

KNOWLEDGE ON DRUG SAFETY AND DRUG UTILIZATION DURING PREGNANCY: A REVIEW OF SYSTEMATIC REVIEWS AND META-ANALYSES

Anshar Timur Samudra¹, Antonius Adji Prayitno Setiadi², Sylvi Irawati^{3*}

¹⁻³Faculty of Pharmacy, University of Surabaya

Email Korespondensi: s.irawati.2912@gmail.com

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ABSTRACT

Drug use all through pregnancy can be beneficial or dangerous to the expectant mother, her fetus, and the baby. Some drugs have a risk of causing disability or death. Pregnant women's lack of knowledge about the harms of drug use during pregnancy can affect the use of these drugs during pregnancy. This study aims to review systematic reviews and meta-analyses regarding knowledge and use of medications during pregnancy in pregnant women. The design of this study is a scoping review using the PubMed database. The studies reviewed are systematic reviews and meta-analyses published in 2014-2024. Of the 1658 search results, five studies met the inclusion criteria. Four systematic reviews discussed drug utilization during pregnancy, and one systematic review addressed the knowledge of pregnant women regarding the use of drugs during pregnancy. The prevalence of antibiotic consumption during pregnancy ranges from 0.04 to 90%. While the prevalence of herbal medicine use in pregnant women varies between 12% and 93%. As many as 93.3% of pregnant women do not know enough about medicines and have gaps in knowledge or information about medicines, whether prescription drugs, over-the-counter drugs, or herbal medicines. Pregnant women's knowledge is also limited about the risks associated with polypharmacy in the first trimester of pregnancy, and there is a relationship between polypharmacy during pregnancy and an increased risk of congenital malformations. In conclusion, the prevalence of herbal medicine and antibiotic use during pregnancy is still relatively high. Most pregnant women do not have a good level of knowledge regarding the use of these medicines during pregnancy.

Keywords: Drug Utilization, Knowledge, Pregnancy

INTRODUCTION

The use of drugs during pregnancy may pose benefits or risks to the mother, fetus, and infant. Some drugs have the risk of causing disability or death of the fetus in the womb, disability or death in the newborn, and disability that appears with age (Navaro *et al.*, 2018). Examples of drugs that cause congenital disabilities include *phenytoin*, *misoprostol*, and

thalidomide (Joint Formulary Committee, 2023). In addition, some drugs increase the risk of the mother experiencing abortion, uterine contractions, bleeding, postpartum depression, or other health problems (Navaro *et al.*, 2018). Examples of drugs that affect uterine contractions include *dinoprostone*, *misoprostol*, and *prostaglandins* (Joint Formulary Committee, 2023).

The FDA risk categories were created based on existing research evidence regarding the safety of their use all through being pregnant, the type of study subjects, and the results of those research. The categories consist of categories A, B, C, D, and X. This labeling requirement aims to provide evidence-based information on the safe use of drugs in pregnancy. Although initially proposed as a method to prevent teratogenic effects, many medicines have been poorly studied in the pregnant population, and thus, their long-term safety is unknown (Wibowo and Brata, 2023).

The lack of evidence on the inappropriate use of drugs in pregnant women can cause several complexities in the fetus and mother. Therefore, the latest Briggs, Towers, and Forinash no longer lists drug recommendations in pregnancy based on the FDA risk categories but instead describes drug use recommendations based on the risk of the drug to the fetus according to the evidence of studies of the drug in pregnant women and/or animals. In addition, the recommendations add information regarding the trimester in which the use of a drug is contraindicated. Examples of some of the new pregnancy drug use recommendation classifications are *compatible*, *no (limited) human data* - *probably compatible*, and *compatible - maternal benefit >> embryo-fetal risk* (Briggs, Towers and Forinash, 2022).

LITERATURE REVIEW

Since 1979, the *Food and Drug Administration* (FDA) imposed a drug risk category on pregnancy in response to the *thalidomide* tragedy. *Thalidomide* is a potent human teratogen. A teratogen is a compound that can cause physical

abnormalities at birth or abnormal development in an embryo or fetus (Cleveland Clinic, 2022). Severe malformations because of *thalidomide* can also contain defects of limbs, axial skeleton, head and face, eyes, ears, tongue, teeth, central nervous system, respiratory, cardiovascular, genitourinary, and gastrointestinal tract in infants. The drug is contraindicated in pregnancy (Briggs, Freeman and Towers, 2017).

The use of drugs in pregnancy can enter the placenta and cause harmful effects on the fetus and in fact there are low molecular weight substances will diffuse freely throughout the placenta as early as five weeks of fetal life. Nearly each substance used for therapeutic purposes can also enter the fetus from the mother. Therefore, the labeling information will contain a risk summary section that combines human and animal data and a clinical considerations section that discusses risk assessment and how to deal with accidental fetal drug exposure and further recommends that pregnant women be warned that they should not consume without the supervision of a physician, unless there is information on the benefits outweighing the risks (Law, Bozzo and Koren, 2010).

Drugs that are said to be teratogens are those that contain medicinal ingredients that can cause physical abnormalities or abnormal development in the embryo or fetus. When patients and doctors consider medication therapy during pregnancy, this is often the fear. Research and prediction of drug toxicity in humans is difficult. The teratogenic properties of a drug are often proven through animal studies. However, these findings may not be relevant for human use of the drug (Wibowo and Brata, 2023).

The lack of knowledge of pregnant women approximately the

risks of using drugs all through pregnancy can affect the use of these drugs during pregnancy. This study aims to *review systematic reviews* and meta-analyses on knowledge and drug use during pregnancy in pregnant women that have been conducted so far.

RESEARCH METHOD

The design of this study was a *scoping review*. This *scoping review* was conducted using the PubMed *database*. The inclusion criteria used in this study were *systematic reviews* and meta-analyses published within the last 10 years (2014-2024), which examined the knowledge and use of drugs during pregnancy in pregnant women in *real-world settings* or the general population or community. The keywords used for searching the PubMed *database* were as follows: (knowledge*[tiab] OR drug utilization[mesh])AND pregnan*[ti]AND (drug*[tiab] OR medicine*[tiab] OR medication*[tiab]) Filters: from 2014 - 2024. Two authors, namely (ATS) and (SI), screened titles and abstracts. If there is a difference of opinion between the first and second authors, it is discussed again with the third author (AAPS). Reporting this *scoping review* uses the reporting method according to the *Preferred Reporting Items for Systematic Reviews and Meta-*

Analyses Extension for Scoping Reviews (PRISMA-ScR) guidelines.

RESULT

An initial search using the PubMed *database* yielded 1,658 articles. As many as 670 articles were excluded because they were not published between 2014 and 2024. After that, researchers screened the titles and abstracts of the remaining 988 articles. The screening process resulted in 5 articles on related topics. Of the five articles, none of the meta-analysis studies discussed the knowledge and use of drugs during pregnancy in pregnant women.

In a search on the PubMed *database* for the last 10 years, four *systematic reviews* were obtained that discussed using drugs all through pregnancy, and one systematic review addressed the knowledge of pregnant women regarding using medications all through pregnancy. Of the four *systematic reviews*, two articles discussed the use of herbal medications in pregnant women, 1 article discussed the use of antibiotics in pregnant women, and 1 article discussed the risk of congenital malformations due to the use of four or more drugs (polypharmacy) during pregnancy. The procedure for preparing this research protocol can be seen in Figure 1.

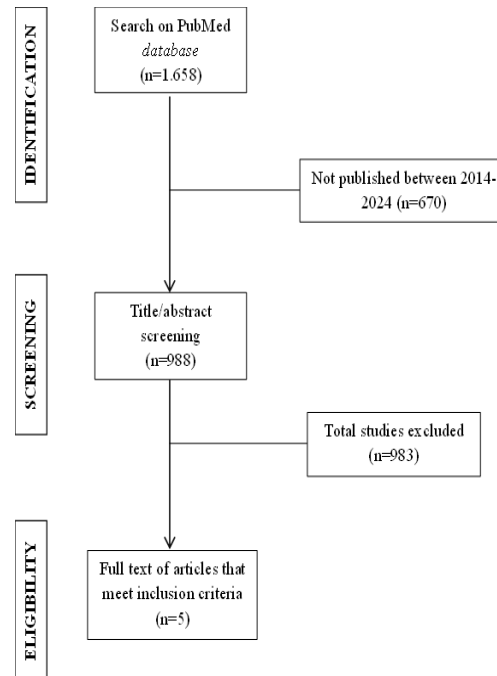


Figure 1. Study Selection with ScR Prisma Diagram

Based on five articles from the search results, all studies were observational. Antibiotic use in pregnant women was grouped based on six regions of the World Health Organization (WHO) classification: Africa, the Americas, the Eastern Mediterranean, Europe, Southeast Asia, and the Western Pacific. Most pregnant women obtain antibiotics from a doctor's prescription and use them throughout pregnancy (Orwa *et al.*, 2024). Two systematic reviews discussed the usage of herbal medication in pregnant women. The studies got here from the Eastern Mediterranean, which included Iran, Saudi Arabia, Palestine, Egypt, Oman, Iraq, and Jordan. All studies were cross-sectional from 2011-2021 (Bouqoufi *et al.*, 2023). Other research on the use of herbal medicine comes from Sub-Saharan African countries: South Africa, Nigeria, Mali, Zimbabwe, Ghana, Ethiopia, Tanzania, Kenya, Uganda, Malawi, Zambia and Ivory Coast.

Commonly used herbal remedies in African countries include *Zingiber officinale*, *Allium sativum*, *Cucurbita pepo* (Cucurbitaceae), *Ricinus communis* (Euphorbiaceae), *Vernonia amygdalina* *Debile* (Asteraceae) and *Garcinia kola* *Heckel* (Clusiaceae) (Mudonhi *et al.*, 2022). Other studies addressed the risk of congenital malformations due to the use of four or more drugs (polypharmacy) during pregnancy. Four out of seven research stated an elevated risk of congenital malformations due to polypharmacy during pregnancy (Thunbo *et al.*, 2022). The last study was a study on the knowledge of pregnant women regarding the use of drugs during pregnancy. All studies are observational and come from Asia, Europe, Africa, North America, Australia, and South America (Kirubarajan *et al.*, 2021). The results of the article search are grouped into Table 1.

Table 1. Summary of Review Characteristics

Author name and year of publication	Purpose of review	Number of studies reviewed	Research designs reviewed	Population and location setting	Results systematic review
Orwa <i>et al.</i> (2024)	To comprehensively analyze all studies published from 2000 onwards documenting the prevalence of contemporary antibiotic consumption during pregnancy	Overall, 116 studies (14 from Africa, 24 from the Americas, six from the Eastern Mediterranean, 57 from Europe, four from Southeast Asia and 11 from the Western Pacific)	67 cohort studies, 43 cross-sectional studies, three case-control studies, two prospective observational studies, and one secondary analysis study. <i>Databases used: PubMed, Web of Science, Embase, and Cochrane.</i>	33,821,194 pregnancies, comprising 80 studies (33,714,431 pregnancies) in population settings and 36 studies (106,763 pregnancies) in hospital settings.	The prevalence of antibiotic consumption at some point being pregnant ranged from 0.04 to 90%, with a pooled estimate of 23.6% (95% CI: 20,1-27,5; $I^2=100\%$). Low-income countries had the very best pooled prevalence of 45.3% (95% CI: 15,4-79,1; $I^2=99,6\%$). Regionally, the Western Pacific had the best pooled prevalence of 34.4% (95% CI: 13.4-64.1; $I^2=100\%$), and Southeast Asia recorded the lowest mixed incidence of 8.2% (95% CI 3.4-18.3; $I^2=92.2\%$).
Bouqoufi <i>et al.</i> (2023)	A systematic literature review on the prevalence of herbal	33 research	The cross-sectional study was conducted from January 2011 to	Of the 33 studies, 19 had been conducted in Iran, 5 in Saudi Arabia, 4 in	The prevalence of herbal medication use in pregnant women various among 19.2%

Author name and year of publication	Purpose of review	Number of studies reviewed	Research designs reviewed	Population and location setting	Results systematic review
	use during pregnancy from the World Health Organization (WHO) Eastern Mediterranean Regional Office.		June 2021. <i>The databases used were PubMed, Scopus, and Web of Science.</i>	Palestine, 2 in Egypt, and one each in Oman, Iraq, and Jordan.	and 90.2%. The maximum generally used herbs that were identified had been Ginger (<i>Thymus vulgaris</i>), (<i>Mentha x piperita</i>), (<i>Salvia officinalis</i>), (<i>Matricaria chamomilla</i>), (<i>Trigonella foenum-graecum</i>), (<i>Nigella sativa</i>), honey, (<i>Cinnamomum verum</i>), (<i>Citrus x aurantium</i>), (<i>Camellia sinensis</i>), (<i>Pimpinella anisum</i>), (<i>Allium sativum</i>) and (<i>Cuminum cyminum</i>).
Mudonhi <i>et al.</i> (2022)	This take a look at the share of pregnant women using traditional medicine in Sub-Saharan Africa, identified	48 research	All studies posted in English (till November 17, 2021) in respectable <i>peer-reviewed</i> journals and available open	Pregnant women in Sub-Saharan African Nations (South Africa, Nigeria, Mali, Zimbabwe, Ghana, Ethiopia, Tanzania,	Traditional medicine is used for various purposes by pregnant women in Sub-Saharan Africa, ranging from 12 to 93%. However, there is still a knowledge gap regarding how

Author name and year of publication	Purpose of review	Number of studies reviewed	Research designs reviewed	Population and location setting	Results systematic review
	the different types of traditional medicine used all through antenatal care and the reasons for their use, and additionally identified the challenges confronted with the aid of pregnant women using traditional medicine in antenatal care.		access. <i>Databases</i> used: Google Scholar, PubMed, Cochrane, HINARI, and WHO Website	Kenya, Uganda, Malawi, Zambia and Ivory Coast)	traditional medication is used and for what purpose all through being pregnant.
Thunbo <i>et al.</i> (2022)	To evaluate the chance of congenital malformations in polymorbid pregnancies due to first-trimester drug use (polypharmacy).	7 research in Finland, Australia, Israel, Netherlands, and Hungary.	4 case-control studies, 2 cohort studies, and one research with an unclear study design. <i>Databases</i> used: PubMed, Scopus,	Pregnant women who use two or more different drugs simultaneously (polypharmacy) without regard to the timing of pregnancy	Four of the seven research reported an elevated risk of congenital malformations compared with unexposed or monotherapy, with odds ratios ranging from 1.1 to >10.0. Pregnant women's information is

Author name and year of publication	Purpose of review	Number of studies reviewed	Research designs reviewed	Population and location setting	Results systematic review
			and Embase	and indications.	limited about the risks associated with first-trimester polypharmacy in polymorbid pregnancies due to scant literature evidence.
Kirubaran et al. (2021)	To characterize pregnant patients' knowledge, attitudes, information sources, and institutional beliefs regarding medication use during pregnancy.	The 34 studies consisted of Asia (n=11), Europe (n=11), Africa (n=5), North America (n=2), Australia (n=2), and South America (n=1). One study included participants from multiple countries and the other analyzed online comments	Observational study. Databases used: Medline, Embase, and CINAHL	11,757 pregnant women	A total of 15 studies analyzed pregnant patients' perceptions regarding their knowledge of medicines. 93.3% of participants were not confident that they knew enough about the use of medicines during pregnancy or wanted to learn more about their safety profiles. The outcomes of most knowledge assessments determined that most of the people of pregnant women had information gaps regarding

Author name and year of publication	Purpose of review	Number of studies reviewed	Research designs reviewed	Population and location setting	Results systematic review
					prescription drugs.

The use of medications during pregnancy requires a high degree of caution. But, medication use by pregnant women all through the first trimester has increased significantly over the last decade. More than 50% of pregnant women report taking at least one medication in the first trimester, that's the critical period for fetal development (Kirubarajan *et al.*, 2021). Self-medication behavior is widespread during being pregnant, with many people taking *over-the-counter* drugs in the course of all trimesters of pregnancy (Thunbo *et al.*, 2022). In a study on the use of over-the-counter medications, more than half of pregnant women in the first trimester used acetaminophen (Liu *et al.*, 2015).

Drugs that pregnant women widely consume during pregnancy include antibiotics, antidepressants, non-steroidal anti-inflammatory drugs (NSAIDs), anti-retroviral treatment, anti-malaria, over-the-counter drugs, and chronic disease drugs. As many as 93.3% of pregnant women did not have sufficient knowledge regarding the use of medications consumed during pregnancy. Most pregnant women also experience information gaps regarding the drugs they consume, including prescription drugs. Many pregnant women do not realize that commonly prescribed drugs can also harm their fetuses, especially if they are also available over the counter (Kirubarajan *et al.*, 2021).

Antibiotics are one of the most usually used drugs all through

pregnancy, accounting for near 40% of prescribed drugs in some studies (Miller *et al.*, 2018). Various antibiotics are prescribed at some stage in being pregnant relying on the sort of contamination present, the most common being penicillins, other beta-lactams, and macrolides (Brandon *et al.*, 2015). Therefore, antibiotic prescribing have to be cautiously assessed and primarily based on each individual, evaluating the advantages and disadvantages for the mom and fetus. Most research (N = 101) reported prevalence for the complete being pregnant duration, even as a minority targeted on one or two trimesters (N = 15). Among all included research, a dominant 69% (N = 80) used a populace-primarily based approach, 88.8% (N = 103) used convenience sampling, and 74.1% (N = 86) retrieved facts from a prescription registry (Orwa *et al.*, 2024).

Prevalence of antibiotic consumption during pregnancy in the regions of Europe (20.3%), Africa (28.6%), Americas (31.8%), Eastern Mediterranean (14.8%), Southeast Asia (8.2%), and Western Pacific (34.4%). There was a marked variation in prevalence as compared to the overall pooled prevalence of 23.6% for systemic antibiotic use throughout being pregnant. A minority of studies showed lower occurrence charges, with some as low as 0.04%. Conversely, a minority of studies suggested higher prevalence charges, as much as 90%. But, upon similarity research, the

outliers had a pooled prevalence of 23.8% (95% CI 19.2-29.3; $I^2=100\%$) (Orwa *et al.*, 2024).

The use of herbal medicine in pregnant women has also increased compared to conventional medicine. This is due to the belief of pregnant women that herbal medicines are natural and free from any side effects compared to traditional medicines. Most pregnant women do no longer get information approximately the use of herbs. In some studies, there is a significant relationship between age and the use of herbal medicine. The variety of pregnancies and children additionally had a substantial relationship with the use of herbal medications. Further, a significant relationship was found among the trimester of pregnancy and using herbal medications. The highest use of herbal medicine occurred in the third trimester, with frequencies various from 15.3% to 60.0%. The motivation for pregnant women to use herbal medicine during pregnancy is because the medicine has been consumed before pregnancy and to save health costs. Some pregnant women also believe that herbal medicines are safe and harmless to the mom and fetus. Almost 58% of pregnant women used herbal medication because it become extra reachable than medical therapy (Bouqoufi *et al.*, 2023).

Pregnant women use herbal medicine to deal with gastrointestinal disorders (inclusive of nausea, vomiting, pain, flatulence, and abdominal pain, flu and cold symptoms, stretch marks), to stimulate labor, increase neonate intelligence, and improve fetal health (Bouqoufi *et al.*, 2023). Another study conducted in South Africa mentioned that herbal medicine is used for the treatment of not unusual problems associated

with pregnancy, such as edema, indigestion, constipation, infection, excessive blood stress, and postpartum restoration (Panganai *et al.*, 2016). Factors influencing the increased use of herbal medicine include culture and beliefs, poverty, low levels of education, long distances to health facilities, and high cost of modern drugs. Some of the problems in the use of herbal medication in pregnant women include that traditional medication is still untested, and its mode of movement or protection isn't acknowledge in the management of being pregnant. In addition, its interaction with drugs and food ate up by means of pregnant women is likewise unknown (Mudonhi *et al.*, 2022).

Knowledge related to teratogenicity affects behavior change in pregnant women, as pregnant women significantly reduce self-medication behavior, ask about medication safety, and comply with drug use guidelines. Pregnant women tend to continue using drugs after obtaining adequate information on drug teratogenicity. There are various sources of information regarding medication use during pregnancy accessed by pregnant women. The most normally accessed resources are drug stores or formal health care companies, consisting of popular practitioners, obstetricians, midwives, pharmacists, friends, family, the internet, and magazines. In addition, healthcare websites and telephone session services have been rated incredibly honest and useful. Any other examined cited that pregnant women chose to take limited medicine because of a loss of information regarding drug safety (Kirubarajan *et al.*, 2021).

A total of 27.6% of pregnant women used four or more medications during pregnancy.

Overall, polypharmacy in being pregnant turned into located to be related to an expanded threat of congenital malformations in comparison to unexposed pregnancies or monotherapy with ORs ranging from 1.1 to >10.0 (95% CI 1.03-326). Lack of drug-related

knowledge is a potential problem for some pregnant women with chronic diseases, such as diabetes, cardiovascular disease, epilepsy, asthma, and rheumatic diseases (Thunbo *et al.*, 2022).

DISCUSSION

In the last 10 years, from the PubMed *database* search, only five *systematic reviews* were obtained that discussed the knowledge and use of drugs during pregnancy in pregnant women. This small number of results is because the authors only used one *database* to search for research articles. *Databases* that have not been included i.e. Scopus, Embase, Medline, Cochrane, Google Scholar, and *Web of Science*. The lack of *databases* led to the lack of systematic review and meta-analysis studies. Only one *systematic review* found by the author discussed the knowledge of pregnant women regarding the use of drugs. Whereas if searched further in the PubMed *database*, many observational studies in various countries discuss the knowledge of pregnant women related to drug use in *real-world* or community *settings*. In addition, the authors also did not find meta-analysis research in the last 10 years. This prevented the authors from providing a more complex analysis of safety, harm, and benefit data related to medication use during pregnancy. Meta-analysis studies are essential for establishing statistical significance to obtain a more accurate estimate of the magnitude of impact.

Drug use during pregnancy is increasing, especially in the use of over-the-counter drugs, prescription drugs, and herbal drugs. Pregnant women's knowledge regarding the use of drugs at some point of being

pregnant is essential. Pregnant women's knowledge related to the drugs they consume and the dangers or side effects of these drugs on the mother and fetus will affect their attitude toward taking these drugs. A higher level of knowledge is associated with a higher likelihood of engaging in self-medication behavior during pregnancy, thus increasing the use of over-the-counter drugs in pregnant women. However, if pregnant women know the risks of over-the-counter drugs, they are less likely to engage in self-medication behavior (Atmadani *et al.*, 2020). Safety information related to consumed drugs is mainly obtained by pregnant women from drug packaging. Many pregnant women feel concerned about capacity risks to the fetus and protection information on drug use. In a few nations, there is a real knowledge gap among pregnant women regarding the teratogenicity and possible negative outcome of drugs on the fetus. Therefore, it is not surprising that many pregnant women feel distrustful of the medical system. One potential consequence of this distrust is the increased use of herbal remedies (Kirubarajan *et al.*, 2021).

According to WHO findings, two-thirds of pregnant women in low-middle-income nations use traditional medications as their primary source of health care (Crockett *et al.*, 2020). A recent survey showed that pregnant women

in the Eastern Mediterranean Regional Office region use a wide variety of herbal medicines, and 65 different species of medicinal plants were reported to be used in traditional medicine during pregnancy. However, the authors did not find any research on the use of herbal medications in the Asian region. At the same time, China and Indonesia have biodiversity and natural products. Many herbal plants can be found in these two countries. In addition, until now, there has still been a culture or belief in the community regarding the use of herbal medicine. Regarding the use of herbal medicine during pregnancy, most pregnant women are from rural areas, homemakers, and have educational qualifications below college (Bouqoufi *et al.*, 2023).

Systematic reviews related to the usage of herbal medications were found in the Eastern Mediterranean region and Sub-Saharan African countries. Where the usage of herbal medications in these two regions is high. However, there is still a knowledge gap regarding the usage of herbal medications during pregnancy. Most pregnant women do not know the effects on the fetus related to the usage of herbal medications. Local cultural factors or hereditary heritage are the cause of the high usage of herbal medications. Family and friends are the primary sources of motivation related to the use of herbal medicine. There is very little literature on the safety of herbal medications used all through pregnancy. To provide care and counseling for patients using herbal medicines, pharmacists need to have sufficient information about the use and safety of herbal medicines and should update their knowledge. This may be carried out by means of supplying training and education to

practising pharmacists via organizing persevering with medical training programs focused at the efficacy, potential dangers, feasible interactions and effects of natural drugs, and key principles carried out to herbal management at some stage in pregnancy.

The usage of antibiotics during pregnancy is also something that needs to be considered. Because there are several types of antibiotics that are dangerous for pregnant women and fetuses. In addition, using antibiotics without a doctor's prescription and clear medical indications also needs to be watched. The *systematic review* also did not measure the danger of side effects due to the wrong use of antibiotics during pregnancy. Overall, there is a lack of health literacy among all pregnant women regarding the use of over-the-counter drugs, herbal remedies, and prescription drugs. Pregnant women often lack an understanding of the side effects associated with drug use, especially overuse, and many pregnant women experience polypharmacy. Evidence regarding the potential risk of congenital malformations in polypharmacy-treated pregnant women is limited. The studies identified have been heterogeneous and did not analyze equal drug combinations, making pooled risk estimates challenging to determine.

CONCLUSIONS

The prevalence of the use of herbal medicines and antibiotics during pregnancy is still relatively high. Most pregnant women do not have a good level of knowledge regarding the use of these drugs during pregnancy. In addition, some pregnant women also do not know the side effects that occur to the mother and fetus due to the use of

these drugs. This is due to the lack of literature related to the use of herbal medicines and antibiotics. There is a knowledge gap in the literature about the risk of congenital malformations due to the use of four or more drugs (polypharmacy) during pregnancy.

Further research is needed to examine the relationship between polypharmacy exposure and the risk of congenital malformations. In addition, it is necessary to expand the database used to search for results of *systematic reviews* and meta-analyses related to knowledge and drug use during pregnancy in pregnant women that have been conducted so far.

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