妊娠期药动学变化与生理药动学模型在妊娠期药动学研究中的应用

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摘要: 妊娠妇女合理用药是医生和药师必须认真对待的临床问题。妊娠期间体内大多数组织器官都会发生解剖和生理学的改变, 从而影响药物的吸收、分布、代谢和排泄等体内过程, 最终导致生物利用度的变化。因此为达到有效治疗浓度, 孕期可能需要剂量调整。过去的十几年中建模与仿真技术在新药研发和临床治疗领域的应用不断扩展, 例如用群体药动学 (population pharmacokinetics, PPK) 和生理药动学 (physiologically based pharmacokinetics, PBPK) 建模方法来设计特殊人群的给药方案。严谨设计和验证的模型能有效弥补临床试验的不足, 为临床研究方案设计提供极有价值的参考, 甚至替代部分临床试验。本文将介绍妊娠期影响药物药动学性质的生理学变化, 并综述PBPK模型在妊娠期药动学研究中的应用进展。

关键词: 妊娠; 药动学; 药物代谢酶; 生理药动学; 建模与仿真

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Changes of pharmacokinetics and application of physiologically based pharmacokinetic modeling in pharmacotherapy during pregnancy

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Abstract: The rational medication in pregnant women is a clinical issue that clinicians and pharmacists must take seriously. Most tissues and organs undergo anatomical and physiological changes during pregnancy that affect the absorption, distribution, metabolism, and excretion of drugs *in vivo*, which ultimately lead to changes in bioavailability. In order to achieve an effective therapeutic concentration, dose adjustment might be required during this period. In the past ten years, the application of modeling and simulation methods in the field of drug development and clinical therapy has continued to expand, for instance, using population pharmacokinetic (PPK) and physiologically based pharmacokinetic (PBPK) modeling to adjust dosage regimen in special populations. Rigorously designed and validated models will effectively make up for the deficiencies of clinical trials, provide valuable references for the design of clinical research, and even replace part of them. This article will introduce the physiological changes that affect the pharmacokinetic properties of the drug during pregnancy and review the progress in the application of PBPK modeling in pharmacokinetic studies in pregnant women.

Key words: pregnancy; pharmacokinetics; drug metabolic enzyme; physiologically based pharmacokinetics; modeling and simulation

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妊娠女性等特殊人群的合理用药一直是药物治疗方面的重要挑战。妊娠期的药物使用必须考虑两点: 一是药物是否可能对胎儿造成不良影响, 尤其是在妊娠早期, 此时胎儿对药物最为敏感; 二是合理给药方案的制定, 以使孕妇获得有效的药物治疗。为了应对妊娠期间不断增加的身体和新陈代谢需求, 女性在妊娠期会经历明显的解剖和生理变化, 如心血管系统、呼吸系统、消化和泌尿系统等, 使得药物在体内的处置过程发生一定改变[1]。这种改变可能导致在临床常规治疗剂量下, 药物的生物暴露量在妊娠期女性中显著降低或升高, 造成治疗不充分或毒性反应的发生。然而, 由于伦理等方面原因, 孕妇通常被药物临床试验排除在外, 导致患者及医务人员在做出药物和剂量选择时缺乏可靠的安全性证据而经常发生超说明书用药的情况[2]。因此, 迫切需要可被监管机构认可的研究手段对妊娠期的药物暴露水平做出准确评估。

在过去的十几年里, 随着计算机技术的迅猛发展, 定量药理学建模与仿真技术, 如生理药动学 (physiologically based pharmacokinetics, PBPK) 模型和群体药动学 (population pharmacokinetics, PPK) 模型, 在新药研发和临床治疗领域也得到了广泛应用。其中PBPK模型可以将系统特异性因素 (如机体的身高体重、肝肾功能差异等) 与药物特异性因素 (清除率、分布容积、代谢途径等) 结合起来, 从而预测药物在不同人群中的药动学特征[3]。本文将介绍妊娠期影响药物药动学性质的生理学变化, 并综述PBPK模型在妊娠期药动学研究中的应用进展。

1 妊娠期影响药物体内过程的生理变化

1.1 药物吸收 妊娠期胃肠蠕动减弱, 胃肠排空时间延长30%～50%, 同时胃酸分泌减少40%, 而黏液分泌增多, 导致胃pH值升高, 这对于弱酸性药物的吸收是不利的。例如, 胃pH升高会使乙酰水杨酸的解离度增大, 导致药物吸收延迟。孕早期妇女中常见的恶心和呕吐可能导致药物的损失[4]。肠道代谢酶和转运体在这个特殊的时期, 可能产生活性变化, 将改变药物通过肠壁有效吸收的比例。妊娠期心排血量和潮气量增大, 导致肺泡对药物的吸收增加, 在吸入给药时应考虑到这一点[5]。另外, 尽管缺乏特定的药物数据, 但一般认为妊娠期血管舒张和增加的局部血流量会促进肌肉注射或皮下注射后的药物吸收[6]。

1.2 药物分布 妊娠妇女体型明显增大, 许多器官的体积随孕期均有不同程度的增大。由于肾素-血管紧张素-醛固酮系统激活, 促进了水钠潴留, 妊娠期妇女的血管内液体容量明显增大。到妊娠结束时, 血浆容量相对基线增大约50%, 这导致水溶性药物的分布容积增大。妊娠期脂肪储存增大, 这将导致脂溶性强的药物在脂肪中的分布容积增大[7]。此外, 血浆蛋白被稀释, 研究报道白蛋白和α1-酸性糖蛋白的血浆浓度随妊娠进展而减小, 因此药物未结合比例可能上升[8,9]。血浆蛋白水平和药物结合能力在分娩时是正常孕前值的70%～80%。妊娠期间部分组织器官的血流供应将有质的飞跃, 例如子宫, 同时血液也将把药物带向胎盘和胎儿, 因此药物在孕妇体内的组织分布相对普通成人可能有一定程度的改变[10]。

1.3 药物代谢 妊娠期代谢酶可能发生显著的活性改变, 根据目前的资料显示, 其中大部分活性上调。例如, Hebert等[11]以14名健康孕妇作为研究对象, 咪达唑仑作为底物, 发现妊娠晚期CYP3A的活性比产后升高约2倍; Hogstedt等[12]通过测定妊娠期和产后美托洛尔在同一批孕妇体内的代谢情况, 发现妊娠期美托洛尔的清除率提高了4～5倍, 提示CYP2D6的活性增加, 后来Wadelius等[13]通过右美沙芬也验证了这一点。相反地, Tracy等[14]发现与产后相比, 咖啡因在整个妊娠期的口服表观清除率明显下降, 表明CYP1A2活性降低。不仅如此, II相代谢酶活性在妊娠期同样会受到一定影响。Pennell等[15]对53例孕妇的305个样本分析表明, 妊娠期总拉莫三嗪和游离拉莫三嗪清除率均显著高于非妊娠期, 妊娠晚期分别增加94%和89%, 考虑可能与代谢酶UGT1A4活性升高相关。主要代谢酶在妊娠期的活性变化趋势及部分底物总结于表1[11-26]。

Table 1 The impact of pregnancy on metabolic enzyme activities. *Extensive metabolisers

Metabolic enzyme	Activity	Substrate	Ref.
CYP1A2	↓	Caffeine	[14, 16]
CYP2A6	↑	Nicotine	[17]
CYP2B6	↑	Methadone	[18]
CYP2C8	↑	Verapamil, fluvastatin	[19]
CYP2C9	↑	Phenytoin	[20]
CYP2C19 *	↓	Proguanil	[21]
CYP2D6 *	↑	Metoprolol, fluoxetine	[12, 13, 22]
CYP2E1	↑	Paracetamol	[23]
CYP3A4	↑	Nifedipine, midazolam	[11, 24]
UGT1A1	↑	Bilirubin	[25]
UGT1A4, UGT2B7	↑	Lamotrigine, morphine	[15, 26]

这些活性的变化可能与妊娠期雌性激素水平上升而影响代谢酶的上游调控因子有关[27-30]。在CYP2A6基因的上游调控区已确定了与雌激素受体α (ERα) 结合的雌激素反应元件[31], 也有报道发现雌激素可以激活小鼠和人肝细胞中的组成型雄甾烷受体 (CAR) [32]。考虑到CAR等核受体参与了许多药物代谢酶基因表达的上调, 雌性激素对这些受体的激活可能在妊娠期

药物代谢改变中起着重要作用。另外, 孕期母体血浆中催乳素水平逐渐升高, 直到足月时达到峰值。催乳素已被证明可以调节多种药物代谢酶的表达。在去卵巢的大鼠中给予羊催乳素, 可通过上调UGT1A6和谷胱甘肽S转移酶 (GST) 的表达, 增加对硝基苯酚的葡萄糖醛酸化代谢[33]。

1.4 药物排泄 妊娠期肾血流量增大25%～50%, 肾小球滤过率增大50%, 因此主要以原形经肾小球滤过排泄的药物很可能肾清除增加[34]。妊娠对参与肾小管分泌和重吸收的肾转运蛋白的影响方面的研究不够充分, 有报道推测肾小管P-糖蛋白 (P-gp)、有机阴离子转运体 (OAT) 和有机阳离子转运体 (OCT) 的活性增强[11,35-37]。但总体而言, 妊娠对转运体的影响方面的研究非常缺乏。

2 妊娠期的药动学变化

一般地, 疾病或特殊生理状态对药物体内过程的影响是上述吸收、分布、代谢、排泄 (ADME) 影响的综合结果。对于妊娠期患者, 多种生理参数发生显著改变, 对药动学的联合作用可以增强或部分或完全抵消。例如, 当孕妇使用咪达唑仑时, 血浆白蛋白浓度降低使游离药物浓度增加, 同时CYP3A4活性升高加上心输出量的增加, 导致咪达唑仑的清除率显著提升[11]。咪达唑仑在健康志愿者中通常被归类为中等肝脏提取率药物, 但随着孕期的增加, 清除率随之升高, 该药在孕晚期的肝脏提取率可达到较高水平[38]。

药物在妊娠期完整的单剂量或多剂量药动学研究不足, 部分报道出自治疗药物监测或机会性取样 (opportunistic sampling) 药动学数据。2015年, Pariente等[39]通过检索MEDLINE、EMBASE、Cochrane Central Register of Controlled Trials和ISI Web of Science等数据库, 对妊娠期药动学文献进行了全面的系统回顾。共纳入189项临床研究, 每项研究都有一组妊娠妇女和一组非妊娠女性或其自身对照 (产后或孕前), 药动学参数变化的信息被提取出来。在此基础上, 作者检索了2016至2020年间公开发表的妊娠期药动学对照研究, 作为前述研究的更新并将结果汇总于表2[11,22,24,26,36,39-128]。近年来抗艾滋病病毒 (HIV) 药物在妊娠期的研究报道较多, 通过合理使用抗HIV药物阻断病毒母婴传播是感染孕妇的重大需求。总的来说, 由于许多肝脏代谢酶的活性上升, 药物在妊娠期清除率 (CL) 增大是较常见的情况, 这可能导致药物暴露水平 (C_{max}/AUC) 的减小和终末期表观分布容积 (V_d) 的上升。部分临床医生倾向于认为妊娠妇女应减少给药剂量, 以避免可能的安全性问题, 然而药动学事实提示不少药物在妊娠期尤其是孕晚期有可能需要增大剂量以满足治疗需求。

3 生理药动学模型在妊娠期药动学研究中的应用

生理药动学 (PBPK) 模型是基于生理学和解剖学基础, 以循环系统的血液流向将各器官或组织相互联结为一个整体, 各器官或组织在实际血流速率和组织/血液分配系数以及药物性质的控制下遵循物质平衡原理来描述药物体内过程的一种药动学分析方法。PBPK模型最常见的应用是模拟药物相互作用和预测特殊人群, 如儿童、孕妇、老年人和肝肾功能异常患者的药动学变化[129]。完整的妊娠PBPK模型基础结构如图1所示。本文将近几年来妊娠PBPK模型研究总结并详述如下。

3.1 抗抑郁药与抗精神病药 舍曲林是一种选择性5-羟色胺再摄取抑制剂, 是治疗抑郁症的一线药物之一。舍曲林在妊娠期的安全性较好, 因此被推荐作为孕妇使用抗抑郁药的优先选择。George等[130]使用常微分方程程序包mrgsolve构建了一个具有肠道、肝脏、血浆和胎盘-胎儿隔室的小型生理模型, 在此基础上建立了舍曲林的PBPK模型, 根据孕龄预测妊娠期舍曲林的剂量。该模型预测了一项临床研究的药动学参数, 其中8名受试者为孕中期, 6名受试者为孕晚期。妊娠期生理和代谢的变化导致舍曲林清除率增大 (在第40孕周时增大143%), 当使用孕前剂量时, 可能导致孕妇剂量不足。作者将该模型开发成一个基于web的交互式给药工具, 可以将PBPK模型的输出结果转化为妊娠阶段最佳舍曲林剂量。

齐拉西酮是一种非典型抗精神病药, 口服后在体内约33%的剂量经CYP3A4代谢清除。Biesdorf等[131]建立了齐拉西酮在普通成人中的PBPK模型, 考虑妊娠引起的血流量、肾小球滤过率、药物代谢和血浆蛋白结合的变化后将该模型外推至妊娠群体。模型预测妊娠6周、20周和34周时齐拉西酮血药浓度与非妊娠女性的水平并无显著差异。因此, 文章认为齐拉西酮在孕期不需要剂量调整。与齐拉西酮不同, 喹硫平与阿立哌唑的稳态血药浓度在孕期不断减小, 两药均主要在肝中经CYP酶代谢清除。Zheng等[132]建立了这两种药物的PBPK模型并在成人群体中通过了模型验证后外推至妊娠群体。模型预测喹硫平与阿立哌唑的药动学在孕晚期完全无法达到治疗浓度窗的要求, 有必要考虑在孕中期和晚期调整给药剂量。建议相对于孕前, 孕晚期妇女使用喹硫平的剂量至少增大1.5倍, 阿立哌唑至少增大1倍。

3.2 抗感染药物 许多抗感染药物, 如喹诺酮类、磺胺类和氨基糖苷类, 不推荐用于孕妇因为它们有潜在的致畸作用。而大多数青霉素类和头孢菌素类在孕妇

Table 2 The pharmacokinetic alterations of drugs during pregnancy. C_{max}: Peak plasma concentration; AUC: Area under the curve; C_{trough}: Steady-state trough concentration; C_{ave}: Average concentration; C_{total}: Total concentration; CL: Clearance; V_d: Volume of distribution; $t_{1/2}$: Elimination half-life; *f*u: Free fraction; C/D: Dose-standardized drug concentration in plasma at a given time; NA: Not available; A, B, C, D, X: The risk to the fetus is escalating from A to X; *: Not consistent among studies

Drug	Pregnancy category	Significant change	Non-significant change	Ref.
Antibiotics				
Amoxicillin	B	CL ↑, $t_{1/2}$ ↓	—	[40]
Ampicillin	B	CL ↑, AUC ↓	—	[41]
Azithromycin	B	V_d ↑	AUC, $t_{1/2}$	[42]
Cloxacillin	B	f_u ↑	—	[43]
Flucloxacillin	B	f_u ↑	—	[43]
Cefazolin	B	CL and V_d ↑	—	[44]
Cefatrizine	B	C_{max} and AUC ↓, $t_{1/2}$ ↑	—	[45]
Cefradine	B	CL ↑, AUC and $t_{1/2}$ ↓	V_d	[44]
Ceftazidime	B	CL ↑	—	[46]
Cefuroxime	B	CL ↑, AUC and $t_{1/2}$ ↓	V_d	[47]
Imipenem	C	CL and V_d ↑, AUC ↓	$t_{1/2}$	[48]
Penicillin V	B	AUC and $t_{1/2}$ ↓	CL, C_{max}	[49]
Piperacillin*	B	CL and V_d ↑, AUC ↓	AUC, C_{max}, $t_{1/2}$	[50−52]
Trimethoprim	C; D (use in labor)	CL and V_d ↑	$t_{1/2}$	[53]
Tazobactam	B	V_d and $t_{1/2}$ ↑	C_{max}, AUC	[51]
Isoniazide*	C	CL ↑	CL, AUC, V_d	[54,55]
Pyrazinamide	C	—	CL, AUC, V_d	[55]
Ethambutol	B	—	CL, AUC, V_d	[55]
Antimalarials				
Artemeter	NA	C_{max} and AUC ↓	—	[56]
Atovaquone	NA	CL and V_d ↑, C_{max}, AUC and C_{trough} ↓	—	[57]
Chloroquine*	C	CL and V_d ↑, AUC and $t_{1/2}$ ↓	CL, AUC, $t_{1/2}$	[58−61]
Lumefantrine*	NA	CL ↑, $t_{1/2}$ ↓	CL, V_d, C_{max}, AUC	[56,62,63]
Mefloquine*	C	CL and V_d ↑, C_{max} ↓	CL, $t_{1/2}$, V_d	[64−66]
Piperaquine*	NA	CL and C_{max} ↑, V_d, AUC and $t_{1/2}$ ↓	CL, AUC, V_d	[67−69]
Hydroxychloroquine	C	V_d ↑	CL, AUC	[70]
Sulfadoxine*	NA	CL ↑, AUC and $t_{1/2}$ ↓	C_{max}, AUC, $t_{1/2}$	[71]
Sedative Hypnotic Drugs				
Diazepam	D	—	CL	[72]
Thiopental	C	CL and V_d ↑	—	[72]
Antiepileptic drugs				
Carbamazepine*	D	CL ↑, f_u ↑	CL, f_u	[73−76]
Lamotrigine	C	CL ↑	—	[77]
Levetiracetam	C	CL ↑	—	[78]
Oxcarbazepine	C	CL ↑, C/D ↓	—	[79]
Phenytoin	D	CL ↑, f_u ↑, C_{total} ↓	—	[80]
Phenobarbital	D	CL ↑, f_u ↑, C_{total} ↓	—	[81]
Topiramate	D	C/D ↓	CL	[82]
Antidepressant/anxiolytic drugs				
Citalopram	C	C_{trough} ↓	—	[83]
Fluoxetine	C	C_{trough} ↓	—	[22]
Paroxetine	C	C_{total} ↓	—	[84]
Venlafaxine	C	C_{total} ↓	—	[85]
Clorazepate	D	CL ↑, C_{max} ↓	—	[86]
Midazolam	D	CL, f_u and V_d ↑, C_{max} and AUC ↓	$t_{1/2}$	[11,87]
Antivirals				
Dolutegravir	NA	—	AUC, C_{max}	[88]
Ledipasvir	NA	—	AUC	[89]
Lopinavir*	NA	CL, f_u and V_d ↑, C_{max}, AUC and $t_{1/2}$ ↓	CL, V_d, $t_{1/2}$, AUC, C_{trough}	[39,90]
Elvitegravir	NA	AUC ↓	—	[91]
Abacavir	C	—	C_{max}, CL, AUC, $t_{1/2}$	[92]
Atazanavir	B	CL ↑, C_{max}, AUC, C_{trough} and $t_{1/2}$ ↓	V_d	[93]
Efavirenz*	D	CL ↑, AUC and C_{trough} ↓	C_{max}, AUC, CL	[94−96]
Emtricitabine*	B	CL ↑, C_{max}, AUC and C_{trough} ↓	C_{max}, $t_{1/2}$, AUC, C_{trough}	[97−99]
Indinavir	C	CL ↑, C_{max}, AUC and C_{trough} ↓	—	[100]
Darunavir	C	CL ↑, AUC and C_{max} ↓	—	[101]

Continued

Drug	Pregnancy category	Significant change	Non-significant change	Ref.
Lamivudine	C	CL ↑	—	[102]
Nevirapine	B	C_{max}, AUC and C_{trough} ↓	—	[103]
Tenofovir*	NA	CL and V_d ↑, C_{ave}, C_{max}, AUC and C_{trough} ↓	C_{max}, $t_{1/2}$, AUC, C_{trough}	[104−106]
Saquinavir*	NA	C_{max} and AUC ↓	CL, C_{max}, $t_{1/2}$, AUC, C_{trough}	[107,108]
Raltegravir*	NA	CL and V_d ↑, C_{max} and AUC ↓	C_{max}, $t_{1/2}$, AUC, C_{trough}	[109,110]
Ritonavir	NA	CL and V_d ↑, C_{max}, C_{trough} and AUC ↓	$t_{1/2}$	[107]
Etravirine	B	CL ↓, AUC ↑	—	[111]
Oseltamivir	NA	—	CL, $t_{1/2}$, AUC	[112]
Cardiovascular drugs				
Atenolol	D	CL ↑	C_{max}, AUC, $t_{1/2}$	[113]
Clonidine	C	CL ↑	NA	[114]
Digoxin	C	CL ↑ and AUC ↓	C_{max}, $t_{1/2}$	[11]
Metildigoxin	NA	CL ↑	—	[115]
Furosemide	C; D (use for gestational hypertension)	CL and V_d ↑, C_{max} ↓	$t_{1/2}$	[116]
Labetalol*	C	CL and V_d ↑	CL, V_d	[117−119]
Metoprolol	C	CL ↑	—	[120]
Nifedipine	C	CL ↑, C_{max} and $t_{1/2}$ ↓	NA	[24]
Sotalol	B	CL ↑	V_d, $t_{1/2}$	[121]
Aspirin	C; D (high dose during late pregnancy)	C_{max} and AUC ↓	—	[122]
Pravastatin	X	CL ↑	—	[123]
Drugs for analgesia and anesthesia				
Ketorolac	NA	CL and V_d ↑	$t_{1/2}$	[124]
Morphine	C; D (high dose in labor)	CL ↑ and $t_{1/2}$ ↓	V_d	[26]
Paracetamol*	B	CL and V_d ↑, AUC, $t_{1/2}$ and C_{trough} ↓	AUC, $t_{1/2}$	[125,126]
Buprenorphin	C	C_{max} and AUC ↓	—	[127]
Methadone	C	CL ↑, AUC and C_{trough} ↓	—	[128]
Others				
Metformin	B	CL and V_d ↑	—	[36]

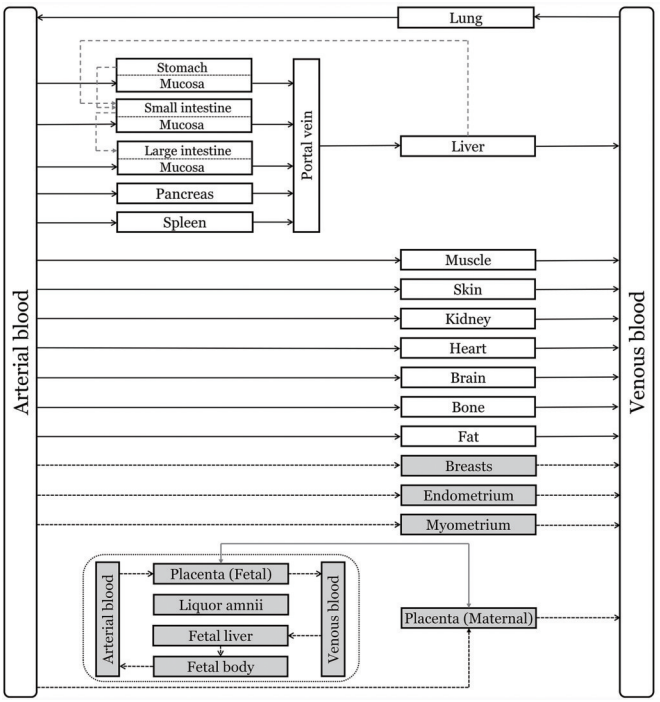

Figure 1 The 27-compartment physiological model of pregnant women. The gray portions are nine gestation-specific compartments

群体中的安全性较好。Dallmann等[8]考察了PBPK模型模拟三种主要经肾排泄的头孢类药物 (头孢唑啉, 头孢呋辛和头孢拉定) 孕期药动学的可靠性。通过对妊娠早中晚三个时期的药动学模拟, 所有预测的血浆浓度值均在观测值2倍误差范围内, 85%在1.25倍误差范围内。该研究建立的妊娠PBPK模型可以预测主要经肾清除的药物在孕妇体内的药动学。

3.3 非甾体抗炎药 Mian等[133]构建了对乙酰氨基酚及其多个代谢产物的妊娠PBPK模型, 这些产物包括经CYP2E1催化的毒性物质乙酰苯醌亚胺 (NAPQI), 葡萄糖醛酸化代谢物和磺酸化代谢物。模型发现与未怀孕的女性相比, 在妊娠期间对乙酰氨基酚血药浓度较低。孕早期原形转化为NAPQI的比例最高, 但缺少NAPQI的毒理学资料, 不能对剂量进行调整。研究者随后通过模型对对乙酰氨基酚的胎盘转运进行了考察[134]。孕妇静脉血中对乙酰氨基酚的暴露水平与胎儿静脉血中对乙酰氨基酚的暴露水平相当。胎儿清除率的预测显示, 转化为磺酸乙酰氨基酚和NAPQI的摩尔剂量中位数分别为0.8%和0.06%。预测脐带动脉血中对乙酰氨基酚的平均浓度为3.6 mg·L^{-1}, 这一浓度远低于导致胎儿动脉导管闭合的参考阈值 (24.47 mg·L^{-1})。

另一种非甾体抗炎药吲哚美辛在体内主要由CYP2C9和UGT2B7代谢。Alqahtani等[135]利用模型考察了孕中期的药物暴露情况。模型和临床数据均反映吲哚美辛在孕中期的清除率明显升高。同时, 作者建立了吲哚美辛浓度与前列腺素E_2代谢产物浓度的PK/PD模型。在妊娠期间, 常规的25 mg剂量不能产生预期的效果, 提示该药在妊娠期间需要调整剂量。

3.4 抗HIV药物 抗HIV药物用于孕妇以期能阻止HIV的母婴传播。Freriksen等[136]将妊娠PBPK建模方法与胎盘药物转移的在体数据相结合, 来模拟新型整合酶抑制剂度鲁特韦在母体和胎儿的暴露情况。模型对孕晚期药物脐带血浓度取得良好的拟合。模型预测50 mg每日一次给药方案下胎儿血药谷浓度高于90%病毒抑制浓度。Mendes等[37]利用模型研究了妊娠对替诺福韦、恩曲他滨和拉米夫定药动学的影响。PBPK模型准确预测了几种药物的主要药动学参数。模型揭示药物的肾小管分泌和肾小球滤过在怀孕期间都发生了改变, 肾清除率的变化与肾血浆流量的变化有关。Schalkwijk等[137]将地瑞那韦胎盘转移数据整合入妊娠PBPK模型, 以模拟和评估足月胎儿地瑞那韦暴露。他们使用人体外胎盘小叶模型来测定地瑞那韦的胎盘清除率。模拟结果显示在600/100 mg每日两次给药方案下, 胎儿群体的谷浓度达到或高于地瑞那韦的半数最大有效浓度 (0.55 mg·L^{-1})。孕妇口服地瑞那韦有助于预防HIV的母婴传播。Liu等[138]建立了恩曲他滨和阿昔洛韦的妊娠PBPK模型, 模型准确预测了临床报道数据。恩曲他滨和阿昔洛韦的母体血药浓度随孕期减小, 在孕晚期减小幅度最大, 但仍能维持有效治疗浓度。通过体外胎盘小叶灌注实验测定药物的胎盘转移, 并整合入模型, 模型预测的脐静脉浓度与观测数据一致。

3.5 阿片类药物 阿片类药物成瘾的治疗, 即脱毒疗法需使用较弱的阿片受体激动剂。丁丙诺啡已被美国FDA批准用于脱毒治疗, 但当前孕妇仍使用普通成人的推荐剂量。该药在体内经多种代谢酶清除, 包括CYP3A4、UGT1A1和UGT2B7。Zhang等[139]在健康成人中建立并验证的丁丙诺菲舌下PBPK模型的基础上, 通过添加胎儿和胎盘隔室以及妊娠生理参数的变化, 将模型外推至孕妇。模型预测的丁丙诺啡药时曲线与报道数据一致。与产后相比, 整个孕期丁丙诺啡暴露量较低, 且在妊娠晚期差异最显著。模型预测表明需要增大剂量或给药频率来维持妊娠期阿片类药物脱毒的疗效。美沙酮也用于阿片类药物成瘾的治疗, 该药在体内经CYP2B6、CYP3A4和CYP2C19等多种酶代谢, 同时约20%经肾脏排泄。Ke等[18]通过不同方式计算了妊娠期CYP2B6和CYP2C9活性的诱导, 和CYP2C19活性的抑制, 并纳入PBPK模型的计算中。该模型预测的单次和多次给药后美沙酮的PK参数与观测数据一致。

3.6 糖皮质激素 倍他米松和地塞米松是研究最广泛的产前激素, 在早产婴儿出生之前给药, 用来加速胎儿肺成熟。在临床试验中, 很少能获得对母体、胎儿和新生儿糖皮质激素PK的定量评估。Ke等[140]使用经验证的PBPK模型来模拟两种激素经不同途径给药 (静注、口服和肌注) 在女性妊娠期的药动学行为, 成功预测了妊娠状态对静脉注射地塞米松和倍他米松药动学的影响, 以及在妊娠期肌肉注射或口服倍他米松的相对生物利用度。结合真实世界证据, PBPK模型对于优化糖皮质激素给药方案十分有用。

3.7 其他 Dallmann等[141]通过PBPK模型考察了经多种途径代谢清除的药物的孕期药动学, 这些药物有咖啡因、咪达唑仑、硝苯地平、美托洛尔、昂丹司琼、格拉司琼、地西泮和甲硝唑。97%的预测平均血浆浓度在实际观测值2倍误差范围内, 63%在1.25倍误差范围内。所有药物的AUC预测误差在1.25倍以内。作者认为, 所提出基于妊娠生理的药动学模型, 可以通过整合妊娠对一种或多种细胞色素P450酶影响的先验知识, 定量预测这些酶代谢底物的药动学。Darakjian等[142]开发了咖啡因在妊娠女性中的PBPK-PD模型,

研究孕妇在怀孕期间的咖啡因摄入量 (高于或低于200 mg) 与血浆中咖啡因含量之间的关系, 以预测3个孕期的咖啡因血药浓度变化及与之关联的PD效应。咖啡因在孕期血药浓度的上升与CYP1A2活性减小有关。模型还预测, 胎儿胎盘隔室的咖啡因水平也因此升高。母体血液中咖啡因含量的增大导致磷酸二酯酶的抑制、环磷酸腺苷的升高和肾上腺素水平的升高, 这可能会增大妊娠失败的风险。

4 结论与展望

尽管许多临床使用的药物尚缺少妊娠期药动学和药效学信息, 但已有的研究证明妊娠期药动学的显著改变是广泛存在的。模型指导的给药方案设计在过去十数年中取得了长足进步, 其中PBPK模型在儿科剂量优化方面的应用已得到药品监管部门推荐。孕妇的生理状况比儿童更加复杂, 而相关报道仍显不足。随着妊娠生理变化相关基础知识的充实和PBPK技术方法的不断进步, PBPK模型能成为预测妊娠期药动学的有力工具, 并有望将研究结果应用于妊娠期药物治疗临床实践当中。在临床研究之前进行计算机模拟也有助于优化首次妊娠期人体PK研究的设计, 包括研究周期的优先顺序、样本大小和剂量选择。当前的妊娠PBPK模型还有待在模拟胎儿的药物暴露方面进行更多考察。为估计药物的胎盘转运, 需要来自模型、体外细胞、离体胎盘灌注或动物和人体内等多方面的数据, 而验证模型则需获得分娩时脐带血的药物浓度数据。另外, 孕妇-胎儿PBPK模型可以补充传统的临床前动物胚胎毒性研究, 在考虑物种生理生化参数的差异后, 确定能产生胚胎毒性暴露水平的药物剂量, 该模型在未来也有待开展更全面系统的研究。

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