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Original article

Metformin versus Low Dose Aspirin in Prevention of Hypertensive Disorders in Pregnant Obese Women

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Abstract

Background: Hypertensive disorders in Pregnant obese women are associated with increased risk of maternal mortality and morbidity, metformin and aspirin have been reported to reduce the risk of them. **Aim of the Work:** to compare the effect of metformin versus low dose aspirin in prevention of hypertensive disorders in pregnant obese patients. **Patients and Methods:** During this study, 345 patients were assessed for eligibility and 300 patients were included in the study (100 in each group). First group received metformin started from 12 to 13 weeks till delivery at dose 1 g /day. Second group received Low dose aspirin at dose 150 mg daily from 12 to 13 weeks till delivery. Third group was the control group. In this study, we followed up each group at ANC visit and all patients were clinically examined. **Results:** Maternal weight gain during pregnancy at weeks 30 and 34 statistically was significantly lowest in metformin group (p value=0.016, <0.001) respectively, Hypertensive disorders of pregnancy, gestational hypertension and Preeclampsia were least frequent in metformin group, followed by aspirin group and most frequent in control group, the differences statistically were significant (p value<0.001, 0, 026, 0.019) respectively, marked lower limb edema was least frequent in metformin group and most frequent in control group, regarding preterm delivery was least frequent

in metformin group, followed by aspirin group and most frequent in control group. **Conclusion:** Prophylactic therapy with a daily dose of 1.0 g of metformin in pregnant obese women without diabetes mellitus from 12 to 13 weeks of gestation until delivery was associated with less hypertensive disorders, less maternal gestational weight gain and less neonatal preterm delivery than that observed with aspirin and control groups.

1. Introduction:

Chronic hypertension during pregnancy, eclampsia, gestational hypertension, and preeclampsia (PE) are all examples of hypertensive disorders of pregnancy, a category of serious pregnancy problems. **[1]**

Among these disorders, PE stands out as the most common. It is characterized by new-onset hypertension, usually after 20 weeks of gestation, along with symptoms spanning multiple systems. These symptoms can include proteinuria, elevated liver enzymes, renal insufficiency, thrombocytopenia, pulmonary edema, seizures (eclampsia), persistent severe headache, and even death for both the mother and the fetus. Fetal hemorrhage (PE) is a major contributor to neonatal and maternal illness and death. **[2]**

Worldwide, preeclampsia affects 2%-8% of pregnancies **[3],** causes 16% of maternal mortality (mostly in low- and middle-income nations), and is the leading cause of induced preterm labor in industrialized nations. **[4].**

Two distinct disease entities, early-onset and late-onset preeclampsia have been identified by some researchers. Conventional wisdom holds that preeclampsia occurs more frequently before 34 weeks of gestation, whereas preeclampsia that occurs at or after this point in time is known as late-onset preeclampsia. While there is some overlap in the presenting features, they are linked to various biochemical indicators, clinical aspects, genetics, and consequences for mothers and their unborn children **[3].**

There is a higher risk of PE for women whose body mass index (BMI) was greater before pregnancy, especially for those whose BMI was greater than 30 kg/m2. **[5].**

Therefore, additional therapeutic options need to be investigated further. Preliminary research has shown that metformin (MET) is both safe and effective in preventing PE during human pregnancies. Women at high risk for prenatal hypertension and preeclampsia, such as those with pregestational diabetes mellitus (PGDM), gestational diabetes, polycystic ovary syndrome (PCOS), or obesity, may benefit from MET. **[6].**

By enhancing cardiovascular function and reducing prenatal weight gain, metformin has the potential to prevent pre-eclampsia. Clinical implications of metformin's effectiveness in avoiding late-onset pre-eclampsia are highly significant, regardless of the underlying mechanism. **[4].**

Since hypertension and coagulation irregularities in PE are partially caused by an imbalance between vasodilating and vasoconstricting prostaglandins, it is sensible to use low-dose aspirin as a preventative measure in women at high risk of getting PE. This could lead to a decrease in the occurrence of the condition. **[5].** It is believed that low-dose aspirin treatment can prevent placental vasoconstriction and pathologic blood coagulation because it suppresses thromboxane formation more than prostacyclin generation. Proteinuric hypertension, preterm

birth, babies born at a low birth weight, and perinatal mortality were all significantly reduced in multiple single-center trials that first looked at women at high risk for preeclampsia. **[1].**

Supporting the idea that aspirin's efficacy is dose-dependent and dependent on gestational age at treatment initiation, a prior meta-analysis from the Cochrane Database found that aspirin at doses greater than 75 mg/d reduced the risk of PE more effectively. **[2].**

2. Patients and Methods:

From December 2021 to October 2022, 300 pregnant women with a high body mass index (BMI) of 30 kg/m2 or higher at their first antenatal care visit were randomly assigned to one of three groups: Metformin, Aspirin, or Control. The trial was conducted at Beni-Suef University hospital after receiving approval from the ethical committee and patients' informed consent.

This study was approved by ethical committee before start of the recruitment and was given the following code FMBSUREC/05122021/Nabawy.

Inclusion criteria:

1. Pregnant patients with high body mass index in first ANC visit (BMI ≥ 30kg⁄m^2) without overt diabetes.
2. Gestational age from 12 to 13 weeks.
3. Singleton pregnancy

Exclusion criteria:

1. History of gestational diabetes mellitus or chronic HTN
2. Major fetal defect.
3. Multifetal pregnancy.
4. History of preeclampsia eclampsia
5. Kidney, liver, heart disease.
6. Hyperemesis gravidarum.
7. Sensitivity to metformin or Aspirin**.**
8. Women which use metformin prior to randomization (those with type II diabetes – polycystic ovary syndrome).
9. Patients with peptic ulcer.

Study procedure:

After obtaining a informed consent from patients together with complete medical history before entering the study, the patients were divided in to three groups, each group 100 patients, First group received metformin started from 12 to 13 weeks till delivery at dose 1 g /day. Second group received Low dose aspirin at dose 150 mg daily from 12 to 13 weeks till one week before delivery. Third group was the control group. In this study, we followed up each group at ANC visit and all patients were clinically examined (Routine examination).

1. Pulse.
2. Blood pressure (Hypertension if blood pressure more than 140/90).
3. Weight (measure by GB Digital Scale), Height and BMI calculation
4. Oedema.
5. Ultrasound and fetal wellbeing tests.

6. Full labs especially to high-risk group (CBC, Urine analysis, serum uric acid, PTT Blood urea nitrogen and creatinine, SGOT, SGPT).
7. Proteinuria (measure albumin in urine to cases with elevated blood pressure).

(IUGR , congenital anomaly)

And the follow up process was in three phases:

a) 1st trimester every 4 weeks.
b) 2nd trimester every 2 weeks.
c) 3rd trimester weekly.

Primary outcome

- Occurrence of PIH

Secondary outcome

1. Gestational weight changes.
2. Preterm labor.
3. Preeclampsia & eclampsia
4. Drug side effect. as metformin side effect as GIT upset (nausea, vomiting, diarrhea) and aspirin side effect (bleeding)
5. Fetal mortality and morbidity (prematurity admission to NICU and other fetal complications

Statistical analysis:

This study used Microsoft Office Excel 2007 and IBM SPSS statistics (Statistical Package for Social Sciences) software version 22.0, IBM Corp., Chicago, USA, 2013 to code, tabulate, and conduct statistical analyses on the obtained data.

Qualitative data was described using number and percentage, whilst quantitative data was described using minimum and maximum range values and mean±SD (standard deviation) for normally distributed quantitative data. A P value less than 0.050 was considered significant, whereas a value greater than or equal to 0.050 was considered non-significant.

3. Results:

Table (1): Comparison between the studied groups regarding baseline demographic characteristics

Characteristics		Metformin (N=100)	Aspirin (N=100)	Control (N=100)	p-value
Age (years)	**Mean±SD**	27.8±4.1	28.2±4.0	28.1±4.2	^0.774
	Range	19.0–37.0	20.0–36.0	18.0–38.0	
BMI (kg/m²)	**Mean±SD**	34.9±2.9	34.9±2.7	34.8±2.6	^0.965
	Range	30.0–43.3	30.3–40.7	30.1–40.9	
Parity	**Nulliparous**	33 (33.0%)	24 (24.0%)	28 (28.0%)	#0.367
	Parous	67 (67.0%)	76 (76.0%)	72 (72.0%)	

*BMI: Body mass index. GA: Gestational age. ^ANOVA test. #Chi square test. *Significant*

Table (1) shows that there are no statistically significant differences between the studied groups regarding baseline demographic characteristics, age, body mass index, parity and gestational age at enrollment.

Table (2): Comparison between the studied groups regarding Hypertensive disorders of pregnancy

Findings	Metformin (N=100)	Aspirin (N=100)	Control (N=100)	p-value
Present	1 (1.0%)a	4 (4.0%)a	15 (15.0%)b	**#<0.001***
Absent	99 (99.0%)	96 (96.0%)	85 (85.0%)	

*#Chi square test. *Significant. Homogenous groups had the same symbol "a, b" based on post hoc Bonferroni test.*

Table (2) showed that: Hypertensive disorders of pregnancy was least frequent in metformin group, followed by aspirin group and most frequent in control group, the differences statistically were significant between control and each of Metformin and Aspirin groups.

Table (3): Comparison between the studied groups regarding gestational hypertension

Findings	Metformin (N=100)	Aspirin (N=100)	Control (N=100)	p-value
Present	1 (1.0%)a	3 (3.0%)ab	9 (9.0%)b	**§0.026***
Absent	99 (99.0%)	97 (97.0%)	91 (91.0%)	

*§Fisher's Exact test. *Significant. Homogenous groups had the same symbol "a, b" based on post hoc Bonferroni test.*

Table (3) showed that: Gestational hypertension was least frequent in metformin group, followed by aspirin group and most frequent in control group, the differences statistically were significant between control and Metformin groups.

Table (4): Comparison between the studied groups regarding preeclampsia

Findings	Metformin (N=100)	Aspirin (N=100)	Control (N=100)	p-value
Present	0 (0.0%)a	1 (1.0%)ab	6 (6.0%)b	**§0.019***
Absent	100 (100.0%)	99 (99.0%)	94 (94.0%)	

*§Fisher's Exact test. *Significant. Homogenous groups had the same symbol "a, b" based on post hoc Bonferroni test.*

Table (4) showed that: Preeclampsia was least frequent in metformin group, followed by aspirin group and most frequent in control group, the differences statistically were significant between control and

Metformin groups.

Table (5): Comparison between the studied groups regarding Hypertensive disorders of pregnancy detection time (week)

Measures	Metformin (N=1)	Aspirin (N=4)	Control (N=14)	p-value
Mean±SD	37.0±0.0a	34.8±3.9ab	28.9±2.0	**<0.001***
Range	37.0–37.0	29.0–37.0	27.0–33.0	

*^ANOVA test. *Significant. Homogenous groups had the same symbol "a, b" based on post hoc Bonferroni test.*

Table (5) showed that: Hypertensive disorders of pregnancy detection time was longest in metformin group, followed by aspirin group and shortest in control group, the differences statistically were significant between control and Metformin groups.

Table (6): Comparison between the studied groups regarding intrauterine growth restriction due to pregnancy induced hypertension

Findings	Metformin (N=100)	Aspirin (N=100)	Control (N=100)	p-value
Present	1 (1.0%)	2 (2.0%)	7 (7.0%)	§0.086
Absent	99 (99.0%)	98 (98.0%)	93 (93.0%)	

§Fisher's Exact test.

Table (6) showed that: Intrauterine growth restriction was least frequent in metformin group, followed by aspirin group and most frequent in control group, the differences statistically were not significant.

Table (7): Comparison between the studied groups regarding preterm delivery due to pregnancy induced hypertension

Findings	Metformin (N=100)	Aspirin (N=100)	Control (N=100)	p-value
Present	0 (0.0%)a	3 (3.0%)ab	6 (6.0%)b	**§0.046***
Absent	100 (100.0%)	97 (97.0%)	94 (94.0%)	

§Fisher's Exact test. *Significant. Homogenous groups had the same symbol "a, b" based on post hoc Bonferroni test.

Table (7) and figure (10) showed that: Preterm delivery was least frequent in metformin group, followed by aspirin group and most frequent in control group, the differences statistically were significant between control and Metformin groups.

Table (8): Comparison between the studied groups regarding gestational diabetes mellitus

Findings	Metformin (N=100)	Aspirin (N=100)	Control (N=100)	p-value
Present	0 (0.0%)	2 (2.0%)	2 (2.0%)	#0.100
Absent	100 (100.0%)	98 (98.0%)	98 (98.0%)	

#Chi square test.

Table (8) showed that: Gestational diabetes mellitus was non-significantly least frequent in metformin group.

Table (9): Metformin side effects among metformin group

Findings	N	%
Present	19	19.0%
Absent	81	81.0%

Total=100

Table (9) showed that: Metformin side effects (nausea, vomiting and diarrhea) occurred in about one fifth (19.0%) of metformin group.

Table (10): Comparison between the studied groups regarding maternal weight (kg)

Time		Metformin (N=100)	Aspirin (N=100)	Control (N=100)	p-value
Baseline	**Mean±SD**	95.5±10.5	95.3±10.2	95.8±9.6	^0.939
	Range	75.2–125.1	72.9–125.8	75.2–117.0	
Week-30	**Mean±SD**	95.9±10.5a	99.1±10.2b	99.7±9.6b	**^0.016***
	Range	75.6–125.7	77.0–129.5	79.0–121.2	
Week-34	**Mean±SD**	96.4±10.5a	101.4±10.2b	101.9±9.6b	**^<0.001***
	Range	76.1–126.3	79.6–131.9	81.2–123.8	

^ANOVA test. *Significant. Homogenous groups had the same symbol “a, b” based on post hoc Bonferroni test.

Table (10) showed that: No statistically significant differences between the studied groups regarding baseline weight. Weight at weeks 30 and 34 was lowest in metformin group, the differences statistically were significant between Metformin group and each of Aspirin and control groups.

3. Discussion:

Estimates put the prevalence of hypertensive illnesses during pregnancy at 8-10%; among pregnant women, 0.9-1.5% have chronic hypertension and 2-8% undergo hypertension as a result of their pregnancy. A small percentage of pregnant women, namely 1% of primiparas, are diagnosed with preeclampsia. The World Health Organization (WHO) estimates that it causes 76,000 maternal fatalities annually, or 16% of all maternal deaths worldwide; these deaths mostly occur in underdeveloped nations. **[7].**

There is a higher risk of PE for women whose body mass index (BMI) was greater before pregnancy, especially for those whose BMI was more than 30 kg/m2. **[5].**

This study aimed to compare the effect of metformin versus low dose aspirin in prevention of hypertensive disorders in pregnant obese patients.

This randomized control trial was conducted at Beni-Suef University hospital from December 2021 till October 2022 and performed on total 300 patients with high body mass index (BMI) in first antenatal care visit ≥ 30kg⁄m without overt diabetes.

Different studies were done comparing the effect of metformin or aspirin on prevention of hypertensive disorders with pregnancy, some of them agree and others differ from our results. However, the present study was the first to compare metformin with aspirin and controls in efficacy in prevent of hypertension disorders in pregnant obese women in the same study as the previous literatures compared the effect of only one drug with controls in prevent of hypertension disorders in pregnant obese women.

For the demographic variables of age, BMI, parity, and gestational age at enrollment (p values = 0.774, 0.965, 0.367, 0.453), the present research found no statistically significant differences between the experimental groups. respectively.

Our study results revealed that Hypertensive disorders of pregnancy, gestational hypertension and Preeclampsia were least frequent in metformin group, followed by aspirin group.

Compared to control group, the differences statistically were significant between control and each of Metformin and Aspirin groups. (p value<0.001, 0.026, 0.019) respectively.

Regarding the occurrence of gestational diabetes was least frequent in metformin group, and most frequent in aspirin and control group, the differences were statistically non-significant (p value =0.100).

Our study results revealed that maternal weight gain during pregnancy at weeks 30 and 34 was lowest in metformin group, the differences statistically were significant between Metformin group and each of Aspirin and control groups ***(p value=0.016, <0.001)*** respectively.

Our study results revealed that 19% of metformin group was complaining of its side effects such as (nausea, vomiting, diarrhea).

The current study revealed that Eclampsia did not occur in any of the study groups.

The impact of metformin on pregnancy outcomes was examined in a randomized controlled trial by Syngelaki et al. **[6].** The trial included 450 non-diabetic pregnant women with a body mass index (BMI) more than 35.

Our findings are supported by Syngelaki et al. **[6],** who found that compared to the placebo group, the metformin group had a decreased incidence of preeclampsia (p value<0.001), and that there was a strong connection between the incidence of preeclampsia and maternal gestational weight gain (P = 0.001).

Also, **Nascimento et al. [8]** conducted a randomized clinical trial that enrolled 357 obese pregnant women (BMI ≥ 30 kg/m2), divided into 2 groups: metformin group and control group to evaluate the use of metformin for pregnancy outcomes.

Nascimento et al. [8] results were in concordance with our results in that pre-eclampsia presented chances of reduction in the incidence in metformin group ***(p < 0.01).***

The purpose of the multicenter randomized controlled trial by Lin et al. **[9]** was to determine if high-risk pregnant women who took 100 mg of aspirin were less likely to experience preeclampsia compared to those who took a placebo. The trial comprised 898 pregnant women.

Contrary to our findings, Lin et al. [9] did not find a statistically significant difference in the incidence of preeclampsia between the aspirin group (16.8% [78/464]) and the control group (17.1% [74/434]); relative risk, 0.986; 95% confidence interval, 0.738-1.317; P=0.924). Concerning adverse outcomes for mothers and babies, there was again no statistically significant difference between the two groups.

Our study results revealed that Hypertensive disorders of pregnancy was lastly detected during pregnancy in metformin group with GA 35.9±2.3 weeks, and firstly detected in control group with GA 30.6±2.8 weeks, the differences statistically were significant between control and Metformin groups ***(p value<0.001).***

Consequently, premature termination of pregnancy (> 34 weeks) was decreased in metformin group.

As a result, preterm delivery was least frequent in metformin group, followed by aspirin group and most frequent in control group, the differences statistically were significant between control and Metformin groups ***(p value= 0, 046)***

Regarding intrauterine growth restriction was least frequent in metformin group, followed by aspirin group and most frequent in control group, the differences statistically were non-significant (p value**0** =.086), with no neonatal mortality and NICU admission recorded.

In agreement with our results, **Syngelaki et al. [6]** revealed that there was no statistically significant difference between the groups in the incidence of adverse fetal or neonatal outcomes of fetal growth restriction, neonatal death which may be explained by that most of pregnant women in metformin and placebo groups (90% and 93.6%) were delivered after 37 weeks of gestation and mode of delivery was mainly vaginal birth that decreased the stress of cesarean delivery.

Nascimento et al. [8] results disagreed with our results in that prematurity but agree with our results regarding SGA and IUGR showed no statistically significant differences among the studied groups.

Contrary to our findings, a randomized placebo-controlled trial by Chiswick et al. **[10]** included 449 obese pregnant women with a body mass index (BMI) of 30 kg/m2 or higher. The trial found that the placebo group had a mean birthweight at delivery of 3463 g (SD 660), while the metformin group had a non-significant effect of 3462 g (548). on the other hand, we found no statistically significant difference between the metformin group (n=7) and the placebo group (n=2) in terms of the combined adverse outcome of miscarriage, termination of pregnancy, stillbirth, or neonatal death (p=0.011).

The strength points of this study:

The fact that no patients were lost to follow-up while pregnant and that the trial used a prospective design are two of its strongest aspects. This is the first research of its kind to examine the efficacy of metformin in preventing hypertensive illnesses and problems during pregnancy, comparing it to aspirin and controls.

The limitations of the study:

It is important to note that the study had certain limitations, such as a smaller sample size compared to other studies, the fact that it was not a multicentric study, and the high likelihood of publication bias. The availability of patients who could participate in the study was also affected by the COVID-19 pandemic, which is another drawback.

4. Conclusion and Recommendations:

Conclusion

From 12–13 weeks of gestation until delivery, pregnant obese women without diabetes mellitus

who took 1.0 g of metformin daily as a preventative measure had fewer hypertensive disorders, fewer neonatal preterm deliveries, and less maternal gestational weight gain compared to the control group and the aspirin group.

Recommendations

Prophylactic therapy with a daily dose of metformin as an alternative to aspirin is recommended in obese pregnant women to decrease weight gain and prevention of hypertensive disorders during pregnancy.

Future prospective studies for the long-term follow up and outcomes of metformin and aspirin during pregnancy are recommended.

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