THE PCOS SOCIETY INDIA

PCOS TUTORIALS

A Post Graduate Certificate Course in PCOS Management

Module 5
PCOS and Pregnancy

Brought to you by The PCOS Society (India)

THE PCOS SOCIETY INDIA

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Module V

PCOS and Pregnancy

Table of Contents

Module Overview

- Women with polycystic ovary syndrome (PCOS) have difficulty conceiving and we have discussed in details infertility associated with PCOS in module 4. In this module we shall discuss about the challenges faced by women with PCOS that conceive.
- These women face higher risk of early and recurrent pregnancy loss (RPL).
- They also have two to three fold higher risk of complications such as gestational diabetes (GDM), hypertension (HTN) in pregnancy and preeclampsia.
- The risk of employing caesarean section for delivery also tends to be higher among women with PCOS for multiple reasons including infertility associated multifetal gestation.
- Further preterm labour may lead to preterm babies who may face the complications of prematurity and may have an extended stay in neonatal intensive care unit (NICU).
- This module will enable the understanding of pathophysiology of these complications during pregnancy; elaborate on investigative work up for diagnosis and prognosis; and discuss the management briefly to assist in successful clinical outcomes following pregnancy among women with PCOS.

Learning Objectives

At the conclusion of this module, the participant will be able to understand:

- Epidemiology of complications in pregnancy that are frequently seen when women with PCOS conceive
- Pathophysiology of complications in pregnancy among women with PCOS
- Diagnosis of complications in pregnancy among PCOS women
- Management of these complications
- How to improve pregnancy outcomes in such cases

PCOS and Pregnancy

PRE-TEST

State whether the following statements are True or False.

1. **Women with PCOS can never get pregnant.**

   True

   False

2. **Women with PCOS have complications in pregnancy only when it is a multifetal gestation.**

   True

   False

3. **When women with PCOS conceive they are at higher risk of pregnancy complications.**

   True

   False

4. **Early and recurrent pregnancy loss occurs more often in women with PCOS as compared to normal women.**

   True

   False

5. **Eclampsia is the only complication with higher frequency in pregnant women with PCOS.**

   True

   False

6. **Higher number of miscarriages occur in obese women with PCOS.**

   True

   False

7. **Metformin has shown to be effective in an insulin-resistant PCOS woman with recurrent miscarriages.**

   True

   False

8. **All women with GDM need to be started on insulin.**

   True

   False

9. **Patients if diagnosed with hypertensive disorders of pregnancy must be admitted to hospital.**

   True

   False

10. **PCOS may contribute to foetal origin of adult diseases.**

    True

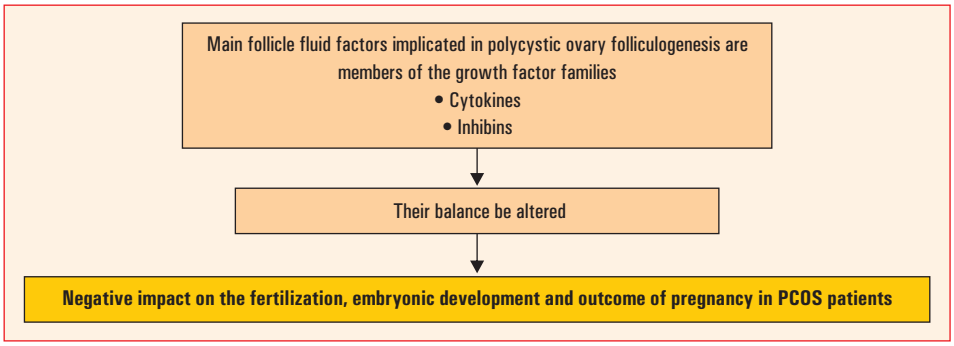
    False

Answers: 1. False; 2. False; 3. True; 4. True; 5. False; 6. True; 7. True; 8. False; 9. False; 10. True

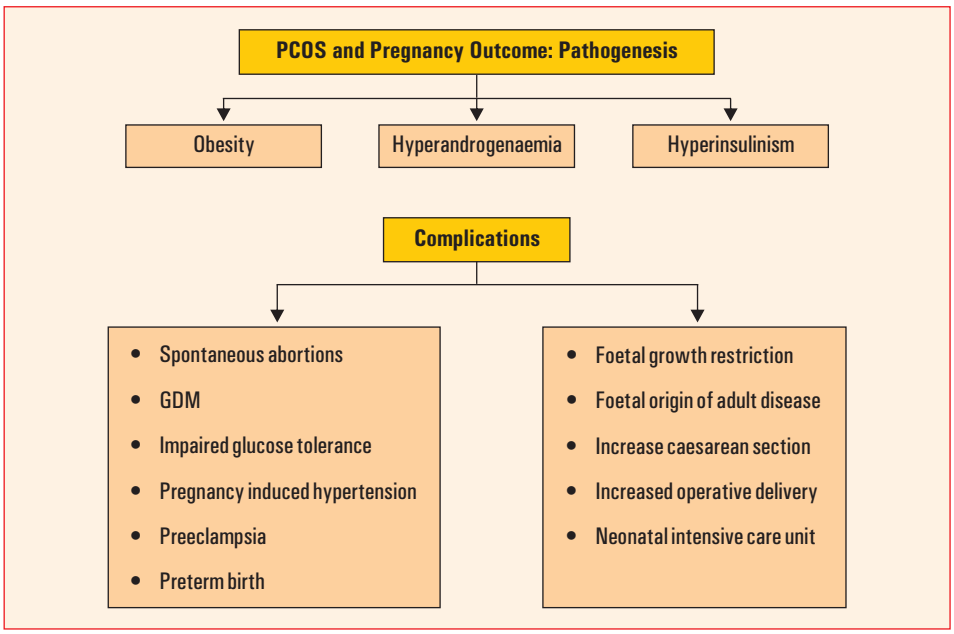
PCOS: Introduction

- PCOS is an endocrinological disorder that is characterized by reduction in all reproductive performances:
  - Chronic anovulatory infertility
  - Increased risk of abortion and
  - Complicated pregnancy
- Women with PCOS present with anovulatory infertility and usually undergo ovulation induction with reported cumulative live-birth rates close to 80%
- Inherent complication of such interventions are:
  - Multiple pregnancy
  - Perinatal morbidity
- Ongoing singleton pregnancy is also associated with a higher risk of pregnancy complications

- PCOS is a heterogeneous and complex disorder that has both adverse reproductive and metabolic implications for affected women.
- This endocrinological disorder is characterized by a reduction in all reproductive performances, including not only chronic anovulatory infertility but also an increased risk of abortion and complicated pregnancy.
- PCOS is a common endocrine disorder during reproductive life, seen in nearly 15% of all women.
- Frequently women with PCOS present with anovulatory infertility and usually undergo ovulation induction with reported cumulative live-birth rates close to 80%.



- However, multiple pregnancies and related perinatal morbidity represent an inherent complication of such interventions.
- Even when an ongoing singleton pregnancy is achieved, there is evidence of higher risk of pregnancy complications in women with PCOS.



- Several meta-analyses and retrospective studies, demonstrated increased risk of Pregnancy induced hypertension (PIH) and preeclampsia, GDM and preterm birth.
- Currently, the pathophysiology of pregnancy complications associated with PCOS is not completely understood. However, it is believed to be directly related to features associated with PCOS itself, such as hyperandrogenism, obesity, insulin resistance, infertility treatment, and placental dysfunction.[1,2]

References:

1. Palomba S, Falbo A, Orio F, *et al.* Metformin hydrochloride and recurrent miscarriage in a woman with polycystic ovary syndrome. *Fertility and Sterility.* 2006;85(5):1511.e3–1511.e5.
2. de Wilde MA, de Ruiter ML, Verhulst SMV, *et al.* Increased rates of complications in singleton pregnancies of women previously diagnosed with polycystic ovary syndrome predominantly in the hyperandrogenic phenotype. *Fertility & Sterility.* 2017;108(2):333–340.

Prevalence of PCOS Induced Complications in Pregnancy

Pregnancy complication	Prevalence in women with PCOS
GDM and associated foetal macrosomia	40–50%
PIH and preeclampsia	5%
SGA	10–15%

Pregnancy complication	Odds ratio	95% Confidence interval
GDM	2.94	1.70–5.08
PIH	3.67	1.98–6.81
Preeclampsia	3.47	1.95–6.17
Preterm birth	1.75	1.16–2.62
Admission to NICU	2.31	1.25–4.26
Perinatal mortality	3.07	1.03–9.21

SGA: Small-for-gestational-age; PIH: Pregnancy-induced hypertension; GDM: Gestational diabetes; NICU: Neonatal intensive care unit

- When pregnancy occurs in women with PCOS, there is a higher incidence of GDM (40% to 50%) and associated fetal macrosomia, gestational hypertensive disorders (such as preeclampsia and PIH) [5%], and birth of small-for-gestational-age (SGA) babies (10% to 15%).[1,2]
- The meta analysis on pregnancy complications in women with PCOS demonstrated a statistically significant higher risk of developing GDM, PIH, preeclampsia and preterm birth (PTB) as shown in the table above.[1,2]
- Their babies had a statistically significant higher risk of admission to a NICU and a higher perinatal mortality unrelated to multiple births.[1,2]

Prevalence of Singleton Pregnancy Complications in Women with PCOS

Complication	Unadjusted OR	95% CI
DM	3.52	1.56–8.0
HDP	3.53	1.70–7.35
APH	1.09	0.40–2.99
Cerclage	0.91	0.19–4.23
PPROM	2.35	0.69–8.03
Cesarean section	0.99	0.58–1.71
SGA $<10^{th}$ percentile	0.99	0.36–2.70
LGA $>90^{th}$ percentile	2.78	1.27–6.10
PTB <32 wk	1.74	0.45–6.72
PTB <37 wk	2.32	1.11–4.86
LBW <1,500 g	1.54	0.41–5.84
LBW <2,500 g	1.34	0.58–3.07
Macrosomia >4,000 g	1.01	0.40–2.55
Malformations	0.91	0.19–4.23
Perinatal mortality	0.91	0.11–7.90

DM: Diabetes; HDP: Hypertensive disorders of pregnancy; APH: Antepartum haemorrhag; PPROM: Preterm premature rupture of the membranes; SGA: Small-for-gestational-age; LGA: arge for gestational age; PTB: preterm birth; LBW: Low birth weight

- The risk of complications continues to be high even in singleton pregnancies among women with PCOS.
- Pregnancy complications in the analysis tabulated above included GDM diagnosed via the 75 g, 2 hr oral glucose tolerance test (OGTT), hypertensive disorders of pregnancy (HDP), including gestational hypertension or preeclampsia as per the International Society for the Study of Hypertension in pregnancy guidelines, antepartum haemorrhage (APH) leading to hospital admission, cerclage placement, preterm premature rupture of the membranes (PPROM), intrauterine fetal demise, and elective or unplanned caesarean section.
- Birth outcome variables included gestational age at delivery, birth weight (g), PTB; <32 and <37 weeks, low birth weight (LBW) [<1,500 and <2,500 g], macrosomia (>4,000 g), small for gestational age (SGA) and large for gestational age (LGA) [$<10^{th}$ and $>90^{th}$ percentiles, respectively], according to Fenton 2013 growth curves, congenital malformations, and perinatal mortality (≤7days).
- It must be noted that there is threefold to fourfold increased risk for HDP (which includes PIH and preeclampsia) and GDM. Further a twofold increased risk of preterm delivery, PPROM is observed in women with PCOS.

- The relative risk (RR) for adverse obstetric or neonatal outcomes was increased (1.7) in patients with PCOS and varied according to the PCOS phenotype (1.93 full-blown PCOS; 2.23 non polycystic ovaries; 0.54 non hyperandrogenic; 0.48 ovulatory phenotypes).[3,4]

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1. Fauser BC, Tarlatzis RW, Rebar RS, *et al.* Consensus on women's health aspects of polycystic ovary syndrome (PCOS): The Amsterdam ESHRE/ASRM-Sponsored 3rd PCOS consensus workshop group. *Fertil. Steril.* 2012;97:28–38.e25.
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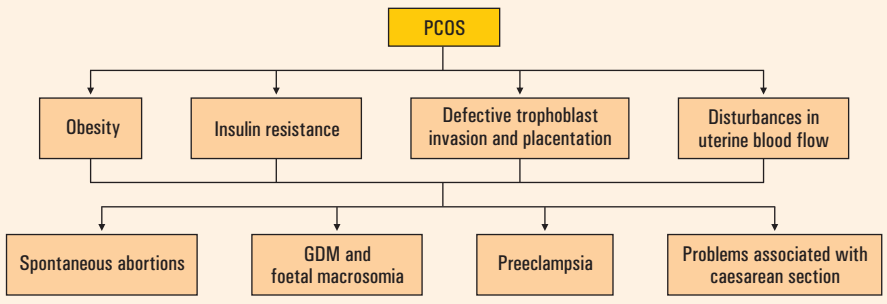
Pathophysiology of Pregnancy Outcomes in PCOS



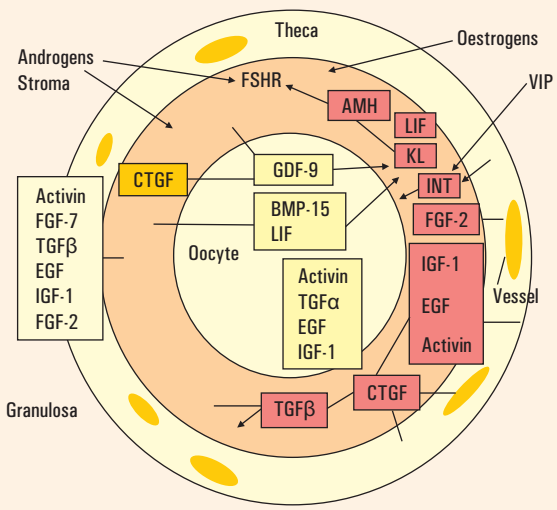
GDM: Gestational diabetes

- The proposed pathophysiology of pregnancy complications is obesity, altered glucose metabolism, and disturbances in uterine blood flow.
- Obesity in its own right is associated with several adverse pregnancy outcomes, including spontaneous miscarriage, preeclampsia, GDM, congenital anomalies (e.g., cardiac and spina bifida), foetal macrosomia, caesarean delivery, and wound complications after caesarean section.
- Insulin resistance partially mediates the effects of obesity on adverse pregnancy outcome.[1,2]
- The spectrum of pregnancy complications seems to have a common denominator: defective trophoblast invasion and placentation.

- In a comparative study between PCOS women and the control group, placental weight, thickness, density and volume were significantly ($P<0.05$) lower in PCOS than in the control group. Further, there was considerable difference noted between the groups in foetal–placental weight ratio.[3]
- Alterations in the impedance to blood flow through the uterine artery may be sustained during the first and middle trimester of pregnancy.[1,2]

Pathophysiology of Pregnancy Complications in Women with PCOS

- Poor oocyte quality due to hyperandrogenaemia, hyperinsulenaemia and aberrant ovarian growth factors–growth differentiation factor (GDF 9) deficit, increased tumor necrosis factor (TNF α), increased expression of endothelial growth factor receptors (EGFR)
- Poor embryo quality due to poor quality oocytes
- Increased oxidative stress and increased follicular fluid homocysteine levels
- Epigenetic influence: increased incidence of CAG repeats and chromosome X inactivation, altered fetal luteinizing hormone (LH) secretion, reproductive and metabolic consequences on the foetus



FSHR: Follicle stimulating hormone receptor; AMH: Anti-müllerian hormone; VIP: Vasoactive intestinal peptide; LIF: Leukemia inhibitory factor; IGF: Insulin-like growth factor; BMP-15: Bone morphogenetic protein-15; GDF-9: Growth differentiation factor 9; TGF-β: Transforming growth factor-β; FGF2: Fibroblast growth factor 2; EGF: Epidermal growth factor; CTGF: Connective tissue growth factor; KL: Kit ligand

- Gene expression of GDF9, an oocyte-derived growth factor affecting theca cell layer formation, is reduced in ovaries of anovulatory PCOS women, linking dysregulated oocyte GDF9 gene expression with altered folliculogenesis.
- Intrafollicular cytokines and growth factors also affect oocyte development.
- Improved oocyte quality accompanies increased levels of granulocyte colony-stimulating factor; interleukins IL-12, IL-6, IL-8, and IL-18; brain-derived neurotropic factor; bone morphogenic protein 2; and amphiregulin, as well as decreased levels of IL-1 and IL-12 and vascular endothelial growth factor isoform.
- It is unclear, however, which cytokines and growth factors in follicular fluid are relevant for determining oocyte quality in PCOS.
- The androgen receptor is located on the X chromosome, and it contains a polymorphic CAG repeat region in exon 1. The length of this CAG repeat region shows an inverse relationship with androgen sensitivity.
- Multiple genome-wide association studies (GWAS) have replaced single gene aetiology of PCOS. GWAS has consistently demonstrated that PCOS is a complex genetic disorder with multiple alleles.
- However there is lack of functional genomics studies to explain the possible pathophysiological significance of identified genetic variants.
- The gonadotropin and gonadotropin receptor variants are nevertheless have a constant association with phenotypic abnormalities in PCOS.[3,4]

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1. Nelson SM, Matthews P, and Poston L. Maternal metabolism and obesity: modifiable determinants of pregnancy outcome. *Hum Reprod Update*. 2010;16:255–275.
2. Fauser BC, Tarlatzis RW, Rebar RS, *et al*: Consensus on women's health aspects of polycystic ovary syndrome (PCOS): The Amsterdam ESHRE/ASRM-Sponsored 3rd PCOS consensus workshop group. *Fertil. Steril*. 2012;97:28–38.e25.
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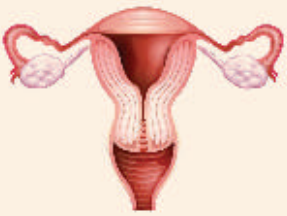
Early and Recurrent Pregnancy Loss in PCOS

- Higher incidence of adverse pregnancy and birth outcomes has been reported among the women with PCOS.
- Women with PCOS have several other risk factors associated with conception, such as obesity, increased age at conception, multifetal gestation use of assisted reproductive techniques and others.
- Recently published retrospective study in *Fertil and Steril*, 2016 investigated whether PCOS was an independent risk factor among singleton conception in women who underwent IVF procedures. The result of the study are shown in the table below:

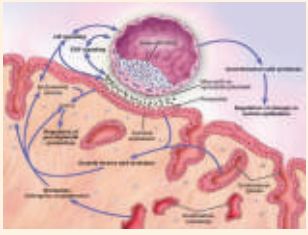
Prevalence of pregnancy complications in women with PCOS

Parameter	Unadjusted OR	95% CI
Singleton pregnancies	1.27	0.91–1.77
Biochemical pregnancy loss	1.45	1.02–2.06
Early clinical pregnancy loss	0.88	0.53–1.48
Ectopic pregnancy	1.63	0.53–5.07
Therapeutic pregnancy termination	10.6	0.96–118.0
Multiple pregnancies	0.28	0.13–0.60

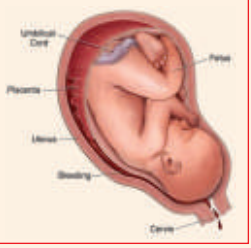
Periconceptional influences



Embryo implantation



Pregnancy outcome



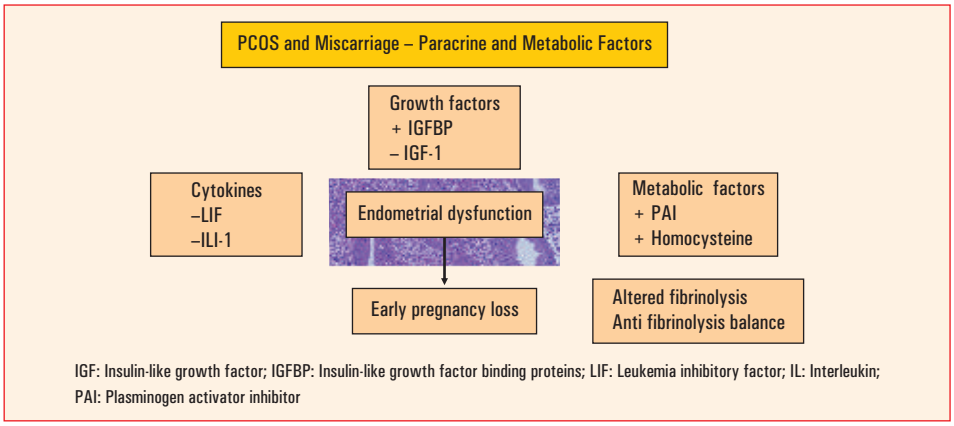
- The study found that after adjusting for differences in maternal age, parity, body mass index (BMI), and time to conception PCOS continued to be an independent risk factor for higher rates of adverse pregnancy outcomes.

Impact of PCOS on Reproductive Outcome

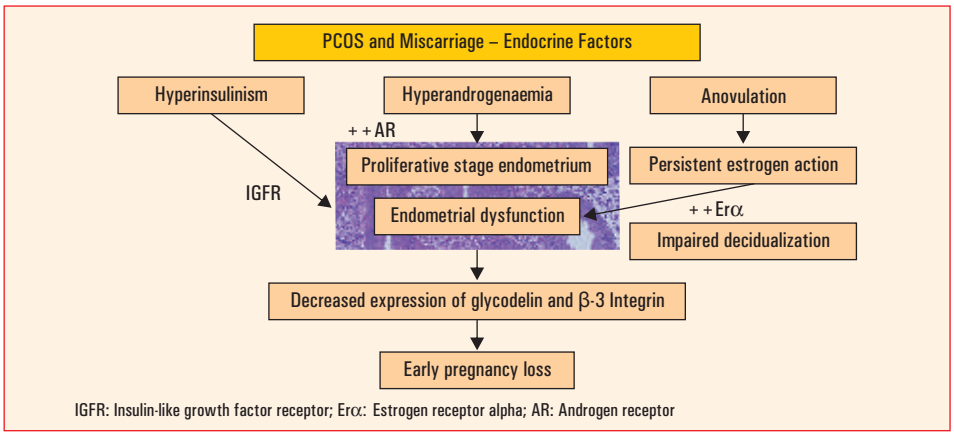
- High incidence of periconceptional damage
- High incidence of miscarriage: 30–50%
- High incidence of negative pregnancy outcome
  - o GDM: 20–30%; PIH: 13.3 %; Fetal growth restriction: 10 –15 %

Results in adverse pregnancy outcomes

Several factors are responsible for adverse outcomes of pregnancy in PCOS[1] as shown in the figure below:



IGF: Insulin-like growth factor; IGFBP: Insulin-like growth factor binding proteins; LIF: Leukemia inhibitory factor; IL: Interleukin; PAI: Plasminogen activator inhibitor



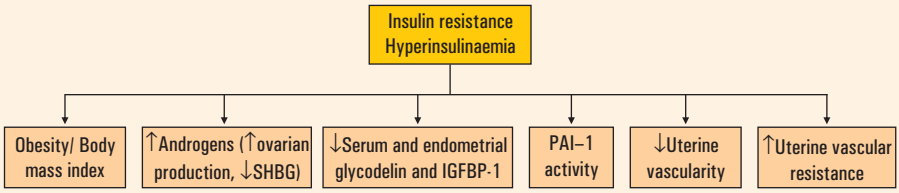
IGFR: Insulin-like growth factor receptor; Erα: Estrogen receptor alpha; AR: Androgen receptor

Potential Contributors to Pregnancy Loss in PCOS Women

Obesity	Placental thrombosis	Endometrial defects	Hyper-androgenaemia	Insulin resistance	Fetal defects
• Independent risk factor for spontaneous abortions	• Elevated Plasminogen activator inhibitor-1 activity is an independent risk factor for pregnancy loss in women with PCOS	• Deficient secretion of endometrial proteins may contribute to pregnancy loss in PCOS o Glycodelin o IGF binding protein-1	• Found associated with pregnancy loss • A negative correlation between plasma androgen concentrations and glycodelin concentrations lead to abnormal endometrial development	• It is an independent risk factor for pregnancy loss in all women • Hyperinsulinaemia acts as a unifying mechanism for pregnancy loss in PCOS	• Chromosomal abnormalities are not common in PCOS

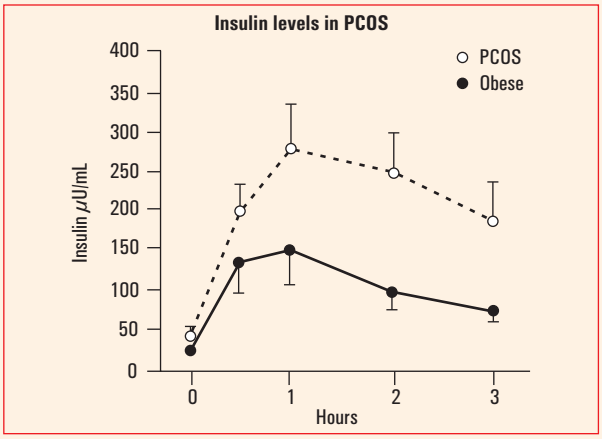
- Foetal chromosomal abnormalities may not be common in PCOS and, hence, other factors may play a more dominant role in pregnancy loss in this syndrome.[3]
- Obesity is one such factor. Significant differences in spontaneous abortion rates between obese women (38.1%; BMI=30 kg/m^2) and normal weight (13.3%; BMI 20–24.9 kg/m^2) or overweight (15.5%; BMI 25–29.9 kg/m^2) women, support the concept that obesity is an independent risk factor for spontaneous abortion.[4]
- High plasminogen activator inhibitor (PAI-1) activity can result in placental bed thrombosis as well as uterine vascular insufficiency. Regarding PAI-1 activity in PCOS, Glueck *et al*. reported that elevated PAI-1 activity is an independent risk factor for miscarriage in women with PCOS.[5]
- A gene defect is not necessary as insulin resistance itself has been shown to increase PAI-1 levels.
- Deficient secretion of endometrial proteins is responsible for 30–50% miscarriages in PCOS. Glycodelin (previously known as PP14) and IGF binding protein-1 (IGFBP-1) are two proteins secreted by the endometrium that appear to play important roles in endometrial receptivity during implantation and early pregnancy.[6]
- Women with PCOS have been shown to have both low serum glycodelin concentrations and serum IGFBP-1 concentrations in pregnancy. Serum glycodelin was 56% lower in women with PCOS during gestational weeks 3–5, 23% lower during weeks 6–8, and similar by weeks 9–11. Serum IGFBP-1 concentrations were 60–70% lower in PCOS during weeks 3–5 and 6–8, and 39% lower during weeks 9–11. This study provided evidence implicating endometrial dysfunction during the periimplantation period as a possible mechanism for early pregnancy loss in PCOS.[7]
- In a double blind, placebo-controlled study of 48 women with PCOS, the insulin-sensitizer metformin significantly increased follicular and luteal phase serum glycodelin and IGFBP-1 concentrations.[8]
- Increased LH was not associated with RPL.[9]
- The plasma concentrations of androgens were significantly higher in women with PCOS, who had recurrent miscarriages compared with normal controls. Likewise, women with recurrent miscarriages who did not have PCOS had significantly higher androgen levels than normal controls, suggesting that an elevated androgen profile by itself is involved with recurrent miscarriages.
- A negative correlation between plasma androgen concentrations and glycodelin concentrations from uterine flushings, suggests that high androgen concentrations may lead to abnormal endometrial development.[9,10]

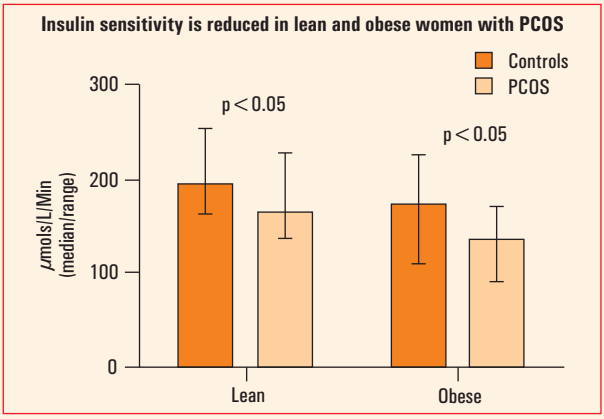
Factors Responsible for Pregnancy Loss Unified by Hyperinsulinaemia with Insulin Resistance

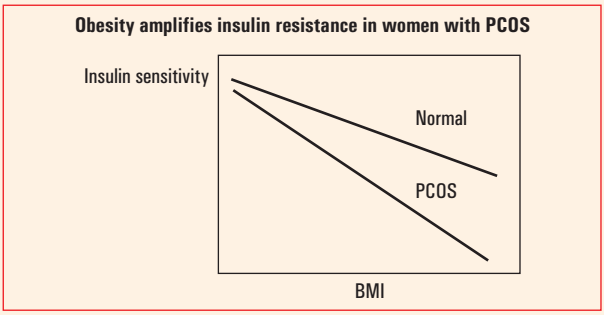


PAI: Plasminogen activator inhibitor; IGFBP: Insulin-like growth factor binding proteins; SHGB: Sex hormone binding globulin

Relation between Insulin Levels and Obesity in PCOS







- As discussed above obesity, hyperandrogenaemia, endometrial defects, increased PAI activity affect implantation and lead to pregnancy loss. All of these factors as shown above have been associated with insulin resistance in presence of hyperinsulinaemia.
- Decreased uterine vascularity and increased vascular resistance are also seen with insulin resistance.
- Hyperinsulinaemia in PCOS women is associated with hyperhomocysteinaemia, independent of BMI alone. [11]
- Homocysteine should be considered as a marker of RPL especially in insulin resistant PCOS women.[12]
- Metformin has shown to be effective in an insulin-resistant PCOS woman with recurrent miscarriages.[13]

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1. Sterling L, Liu J, Okun N, *et al.* Pregnancy outcomes in women with polycystic ovary syndrome undergoing *in vitro* fertilization. *Fertil. Steril*. 2016;105(3):791–797.e2.
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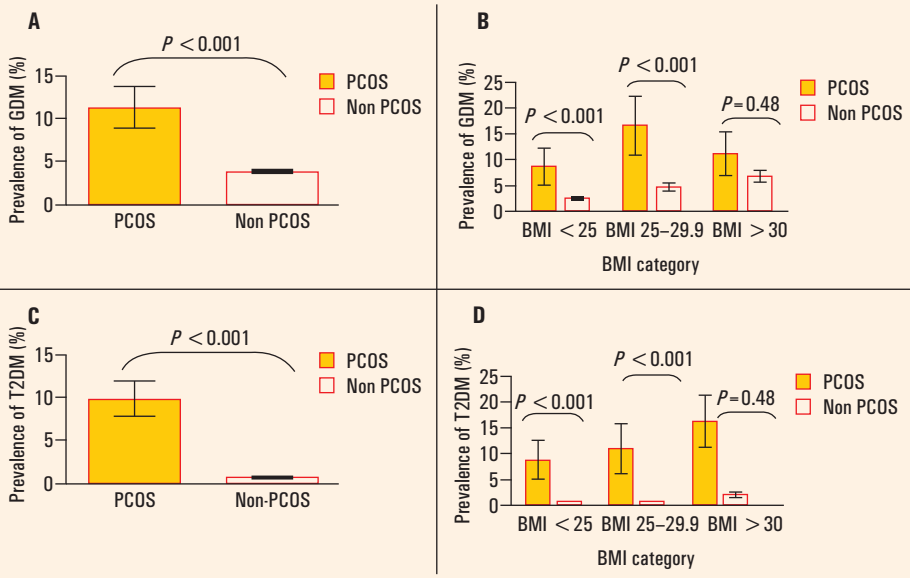
Gestational Diabetes in PCOS

	Prevalence		*P* value
	Women with PCOS	Women without PCOS	
Gestational diabetes	11.2%	3.8%	< .001
Type 2 diabetes mellitus	5.1%	0.3%	< .001

- The prevalence of GDM and type 2 diabetes mellitus (T2DM) was 11.2% and 5.1% in women with PCOS and 3.8% and 0.3% in women without PCOS, respectively ($P < .001$) for both.
- PCOS was associated with increased odds of GDM and T2DM.[1]
- In a subgroup analysis, maternal complications were statistically significantly higher in women with hyperandrogenic (defined as a free androgen index >4.5) PCOS compared to those with normoandrogenic PCOS (45% vs. 24%; $P=.003$).
- No statistically significant differences were observed between these groups regarding neonatal complications.[2]

Prevalence of Gestational Diabetes and Type 2 Diabetes in Pregnancy

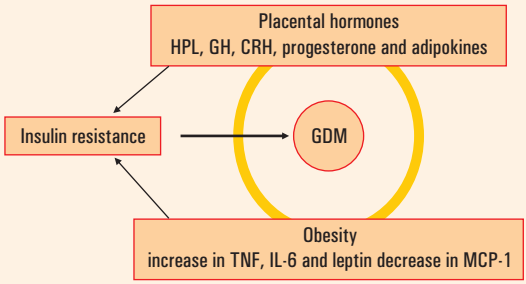


- After adjusting for age, BMI, HTN, smoking, and demographic factors, the odds of GDM (odds ratio 2.1, 95% CI 1.1–3.9, $P = .02$) and T2DM (odds ratio 8.8, 95% CI 3.9–20.1, $P < .001$) remained increased in women reporting PCOS. [1,2]

Conversion Rates for Glucose Tolerance

- Women with normal glucose tolerance at baseline had a 16% conversion to IGT per year
- Women with baseline IGT had a 6% conversion rate over 3 years, or 2% per year to DM
- 9.3% converted from normal to IGT over 6.2 years
- 7.4% converted from normal to T2DM
- 5.4% converted from IGT to T2DM [3]

Pathophysiology of Gestational Diabetes in PCOS Women



GDM: Gestational diabetes; HPL: Human placental lactogen; GH: Growth hormone; CRH: Corticotropin-releasing hormone; MCP: Monocyte chemoattractant protein; IL: Interleukin; TNF: Tumor necrosis factor

- Altered human placental lactogen (hPL), placental growth hormone (GH), corticotropin-releasing hormone (CRH), progesterone and adipokines (TNF alpha) result in insulin resistance and lead to GDM. [4]
- In presence of obesity there is increase in TNF, IL-6 and leptin and decrease in monocyte chemoattractant protein (MCP-1) which further adds to the insulin resistance.
- The increased rates of GDM may relate to placental hormone-mediated exacerbation of pre-existing insulin resistance.
- Higher rates of GDM among the PCOS population have been observed irrespective of BMI.

Adverse Outcomes Associated with Gestational Diabetes

Outcome	Relative risk
Maternal	
Subsequent development of type 2 diabetes mellitus	7.4
Gestational hypertension	1.6
Preeclampsia	1.5
Cesarean delivery	1.3
Foetal	
Shoulder dystocia/birth trauma	2.9
Macrosomia	1.6
Subsequent adolescent and childhood overweight	1.5
Birth defects	1.2
Hyperbilirubinaemia	*
Hypoglycaemia	*

- GDM has health implications for the mother and foetus during pregnancy and later in life.
- These adverse outcomes have been mentioned above.[5]

Screening and Diagnostic Test for Gestational Diabetes

- In India DIPSI (Diabetes in Pregnancy Study Group in India) guidelines is recommended for screening and diagnosis of GDM
- It is conducted in non-fasting state screened during gestational period of 24 –28 weeks
- 75 g of glucose is used
- Venous blood samples are collected after 2 hr
- DIPSI diagnostic criteria is a 2 hr value ≥ 140 mg/dL
- This method holds the convenience of being a single step, nonfasting procedure
- DIPSI criteria was found to be comparable to WHO criteria for sensitivity and specificity in diagnosing and screening GDM[6]

- In India modified 75 g glucose test as mentioned in DIPSI guidelines is recommended for screening and diagnosis of GDM:
  - The test can be conducted in nonfasting state (irrespective of the time of last meal)
  - 75 g of glucose dissolved in 300 mL of water is administered and time noted
  - Venous blood samples are collected after 2 hr and subjected to centrifugation and analyzed in a semi automated analyzer.
  - DIPSI diagnostic criteria is a 2 hr value ≥ 140 mg/dL
  - This method holds the convenience of being a single step, nonfasting procedure
- DIPSI criteria was found to be comparable to WHO criteria for sensitivity and specificity in diagnosing and screening GDM.[6,7]

Management of Gestational Diabetes for Euglycaemia

Medical nutrition therapy (MNT)	Pharmacotherapy
• **Balanced diet** o 25 kcal/kg of ideal body weight for gestational age among overweight or obese women and o 30 kcal/kg among normal weight women • Never less than 1,500 kcal for pregnant women • Total energy : 45%–48% from complex carbohydrates, 20%–21% from proteins, and 30%–32% lipids • The total energy intake modified according to the progression of pregnancy at 4-week intervals.	• Insulin or oral anti hyperglycaemic agents may be used for failed MNT • Metformin and glyburide are considered safe and effective in pregnancy and lactation • Acarbose has less than 2% absorption in maternal circulation and has been recently added to the oral hypoglycaemic agent (OHA) used in pregnancy • Initial dose of insulin is 0.3–1.0 U/kg of body weight • The pharmacotherapeutic dosage is modified to achieve o Fasting plasma glucose <95 mg/dL and o 1hr postprandial glucose <130 mg/dL or o 2hr postprandial glucose <120 mg/dL

- For maintaining the blood glucose levels the above plan is followed.
- MNT is the first step which if fails pharmacotherapy with insulin or OHA needs to be considered.[8]
- Traditionally insulin has been the gold standard for treatment of hyperglycaemia during pregnancy, when lifestyle measures are unable to alone maintain the glycaemic control during pregnancy. However, recent evidences support the use of OHA (metformin and glyburide) as safe and acceptable alternatives.
- US Food and Drug Administration (FDA) has not approved any OHA for treatment of diabetes in pregnancy.
- However UK National Institute for Health and Care Excellence (NICE) guidelines consider metformin and glyburide safe in pregnancy and lactation.
- The Endocrine society provides guidelines regarding use of OHAs (metformin and glyburide) in pregnancy.[9]

Recommendations on Use of Oral Anti Hyperglycaemic Agents in Mild Gestational Diabetes

For glycaemic control in women with GDM who fail 1 week trial of MNT and exercises

Metformin

- Used alone or as an adjunct to insulin
- During preconception period and during pregnancy [8]

Myoinositol

- Supplementation during first trimester, in obese pregnant women
- Reduces the incidence in GDM through reduction in insulin resistance [9]

Glibenclamide (Glyburide)

- Can be used as oral anti hyperglycaemic agent
- Higher incidence of hypoglycaemia [10]

Metformin

- NICE guidelines recommend that metformin may be used alone or as an adjunct to insulin in preconception period and during pregnancy [8]

Myoinositol

- Supplementation with myoinositol from the first trimester, in obese pregnant women appeared to reduce the incidence in GDM through a reduction in insulin resistance [9]

Glibenclamide (Glyburide)

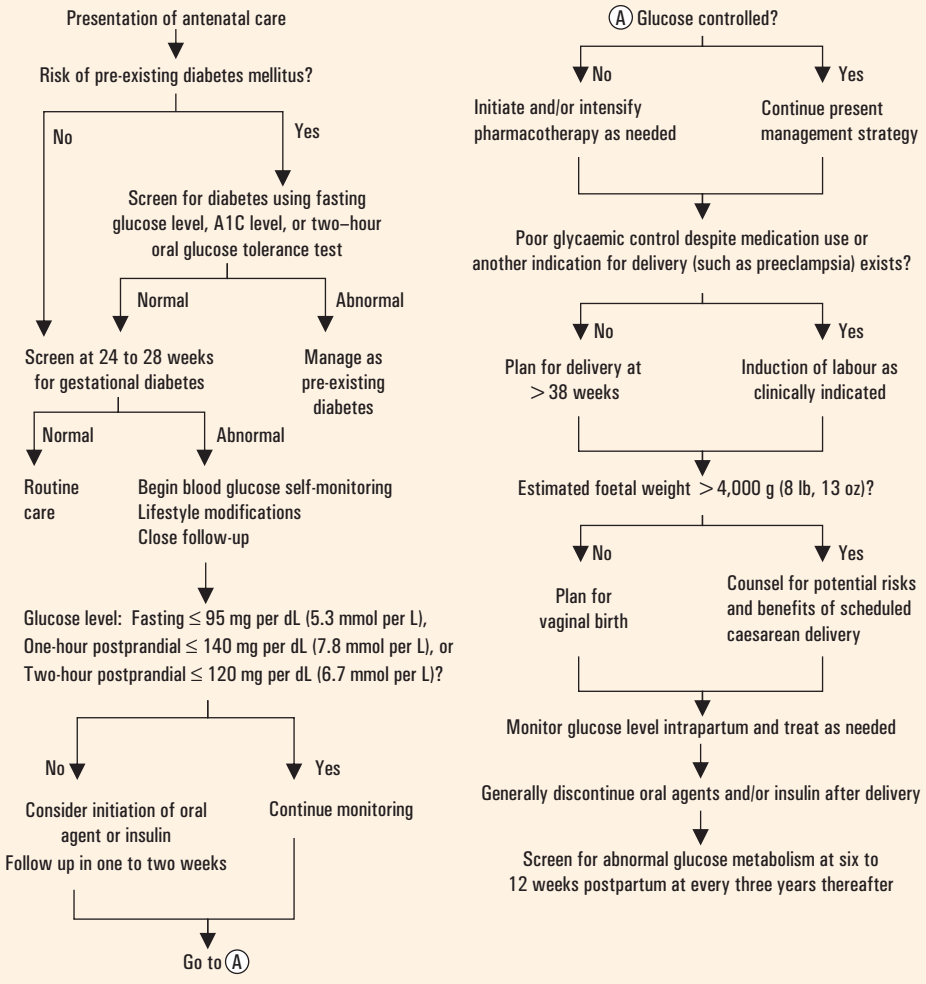
- It can also be used as oral anti hyperglycaemic agent however due to possible hypoglycaemia; it is not a preferred choice [10]

Oral Anti Hyperglycaemic Agents

	Glibenclamide	Metformin
Degree of hyperglycaemia	++	+
Predominantly fasting hyperglycaemia		+
Predominantly postprandial hyperglycaemia	+	
Risk of hypoglycaemia	High risk	Safe
Gastro-intestinal intolerability	-	Possible
Effect of insulin resisitance	-	+
Effect on weight	Weight gain	Weight neutral
Frequency of administration	Once/twice daily	Once/thrice daily (sustained resistance)

- Endocrine society suggests glibenclamide is the first option for management of GDM. However, this support may be controversial.
- Metformin crosses the placenta but has evidence of favourable effects on children when compared with insulin group, however no such data is available for glibenclamide.
- There are no human studies available on use of acarbose in GDM, hence is not recommended yet.
- Insulin is not transferred through placenta or secreted into breast milk and therefore, remains the optimal anti-diabetic treatment during pregnancy and lactation.[11,12,13]

Algorithm for Management of Gestational Diabetese



- The above algorithm guides the management of GDM.
- Screening and continued monitoring are the important pillars for achieving satisfactory medical outcomes in these women.
- The birth plan will be based on presence of other complications of pregnancy, blood glucose control and estimated foetal weight
- Postpartum follow-up helps defer the development of T2DM, which occurs over time in 15 to 50% of women with GDM.[14]
- These patients should be screened at follow up as mentioned above. [15]

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Hypertensive Disorder of Pregnancy

Chronic hypertension in pregnancy

- Blood pressure ≥ 140/90 mmHg
- Without proteinuria
- Present since before pregnancy, diagnosed before 20 weeks of gestation

PIH/ Gestational hypertension

- Blood pressure ≥ 140/90 mmHg
- Without proteinuria
- After 20 weeks gestation on two or more occasions (at least 6 hr apart)

Preeclampsia

- Blood pressure ≥ 140/90 mmHg
- In combination with proteinuria >0.3 g/24 hr
- After 20 weeks gestation

Preeclampsia superimposed on chronic hypertension in pregnancy

- Blood pressure > 140/90 mmHg before 20 weeks of pregnancy
- Proteinuria develops after 20 weeks of pregnancy
- 12 weeks postpartum the proteinuria resolves but hypertension continues

Eclampsia

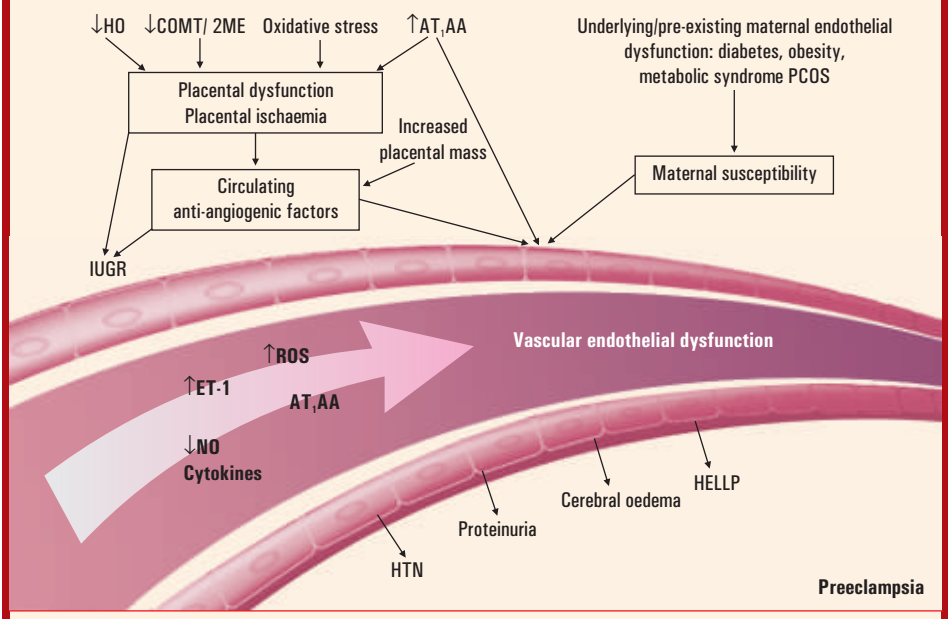
- Convulsive disorder of pregnancy

- The classification of HDP is mentioned above.[1]
- PIH and preeclampsia are the most common types of hypertensive disorders seen in women with PCOS.
- The prevalence rates of HDP are 3–32%.[2]

- Findings of prevalence of HDP from a recent study published in the journal *Fertility and Sterility*, 2017 issue is given in the table below.

	Prevalence rates		*P* value	Adjusted OR
	Women with PCOS	Women without PCOS		
Hypertensive disorders of pregnancy	19.7	6.5 %	0.004	4.25

Pathophysiology of Hypertensive Disorders Of Pregnancy



HO: Heme oxygenase; COMT: catechol-o-methyltransferase; 2-ME: 2-methoxyestradiol; AT_1-AA: Angiotensin II type 1 receptor autoantibodies; ET-1: Endothelin-1; ROS: Reactive oxygen species; NO: Nitric oxide; IUGR: Intrauterine growth restriction; HTN: Hypertension; HELLP: Hemolysis elevated liver enzymes nd low platelet count occurring in pregnancy; PCOS: Polycystic ovary syndrome

Common mechanisms involved in preeclampsia :

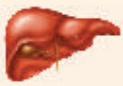
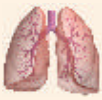
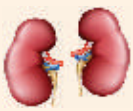
- Increase in oxidative stress
- Diffuse endothelial dysfunction
- Alterations in inflammatory mediators, and
- Abnormalities in the renin-angiotensin system

Several mechanisms have been implicated as potential causes of preeclampsia and eclampsia.

- Common mechanisms include an increase in oxidative stress, diffuse endothelial dysfunction, alterations in inflammatory mediators, and abnormalities in the renin-angiotensin system.

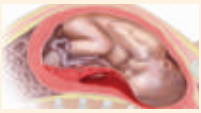
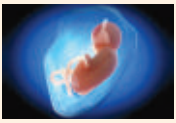
- Insulin resistance, obesity, hyperandrogenemia, aberrant cytokines TNF alpha and GF, lead to endothelial dysfunction resulting in increased incidence of PIH.[3]
- Preeclampsia typically disappears after delivery; the placental foetal unit is the most likely cause.
- Increase in tyrosine kinase-1 and reduced levels of placental and vascular endothelial growth factor is found in women prone to developing pre-eclampsia.
- In a normal pregnancy, the placenta produces renin, which leads to increased activity in the renin-angiotensin system. It was recently discovered in preeclamptic patients that an IgG autoantibody interacts with the angiotensin type one (AT_1) receptor leading to its activation.[4,5]
- Not only does this increase blood pressure, it also mediates coagulation via tissue factor and the fibrinolytic system, induces reactive oxygen species, and influences fms-like tyrosine kinase -1 secretion.[4,6]
- Prostaglandin aberrations causing a decrease in prostacyclin production. It has been found on studying urinary metabolites in preeclamptic patients. During normal pregnancy, there is an increase in the ratio of endothelial cell-produced prostacyclin and platelet-produced thromboxane, resulting in a vasodilatory state. In preeclampsia this ratio is reversed, promoting vasoconstriction and a proaggretory state.[4,5]

Complications of Preeclampsia

Maternal	
	CNS • Seizures, cerebral oedema/ hemorrhage, stroke
	Hepatic • Failure/ rupture, subcapsular haemorrhage
	Haemotological • DIC, HELLP syndrome
	Lungs • Pulmonary oedema
	Renal • Oliguria, renal failure, proteinuria: hypoproteinaemia (glomerular injury)

DIC: Disseminated intravascular coagulation; HELLP: Hemolysis elevated liver enzymes and low platelet count occurring in pregnancy

Complications of Preeclampsia

Foetal	
	• Preterm delivery
	• Still birth (IUFD)
	• Placental abruption
	• Uteroplacental insufficiency; hypoxic neurological injury; IUGR; oligohydramnios

IUFD: Intrapartum foetal distresss; IUGR: Intrauterine growth restriction

- High blood pressure can lead to several complications associated with cerebrovascular, hepatic, haematological and renal compromise which is proportional to the degree of blood pressure elevation.
- The complications of preeclampsia for both mother and foetus have been described above
- The most dangerous complication of preeclampsia is eclampsia.[7]

Management of Hypertensive Disorders in Pregnancy

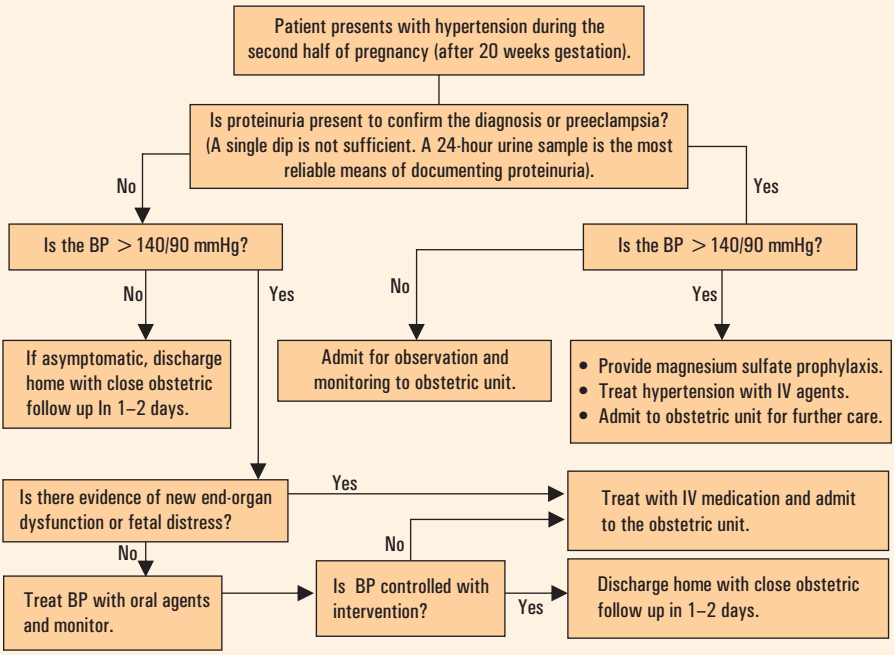
The table given below describes the common protocols for anti-hypertensive medications used in patients with severe HTN in pregnancy.

Agent	Protocol	Side Effects
Labetalol	20 to 40 mg IV every 10 minutes or 20 mg IV doubled every 10 minutes to max of 80 mg IV until goal blood pressure achieved	Flushing, light headedness, palpitations, scalp tingling
Hydralazine	5 mg IV every 10 minutes. May increase to 20 mg IV or 10 mg IM followed by 10 mg increases every 15–20 minutes to a maximum of 30 mg IM until goal blood pressure achieved	Headache, flushing, light headedness, nausea, palpitations

Management of hypertensive disorders in pregnancy (contd...)

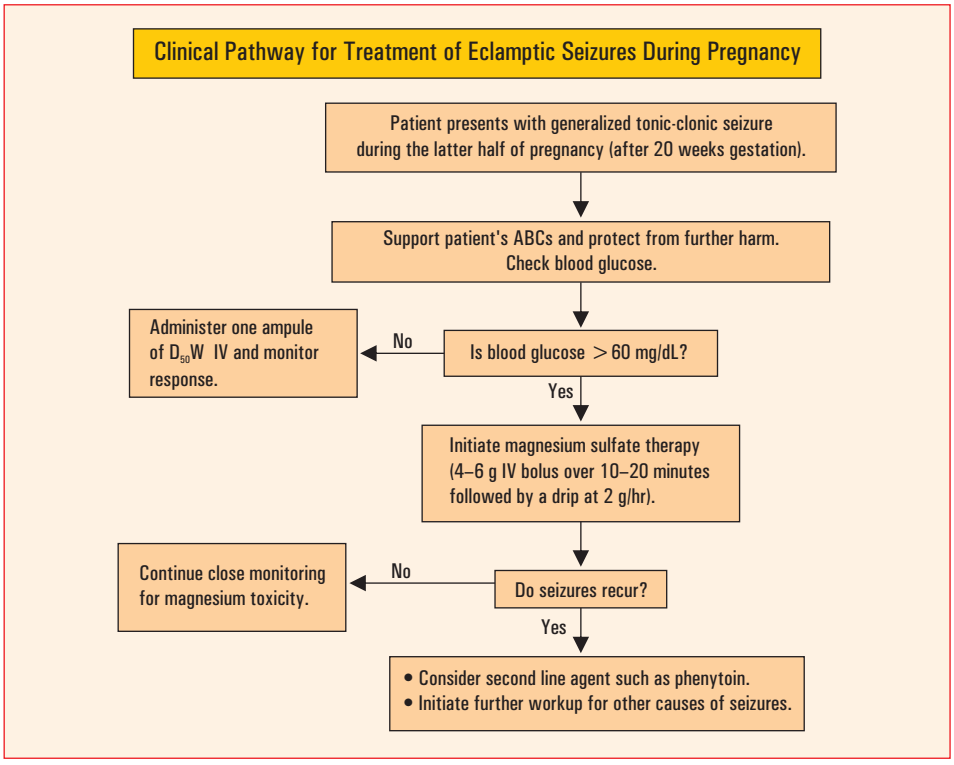
Agent	Protocol	Side Effects
Nifedipine	10 to 20 mg orally every 30 minutes to a maximum dose of 50mg in one hour of goal blood pressure achieved	Flushing, nausea, vomiting
Nitroprusaide	0.25 mcg/kg/min IV titrated every 3 to 5 minutes to a maximum dose of 5 mcg/kg/min IV until goal blood pressure achieved	Cyanide production
Nitroglycerin	5 mcg/min IV titrated every 3 to 5 minutes to a maximum dose of 100 mcg/min IV until goal blood pressure achieved	Headache, trachycardia, methemoglobinaemia, increased intracranial pressure

Clinical Pathway for Management of Hypertensive Disorders of Pregnancy



These clinical pathway are intended to supplement, rather than substitute for, professional judgement and may be changed depending upon a patients individual needs. Failure to comply with these pathways does not represent a breach of the standard of care.

- The above algorithm describes the clinical pathway for the management of HDP
- Based on the severity of blood pressure elevation patient may be treated on outpatient department basis or admitted in severe cases
- Mild increase in blood pressure may not need pharmacotherapy
- In cases with severe preeclampsia IV labetalol is recommended
- For patients on anti-hypertensive blood pressure goals in pregnancy must be systolic pressure of 130 to 150 mmHg and diastolic pressure of 80 to 100 mmHg
- Prophylactic step are taken to prevent eclampsia as mentioned above
- Close monitoring and timely intervention is the key to prevent serious complications of HDP
- Eclampsia is one of the most dreaded presentation of HDP
- Clinical pathway for management of eclamptic seizures in pregnancy is briefly discussed in the algorithm given below[8]



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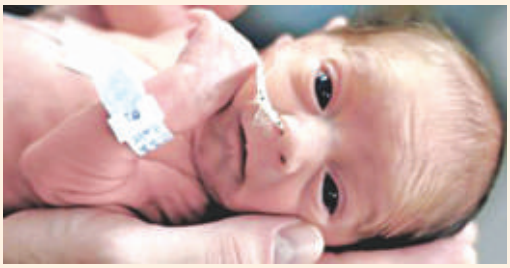
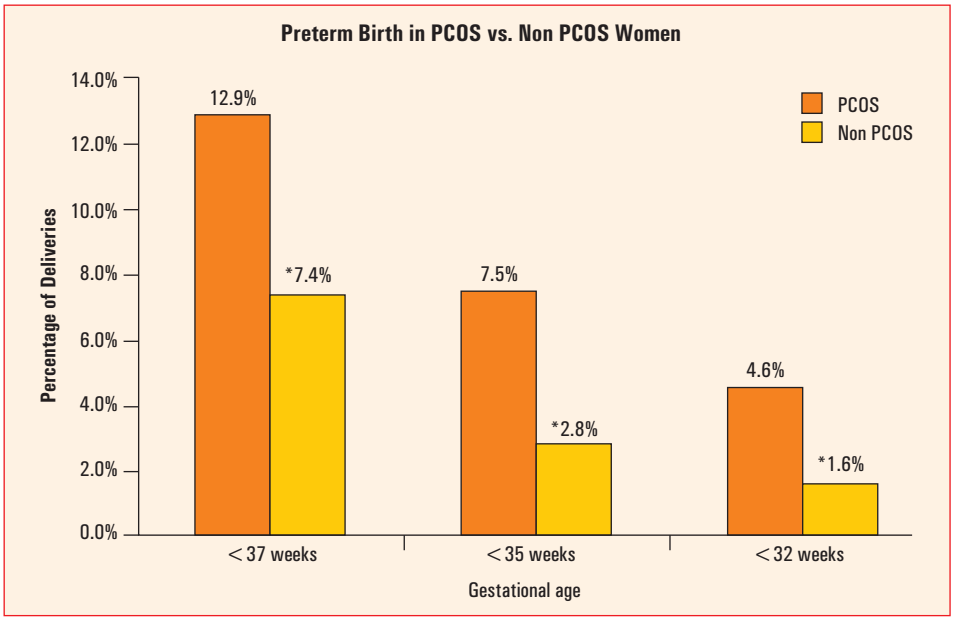
Preterm Delivery

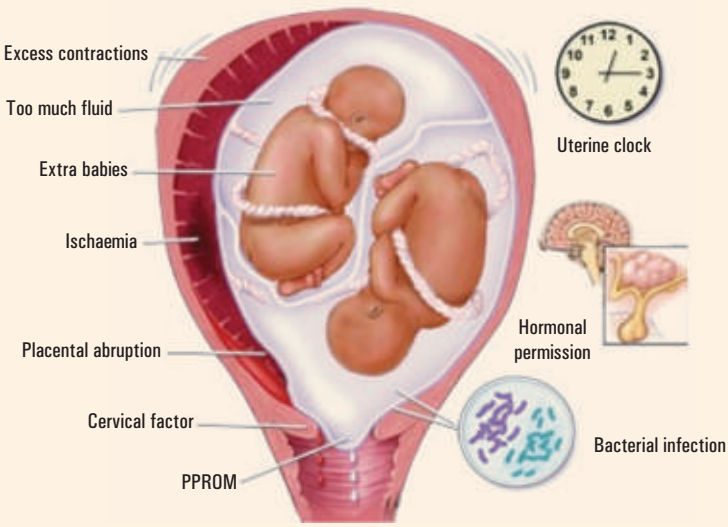


- Delivery between the 22nd and 37th week of gestation is called preterm.
- Neonatal complications such as prolonged stay in the incubator, necessity for glucose infusions or neonatal jaundice are common association with PTB.



- A higher proportion of PCOS women delivered preterm (12.9%) compared to non PCOS women as seen in the figure above; with the majority of cases due to spontaneous PTB.
- Higher rate of late PTB <37 weeks is seen among PCOS subjects is seen without differences in rates of cerclage, PPROM, as compared to PTB <32 weeks.
- PCOS has been characterized by a similar state of chronic low-grade inflammation, as seen among women with SGA babies.
- Insulin resistance, visceral adiposity, hyperandrogenism, and resultant increased production of specific cytokines and chemokines including TNF-α, IL-6 and IL-1, adhesion molecules implicated in endothelial dysfunction, follistatin and C-reactive protein contribute to higher prevalence of SGA babies among women with PCOS.

Preterm Birth Causes and Risk Factors



PPROM: Preterm premature rupture of the membranes

- Higher levels of inflammatory cytokines were found in amniotic fluid of women in premature labour.
- Underlying inflammatory mediators associated with PCOS may also contribute to predisposition for PTB.
- Women with infertility which is a common association among PCOS women may also contribute for higher risk for PTB than spontaneously conceived pregnancies.
- Increased antenatal surveillance and facilitated access to higher levels of perinatal and neonatal services should be considered for pregnant women with PCOS.

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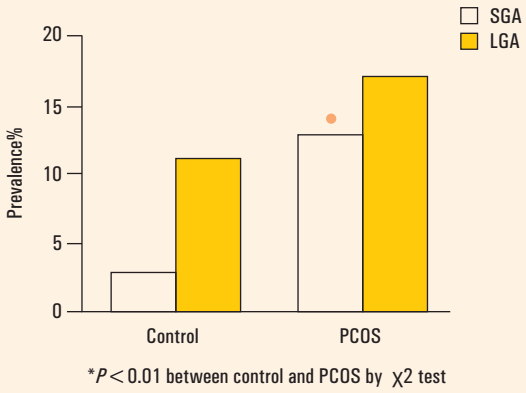
Impact on Foetus: Low Birth Weight Babies and Foetal Origin of Adult Disease

- The spectrum of low birth weight babies (LBW) includes SGA, IUGR, and very low birth weight (VLBW) infants, some who are not only born prematurely but at times also with superimposed IUGR.
- SGA is defined as a birth weight or birth length less than the 10thpercentile with respect to gestational age
- IUGR refers to an infant who does not reach his or her predetermined genetic potential because of some pathologic insult
- Although IUGR infants may be SGA, all SGA infants are not necessarily IUGR.[1]

Small for Gestational Age Foetus in Pregnant Women with PCOS



Prevalence of SGA and LGA infants born to control mothers and mothers with PCOS.

- Pregnant women with PCOS have more than double the risk of giving birth to SGA babies.
- IUGR is caused in 10–15 % of pregnant women with PCOS.

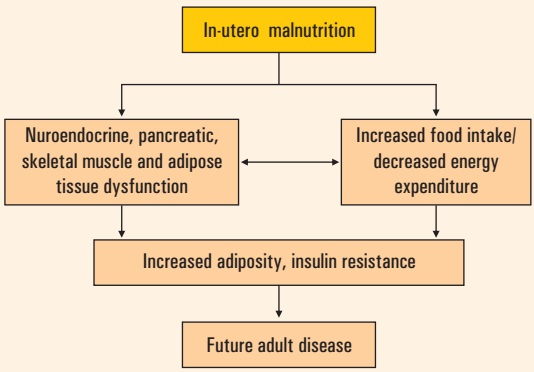
- Mothers with PCOS showed a significantly higher prevalence of SGA newborns which cannot be completely attributed to pregnancy complications, and seems to be more related to the PCOS condition of the mother.
- Pregnant women with PCOS are more than twice likely to give birth to SGA children than healthy women.[2]

- Foetal growth restriction is seen in 10–15 % of pregnant women with PCOS.
- SGA may be linked to insulin resistance and insulin-dependent growth dysfunction.
- Therefore, PCOS pregnant women are patients of special obstetrical care.[3]

Pathogenesis of Foetal Origins of Adult Disease (FOAD)

Chronic diseases associated with FOAD

- Obesity
- Type 2 diabetes mellitus
- Cardiovascular disease
- Hypertension
- Kidney disease
- Premature pubarche
- PCOS
- Dyslipidaemia
- Short stature
- Osteoporosis



- Prenatal and postnatal periods are exquisitely sensitive to any factor that can affect growth. These are periods of exponential cell replication, division, and growth.
- Infants born SGA are at increased risk for developing obesity, T2DM, cardiovascular disease (CAD), HTN, kidney disease, premature pubarche, and PCOS, dyslipidaemia, short stature, and osteoporosis.
- Many of these phenotypic changes are known to be secondary to or associated with insulin resistance which is inherent in women with PCOS.[1]
- FOAD is due to altered developmental physiology caused by undernutrition, hypoxia, infection and stress hormones.[4]
- High oxidative status of mother during pregnancy in women with PCOS has a significant influence over the development of the chronic diseases associated with FOAD.[5]
- There is robust evidence that a hyperandrogenic intra-uterine environment 'programmes' the genes concerned with ovarian steroidogenesis, insulin metabolism, gonadotrophin secretion and ovarian follicle development resulting in the development of PCOS in adult life.[4]

References:

1. Calkins K and Devaskar SU. Fetal Origins of Adult Disease. *Curr Probl Pediatr Adolesc Health Care*. 2011;41(6):158–176.
2. Sir Peterman- T, Hitchsfield C, Maliqueo M, *et al*. Birth weight in offspring of mothers with polycystic ovarian syndrome. *Human Reproduction*. 2005;20(8)2122–2126.
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4. Fillipou P and Homburg R. Is foetal hyperexposure to androgens a cause of PCOS. *Human Reproduction Update*. 2017;23(4):421–432.
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Recommendations to Improve Outcome of Pregnancy

- Preconceptual assessment of BMI, BP and OGTT
- Screen for GDM at 24–28 weeks of gestation
- Metformin can be used in preconception period and during pregnancy
- Myoinositol supplementation reduces insulin resistance and its use in the first trimester, for obese pregnant women with PCOS may reduce the chances of development of GDM

- The Endocrine Society, USA Clinical Practice Guidelines recommends pre-conceptual assessment of BMI, BP and OGTT.[1]
- Indian guidelines recommend a pregnant woman should be screened for glucose tolerance in the first trimester, if normal then again should be tested for GDM around 24th–28th week using DIPSI criteria and finally around 32nd – 34th week.[2]
- Clinical evidence suggests metformin is safe and effective during periconception period and pregnancy.[3]
- Study have found that use of myoinositol in obese women with PCOS can reduce the risk of development of GDM.[4]

- CoPPer study is a follow-up study of women diagnosed with PCOS .

Study Design

- 50 consecutive pregnant women
- Preconception standardized evaluation
  - o Biometry
  - o Endocrinology
  - o Metabolic features, including OGTT
  - o Ultrasound
- OGTT at 24–26 weeks

References:

1. Legro SR, Arslanian AS, Ehrmann AD, *et al.* Endocrine society. diagnosis and treatment of polycystic ovary syndrome: an endocrine society clinical practice guideline. *J. Clin. Endocrinol. Metab*. 2013;98(12):4565–4592.
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3. Nice Guidelines. Diabetes in pregnancy: management from preconception to the postnatal period. Available at: https://www.nice.org.uk/guidance/ng3/chapter/1-recommendations. Last accessed on: Sept 20, 2017.
4. D'Anna R, Di Benedetto A, Scilipoti A, *et al*. Myoinositol supplementation for prevention of gestational diabetes in obese pregnant women: a randomized controlled trial. *Obstet Gynecol*. 2015;126(2):310–5.

Conclusion

- When women with PCOS conceive whether it's a multifetal gestation or a singleton pregnancy, a higher risk of pregnancy complications is involved.
- Currently, the pathophysiology of pregnancy complications associated with PCOS is not completely understood yet hyperandrogenism, obesity, insulin resistance, infertility treatment, and placental dysfunction are believed to be the associated causes.
- Women with PCOS are at higher risk of early pregnancy loss, recurrent pregnancy loss, gestational diabetes, hypertensive disorders of pregnancy, preterm delivery, foetal growth restriction.
- Vigilance to screen and identify these complications and institution of appropriate management preferably by experts in the field is necessary for successful outcomes for both the mother and the foetus.

Key Points

- Women with PCOS who desire a pregnancy may be at increased risk for adverse pregnancy outcomes, and this may be exacerbated by obesity and/or insulin resistance (level B).
- Health should be optimized before conception, with advice about smoking cessation, lifestyle, diet, and appropriate vitamin supplementation (e.g., folic acid).
- Several factors contribute to early and recurrent loss of pregnancy in women with PCOS.
- Women with PCOS should be observed closely during pregnancy as they may be at increased risk for the development of gestational diabetes, gestational hypertension, and associated complications (level B).
- Pregnancy-associated risks are greater in women diagnosed by more classic (National Institutes of Health) criteria as opposed to nonhyperandrogenic women (level B).
- Babies born from women with PCOS may have increased morbidity and mortality (level B).
- Metformin may be safe alternative in women with mild gestational diabetes who failed one week of trial with medical nutrition therapy.

Suggested Readings

1. Dumesic DA, Oberfield SE, Stener-Victorin E, *et al*. Scientific statement on the diagnostic criteria, epidemiology, pathophysiology, and molecular genetics of polycystic ovary syndrome. *Endocr Rev*. 2015;36(5):487–525.
2. de Wilde MA, de Ruiter ML, Verhulst SMV, *et al*. Increased rates of complications in singleton pregnancies of women previously diagnosed with polycystic ovary syndrome predominantly in the hyperandrogenic phenotype. *Fertility & Sterility*. 2017;108(2):333–340.
3. Palomba S, Falbo A, Russo T, *et al*. Pregnancy in women with polycystic ovary syndrome: the effect of different phenotypes and features on obstetric and neonatal outcomes. *Fertil Steril*. 2010;94(5):1805–11.
4. Malik S, Jain K, Shah D, *et al*. Management of polycystic ovary syndrome in India. *Fertil Sci Res*. 2014;1:23–43.

Notes

PCOS and Pregnancy

POST-TEST

1. **Women with PCOS can:**
   a. Get pregnant only if they undergo IVF
   b. Get pregnant only if they undergo ovulation induction
   c. Get pregnant spontaneously or with ovulation induction and other assisted reproductive techniques
   d. Never get pregnant
2. **The possible complications of pregnancy are:**
   a. Gestational diabetes
   b. Hypertensive disorders of pregnancy
   c. Preterm delivery
   d. All of the above
   e. None of the above
3. **Which of the following is untrue?**
   a. Singleton pregnancies have no complications in women with PCOS
   b. Hyperandrogenism, insulin resistance, obesity may contribute to the pathophysiology of PCOS
   c. Women with PCOS have higher proportion of both SGA and LGA babies
   d. All of the above
   e. None of the above
4. **Which of the following is the cause of pregnancy complications**
   a. Poor oocyte quality
   b. Poor embryo quality
   c. High oxidative stress
   d. All of the above
   e. None of the above
5. **Which of the following has not been associated as a cause of early pregnancy loss in women with PCOS?**
   a. Obesity and insulin resistance
   b. Higher plasma levels of androgens
   c. Low levels of glycodelin
   d. Increased levels of luteinizing hormone

6. **GDM in women with PCOS is more prevalent among:**

   a. All women with PCOS

   b. Obese women with PCOS

   c. Hyperandrogenic women with PCOS

   d. b and c

   e. None of the above

7. **Prevalence of hypertensive disorders of pregnancy among pregnant women with PCOS is:**

   a. Half of that seen among the normal population

   b. Thrice of that seen among the normal population

   c. Ten times of that seen among the normal population

   d. Same as that seen among the normal population

8. **Which of the following chronic diseases are hypothesized to have foetal origins ?**

   a. Obesity

   b. Hypertension

   c. Coronary artery disease

   d. Osteoporosis

   e. All of the above

   f. None of the above

9. **The following must be assessed in all women with PCOS who are planning to conceive, except:**

   a. BP

   b. Oral glucose tolerance test

   c. Blood glucose

   d. Phenylketonuria screening

10. **In women with PCOS who have experienced a miscarriage, you should check serum homocysteine levels for identification and treatment of hyperhomocystenemia mediated repeated pregnancy losses.**

    a. True

    b. False

Answers: 1. c; 2. d; 3. a; 4. d; 5. d; 6. d; 7. b; 8. e; 9. d; 10. a

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