Problems in PCOS pregnancy

- Miscarriage
- Pre-eclampsia
- PIH
- Cesarean Section
- Gestational Diabetes
- Preterm labour
- Admission to NICU
- Prematurity
- Perinatal mortality
Problems with PCOS Pregnancy
Problems with PCOS Pregnancy

Metformin! Metformin! Metformin!
We have heard so much good about Metformin and I give up!
But, before I do.............
Can you recognise the woman in this picture?
People think Sachin dressed up as a lady in sari for some fancy dress competition!
Google image of India on Diwali night!
No!

This image was based on data collected by the VIIRS 'day-night band' which detects light in a range of wavelengths from green to near-infrared!
It is easy to believe!....especially when you want to!!!

Check the evidence first!
It all started like this…….

The main problem with PCOS is Insulin Resistance. If IR is tackled with Metformin, all problems secondary IR gets tackled.
Metformin

Stimulates AMPK
- Inhibits lipogenic enzymes
- Activates GLUT-4
- Decreases lipogenesis
- Increases fatty acid oxidation
- Increases basal glucose uptake

Activates Insulin Signalling
- Increases insulin-dependent glucose uptake

Decreased Insulin Resistance
Why is Metformin continued during pregnancy?

- To reduce Pre-eclampsia
- To reduce GDM
- To reduce Preterm Labour
Metformin is being used indiscriminately throughout pregnancy. After all it is useful, supposedly safe and has no worrisome side effects.
Metformin is the new Vitamin!
Metformin to reduce PE, PTL, GDM

But,

Metformin was, and is not approved for this indication

Evidence is lacking!
Use of Metformin is supported by unclear and non-powered data
Metformin reduces risk of GDM

Metformin throughout pregnancy

- GDM incidence ↓ from 30% to 12% (Glueck 2002, 2004, 2007)
- No significant effect, but less complications of pregnancy in the metformin group (Vanky 2004)

Controversial results
Why are there such controversial results?
Why are there controversial results?

Most of the studies were retrospective or prospective of cohorts or case control studies or observation researches and conducted at single center.

- Subject group might be the same - conducted in the same country
- Selection bias. Large observed and unobserved differences in patients between the treatment and control groups. This is ruled out in RCTs.
Metformin Versus Placebo from First Trimester to Delivery in Polycystic Ovary Syndrome: A Randomized, Controlled Multicenter Study

Eszter Vanky, Solhild Stridsklev, Runa Heimstad, Pål Romundstad, Kristin Skogøy, Odrun Kleggetveit, Sissel Hjelle, Philip von Brandis, Torunn Eikeland, Karin Flo, Kristin Flaten Berg, Gabor Bunford, Agnethe Lund, Cecilie Bjerke, Ingunn Almås, Ann Hilde Berg, Anna Danielson, Gulim Lahnami, and Sven Magnus Carlsen*

Context: Metformin is widely prescribed to pregnant women with polycystic ovary syndrome (PCOS) in an attempt to reduce pregnancy complications. Metformin is not approved for this indication, and evidence for this practice is lacking.

Objectives: Our objective was to test the hypothesis that metformin, from first trimester to delivery, reduces pregnancy complications in women with PCOS.

Design and Setting: We conducted a randomized, placebo-controlled, double-blind, multicenter study at 11 secondary care centers.

Participants: The participants were 257 women with PCOS, in the first trimester of pregnancy, aged 18–42 yr.

Intervention: We randomly assigned 274 singleton pregnancies (in 257 women) to receive metformin or placebo, from first trimester to delivery.

Main Outcome Measures: The prevalence of preeclampsia, gestational diabetes mellitus, preterm delivery, and a composite of these three outcomes is reported.
Best study

• Randomized
• Double blind
• Placebo controlled
• Multicentric
Best study

- 257 PCOS women
- 18-42yrs
- Randomized to placebo and Metformin
- First trimester to delivery
- Outcomes: Pre-eclampsia, GDM, Pre-term delivery
<table>
<thead>
<tr>
<th>Primary End points</th>
<th>Metformin [n (%)]</th>
<th>Placebo [n (%)]</th>
<th>Risk difference (%)</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preeclampsia</td>
<td>10/135 (7.4)</td>
<td>5/135 (3.7)</td>
<td>3.7</td>
<td>-1.7–9.2</td>
<td>0.18</td>
</tr>
<tr>
<td>Preterm delivery(^a)</td>
<td>5/135 (3.7)</td>
<td>11/135 (8.2)</td>
<td>-4.4</td>
<td>-10.1–1.2</td>
<td>0.12</td>
</tr>
<tr>
<td>New GDM</td>
<td>22/125 (17.6)</td>
<td>21/124 (16.9)</td>
<td>0.8</td>
<td>-8.6–10.2</td>
<td>0.87</td>
</tr>
<tr>
<td>Composite primary endpoints</td>
<td>35/135 (25.9)</td>
<td>33/135 (24.4)</td>
<td>1.5</td>
<td>-8.9–11.3</td>
<td>0.78</td>
</tr>
</tbody>
</table>
Why isn’t Metformin effective?

Is it the effect of Obesity?

Metformin is ineffective in massive obesity (BMI ≥ 35 kg/m^2)?

First weight loss, then metformin when BMI < 35 kg/m^2? (Balen et al. 2006)
Post hoc analysis

Subgroups stratified according to body mass index (BMI) of 30 kg/m² or lower and BMI higher than 30 kg/m² showed no difference between the study groups.
Metformin in preventing GDM

Metformin, an insulin sensitizing drug, used successfully in the treatment of Diabetes did not reduce the prevalence of GDM.

- GDM prevalence was 17.6% in the metformin group and 16.9% in the placebo group (0.8%, 95% CI, -8.6 to 10.2) (P=0.87).
Why was Metformin unsuccessful in preventing GDM

Diet and lifestyle management in both groups may have reduced the effect of metformin on glucose homeostasis.
Metformin and Preterm delivery

Preeclampsia prevalence was 7.4% in the metformin group and 7% in the placebo group (3.7%; 95% CI, -1.7–9.2) (P=0.18). 
Why is Metformin not useful for preventing Pre eclampsia in PCOS women

Etiopathogeneis of Pre eclampsia

- Abnormal vascular response to placentation
- Chronic systemic inflammation
- Increased sympathetic tone and vascular smooth muscle growth and involves compliance of blood vessels
Metformin and Pre-eclampsia

Pre-eclampsia - blood flow through the uterine arteries is affected.

RCT - Mid-pregnancy Doppler ultrasound of the uterine artery in metformin versus placebo-treated PCOS women.

Metformin treatment does not affect uterine artery flow during gestation.

Metformin in preventing Preterm labour

Preterm delivery was defined as delivery before gestational wk 37. No significant difference in Preterm delivery between Metformin and Placebo controlled group. 3.7% in the metformin group and 8.2% in the placebo group (4.4%, 95% CI, 10.1 – 1.2) (P = 0.12)
Metformin in preventing Preterm labour

Metformin may aid in prevention of preterm birth by ameliorating oxidative stress and chronic inflammation.

But, the etiopathogenesis of Preterm labour is complex and can be due to:

- Faulty placentation
- Intrauterine infection
- Immunologic factors
- Cervical incompetence
- Maternal factors - uterine factors, trauma and surgery
- Fetal anomalies
- Idiopathic conditions
Metformin may be useful in PCOS (other indications)
What do we do when RCTs and Non RCTs produce controversial results?

Evidence of data derived from multiple RCTs or meta-analyses is stronger than data derived from a single randomized trial or unrandomized studies.
Effect of Metformin Intervention during Pregnancy on the Gestational Diabetes Mellitus in Women with Polycystic Ovary Syndrome: A Systematic Review and Meta-Analysis

Zhihong Zhuo,1,2 Aiming Wang,3 and Huimin Yu2

1 Southern Medical University, Guangzhou 510000, China
2 Ningbo No. 2 Hospital, Ningbo 315010, China
3 Navy General Hospital of Chinese PLA, Beijing 100000, China

Correspondence should be addressed to Aiming Wang; one.army@sina.com

Received 22 March 2014; Revised 20 April 2014; Accepted 23 April 2014; Published 21 May 2014

Academic Editor: Raffaele Marfella

Copyright © 2014 Zhihong Zhuo et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Metformin is an effective insulin sensitizer treating type 2 diabetes mellitus. However, the functional consequences of metformin administration throughout pregnancy on gestational diabetes mellitus (GDM) with polycystic ovary syndrome (PCOS) have not been assessed. We therefore performed a meta-analysis and systematic review to determine the effect of metformin on GDM in PCOS. A meta-analysis was performed on the published studies before December, 2013. Meta-analysis examined whether metformin could reduce GDM occurrence in PCOS with a fixed effect model. The odds ratio (OR) with 95% confidence interval (95% CI) was calculated.
Effect of Metformin on GDM in PCOS Pregnancy

5 RCTs
8 Non-RCTs
13 Studies in all

Result: Effectiveness analysis demonstrated that in total, there was no significant availability of metformin on GDM in PCOS in contrast to placebo (OR = 1.07, 95% CI 0.60–1.92)

Imp: No statistically significant benefit of metformin administration on the DM risk in PCOS
Diabetes Prevention program

27 center RCT

Clinical trial to determine whether lifestyle intervention or Metformin pharmacotherapy would prevent or delay the onset of diabetes in individuals with impaired glucose tolerance (IGT).

- **Lifestyle** (Just 7% wt loss / wt maintenance and Brisk walking for 150 min a week)
- **Metformin** – 850mg twice daily
DPP: Reduction in Incidence of Diabetes with Lifestyle Intervention or Metformin

Trial was discontinued 1 year early because of clear results

Patients Developing Diabetes in Mean 3-Year Follow-up (%)

- **Diet + Exercise**: 14 (58% reduction)
- **Metformin**: 22 (31% reduction)
- **Placebo**: 29

5-7% reduction in body weight; exercise 30 min/d

If we can achieve something WITHOUT a DRUG and even BETTER than a DRUG,

Why use a DRUG and that also in Pregnancy?

After all, Life style modification have proven benefits in PCOS
To use the words of Dr. Richard Legro

“Metformin lost the mantle of a medication, to be used judiciously for specific indications, and became instead a new vitamin, to be used ubiquitously to enhance every reproductive process in women with PCOS”
To use the words of Richard Legro

However, if metformin is to be given during pregnancy, let it be given as a drug and not as a vitamin. Future trials can identify pregnant women who are likely to benefit from Metformin. In the meantime take Metformin off the vitamin rack of pregnancy and put it back in the research pharmacy.
Effect of Metformin on the offspring
Effect of Metformin on the offspring

- No teratogenic effect
- No hypoglycemia
- Fat distribution in the offspring: subcutaneous - favourable
Metformin has no ill effect on the Offspring

Impact of metformin on reproductive tissues: an overview from gametogenesis to gestation

Ann Transl Med 2014;2(6):55

Michael J. Bertoldo*, Melanie Faure*, Joelle Dupont, Pascal Froment

Unité de Physiologie de la Reproduction et des Comportements, Institut National de la Recherche Agronomique, Centre Val de Loire, UMR85, 37380 Nouzilly, France
*These authors contributed equally to this work.

Correspondence to: Dr. Pascal Froment. Unité de Physiologie de la Reproduction et des Comportements, Institut National de la Recherche Agronomique, 37380 Nouzilly, France. Email: pascal.froment@tours.inra.fr.

Abstract: Metformin is an oral anti-hyperglycemic drug that acts as an insulin sensitizer in the treatment of diabetes mellitus type 2. It has also been widely used in the treatment of polycystic ovary syndrome (PCOS) and gestational diabetes. This drug has been shown to activate a protein kinase called 5’ AMP-activated protein kinase
Effect of Metformin on Gonads

- Metformin inhibits the mitochondria respiratory chain
- Anaerobic respiration and an increase in lactate secretion
- Lactate is the primary energy substrate for male germ cells and is produced by the Sertoli cells.
in utero metformin-exposed newborns presented with a decrease in testis size, tubule diameter and a lower Sertoli cells number.

These results raise some questions about the harmlessness of metformin on gonad development and the fertility of the progeny from treated mothers, where we have no data at this time.
Literature says metformin is safe to use during pregnancy with respect to immediate pregnancy outcomes. However, we still do not have adequate data to say with any certainty that metformin does not have any adverse effects for whole of life health. There are questions of safety in terms of fetal testicular development.
Use Metformin indiscriminately now

And you might wake up to a population of infertile men!!!
Thalidomide tragedy of the functional kind!