine and tar, but

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the by-products of tobacco combustion are more damaging to the fetus than nicotine itself. Studies have shown that smoking (including passive smoking) can lead to a variety of adverse pregnancy outcomes, such as preterm birth, placental abruption, stillbirth and fetal growth restriction, and can set the stage for a variety of diseases in the offspring after birth. These smoking-related fetal diseases all have one thing in common: they are permanent, for many of them, only symptomatic treatment is currently available. This article will focus on the advances in research on the adverse pregnancy outcomes and adverse effects of smoking on the health of the offspring, with a view to raising awareness and reducing the adverse effects of smoking.

Keywords

Smoking, Adverse Pregnancy Outcomes, Second-Hand Smoke, Offspring Health

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1. 引言

吸烟在公民中比较普遍，并对其自身和子代的健康造成了一定的危害。值得关注的是，除了主动吸烟的人群外，还有相当多的人群暴露于无形的吸烟环境中，即所谓的二手烟(Secondhand Smoke, SHS)。二手烟包括吸烟者呼出的主流烟雾和烟草燃烧产生的副流烟[1]。SHS 暴露的重要来源是工作场所，允许吸烟的公共场所和吸烟者所在的房屋与车辆等。其中，房屋与车辆是儿童和孕妇最可能接触 SHS 的场所[2]。目前，从烟草烟雾中已鉴定出 7000 多种化学物质，其中包括 70 余种致癌物质[3]。在当今社会，香烟是合法的毒药，不仅损害自身的健康，也对子代的身心健康造成一定的危害。不管是主动吸烟，还是被动吸烟，均对人们，尤其是处于妊娠期的妇女和其子代的身心健康，带来巨大的风险[4]。现就吸烟对妊娠结局及子代健康的影响进行综述，以期引起社会的重视，减少吸烟导致的不良影响。

2. 吸烟对妊娠相关结局的影响

2.1. 吸烟可导致生育力下降

2.1.1. 吸烟导致流产率和早产率增加

对于育龄妇女而言，主动吸烟和被动吸烟均与生育率降低有密切关联[5]。有些研究一致认为，妇女吸烟在其孕期更容易发生流产。与非吸烟者相比，吸烟的妇女发生流产的可能性增加近 33% [6] [7] [8]。英国一项研究表明，孕期吸烟的孕妇其死产率将增加 23% [9] [10]。怀孕期间吸烟的女性可导致胎儿发生宫内感染的可能性增加 50%以上，因为吸烟者的绝对危险度减少率(Absolute Risk Reduction, ARR)比不吸烟者高 1.67 [10]。在我国农村进行的一项基于人群的回溯性队列研究表明，父亲吸烟与孕妇自发性流产有关[10]。因此，在备孕期间，尤其是孕期，父母双方均应戒烟。Dahlin 等人进行的一项基于人群的队列研究显示，孕期吸烟的孕妇发生极早早产(<28 周)是孕期父母未吸烟的 1.91 倍，但孕妇在早孕期戒烟没有增加早产的风险[11]。这表明及早戒烟对避免早产是有重要意义的。

2.1.2. 吸烟可导致男性生育力下降

吸烟可严重影响男性生育力，却没有引起大家的足够重视。尼古丁作为烟草中的主要有害物质，在吸烟者的血清和精液中均可被检测到，尼古丁的含量和烟草暴露剂量呈正相关[12]。可替宁是尼古丁的代

谢产物,也是烟草中的生物碱。研究证明尼古丁的毒理学作用呈剂量依赖性[13]。体外研究发现,低浓度($\leq 1 \text{ mmol}\cdot\text{ml}^{-1}$)的尼古丁和可替宁均可抑制精子的活力,较高浓度($\geq 1 \text{ mmol}\cdot\text{ml}^{-1}$)的尼古丁会显著降低精子的运动和活力[14]。Condorelli 等人报道,从体外低浓度($1 \text{ ng}\cdot\text{ml}^{-1}$)开始,尼古丁以浓度依赖的方式抑制精子的运动[15]。在较高的浓度下,尼古丁可促进精子凋亡,DNA 碎片化[15]。以上研究表明,尼古丁是烟草烟雾中直接损害男性生育力的有害成分。

2.1.3. 吸烟可导致人工辅助生殖技术胚胎成活率降低

辅助生殖技术(Assisted Reproductive Technology, ART)是用于治疗不孕不育症的生殖技术。ART 包括体外受精(In Vitro Fertilization, IVF)、胞浆内精子显微注射技术(Intracytoplasmic Sperm Injection, ICSI)和配子输卵管内移植技术(Gamete Intrafallopian Transfer, GIFT)。有研究表明,男性吸烟是影响 IVF 患者妊娠结局的有害因素[16]。Zitzmann 等人对 153 对 ICSI 和 148 对 IVF 夫妇的研究中发现,吸烟可导致辅助生殖技术成功率降低[17]。配偶吸烟时,从孕妇身上提取的卵母细胞数量可减少 46%,这很可能是由于女性的被动吸烟所致[18]。Wesselink 等人的一项前瞻性研究中发现,高剂量、长时间吸烟者的生育力显著降低[19]。另有一项关于吸烟对辅助生殖影响的 Meta 分析表明,与非吸烟者相比,在女性吸烟人群中检测到了显著的不良结果,包括每个周期的活产率和临床妊娠率降低,回收的卵母细胞数和平均受精率均下降,并且每次怀孕的流产率却显著增加[20]。这表明女性吸烟对辅助生殖技术的结果具有显著的负面影响,并强烈建议女性吸烟者在使用人工辅助生殖技术怀孕之前戒烟,这将使孕妇和胎儿大大受益。

2.2. 吸烟可导致胎儿宫内发育迟缓

胎儿宫内发育迟缓是吸烟诱发的重要的病理生理改变。一项巴西开展的关于孕期暴露于烟草烟雾的研究表明,新生儿平均出生体重减少了 223.4 g,身高减少了 0.94 cm,头围减少了 0.69 cm [21]。与使用非法药物的吸烟者相比,使用非法药物且不吸烟的孕妇中,新生儿的平均出生体重增加了 317 g [21]。吸烟母亲孕育的婴儿的出生体重显著降低,而新生儿低出生体重($< 2500 \text{ g}$)是预测婴儿死亡的关键指标。美国的研究人员对 265 名婴儿的出生体重进行了统计,结果表明,戒烟比限制非法使用毒品对出生体重的影响更大[21]。McCowan 等人的一项前瞻性队列研究表明:在怀孕 15 周之前停止吸烟的妇女中,自发早产率和小于胎龄儿的比例与不吸烟者没有差异[22]。以上研究表明如果尽早停止吸烟,这些严重的不良反应或许是可逆的。

2.3. 吸烟可导致胎盘早剥的风险增加

胎盘早剥是一种严重的产科并发症,高危因素包括高龄产妇、多胎、先兆子痫、宫内感染、长时间破膜等。怀孕期间吸烟也被证明与胎盘早剥相关,已有相关研究表明,与未吸烟孕妇相比,妊娠期间母亲吸烟发生胎盘早剥的风险显著增加[7]。吸烟与胎盘早剥之间存在很强的剂量依赖性,其胎盘早剥的风险随着每天吸烟的次数增加而增加[23]。在一项研究中,每天吸 1~9 支烟的孕妇发生胎盘早剥的风险增加近 90%,而每天抽 10 支或更多支烟的孕妇发生胎盘早剥的风险将增加 120% [24]。另有研究表明,父亲吸烟也会使孕妇发生胎盘早剥的风险增加一倍[25]。如果夫妻双方都是吸烟者,则风险将增加近五倍[25]。这可能是由于孕妇被动暴露于烟草烟雾的环境中引起。尽管吸烟与胎盘早剥之间的关联机制目前尚未阐明,但是吸烟诱发的低氧血症导致的子宫胎盘循环变化可能在其中发挥了一定的作用,直接作用是尼古丁通过介导羧基血红蛋白干扰氧合作用,进而导致子宫和脐动脉的血管收缩作用增强。尼古丁,可替宁和一氧化碳等有害物质可迅速通过胎盘组织进入胎儿血液[26]。吸烟引起的子宫灌注不足可导致与胎盘慢性低氧相类似的病变[27]。这些损害在胎盘包括胎盘微梗塞、动脉粥样硬化、蜕膜坏死和萎缩性胎盘绒毛[26]。吸烟引起的血管脆性增加可能导致动脉破裂最终导致胎盘早期剥离[27]。吸烟还会增加血浆中

同型半胱氨酸的水平[28],可能在胎盘早剥中发挥一定的作用。高同型半胱氨酸血症可引起内皮细胞损伤和功能障碍,导致局部血栓形成和胎盘血管床的缺陷。由此可见吸烟是造成胎盘早剥的一个重要危险因素。

2.4. 吸烟与妊娠期高血压和先兆子痫的关系

妊娠期高血压(Gestational Hypertension, GH)多发生于妊娠 20 周后至产前 48 h 内。血脂异常,炎症,氧化应激作为 GH 和先兆子痫(Preeclampsia, PE)发病机制的主要危险因素[29]。England 等人的系统审查(涵盖 1959~2006 年的 48 项流行病学研究)和 Conde-Agudelo 等人的系统审查(涵盖 1966~1998 年的 35 项研究)均表明,孕期吸烟与 PE 之间的反比关系[30]。然而,一些研究表明,怀孕期间吸烟会增加妊娠期患高血压的风险[31][32][33]。在一项基于人群的队列研究中,Bakker 等人发现,妊娠头三个月吸烟导致的 PE 风险略有增加[33]。Rauchfuss 等人对 508 名 16~22 周的单次怀孕女性进行的前瞻性研究中发现,从不吸烟和怀孕期间减少吸烟次数的女性患 GH 的风险最低,而在怀孕前或怀孕期间戒烟的女性患 PE 的风险也会增加[34]。

有一些机制可以解释吸烟者的 GH 和 PE 风险增加。一般来说,由吸烟(烟草烟雾成分引起的)引起的血管病变可能会影响与胎盘发育相关的过程,并损害母亲血管内皮的结构和功能。研究表明,接触烟草烟雾会引发各种器官的炎症反应和氧化应激,并导致血栓损伤事件[35]。首先,已有研究表明,具有抗氧化特性的微量营养素水平较低(例如硒)可能会增加 GH 的风险[36][37]。同时,吸烟也与孕妇体内低浓度的硒有关[38],吸烟者中铅和镉含量的增加可能导致与重金属结合的抗氧化硒浓度降低[39]。胎盘镉水平增加也与 PE 风险增加有关[40]。其次,烟草烟雾可能会影响内皮细胞的氧化损伤(内皮细胞会合成内源性一氧化氮,具有血管舒张作用),这可引起血管收缩和血管扩张因子作用之间的不平衡[41]。最后,尼古丁可通过作用于心血管系统增加血压[42]。然而,为什么在怀孕期间戒烟会增加高血压的风险,这仍然无法解释,这需要在大型样本中进行测试。

还有一些机制可以解释吸烟者 PE 风险的降低[31]。例如,尼古丁可以通过乙酰胆碱受体亚基($\alpha 7$ -nAChR)产生抗炎作用,抑制促炎细胞因子的产生,可减轻胎盘缺血引起的高血压。外源性一氧化碳可能具有免疫抑制作用,并具有降低血管张力的特性[42]。研究发现,烟草烟雾成分降低了 sFlt-1(胎盘上皮细胞释放的一种抗血管生成因子)的剂量依赖性水平,既往研究表明,妊娠早期 sFlt-1 水平越高,发生 GH、PE 的风险越高[31]。尼古丁会抑制血栓素 A2 的产生,这也许可以解释吸烟者患 PE 风险降低的原因。尼古丁可通过影响血管收缩性前列腺素的产生而降低血浆容量[31]。

对于吸烟与妊娠期高血压和先兆子痫的关系,既往的研究有两种不同的结论,可能是烟草烟雾的不同成分在不同的过程起作用,或者它们对同一细胞过程可能有不同的作用,这还需要进一步论证研究。

3. 吸烟对子代健康的影响

3.1. 吸烟可导致后代骨折风险增加

有研究表明,产前吸烟与婴儿出生后骨折发生率增加有关[43]。母体孕期吸烟与胎儿生长有限,尤其是胎儿骨骼的生长发育存在一定的因果关系。有研究推测,孕期吸烟可降低母体肠道的钙吸收能力,导致经由胎盘-脐带运输到胎儿的钙水平减少,从而影响胎儿骨骼的发育[44]。此外,烟草烟雾中的镉等成分也会对胎儿产生直接的毒性作用[45]。母亲吸烟可通过作用宫内编程的生长激素/胰岛素样生长因子-1 轴,进而对出生后子代的骨骼发育产生长期的不良影响[46]。因此,孕期吸烟的母亲会显著增加其子代骨骼发育受损的风险。

3.2. 吸烟导致子代遗传学改变

孕妇孕期主动吸烟或被动暴露于二手烟, 不仅对母亲而且对胎儿的基因和细胞水平都具有巨大的负面影响。2012年, 美国开展的一项有关孕期吸烟和不良妊娠结局的研究指出, 表观遗传与细胞遗传的改变在胎儿畸形的发病机理中起着重要作用[47]。在这项研究中, 在怀孕期间吸烟的母亲的后代在出生时就出现了一组基因甲基化变化(细胞色素 p450 1A1, AHRR 和 GFI1)。这些基因在芳香烃信号通路中均可介导烟草烟雾有毒成分的清除和解毒[47]。Kareli 等人的研究表明, 孕妇孕期吸烟可导致新生儿 DNA 损伤, 引起染色体不稳定, 并且这种损害可与环境、化学物质等相关基因诱变物质协同作用, 甚至可能会导致子代相关癌症的发生率增加[48]。

3.3. 孕妇吸烟可导致子代患精神、神经疾病风险增加

3.3.1. 孕妇吸烟可导致子代发生精神疾病风险增加

孕期吸烟也可导致子代的神经发育受损, 出现一定的精神行为异常或障碍。有研究为孕期吸烟引起后代双相情感障碍提供了新证据[49]。该研究指出, 孕期吸烟暴露可显著增加胎儿致畸率, 导致子代出生后罹患严重精神疾病的风险增加[49]。烟草中重要组分尼古丁和一氧化碳可通过胎盘, 直接或间接地影响胎儿的神经发育[50]。最近芬兰的一项出生队列研究发现, 孕期吸烟的孕妇其后代在童年具有较多的情绪和行为问题, 精神治疗相关药物的使用率亦较高[51]。产前烟草暴露也可破坏肾上腺轴和感觉门控开关, 导致婴儿期的认知力和注意力受损[52]。尼古丁暴露也可能限制胎盘血流量, 使胎儿处于营养不良和低出生体重的风险中, 这怀疑也是双相情感障碍发展的原因。因此, 烟草暴露对子代精神疾病相关的影响是通过多种途径共同起作用的。

3.3.2. 孕妇孕期吸烟导致子代神经病学改变

孕妇长期暴露于烟草烟雾中对儿童神经发育及其行为的各种不利影响, 已成为近年来一些研究的焦点。有研究表明, 孕妇在怀孕期间吸烟与胎儿生长受限和大脑容量减少有关, 并已证实孕期吸烟的妇女其胎儿小脑和胼胝体密度降低, 这些研究表明, 在信息处理过程中, 胎儿大脑不同部位的协调能力下降, 对外部刺激做出充分反应的能力下降[53]。一项 2011 年开展的队列研究, 该研究评估了 1019 名婴儿的各种认知功能, 如一般推理, 视觉运动整合, 语言能力和语言理解能力, 结果表明, 怀孕前吸烟可导致子代认知执行能力下降, 即使该妇女在受孕前已经停止吸烟, 其后代的认知表现仍未见明显改善[54]。

3.4. 孕妇烟草暴露可导致子代发生龋齿的风险增加

日本一项横断面研究表明, 与怀孕期间未吸烟者相比, 孕前三个月的母亲吸烟与儿童龋齿患病率增加显著相关, 与孕妇产前产后未有烟草暴露史的孕妇相比, 产前产后存在烟草暴露的孕妇生产的儿童患龋齿的几率更高[55]。然而日本一项回顾性队列研究表明, 婴儿 4 个月大暴露在烟草烟雾中, 患龋齿的风险增加了约 2 倍, 然而母亲在怀孕期间吸烟的影响在统计学上并不显著[56]。这两项研究结果的差异可能是由于刷牙等生活方式的差异所造成的。龋齿的主要病因是牙齿中的牙釉质晶体与潜在在牙齿表面的口腔细菌发酵所产生的酸接触, 牙釉质的钙化受到抑制, 在牙齿表面发育缺陷处, 产生酸的斑块增多。另有日本的一项横断面发现孕妇孕期吸烟并且子代出生后暴露于烟草烟雾中较孕妇孕期吸烟而子代出生后家庭禁烟发生龋齿的风险增加 2.14 [57]。这表明孕妇的二手烟烟草暴露也是导致子代发生龋齿的一个重要的危险因素, 故应倡导家庭戒烟。这可能是由于烟草烟雾暴露增加了牙齿对酸的敏感性, 影响牙齿和口腔内的微生物所造成的。

3.5. 孕妇孕期吸烟可导致子代肥胖的风险增加

多项研究均指出母亲孕期吸烟可导致子代在儿童期的体重指数(Body Mass Index, BMI)呈线性增长[58]。宫内香烟暴露会导致子代出生后在儿童期的 BMI、脉搏率、腰围和腰臀比等指标均显著增加[59]。与母亲从不吸烟的孩子相比,在孩子一生中其他时间吸烟但在怀孕期间没有吸烟的母亲的后代具有相似的平均危险因素。由此可见若采取有效措施使孕妇孕期禁烟,可减少子代肥胖的风险。

3.6. 孕妇孕期吸烟可能影响胎儿肾脏的发育

孕妇孕期吸烟也可影响胎儿肾脏的发育。荷兰一项针对 1072 名儿童的前瞻性队列研究发现,胎儿肾脏容量与孕期香烟暴露的数量之间存在明显的剂量依赖性关系[60]。研究人员发现,与每天吸食少于五支烟的女性相比,孕妇每天吸食十支烟可导致胎儿的肾脏容量显著减少[60],并且孕期母体吸烟可导致后代在成年后罹患肾脏疾病和高血压的风险增加。

3.7. 孕妇孕期吸烟导致子代呼吸系统疾病增加

McEvoy 等人发现,孕产妇吸烟对子代肺功能的主要影响是呼气量减少,呼吸顺应性降低,导致儿童呼吸道疾病的患病率和住院率均显著增加[61]。尼古丁是烟草中影响肺部发育的主要成分,孕期暴露电子烟对胎儿的肺部发育也同样具有很大的危害。美国密歇根州底特律的一项研究证实,孕期吸烟与子代出生后肺功能的下降密切相关[62]。1987 年至 2004 年,针对华盛顿州进行的一项回顾性病例分析发现,母体孕期吸烟出生的子代在幼儿期呼吸道感染而引起的儿科住院率和死亡率显著增加[63]。由此可见,若孕妇孕期戒烟将大大减少子代患呼吸系统疾病的风险。

3.8. 戒烟之必要性

孕期烟雾暴露对妊娠结局和子代健康的不良影响不仅仅是孕妇吸烟所导致的,孕前孕期家庭和生活环境中的二手烟同样会产生危害,甚至危害更大。我们应鼓励有生育要求的女性在怀孕前戒烟,使她们充分认识到吸烟所造成的不良后果。尼古丁贴片等尼古丁替代疗法其对戒烟的影响很小,其影响可能是由于造成孕妇在孕期减少吸烟所致,故不提倡。总之,决策者和公众必须关注限制家庭和公众烟草接触以及二手烟接触,以保护幼儿和孕妇自身的健康。全球重要的无烟政策,健康宣传运动和行为干预措施是有用的,并且应该是强制性的。

综上所述,关于孕妇孕期烟草暴露主要有以下几种结局的负面影响:早产,流产,生育力下降,胎儿生长受限,低出生体重,胎盘早剥,子代骨折风险增加,子代遗传学改变,子代患精神、神经系统疾病的风险增加,子代发生龋齿的风险增加,子代肥胖,子代肾脏发育异常,子代呼吸系统疾病增加。虽然孕期孕妇吸烟对妊娠相关结局起主要作用,但在孕前、产后吸烟以及二手烟暴露也会对孕妇及子代产生负面影响,甚至危害更大。另外也有研究表明吸烟与胎膜早破、前置胎盘、胎盘植入等相关,这还需要进一步研究。在临床上,我们应及时告知孕妇及其家属吸烟的危害,尽可能减少其对子代的危害。

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