



Mrs S, 27 yr old Primigravida with PCOS, BMI- 31, On Folic acid and Metformin, Conceive with OI Beaming with happiness, she asks her obstetrician, “What about Metformin, Doctor? Should I continue it?”



Is It Safe To
TAKE METFORMIN
During Pregnancy

Look Before You Leap



Do you know what happens when you always look before you leap?" She reached out and touched his hand before hurrying toward the door. "You hardly ever make the jump.

Nora Roberts

What is Metformin?

Metformin is a Biguanide used to control blood glucose levels in Type 2 Diabetes

US FDA Pregnancy Category 2

It is an insulin sensitizer

It crosses the placenta



How does Metformin act?

- It decreases the absorption of dietary carbohydrates from the intestines
- It reduces the production of glucose by the liver-reduced Gluconeogenesis
- **Third, and perhaps most importantly, metformin increases the sensitivity of muscle cells to insulin**

What are the issues here?

An obese PCOS pregnant patient
Pregnancy complications in patients with PCOS
Will Metformin help reduce these complications



Should we continue Metformin?

What does evidence say?

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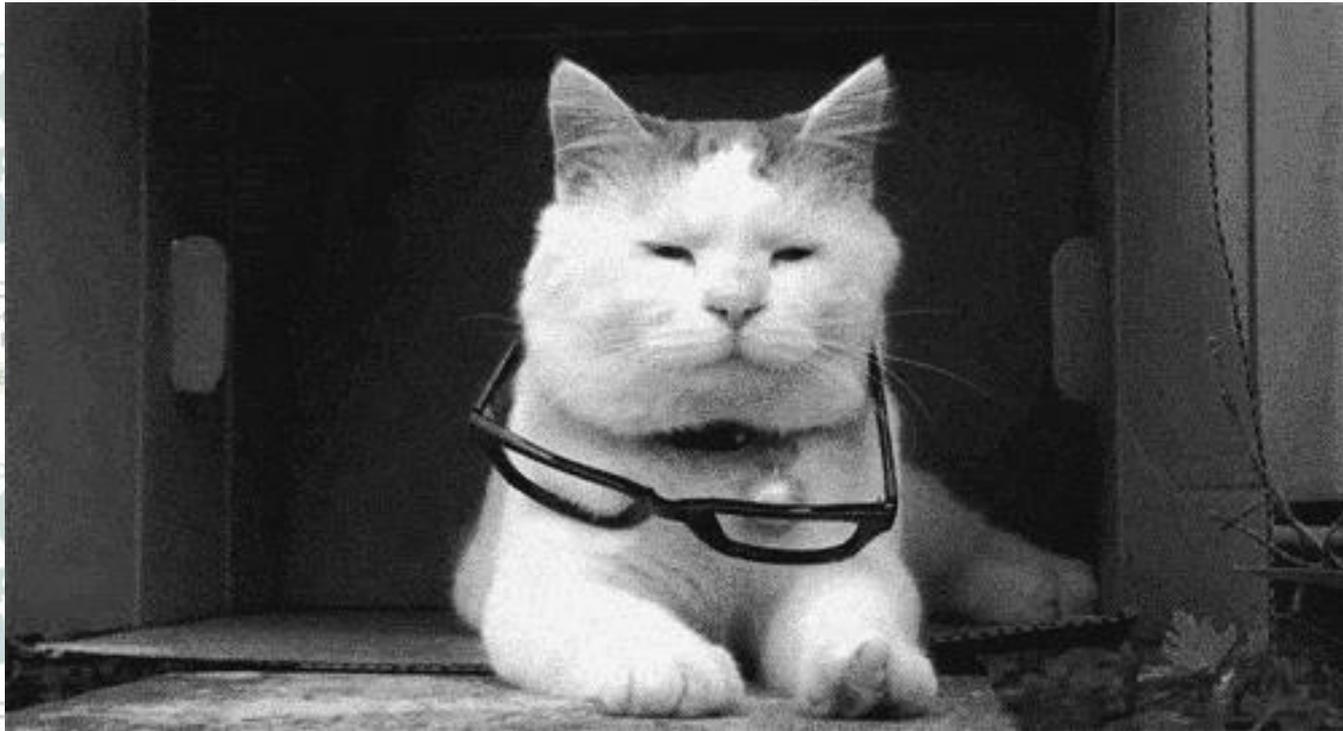
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Pregnancy in PCOS is at increased risk of....

P

- Insulin Resistance
- Hyperandrogenemia

C

- GDM- 40-50%
- PIH -10-30%

OS

- Early Miscarriage- 5 fold more
- Preterm Birth- 6-15%

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Pregnancy in PCOS is a

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Early pregnancy loss in pregnancy in PCOS

Chromosomal Abnormalities – uncommonly seen

Hyperinsulinemia and hyperandrogenemia – more often implicated

Does Metformin decrease EPL?- Yes!

Pregnancy loss in the first trimester reduced from **41.9%** in the untreated group to **8.8%** in the Metformin group

Jakubowicz et al, **Effects of Metformin on early pregnancy loss in the polycystic ovary syndrome**; J Clin Endocrinol Metabolim, 2002

Khattab S, et al. **Metformin reduces abortion in pregnant women with polycystic ovary syndrome**. Gynecol Endocrinol 2006;

Metformin is safe! It is not teratogenic!



Pooling analysis - control group had a malformation rate of **7.2%**, compared to **1.7%** in the metformin group, strongly supporting metformin's safety during pregnancy

G. G. Briggs, *Drugs in Pregnancy and Lactation*, 2002

C. Gilbert et al, "Pregnancy outcome after first-trimester exposure to metformin: a meta-analysis," *Fertility and Sterility*, 2006

Nexus between PCOS & GDM

Obesity and PCOS are independent risk factors for GDM
GDM complicates 40 to 50% of pregnancies in PCOS

Higher pre-pregnancy BMI favours GDM

Increased Insulin Resistance

40% in lean & almost 100% in obese PCOS

Decreased expression of GLUT4 & Adiponectin, a hormone with insulin-sensitizing activity in PCOS

Nexus between PCOS and Type 2 DM

Higher risk of Type 2 Diabetes in
-- 10% of women shortly after delivery and
-- 40% by 10-years after GDM

Does Metformin prevent GDM?- YES

10-fold reduction in GDM seen in pregnant women with PCOS

Only **3%** of the metformin group developed GDM compared to **31%** in the non-metformin group

Glueck CJ, Wang P, Kobayashi S, et al. **Metformin therapy throughout pregnancy reduces the development of gestational diabetes in women with polycystic ovary syndrome.** Fert Steril 2002

Khattab S, Mohsen IA, Aboul Foutouh I, et al. **Can metformin reduce the incidence of gestational diabetes mellitus in pregnant women with polycystic ovary syndrome? Prospective cohort study.** Gynecol Endocrinol. 2011

De Leo V, et al. **The administration of metformin during pregnancy reduces polycystic ovary syndrome related gestational complications.** Eur J Obstet Gynecol Reprod Biol 2011

RCTs of metformin in pregnant PCOD

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First author	Year	Number of patient	Duration of metformin intake	Results
Vanky <i>et al.</i>	2004	40	Conception to delivery	Reduced severe pregnancy complications in metformin arm (0% vs. 32%; $P=0.01$)
Begum <i>et al.</i>	2009	59	Preconception to delivery	9 fold reduced GDM in the metformin arm (3.4% vs. 30% in control)
Vanky <i>et al.</i>	2010	273	First trimester to delivery	Fewer preterm delivery (3% vs. 11% in placebo, $P<0.01$) and less maternal weight gain in the metformin arm
Morin-Papunen <i>et al.</i>	2012	320	Preconception to the first trimester	Higher live birth rates in the metformin arm ($P=0.014$)

PCOD: Polycystic ovarian disease, GDM: Gestational diabetes mellitus, RCT: Randomized controlled trial

There are more benefits!

- **Does not act on pancreas, does not decrease insulin secretion, does not cause hypoglycemia**
- **Prevents or delays the onset of diabetes, George Washington University study- 3,234 non-diabetics with impaired glucose tolerance were given metformin, placebo, or lifestyle recommendations. The incidence of diabetes in the metformin group was 31% less than in the placebo group on follow up**

S Afr Med J 1980 Nov 15;58(20):795-802, "Pregnancy in established non-insulin-dependent diabetics. A five-and-a-half year study at Groote Schuur Hospital" by Coetzee EJ, Jackson WP.

Metformin can decrease Preterm Births too!

Vanky et al (2004) demonstrated a **22.7%** decrease in premature birth rate in the metformin group as compared to controls

Preterm birth prevalence was **3.7%** in the metformin group and **8.2%** in the placebo group

Vanky et al, **Metformin Versus placebo from first trimester to delivery in polycystic ovary syndrome: a randomized, controlled multicenter study**," Journal of Clinical Endocrinology and Metabolism, 2010

More maternal benefits!

- Maternal lipids, C-reactive protein levels not altered
- Uterine artery flow during gestation not affected
- Incidence of surgical delivery reduced
- Maternal weight gain reduced

Niromanesh et al, Diabetes Research and Clinical Practice, 2012

H. Ijäs et al, An International Journal of Obstetrics and Gynaecology, 2011

Stridsklev et al, Midpregnancy **Doppler ultrasound of the uterine artery in metformin- versus placebo-treated PCOS women: a randomized trial,** The Journal of Clinical Endocrinology & Metabolism

Not just the mother, the neonate benefits too!

Metformin throughout pregnancy has been associated with

- **Diminished neonatal hypoglycaemia**
- **Decreased prevalence of FGR**
- **Reduced rates of macrosomia**
- **Absence of IUFDs or stillbirths**
- **Increased live birth rates**

S Bolton et al, European Journal of Pediatrics, 2009

F H Nawaz et al, **Does continuous use of Metformin throughout pregnancy improve pregnancy outcomes in women with polycystic ovarian syndrome?**, Journal of Obstetric and Gynecology Research, 2008

Metformin is safe during breastfeeding too!

The **growth** and **motor-social skills** of breast-fed children of women with PCOS taking metformin have been demonstrated to be similar to those of formula-fed infants, **with no abnormalities**

S Bolton, European Journal of Pediatrics, 2009

C J Glueck et al, Journal of Pediatrics, 2006

MIG Trial

- Largest RCT evaluating the role of metformin in GDM
- **371** women on metformin from 20-33 weeks
- **378** women on insulin
- Dose of metformin upto 2500 mgs daily
- 46.3% of metformin group required additional insulin for glycemic control
- Primary outcomes-neonatal hypoglycaemia, RDS, need for phototherapy, birth trauma, low APGAR score, prematurity

MIG Trial

- **Severe neonatal hypoglycaemia-insulin** group-30/370, compared to 12/363 in the metformin group
- **Maternal weight gain** was more in the insulin group
- No maternal or neonatal lactic acidosis reported
- All other parameters were almost similar
- **Pts preferred metformin over insulin**

J. A. Rowan, MIG Trial, 2007

Rowan JA et al, Diabetes Care. 2011

J. C. Silva, Journal of Perinatal Medicine, 2012

MIG TOFU Trial

MIG TOFU- at 2 yrs - increased subcutaneous upper limb fat, subscapular and biceps skin folds were found in metformin children

Visceral fat was not increased

Ponderal Index did not differ in the 2 groups

Over the short term, metformin does not seem to be harmful with regards to early motor, linguistic, or social development



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Indian Journal of Endocrinology and metabolism, 2015

Author	Year	Region	Number of patient	Primary outcome	Results
Hellmuth <i>et al.</i>	2000	Denmark	118	Maternal, neonatal outcome	Significantly increased in preeclampsia (32 vs. 7 vs. 10%, $P<0.001$) in mother treated with metformin compared to glibenclamide or insulin. Perinatal mortality also significantly increased (11.6 vs. 1.3%, $P<0.02$) in the metformin arm compared to those not treated with metformin
Ekpebegeh <i>et al.</i>	2007	South Africa	379	Glycemic control, perinatal outcome	Perinatal mortality less in the insulin group ($P=0.003$) compared to oral drugs
Tertti <i>et al.</i>	2008	Finland	173	Maternal, neonatal outcome	No difference in any outcome except neonatal hypoglycemia higher in insulin ($P=0.03$)
Balani <i>et al.</i>	2009	UK	127	Maternal, neonatal outcome	Metformin group had less weight gain ($P<0.001$) and improved neonatal outcome ($P<0.01$) compared to insulin. Preterm birth more common in insulin arm (10% vs. 0%; $P=0.01$)
Rai <i>et al.</i>	2009	India	60	Glycemic control, perinatal outcome	Better glucose control in the metformin arm throughout pregnancy more so in first week ($P=0.03-0.007$). Significant increase in NICU admission and cost of therapy in insulin arm
Goh <i>et al.</i>	2011	US	1269	Maternal, neonatal outcome	Metformin group had better glycemic control, fewer preterm delivery (12.5% vs. 19.2%; $P=0.005$), and improved neonatal outcome ($P=0.004$)
Gandhi <i>et al.</i>	2012	UK	592	Maternal, neonatal outcome	No difference except significantly less macrosomia (8.2% vs. 14.3%; OR=0.56, 95% CI=0.33-0.99) and lower BW >90 th centile (14.8% vs. 23.7%; OR=0.56, 95% CI=0.37-0.85) in metformin arm

NICU: Neonatal intensive care unit, OR: Odds ratio, CI: Confidence interval, BW: Birth weight

The Role of Metformin in Metabolic Disturbances during Pregnancy: Polycystic Ovary Syndrome and GDM

Joselyn Rojas et al, International Journal of Reproductive Medicine, Volume 2014

- Has a better postpartum metabolic prognosis for both mothers and their offspring
- Reduces pregnancy complications

Effects of metformin on pregnancy outcomes in women with polycystic ovary syndrome- A Meta-analysis, Sept 9, 2016, Medicine
Marques P et al, **Metformin safety in the management of Gestational diabetes**, Endo Pract 2014

Boomsma CM et al, **A Meta-analysis of pregnancy outcomes in women with polycystic ovary syndrome**, Human Reprod Update 2006

“There is no rose without a thorn”



Side Effects of Metformin

Malaise & fatigue: in 10%- 25% of women

GI disturbance: 30% of women

Vitamin B12 malabsorption: 10%-30% show reduced vitamin B12 absorption as Metformin interferes with the ability of the stomach cells to absorb the intrinsic factor-vitamin B12 complex

Is this important?

B12 is required for synthesis of DNA, for proper growth and function of every cell in the body

By reducing absorption of vitamin B12, Metformin may **increase homocysteine levels**, since Vitamin B12, vitamin B6 and folic acid are responsible for metabolizing homocysteine into less potentially harmful substances

Supplementation of these vitamins can prevent increased Homocysteine levels

Side Effects of Metformin

Anaemia: By preventing optimal absorption of vitamins B12 and folic acid, metformin could induce or contribute to megaloblastic anaemia.

Although **anaemia is not common among people taking metformin**, it remains a risk for those whose B12 and folic acid levels were already low when metformin therapy was started

Gestational diabetes: an alternative to insulin therapy? [Diabete gestationnel: une alternative a l'insulinothérapie.] Presse Med 2001 Feb 3

Green MF et al, **Oral hypoglycemic drugs for gestational diabetes**, N England J Med 2000

Metformin and Pre-eclampsia

Preeclampsia prevalence was **7.4%** in the metformin group and **3.7%** in the placebo group. Perhaps Metformin is unable to effectively modify faulty placentation, the root cause of pre-eclampsia.

Vanky et al, **Metformin Versus placebo from first trimester to delivery in polycystic ovary syndrome: a randomized, controlled multicenter study**,” Journal of Clinical Endocrinology and Metabolism, 2010

METFORMIN



P

- Insulin Resistance
- Hyperinsulinemia



C

- Type 2 Diabetes, GDM
- PIH, PTL



OS

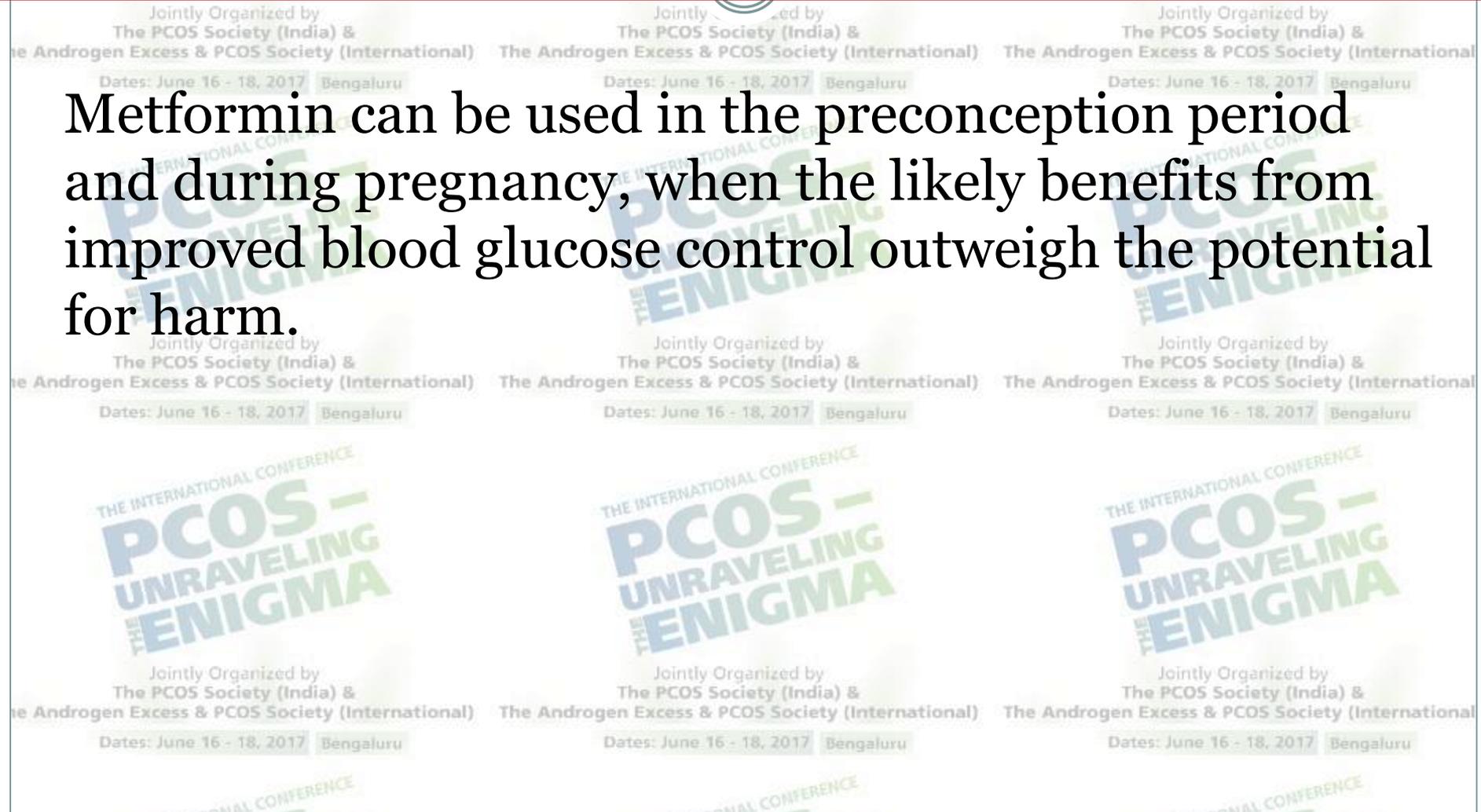
- Early Miscarriage
- Obesity

Effects of metformin on pregnancy outcomes in women with polycystic ovary syndrome---A meta-analysis-Xian-Ling Zeng, Medicine (Baltimore). 2016 Sep

Metformin in women with PCOS throughout pregnancy could increase the possibility of term delivery, VD and reduce the risk of EPL, preterm labor, GDM and PIH, with no serious side effects. Moreover, metformin was not teratogenic based on the limited data. So we may recommend metformin treatment for women with PCOS during the whole pregnancy period as it is quite beneficial and safe for both mothers and babies.

New NICE Guidelines 2015

Metformin can be used in the preconception period and during pregnancy, when the likely benefits from improved blood glucose control outweigh the potential for harm.



Indian Journal of Endocrinology and metabolism, 2015

There are several parts in the world including India, where insulin may not be easily available, apart from various logistic and other psycho-socio-economic issues.

These could be the situations, where metformin use can be desirable. At any point of time, adverse effects of untreated hyperglycemia will be worse than treating with metformin.



Mrs S, 27 yr old Primigravida with PCOS, BMI- 31, On Folic acid and Metformin, Conceive with OI Beaming with happiness, she asks her obstetrician, **“What about Metformin, Doctor? You didn’t give me an answer, Doctor. Should I continue it?”**



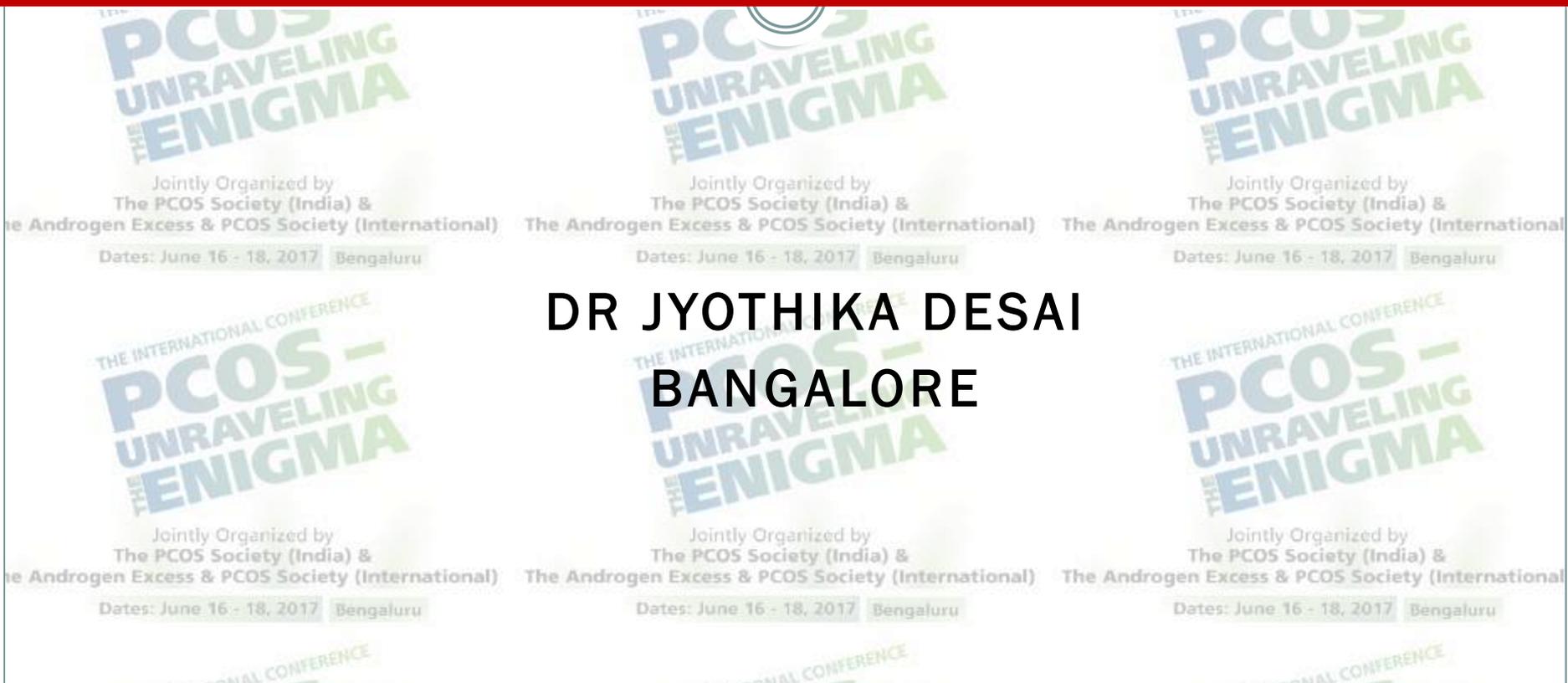
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Should Metformin be continued in pregnancy?



DR JYOTHIKA DESAI
BANGALORE

OF COURSE
YES!

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