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Evaluation of Addition Of Sildenafil Citrate On Fetal Growth And Doppler Indices In Treatment of Pregnancy Induced Hypertension

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Abstract:

Pregnancy induced hypertension (PIH) is the most common complication during pregnancy and it affects up to 12% of pregnancies. It is the leading cause of maternal and fetal morbidity and mortality (1). Sildenafil is a potent and selective inhibitor of cGMP .which results in increased levels of cGMP, leading to smooth muscle relaxation thus mediating improved uteroplacental perfusion and increased fetal growth (12). **Objectives:** This study is to evaluate effect of sildenafil citrate on fetal growth and Doppler indices in treatment of pregnancy induced hypertension **Setting:** Department of Obstetrics &Gynecology, Beni-Suef University Hospital. **Methods:** Patients were divided into two groups: Group A (sildenafil group) were offered Sildenafil 20 mg t.i.d. with a plenty of fluids until delivery in addition to traditional treatment. Group B (Placebo group) received placebo drug with the same shape and texture as sildenafil citrate in addition to traditional treatment. **Main outcome measures:** Utero placental perfusion, fetal growth and maternal and fetal safety. **Results:** Sildenafil treatment was associated with a significant decrease of SBP between the two time points (P-value<0.001), a significant decrease of DBP between the two time points (P-value<0.001) and increase in estimated fetal weight by ultrasound (P<0.001). **Conclusions:** Despite limited data, overall there does not appear to be any severe adverse maternal side effects nor any increase in the rate of stillbirths, neonatal deaths attributed to SC.

Keywords: sildenafil, pregnancy induced hypertension, IUGR, Doppler indices.

1. Introduction:

Pregnancy induced hypertension (PIH) is the most common complication during pregnancy and it affects up to 12% of pregnancies. It is the leading cause of maternal and fetal morbidity and mortality (1).

Pregnancy induced hypertension (PIH) is defined as hypertension (blood pressure ≥ 140/90 mmHg) with or without proteinuria (≥ 300 mg / 24hours) emerging after 20 weeks gestation (11).

Hypertensive disorders of pregnancy are frequently encountered complications of pregnancy and have a number of possible aetiologies. The International Society for the Study of Hypertension in Pregnancy (ISSHP) classifies hypertension in pregnancy as follows: chronic hypertension, gestational hypertension, preeclampsia- de novo or superimposed on chronic hypertension, or white coat hypertension (10).

It has many fetal and maternal complications. The most common complication of PIH is intra uterine growth retardation (IUGR). Other fetal complications are oligohydraminos , intrauterine fetal death, placental infarcts, and abruption. It is therefore desirable to know the accurate changes in utero-placental and fetal circulation to predict perinatal outcome and help in appropriate intervention (6).

Sildenafil is a potent and selective inhibitor of cGMP-specific phosphodiesterase type 5 (PDE5), which is responsible for degradation of cGMP which results in increased levels of cGMP, leading to smooth muscle relaxation (vasodilation) (15).

Evidence that vasodilation of the uterine circulation is impaired in PIH, which may be attributed in part to reduce NO-mediated vasodilation. In addition, these studies suggest that PDE5 inhibition by Sildenafil may be able to improve uterine artery vasodilation, thus mediating improved uteroplacental perfusion and increased fetal growth (12).

Also fetal growth monitoring is essential in patients with PIH for early prediction and detection of fetal complications, the average singleton fetus weighs about 80 grams (2.8 ounces) by the end of the first trimester and grows increasingly faster after 22 weeks to reach a maximum growth rate of almost 220 grams (7.8 ounces) per week by 35 weeks . Growth then slows down and is about 185 grams (6.5 ounces) per week by 40 weeks (14).

Doppler velocimetry of the utero-placental and feto-placental circulation can be used to further investigate such complications of pregnancy as fetal growth restriction and other forms of fetal distress that result from fetal hypoxemia or asphyxia (3).

2. Patients and Methods:

This study carried out in Beni_Suef university hospital after the approval of the research Ethics Committee, A prospective randomized control study conducted at obstetrics and gynecology department of Beni_suef university hospital from January 2019 till January 2020.

The study population included pregnant women recruited from the outpatient Obstetrics clinic or emergency room or admitted to department after proper counseling. Using two groups with 30 patients in each group as follows:

1. Study group (Sildenafil group): We offered Sildenafil citrate (20 mg orally three times daily until delivery) as innovative therapy to 30 women with PIH in addition to antihypertensive drugs and other drugs like MgSO4, Omega-3.

2.Placebo group: We offered placebo which is a vitamin the same in shape and texture in addition to antihypertensive drugs and other drugs like MgSO4, Omega-3 to 30 women with PIH.

2.1 Inclusion criteria:

1. Pregnant women beyond 20weeks of gestation.
2.Singleton pregnancy.
3.Systolic blood pressure≥140mmHg or diastolic blood pressure ≥ 90mmHg measure on two occasions 6 hours or more apart.
4. Without proteinuria or proteinuria +1 will be included in the study.

2.2 Exclusion criteria:

1.Women with pre-existing chronic hypertension.
2.When urgent delivery is indicated.

3.Women with kidney disease.
4.Smoking, Drug or alcohol abusers.
5.Women who had twins or multiple fetuses.

2.3 All patients were subjected to: All women were subjected to:

1.Full history taking & examination.

2.Investigations: CBC, urine analysis, bleeding profile, kidney function test and liver function test were done.

3.Ultrasound scan:

All women underwent Trans-abdominal Ultrasound which was performed with (Mindray N2) as follows:

-Fetal biometry: by measuring biparietal diameter (BPD), Femur length (FL) and Abdominal circumference (AC). Average gestational age and effective fetal weight will be then calculated.

- Liquor assessment.

- Doppler ultrasound: including umbilical artery and middle cerebral artery blood flow was performed, assessing the various Doppler indices: Pulsatility index (PI), Resistive index (RI) and Systolic diastolic ratio (S/D ratio) in umbilical and middle cerebral arteries as well

as MCA/UA ratio compared to the standard normograms.

Study group (Sildenafil group): Each participant received a 20 mg tablet of sildenafil citrate orally three times daily until delivery

Placebo group: Each participant received placebo (which is a vitamin the same in shape and texture) orally three times daily until delivery.

Each patient was instructed for bed rest and nutritional supplementation including excessive oral fluid intake around the time of each tablet ingestion with the aim of increase of amniotic fluid index and minimizing the effects of the possible blood redistribution suggested by Miller et al., (2009). Pregnancy was allowed to continue until fetal maturity if fetal growth continues and fetal evaluation remains normal. Both mother and baby were followed up for 30 days after delivery.

Each participant was weekly submitted to:

a. Umbilical and middle cerebral arteries Doppler indices.

b. Ultrasonic fetal growth assessment: Growth of BPD, HC, AC, FL, and EFW (Estimated fetal weight).

c. Fetal movements monitored and counted by the patient and if at any time, there was decrease in the activity and motion of the fetus, assessment of the fetal well-being should be considered.

d. Amniotic Fluid Index Technique: Using the umbilicus as one reference point, the uterus was divided into upper and lower halves. The linea nigra was then used to divide the uterus into right and left halves. A transducer was then placed on the maternal abdomen along the longitudinal axis of the mother. The transducer head was perpendicular to the floor. One should be careful to maintain a perpendicular relationship to avoid a falsely enlarged amniotic fluid pocket. The vertical diameter of the largest pocket, once identified, was measured. The numbers obtained from each quadrant were summed. This summation represented the amniotic fluid index, in centimeters. Oligohydramnios would be consistent with an amniotic fluid index of less than 5 cm, and polyhydramnios would be consistent with an amniotic fluid index in excess of 25.0 cm (7).

Examination of the newborn, after resuscitation and establishment of respiration, Apgar score were calculated, and the newborn were examined carefully for any congenital malformation or any disorder as birth trauma for early management.

Primary outcome measures:

1. Uteroplacental perfusion as measured by Doppler velocimetry.
2. Fetal growth.
3. Maternal and fetal safety.

Secondary outcome measures:

1. Gestational age at delivery.
2. Birth weight.
3. Neonatal complications.

3. Results:

A prospective randomized control study conducted at obstetrics and gynecology department of Beni_Suef university hospital from January 2019 till January 2020.

The study population included pregnant women recruited from the outpatient Obstetrics clinic or emergency room or admitted to department after proper counseling. Using two groups with 30 patients in each group as follows:

Study group (Sildenafil group): We offered Sildenafil citrate (20 mg orally three times daily until delivery) as innovative therapy to 30 women with PIH in addition to antihypertensive drugs and other drugs like MgSO4, Omega-3.

Placebo group: We offered placebo which is a vitamin the same in shape and texture in addition to antihypertensive drugs and other drugs like MgSO4, Omega-3 to 30 women with PIH.

The analyzed data were collected and tabulated, and the following results were obtained.

Table (1): Summarizes the relevant patients' Associated medical disorders of the patients who received Sildenafil (Group A) or placebo treated (group B)

	Group A (Sildenafil Group) Frequency (%)		**Group B (Placebo Group) Frequency (%)**		**Test of significance**	**P-value**
Associated medical disorders	NO	23 ±76.7%	NO	19 ±63.3%	Chi square (χ^2) test $\chi 2(2, N= 60) = 1.4$	0.5
	Diabetic	5 ±16.6%	Diabetic	7 ±23.4%		
	Chronic Hypertension	2 ±6.7%	Chronic Hypertension	4 ±13.3%		

These data shows that there was no statistical significant difference between the 2 groups regarding associated medical disorders

Table (2): Clinical parameters in both groups: Sildenafil (Group A) or placebo treated (group B)

	Group A (Sildenafil group)	**Group B (Placebo group)**	**Test of significance**	**P-value**
	Mean (SD)	Mean (SD)		
Systolic blood pressure Before	143.8 ±5.8	141.3 ±6.7	**Independent-samples Mann-Whitney U test**	0.69
Systolic blood pressure After 2 hours	118.2 ±4.3	126.8 ±6		≤0.001
Diastolic blood pressure Before	93.8 ±3.6	90.3 ±1.8		0.8
Diastolic blood pressure After 2 hours	72.5 ±2.5	79.3 ±1.7		≤0.001
Maternal Pulse Before	82.8 ±3.4	83.5±3.5		0.52
Maternal Pulse After 2 hours	91.4 ±3.6	81.9 ±2.9		≤0.001
Fetal heart rate Before	135.8 ±9.8	131.97 ±4		0.28
Fetal heart rate After 2 hours	137.9 ±10	131.5 ±5		0.01

Mixed model ANOVA is used to test the time effect (repeated measures over time) and the grouping factor effect (sildenafil group and placebo group) and also to determine the interaction between timing and or the grouping factor.

SBP: There are significant statistical differences across the two time points **(P-value<0.001)** and there was significant differences between groups regarding the **SBP (P-value=**0.003). Also there was a significant interaction between the time and groups **(P-value<0.001).** Following up this interaction indicated that there was no significant difference between groups at baseline (p-value**=0.76**) and between the placebo group over time (P-value=0.6).Only the sildenafil group showed a significant decrease of **SBP** between the two time points **(P-value<0.001).**

DBP: There are significant statistical differences across the two time points **(P-value<0.001)** and there was significant differences between groups regarding the **DBP (P-value<0.001**). Also there was a significant interaction between the time and groups **(P-value<0.001).** Following up this interaction indicated that there was no significant difference between groups at baseline (p-value**=0.5**) and between the placebo group over time (P-value=0.14).Only the sildenafil group showed a significant decrease of **DBP** between the two time points **(P-value<0.001).**

Pulse: There are significant statistical differences across the two time points **(P-value<0.001)** and significant differences between groups regarding the **Pulse (P-value<<0.001).** Also there was a significant interaction between the time and groups **(P-value<0.001).** Following up this interaction indicated that there was no significant difference between groups at baseline (p-value**=0.41**); the placebo group didn't have a statistically significant change over time **(p-value-0.91).**

On contrast the mean **Pulse** of sildenafil group increased significantly over time **(p-value<0.01)**.

So this table concludes that this noticeably increase of **Pulse** among sildenafil group is due to sildenafil.

FHR: There are no significant statistical differences across the two time points **(P-value-0.12)**, but significant differences between groups regarding the **FHR (P-value=.011).** Also there was a significant interaction between the time and groups **(P-value=0.014).** Following up this interaction indicated that there was no significant difference between groups at baseline (p-value**=0.06**); the placebo group didn't have a statistically significant change over time **(p-value-0.5).**

On contrast the mean **FHR** of sildenafil group increased significantly over time **(p-value0.005)**.

Table (3) Comparison between umbilical artery PI before and after 2 hours and after 2 weeks among sildenafil group and placebo group :

Umbilical artery PI	Sildenafil group	Placebo group	Test of significance	P value
Before	0.95±0.17	0.92±0.11	**Independent-**	0.46
After 2 hours	0.93±0.12	0.92±0.11	**samples Mann-**	0.79
After 2 weeks	0.94±0.1	0.93±0.11	**Whitney U test**	0.94

Table (4) Comparison between umbilical artery RI before and after 2 hours and after 2 weeks among sildenafil group and placebo group:

Umbilical artery RI	Sildenafil group	Placebo group	Test of significance	P value(before after)
Before	0.68±0.03	0.68±0.02	**Independent-samples Mann-Whitney U test**	0.39
After 2 hours	0.67±0.02	0.69±0.03		0.13
After 2 weeks	0.68±0.02	0.69±0.025		0.56

Data is expressed as **mean ±SD** ***P-value is statistically significant**

Mixed model ANOVA is used to test the time effect (repeated measures over time) and the grouping factor effect (sildenafil group and placebo group) and also to determine the interaction between timing (pre-post) and or the grouping factor.

shows that:

Umbilical artery PI: There are no significant statistical differences across the three time points **(P-value<0.21)** and also, there was no significant differences between groups regarding the **Umbilical artery PI (P-value=**0.65). Also there was no significant interaction between the time and groups **(P-value=0.3).**

Umbilical artery PI: There are significant statistical differences across the three time points **(P-value=0.008)** and also, there was no significant differences between groups regarding the **Umbilical artery PI (P-value=**0.19). Also there was no significant interaction between the time and groups **(P-value=0.4).**

Table (5) Comparison between middle cerebral artery PI before, after 2 hours and after 2weeks among sildenafil group and placebo group:

MCA PI	Sildenafil group	Placebo group	Test of significance	P value(before after)
Before	2.23±0.25	2.15±0.27		0.26
After 2 hours	2.22±0.24	2.17±0.26	**Independent-samples Mann-Whitney U test**	0.52
After 2 weeks	2.3±0.19	2.19±0.24		0.12

Table (6) Comparison between middle cerebral artery RI before, after 2 hours and after 2weeks among sildenafil group and placebo group:

MCA RI	Sildenafil group	Placebo group	Test of significance	P value(before after)
Before	0.84±0.019	0.83±0.015	**Independent-samples Mann-Whitney U test**	0.24
After 2 hours	0.83±0.024	0.84±0.02		0.3
After 2 weeks	0.84±0.027	0.83±0.014		0.59

Data is expressed as **mean ±SD** ***P-value is statistically significant**

Mixed model ANOVA is used to test the time effect (repeated measures over time) and the grouping factor effect (sildenafil group and placebo group) and also to determine the interaction between timing (pre-post) and or the grouping factor.

shows that:

Middle cerebral artery PI : There are significant statistical differences across the 3 time points **(P-value=0.013)** Also there was a no significant interaction between the time and groups **(P-value=0.3).** Following up this interaction indicated that there was significant difference PI at baseline between baseline and after 2 weeks (P-value=0.03).

Middle cerebral artery RI: There are no significant statistical differences across the 3time points **(P-value=0.92)** and no significant differences between groups regarding the **Middle cerebral artery RI (P-value=0.69).** But there was a significant interaction between the time and groups **(P-value<0.038) .**

Table (7) Comparison between increase in fetal body weight 1st 2weeks before sildenafil or placebo and 2nd and 3rd 2 weeks after sildenafil or placebo among sildenafil group and placebo group:

EFW	Sildenafil group	Placebo group	Test of significance	P value(before after)
Before	1565±145	1532±151	**Independent-samples Mann-Whitney U test**	0.311
After 2 Weeks	1739±128	1698±157		0.35
After 4 weeks	1933±134	1873±135		0.087

Data is expressed as **mean ±SD** ***P-value is statistically significant**

Mixed model ANOVA is used to test the time effect (repeated measures over time) and the grouping factor effect (sildenafil group and placebo group) and also to determine the interaction between timing (pre-post) and or the grouping factor.

Shows that there are significant statistical differences across the three time points **(P-value=0.01)** and but neither was significant differences between groups regarding increase in fetal body weight **(P-value=0.21).** Nor-significant interaction between the time and groups **(P-value=0.32).**

Table (8) Complaints (that may be Side effects of sildenafil) among the intervention group (sildenafil) compared to placebo group:

Complaints		**Groups**		**P-value**
		Sildenafil group	**Placebo group**	
Proteinuria	**No**	24(80%)	26(86.7%)	0.48
	Yes	6(20%)	4(13.3%)	
Headache	**No**	20(66.7%)	27(90%)	0.028*
	Yes	10(33.3%)	3(10%)	
Epigastric discomfort	**No**	22(73.3%)	24(80%)	0.54
	Yes	8(26.7%)	6(20%)	
Visual disturbance	**No**	28(93.3%)	30(100%)	0.15
	Yes	2(6.7%)	0	
Vomiting	**No**	27(90%)	29(96.3%)	0.3
	Yes	3(10%)	1(3.3%)	
Uterine Contractions	**No**	24(80%)	26(86.7%)	0.49
	Yes	6(20%)	4(13.3%)	
Decreased fetal movements	**No**	30(100%)	28(93.3%)	0.15
	Yes	0	2(6.7%)	

Data is expressed as number and percent *** P-value is significant <0.05

Chi square test was used to test the difference between the two groups regarding different complaints. Table (7) showed that there was a highly statistically significant difference between the two groups regarding headach (P-value=0.028) as 10(33.3%) of sildenafil group had headache whilst only 3(10%) of placebo group had headache.

Table (9) Comparison between both groups regarding Mode of delivery:

	Groups		P-value
	Sildenafil group	**Placebo group**	
CS	10(33.3%)	12(40%)	0.6
Vaginal delivery	20(66.7%)	18(60%)	

Mode of delivery show no statistical significance between 2 groups

Table (10) Comparison between both groups regarding neonatal outcomes:

Outcome		Groups		P-value
		Sildenafil group	**Placebo group**	
Admission to newborn nursery	**Yes**	4(13.3%)	6 (20%)	0.488
	No	26(86.7%)	24(80%)	

Data is expressed as number and Chi square test was used to test the difference between the two groups regarding neonatal outcomes

Table (11) Comparison between both groups regarding the gestational age at delivery:

		Groups		P-value
		Sildenafil group	**Placebo group**	
Gestational age at delivery	**Less than 37 weeks**	3(10%)	4(13.3%)	0.68
	More than 37 weeks	27(90%)	26(86.7%)	

The study found no statistical difference of PTL among 2 groups

4. Discussion:

Pre−eclampsia affects 2- 8% of all pregnancies world wide. In Egypt, the prevalence of pre−eclampsia was 10.7% in a community−based study (4). The treatment tested in our study was Sildenafil citrate, a phosphodiesterase-5 (PDE5) inhibitor; PDE5 is a down-stream modulator of the vasodilator NO (Nitric oxide). NO plays a vital role in mediating vasodilation, which facilitates adequate fetoplacental perfusion (8) .This adaptation appears to be missing in arteries taken from women with PE (pre-eclampsia) a condition with almost identical pathology to that underlying IUGR ,so studies suggest that PDE5 inhibition by Sildenafil may be able to improve uterine

artery vasodilatation, thus mediating improved uteroplacental perfusion and increased fetal growth (12)**.**

We conducted a prospective randomized control trial included 60 women to evaluate the effect of sildenafil citrate on maternal clinical parameters, fetal growth and Doppler indices in treatment of mild pre-eclampsia. They were followed-up at 2hours, 1 week, 2 weeks and one month, and the data was analyzed.

There were no significant differences between the two groups in terms of age, gravidity, parity, BMI, gestational age, AFI, and associated medical co-morbidities before receiving sildenafil to ascertain that the outcomes will be related mainly to the selected intervention.

Regarding Changes in clinical parameters, In the present study sildenafil treatment was associated with a significant decrease of SBP, a significant decrease of DBP and significant increase in the maternal Pulse and FHR of sildenafil group after 2 hours (p-value<0.01).

Similarly, (9) reports a significant blood pressure–lowering effect of sildenafil is present during pre-eclampsia.

Regarding the effect of sildenafil on uteroplacental circulation as determined by Doppler ultrasound study of umbilical and middle cerebral arteries: In the present study, there was no significant effect in pulsatility index (PI) and resistance index (RI) of both umbilical artery and MCA. On the contrary (2), demonstrated a significant decrease in systolic/ diastolic ratios and PI for the umbilical artery and a significant increase in middle cerebral artery PI.

Regarding fetal growth: There are no significant statistical differences across the two time points **(P-value=0.35& 0.087).** Although **Premalatha et al.** reported increased abdominal circumference measurements by ultrasound. They conducted their trial between 2012 and 2015 on 100 women given sildenafil for severe early and late IUGR.

Regarding maternal side effects Headache ---there was a significant increase in the number of patients who developed headache in the intervention group (33.3%) than in the placebo group (10%). Both (13). Studies reported the high incidence of headache among the majority of patients who received sildenafil citrate. Our study did not report any other differences between the study groups about the maternal adverse effects.

Although we did not report any significant differences between the intervention and placebo groups in the neonatal outcome (birth weight, NICU admission and time of delivery), same reported by (13). On the other hand (5) demonstrated improvement of neonatal outcome.

A meta-analysis by (9) did not mention any worsening neonatal outcomes and, in fact, reported that sildenafil citrate had better neonatal outcomes in animal and human studies.

Recently, the multicentre **STRIDER** trial that studies the effect of sildenafil citrate in early IUGR was suspended and reported that sildenafil citrate patients had higher risks for neonatal deaths due to rebound pulmonary hypertension in these neonates caused by cessation of sildenafil citrate after delivery leading to neonatal respiratory distress and death. These results were not reported by any other studies before.

Thus, larger randomized studies at wide scale are needed to follow up neonates for any adverse effects of the drug. A strengths of our study are the large sample size compared with most of previous RCTs done and the high follow-up rate, largely achieved by professional study staff.

Our study may be limited by the lack of measuring maternal concentrations of sildenafil during therapy. This measurement would have been useful to compare the in vivo concentration with the effective concentrations needed to dilate maternal uteroplacental vascular endothelium. Also, further studies including: the dose, frequency of administration, timing in gestational age, selection and exclusion criteria that will optimize the effects and results of sildenafil citrate as a treatment for mild preeclampsia.

Finally, limitations of the current study that umbilical artery PH was not measured after delivery for accurate assessment of neonatal outcome due to low facilities in our hospital.

5. Conclusion and Recommendations:
Conclusion: This study showed the safety of the use of sildenafil citrate in addition to other antihypertensive drugs in the management of mild pre-eclampsia.

Recommendations: Sildenafil treatment may offer anew opportunity to improve perinatal outcomes, for pregnancies complicated by PIH. However, these observations require further studies on wide scale. Other studies are required to evaluate the long term consequences of sildenafil administration.

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