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SYSTEMATIC REVIEW

Benefits of Low-Dose Aspirin During Pregnancy: A Systematic Review

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Abstract: Low-dose aspirin therapy (LDA) is reported to give good results on the outcome of pregnancy. This systematic review study aims to find out in what cases the role of LDA can be given, the amount of dose and duration of administration and the final results of various studies that have been conducted. Researchers used a systematic literature study with the help of Publish or Perish, Mendeley and Microsoft Excel applications in a literature search from Google Scholar with the keyword low dose aspirin related to pregnancy. Of the 200 articles taken, after conducting a systematic assessment, 21 articles were included in the inclusion criteria that discussed 4 topics, namely pre-eclampsia, current pregnancy loss, healthy pregnancy and inflammatory cases in pregnancy. From the results of the review, it can be concluded that low-dose aspirin can be used and is beneficial in preventing and treating some complications in pregnancy. Its administration can be given before conception until gestational age reaches 36 weeks with a dose range of 50 mg to 150 mg per day.

Keywords: Low-dose aspirin, LDA, pregnancy

INTRODUCTION

A healthy pregnancy is the hope of every pregnant woman, so it is hoped that the pregnancy process can be passed properly and a healthy child is born.[1,2] However, complications in pregnancy are often reported to occur in some cases of pregnancy so therapeutic efforts have been made both pharmacologically and non-pharmacologically therapy.[3],[4],[5]

One pharmacological therapy that is widely done is the administration of low-dose aspirin (LDA) to overcome several kinds of complications in pregnancy.[6,7]

Various benefits of giving low-dose aspirin have been published in reputable journals, but it is necessary to know in what cases the benefits of low-dose aspirin are given to overcome pregnancy complications, how many doses are given, whether research on the use of low-dose aspirin has been studied in many countries and how the results obtained are interesting to know so that it is hoped that the use of low-dose aspirin can be applied correctly.

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administration and the final results of various studies that have been conducted

METHODS

This Systematic review study uses the Publish or Perish application, selecting articles from Google Scholar sources using the keyword low dose aspirin related pregnancy with a range of 2019 to 2023. The search results are then copied using the Mendeley application to obtain a complete bibliography of writing. The results of Mendeley's data are then exported into Microsoft Excel and classified based on inclusion criteria, namely, articles must come from Scopus-indexed journals with quartiles 1 and 2, are research articles, articles have been cited at least 5 times, articles must be related to the use of low dose aspirin in pregnancy. Articles that enter the inclusion criteria are equipped with data according to the objectives and research problems, and then the flow of this systematic study is added in prism diagrams and literature search results tables for further study and discussion to get conclusions.

RESULTS

From the results of a systematic review of 200 articles selected using the Publish or Perish Application, 21 articles were included in the inclusion criteria, The systematic step in the literature search can be seen in the prism diagram in Figure 1.

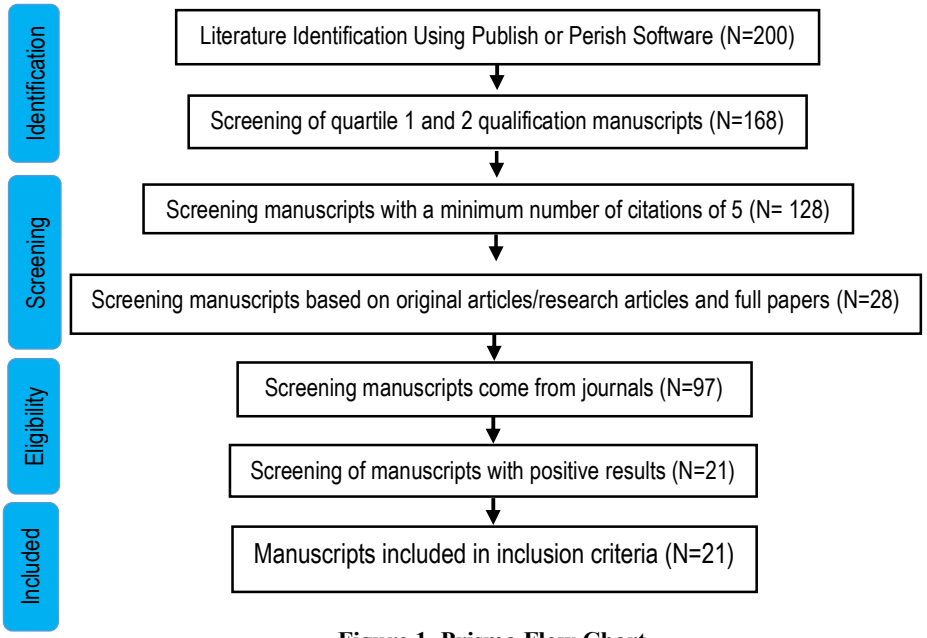

Figure 1. Prisma Flow Chart

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Twenty-one articles included in the inclusion criteria were then collected using Microsoft Excel and can be seen in Table 1.

Table 1. Results of systematic literature search included in inclusion criteria about the benefits of low-dose aspirin during pregnancy

No.	Cites	Study	Yr	Source	Qrtl	Publisher	Case	Study Design	N	Origin	Dose
1	182	Hoffman MK et all [8]	2020	Obstetrical and Gynaecological Survey	2	Elsevier	Pre-Eclampsia	RCT	11,976	Congo, Guatemala, India, Kenya, Pakistan, Zambia	81 mg
2	35	Lu C, et all[9]	2019	Journal of Maternal-Foetal and Neonatal Medicine	2	Taylor &Francis	RPL	RCT	1251		81-100 mg
3	30	Lin L, et all[10]	2019	Journal of Cellular Physiology	1	Wiley Online Library	Pre-Eclampsia	cohort	10	China	0.005–0.5 mM
4	24	Gu W, et all [11]	2020	European Journal of Obstetrics and Gynecology and Reproductive Biology	2	Elsevier	Pre-Eclampsia	RCT	1105	China	25,50,75 mg

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No.	Cites	Study	Yr	Source	Qrtl	Publisher	Case	Study Design	N	Origin	Dose
5	22	Finneran MM. et all [12]	2019	American Journal of Obstetrics and Gynaecology	1	Elsevier	Pre-Eclampsia	cohort	1002	USA	60mg
6	22	Kalafat E, et all [13]	2020	American Journal of Obstetrics and Gynaecology	1	ajog.org	Pre-Eclampsia	cohort	630	UK	75mg, 150 mg
7	21	Madani T, et all[14]	2019	Journal of Obstetrics and Gynaecology Research	2	Wiley Online Library	Pregnancy rate, FET	RCT	60	Iran	100mg
8	19	Naimi. et all[15]	2021	Annals of Internal Medicine	1	acpjournals.org	Pregnancy	Cohort	1227	USA	81 mg
9	16	Zvanca ME, et all[16]	2019	Journal of Maternal-Foetal and Neonatal Medicine	2	Taylor &Francis	Low-risk pregnancy	Retrospective	128	Romania	75 mg, 100 mg
10	15	Wang T, et all[6]	2020	International Journal of Gynaecology and Obstetrics	1	Wiley Online Library	RPL	RCT	571	China	50 mg

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No.	Cites	Study	Yr	Source	Qrtl	Publisher	Case	Study Design	N	Origin	Dose
11	15	Karadağ C, et all [17]	2020	Journal of Maternal-Foetal and Neonatal Medicine	2	Taylor &Francis	RPL	RCT	174	Turkey	100 mg
12	15	van Montfort P, et all[18]	2020	Acta Obstetricia et Gynecologica Scandinavica	1	Wiley Online Library	Pre-Eclampsia	cohort	306	Netherlands	80-100 mg
13	14	Huai J, et all[19]	2021	Journal of Clinical Hypertension	2	Wiley Online Library	Pre-Eclampsia	RCT	898	China	100 mg
14	14	Levine LD, et all[20]	2019	Canadian Journal of Physiology and Pharmacology	2	cdnsciencepub.com	Inflammation	RCT	1228	USA	81 mg
15	11	Wang M, et all[21]	2019	Clinical Immunology	1	Elsevier	Recurrent pregnancy loss (RPL)	cohort	120	China	50-75 mg
16	11	Walsh SW, et all[22]	2020	Reproductive Sciences	2	Springer	Pre-eclampsia	cohort	36	USA	81 mg

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No.	Cites	Study	Yr	Source	Qrtl	Publisher	Case	Study Design	N	Origin	Dose
17	11	Wheeler SM, et all [23]	2022	JAMA Network Open	1	jamanetwork.com	Pre-eclampsia	cohort retrospective	3,695,019	USA	81 mg
18	9	Theilen LH, et all[24]	2020	American Journal of Obstetrics and Gynecology	1	Elsevier	Pregnancy complication	RCT	1185	USA	81 mg
19	5	Wang M, et all[25]	2021	Journal of Nephrology	1	Springer	Pre-Eclampsia	Retrospective	287	China	75-100 mg
20	5	Xiqi Li, et all [26]	2021	Hypertension	1	Am Heart Assoc	Pre-Eclampsia	RCT	198	China	150 mg
21	5	Sun S, et all [27]	2021	International Journal of Gynecology and Obstetrics	1	Wiley Online Library	RPL	Cohort	202	China	50-75 mg

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From the results of the literature search, the use of low-dose aspirin therapy was most widely carried out in cases of pre-eclampsia with a total of 11 articles (52%), and the use of low-dose aspirin was also given in cases of recurrent pregnancy loss (RPL) as many as 4 articles (24%), and the use of low-dose aspirin for health pregnancy efforts was found to be 4 articles (19%). and inflammatory cases in pregnancy are also as many as 1 article (5%).

The total number of samples involved in this systematic literature study was 3,717,613 research subjects from various countries

The country of origin where the research was conducted was China 9 articles (43%), USA 6 articles (29%), the Netherlands 1 article (5%), Turkey 1 article (5%), Romania 1 article (5%), Iran 1 article (5%), United Kingdom 1 article (5%), Interstate (Congo, Guatemala, India, Kenya, Pakistan, Zambia) 1 article (5%).

The most common types of studies conducted on low-dose aspirin use research were randomized clinical trials (RCT) 10 articles (48%), cohort 8 articles (38%), retrospective studies 2 articles (10%), retrospective cohort 1 article (5%)

Low-dose aspirin used in many studies ranges from 50 mg to 150 mg, with varying lengths of administration, starting from before conception to the end of pregnancy.

DISCUSSION

Low Dose Aspirin and Pre-Eclampsia

The pathophysiology of pre-eclampsia in pregnant women is explained in several approaches, one of which is due to ischemia, hypoxia in the placenta and the secretion of soluble fms-like tyrosine kinase 1 (sFlt1) enzyme into the maternal circulation.[10,28,29] Low-dose aspirin administration decreased hypoxia induced by sFlt1 production and c-Jun NH_2-terminal kinase/protein-1 activator (JNK/AP-1) pathway mediating sFlt1 induction.[10,30] Low-dose aspirin (LDA) administration can directly decrease the expression of AP-1 factor, and this decreases sFlt1 production.[10] So it can be concluded that LDA works against trophoblast and endothelial dysfunction and revealed that LDA mediates the process of inhibition of sFlt1 secretion via JNK/AP-1 pathway which is a molecular mechanism to prevent pre-eclampsia.[10] In addition to JNK / AP-1 pathway, in another theory, it was revealed that the occurrence of pre-eclampsia as a result of the creation of imbalance conditions in prostacyclin levels and thromboxane B2 (TXB2) which is the key to pre-eclampsia, so that LDA administration can reduce TXB2 levels that increase in women who predispose to pre-eclampsia such as in women who are obese during pregnancy.[12,31–34] In a study conducted by Wei Gu in China where it was found that the effectiveness of LDA in preventing pre-eclampsia and other complications in pregnancy is directly proportional to the size of the dose given. [11] Low-dose aspirin in terms of prevention of pre-eclampsia is best given before 16 weeks of gestation. [23]

Low Dose Aspirin and Recurrent Pregnancy Loss (RPL)

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Recurrent pregnancy loss (RPL) is a failure in pregnancy more than two or more times, this can occur in 2-5% of pregnant women. [10.11,17] Several theories have been proposed to explain the aetiology of RPL including genetic, chromosomal, immunological, endocrinological, anatomical and structural factors.[17,35–37] One of the etiologists of RPL can be explained by poor endometrial receptivity resulting in inadequate perfusion of the uterus that triggers endometrial and sub-endometrial hypoxia.[6] Patients with RPL experience thinning of endometrial thickness as well as obstruction of uterine arteries and endometrial blood flow. [6] LDA administration can improve uterine artery condition and endometrial perfusion in RPL patients by increasing the flow rate in the uterine and endometrial arteries. [6] Low-dose aspirin blocks thromboxane A2 (TXA_2) synthesis and prevents platelet aggregation and vasoconstriction from occurring.[12,38,39] Another theory that explains the occurrence of RPL is the manifestation of genetic mutations in factor V Leiden (FVLM) this causes thrombophilia which is a predisposing factor for various disorders in pregnancy such as the high risk of suffering from pre-eclampsia, intrauterine fetal growth restriction, placental absorption and premature birth.[17,40] From an immunological point of view, it is explained that RPL occurs as a manifestation of the anti-phospholipid immune syndrome (APS), where the pathophysiology of this syndrome is the occurrence of haemostasis disorders of T-helper cytokine 1 (Th1), namely IL-2 and interferon (IFN)-γ and or Th2, namely interleukin (IL)-4 and IL-10, but overexpression occurs which causes changes in the immune response which is believed to damage the placental villi and embryonic tissue which adversely affects the implantation process and the development of fertilization results that manifest in impaired embryonic growth which ultimately leads to the appearance of side effects in pregnancy. [21,41–45] In the case of RPL in addition to single LDA administration, combination treatment with low molecular weight heparin (LMWH) can also be given. [17,21,46–49]

Low Dose Aspirin and Health Pregnancy

In one study conducted by Madani T et all, it was found that giving low-dose aspirin to women who will undergo IVF with the frozen-thawed embryo transfer (FET) cycles method, resulted in better pregnancy, implantation, and live birth rates without changing uterine hemodynamic or endometrial thickness.[14] Low-dose aspirin (LDA) therapy begins midway through the luteal phase of the previous cycle, significantly improving ovarian blood flow velocity, ovarian responsiveness, and implantation and pregnancy rates. [14]

Another condition in the form of high oestrogen levels associated with ovarian stimulation can increase platelets and coagulation activity leading to a state of procoagulant where this condition is known as thrombophilia, it causes the formation of local micro thrombosis at the implantation site, which consequently impairs the ability of syncytiotrophoblast to connect with the

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mother's blood vessels resulting in poor placental perfusion.

Research conducted by Naimi et all found that giving low-dose aspirin at least 4 times 1 week before conception to 36 weeks of pregnancy was able to increase β-hCG levels as a marker of pregnancy and reduce the occurrence of abortion in the population of women who experience recurrent pregnancy loss, this increases live births to above 30%. [15]

In another study, it was found that giving low-dose aspirin before entering 11 weeks of pregnancy had a good effect on pregnancy, as evidenced by the increase in β-hCG and Pregnancy-associated plasma protein A (PAPPA) as the main biomarkers in first-trimester pregnancy as markers of a good pregnancy. [16]

Low-Dose Aspirin and Inflammation

Inflammation has been identified to play an important role in the manifestations of pregnancy. [20] Systemic biomarkers such as high-sensitivity C-reactive protein (hs-CRP) are associated with complications in pregnancy such as pre-eclampsia, pre-term delivery, pregnancy loss and intrauterine growth restriction.[20,50] A study conducted by Lindsay D et all, by examining the levels of hsCRP biomarkers in various pregnancy conditions, found that low-dose aspirin therapy from preconception to 36 weeks gestation in women who had a history of complications in pregnancy showed a decrease in hrCRP levels which turned out to be directly proportional to the low pregnancy complications that occurred and the increase in good birth manifestation. [20]

CONCLUSION

Low-dose aspirin can be used and is beneficial in preventing and treating some complications in pregnancy. Its administration can be given before conception until gestational age reaches 36 weeks with a dose range of 50 mg to 150 mg per day.

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