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Sildenafil plus Low Dose Aspirin for Prevention of Preeclampsia: A Randomized Controlled Trial

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Abstract

Objective: To compare between the efficacy of the use of oral sildenafil plus low dose aspirin versus the use of oral low dose aspirin alone in pregnancy as preventive measure in women at risk for preeclampsia (PE). **Design:** A randomized clinical trial. **Setting:** Outpatient Obstetric clinic of Ain Shams University Maternity Hospital. **Population or sample:** Women at gestational age of ≤16 weeks who at risk for PE between June 2018 and June 2019. **Methods:** Participants were randomly allocated into two groups: Group I Included 200 women who received a 25 mg tablet of oral sildenafil citrate tid until delivery plus 100 mg tablet of aspirin orally once daily until gestational age of 36 weeks, Group II Included 200 women who received a 100 mg tablet of aspirin orally once daily until gestational age of 36 weeks. **Main Outcome Measures:** Incidence of preeclampsia diagnosed per ACOG criteria. **Results:** The incidence of PE in both groups showed no statistically significant difference. The incidence of PE in the first group is 11.0%, and it is 12.0% in the second group (p-value 0.754). **Conclusion:** The addition of sildenafil citrate to low dose aspirin had no impact on the prevention of preeclampsia for women at risk of PE, in addition, sildenafil did not improve maternal and fetal outcomes.

Keywords

Preeclampsia, Hypertension, Placental Disease, Pregnancy Complications, Aspirin, Sildenafil Citrate

1. Introduction

Pregnancy is characterized by significant metabolic and hemodynamic changes

that begin early in the gestational period. Major hemodynamic changes include an increase in the cardiac output during the first trimester, sodium and water retention leading to plasma volume expansion with a peak around week 30, and reductions in the systemic vascular resistance and systemic blood pressure [1]. The reduction of the systemic vascular resistance is around 25% and is due to the increase in vasodilating agents, like nitric oxide and prostacyclin production, and the decrease in the sensitivity to norepinephrine and angiotensin [1]. The diastolic blood pressure begins to decrease from the 7th week of gestation, with a 10 mmHg decline between the 24th-26th gestation weeks, returning to normal values during the third trimester [2]. These are some of the changes that can occur during pregnancy.

Hypertension is the most prevalent maternal complication worldwide (several studies estimate that it affects 7% - 10% of all pregnancies) [3], and it is associated with a significant morbidity and mortality of the mother and fetus. In fact, hypertension is the second largest cause of direct maternal death worldwide (14% of the total) [4], and it is estimated that 192 people die every day because of hypertensive disorders in pregnancy [5].

In Latin America and the Caribbean, hypertensive disorders are responsible for almost 26% of maternal deaths, whereas in Africa and Asia they contribute to 9% of deaths. Although maternal mortality is much lower in high-income countries than in developing countries, 16% of maternal deaths can be attributed to hypertensive disorders [6].

Pre-eclampsia and eclampsia are two hypertensive disorders of pregnancy, considered as major causes of maternal and perinatal morbidity and mortality [7]. These diseases affect between 3% and 5% of all pregnancies and account for more than 60,000 maternal and 500,000 fetal deaths per year worldwide [8].

Preeclampsia is a disorder of pregnancy associated with new-onset hypertension, which occurs most often after 20 weeks of gestation and frequently near term. Although often accompanied by new-onset proteinuria, hypertension and other signs or symptoms of preeclampsia may present in some women in the absence of proteinuria [9]. Reliance on maternal symptoms may be occasionally problematic in clinical practice. Right upper quadrant or epigastric pain is thought to be due to periportal and focal parenchymal necrosis, hepatic cell edema, or Glisson's capsule distension, or a combination. However, there is not always a good correlation between the hepatic histopathology and laboratory abnormalities [10]. Similarly, studies have found that using headache as a diagnostic criterion for preeclampsia with severe features is unreliable and nonspecific. Thus, an astute and circumspect diagnostic approach is required when other corroborating signs and symptoms indicative of severe preeclampsia are missing [11]. Of note, in the setting of a clinical presentation similar to preeclampsia, but at gestational ages earlier than 20 weeks, alternative diagnoses should be considered including but not limited to thrombotic thrombocytopenic purpura, hemolytic-uremic syndrome, molar pregnancy, renal disease or au-

toimmune disease.

Although hypertension and proteinuria are considered to be the classical criteria to diagnose preeclampsia, other criteria are also important. In this context, it is recommended that women with gestational hypertension in the absence of proteinuria are diagnosed with preeclampsia if they present with any of the following severe features: thrombocytopenia (platelet count less than 100,000 × 10 9/L); impaired liver function as indicated by abnormally elevated blood concentrations of liver enzymes (to twice the upper limit of normal concentration); severe persistent right upper quadrant or epigastria pain and not accounted for by alternative diagnoses; renal insufficiency (serum creatinine concentration greater than 1.1 mg/dl or a doubling of the serum creatinine concentration in the absence of other renal diseases); pulmonary edema; or new-onset headache unresponsive to acetaminophen and not accounted for by alternative diagnoses or visual disturbances. Gestational hypertension is defined as a systolic blood pressure of 140 mmHg or more or a diastolic blood pressure of 90 mmHg or more, or both, on two occasions at least 4 hours apart after 20 weeks of gestation in a woman with a previously normal blood pressure [12]. Women with gestational hypertension with severe range blood pressures (a systolic blood pressure of 160 mmHg or higher, or diastolic blood pressure of 110 mmHg or higher) should be diagnosed with preeclampsia with severe features. These severe ranges of blood pressure or any of the severe features increase the risk of morbidity and mortality [13]. It is known that pre-eclampsia and eclampsia are the hypertensive disorders that involve the most significant health risks for the pregnant woman and the fetus. In this context, it is imperative to evaluate whether all possible and necessary measures are being taken correctly in terms of prevention, maintenance, and treatment of the disease.

Aspirin (acetylsalicylic acid) is a non-steroidal anti-inflammatory drug (NSAID) that works primarily through its inhibition of two cyclooxygenase is enzymes (COX-1 and COX-2), which are necessary for prostaglandin biosynthesis. The COX-1 isoform is present in the vascular endothelium and regulates the production of prostacyclin and thromboxane A2, prostaglandins with opposing regulatory effects on vascular homeostasis and platelet function. Prostacyclin is a potent vasodilator and inhibitor of platelet aggregation, whereas thromboxane A2 (TXA2) is a potent vasoconstrictor and promotes platelet aggregation. The effect of aspirin on COX-dependent prostaglandin synthesis is dose dependent. At lower dosages (60 - 150 mg/day) aspirin irreversibly acetylates COX-1, resulting in decreased platelet synthesis of TXA2 without affecting vascular wall production of prostacyclin [14]. At higher doses, aspirin inhibits both COX-1 and COX-2, effectively blocking all prostaglandin production. Evidence suggesting that an imbalance in prostacyclin and TXA2 metabolism was involved in the development of preeclampsia prompted the initial studies of aspirin for preeclampsia prevention because of its preferential inhibition of TXA2 at lower doses [15]. Whether low-dose aspirin improves early placental perfusion is unknown,

and likewise, the precise mechanism by which low-dose aspirin prevents preeclampsia in some women is also uncertain [16].

Sildenafil is a phosphodiesterase5inhibitor (PDE5), which enhances NO- mediated effects by inhibiting cyclic guanosine monophosphate degradation. During pregnancy, NO activity increases, mediating essential vascular adaptation, such as reducing maternal peripheral vascular resistance [17] and creating the low-resistance/high-caliber utero-placental unit needed to provide adequate blood flow to the fetus [18]. Increasing NO availability during pregnancy might overcome deficits in placental and systemic NO reported in FGR and preeclampsia and thereby improve placental function and maternal endothelial function [19]. Moreover, sildenafil might counterbalance vascular dysfunction because of augmented vasoconstrictors and antiangiogenic factors [20]. Because no pronounced maternal and fetal side effects were observed in pregnant women using sildenafil for pulmonary artery hypertension, [21] transition of sildenafil from preclinical to clinical studies was established for the indications FGR and preeclampsia. The first prospective studies and small clinical trials show beneficial effects of maternal oral sildenafil treatment on fetal growth [13] and maternal blood pressure (BP) [22] at fairly low dosages.

2. Methods

The current study was a parallel groups, randomized comparative clinical trial, which was performed between June 2018 and June 2019 at a large tertiary referral university hospital. The study population was a consecutive series of participant between 18 and 40 years, all of them are Egyptians, Some of them are nulliparous and others are parous, some of them are singleton pregnancy and others are of multiple gestations, also some of them are medically free and others have chronic diseases and autoimmune diseases. Pregnant women with foetus of congenital anomaly are excluded from the study.

Sample Size Calculation: Sample size was calculated using PASS 11.0 sample size calculator and based on a study carried out by ***Kamil et al.*** **(2018)** [23]; also according to ***ACOG*** **(2018)** [24] that mentioned that preeclampsia was observed in 1.6% participants in the acetylsalicylic acid group, compared with 8.0% those at risk for preeclampsia. Group sample sizes of **200** women at risk for preeclampsia in group one (Sildenafil + Aspirin group) and **200** women at risk for preeclampsia in group two (Aspirin group) achieve 80% power to detect a difference between the group proportions of −0.0640. The proportion in group one (the treatment group) is assumed to be 0.0160 under the null hypothesis and 0.008 under the alternative hypothesis. The proportion in group two (the control group) is 0.0800. The test statistic used is the two-sided Z test with pooled variance. The significance level of the test was targeted at 0.0500. The significance level actually achieved by this design is NA.

400 women were invited to participate in the study according to the inclusion and exclusion criteria as follow.

2.1. Inclusion Criteria

Pregnant women at gestational age of ≤16 weeks are distributed into:

Women high risk for preeclampsia (If the women has one or more of these high-risk factors) [25] which include:

- History of preeclampsia, especially when accompanied by adverse outcome, among parous women, the risk of PE in subsequent pregnancies depends on a prior history of PE. This relative risk for subsequent PE ranges from 7 to 10 times higher in a second pregnancy.
- Multifetal gestation (Preeclampsia is more common in women who are carrying twins, triplets or other multiples).
- Chronic hypertension (≥140/90 mmHg or medication for hypertension before 20 weeks of gestation).
- Preexisting type 1 or type 2 diabetes.
- Renal disease.
- Autoimmune disease {systemic lupus—antiphospholipid syndrome}.

Recently, a systematic review and meta-analysis evaluated clinical risk factors at less than or equal to 16 weeks of gestation in 25,356,655 pregnant women in 27 countries. Patients with a history of chronic hypertension have a higher risk of developing PE than those without this condition (relative risk [RR] 5.4; 95% CI, 4.0 - 6.5). Pre-existing diabetes mellitus, APS, SLE, and chronic kidney disease are also associated with an increased risk of developing PE (RR 3.7; 95% CI, 3.1 - 4.3; RR 2.8; 95% CI, 1.8 - 4.3; RR 2.5; 95% CI, 1.0 - 6.3; and RR 1.8; 95% CI, 1.5 - 2.1, respectively).

Women moderate risk for preeclampsia (If women have more than one of these moderate risk factors) [25] which include:

- Nulliparous women, the increased risk of developing PE have been widely reported. One systematic review reported that the risk of PE is increased three-fold in nulliparous women.
- Obesity {Body mass index greater than 30 kg/m^2}.
- Family history of preeclampsia, although most cases of PE are sporadic, a familial susceptibility to PE has been documented. Daughters or sisters of women with PE are 3 - 4 times more likely to develop the condition than women without a family history.
- Sociodemographic characteristics {African—American—low socioeconomic status}, the risk of PE was significantly higher in women of Afro-Caribbean and South Asian racial origin compared with white women.
- Advanced maternal age, defined as age greater than or equal to 35 years at the time of delivery, is associated with 1.2 to 3-fold increased risk of developing PE.
- Personal history factors {low birth weight—small for gestational age—previous adverse pregnancy outcome—more than ten years pregnancy interval}. Interpregnancy intervals of less than 12 months or greater than 72 months are associated with higher risk of PE development compared with interpregnan-

cy intervals of 12 - 23 months.

2.2. Exclusion Criteria

- Gestational age > 16 wks.
- Gestational age < 12 wks.
- According to the use of aspirin.
  - Allergy to aspirin.
  - A history of one of the following: asthma, peptic ulcer, inflammatory bowel disease, rheumatoid arthritis, haemophilia or thrombophilia.
- According to the use of sildenafil.
  - Allergy to sildenafil.
  - A history of one of the following:
    - ✓ Unpredictable Severe Constricting Chest Pain.
    - ✓ Narrowing of the Aortic Heart Valve.
    - ✓ Hypertrophic cardiomyopathy.
    - ✓ Life-Threatening Irregular Heart Rhythm.
    - ✓ Chronic heart failure.
    - ✓ Abnormally low blood pressure.
    - ✓ Liver problems.
    - ✓ Severe renal impairment.
    - ✓ Sickle Cell Anemia.

After good history taking and detailed examination, ultrasound scanning and laboratory investigation was done; Participants were randomly allocated into two groups:

Group I: "Sildenafil citrate plus oral low dose aspirin group" included 200 women who received a 25 mg tablet of sildenafil citrate (silden 25 mg, EIPICO, EGYPT) orally three times daily until delivery plus 100 mg tablet of aspirin (Aspirin® Protect 100 mg, BAYER, GERMANY) orally once daily until gestational age of 36 weeks.

Group II: "Aspirin group" included 200 women who received a 100 mg tablet of aspirin (Aspirin® Protect 100 mg, BAYER, GERMANY) orally once daily until gestational age of 36 weeks.

400 opaque envelopes had been numbered serially and enveloped the corresponding letter which denoted the allocation be put according to randomization table. Then all envelopes were closed and put in one box. When the first patient arrived, the envelope was opened and the participant was allocated according to letter inside.

In the first group, after good history taking and detailed examination, ultrasound scanning and laboratory investigation was done; the participant received a 25 mg tablet of sildenafil citrate (silden 25 mg, EIPICO, EGYPT)orally three times daily until delivery plus 100 mg tablet of aspirin (Aspirin® Protect 100 mg, BAYER, GERMANY) orally once daily until gestational age of 36 weeks.

In the second group, also after good history taking and detailed examination,

ultrasound scanning and laboratory investigation was done, the participant received a 100 mg tablet of aspirin (Aspirin® Protect 100 mg, BAYER, GERMANY) orally once daily until gestational age of 36 weeks.

All Participants Will Be Followed up by:

Measuring blood pressure: Sphygmomanometry is the recommended method for blood pressure measurement during pregnancy. The patient should be relaxed prior to measurement. After 5 minutes has elapsed, the participant's blood pressure should be read while she is in a sitting position, with her legs uncrossed and her back supported. The participant's arm should beat the level of the right atrium of the heart. If the participant's upper arm circumference is 33 cm or greater, a large blood pressure cuff should be used. Clinicians should avoid measuring blood pressure in the upper arm in the left lateral position because this position falsely lowers blood pressure readings. Blood pressure measurements should be obtained during each prenatal care visit throughout pregnancy. If a patient has an elevated blood pressure reading, the reading should be confirmed with repeated measurements.

Laboratory investigations: Complete blood count, urine analysis, liver function tests, and kidney function tests.

Ultrasonic fetal growth assessment: Growth of bi-parietal diameter (BPD), head circumference (HC), AC, femur length (FL), HC/AC ratio, FL/AC ratio and EFW.

Participants were diagnosed according to a recently revised criteria for the diagnosis of preeclampsia which includes elevated blood pressure (≥140/90 mmHg on 2 occasions 4 hours apart, after 20 weeks of gestation) and either proteinuria (≥300 mg/dl on a 24-hour urine protein test, protein to creatinine ratio of ≥ 0.3 [each measured as mg/dl], or urine protein dipstick reading ≥ 2 if quantitative analysis is not available) or, in the absence of proteinuria, thrombocytopenia, renal insufficiency, impaired liver function, pulmonary edema, or cerebral or visual symptoms.

The patients were informed to return to the hospital if they were complaining from right upper quadrant pain, epigastria pain, and new-onset headache unresponsive to acetaminophen and not accounted for by alternative diagnoses or visual disturbances.

2.3. Statistical Analysis

Data were analyzed using IBM© SPSS© Statistics version 23 (IBM© Corp., Armonk, NY).

Continuous numerical variables were presented as mean and SD and inter-group differences were compared using the unpaired t-test.

Categorical variables were presented as number and percentage and differences were compared using the Pearson chi-squared test or Fisher's exact test as appropriate. Ordinal variables were compared using the chi-squared test for trend.

Multivariable binary logistic regression analysis was used to test the relation

between addition of sildenafil to low-dose aspirin and the incidence of preeclampsia as adjusted for other confounding factors.

P-values < 0.05 are considered statistically significant.

3. Results

Among the 400 women recruited at baseline, 8 women withdrew and discontinued treatment before delivery, 5 in the first group (2.5%) and 3 in the second group (1.5%), also 17 women lost to follow up, 10 in the first group (5%) and 7 in the second group (3.5%). In total, 46 women developed preeclampsia, 22 in the first group (11%) and 24 in the second group (12%). Accordingly the incidence of PE in both groups showed no statistically significant difference (p-value 0.754). Baseline characteristics did not differ statistically between the two groups (Table 1). The obstetric history of the two groups showed no statistically significant difference. The difference in parity was comparable between the two groups (p-value = 0.297). Also the history of previous miscarriages was comparable between the two groups (p-value = 0.082) (Table 2).

Table 1. Demographic characteristics of both study groups.

Variable	Sildenafil plus low-dose aspirin (n = 200)		Low-dose aspirin only (n = 200)		P-value*
	Mean	SD	Mean	SD	
Age (years)	29.1	5.5	29.1	5.7	0.943
BMI (kg/m^2)	25.62	5.01	25.70	4.99	0.883

Data are mean and standard deviation (SD). *Unpaired t-test. BMI, body mass index.

Table 2. Obstetric history of both study groups.

Variable		Sildenafil plus low-dose aspirin (n = 200)		Low-dose aspirin only (n = 200)		P-value*
		N	%	N	%	
Parity	**P0**	29	14.5%	39	19.5%	0.297
	P1	49	24.5%	49	24.5%	
	P2	59	29.5%	54	27.0%	
	P3	35	17.5%	33	16.5%	
	P4	26	13.0%	22	11.0%	
	P5	2	1.0%	3	1.5%	
Previous miscarriages	**Nil**	76	38.0%	64	32.0%	0.082
	1 Miscarriage	98	49.0%	98	49.0%	
	2 Miscarriages	26	13.0%	38	19.0%	

Data are number (n) and percentage (%). *Chi-squared test for trend.

There is no statistically significant difference between the prevalence of risk factors for preeclampsia in both study groups (Table 3, Table 4). But we noted that the past history of preeclampsia, family history of preeclampsia and chronic hypertention play important role in developing preeclampsia more than other risk factors. In our study we suggest that chronic hypertention is the most significant factor for preeclampsia.

According to the secondary maternal outcomes in both study groups, Table 5 shows equal incidence of early PE in both groups with (p-value 1.000) which is statistically insignificant. As regards incidence of severe PE in both groups is also statistically insignificant with (p-value 0.792). The incidence of gestational hypertension in both groups is comparable as it is 10.0% in the first group and 8.0 % in the second group but also it is statistically insignificant. Finally the incidence of APH is statistically insignificant in both groups with (p-value 0.760).

Table 3. Prevalence of risk factors for preeclampsia in both study groups.

Variable		Sildenafil plus low-dose aspirin (n = 200)		Low-dose aspirin only (n = 200)		P-value*
		n	%	n	%	
Risk factor for PE	Age ≥ 35 years	39	19.5%	40	20.0%	0.900
	BMI ≥ 30 kg/m^2	39	19.5%	40	20.0%	0.900
	Primigravida	29	14.5%	39	19.5%	0.183
	Past history of PE	49	24.5%	53	26.5%	0.646
	Family history of PE	26	13.0%	18	9.0%	0.201
	Multifetal gestation	35	17.5%	26	13.0%	0.211
	Chronic hypertension	36	18.0%	33	16.5%	0.691
	DM type 1 or 2	23	11.5%	33	16.5%	0.150
	CKD	28	14.0%	24	12.0%	0.552
	Autoimmune disease	28	14.0%	27	13.5%	0.885
	Sociodemographic risk factors	200	100.0%	200	100.0%	NA
	LBW, SGA or >10 years IPI	26	13.0%	29	14.5%	0.663
Number of risk factors	2 RF	103	51.5%	99	49.5%	0.950
	3 RF	71	35.5%	75	37.5%	
	4 RF	17	8.5%	21	10.5%	
	5 RF	9	4.5%	4	2.0%	
	6 RF	0	0.0%	1	0.5%	

Data are number (n) and percentage (%). NA = test not applicable. *Pearson chi-squared test unless otherwise indicate. §Chi-squared test for trend. PE, preeclampsia. DM, diabetes mellitus. CKD, chronic kidney disease. LBW, low birth weight. SGA, small for gestational age. RF, risk factors.

According to the fetal and neonatal outcomes in both study groups, Table 6 shows no statistically significant difference between both groups as regards miscarriage, PTB, Still birth, NICU admission, and Neonatal death. Although the difference in SGA was comparable between the two groups (p-value = 0.283), SGA incidence shows no statistically significant difference between both groups.

Table 7 shows the results of multivariable binary logistic regression analysis for the relation between addition of sildenafil to low-dose aspirin and the incidence of preeclampsia as adjusted for the number of risk factors for preeclampsia.

Table 4. Incidence of preeclampsia in both study groups.

Variable	Sildenafil plus low-dose aspirin (n = 200)		Low-dose aspirin only (n = 200)		P-value*
	n	%	n	%	
Preeclampsia	22	11.0%	24	12.0%	0.754

Data are number (n) and percentage (%). *Pearson chi-squared test.

Table 5. Secondary maternal outcomes in both study groups.

Variable	Sildenafil plus low-dose aspirin (n = 200)		Low-dose aspirin only (n = 200)		P-value*
	n	%	N	%	
Early PE	6	3.0%	6	3.0%	1.000
Severe PE	7	3.5%	8	4.0%	0.792
Gestational hypertension	20	10.0%	16	8.0%	0.485
APH	6	3.0%	5	2.5%	0.760
Withdrawal from study	5	2.5%	3	1.5%	0.724§
Loss to follow-up	10	5.0%	7	3.5%	0.457

Data are number (n) and percentage (%). *Pearson chi-squared test unless otherwise indicated. §Fisher's exact test, PE, preeclampsia. APH, antepartumhaemorrhage.

Table 6. Fetal and neonatal outcomes in both study groups.

Variable	Sildenafil plus low-dose aspirin (n = 200)		Low-dose aspirin only (n = 200)		P-value*
	n	%	n	%	
Miscarriage	4	2.0%	6	3.0%	0.522
SGA	9	4.5%	14	7.0%	0.283
PTB	11	5.5%	9	4.5%	0.646
Still birth	2	1.0%	6	3.0%	0.284§
NICU admission	17	8.5%	13	6.5%	0.448
Neonatal death	6	3.0%	4	2.0%	0.522

Data are number (n) and percentage (%). *Pearson chi-squared test unless otherwise indicated. §Fisher's exact test, SGA, small for gestational age. PTB, preterm birth. NICU, neonatal intensive care unit.

Table 7. Multivariable binary logistic regression analysis for the relation between addition of sildenafil to low-dose aspirin and the incidence of preeclampsia as adjusted for the number of risk factors for preeclampsia.

Variable	B	SE	Wald	df	P-value	Odds ratio	95% CI for OR	
							Lower	Upper
Sildenafil (=1)*	0.141	0.336	0.176	1	0.675	1.152	0.596	2.227
Number of risk factors	1.100	0.184	35.740	1	<0.001	3.003	2.094	4.306
Constant	−5.343	0.641	69.476	1	<0.001	0.005		

B = regression coefficient, SE = standard error, df = degree of freedom, OR = odds ratio, 95% CI = 95% confidence interval. *Referenced to no sildenafil (=0).

After adjustment for the number of risk factors, there was no statistically significant relation between addition of sildenafil and the incidence of preeclampsia (odds ratio = 1.152, 95% CI = 0.596 to 2.227, P-value = 0.675).

4. Discussion

Preeclampsia is a multisystem, pregnancy-related disorder characterized by de-novo hypertension and proteinuria and/or other maternal organ dysfunction after 20 weeks of gestation. It is a major cause of maternal and fetal mortality in both low and middle-level income countries that requires early detection and control. According to recent global figures, about 3% - 5% of pregnant women are expected to develop preeclampsia with high annual mortality rate [26].

Disruptions in the restoration of placenta vessels and decreasing blood flow to the placental cause preeclampsia. Women with a history of preeclampsia are more likely to have vascular disorders in the future. Most existing therapeutic approaches are for the time when preeclampsia has already been diagnosed and are applied to help relieve maternal and fetal complications. Considering the pathogenesis of the disease, a preventive approach can be made to the pathogenesis of the disease, as well as to the prevalence of clinical disease [27].

Low-dose aspirin (LDA) treatment is currently one of the key interventions for the prevention of PE. Reduction of PE risk has been shown at aspirin dosages between 80 and 150 mg/day. Several obstetric authorities recommend LDA for women with an increased PE risk. Nevertheless, the use of LDA alone does not results in optimum decrease in the risk of PE in many settings [28].

Sildenafil citrate has been used for increasing utero-placental perfusion in cases with intrauterine growth restriction (IUGR), which makes it a promising drug in the management of mild pre-eclampsia. Its action is similar to the action of nitric oxide, which is a potent vasodilator, especially for the venules, besides inhibiting platelet aggregation. During pregnancy nitric oxide is synthesized in utero placental tissues and endothelial cells, helping to maintain low vascular resistance in the utero-placental and feto-placental circulations [23].

Nevertheless, there is no adequate information about the combination of LDA and sildenafil citrate for reducing the risk of preeclampsia. Thus, Our study was

conducted to compare two modalities of therapies with different mechanisms directed to increase uteroplacental perfusion and thereafter preventing incidence of preeclampsia and improving perinatal outcome in patients whom vascular insufficiency is suspected, sildenafil citrate (a vasodilator drug) and LDA (antithrombotic drug) combination versus low dose aspirin (antithrombotic drugs) alone.

4.1. Main Findings

Regarding the primary outcome of the present study, we demonstrated that there was no statistically significant difference between LDA plus sildenafil and LDA alone groups in terms of incidence of preeclampsia. The incidence of preeclampsia was 11% and 12% in LDA plus sildenafil and LDA alone, respectively.

4.2. Strengths and Limitations

The limitations in this study that it was a single center study with small sample size. Another important limitation is the lack of a placebo group. To our knowledge it is the first study to compare Sildenafil Citrate plus low dose aspirin versus low dose aspirin alone with promising effect in preventing the recurrence of placental mediated diseases by different mechanisms of action that target many causes of placental dysfunction.

Sildenafil Citrate as the most widely investigated drug for FGR with the surprising results of the keenly awaited STRIDER trials raising concerns that sildenafil has no impact on FGR and may even be harmful.

4.3. Interpretation (in Light of Other Evidence)

The present study was an interventional, comparative, study that included and followed 400 pregnant women with risk of pre-eclampsia. The women were recruited from outpatient clinic and patients admitted in Ain Shams university hospital in Obstetrics and Gynecology department. Eligible women were divided into two groups: Group A: 200 pregnant women receiving LDA plus sildenafil citrate, Group B: 200 pregnant women receiving LDA alone.

It has been previously reported that the rate of preeclampsia showed a consistent increase with advanced maternal age [29]. In the present study, the mean age of at-risk women was 29.1 years old; with no significant difference between both groups indicating adequate allocation of the women with no selection bias.

In their registry-based analysis, ***Lamminpää and colleagues* (2012)** reported that the mean age of 15,437 women were at-risk of preeclampsia, was 26.6 ± 4.2 years. [30]

Likewise, ***McLaughlin and colleagues* (2017)** included pregnant women at high risk of preeclampsia. The maternal mean age was 32 ± 0.7 years old. [31]

Many risk factors, besides maternal age, increase the risk of preeclampsia such as obesity, history of previous preeclampsia, chronic kidney disease, autoim-

mune diseases, diabetes, or chronic hypertension [32]. Nulliparous women have a three-fold higher risk of preeclampsia compared with multiparous women [33]. This high risk of preeclampsia was attributed to limited exposure to partner's sperm among nulliparous women [34] [35].

In the present study, we found that considerable proportions of women in both groups had age ≥35 years, BMI ≥30 kg/m^2, primigravida, past history of PE, family history of PE, multifetal gestation, chronic hypertension, diabetes, CKD, autoimmune disease, and sociodemographic risk factors; with no significant difference between both groups indicating adequate allocation of the women with no selection bias.

In line with our findings, ***Groom and colleagues* (2017)** conducted an open-label randomized controlled trial in 5 tertiary care centers in 3 countries on women who deemed to be at high risk of preeclampsia. A considerable proportion of women had advanced age, obesity, nulliparity, family history, chronic hypertension, and diabetes [36].

Regarding the primary outcome of the present study, we demonstrated that there was no statistically significant difference between low dose aspirin plus sildenafil and low dose aspirin alone groups in terms of incidence of preeclampsia. The incidence of preeclampsia was 11% and 12% in low dose aspirin plus sildenafil and low dose aspirin alone, respectively.

In concordance with our findings, ***Mousa et al.* (2019)** conducted a study at Al-Azhar University Hospitals from March 2017 to March 2019. One hundred patients (50 in each arm of the study), who had or have a high-risk pregnancy, were selected and enrolled into a randomized clinical trial to receive low dose aspirin plus sildenafil or low dose aspirin alone. There was no statistically significant difference between low dose aspirin plus sildenafil and low dose aspirin along groups in terms of incidence of preeclampsia [37].

To our knowledge, no other studies assessed the role of low dose aspirin plus sildenafil in prevention of preeclampsia. However, other reports assessed sildenafil or low dose aspirin.

For example, ***Odibo and colleagues* (2015)** conducted a randomized, double-blind, placebo-controlled trial of aspirin for women with risk factors for preeclampsia. There was no evidence that the primary outcome of pre-eclampsia was prevented by low dose aspirin [38] (relative risk (RR) 0.88, 95% CI 0.21 - 3.66).

Likewise, ***Villa and colleagues* (2013)** studied the effect of aspirin in the prevention of pre-eclampsia in high-risk women. A total of 152 women with risk factors for pre-eclampsia and abnormal uterine artery Doppler velocimetry. Low dose aspirin did not reduce the rate of pre-eclampsia (relative risk [RR] 0.7, 95% CI 0.3 - 1.7); gestational hypertension (RR 1.6, 95% CI 0.6 - 4.2); early-onset pre-eclampsia (diagnosed <34 + 0 weeks of gestation) (RR 0.2, 95% CI 0.03 - 2.1); or severe pre-eclampsia (RR 0.4, 95% CI 0.1 - 1.3) [39].

***Rossi and Mullin* (2011)** reviewed literature about the efficacy of low dose

aspirin to prevent pre-eclampsia in women at high and low risk. Fifteen studies were pooled. Low dose aspirin did not decrease the incidence of pre-eclampsia in high-risk (396/5025 - 8% versus placebo: 464/5027 - 9%; P = 0.05; OR: 0.72; 95% CI: 0.51 - 1.00) and low-risk (137/4939 - 3% vs placebo: 166/4962 - 3%; P = 0.10; OR: 0.82; 95% CI: 0.65 - 1.04) women [40].

***Cantu and colleagues* (2015)** explored whether low dose aspirin is more effective in women at increased risk when initiated before 16 weeks' gestation or given to non-obese women. Of 2503 women, 461 (18.4%) initiated low dose aspirin < 16 weeks. low dose aspirin effect was not better when initiated < 16 weeks (RR: 0.93, 95% CI: 0.67 - 1.31) versus ≥ 16 weeks (RR: 0.90, 95% CI: 0.75 - 1.08), (p value for interaction = 0.87). Similarly, low dose aspirin effect was not better in non-obese (RR: 0.91, 95% CI: 0.7 - 1.13) versus obese women (RR: 0.89, 95% CI: 0.7 - 1.13), (p value for interaction = 0.85) [41].

***Bujold et al.* (2010)** conducted a meta-analysis (11,348 women) of 27 studies in which the time of start of aspirin could be identified. They found a significant reduction of the incidence of pre-eclampsia. When aspirin was started at 16 weeks of gestation or earlier (n = 764), 36 women developed pre-eclampsia, and in the control group 80 women developed pre-eclampsia (relative risk 0.47, 95% CI 0.34 - 0.65), with little if any heterogeneity between the studies. If aspirin was started after 16 weeks of gestation (n = 10,584) there was no reduction of the incidence of pre-eclampsia (relative risk 0.81, 95% CI 0.63 - 1.03) [42].

As regard sildenafil citrate, ***Sharp and colleagues* (2018)** did a superiority, placebo-controlled randomized trial in 19 fetal medicine units in the UK. We used random computer allocation (1:1) to assign women with singleton pregnancies between 22 weeks and 0 days' gestation and 29 weeks and 6 days' gestation and severe early-onset fetal growth restriction to receive either sildenafil 25 mg three times daily or placebo until 32 weeks and 0 days' gestation or delivery. Sildenafil did not decrease the incidence of pre-eclampsia in high-risk [43].

***Ferreira et al.* (2019)** did a systematic review to evaluate the benefits of using sildenafil in pregnancy. Randomized clinical trials which used sildenafil for treatment or prevention of obstetric diseases compared with placebo were selected. The pre-eclampsia did not show any statistical significance. This may be due to the small number of patients used in each study and the great heterogeneity between the groups [44].

As regard to fetal outcomes, we found no significant difference between sildenafil plus low dose aspirin versus low dose aspirin alone in terms of miscarriage, SGA, preterm labor, still birth, NICU admission, and neonatal death.

***Kamel and colleagues* (2019)** investigated the safety of sildenafil citrate in managing hypertensive disorders of pregnancy. In a randomized, double-blind, placebo-controlled trial, 122 singleton pregnancies with mild pre-eclampsia between 28 and 36 weeks of gestation were randomized to either use oral sildenafil citrate tablets with antihypertensive or antihypertensive alone. The intervention group has an insignificant lower incidence of intrauterine growth restriction

than the placebo group [23].

Likewise, **Trapani and colleagues and Samangaya and colleagues** studies found no significant difference between sildenafil and placebo in terms of birth weight, Apgar score at the first minute, and length of stay in NICU [22] [45].

Strategies to prevent preeclampsia have been studied extensively over the past 30 years [46] [47] [48] [49]. To date, no intervention has been proved unequivocally effective at eliminating the risk of preeclampsia. With regard to nutritional interventions, evidence is insufficient to demonstrate effectiveness for vitamins C and E [50], fish oil [51], garlic supplementation [52], vitamin D [53], folic acid, [54] or sodium restriction [55] for reducing the risk of preeclampsia. A meta-analysis of 13 trials (15,730 women) reported a significant reduction in preeclampsia with calcium supplementation, with the greatest effect among women with low-baseline calcium intake [56]. Yet, this is not the case in the United States or other developed countries. Likewise, data do not support effectiveness of bed rest and, thus, it should not routinely be recommended [57].

The use of metformin for the prevention of preeclampsia has been suggested. In a meta-analysis of five randomized controlled trials comparing metformin treatment (n5611) with placebo and control (n5609), no difference in the risk of preeclampsia was found (combined/pooled risk ratio, 0.86; 95% CI, 0.33 - 2.26; P5.76; I2566%) [58]. Because preeclampsia was a secondary outcome in most studies in this meta-analysis, the effect of metformin needs to be assessed by a study designed to evaluate the reduction in the prevalence of preeclampsia as a primary endpoint. In the meantime, the use of metformin for the prevention of preeclampsia remains investigational, as is the use of sildenafil and statins.

5. Conclusions

The addition of sildenafil citrate to low dose aspirin had no impact on the prevention of preeclampsia for women at risk of PE, in addition, sildenafil did not improve maternal and fetal outcomes.

Sildenafil citrate prophylaxis is not recommended for prevention of PE and it should not be prescribed for this indication outside of research studies with explicit participants consent. Nevertheless, further large-scale studies are still needed to confirm our findings.

Low-dose aspirin (100 mg/day) prophylaxis is recommended in women at high risk of preeclampsia and should be initiated between 12 weeks and 28 weeks of gestation (optimally before 16 weeks) and continued daily until delivery, Low-dose aspirin prophylaxis is not recommended solely for the indication of prior unexplained stillbirth, in the absence of risk factors for preeclampsia, Low-dose aspirin prophylaxis is not recommended for prevention of fetal growth restriction, in the absence of risk factors for preeclampsia.

Low-dose aspirin prophylaxis is not recommended for the prevention of spontaneous preterm birth, in the absence of risk factors for preeclampsia, Low-dose aspirin prophylaxis is not recommended for the prevention of early

pregnancy loss.

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Contribution to Authorship

All authors contributed to drafting of the original study protocol and to the analysis and interpretation of the data.

All authors commented and approved the final version.

Details of Ethics Approval

The study was approved from the local ethical and research committee of Ain Shams University Maternity Hospital

All research was conducted in accordance with the ethical principles for medical research involving human subjects of the world medical association (WMA; Declaration of Helsinki), as revised during the 95th WMA general assembly held in Seoul, South Korea in October 2008.

After confirming the inclusion criteria, written informed consent was obtained from all participants before recruitment in the study after explaining the purpose and procedure of the study and informing them the risk of intrapartum and postpartum hemorrhage, need for blood transfusion, injury to adjacent pelvic organs specifically lower urinary tract damage and possible need for hysterectomy to control massive postpartum hemorrhage

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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