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Does Metformin Use During Pregnancy Effectively Reduce the Rate of Early Pregnancy Loss in Women with Polycystic Ovary Syndrome?

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ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine “Does Metformin use during pregnancy effectively reduce the rate of early pregnancy loss in women with polycystic ovary syndrome?”

STUDY DESIGN: This review is based on two primary double-blind, randomized controlled trials and a prospective controlled trial that was not randomized or blinded to evaluate whether metformin, a medication used to manage PCOS, can also prevent early pregnancy loss in women with PCOS.

DATA SOURCES: All articles used were published in English, in peer-reviewed journals, and located through PubMed, OVID and COCHRANE databases..

OUTCOMES MEASURED: Each of the three trials included evaluated the effectiveness of metformin at preventing pregnancy loss and premature labor in patients with PCOS, as well as safety of administering the drug during pregnancy. Sohrabvand et al solely focused on early pregnancy loss, with other studies following pregnancy to term.

RESULTS: Two double-blind randomized controlled trials and one prospective controlled trial were included in this review. Results from the Vanky et al (2004) study demonstrated a 22.7% decrease in premature birth rate in metformin group as compared to control. Sohrabvand et al also presented a statistically significant decrease in current miscarriage rate in groups taking metformin up to 8 weeks and 12 weeks, of gestation ($p = 0.008$ and $p = 0.002$, respectively) as compared to previous miscarriage rate. Vanky et al (2010) analyzed a multicenter trial, but its results differed in that a statistically significant decrease in preterm labor could only be appreciated after a subgroup analysis was performed of participants deemed to have good and acceptable compliance (7.4% decrease, $p = 0.03$). The recommendation made in this last trial was not in favor of metformin usage due to a perceived overall lack of benefit.

CONCLUSIONS: Two of the three trials in this review support the use of metformin during pregnancy in women with PCOS as means of preventing pregnancy loss or premature labor. Various factors, such as tighter monitoring throughout pregnancy, and inconsistencies in pre-pregnancy metformin intake could have affected the results within this patient population.

KEY WORDS: polycystic ovary syndrome, miscarriage, pregnancy

INTRODUCTION

Polycystic ovary syndrome (PCOS) is otherwise known as Stein Leventhal Syndrome. It carries no specific predilection for race or ethnicity, and is a multifactorial disorder characterized by anovulation, polycystic ovaries, insulin resistance, and hyperandrogenism.[1] It can result in numerous complications, and one of them, early pregnancy loss, is the focus of this paper.[2] This paper is primarily based on two double-blind, randomized controlled trials and a prospective controlled trial that was not randomized or blinded to evaluate whether metformin, a medication used to manage PCOS, can also prevent early pregnancy loss in women with PCOS.

PCOS and its related complications are relevant to the Physician Assistant practicing today due to the vast proportion of female patients plagued by the disorder. Based on data from 2003-2008, the number of PCOS-related doctor office visits reached an astounding total of 2,328,000 visits, with a mean yearly number of 516,000 visits.[3] Because of these factors, PCOS has also proved to be quite an expensive condition to manage. The most recent data regarding cost of PCOS-related complaints spans the period between 2003-2008, and demonstrated a total cost of $1.16 billion annually.[3] Overall, PCOS affects 5-10% of the female population in the US, a pretty significant percentage, especially when its consequences and related disorders are considered: diabetes mellitus, infertility, metabolic syndrome, and cardiovascular disease. Early pregnancy loss is the focus in this paper, and is also a frustrating aspect of PCOS, as becoming pregnant alone can prove to be quite a challenge.[1]

The exact cause of PCOS is unknown, but it has been attributed to a pattern of genetic inheritance, as it tends to be seen more frequently among relatives.[1] The role of PCOS in leading to infertility, as well as early pregnancy loss, is multifactorial and is strongly believed to be caused by the combination of hyperandrogenism, alterations in gonadotropin secretion, and the insulin resistance, among other things.[4]

In treatment of PCOS, initially a trial of diet and exercise aimed at weight loss is recommended,

as women with PCOS are typically overweight. Often, achieving a healthy weight is enough to relieve some of the symptoms associated with the disorder. If poorly controlled by diet and exercise, insulin resistance is managed with metformin, and frequently has favorable outcomes in restoring ovulation as well.[1] If additional help is needed for stimulation of ovulation, clomiphene citrate can be used.[1] Management of potential cardiovascular and metabolic syndrome complications is addressed as well in the form of pushing for weight loss, and supplementing with pharmacotherapy as deemed appropriate.[1]

Often, the above mentioned treatments are enough to adequately manage the disorder. However, it is widely known that even with appropriate management, women with PCOS often have a very hard time achieving a pregnancy. As if that were not enough, maintaining that pregnancy can additionally prove to be futile, as early pregnancy loss is quite common in these patients.[5] Numerous interventions have been looked at as a potential 'remedy' for prevention of this complication, but not many have shown success. The studies evaluated in this paper demonstrate that metformin, a drug given to manage anovulation and hyperinsilunemia in PCOS, can be continued after the patient becomes pregnant and has actually shown a positive outcome related to maintenance of the pregnancy.[5]

OBJECTIVE

The objective of this selective EBM review is to determine “Does Metformin use during pregnancy effectively reduce the rate of early pregnancy loss in women with polycystic ovary syndrome?”

METHODS

The studies that were used to answer this question all fit the following criteria: the populations studied consisted of women of reproductive age, 18-45 years old, and diagnosed with PCOS, who also had a confirmed viable pregnancy. The intervention used was a dose range of Metformin 500-850mg given three times a day to the treatment group. The comparison group in the studies received a visually matched placebo. Additionally, previous history of miscarriages in these women was used for

comparison with the outcomes after the trial with metformin. Outcomes that were measured surrounded the efficacy of metformin in helping to maintain a viable pregnancy past the first trimester without complications or pregnancy loss. Types of studies used in this systematic review included two double-blind, randomized controlled trials and a prospective controlled trial that was not randomized or blinded.

Key words that were used in searching for appropriate studies included metformin, pregnancy and PCOS. All articles used were published in English, in peer-reviewed journals, and located through PubMed, OVID and COCHRANE databases. The articles/studies were researched by the author, and selected based on the type of trial conducted, focus on patient-oriented outcomes (POEMs), and of course their direct relevance to the clinical question presented. Inclusion criteria for the systematic review included randomized, controlled, double-blind studies, as well as controlled trials that were not randomized, included POEMs, and had a publish date after 1996. Exclusion criteria included studies that were comparing metformin with other drugs in prevention of pregnancy loss in PCOS, or using metformin in combo with another drug. Reluctance to take drugs during pregnancy, known alcohol abuse, previous diagnosis of diabetes mellitus, and treatment with oral glucocorticoids or other drugs known to interfere with metformin were exclusion criteria for the subjects recruited for the studies. Summary of statistics that were reported or used were relative risk reduction (RRR), absolute risk reduction (ARR), number needed to treat (NNT), confidence intervals, and p-values.

Demographics and characteristics of the studies utilized for this review are displayed in Table 1.

Table 1. Demographics and characteristics of included studies

Study	Type	# Pts	Age	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Vanky[6], 2004	Double blind, placebo controlled RCT	40	28-33	Diagnosis of PCOS before the actual pregnancy; Age 18-40 years old; Gestational age between 5 and 12 weeks	Liver disease; Creatinine >130mmol/l Known alcohol abuse; History of diabetes mellitus; Fasting plasma glucose >5.6 mmol/l; Treatment with oral glucocorticoids or use of drugs known to interfere with metformin	2	Randomized to receive metformin (850mg) or visually matched placebo BID initiated with diagnosis of pregnancy and continued throughout gestation
Vanky[5], 2010	Double blind, placebo controlled multicenter RCT	257	18-42	PCOS diagnosed according to the Rotterdam criteria; Age 18-45 yrs; Gestational age between 5 and 12 weeks; A singleton viable fetus shown on ultrasonography	Alanine aminotransferase higher than 90 IU/liter; Serum creatinine concentration higher than 1.70 mg/dl; Known alcohol abuse; Previously diagnosed diabetes mellitus or fasting serum glucose higher than 126 mg/dl at the time point of inclusion; Treatment with oral glucocorticoids, or use of drugs known to interfere with metformin	12	Randomized to receive metformin (500 mg) or visually matched placebo BID
Sohrabvand[7], 2009	RCT	75	22-33	Pregnant women with history of infertility that was solely due to PCOS, based on Rotterdam criteria and confirmed by physician; Received metformin along with other ovulation-inducing drugs prior to pregnancy	Reluctance to take drugs during pregnancy	0	Randomized to receive metformin (500mg TID) until 5-6 weeks gestation in in Group A, 8 weeks gestation in Group B, and until 12 weeks of gestation in Group C., after which it was entirely discontinued.

OUTCOMES MEASURED

Of the various outcomes assessed in these trials, the ability of maintaining a pregnancy past the first trimester in women with PCOS taking metformin, as well as adverse reactions associated with taking the drug were the main point of focus. All outcomes were based on patient-oriented evidence that mattered (POEMs). Vanky et al (2004) initially compared the incidence of pregnancy complications in women with PCOS who were taking metformin with those who took an identically matched placebo, including premature delivery, gestational diabetes mellitus (GDM) and thrombotic events.[6] Sohrabvand et al compared the occurrence of miscarriage among three separate groups of participants which either discontinued metformin after diagnosis of pregnancy, continued taking it until week 8 of gestation, or week 12 of gestation.[7] The study additionally compared previous history of miscarriage in the participants with its occurrence during the trial. Vanky et al (2010) compared metformin and placebo groups in terms of the occurrence of premature delivery or miscarriage, preeclampsia, new GDM, and other complications of pregnancy.[5]

RESULTS

Among all trials used in this review, dichotomous data was used to assess the outcomes measured. In the first trial by Vanky et al (2004) it was discovered that the only cases of pre-term delivery occurred within the placebo group, with no cases of miscarriages or preterm delivery occurring within the metformin group.[6] (Table 2) Table 2 also demonstrates that there was no statistical difference among the patient characteristics in the two groups, including their previous history of miscarriage. Whereas no p-value was provided for this significant finding, the RRR was calculated to be 100%, ARR was 22%, and NNT was 5 patients (Table 3). This NNT suggests that for every 5 patients treated with 850mg of Metformin once daily for first week and twice daily for all subsequent weeks of pregnancy, preterm delivery would be prevented in one additional woman with PCOS, than when treated with placebo. This study additionally suggested that metformin is safe in pregnancy, as it

did not appear to contribute to any severe pregnancy complications. A statistically significant p-value of 0.01 supports this conclusion, as 32% of women within the control group suffered severe pregnancy or post-partum complications, with complete absence of these complications in the metformin group.[6] There were 2 drop-outs from this trial, one due to inconvenient traveling distance, and the other due to motivation failure; none withdrew due to complications or intolerance of metformin.[6]

Table 2. Selected patient characteristics at inclusion and results of trial [6]

	Metformin	Placebo	*P*
# of Participants	18	22	–
# of Former Pregnancies (%)	11 (61)	11 (50)	0.8
# of Former Pregnancy Losses (%)	7 (39)	10 (54)	0.5
Metformin Treatment at Conception (%)	8 (44)	11 (50)	0.7
Gestational age at birth in days (SD)	282 (8)	266 (36)	0.06
# of Pre-term deliveries (%)	0 (0)	5 (23)	–

Table 3. Analysis of efficacy of Metformin in prevention of preterm labor in PCOS

	Relative risk reduction (RRR)	**Absolute risk reduction (ARR)**	**Number needed to treat (NNT)**
Vanky[6], 2004	100%	1/.22	4.54 = 5 patients

Sohrabvand et al stratified its participants into three groups based on the clinic in which they were initially interviewed.[6] There were 25 participants within each group, and none dropped out. Conception within this patient population was assisted with a regimen of clomiphene citrate and 1500mg metformin daily. Aside from comparison of the trial outcomes of each group, previous history of miscarriage was additionally compared with miscarriage occurrences during the trial. Within Group A, among participants who discontinued the metformin upon diagnosis of pregnancy, there was 1 miscarriage compared with 6 former pregnancy losses, demonstrating a statistically insignificant p-value of 0.06. Group B was administered metformin until the 8th week of gestation, and resulted in 1 miscarriage compared with a history of 8 total pregnancy losses among the group. Group C continued

taking metformin until week 12 of gestation, and resulted in 2 miscarriages compared with a history of 10 total miscarriages. The p-values for both Group B and C were statistically significant at 0.008 and 0.002, respectively(Table 4). These findings demonstrated the efficacy of metformin on two separate levels, as it appears to have reduced miscarriage history within the individual groups, as well as within the groups that continued taking metformin after the diagnosis of pregnancy.[7]

Table 4. Patient Characteristics at Inclusion and Results of Trial[7]

	Group 1	**Group 2**	**Group 3**	***P* value**
# of Participants	25	25	25	–
Age (SD)	27.96 (5.7)	28.72 (3.57)	26.8 (3.88)	0.115
Results	**Group 1**	**Group 2**	**Group 3**	
# of Former Pregnancy Losses (%)	6 (20)	8 (32)	10 (40%)	
# of Current Miscarriage (%)	1 (4)	1 (4)	2 (8)	
P value	0.06	0.008	0.002	

Vanky et al (2010), a randomized controlled multicenter study, initially recruited 364 participants for its trial, however, 32 were excluded due to inability to meet inclusion criteria, and 58 did not desire participation. Following randomization, a single participant from the experimental group was additionally excluded due to a 21-hydroxylase deficiency diagnosis.[5] Within the placebo group 3 patients were lost to follow-up due to miscarriages, resulting in a total of 135 participants within each arm of the trial. Primary endpoints of this trial included preterm delivery, and demonstrated a reduction of preterm delivery rate from 8.2% within the placebo group to 3.7% within the experimental arm, a finding that was determined to be not statistically significant ($p = 0.12$) (Table 5). However, of the 270 participants within the study, 80.2%, or 216 women, were determined to have good and acceptable compliance, resulting in performance of a per protocol analysis.[5] The analysis showed a statistically significant ($p = 0.03$) decrease in preterm birth occurrence among the two groups, demonstrating a 7.4% decrease (CI=0.9–1.2), as compared with the previous 4.5% (CI=-10.1–1.2). RRR was calculated

to be 73%, ARR was 7.4%, and NNT was 14 patients, indicating that 14 pregnant women with PCOS would have to be treated with metformin to successfully prevent preterm labor in one additional woman (Table 6). No differences could be appreciated between the two groups in terms of preeclampsia and GDM in either the primary endpoints or the per protocol subgroup analysis, as demonstrated by p-values that were all statistically insignificant.[5]

Table 5.

Preterm Delivery / Miscarriage Occurrence	Metformin (%)	Placebo (%)	95% CI	*P* value
Primary endpoints	5/135 (3.7)	11/135 (8.2)	-10.1–1.2	0.12
Subgroup analysis	3/108 (2.8)	11/108 (10.2)	0.9–13.9	0.03

Table 6. Analysis of efficacy of Metformin in prevention of preterm labor in PCOS

	Relative risk reduction (RRR)	Absolute risk reduction (ARR)	Number needed to treat (NNT)
Vanky[6], 2010	73%	1/.074	13.5 = 14 patients

DISCUSSION

Metformin is a drug belonging to the biguanide class, and is most widely known as the antidiabetic drug used in management of Type 2 diabetes mellitus. It was initially created to help control blood glucose levels in diabetics, however its use today spans across a spectrum of disorders involving insulin resistance.[8] Metformin's mechanism of action mainly involves decreasing hepatic glucose production, however it also increases insulin sensitivity and glucose metabolism within certain organs and tissues, such as muscle, liver, and intestine. Within the intestine this metabolism results in a byproduct, lactate, which is typically taken up by the liver and used in the process of hepatic gluconeogenesis. The exact molecular mode of action of metformin is not certain, but known to involve the enzyme AMP-activated protein kinase (AMPK), Peutz-Jeghers protein, and LKB1. In addition to those mechanisms, metformin is also known to promote lowering of lipid levels and aiding in weight loss and management. Its action at decreasing blood glucose levels, managing insulin

resistance, and also decreasing androgen levels is believed to be the key in helping to manage PCOS-related complications such as anovulation and infertility[5,7].

Perhaps the most common side effects of metformin are gastrointestinal in nature, and include abdominal discomfort, nausea, possible vomiting, diarrhea, and a metallic taste in the mouth[8]. Vanky et al (2010) mentioned diarrhea and bloating as being more prevalent within the metformin group, with abdominal discomfort and nausea being equally prevalent[5]. Vanky et al (2004) also mentioned nausea and abdominal discomfort as being equally prevalent among the two groups, however no participants dropped out of the study due to the side effects, and were instead told to take half the original dose of metformin[5].

Another side effect of metformin is lactic acidosis, and although it may mimic the gastrointestinal side effects, it is much more serious[8]. Symptoms include abdominal pain, nausea, vomiting, hypotension, and hyperventilation[8]. Metformin contributes to this condition in two ways: by increasing lactate production in the intestine, as previously mentioned, and by decreasing hepatic uptake of lactate[8]. This complication, however, is more associated with metformin overdose, kidney, lung, and liver disease, and wasn't present in any of the trials included in this review[8].

Sohrabvand et al study was perhaps the only one in this review to directly address the effect of metformin on early pregnancy loss, as both of the Vanky et al trials looked at premature birth as a potential complication of pregnancy, and addressed other effects of metformin in pregnancy. Regardless of the initial trial goal, the final results of all the studies included in this review point to a favorable outcome, as metformin appears to have decreased the incidence of both early pregnancy loss and premature birth in the participants, as long as compliance with treatment was a factor. However, the largest of the three trials, Vanky et al (2010), does not conclude that there is a worthy “benefit of the drug on study endpoints, and speaks against this practice.”[5] The supposed benefit of metformin here was only evident in the fewer number of preterm births after the subgroup analysis was performed,

with absolutely no statistically significant difference in either the primary endpoints analysis or the subgroup analysis of other pregnancy complications.[5] The authors therefore attributed the supposed benefit to a "tight and thorough pregnancy follow-up and...diet and lifestyle intervention."[5] The smaller trials did attribute the reduction in preterm births and miscarriage to metformin, however, the sample size was cited as not adequately large enough to conclude the definitive benefit. Worthy of mention is the finding that metformin treatment appears to be safe in pregnant women with PCOS among all three trials.[5,6,7]

There are limitations to this study which lead to a potential doubt about the certainty of metformin as playing a definitive role in prevention of early pregnancy loss. One limitation is that all participants in the trials received comprehensive counseling and health care throughout the duration of the trial. This comprehensive health care and follow-up is not necessarily provided to all women receiving prenatal care outside the scope of the trials, and may have contributed to a better outcome of the pregnancy. Additionally the results may have been skewed by a either a more intense disease course or a milder one of study participants, as compared to other women with PCOS. Yet another factor consider is pre-pregnancy therapy with metformin, and the different times and gestational ages at which metformin therapy was initiated.

CONCLUSIONS

Among the data presented in the three trials used for this review metformin appears to be effective in reducing early pregnancy loss in women with PCOS. However there are inconsistencies present in data interpretations within these trials, which calls for more investigation to be performed. Benefits of metformin have been proven in non-pregnant patients with PCOS, and metformin does appear to be safe in pregnancy, which has facilitated its use during pregnancy regardless of its inconsistent pattern of benefits. Perhaps an entirely separate recommendation could be made to increase the quality of prenatal care among women with PCOS, as this was cited as a possible hidden

“benefit” of metformin. Future studies should be performed to additionally evaluate the benefit of metformin in preventing pregnancy loss or premature delivery, and should further refine the study population by including women who have a similar pre-pregnancy history with metformin administration, and in whom metformin is initiated preconception and continued through the diagnosis of pregnancy. Compliance with treatment should be strongly encouraged to maximize the consistency of data results.

REFERENCES:

1. Tzadik M, Purcell K, Wheeler JE. Chapter 40. Benign Disorders of the Ovaries & Oviducts. In: DeCherney AH, Nathan L, eds. *CURRENT Diagnosis & Treatment Obstetrics & Gynecology*. 10th ed. New York: McGraw-Hill; 2007. http://www.accessmedicine.com/content.aspx?aID=2389603. Accessed September 11, 2012.

2. Glueck CJ, Wang P, Goldenberg N, Sieve-Smith L. Pregnancy outcomes among women with polycystic ovary syndrome treated with metformin. *Hum. Reprod. 2002;17(11):2858-2864*

3. Jason J. Polycystic ovary syndrome in the United States: clinical Visit Rates, characteristics, and cssociated health care costs. *Arch Intern Med.* 2011;171(13):1209-1211. http://archinte.jamanetwork.com/article.aspx?articleid=1105819. Accessed September 28, 2012.

4. Hoffman BL, Schorge JO, Schaffer JI, Halvorson LM, Bradshaw KD, Cunningham FG, Calver LE. Chapter 17. Polycystic Ovarian Syndrome and Hyperandrogenism. In: Hoffman BL, Schorge JO, Schaffer JI, Halvorson LM, Bradshaw KD, Cunningham FG, Calver LE, eds. *Williams Gynecology*. 2nd ed. New York: McGraw-Hill; 2012. http://www.accessmedicine.com/content.aspx?aID=56703811. Accessed September 28, 2012.

5. Vanky,E.; Stridsklev,S.; Heimstad,R, et al. Metformin versus placebo from first trimester to delivery in polycystic ovary syndrome: a randomized, controlled multicenter study. *J Clin Endocrinol Metab.* 2010;95(12):E448-55

6. Vanky E, Salvesen KA, Heimstad R, Fougner KJ, Romundstad R, Carlsen SM. Metformin reduces pregnancy complications without affecting androgen levels in pregnant polycystic ovary syndrome women: results of a randomized study. *Hum Reprod.* 2004;19(8):1734-1740.

7. Sohrabvand F, Shariat M, Haghollahi F, Bagheri B. Effect of Metformin on Miscarriage in Pregnant Patiens with Polycystic Ovary Syndrome. *West Indian Med J.* 2009;58(5):433-436.

8. McCulloch D. Metformin in the treatment of diabetes mellitus. Up to Date. http://www.uptodate.com/contents/metformin-in-the-treatment-of-diabetes-mellitus. Updated 2012. Accessed December 8, 2012.