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2017-18

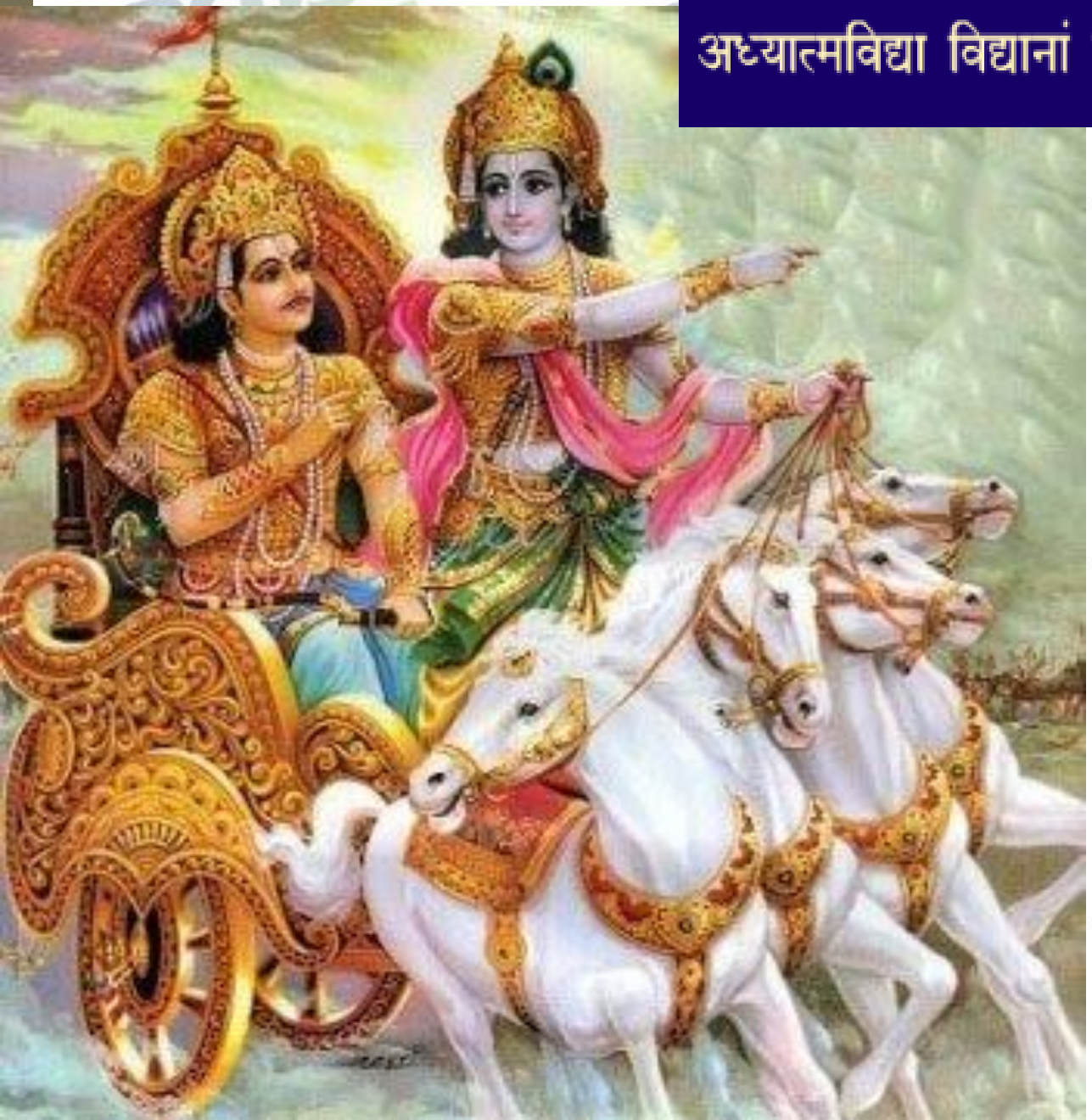
National coordinator, Family welfare committee, FOGSI:

Joint Secretary, Indian Menopause Society, Bangalore Chapter, 2016-2018.

Member of FOGSI Youth cell, Endometriosis and safe motherhood Committee.

Special interests : Maternal medicine, Endoscopic and vaginal surgery, Menopausal medicine, population stabilization.

The Gita,



सर्गाणामादिरन्तश्च मध्यं चैवाहमर्जुन ।
अध्यात्मविद्या विद्यानां वादः प्रवदतामहम् ॥ ३२ ॥

Of creations, I am the beginning, the middle and the end;
Of knowledge I am knowledge of the Supreme Self;
Among speakers, I am words that are unbiased and in pursuit of truth.

Of Arguments, I am the logical conclusion.

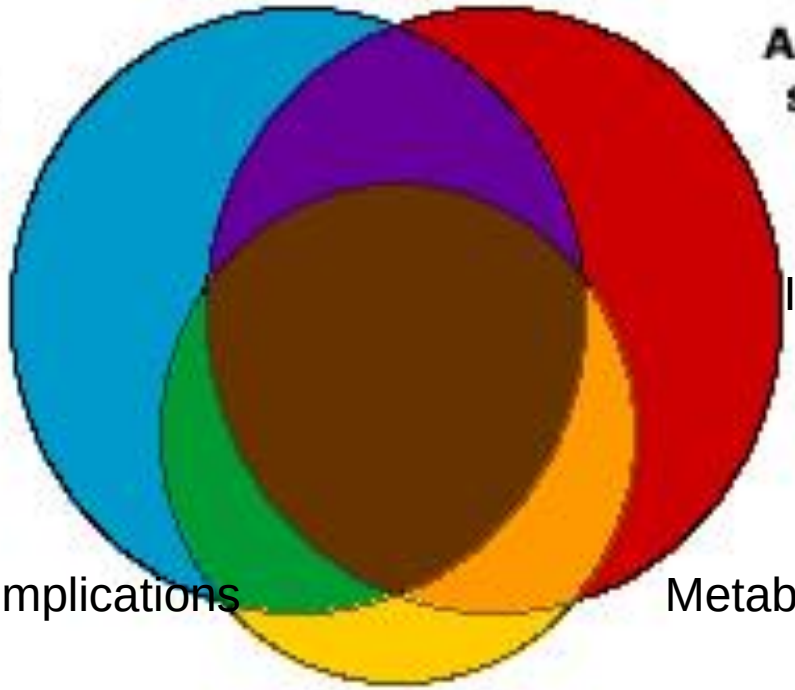
Is PCOS associated with a higher pregnancy loss ?

Of Course !

Yes indeed !

PCOS in the Indian context

- Epidemic proportions
- Emergent public health problem.
- Lack of strong public and academic discourse
- Gargantuan, yet ill-recognized problem, poorly understood.
- Often not well managed



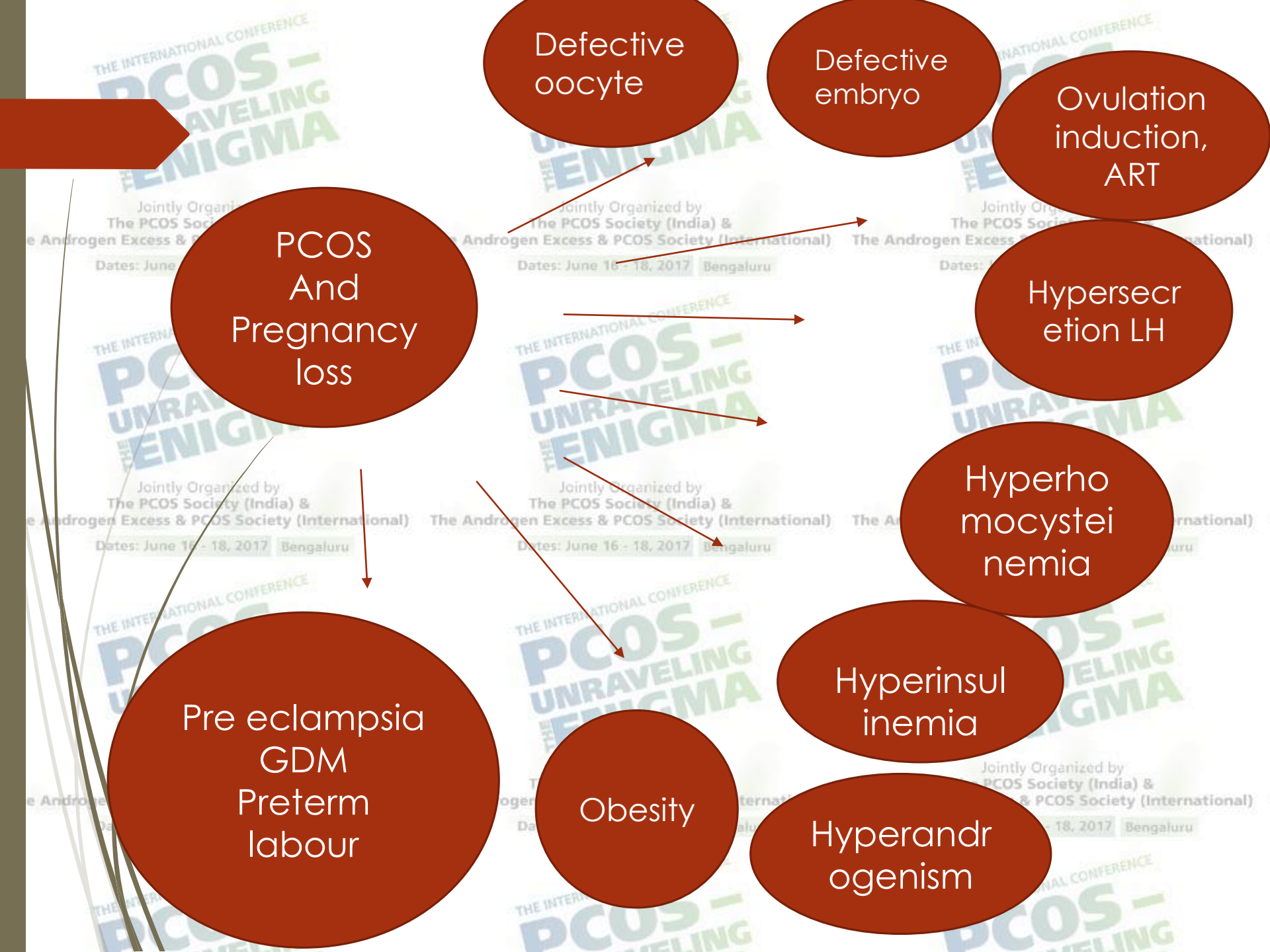
Complex Heterogeneity

NIH (USA) Evidence-based Methodology Workshop on PCOS in December 2012,

- *PCOS is a very common disorder (the prevalence ranges from 6 to 20% depending on the criteria used*
- ***While supporting the Rotterdam definition as the most inclusive and appropriate in a global context, it was suggested that a more appropriate, less 'ovary-centric' name for the syndrome should be considered.***

Phenotypes of PCOS (ESHRE-ASRM)

- *Four different phenotypes of PCOS are now identified:*
- ***hyperandrogenism (clinical or biochemical) and CA - H-CA***
- ***hyperandrogenism and polycystic ovaries on ultrasound - but with ovulatory cycles - H-PCOm***
- ***CA and polycystic ovaries without hyperandrogenism- CA-PCOm***
- ***hyperandrogenism, CA and polycystic ovaries- H-CA-PCOm.***
- 2011, The Amsterdam ESHRE/ASMR- 3rd PCOS Consensus Workshop Group


Defective oocyte
Defective embryo
Ovulation induction, ART
PCOS And Pregnancy loss
Hypersecretion LH
Hyperhomocysteinemia
Pre eclampsia GDM Preterm labour
Hyperinsulinemia
Obesity
Hyperandrogenism

BMJ. 2011 Oct 13;343:d6309. doi: 10.1136/bmj.d6309.

Risk of adverse pregnancy outcomes in women with polycystic ovary syndrome: population based cohort study.

Roos N[1], Kieler H, Sahlin L, Ekman-Ordeberg G, Falconer H, Stephansson O.

Author information

Abstract

OBJECTIVE: To study the risk of adverse pregnancy outcomes in women with polycystic ovary syndrome, taking into account maternal characteristics and assisted reproductive technology.

DESIGN: Population based cohort study.

SETTING: Singleton births registered in the Swedish medical birth register between 1995 and 2007.

PARTICIPANTS: By linkage with the Swedish patient register, 3787 births among women with a diagnosis of polycystic ovary syndrome and 1,191,336 births among women without such a diagnosis.

MAIN OUTCOME MEASURES: Risk of adverse pregnancy outcomes (gestational diabetes, pre-eclampsia, preterm birth, stillbirth, neonatal death, low Apgar score (<7 at five minutes), meconium aspiration, large for gestational age, macrosomia, small for gestational age), adjusted for maternal characteristics (body mass index, age), socioeconomic factors (educational level, and cohabitating with infant's father), and assisted reproductive technology.

RESULTS: Women with polycystic ovary syndrome were more often obese and more commonly used assisted reproductive technology than women without such a diagnosis (60.6% v 34.8% and 13.7% v 1.5%). Polycystic ovary syndrome was strongly associated with pre-eclampsia (adjusted odds ratio 1.45, 95% confidence interval 1.24 to 1.69) and very preterm birth (2.21, 1.69 to 2.90) and the risk of gestational diabetes was more than doubled (2.32, 1.88 to 2.88). Infants born to mothers with polycystic ovary syndrome were more prone to be large for gestational age (1.39, 1.19 to 1.62) and were at increased risk of meconium aspiration (2.02, 1.13 to 3.61) and having a low Apgar score (<7) at five minutes (1.41, 1.09 to 1.83).

CONCLUSIONS: Women with polycystic ovary syndrome are at increased risk of adverse pregnancy and birth outcomes that cannot be explained by assisted reproductive technology. These women may need increased surveillance during pregnancy and parturition.

Evidence for etiological factors for pregnancy loss In PCOS

Population based cohort study(Sweden) 3787patients

- ***PCOS was strongly associated with pre-eclampsia (adjusted OR 1.45, 95% CI: 1.24-f1.69),***
- ***preterm birth (2.21, 1.69 to 2.90),***
- ***more than double risk of GDM (2.32, 1.88 to 2.88),***
- ***and birth of large for gestational age infants (1.39, 1.19 to 1.62).***

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PLOS ONE

Recurrent Pregnancy Loss in Polycystic Ovary Syndrome: Role of Hyperhomocysteinemia and Insulin Resistance

Pratip Chakraborty[1☯], S. K. Goswami[2☯], Shweta Rajani[2], Sunita Sharma[2], Syed N. Kabir[3], Baidyanath Chakravarty[2], Kuladip Jana[4*]

1 Department of Infertility, Institute of Reproductive Medicine, Kolkata, India, **2** Department of Assisted Reproduction, Institute of Reproductive Medicine, Kolkata, India, **3** Reproductive Biology Research, CSIR-Indian Institute of Chemical Biology, Jadavpur, Kolkata, India, **4** Division of Molecular Medicine, Bose Institute, P 1/12, Calcutta Improvement Trust Scheme VIIM, Kolkata, West Bengal, India

Abstract

Recurrent pregnancy loss (RPL) in polycystic ovary syndrome (PCOS), which occurs in ~50% of total pregnancies is a frequent obstetric complication. Among the several hypotheses, insulin resistance (IR), obesity and hyperhomocysteinemia (HHcy) play significant role/s in RPL. This study was conducted to assess the link between elevated levels of homocysteine and IR in PCOS-associated women with RPL in Kolkata, India. A retrospective study was conducted of one hundred and twenty six PCOS women (<30 years) who experienced two or more spontaneous abortions during the first trimester presenting to Institute of Reproductive Medicine (IRM) in Kolkata during the period of March 2008 through February 2011. One hundred and seventeen non-PCOS subjects with matching age range were randomly chosen as controls. Incidence of HHcy and IR was 70.63% (n = 89) and 56.34% (n = 71), respectively, in RPL-affected PCOS population which was significantly higher ($p<0.04$; $p<0.0001$) when compared to the non-PCOS set (HHcy: 57.26%; IR: 6.83%). Rates of miscarriage were significantly higher ($p<0.008$; $p<0.03$) in hyperhomocysteinemia-induced miscarriage when compared to the normohomocysteinemic segment (PCOS: 70.63% vs.29.36% & non-PCOS: 57.26% vs. 42.73%) along with the insulin resistant ($p<0.04$; $p<0.0001$) population (PCOS: 70.63% vs. 56.34% & non-PCOS: 57.26% vs. 6.83%) in both groups. A probabilistic causal model evaluated HHcy as the strongest plausible factor for diagnosis of RPL. A probability percentage of 43.32% in the cases of HHcy- mediated RPL suggests its increased tendency when compared to IR mediated miscarriage (37.29%), further supported by ROC-AUC (HHcy: 0.778*vs.* IR: 0.601) values. Greater susceptibility towards HHcy may increase the incidence for miscarriage in women in India and highlights the need to combat the condition in RPL control programs in the subcontinent.

Citation: Chakraborty P, Goswami SK, Rajani S, Sharma S, Kabir SN, et al. (2013) Recurrent Pregnancy Loss in Polycystic Ovary Syndrome: Role of Hyperhomocysteinemia and Insulin Resistance. PLoS ONE 8(5): e64446. doi:10.1371/journal.pone.0064446

Editor: Stephen Franks, Imperial College London, United Kingdom

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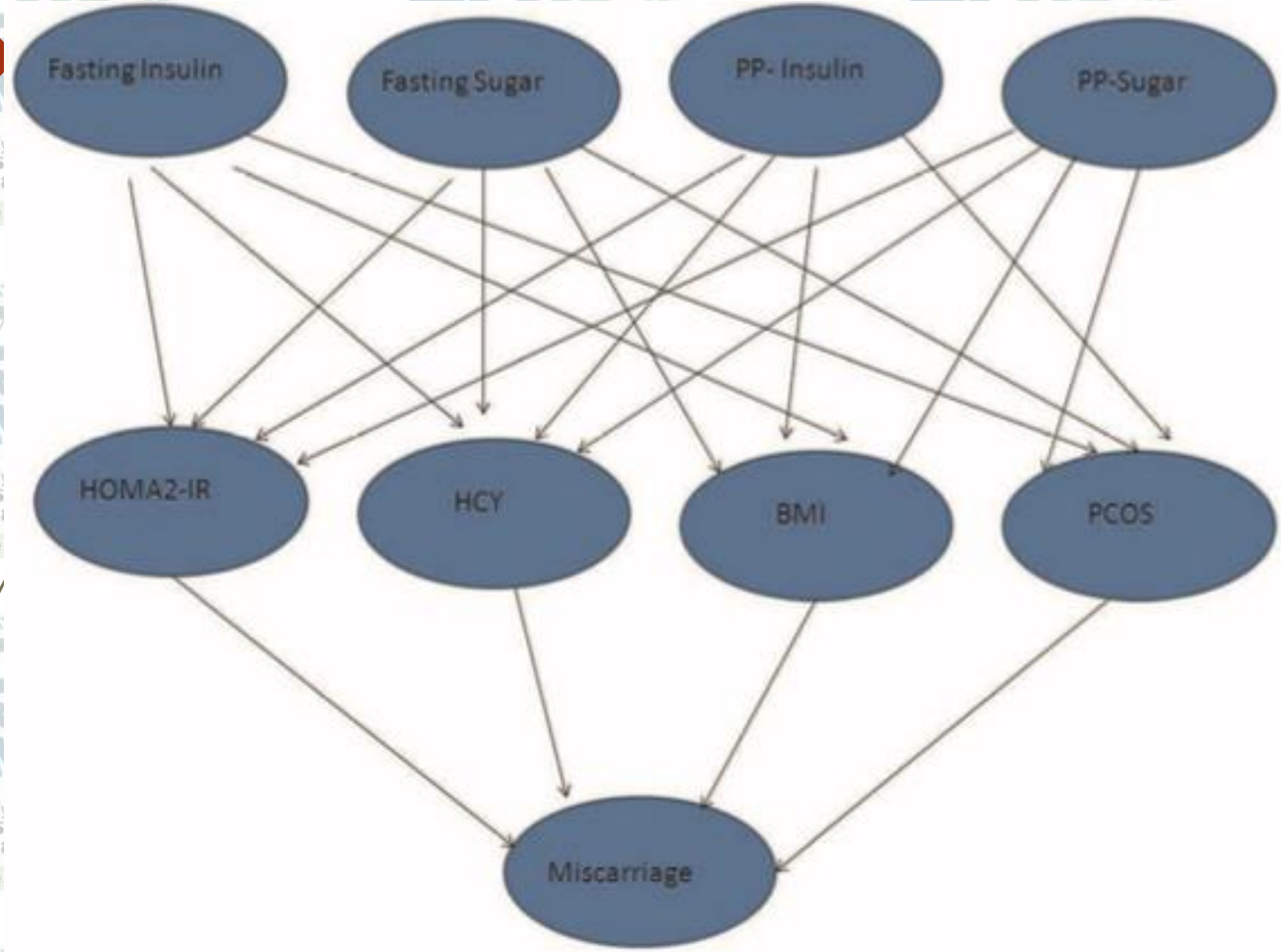
☯ These authors contributed equally to this work.

Probabilistic Model



Hyperhomocysteinemia, the culprit

- Increased thrombosis caused by HHcy resulting microthrombi formation in the vessel bed of the placenta can impair sustained placental function .
- These microthrombi may cause multiple placental infarctions and subsequently maternal complications of pregnancy.
- Apart from the thrombogenic effect of elevated Hcy on pregnancy in women with PCOS, few recent studies have also implicated the adverse effect of high serum or follicular fluid Hcy levels on defect in folliculogenesis , embryo quality , oocyte numbers and oocyte maturation , that may have future bearings on the establishment and maintenance of pregnancy.

Mechanisms leading to pregnancy failure in PCOS

- **HHcy** may lead to premature vascular disease, i.e., early damage to decidual or chorionic vessels - disturbed implantation of the conceptus
- Hypofibronolysis associated with **high (PAI-1)** aggravated by HHcy, eventually causing thrombosis.
- Plasma PAI-1 levels are associated with dyslipidemia, hyperinsulinemia and hypertension , **Higher risk of pre eclampsia**
- **Hyperinsulinemia** - pathway for the effect of obesity on some reproductive abnormalities - through its effect on androgen production.
- Association between IR and Hhcy
- Higher risk of GDM
- Prematurity
- Neonatal problems

Am J Obstet Gynecol. 2011 Jun;204(6):558.e1-6. doi: 10.1016/j.ajog.2011.03.021. Epub 2011 Mar 16.

Pregnancy outcomes in women with polycystic ovary syndrome: a metaanalysis.

Kjerulff LE[1], Sanchez-Ramos L, Duffy D.

Author information

Abstract

OBJECTIVE: The purpose of this study was to examine which maternal and neonatal complications are associated with polycystic ovary syndrome (PCOS) in pregnant women.

STUDY DESIGN: The studies that were included compared pregnancy outcomes between women with PCOS and those without diagnosed PCOS. Our primary outcomes included gestational diabetes mellitus, pregnancy-induced hypertension, and preeclampsia. Secondary outcomes included cesarean delivery rates, operative vaginal delivery rates, preterm delivery, small-for-gestational-age (SGA) infants and large-for-gestational-age infants.

RESULTS: We found that PCOS in pregnancy was associated with higher rates of gestational diabetes mellitus, pregnancy-induced hypertension, preeclampsia, preterm delivery, cesarean delivery, operative vaginal delivery, SGA, and large-for-gestational age. Only gestational diabetes mellitus, pregnancy-induced hypertension, preeclampsia, preterm delivery, and SGA infants were found to be statistically significant.

CONCLUSION: This metaanalysis confirms the higher association of pregnancy complications and PCOS compared with patients who do not have PCOS. Additionally, there may be a stronger association between PCOS and hypertensive disorders than has been shown previously.

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Increased prevalence of insulin resistance in women with a history of recurrent pregnancy loss

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Division of Reproductive Endocrinology, Department of Obstetrics and Gynecology, University of Tennessee Health Science Center, Memphis, Tennessee

Objective: To determine whether insulin resistance is associated with recurrent pregnancy loss (RPL).

Design: Single center, case-controlled, prospective study.

Setting: University-associated reproductive endocrinology clinical practice.

Patient(s): Seventy-four nonpregnant, nondiabetic women with RPL. Controls were 74 fertile, nonpregnant, nondiabetic women without RPL who had at least one live infant, and were matched by age, race, and body mass index (BMI).

Intervention(s): Both groups consented to obtaining fasting insulin and glucose levels.

Main Outcome Measure(s): Insulin resistance was defined as a fasting insulin level >20 μU/mL or a fasting glucose to insulin ratio of <4.5.

Result(s): Among the 74 women with RPL, 20 (27.0%) demonstrated insulin resistance, whereas only 7 of 74 (9.5%) of the matched controls were insulin resistant (odds ratio 3.55; 95% confidence interval 1.40–9.01). The RPL and control groups were similar with respect to age, ethnicity, and BMI. The RPL and control groups had similar fasting glucose levels and glucose-to-insulin ratios. However, fasting insulin levels ≥20 μU/mL were statistically different between the two groups (odds ratio 3.92).

Conclusion(s): Women with RPL have a significantly increased prevalence of insulin resistance when compared with matched fertile controls. (Fertil Steril® 2002;78:487–90. ©2002 by American Society for Reproductive Medicine.)

Key Words: Insulin resistance, recurrent pregnancy loss, fasting insulin, miscarriage

Received November 7, 2001; revised and

RPL in PCOS: Results of retrospective studies and RCTs.

- Hhcy, IR and Obesity
- Significantly higher incidence

  HHcy (70.63% vs. 57.26%, $p < 0.04$)

  IR (56.34% vs. 6.83%, $p < 0.0001$)

  PCOS compared to controls.

  probability percentage: HHcy=43.32%,IR=37.29%).
- Significantly higher risk for development of GDM in PCOS women than those without (OR: 2.89, 95% CI: 1.68-4.98),
- RCT - PCOS treated with metformin found no difference in the prevalence of pre-eclampsia ($p = 0.18$), preterm delivery ($p = 0.12$), or prevalence of GDM ($p = 0.87$) compared to controls during pregnancy.

Hyperhomocysteinemia and RPL in PCOS, The solution !

- *HHcy mediated RPL - substantial role in spontaneous abortion of sub-continental women.*
- *Studies - folic acid, Vit B6 & B12 supplementation, and LMWH (unpublished)observations in improving pregnancy outcomes in women with HHcy.*
- *Identify and actvely treat HHcy in these women at high risk of subsequent miscarriage.*
- *Further studies - assess efficacy of vitamins/anticoagulation in prevention of microthrombi in the placental bed.*

- **Diagnosis and Treatment of Polycystic Ovary Syndrome: An Endocrine Society Clinical Practice Guideline**

  Richard S. Legro Silva A. Arslanian David A. Ehrmann Kathleen M. Hoeger M. Hassan Murad Renato Pasquali Corrine K. Welt

- J Clin Endocrinol Metab (2013) 98 (12): 4565-4592.
- **Pregnancy complications**
- Because women with PCOS are at increased risk of pregnancy complications (gestational diabetes, preterm delivery, and pre-eclampsia exacerbated by obesity, we recommend preconceptual assessment of body mass index (BMI), blood pressure, and oral glucose tolerance
- **Values and preferences**
- We believe that a priority should be placed on reducing the overall increased morbidity from pregnancy complications such as gestational diabetes, pre-eclampsia, and preterm delivery in women with PCOS. Whether these increased risks are due to PCOS itself or the features associated with PCOS such as IR or obesity requires further study.

2002

Effects of Metformin on Early Pregnancy Loss in the Polycystic Ovary Syndrome

DANIELA J. JAKUBOWICZ, MARIA J. IUORNO, SALOMON JAKUBOWICZ, KATHERINE A. ROBERTS, AND JOHN E. NESTLER

Hospital de Clinicas Caracas and Central University of Venezuela (D.J.J., S.J.), Caracas 1040, Venezuela; and Departments of Medicine (M.J.I., K.A.R., J.E.N.) and Obstetrics and Gynecology (J.E.N.), Medical College of Virginia, Virginia Commonwealth University, Richmond, Virginia 23298-0111

Polycystic ovary syndrome is the most common form of female infertility in the United States. In addition to poor conception rates, pregnancy loss rates are high (30–50%) during the first trimester. We hypothesized that hyperinsulinemic insulin resistance contributes to early pregnancy loss in the syndrome, and that decreasing hyperinsulinemic insulin resistance with metformin during pregnancy would reduce the rate of early pregnancy loss.

We conducted a retrospective study of all women with polycystic ovary syndrome who were seen in an academic endocrinology clinic within the past 4.5 yr and who became pregnant during that time.

Sixty-five women received metformin during pregnancy (metformin group) and 31women did not (control group). The early pregnancy loss rate in the metformin group was 8.8% (6 of 68 pregnancies), as compared with 41.9% (13 of 31 pregnancies) in the control group ($P < 0.001$). In the subset of women in each group with a prior history of miscarriage, the early pregnancy loss rate was 11.1% (4 of 36 pregnancies) in the metformin group, as compared with 58.3% (7 of 12 pregnancies) in the control group ($P = 0.002$).

Metformin administration during pregnancy reduces first-trimester pregnancy loss in women with the polycystic ovary syndrome. (*J Clin Endocrinol Metab* 87: 524–529, 2002)

Existing guidelines and recommendations Endocrine society, USA, RCOG

- **Preconceptional :**
- In women with PCOS planning to have children, it is recommended to screen for markers of obesity, hypertension and IR to reduce the risk of pregnancy related complications ***Grade A, EL 3.***
- pre-conceptual assessment of BMI, BP and OGTT
- **During Pregnancy :**
- screening for GDM < 20 wks of gestation, in PCOS women requiring ovulation.
- suggest against the use of metformin as first-line treatment for pregnancy complication, it is recommended not to use metformin therapy only during pregnancy until specific evidence on beneficial effects is demonstrated

  Grade B, EL 3.
- In women with PCOS who have experienced a miscarriage, it is suggested to assess serum homocysteine levels for identification and treatment of hyperhomocystenemia mediated repeated pregnancy losses

  Grade B, EL 3.

- Roos N, Kieler H, Sahlin L, Ekman-Ordeberg G, Falconer H, Stephansson O. Risk of adverse pregnancy outcomes in women with polycystic ovary syndrome: Population based cohort study. BMJ. 2011; 343: d6309.
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- 143.
- Kjerulff LE, Sanchez-Ramos L, Duffy D. Pregnancy outcomes in women with polycystic ovary syndrome: a metaanalysis. Am. J. Obstet. Gynecol. 2011; 204 (6): 558. e1-6.
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- 144.
- Maryam K, Bouzari Z, Basirat Z, Kashifard M, Zadeh MZ. The comparison of insulin resistance frequency in patients with recurrent early pregnancy loss to normal individuals. BMC. Res. Notes. 2012; 5: 133.
-

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

- BACKGROUND: We sought to determine whether metformin, which had facilitated conception in 72 oligoamenorrhoeic women with polycystic ovary syndrome (PCOS), would safely reduce the rate of first trimester spontaneous abortion (SAB) and increase the number of live births without teratogenicity.
- METHODS: Seventy-two oligoamenorrheic women with PCOS conceived on metformin (2.55 g/day). They were prospectively assessed in an outpatient clinical research centre. Outcome measures included number of first trimester SAB, live births, normal ongoing pregnancies>or=13 weeks, gestational diabetes (GD), congenital defects (CD), birthweight and height, as well as weight, height, and motor and social development during the first 6 months of life.
- RESULTS: Of the 84 fetuses, to date there have been 63 normal live births without CD (75%), 14 first trimester SAB (17%), and seven ongoing pregnancies>or=13 weeks with normal sonograms without CD (8%). Previously, without metformin, 40 of the 72 women had 100 pregnancies (100 fetuses) with 34 (34%) live births and 62 (62%) first trimester SAB. In current pregnancies on metformin inthese 40 women (46 pregnancies, 47 fetuses), there have been 33 live births (70%), two pregnancies ongoing>/=13 weeks (4%), and 12 SAB (26%) (P<0.0001). There was no maternal lactic acidosis, and no maternal or neonatal hypoglycaemia.
- CONCLUSIONS: Metformin therapy during pregnancy in women with PCOS was safely associated with reduction in SAB and in GD, was not teratogenic, and did not adversely affect birthweight or height, or height, weight, and motor and social development at 3 and 6 months of life.

Mechanisms of action of Metformin

- ***Reduces Hyperandrogenemia***
- ***Reduces Hyperinsulinemia(adversely affects implantation environment by decreasing expression of glycodelin and IGF binding protein-1)***
- ***Metformin decreases circulating PAI-1 (Increased PAI-1 activity independent risk factor for miscarriage in women with PCO hypofibrinolytic state).***

Can Metformin help?

Reduce risk of early miscarriage *in pregnant women with PCOS*

Small observational studies - shown benefits

RCTs - no benefit.

Meta-analysis of 17 trials in women with PCOS - no effect of metformin was seen on the risk of pregnancy loss.

Preventing loss in later pregnancy?

- ***Improving insulin sensitivity***
- **Effect in men and non pregnant women**
- Metformin is associated with an improvement in glucose levels and a reduction in blood pressure and low-density lipoprotein (LDL).
- In addition it may delay or prevent conversion of IGT to type 2 diabetes mellitus.

Current evidence on Metformin

- We suggest against the use of metformin during pregnancy to prevent gestational diabetes mellitus (GDM) (**Grade 2B**).
- We also suggest against the routine use of metformin to prevent pregnancy loss in women with PCOS (**Grade 2C**).

- **Metformin for treatment of the polycystic ovary syndrome**:
- **Authors** : Robert L Barbieri, MD, David A, Ehrmann, MD

Conclusions

- ***PCOS and reproductive wastage : The link is real***
- ***Solutions not clear !***
- ***Current GCPR -available are more for the white caucasian female***
- ***Our dream - current clinical practices to transition to a comprehensive standardized evidence-based approach to PCOS care paradigm across treatment settings in India.***
- ***Aim - harness the mutual synergies in a modern multidisciplinary clinical setting to deliver quality PCOS care***
- ***Generate evidence***

Thank You


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Dates: June 16 - 18, 2017
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