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RESEARCH ARTICLE

Pregnancy-Associated Changes in Pharmacokinetics: A Systematic Review

Gali Pariente[1], Tom Leibson[1], Alexandra Carls[1], Thomasin Adams-Webber[2], Shinya Ito[1,3,4,5]*, Gideon Koren[6]

1 Division of Clinical Pharmacology and Toxicology, Hospital for Sick Children, Toronto, Ontario, Canada, **2** Hospital Library, Hospital for Sick Children, Toronto, Ontario, Canada, **3** Research Institute, Hospital for Sick Children, Toronto, Ontario, Canada, **4** Department of Paediatrics, University of Toronto, Toronto, Ontario, Canada, **5** Department of Pharmacology & Toxicology, University of Toronto, Toronto, Ontario, Canada, **6** Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, Ontario, Canada

* Shinya.ito@sickkids.ca

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Abbreviations: AUC, area under the curve; C/D ratio, concentration-to-dose ratio; DHA, dihydroartemisinin; OTC, over-the-counter; PK, pharmacokinetics; UGT, uridine 5′-diphospho-glucuronosyltransferase.

Abstract

Background

Women are commonly prescribed a variety of medications during pregnancy. As most organ systems are affected by the substantial anatomical and physiological changes that occur during pregnancy, it is expected that pharmacokinetics (PK) (absorption, distribution, metabolism, and excretion of drugs) would also be affected in ways that may necessitate changes in dosing schedules. The objective of this study was to systematically identify existing clinically relevant evidence on PK changes during pregnancy.

Methods and Findings

Systematic searches were conducted in MEDLINE (Ovid), Embase (Ovid), Cochrane Central Register of Controlled Trials (Ovid), and Web of Science (Thomson Reuters), from database inception to August 31, 2015. An update of the search from September 1, 2015, to May 20, 2016, was performed, and relevant data were added to the present review. No language or date restrictions were applied. All publications of clinical PK studies involving a group of pregnant women with a comparison to nonpregnant participants or nonpregnant population data were eligible to be included in this review. A total of 198 studies involving 121 different medications fulfilled the inclusion criteria. In these studies, commonly investigated drug classes included antiretrovirals (54 studies), antiepileptic drugs (27 studies), antibiotics (23 studies), antimalarial drugs (22 studies), and cardiovascular drugs (17 studies). Overall, pregnancy-associated changes in PK parameters were often observed as consistent findings among many studies, particularly enhanced drug elimination and decreased exposure to total drugs (bound and unbound to plasma proteins) at a given dose. However, associated alterations in clinical responses and outcomes, or lack thereof, remain largely unknown.

Conclusion

This systematic review of pregnancy-associated PK changes identifies a significant gap between the accumulating knowledge of PK changes in pregnant women and our

understanding of their clinical impact for both mother and fetus. It is essential for clinicians to be aware of these unique pregnancy-related changes in PK, and to critically examine their clinical implications.

Author Summary

Why Was This Study Done

- Pregnant women take a variety of medications, including prescription and over-the-counter medications, with an estimated prevalence of greater than 90%.
- Some studies have demonstrated significant changes in pharmacokinetics (absorption, distribution, metabolism, and excretion of drugs) during pregnancy and resultant clinical impact, but others have not, which calls for critical assessment of the evidence.

What Did the Researchers Do and Find?

- We conducted a systematic review, and identified 198 studies, involving 121 different medications, that fulfilled the inclusion criteria.
- Decrease in drug exposure mainly due to increased elimination was frequently observed across the drug classes.
- There is a lack of studies describing changes in clinical outcomes, or the lack thereof, associated with altered pharmacokinetics during pregnancy.

What Do These Findings Mean?

- A significant gap exists between our knowledge of pharmacokinetic changes in pregnancy and their clinical consequences.
- It is essential for clinicians to be aware of these pregnancy-related changes in pharmacokinetics, and to critically examine their potential clinical implications.

Introduction

Women frequently take a variety of medications during pregnancy, including prescription, over-the-counter (OTC), and herbal agents [1,2]. During the last three decades the average number of medications (prescription and nonprescription) used per woman in North America during the first trimester increased by 60% from 1.6 to 2.6 [3]. More recently, from 2006 to 2008, over 80% of women reported using at least one medication during the first trimester, and over 90% reported using at least one medication at any point during their pregnancy [3]. Other studies have demonstrated increased rates of use of various OTC medications in the first, second, or third trimester of pregnancy compared to the prepregnancy period [4]. While some

studies have found that the proportion of women receiving at least one prescription medicine increases from the first to third trimester of pregnancy [5,6], others have found that rates of prescription drug use are highest in the first trimester of pregnancy [1,7]. The most common medications used in pregnancy are nonprescription or OTC medications [4]. A longitudinal study aimed at identifying the medications that are most often consumed during pregnancy demonstrated that 95.8% of participants took prescription medications, 92.6% self-medicated with OTC medications, and 45.2% used herbal medications [2].

Most organ systems are affected by substantial anatomical and physiological changes during pregnancy. Such pregnancy-related changes are observed in decreased gastrointestinal motility and increased gastric pH (impacting absorption), increased total body water and plasma volume and decreased concentrations of drug-binding proteins (affecting the apparent volume of distribution and, in some cases, clearance rates), increased glomerular filtration rate (increasing renal clearance), and altered activity of drug-metabolizing enzymes in the liver (affecting hepatic clearance). Overall, these changes in physiological indices take place progressively during gestation (reviewed in [8] and [9]). The increases in cardiac output, total body water, fat compartment, and glomerular filtration rate, together with the decrease in plasma albumin concentration and altered activity of drug-metabolizing enzymes, are all reported to peak during the third trimester (reviewed in [8] and [10]). Table 1 presents typical pregnancy-related changes in organ function leading to altered pharmacokinetics (PK) [10–16]. Changes during pregnancy in drug metabolism by cytochrome P450 isoenzymes (i.e., CYP3A4, CYP2D6, CYP2C9, CYP1A2, and CYP2C19) and by uridine 5′-diphospho-glucuronosyltransferase (UGT) isoenzymes (i.e., UGT1A4 and UGT2B7) have also been demonstrated (Table 2) [10,17–20].

For some drug classes, a large number of PK clinical trials during pregnancy are available in the literature [29–34]. A recent review noted that, since 2008, about a third of these trials investigated drugs used in the treatment of acute labor and delivery issues, another third investigated drugs used in infectious disease treatment during pregnancy, and the remaining third investigated drugs used for various antepartum indications [35]. However, for the large majority of drugs used during pregnancy, there is little or no information available regarding PK changes or dosage requirements during pregnancy [35]. Moreover, it is often unclear if observed PK changes lead to alterations in drug efficacy and/or adverse effect profiles. Given the complexity of the field, the lack of clear understanding of the clinical significance of PK changes, and

Table 1. Physiological changes during pregnancy: effects on drug disposition [10–16].

Parameter	Consequences
Delayed gastric emptying and increased gastric pH	Altered drug bioavailability and delayed time to peak levels after oral administration
Increased cardiac output	Increased hepatic blood flow; increased elimination for some drugs
Increased total body water, extracellular fluid	Altered drug disposition; increased V_d for hydrophilic drugs
Increased fat compartment	Decreased elimination of lipid-soluble drugs; increased V_d for hydrophobic drugs
Increased renal blood flow and glomerular filtration rate	Increased renal clearance
Decreased plasma albumin concentration	Increased free fraction of drug
Altered CYP450 and UGT activity	Altered oral bioavailability and hepatic elimination

UGT, uridine diphosphate glucuronosyltransferase; V_d, volume of distribution.

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Table 2. Reported effects of pregnancy on hepatic enzyme activity.

Enzyme	Effect of Pregnancy [Reference]	Substrate Examples
CYP1A2	Decreased [18]	Paracetamol, propranolol, theophylline
CYP2B6	Increased [21]	Methadone, efavirenz, sertraline
CYP2C8	Increased [22]	Verapamil, fluvastatin
CYP2C9	Increased [23,24]	Glyburide, phenytoin
CYP2C19	Decreased [23,25]	Proguanil, indomethacin, citalopram, escitalopram
CYP2D6	Increased [17]	Alprenolol, codeine, fluoxetine
CYP2E1	Increased [26]	Disulfiram, theophylline
CYP3A4	Increased [27]	Darunavir, citalopram
Uridine 5′-diphospho-glucuronosyltransferases	Increased [28]	Lamotrigine, morphine

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renewed recognition of the need to rationalize drug therapy for pregnant and lactating women, it is imperative to systematically examine existing data on PK changes in pregnancy and their potential clinical impact.

The objective of this study was to systematically identify all existing evidence of PK changes during pregnancy in the context of clinical significance. We hypothesized that known physiological changes occurring during pregnancy and associated PK alterations could consequently be translated into changes in dosing guidelines.

Methods

This research involved a structured review of the literature, according to the PRISMA guidelines [36] (S1 Checklist).

Search Strategy

Searches were conducted in MEDLINE (Ovid), Embase (Ovid), Cochrane Central Register of Controlled Trials (Ovid), and Web of Science (Thomson Reuters) from database inception to August 31, 2015 (S1 Table). An update of the search from September 1, 2015, to May 20, 2016, was performed, and relevant data were retrieved and added to the review (S2 Table). Text words and, where applicable, database subject heading fields (e.g., MeSH) were used for the following concepts: pregnancy AND pharmacokinetics OR dosing OR clearance OR distribution OR absorption OR metabolism OR excretion OR Cmax OR Tmax OR Ctrough OR AUC OR Vd OR t1/2 OR protein binding AND specific study types (randomized controlled trial, non-randomized controlled clinical trial, cohort study, case–control study, or case series). Truncation symbols were used with the text words, when appropriate, to capture variations in spelling and word endings. Subsequently, we reviewed the identified studies and examined their references to identify further potential articles. Information available from relevant conferences was also reviewed. No publication date, language, or location restrictions were applied.

Study Selection

In order to locate all published literature, we established a set of criteria to define types of studies to be reviewed. Inclusion criteria were as follows: (1) the study reported dosing data or at least one PK parameter of interest in pregnant women; (2) a comparison of the dosing data or PK parameter between pregnant and nonpregnant women was done; and (3) the data are described in the form of a peer-reviewed randomized controlled trial, non-randomized controlled clinical trial, cohort study, case–control study, or case series. The review did not cover animal studies, case reports, or studies containing no original research or data. Retrieved

articles were inspected by two independent reviewers (G. P. and T. L.) to determine whether they met the inclusion criteria. In cases where the eligibility of the study was unclear, it was reviewed by a third independent reviewer (G. K.). The full texts were retrieved and read in full.

Data Extraction

The data extractors (G. P. and T. L.) reviewed each of the included studies independently and extracted data according to the predetermined guidelines, using a predesigned data extraction form. When needed, authors of the included studies were contacted for missing data; however, none of the authors who were contacted for more information responded. Data from studies presented in multiple publications were identified to avoid duplications and were reported as a single study, with all other relevant publications listed.

Data Presentation and Analysis

Results of the literature search. The results from each step of the review process are documented in a PRISMA flow diagram (Fig 1), with an overall summary of the number and types of articles included in the review.

When more than one study reported the same PK parameter(s) for the same drug, these parameters were examined for consistency in the change direction (i.e., decrease, increase, or no change). When study data were presented by trimester, the PK parameters obtained during the third trimester were selected for this study because the majority of the pregnancy-associated physiological changes peak during the third trimester.

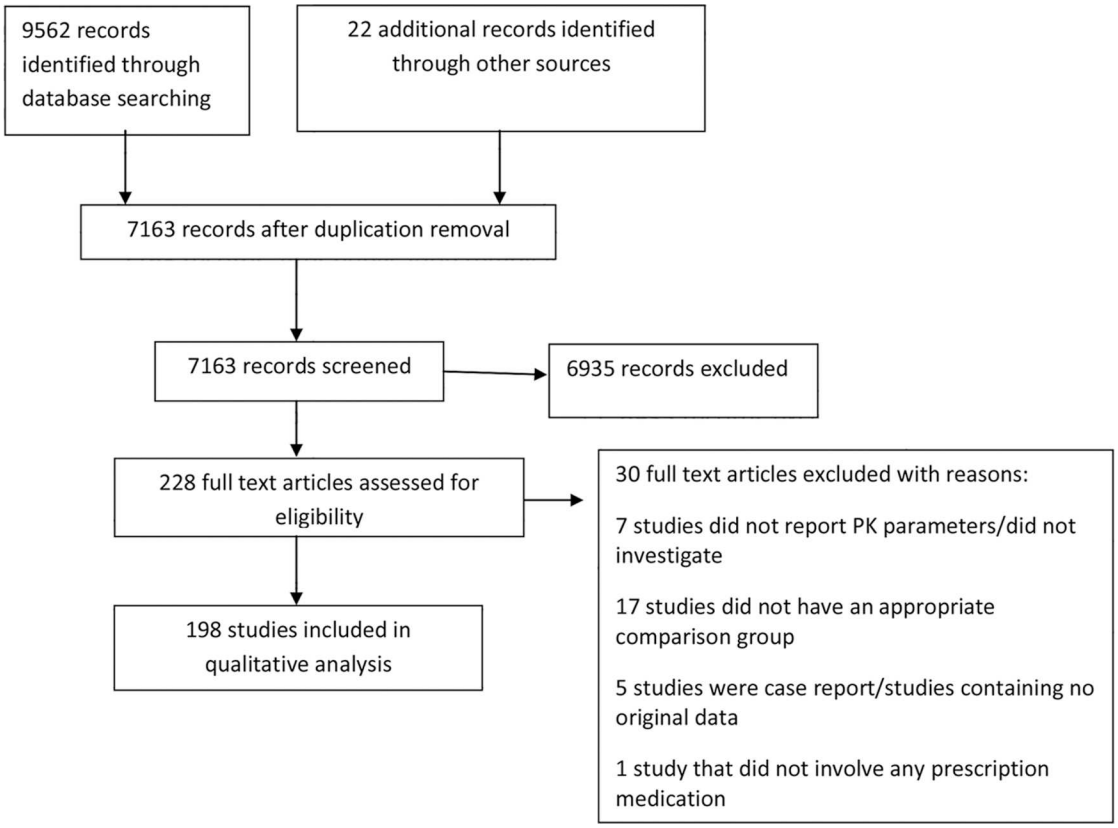

Fig 1. Flow diagram of numbers of studies screened, assessed for eligibility, and included in the review. PK, pharmacokinetics.

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Drugs were divided into two major categories according to between-study agreement of directions of statistically significant changes in PK parameters. If statistically significant pregnancy-associated changes in PK parameters were in the same direction (e.g., increase in clearance and decrease in volume of distribution) among the studies for all reported PK parameters, we categorized the drug as "consistent." On the other hand, a drug was categorized as "inconsistent" if at least one study reported a statistically significant change in a PK parameter in the opposite direction (e.g., increased Cl in one study and decreased Cl in the other). The potential source of inconsistency is speculated on and addressed in the Discussion. Note that the definition of the categories described above is based on statistically significant changes of PK parameters, but statistically non-significant changes are also presented, for completeness. In addition, if only one study showed a statistically significant PK parameter change for a drug, the drug was included in the "consistent" category for simplicity of the data presentation, even though the PK parameters were reported in only one study.

Quality assessment. The quality of each accepted article was assessed using the ClinPK checklist [37] for assessing methodological quality in clinical PK studies (Table 3).

No discrepancies exist between the original protocol and the final data analyses.

Results

Literature Retrieval

The search strategy for the comprehensive systematic review retrieved 9,562 articles, and after removing duplicates, the first screen on title and abstract was performed on 7,163 articles (Fig 1). For 6,935 of these, the title or abstract clearly indicated that the topic of the article was not relevant to the review question or did not satisfy one of the inclusion criteria. The remaining 228 articles were screened using the full text, applying the full set of eligibility criteria. After applying the eligibility criteria, 202 articles containing comparisons of PK parameters of different drugs between pregnant and nonpregnant women were eligible for inclusion. Twenty-six studies were excluded because they didn't report PK parameters, didn't include a comparison group, or were either review papers or case reports (S3 Table). Following review, four further articles were excluded because they duplicated the same outcome domain, in the same cohort, as another article. The remaining 198 articles were included in the data extraction for the comprehensive systematic review. Twenty-two additional articles were identified using a monthly update search between September 1, 2015, and May 20, 2016. Hence, this review article summarizes the results of a total of 198 studies, involving 121 different medications, reporting comparisons of different PK parameters and dosing data between pregnant and nonpregnant cohorts.

Reviewed studies were found to vary widely in both design and quality (S4 Table). There were some differences in the stages of pregnancy in which the women were investigated; while most of the studies provided third trimester results, others reported results from both the second and the third trimesters together [38–42] or separately [43–46], and a few reported results from all trimesters together [47] or separately [48]. Two studies reported only first trimester results [49,50].

Studies Comparing Pregnant and Nonpregnant Women for Each Drug Class

Certain drug classes were far more commonly investigated during pregnancy than others (Fig 2). Approximately one-half of the studies (48%) addressed medications given chronically during pregnancy. Of the studies of chronic medications, 54 studies focused on drugs for HIV

Table 3. ClinPK checklist for assessing methodological quality in clinical pharmacokinetic studies [37].

Section	Checklist Item Number	Checklist Item
Title/abstract	1	The title identifies the drug(s) and patient population(s) studied.
	2	The abstract minimally includes the name of the drug(s) studied, the route of administration, the population in whom it was studied, and the results of the primary objective and major clinical pharmacokinetic findings.
Background	3	Pharmacokinetic data (i.e., absorption, distribution, metabolism, excretion) that [are] known and relevant to the drugs being studied [are] described.
	4	An explanation of the study rationale is provided.
	5	Specific objectives or hypotheses [are] provided.
Methods	6	Eligibility criteria of study participants are described.
	7	Co-administration (or lack thereof) of study drug(s) with other potentially interacting drugs or food within this study is described.
	8	Drug preparation and administration characteristics including dose, route, formulation, infusion duration (if applicable), and frequency are described.
	9	Body fluid or tissue sampling (timing, frequency, and storage) for quantitative drug measurement is described.
	10	Validation of quantitative bioanalytical methods used in the study [is] referenced or described if applicable.
	11	Pharmacokinetic modeling methods and software used are described, including assumptions made regarding the number of compartments and order of kinetics (zero, first, or mixed order).
	12	For population pharmacokinetic studies, covariates incorporated into pharmacokinetic models are identified and described.
	13	Formulas for calculated variables (such as creatinine clearance, body surface area, AUC, and adjusted body weight) are provided or referenced.
	14	The specific body weight used in drug dosing and pharmacokinetic calculations [is] reported (i.e., ideal body weight versus actual body weight versus adjusted body weight).
	15	Statistical methods including software used are described.
Results	16	Study withdrawals or subjects lost to follow-up (or lack thereof) are reported.
	17	Quantification of missing or excluded data is provided if applicable.
	18	All relevant variables that may explain inter- and intra-patient pharmacokinetic variability (including: age, sex, end-organ function, ethnicity, weight or BMI, health status or severity of illness, and pertinent co-morbidities) are provided with appropriate measures of variance.
	19	Results of pharmacokinetic analyses are reported with appropriate measures of precision (such as range or 95% confidence intervals).
	20	Studies in patients receiving extracorporeal drug removal (i.e., dialysis) should report the mode of drug removal, type of filters used, duration of therapy, and relevant flow rates.
	21	In studies of drug bioavailability comparing two formulations of the same drug, F (bioavailability), AUC, Cmax (maximal concentration), and Tmax (time to maximal concentration) should be reported.
Discussion/ conclusion	22	Study limitations describing potential sources of bias and imprecision where relevant should be described.
	23	The relevance of study findings (applicability, external validity) is described.
Other information	24	Funding sources and conflicts of interest for the authors are disclosed.

All the items presented in the table correspond to the original checklist as published in [37].

AUC, area under the curve; BMI, body mass index.

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treatment and vertical transmission prevention, 27 studies focused on antiepileptic drugs, 17 studies focused on drugs related to cardiovascular disorders, and nine studies focused on drugs for endocrine disorders. An additional eight studies investigated antidepressants and anxiolytic drugs, five other studies focused on drugs involved in addiction management, and two studies described drugs treating immunological conditions. In comparison, 84 studies addressed drugs used in the treatment of acute issues during pregnancy; among them, 23 studies addressed antibiotics, 22 studies addressed antimalarial medications, 13 studies addressed analgesics or anesthetic drugs, and eight studies addressed antithrombotic drugs in pregnancy. Fifty-one studies

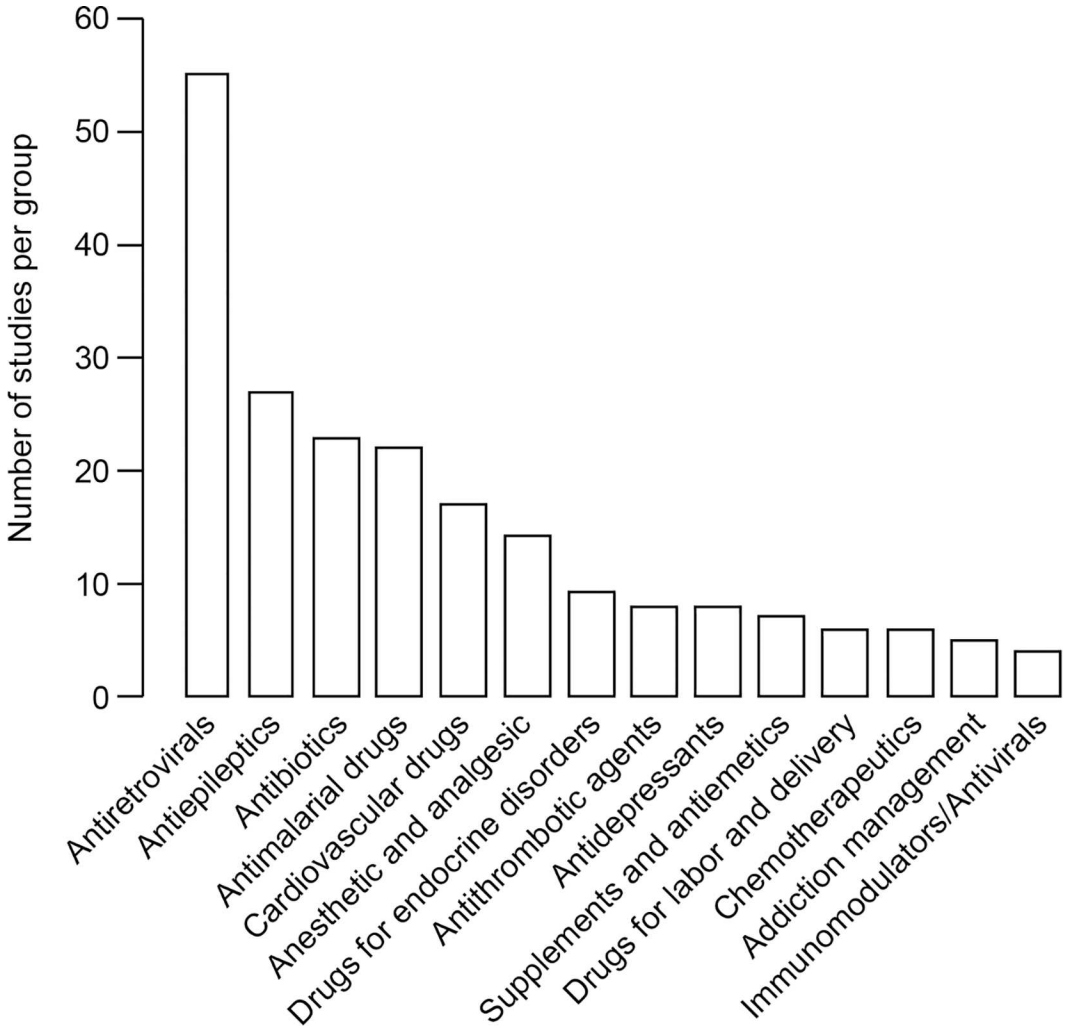

Fig 2. Number of studies comparing pregnant and nonpregnant women for each drug class.

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investigated more than one drug. Among the antiretroviral class, all studies but one presented women living with HIV infection who were treated with more than one antiretroviral medication. Eleven of 22 studies investigating antimalarial drugs described more than one drug given to the same patient population. Four of 27 studies investigating antiepileptic drugs described more than one drug given to the same patient population. Other drug classes that reported results of pregnant women taking more than one drug included antibiotics (four studies), anesthesia and analgesia drugs (one study), and antiemetics (one study).

Reported Pharmacokinetics Parameters

PK parameters of interest as defined by our search terms were the following: elimination half-life ($t_{1/2}$), clearance (Cl), C_{max}, C_{trough}, concentration-to-dose ratio (C/D ratio), area under the curve (AUC), volume of distribution (V_d), and protein binding (i.e., free fraction). The majority of the studies reported on various combinations of some of these PK parameters of interest (Table 4). The most frequently reported PK parameter was Cl, followed by AUC, $t_{1/2}$, and C_{max} with 116, 103, 88, and 87 counts, respectively. In most of the studies that focused on the free fraction of a drug in plasma, the free fraction was the only PK parameter reported in the study.

Table 4. Pharmacokinetics parameters—data count.

Category	PK Parameter	Number of Studies
Dose independent	$t_{1/2}$ (elimination half-life)	88
	Cl (clearance)	116
Dose dependent	C_{trough}	48
	V_d (volume of distribution)	62
	T_{max}	63
	C_{max}	87
	AUC (area under the curve)	103
	Free fraction in plasma	15

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While Cl and AUC were the most frequently reported parameters, both parameters were reported for only 46% of the drugs. Whereas more than half of the drugs (53%) were described with both the Cl and the $t_{1/2}$, only 16% of the drugs included C_{trough}, C_{max}, and AUC. The latter group mostly consisted of antiretroviral drugs. C_{max} and AUC were described together for 30% of the drugs.

Pharmacokinetics Parameters That Are Vital for Dosing Decision Support in Pregnancy

We clustered the different PK parameters into three groups. (1) Distribution parameters are V_d and percent of free fraction. V_d defines how widely the drug is spread in the body. Larger V_d causes lower peak plasma concentration (C_{max}) and also longer elimination half-life. Percent free fraction represents the fraction (percent) of the drug in plasma that is unbound to plasma proteins and, therefore, likely to be pharmacologically active. (2) Exposure parameters are C_{max}, C_{trough}, AUC, C/D ratio. These represent indices of plasma drug concentrations. C_{max} and C_{trough} are the highest and lowest levels within a dosing interval, respectively. AUC is literally the area bounded by the drug concentration–time curve and the x-axis, equivalent to an average drug concentration over time. C/D ratio is the dose-standardized drug concentration in plasma or serum at a given time. By and large, these parameters signify drug exposure levels at a given time point or on average, thereby potentially serving as a surrogate for drug effects. (3) Elimination parameters are $t_{1/2}$ and clearance. Half-life is related to the velocity of a drug's disappearance from plasma/serum. Clearance is an index of drug elimination capacity: higher clearance results in a smaller AUC and a shorter elimination half-life, reducing drug exposure levels.

Tables 5–18 provide information regarding changes in PK parameters (weight-standardized values, if available) during pregnancy compared to the nonpregnant state, assorted by drug classes and the data agreement definitions provided above. In these tables, non-significant results are shown together with statistically significant results (in bold). When a certain PK parameter was reported by several studies, the median value and the range in parentheses are provided. The quality column represents the quality score that was assigned to the study, according to the ClinPK Statement checklist. If the drug was investigated in more than one study, the quality column presents the average quality score of all the studies. Among the frequently investigated drug classes (antibiotics, antidepressants, antiepileptics, cardiovascular drugs, antiretrovirals, and antimalarials), studies have demonstrated enhanced elimination together with a decrease in exposure in pregnancy, indicating decreased availability of the drugs in pregnant women compared to nonpregnant women so far as total drug levels (bound plus unbound) are concerned.

Table 5. Antibiotics: consistent/single studies of pregnancy-associated pharmacokinetic changes (percent calculated as pregnant/nonpregnant values).

Drug [Reference]	Number of Studies	Total Number of Women (Nonpregnant/ Pregnant)	Average Quality (24 Items)	Distribution Parameters	Exposure Parameters	Elimination Parameters	Trimester
Amoxicillin [43]	1	16/16	22	NR	NR	**Cl 140%, $t_{1/2}$ 81%**	3rd
Azithromycin [47,51]	2	54/84	19.5	**V_d 121%**[&]	AUC 90%[&]	$t_{1/2}$ 101%[&]	1st–3rd
Cefatrizine [52]	1	20/20	19	NR	**C_{max} 55%, AUC 57%**	**$t_{1/2}$ 163%**	2nd
Cefazolin [39,53,54]	3	10[$]/54	18.6	V_d 80% (72%–89%)[&], **free fraction 131%**[&]	AUC 68%[&]	Cl 102% (65%–140%)[&], **$t_{1/2}$ 65%**[&], $t_{1/2}$ 131%[&]	2nd–3rd
Cefoperazone [55]	1	9/11	13	**Free fraction 208%**	NR	NR	3rd
Cefradine [54]	1	12/12	19	V_d 113%	**AUC 62%**	**Cl 154%, $t_{1/2}$ 73%**	1st–3rd
Ceftazidime [56]	1	12/12	16	NR	NR	**Cl 165%**	3rd
Cefuroxime [57]	1	7/7	13	V_d 109%	**AUC 69%**	**Cl 142%, $t_{1/2}$ 75%**	1st–3rd
Cloxacillin [48,58]	2	14/33	13.5	**Free fraction 154% (146%–162%)**	NR	NR	3rd
Flucloxacillin [58]	1	7/22	11	**Free fraction 148%**	NR	NR	3rd
Imipenem [59]	1	6/7	15	**V_d 249%**	**C_{max} 34%, AUC 41%**	**Cl 287%,** $t_{1/2}$ 87%	3rd
Mecillinam [60]	1	6/10	17	**V_d 224%**	C_{max} 85%, AUC 85%	Cl 103%, **$t_{1/2}$ 142%**	3rd
Moxifloxacin [61]	1	9/6	11	**V_d 329%**	**C_{max} 31%, AUC 21%**	**$t_{1/2}$ 63%**	3rd
Penicillin V [62]	1	6/6	16	NR	C_{max} 96%, **AUC 60%**	Cl 118%, **$t_{1/2}$ 30%**	3rd
Piperacillin [63–65]	3	11/18	12.3	**V_d 161%,** V_d 145% (136%–155%)	**C_{max} 50%**[&], C_{max} 57%[&], **AUC 61%**[&], AUC 110%[&]	**Cl 284%,** Cl 130% (96%–165%), $t_{1/2}$ 86% (70%–135%)	3rd
Trimethoprim [66]	1	8/10	11	**V_d 407%**	NR	**Cl 346%,** $t_{1/2}$ 100%	2nd–3rd
Tazobactam [64]	1	6/5	13	**V_d 150%**	C_{max} 75%, AUC 106%	**$t_{1/2}$ 156%**	3rd

Significant results are marked in bold.

[&]Parameter not reported in all studies.

[$]Comparison group in one study is published data.

NR, not reported.

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Table 19 shows drugs for which all the studies (36) reported no statistically significant PK differences between pregnant and nonpregnant women. Most of the drugs presented in Table 19 were only investigated in one study, while sertraline, propranolol, quinine folic acid and vitamin D3 were each presented in two publications. For sertraline, statistically non-significant decreases in the exposure parameters were reported [70,217]. In the case of propranolol, mean elimination half-life in pregnancy was shorter in both studies, but the exposure parameter (AUC) changes were not consistent; non-significant increase in the AUC [218] versus non-significant decrease in AUC [219]. Consistent but non-significant increase in Cl was reported for quinine [189,220–222]. Plasma folate concentrations showed no statistically significant changes [221,222], but conflicting change directions were seen in the mean values, depending on the dose [222]. Similarly, vitamin D3 showed conflicting change directions in exposure parameters, which were statistically non-significant [223,224].

Table 6. Antibiotics: inconsistent studies of pregnancy-associated pharmacokinetic changes (percent calculated as pregnant/non-pregnant values).

Drug [Reference]	Number of Studies	Total Number of Women (Nonpregnant/ Pregnant)	Average Quality	Distribution Parameters	Exposure Parameters	Elimination Parameters	Potential Sources for Inconsistency	Trimester
Ampicillin [67,68]	2	32/35	11.5	V_d 96%[&]	C_{trough} 108%[&], **AUC 79%**[&]	**Cl 122%**[&], **inconsistent data for $t_{1/2}$**[#]	Comparison group selection	3rd

Significant results are marked in bold.

[&]Parameter reported in one study.

[#]Numbers not provided.

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Sixty of the total 218 PK observations (27.5%) reported changes in either the elimination parameters or exposure parameters. Seven PK observations (3.2%) did not report either exposure or elimination parameters. Among the 116 PK observations reporting changes in both elimination and exposure, 79.3% (92) demonstrated increased elimination together with decreased exposure in pregnant women compared to the nonpregnant population.

Discussion

In this first systematic review, to our knowledge, of pregnancy-associated PK changes, we were able to obtain a clear overview of the landscape of the field. Now that trends of pregnancy PK change have been mapped in major drug categories and responsible metabolism or transport pathways, existing knowledge gaps critical for patient management can be addressed by the combined efforts of regulatory agencies, academia, and industry. As many women presently delay childbearing to an older age [243] and the frequency of medical conditions seen during pregnancy among older women is dramatically greater than that of younger women [244], the

Table 7. Antidepressant/anxiolytic drugs: consistent/single studies of pregnancy associated pharmacokinetic changes (percent calculated as pregnant/nonpregnant values).

Drug [Reference]	Number of Studies	Total Number of Women (Nonpregnant/Pregnant)	Average Quality	Distribution Parameters	Exposure Parameters	Elimination Parameters	Trimester
Citalopram [69,70]	2	16/16	15	NR	**C_{trough} 59%**[&]	NR	3rd
Fluoxetine [71]	1	11/8	16	NR	**C_{trough} 39%**	NR	3rd
Paroxetine [72]	1	12/12	11	NR	**Lower concentrations**[β]	NR	3rd
Venlafaxine [73])	1	7/7	16	NR	**Concentrations 87%**	NR	3rd
Clorazepate [74]	1	7/7	17	NR	**C_{max} 51%**	**Cl 209%,** $t_{1/2}$ 50%	3rd
Midazolam [75,76]	2	23/21	18	**V_d 112%[&], free fraction 163%**[&]	**C_{max} 68%[&], AUC 53%**[&], AUC 62%[&]	**Cl 184% (159%–210%),** $t_{1/2}$ 87% (79%–96%)	3rd

Significant results are marked in bold.

[&]Parameter not reported in all studies.

[β]Numbers were not provided.

NR, not reported.

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Table 8. Antiepileptic drugs: consistent/single studies of pregnancy associated pharmacokinetic changes (percent calculated as pregnant/non-pregnant values).

Drug Reference]	Number of Studies	Total Number of Women (Nonpregnant/ Pregnant)	Average Quality (24 Items)	Distribution Parameters	Exposure Parameters	Elimination Parameters	Trimester
Carbamazepine [77–85]	9	128/130	11.7	**Free fraction 116% (113%–119%)[&], free** fraction 101% (95%–107%)[&]	**Total concentration 79%[&]**	**Cl 127% (116%–140%)[&]**, Cl 110% (108%–112%)[&]	1st–3rd
Lamotrigine [83,86–93]	9	208/241	15.7	NR	**C/D ratio 34%[&]**	**Cl 212% (185%–240%)[&]**	3rd
Levetiracetam [16,83,94,95]	4	47/47	14	NR	**C/D ratio 45% (39%–52%)[&]**	**Cl 269% (197%–342%)[&]**	3rd
Oxcarbazepine [83,96–98]	4	28/28	13.7	NR	**Lower concentration and C/D ratio[&,β]**	Cl 237%[&]	3rd
Phenytoin [81,82,84,99]	4	82/78	12.5	**Free fraction 126%[&]**	**Total concentration 67% (51%–84%)[&]**	**Cl 145% (130%–160%)[&]**	1st–3rd
Phenobarbital [81]	1	11/11	9	**Free fraction 112%**	**Total concentration 53%**	**Cl 125%**	3rd
Topiramate [83,100,101]	3	21/25	16	NR	**C/D ratio 60% (57%–64%)[&]**	Cl 110%[&]	3rd

Significant results are marked in bold.

[&]Parameter not reported in all studies.

[β]Numbers were not provided.

NR, not reported.

doi:10.1371/journal.pmed.1002160.t008

results of this review raise the question of whether there are sufficient data to manage these health issues appropriately during pregnancy.

Recently, the most commonly used medications in the first trimester were reported [245]. Results from 5,381 mothers identified 54 different medications used in the first trimester by at least 0.5% of pregnant women. The most commonly used prescription medications reported fell into the categories of antibiotics, analgesics, antiemetics, antidiabetic medications, and antidepressants. Among those 54 most commonly used medications, only a few had adequate data available to assess PK characteristics and dosing recommendation during pregnancy, as demonstrated by our present study results.

Table 9. Drugs for analgesia and anesthesia: consistent/single studies of pregnancy-associated pharmacokinetic changes (percent calculated as pregnant/nonpregnant values).

Drug [Reference]	Number of Studies	Total Number of Women (Nonpregnant/ Pregnant)	Average Quality (24 Items)	Distribution Parameters	Exposure Parameters	Elimination Parameters	Trimester
Ketorolac [102]	1	8/8	16	**V_d 134%**	NR	**Cl 150%,** $t_{1/2}$ 108%	3rd
Morphine [103]	1	6/8	19	V_d 92%	**AUC 96%**	**Cl 169%, $t_{1/2}$51%**	3rd
Paracetamol [49,102,104–107]	6	52/85	18.1	**V_d 182%[&]**	**C_{trough} 56%[&]**, C_{max} 87% (42%–96%)[&], **AUC 72%[&]**, AUC 83%[&]	**Cl 142% (132%–196%), $t_{1/2}$ 80%[&]**, $t_{1/2}$ 95% (72%–119%[&]	1st + 3rd

Significant results are marked in bold.

[&]Parameter not reported in all studies.

NR, not reported.

doi:10.1371/journal.pmed.1002160.t009

Table 10. Drugs for analgesia and anesthesia: inconsistent studies of pregnancy-associated pharmacokinetic changes (percent calculated as pregnant/nonpregnant values).

Drug [Reference]	Number of Studies	Total Number of Women (Nonpregnant/ Pregnant)	Average Quality	Distribution Parameters	Exposure Parameters	Elimination Parameters	Potential Sources for Inconsistency	Trimester
Propofol [108–110]	3	22/26	15	V_d 88% (79%–98%)[&]	C_{max} 141%)[&]	**Inconsistent data for Cl**[&,#], $t_{1/2}$ 80.5% (80%–81%)[&]	Different sampling period	3rd

Significant results are marked in bold.

[&]Parameter not reported in all studies

[#]Number not provided.

doi:10.1371/journal.pmed.1002160.t010

Although our study strived to identify all available studies describing PK changes occurring in pregnancy, the total number of these studies was relatively small. Widespread exclusion of pregnant women from clinical studies is most probably the major reason for this limitation.

Changes such as increased clearance, reduced half-life, and reduced AUC in pregnancy have been described for many drugs. These PK alterations generally lead to lower drug concentrations in plasma, decreasing maternal target exposure to drug molecules. However, whether these PK changes compromise efficacy is not necessarily certain. Indeed, the total (unbound plus bound fractions) serum concentration of a drug does not necessarily reflect its activity, as lowered plasma albumin concentration during pregnancy may increase free "active" drug concentrations, depending on the PK characteristics of the drug. Moreover, the impact of maternal dose modifications on fetal exposure requires careful planning.

Published data were inconsistent for several medications, preventing this review from defining a certain direction in PK changes. These conflicting results were seen among the antimalarial drugs (pyrimethamine [199,200], sulfadoxine [199,200], and dihydroartemisinin (DHA) [192–194,197,198]), antithrombotic drugs (unfractionated heparin [113,114] and low-molecular-weight heparin [46,114–117]), and other drugs (ampicillin [67,68] and doxorubicin [205,216]). We will discuss these drugs in detail in the following section. Also, we confirmed that the current understanding of pregnancy-associated decrease in CYP1A2 and CYP2C19 activities is not based on large studies. These findings require further validation before making clinical recommendations.

For patients who are indicated to undergo routine therapeutic drug monitoring for clinical decision making and dose titration, pregnancy may be a challenging period in which serum drug levels may decrease below the target value despite adequate adherence by patients to their regimen. As we discussed above, decrease in drug exposure levels (e.g., reduction in serum

Table 11. Antithrombotic drugs: consistent/single studies of pregnancy-associated pharmacokinetic changes (percent calculated as pregnant/ nonpregnant values).

Drug [Reference]	Number of Studies	Total Number of Women (Nonpregnant/Pregnant)	Average Quality (24 Items)	Distribution Parameters	Exposure Parameters	Elimination Parameters	Trimester
Antipyrine [111]	1	6/4	13	NR	NR	**Cl 242%, $t_{1/2}$ 44%**	3rd
Aspirin [112]	1	11/10	18	NR	**C_{max} 68%,** AUC 76%	NR	3rd

Significant results are marked in bold.

NR, not reported.

doi:10.1371/journal.pmed.1002160.t011

Table 12. Antithrombotic drugs: inconsistent studies of pregnancy-associated pharmacokinetic changes.

Drug [Reference]	Number of Studies	Total Number of Women (Nonpregnant/ Pregnant)	Average Quality	Distribution Parameters	Exposure Parameters	Elimination Parameters	Potential Sources for Inconsistency	Trimester
Heparin [113,114]	2	12/12	17	NR	C_{trough} 400%[&], **inconsistent data for C_{max} and AUC[#]**	Cl 72%[&]	Different population (healthy versus non-healthy pregnant women), different dosing regimens	2nd–3rd
Low-molecular-weight heparin [46,114–117]	5	86/134	15.8	**V_d 119%[&]**, V_d 162%[&]	C_{trough} 300%[&], **inconsistent data for C_{max} and AUC[#]** (equivalent to anti-Xa activity)	**Cl 133% (117%–150%)[&]**, Cl 219%[&]	Different underlying disease, prophylactic versus therapeutic doses, different time points of blood sampling	3rd

Significant results are marked in bold.

[&]Parameter not reported in all studies.

[#]Number not provided.

NR, not reported.

doi:10.1371/journal.pmed.1002160.t012

Table 13. Cardiovascular drugs: consistent/single studies of pregnancy-associated pharmacokinetic changes (percent calculated as pregnant/ nonpregnant values).

Drug [Reference]	Number of Studies	Total Number of Women (Nonpregnant/Pregnant)	Average Quality (24 Items)	Distribution Parameters	Exposure Parameters	Elimination Parameters	Trimester
Atenolol [118,119]	2	27/27	18.5	NR	C_{max} 93%[&], AUC 96%[&]	**Cl 131%[&], $t_{1/2}$ 85%[&]**	3rd
Clonidine [120]	1	0[!]/17	16	NR	NR	**Cl 179%**	3rd
Digoxin [75]	1	12/12	18	**Free fraction 106%**	C_{max} 72%, **AUC 78%**	**Cl 157%,** $t_{1/2}$ 82%	3rd
Fenoterol [121]	1	5/9	15	**V_d 58%**	NR	Cl 93%	2nd–3rd
Furosemide [122]	1	NR/9	11	**V_d 188%**	**C_{max} 41%**	**Cl 165%,** $t_{1/2}$ 111%	3rd
Labetalol [123–125]	3	64/75	18	**Higher V_d[#,&]**, V_d 58%[&]	NR	**Higher Cl[#,&]**, Cl 71%[&], $t_{1/2}$ 96%	3rd
Metildigoxin [126]	1	1/8	14	NR	NR	**Cl 130%**	3rd
Metoprolol [127]	1	8/8	17	NR	**Concentration 25%**	NR	3rd
Nifedipine [128]	1	0[!]/15	15	NR	**C_{max} 52%**	**Cl 408%, $t_{1/2}$ 37%**	3rd
Penbutolol [40]	1	10/11	13	**Free fraction 114%**	NR	NR	2nd–3rd
Sotalol [129]	1	6/6	18	V_d 108%	AUC 60%	**Cl 160%,** $t_{1/2}$ 70%	3rd

Significant results are marked in bold.

[&]Parameter not reported in all studies.

[!]Data compared to published reports.

[#]Numbers not provided.

NR, not reported.

doi:10.1371/journal.pmed.1002160.t013

Table 14. Antiretroviral drugs: consistent/single studies of pregnancy-associated pharmacokinetic changes (percent calculated as pregnant/nonpregnant values).

Drug Reference]	Number of Studies	Total Number of Women (Nonpregnant/ Pregnant)	Average Quality (24 Items)	Distribution Parameters	Exposure Parameters	Elimination Parameters	Trimester
Abacavir [130]	1	25/25	19	NR	**C_{max} 90%,** AUC 109%	Cl 91%, $t_{1/2}$ 102%	3rd
Atazanavir [131–137]	7	292/287	18.4	V_d 74% (73%–154%)[&]	**C_{trough} 54% (43%–66%)[&]**, C_{trough} 79% (49%–132%), **C_{max} 65% (60%–90%)[&]**, C_{max} 73% (63%–99%)[&], **AUC 72% (64%–73%)[&]**, AUC 78% (62%–93%)[&]	**Cl 172% (136%–207%)[&], $t_{1/2}$ 71% (65%–85%)[&]**, $t_{1/2}$ 84% (66%–100%)[&]	3rd
Darunavir [138–140]	3	85/99	19.3	NR	C_{trough} 87% (82%–92%), **C_{max} 73% (71%–78), AUC 75% (61%–79%)**	**Cl 150% (137%–163%),** Cl 128% (121%–136%), $t_{1/2}$ 118%[&]	3rd
Didanosine [141]	1	20/20	19	V_d 119%[&]	C_{max} 96% (92%–101%), AUC 83%[&]	**Cl 127%,** Cl 79%, $t_{1/2}$ 98% (93%–103%)	3rd
Efavirenz [142–144]	3	269/112	20	NR	**C_{trough} 69% (49%–90%)[&]**, C_{max} 88% (71%– 106%)[&], **AUC 70%[&]**, AUC 95%[&]	**Cl 123% (104%–142%)[&]**	1st -3rd
Emtricitabine [145–147]	3	159/143	19.6	V_d 110%[&]	**C_{trough} 68%[&]**, C_{trough} 92%[&], **C_{max} 88%[&]**, C_{max} 100%[&], **AUC 73%,** AUC 83% (82%–84%)	**Cl 121% (117%–140%),** $t_{1/2}$ 96% (92%–100%)[&]	3rd
Indinavir [148–150]	3	42/47	14.6	NR	**C_{trough} 36% (26%–46%)[&], C_{max} 51% (35%–67%)[&], AUC 59% (26%–82%)**	**Cl 215% (167%–344%)**	2nd–3rd
Lamivudine [151]	1	47/114	17	NR	NR	**Cl 122%**	2nd–3rd
Lopinavir [45,142,152–162]	13	550/454	18	**V_d 173%[&]**, V_d 85%[&], **free fraction 117%[&]**	**C_{trough} 62% (34%–76%)[&]**, C_{trough} 70% (68%–119%)[&], **C_{max} 73% (54%–75%)[&]**, C_{max} 83% (75%–92%)[&], **AUC 66% (57%–74%)[&]**, AUC 77% (71%–84%)[&]	**Cl 206% (174%–261%)[&]**, Cl 140% (119%–147%)[&], **$t_{1/2}$ 63%[&]**, $t_{1/2}$ 80% (70%–106%)[&]	2nd–3rd
Nelfinavir [42,149,163–168]	8	207/191	17.2	**V_d 71%[&]**, V_d 106% (90%–123%)[&]	**C_{trough} 52% (23%–79%)[&]**, C_{trough} 75% (60%–90%)[&], **C_{max} 73% (69%–77%)[&]**, C_{max} 74% (63%–77%)[&], **AUC 72% (61%–79%)[&]**, AUC 69% (53%–76%)[&]	**Cl 139% (125%–153%)[&]**, Cl 157% (100%–170%)[&], **$t_{1/2}$ 70% (66%–71%)[&]**, $t_{1/2}$ 76%[&]	2nd–3rd
Nevirapine [169–171]	3	192/86	19.6	NR	**C_{trough} 79%[&], C_{max} 79%[&], AUC 79%[&]**	NR	2nd–3rd
Raltegravir [172,173]	2	56/62	17.5	V_d 144% (138%–151%)	C_{trough} 92% (64%–120%), **C_{max} 58%,** C_{max} 81%, **AUC 46%,** AUC 70%	Cl 178% (142%–214%), $t_{1/2}$ 101% (100%–102%)	3rd
Ritonavir [38,45,133–135,139,148,155–160,174–177]	17	324/394	18	**V_d 253% (234%–273%)[&]**, V_d 190% (121%–252%)[&]	**C_{trough} 56% (42%–100%)[&]**, C_{trough} 66% (34%–100%)[&], **C_{max} 49% (32%–70%)[&]**, C_{max} 58% (44%–101%)[&], **AUC 53% (36%–71%)[&]**, AUC 55% (35%–82%)[&]	**Cl 228% (168%–282%)[&]**, Cl 151% (119%–206%)[&], $t_{1/2}$ 94% (60%–150%)[&]	2nd–3rd
Saquinavir [38,174–176]	4	45/69	18	V_d 91%[&]	C_{trough} 74% (30%–107%)[&], **C_{max} 34%,** C_{max} 82% (79%–93%), **AUC 64%,** AUC 83% (43%–94%)	Cl 100% (81%–154%)[&], $t_{1/2}$ 97% (92%–112%)	2nd–3rd
Sulfadoxine [178]	1	10/28	17	V_d 113%	**AUC 56%**	**Cl 178%, $t_{1/2}$ 57%**	2nd

(*Continued*)

Table 14. (*Continued*)

Drug Reference]	Number of Studies	Total Number of Women (Nonpregnant/ Pregnant)	Average Quality (24 Items)	Distribution Parameters	Exposure Parameters	Elimination Parameters	Trimester
Tenofovir [44,145,179,180]	4	246/155	18.5	**V_d 128**[&]	**C_{trough} 83% (78%–88%)**[&], C_{trough} 93%[&], **C_{max} 84%**[&], C_{max} 91% (82%–100%)[&], **AUC 79% (77%–80%)**[&], AUC 80% (66%–94%)[&]	**Cl 125% (123%–127%)**[&], **$t_{1/2}$ 129%**[&], $t_{1/2}$ 100%[&]	1st–3rd

Significant results are marked in bold.

[&]Parameter not reported in all studies.

NR, not reported.

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concentrations and AUC) in pregnancy may not necessarily alter clinical outcomes. The decision to change dosing schedules in patients based on therapeutic drug monitoring and/or knowledge of PK changes in pregnancy should be associated with critical assessment of the risks of therapeutic failure and adverse effects.

Fifty-one studies included in our review investigated more than one drug. Among the antiretroviral class, all studies but one presented women with HIV infection who were treated with more than one antiretroviral medication. The only study that examined a single antiretroviral

Table 15. Antimalarial drugs: consistent/single studies of pregnancy-associated pharmacokinetic changes (percent calculated as pregnant/nonpregnant values).

Drug [Reference]	Number of Studies	Total Number of Women (Nonpregnant/ Pregnant)	Average Quality (24 Items)	Distribution Parameters	Exposure Parameters	Elimination Parameters	Trimester
Artemeter [181,182]	2	22/46	19	NR	**C_{max} 52%[&], AUC 31%[&]**	NR	2nd–3rd
Atovaquone [183]	1	0[I]/9	18	**V_d 217%**	**C_{trough} 22%, C_{max} 37%, AUC 21%**	**Cl 821%**	2nd–3rd
Chloroquine [184–187]	4	50/70	18.7	**V_d 106%**[&]	C_{max} 106% (76%–137%), **AUC 74%**[&], AUC 81% (72%–91%)[&]	**Cl 138% (133%–144%)**[&], Cl 110%[&], **$t_{1/2}$ 91%**[&], $t_{1/2}$ 86%[&]	2nd–3rd
Lumefantrine [181,182,188,189]	4	56/188	19.2	V_d 90%[&]	**Lower concentration**[&,β], C_{max} 101% (100%–103%)[&], AUC 97% (90%114%)[&]	**Higher Cl**[&,β], Cl 88%[&], **$t_{1/2}$ 81%**[&], $t_{1/2}$ 151%[&]	2nd–3rd
Mefloquine [190–192]	3	32/53	17.6	**V_d 108%**[&], V_d 121%[&]	**C_{max} 77%**[&], C_{max} 103%[&], AUC 112%	**Cl 162%,** Cl 104% (100–109%), **$t_{1/2}$ 134%,** $t_{1/2}$ 78% (68%–88%)	1st–3rd
Piperaquine [193–195]	3	81/80	19	**V_d 66% (63%–68%),** V_d 93%	**C_{max} 134%**[&], C_{max} 126%[&], **AUC 66%,** AUC 103% (110%–117%)[&]	**Cl 137%,** Cl 93% (90%–96%), **$t_{1/2}$ 72% (69%–90%)**	2nd–3rd
Proguanil [183,196]	2	4[I]/19	16.5	**V_d 109%**	C_{trough} 101%[&], C_{max} 80% (65%–95%), AUC 77% (60%–95%)	Cl 116% (73%–160%), **$t_{1/2}$ 71%,** $t_{1/2}$ 123%	2nd–3rd

Significant results are marked in bold.

[&]Parameter not reported in all studies.

[I]Data compared to published reports.

[β]Numbers were not provided.

NR, not reported.

doi:10.1371/journal.pmed.1002160.t015

Table 16. Antimalarial drugs: inconsistent studies of pregnancy-associated pharmacokinetic changes (percent calculated as pregnant/nonpregnant values).

Drug [Reference]	Number of Studies	Total Number of Women (Nonpregnant/ Pregnant)	Average Quality	Distribution Parameters	Exposure Parameters	Elimination Parameters	Potential Sources for Inconsistency	Trimester
DHA (active metabolite of artesunate) [192–194,197,198]	5	169/184	18.5	**V_d 67%,** V_d 97% (74%–108%)	**AUC 106% (82%–129%),** AUC 88% (81%–112%), C_{max} 113% (92%–114%)[&]	**Cl 95% (80%–110%),** Cl 106% (89%–123%), **$t_{1/2}$ 79%,** $t_{1/2}$ 84% (76%–97%)	Different disease severity, different pregnancy and nonpregnancy stages	2nd–3rd
Pyrimethamine [199,200]	2	107/127	19.5	**Inconsistent data for V_d[#]**	**C_{max} 149% (142%–159%)[&], inconsistent data for AUC[#]**	**Inconsistent data for Cl[#], $t_{1/2}$ 160% (132%–189%),** $t_{1/2}$ 107%	Different study designs, quality and quantity of controls and genetic variations	2nd–3rd
Sulfadoxine [199,200]	2	107/127	19.5	**Inconsistent data for V_d[#]**	**C_{max} 135%[&],** C_{max} 92%[&], **AUC 83% (67%–99),** AUC 83%	**Cl 125% (100%–151%),** Cl 125%, **$t_{1/2}$ 80% (74%–86),** $t_{1/2}$ 89%	Different study designs, quality and quantity of controls and genetic variations	2nd–3rd

Significant results are marked in bold.

[&]Parameter not reported in all studies.

[#]Number not provided.

doi:10.1371/journal.pmed.1002160.t016

drug is also the earliest study from this class, investigating zidovudine during pregnancy (published in 1993) [231]. The authors noted that in those 51 studies, no drug that interfered with absorption, elimination, distribution, etc., was included. In addition, as per Health Canada, the US Centers for Disease Control and Prevention, and the World Health Organization, antiretroviral therapy, when indicated, includes at least three agents. Therefore, it is most natural to have multiple drugs on board when conducting a PK study in HIV-positive cohorts.

Clinical Outcome Data

The focus of the present systematic review is on PK data in pregnancy as a first step toward improving drug therapy in this orphan population. Although clinical outcomes were not reported in many of these PK studies, we identified several studies with such information.

For lamotrigine and indinavir, pregnancy-related changes in the clinical endpoints were in agreement with the observed PK changes [88,148]. Others have found significant PK changes and yet no clinical correlation was demonstrated (emtricitabine [145], levetiracetam [16], and topiramate [101]). Interestingly, while the PK-clinical correlation of some drugs was consistent among different studies (e.g., lamotrigine [86,88,91]), this was not the case for others (e.g., oxcarbazepine [96,97]). The scope of studies to investigate both PK and clinical outcome data seems to be dependent on drug class. For example, none of the studies that investigated antibiotics [47,52,53] or anesthetic and analgesic drugs [102] provided data on clinical outcomes. On the other hand, studies of addiction management drugs and antidepressant drugs reported clinical data, showing a positive correlation between decreased drug exposure and diminished clinical effects in pregnancy [70,202]. A study investigating cardiovascular drugs that reported clinical outcomes did not demonstrate significant positive clinical correlations [127]. The three drug groups that provided the richest evidence regarding clinical correlation were the antiretrovirals, antimalarials, and antiepileptics. In the case of antiretrovirals, all studies had showed decreased drug exposure in pregnancy due to PK changes. While most of these studies reported

Table 17. Miscellaneous classes: consistent/single studies of pregnancy associated pharmacokinetic changes (percent calculated as pregnant/nonpregnant values).

Class	Drug [Reference]	Number of Studies	Total Number of Women (Nonpregnant/ Pregnant)	Average Quality (24 Items)	Distribution Parameters	Exposure Parameters	Elimination Parameters	Trimester
Addiction management	Buprenorphine [201]	1	3/3	20	NR	**C_{max} 15%, AUC 12%**	NR	3rd
	Methadone [202–204]	3	37/56	17.3	NR	**C_{trough} 30%[&], AUC 25%[&]**	**Cl 165% (155%–175%),** Cl 190%	2nd–3rd
Anticancer Chemotherapy	Carboplatin [205]	1	2/2	10	**V_d 138%**	**C_{max} 63%, AUC 58%**	**Cl 165%, $t_{1/2}$ 82%**	2nd–3rd
	Cisplatin [206]	1	6/6	13	**Free fraction (8 h) 179%**	NR	NR	3rd
	Epirubicin [205]	1	4/4	11	**V_d 121%**	**C_{max} 60%, AUC 72%**	**Cl 142%, $t_{1/2}$ 85%,**	2nd–3rd
	Paclitaxel [205]	1	2/5	11	**V_d 167%**	**C_{max} 54%, AUC 83%**	**Cl 120%, $t_{1/2}$ 133%**	2nd–3rd
Drugs for endocrine disorders	Insulin [207]	1	10/10	15	NR	NR	**Cl 80%**	3rd
	Metformin [208–210]	3	23/69	18.3	V_d 118%[&]	**AUC 73%[&]**	**Cl 131%[&]**, $t_{1/2}$ 107%[&]	3rd
	Thyroid releasing hormone [211]	1	8/24	17	**V_d 146%**	**C_{max} 68%, AUC 45%**	**Cl 192%, $t_{1/2}$ 68%**	2nd–3rd
	Vasopressin [212]	1	6/6	15	NR	NR	**Higher metabolic clearance rate[#]**	3rd
Labor and delivery	Ritodrine [213]	1	10/10	12	NR	C_{max} 80%, **AUC 72%**	NR	2nd–3rd
	Terbutaline [214]	1	3/3	10	NR	NR	**Cl 133%**	3rd
	Nifedipine [215]	1	0[I]/8	21	**Larger V_d[#]**	NR	**Shorter $t_{1/2}$[#]**	2nd–3rd

Significant results are marked in bold.

[&]Parameter not reported in all studies.

[#]Numbers were not provided.

[I]Data compared to published reports.

NR, not reported.

doi:10.1371/journal.pmed.1002160.t017

Table 18. Miscellaneous classes: inconsistent studies of pregnancy-associated pharmacokinetic changes (percent calculated as pregnant/non-pregnant values).

Class	Drug [Reference]	Number of Studies	Total Number of Women (Nonpregnant/ Pregnant)	Average Quality	Distribution Parameters	Exposure Parameters	Elimination Parameters	Potential Sources for Inconsistency	Trimester
Anticancer chemotherapy	Doxorubicin [205,216]	2	5/14	15	**V_d 129%[&]**	**C_{max} 66%[&], AUC 75%[&]**	**Inconsistent data for Cl[#]**, $t_{1/2}$ 101% (100%–102%)	Comparison group selection, numbers too small to draw conclusions	2nd–3rd

Significant results are marked in bold.

[&]Parameter not reported in all studies.

[#]Numbers not provided.

doi:10.1371/journal.pmed.1002160.t018

Table 19. Non-significant pharmacokinetic differences between pregnant and nonpregnant women.

Class	Drug [Reference]	Number of Studies	Total Number of Women (Nonpregnant/ Pregnant)	Average Quality	Distribution Parameters	Exposure Parameters	Elimination Parameters	Trimester
Antibiotics	Azlocillin [65]	1	4/7	9	V_d 62%	C_{max} 327%	Cl 64%, $t_{1/2}$ 90%	2nd
	Cefotiam [225]	1	6/14	15	V_d 246%	NR	Cl 260%, $t_{1/2}$ 132%	3rd
	Ceftriaxone [53]	1	4/18	18	V_d 81%	NR	Cl 50%, $t_{1/2}$ 183%	3rd
	Gentamicin [53]	1	4/18	18	V_d 75%	NR	Cl 105%, $t_{1/2}$ 76%	3rd
	Sulbactam [68]	1	10/10	14	V_d 87%	C_{trough} 96%, AUC 78%	Cl 117%, $t_{1/2}$–87%	3rd
Antidepressants	Sertraline [70,217]	2	9/12	14	NR	C_{max} 54%, AUC 40%	NR	3rd
Analgesia and anesthesia drugs	Metamizole [226]	1	8/7	11	V_d 120%	C_{max} 149%, AUC 118%	Cl 73%, $t_{1/2}$ 89%	3rd
	Atracurium [227]	1	8/8	17	V_d 97%	NR	Cl 105%, $t_{1/2}$ 91%	NR
	Bupivacaine [228]	1	6/6	16	NR	C_{max}140%, AUC 155%	$t_{1/2}$ 111%	3rd
	Pethidine [229]	1	11/13	13	V_d 106%	C_{max} 51%, AUC 65%	Cl 105%, $t_{1/2}$ 179%	3rd
Cardiovascular drugs	Alprenolol [48]	1	4/11	15	Free fraction 128%	NR	NR	3rd
	Propranolol [218,219]	2	19/19	17	V_d 70%[&]	AUC 99% (97%–101%)	Cl 106%[&], $t_{1/2}$ 79% (70%–88%)	3rd
Antiemetics	Pyridoxine [50]	1	18/56	19	NR	NR	Cl 108%	1st
	Doxylamine [50]	1	18/56	19	NR	NR	Cl 80%	1st
	Ondansetron [230]	1	20/40	20	NR	NR	NR	3rd
Antiretrovirals	Pyrimethamine [178]	1	9/28	17	V_d 93%	AUC 82%	Cl 120%, $t_{1/2}$ 93%	2nd
	Zidovudine [231]	1	0[!]/8	16	NR	NR	NR	3rd
Drugs for endocrine disorders	Mifepristone (RU 4861) [232]	1	9/36	17	V_d 138%	C_{max} 83%, AUC 77%	Cl 140%	1st–3rd
	Propylthiouracil [233]	1	6/6	13	NR	AUC 52%	NR	3rd
	Thyroxine [234]	1	16/16	11	NR	No change in required dose	NR	1st–3rd
Drugs for immune disorders	Intravenous immunoglobulin [235]	1	5/5	19	NR	C_{trough} 108%, C_{max} 111%, AUC 102%	NR	2nd
Antimalarial drugs	Amodiaquine [236]	1	18/24	17	NR	C_{max} 102%, AUC 108%	Cl 92%, $t_{1/2}$ 104%	2nd–3rd
	Quinine [189,220,237]	3	8[!]/49	19	NR	C_{max} 138%[&]AUC 88%[&]	Cl 120%[&], $t_{1/2}$ 110%[&]	1st–3rd
Labor and delivery	Atosiban [238]	1	0[!]/8	15	NR	NR	NR	2nd–3rd
	Oxytocin [239]	1	6/10	15	NR	NR	NR	3rd
	Salbutamol [240]	1	0[!]/5	14	NR	AUC 82%	Cl 104%	2nd–3rd

(*Continued*)

Table 19. (*Continued*)

Class	Drug [Reference]	Number of Studies	Total Number of Women (Nonpregnant/ Pregnant)	Average Quality	Distribution Parameters	Exposure Parameters	Elimination Parameters	Trimester
Supplements	Folic acid [221,222]	2	24/24	18	NR	Plasma folate concentrations[#]	Urine excretion[#]	2nd–3rd
	Iron [241]	1	9/10	11	V_d 70%	C_{max} 134%, AUC 194%	Cl 45%, $t_{1/2}$ 147%	2nd–3rd
	Vitamin D3 [223,224]	2	50/55	18.5	NR	C_{max} 94%[&], AUC 106%[&]	NR	3rd
Antiviral drugs	Acyclovir [242]	1	10/15	11	NR	C_{trough} 133%, C_{max} 100%	NR	3rd
	Oseltamivir [41]	1	23/16	15	V_d 119%	AUC 104%	Cl 92%, $t_{1/2}$ 103%	1st–3rd

[&]Parameter not reported in all studies.

[!]Data compared to published reports.

[#]Numbers not provided.

NR, not reported.

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adequate viral suppression and no mother-to-child HIV transmission [132,135,138], one study reported an increased viral load during pregnancy, with a few cases of neonatal transmission of the virus [150]. Conflicting clinical results were also reported for antimalarial drugs: while some studies reported equal parasite clearance time or no increase in treatment failure in spite of decreased exposure [182], others demonstrated a positive correlation between the decreased exposure and poor clinical outcome, reporting an increase in treatment failure or a decrease in post-treatment prophylactic effect [181,195].

Our review has highlighted those medications that have relatively consistent PK change directions in pregnancy. This collection of PK data could prove to be a decision support base for future attempts to tailor medication prescription for pregnant women to achieve target serum concentrations; however, one must take into account that many studies often report undiminished drug efficacy despite the aforementioned pregnancy-associated PK changes [132,135,138,145,146,163,172,177].

Drugs with a Consistent Pharmacokinetics Change Direction

For the vast majority of drugs (114), data gathered in this review are consistent among studies. Although not all studies presented a full set of PK parameters, the evidence exists to support the notion that in pregnancy, drug exposure levels per given dose are decreased for most medications. In addition, lower plasma protein binding (higher free drug level) is a consistent finding. This tandem trending of higher Cl rate, higher V_d, and higher free fraction is observed for most drugs except for those metabolized by CYP1A2 and CYP2C19, which show a trend toward decreased metabolism during pregnancy.

Drugs with Variable Pharmacokinetic Change Directions

Studies of seven drugs were found to yield conflicting PK results among studies in pregnancy. Three of these drugs are part of the antimalarial drug group (pyrimethamine [199,200], sulfadoxine [199,200], and DHA [192–194,197,198]), two are antithrombotic drugs (unfractionated heparin [113,114] and low-molecular-weight heparin [46,114–117]), one is an antibiotic

(ampicillin [67,68]), and the last is an anticancer chemotherapeutic drug (doxorubicin [205,216]). The average quality score of the consistent antibiotic and antithrombotic studies tended to be higher than the quality score of the inconsistent studies from the same group (14.4 versus 11.5, $p < 0.05$, and 16.4 versus 15.5, $p = 0.119$, for the antibiotic and antithrombotic drugs, respectively). Nevertheless, the average quality score of the consistent studies was not higher than that of the inconsistent studies for both the antimalarial drugs (18.2 versus 19.1, $p = 0.62$) and the anticancer chemotherapeutics (11.5 versus 14.5: averages). Thus, variability of quality scores cannot account for the inconsistent PK directions that were demonstrated.

Ampicillin [67,68]. The pregnancy PK of ampicillin had been reported in two studies [67,68]. Both studies presented PK parameters during delivery and demonstrated conflicting results regarding the half-life of elimination. While the elimination half-life presented in one study [67] was longer among pregnant women compared to the control group (58.3 min versus 44.8 min, respectively), the other study [68] demonstrated a difference in the opposite direction (52.4 min versus 69.9 min, respectively). We believe that one of the potential sources for these conflicting results is the choice of control group: while the control group in the former [67] comprised healthy nonpregnant individuals, the post-pregnant women (who may be still under some influence of pregnancy-associated physiological changes) served as their own control in the latter study [68].

Pyrimethamine and sulfadoxine [199,200]. The pregnancy PK of this antimalarial drug combination had been studied in Papua New Guinea [199] and in four African countries (Mozambique, Sudan, Zambia, and Mali) [200]. These two publications present conflicting results. Concerning pyrimethamine, the Papua New Guinea time-concentration plots showed average pregnancy levels to be lower at most time points than the nonpregnant comparison, while data from the African countries indicated the opposite (measurements in pregnancy were higher). This same phenomenon was also evident in some, but not all, data reported on sulfadoxine.

Appraising the methodologies used by these two research groups, we have identified a potential source for this conflict regarding the raw data. In both studies, pregnancy was associated with significant anemia, and both papers (Table 1) reported an average reduction of ~20% in hemoglobin values during pregnancy. However, while the Papua New Guinea study used plasma for drug assays, the African study used whole blood from dried blood spots, with no correction for hematocrit values. This limitation of the dried blood spot method may have caused an overestimation of drug levels per blood spot area in pregnant women in the African study, as a result of a relative abundance of plasma per blood spot due to severe anemia [246]. Although there are likely to be other factors contributing to the discrepancies between the two studies, we speculate that the difference in the sample matrix is the major cause, and that pyrimethamine and sulfadoxine apparent clearance is higher during pregnancy. This also highlights the importance of methodological standardization in PK studies, including sample analysis procedures.

Dihydroartemisinin [192–194,197,198]. Five studies met the inclusion criteria that investigated the effect of pregnancy on the PK of DHA, the active metabolite of artesunate, for severe malaria (Table 16). Inconsistencies in PK parameter changes exist in the AUC and clearance of DHA; a statistically significant reduction in AUC (decreased exposure) and an increase in oral clearance in pregnancy were observed in one study [197], while the change directions were opposite in the other [198]. However, this can be explained by increased disease severity at PK sampling in the latter [198], as systemic exposure of DHA is higher in infected patients with a severe course of malaria than in those with a mild course [198,247]. The increased DHA exposure in acute malaria during pregnancy after oral artesunate is probably a result of increased bioavailability due to decreased presystemic elimination through glucuronidation in

the intestine [198]. Hepatic metabolism of DHA occurs through enzymes such as CYP2B6, UGT1A9, and UGT2B7, but data on these isoenzymes in pregnant women with acute infection are still limited.

Low-molecular-weight heparin [46,114–117] and heparin [113,114]. Six studies investigated the PK of heparin and low-molecular-weight heparin by using factor anti-Xa activity as a surrogate marker of enoxaparin ($n = 2$), dalteparin ($n = 3$), and unfractionated heparin ($n = 2$) in pregnant women (Table 12). The statistically significant discrepancies in the pharmacokinetic parameters can be mainly attributed to the different study designs, dosing regimens, and indications for heparin in the study population (therapeutic versus prophylactic administration). However, the most important parameter in these studies is the C_{max} (2–4 h after administration) of the factor anti-Xa activity because it determines whether the woman is properly controlled for thromboembolic events. Studies with a dose increase design had an increase in the C_{max} of anti-Xa activity [114,116]. The remaining studies revealed lower C_{max} values during pregnancy, even with higher doses [46,113,115,117]. Those studies [46,114,117] showed higher clearance during pregnancy, which was statistically significant in two of them [46,117]. The recommended therapeutic range of 0.6–1.0 IU/ml [248] was achieved in only half of the population in one of the two studies [117]. It should be noted that the Barbour et al. [116] study compared women in the third trimester to women in early pregnancy (as the control group). Peak levels of anti-Xa activity (equivalent to C_{max}) were 0.63 IU/ml in early pregnancy versus 0.69 IU/ml in the third trimester. These control values were somewhat higher than the C_{max} values reported for the other nonpregnant populations in the other studies [46,114,115].

Study Limitations

Most studies that demonstrated significant PK changes had relatively small sample sizes. The mixture of small sample sizes with different pharmacological/research methodologies poses substantial challenges to comparing and summarizing their study results. Another limitation stems from the fact that, for many drugs, pregnancy-related PK changes were considered to be significant on the basis of a single study, often of low quality, with small numbers of women and a small subset of PK parameters. Although we show single studies with statistically significant results in the "consistent" category for simplicity of presentation, single studies do not inform on the consistency of the changes. Further replication studies are required. The quality assessment of the studies included in this review was performed using the ClinPK checklist for assessing methodological quality in clinical PK studies. This checklist provides meticulous guidelines for quality assessment, but having been only recently published, it will need refinement and external validation.

We are acutely aware of the fact that by excluding studies lacking a comparison group of nonpregnant women we may miss a significant amount of PK data. However, in the context of our research question, we find it imperative to not only document certain kinetic patterns but also provide quantitative or semiquantitative estimates of the extent and directionality of those pregnancy-associated PK changes. Comparing cohort data for pregnant women to normal population averages would expose our study to a multitude of biases, mainly due to the fact that the most dominant contributors to the "normal population" PK parameter values, in textbooks and seminal papers, are healthy men (Lexicomp and Micromedex databases, for example, report "adult" data with no gender, yet the citation lists are rich with male volunteer publications). Moreover, in the majority of studies included in this systematic review, pregnant women served as their own controls (in the prepregnancy or postpartum state), which isolates the pregnancy as the most dominant factor in the assessment.

Lastly, trimester-specific PK changes were difficult to summarize. While most of the studies provided third trimester results, others reported separate results from the second and third trimesters, and few reported separate results from all trimesters. Physiological changes in pregnancy take place progressively during gestation (reviewed by Costantine [8] and Loebstein et al. [9]). As such, we hypothesized that this would lead to trimester-specific differences in drug disposition. Unfortunately, however, many studies in this review did not report trimester-specific changes, which could possibly have contributed to the conflicting PK results in some studies described above.

Conclusions

Our systematic analyses confirmed that many drugs are subject to pregnancy-associated PK changes, which may alter plasma/serum drug concentration profiles. However, we have also found a paucity of clinically useful data on whether dose adjustment is necessary for these PK changes. Where such PK studies were done, generally only a few PK parameters were estimated, sample sizes were small, and maternal and/or fetal outcomes were not examined. Further studies that address these limitations are needed to optimize drug therapy for pregnant women.

Supporting Information

S1 Checklist. PRISMA checklist for reporting systematic reviews.
(DOC)

S1 Table. Search strategy.
(DOCX)

S2 Table. Updated search strategy.
(DOCX)

S3 Table. Non-included full text studies with their reasons.
(DOCX)

S4 Table. Extracted data.
(XLSX)

Author Contributions

Conceptualization: GK GP TL.

Data curation: TAW.

Formal analysis: GP TL AC SI.

Investigation: GP.

Methodology: GP TL TAW.

Project administration: SI.

Resources: TAW.

Supervision: SI GK.

Validation: GP AC.

Visualization: GP TL SI.

Writing – original draft: GP TL AC TAW SI.

Writing – review & editing: SI GK.

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