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

The Journal of Clinical Endocrinology & Metabolism, 2002, by The Endocrine Society
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?
Pregnancy in PCOS is at increased risk of:

- Insulin Resistance
- Hyperandrogenemia

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

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

Metformin in polycystic ovary syndrome, Annals of the New York Academy of Sciences, 14 September 2010
Pregnancy in PCOS is a challenge.
Early pregnancy loss in pregnancy in PCOS

Chromosomal Abnormalities – uncommonly seen

Hyperinsulinemia and hyperandrogenemia – more often implicated

Pregnancy outcomes and the effect of Metformin in women with PCOS, AOGS, May 2012
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 etal, 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
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


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


Does Metformin prevent GDM?- YES
## RCTs of metformin in pregnant PCOD

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

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.

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
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


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.

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
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

Ijäs H, A follow-up of a randomised study of metformin and insulin in GDM: growth and development of the children at the age of 18 months BJOG. 2015
Indian Journal of Endocrinology and Metabolism, 2015
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Region</th>
<th>Number of patient</th>
<th>Primary outcome</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hellmuth et al.</td>
<td>2000</td>
<td>Denmark</td>
<td>118</td>
<td>Maternal, neonatal outcome</td>
<td>Significantly increased in preeclampsia (32 vs. 7 vs. 10%, (P&lt;0.001)) in mother treated with metformin compared to glibenclamide or insulin. Perinatal mortality also significantly increased (11.6 vs. 1.3%, (P&lt;0.02)) in the metformin arm compared to those not treated with metformin</td>
</tr>
<tr>
<td>Ekpebegh et al.</td>
<td>2007</td>
<td>South Africa</td>
<td>379</td>
<td>Glycemic control, perinatal outcome</td>
<td>Perinatal mortality less in the insulin group ((P=0.003)) compared to oral drugs</td>
</tr>
<tr>
<td>Tertti et al.</td>
<td>2008</td>
<td>Finland</td>
<td>173</td>
<td>Maternal, neonatal outcome</td>
<td>No difference in any outcome except neonatal hypoglycemia higher in insulin ((P=0.03))</td>
</tr>
<tr>
<td>Balani et al.</td>
<td>2009</td>
<td>UK</td>
<td>127</td>
<td>Maternal, neonatal outcome</td>
<td>Metformin group had less weight gain ((P&lt;0.001)) and improved neonatal outcome ((P&lt;0.01)) compared to insulin. Preterm birth more common in insulin arm (10% vs. 0%; (P=0.01))</td>
</tr>
<tr>
<td>Rai et al.</td>
<td>2009</td>
<td>India</td>
<td>60</td>
<td>Glycemic control, perinatal outcome</td>
<td>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</td>
</tr>
<tr>
<td>Goh et al.</td>
<td>2011</td>
<td>US</td>
<td>1269</td>
<td>Maternal, neonatal outcome</td>
<td>Metformin group had better glycemic control, fewer preterm delivery (12.5% vs. 19.2%; (P=0.005)), and improved neonatal outcome ((P=0.004))</td>
</tr>
<tr>
<td>Gandhi et al.</td>
<td>2012</td>
<td>UK</td>
<td>592</td>
<td>Maternal, neonatal outcome</td>
<td>No difference except significantly less macrosomia (8.2% vs. 14.3%; OR=0.56, 95% CI=0.33–0.99) and lower BW &gt;90th centile (14.8% vs. 23.7%; OR=0.56, 95% CI=0.37–0.85) in metformin arm</td>
</tr>
</tbody>
</table>

NICU: Neonatal intensive care unit, OR: Odds ratio, CI: Confidence interval, BW: Birth weight
Review Article
The Role of Metformin in Metabolic Disturbances during Pregnancy: Polycystic Ovary Syndrome and GDM
Joselyn Rojas etal, 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 etal, Metformin safety in the management of Gestational diabetes, Endo Pract 2014

Boomsma CM etal, 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
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.

**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"
• Insulin Resistance
• Hyperinsulinemia

• Type 2 Diabetes, GDM
• PIH, PTL

• Early Miscarriage
• Obesity

Metformin in polycystic ovary syndrome, Annals of the New York Academy of Sciences, 14 September 2010
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.
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.
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, conceives 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?”
Should Metformin be continued in pregnancy?

DR JYOTHIKA DESAI
BANGALORE
OF COURSE
YES!
YAAAAAAAASSSSSSSSS