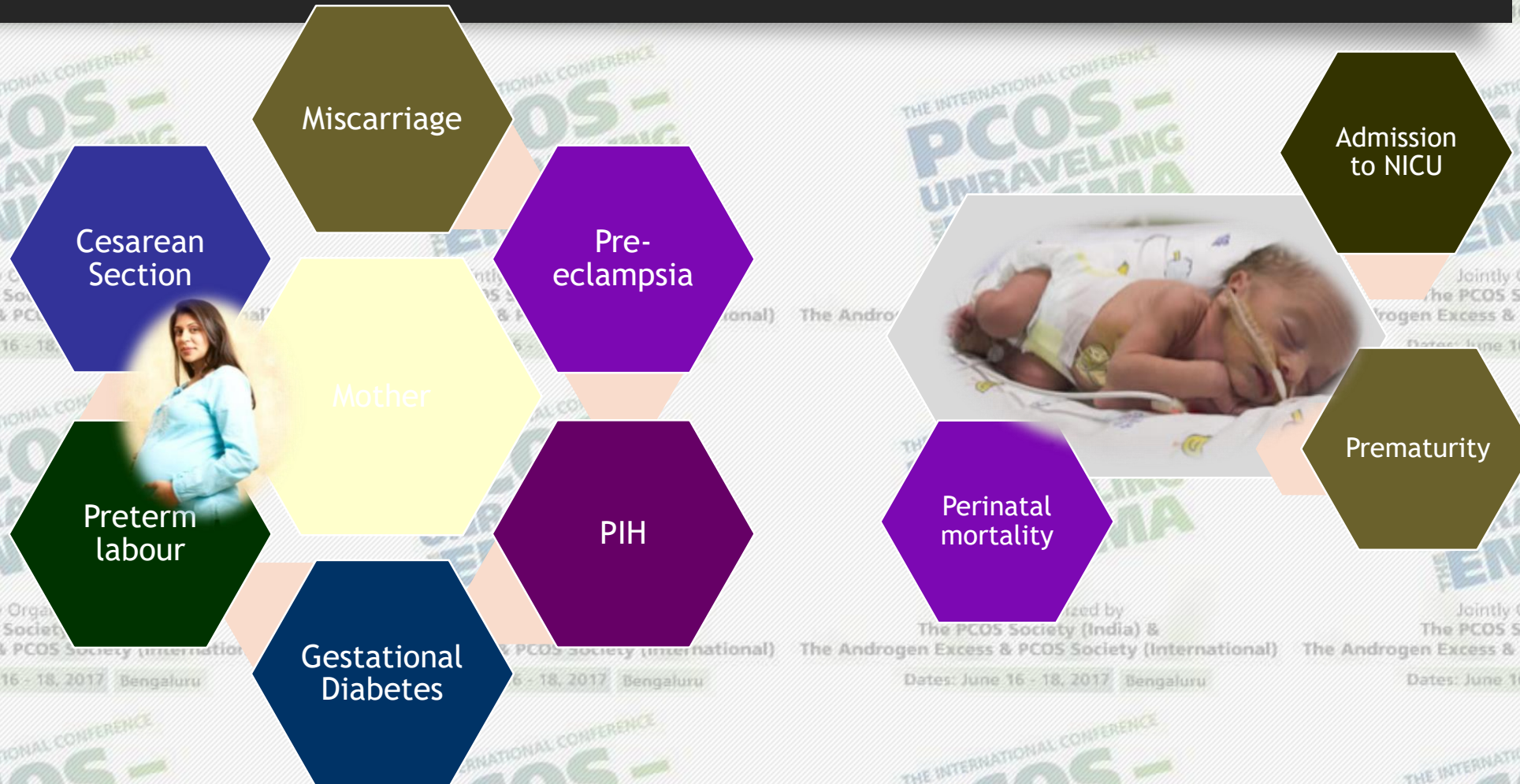


Problems in PCOS pregnancy



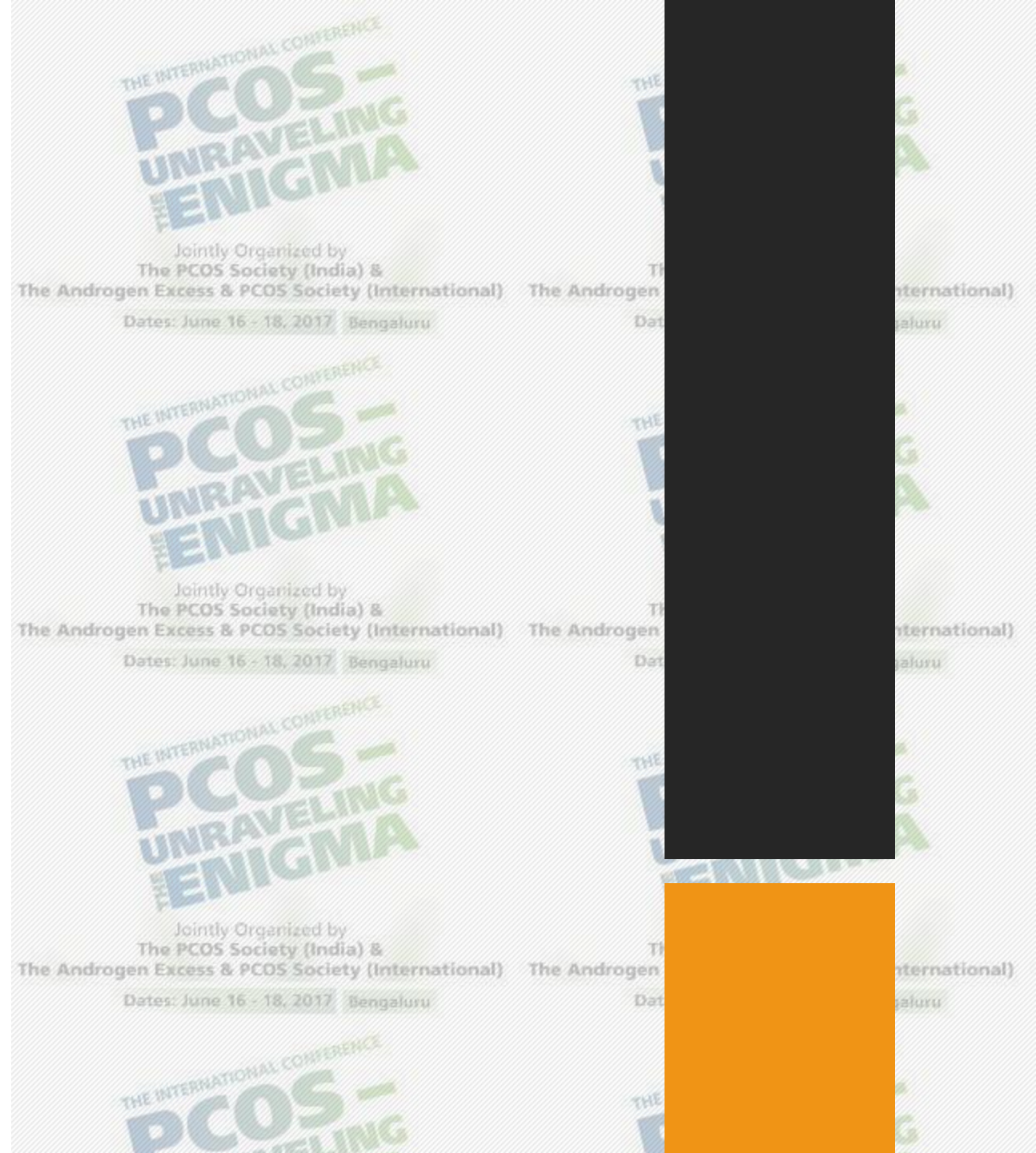
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Problems with PCOS Pregnancy



Problems with PCOS Pregnancy

Metformin! Metformin! Metformin!



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We have heard so much good about Metformin

I give up!



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But, before I do.....

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Can you recognise the woman in this picture?

People think Sachin dressed up as a lady in sari for some fancy dress competition!

Image Credit: pakpassion

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Google image of India on Diwali night!



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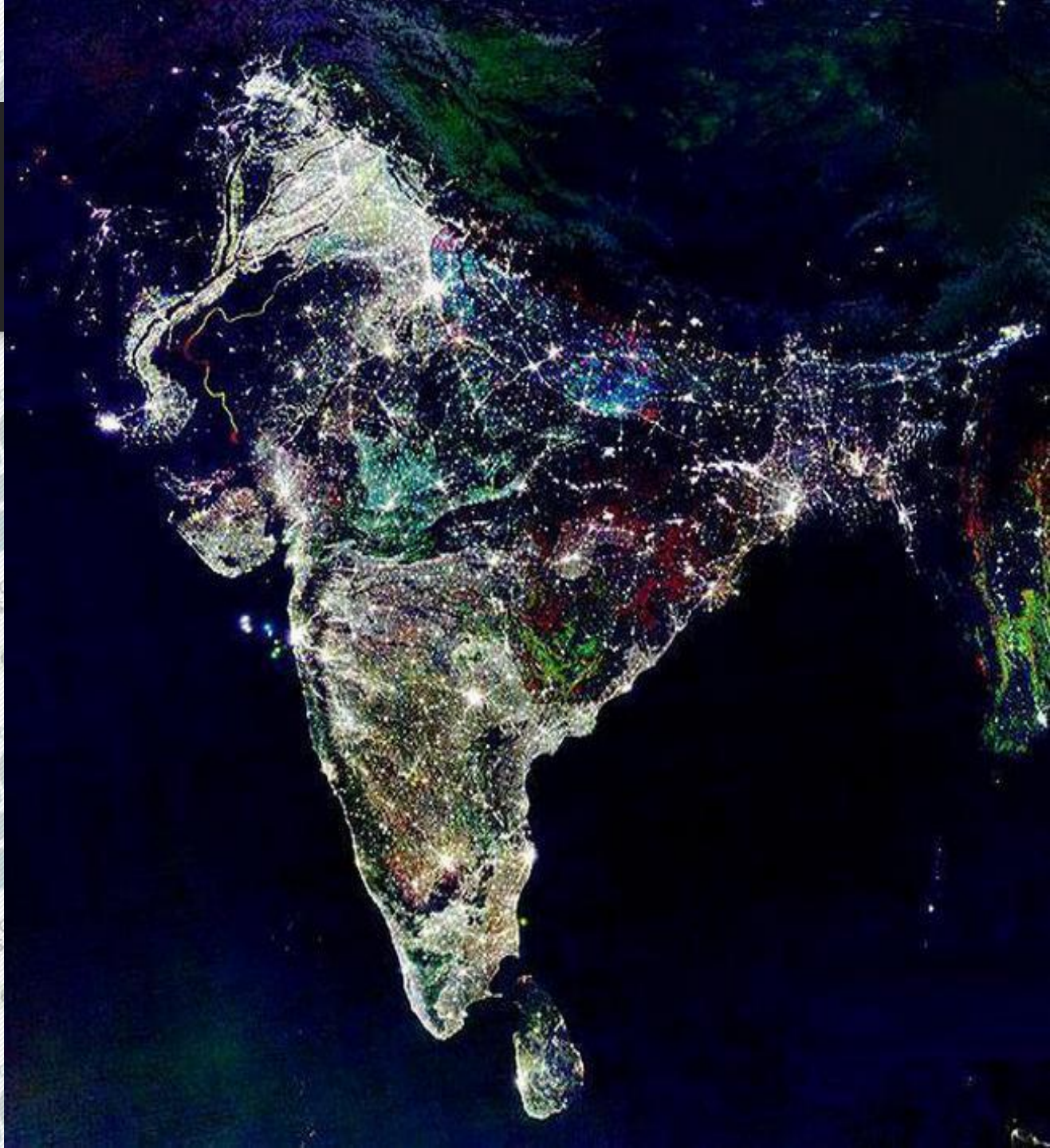
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No!

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!



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It is easy to believe!...especially when you want to!!!

Check the evidence first!

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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

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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

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Why is Metformin continued during pregnancy?

- To reduce Pre eclampsia
- To reduce GDM
- To reduce Preterm Labour

Metformin is being used indiscriminately through out pregnancy. After all it is useful, supposedly safe and has no worrisome side effects.

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Metformin is the new Vitamin!



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Metformin to reduce PE, PTL, GDM

But,

Metformin was, and is not approved for this indication

Evidence is lacking!

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Use of Metformin is supported by unclear and non-powered data

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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

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Why are there such controversial results?

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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 or multiple centers, and many studies included a small number of women
- 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

Best study

- Randomized
- Double blind
- Placebo controlled
- Multicentric



Best study

- 257 PCOS women
- 18-42yrs
- Randomized to placebo and Metformin
- First trimester to delivery
- Outcome: Pre-eclampsia, GDM, Pre-term delivery

Primary End points

	Metformin [n (%)]	Placebo [n (%)]	Risk difference (%)	95% CI	P value
Preeclampsia	10/135 (7.4)	5/135 (3.7)	3.7	-1.7-9.2	0.18
Preterm delivery ^a	5/135 (3.7)	11/135 (8.2)	-4.4	-10.1-1.2	0.12
New GDM	22/125 (17.6)	21/124 (16.9)	0.8	-8.6-10.2	0.87
Composite primary endpoints	35/135 (25.9)	33/135 (24.4)	1.5	-8.9-11.3	0.78

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Why isn't Metformin effective?

Is it the effect of Obesity?

Metformin is ineffective in massive obesity ($BMI \geq 35 \text{ kg/m}^2$)?

First weight loss, then metformin when $BMI < 35 \text{ kg/m}^2$? (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, -8.6-10.2) (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 3.7% 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

Etiopathogenesis 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

Stridsklev S. et al. *a randomized trial. The Journal of Clinical Endocrinology & Metabolism.* 2014;99:972-977

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 – complex

• Placental dysfunction

• 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)

But once size doesn't fit all



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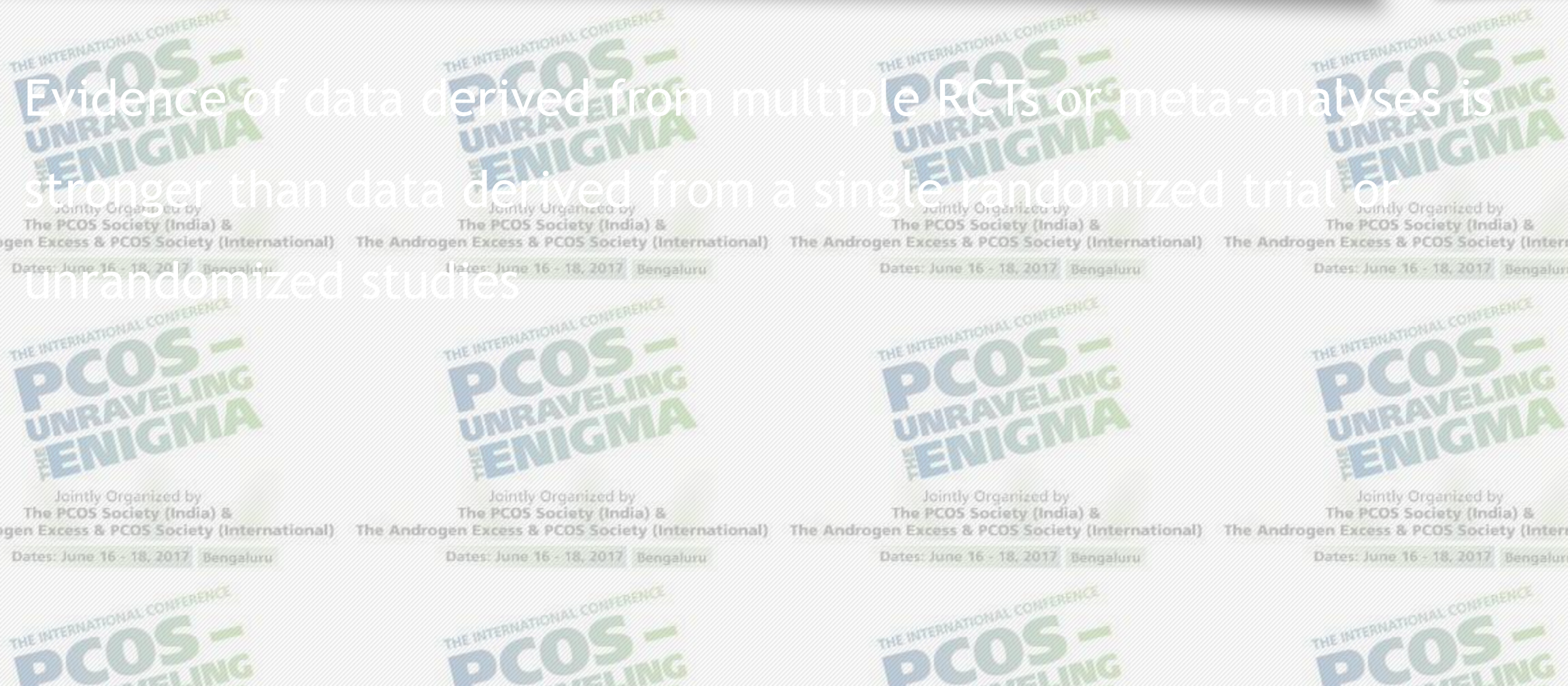
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What do we do when RCTs and Non RCTs produce controversial results?

Evidence of data derived from multiple RCTs or meta-analyses is stronger than data derived from a single randomized trial or unrandomized studies



Review Article

Effect of Metformin Intervention during Pregnancy on the Gestational Diabetes Mellitus in Women with Polycystic Ovary Syndrome: A Systematic Review and Meta-Analysis

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Academic Editor: Raffaele Marfella

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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 system 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

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

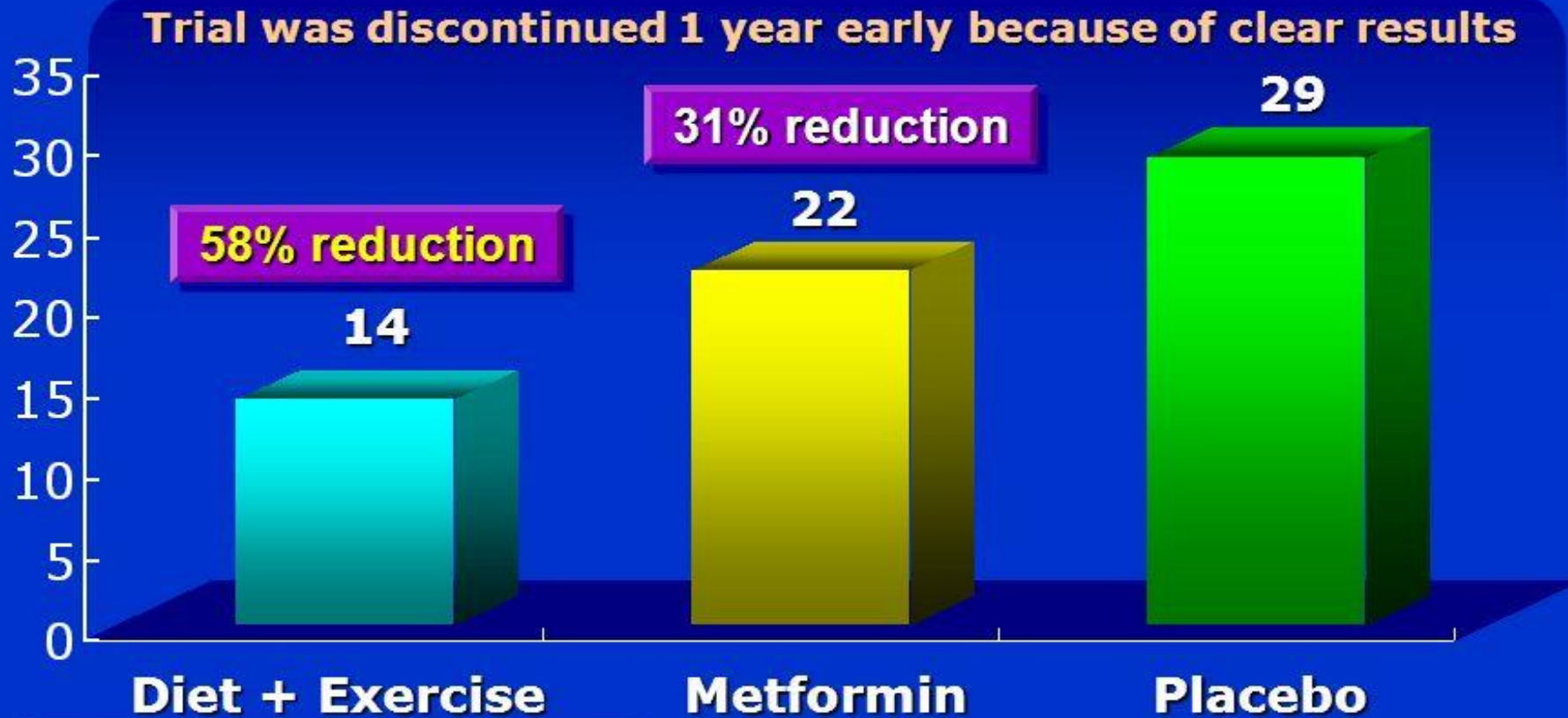
27 center RCT

Clinical trial to determine whether lifestyle intervention or Metformin pharmacol 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 150min a week)
- Metformin 850mg twice daily

DPP: Reduction in Incidence of Diabetes with Lifestyle Intervention or Metformin

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



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

Knowler WC, et al. *N Engl J Med* 2002;346:393-403.

Slide Source:
Lipids Online Slide Library
www.lipidsonline.org

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”*



[J Clin Endocrinol Metab.](#) 2010 Dec; 95(12): 5199–5202.

PMCID: PMC2999976

doi: [10.1210/jc.2010-2301](https://doi.org/10.1210/jc.2010-2301)

Metformin during Pregnancy in Polycystic Ovary Syndrome: Another Vitamin Bites the Dust

[Richard S. Legro](#)

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.”

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Dates: June 16 - 18, 2017 | Bengaluru

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Effect of Metformin on the offspring

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Effect of Metformin on the offspring

- No Teratogenic effect
- No hypoglycemia
- Normal 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

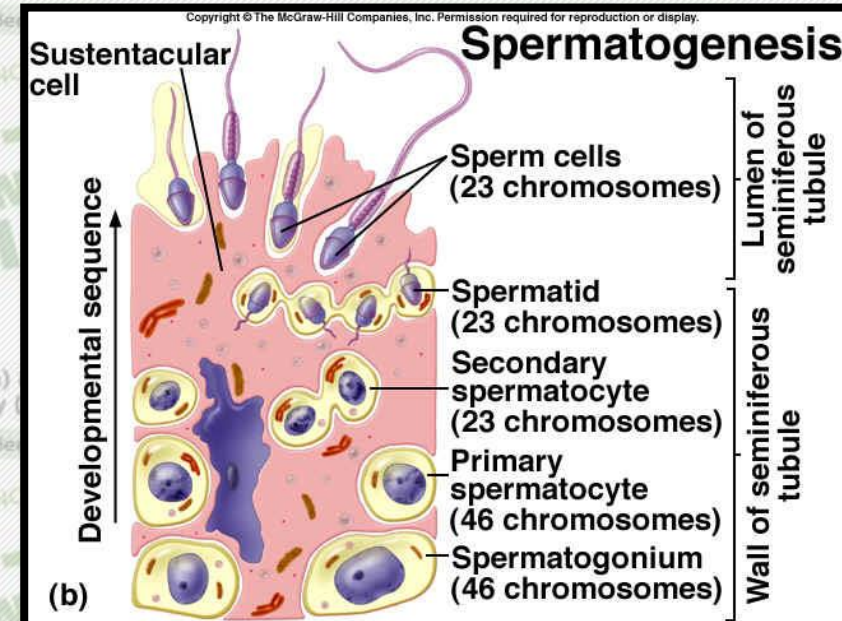
*These authors contributed equally to this work.

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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 new borns presented with a decrease in testis size, tubule diameter and a lower Sertoli cells number.

• These results raise some questions about harmfulness 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.

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Use Metformin indiscriminately now

And you might wake up to a population of infertile men!!!

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Thalidomide tragedy of the functional kind!



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