# Adverse Effect and Drug Interaction Of Metformin In PCOS

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## Abstract:

Originally called the Stein–Leventhal syndrome, PCOS stands for polycystic ovarian syndrome. An enlargement of the ovaries filled with numerous tiny cysts, which are actually immature follicles, is the hallmark of this dangerous illness, which primarily affects females. There are connections between PCOS and ovulation, irregular menstruation, infertility, and insulin intolerance. The symptoms of PCOS can include weight gain, hirsutism, and acne. Endometrial cancer, obesity, Type 2 diabetes, dysfunctional uterine bleeding, high cholesterol, and cardiovascular diseases are among the health issues that arise when the condition gets worse. Nowadays, pharmacological therapies and lifestyle modifications are the standard of care for PCOS treatment in women. Dietary modifications and increased physical activity are the recommended lifestyle adjustments for PCOS treatment. The best treatment for PCOS is changing one's lifestyle, despite the abundance of medications available. Exercise and weight loss are two of the best ways to treat PCOS without having to worry about unfavorable side effects.Natural polyphenols have been used for decades to manage hormonal problems.

**Keywords :- PCOS drug Therapy , Insulin Resistance, Hirsutism ,Menopause , Lactic acidosis , Metformin ,Drug interactions.**

## Introduction :

Polycystic ovarian syndrome (PCOS) is the most common endocrinopathy affecting 5-10% of women of reproductive age, with an estimated 5 million women worldwide impacted. It is characterized by polycystic ovarian morphology, oligo-ovulation, and hyperandrogenism. Most PCOS patients also exhibit insulin resistance, which contributes to increased androgen production. Dysfunctional adipose tissue is linked to this insulin resistance[1].

PCOS is associated with various comorbidities such as obesity, acne, infertility, cardiovascular disease, type 2 diabetes, dyslipidemia, and endometrial cancer. It is also linked to mood and eating disorders. Despite these challenges, PCOS may persist due to evolutionary advantages in the past, including smaller family sizes, reduced childbirth mortality, increased muscle mass, and enhanced energy storage[2].

Treatment goals focus on restoring ovulation and reducing hyperandrogenic symptoms. The development of PCOS is influenced by both genetic and environmental factors. The pharmacologic management of PCOS is examined in the context of these complications and treatment objective[3].

## Etiology :

PCOS is a heterogeneous disorder influenced by both genetic and environmental factors. It is classified as oligogenic, with a tendency to cluster in families, often following autosomal dominant patterns. Epigenetic modifications (changes in gene expression without altering DNA sequence) also play a role[4].

Environmental factors, such as exposure to endocrine-disrupting chemicals (EDCs), contribute to PCOS risk. Prolonged exposure to EDCs from pregnancy through adolescence can increase PCOS susceptibility[5].

Stress, both physical and emotional, negatively affects mental health in PCOS patients, leading to adipocyte hypertrophy and hyperplasia[6].

Low vitamin D levels can worsen PCOS and associated comorbidities. Vitamin D enhances insulin sensitivity by regulating insulin receptor activity and controlling intracellular calcium, which is crucial for insulin signaling. Conversely, vitamin D deficiency can cause inflammation and insulin resistance. Additionally, vitamin D inhibits the AMH promoter, which may play a role in PCOS development[7].

**Diagnosis :[8],[9]**

| NICHD/NIH Criteria (1990) | ESHRE/ASRM Rotterdam Criteria (2003) | Androgen Excess Society (AES) Criteria (2006) |
|---|---|---|
| Hyperandrogenism<br>Oligo-ovulation/anovulation<br>Exclusion of other related disorders | Hyperandrogenism<br>Oligo-ovulation/anovulation<br>Polycystic ovaries | Hyperandrogenism<br>Oligo-ovulation/anovulation<br>Polycystic ovaries<br>Exclusion of other related disorders |

**Symptoms and Indications:**

- large ovaries filled with a lot of tiny cysts
- irregular cycles of menstruation ,
- Pelvic discomfort ,
- The hirsute ,
- Alopecia ,
- ANCHOSTISIS NIGRICA ,
- Skin tags ,[8].

**Pathophysiology :**

The pathophysiology of PCOS involves defects in the hypothalamic-pituitary axis, insulin regulation, and ovarian function. Although the exact cause is unknown, insulin resistance and obesity are commonly associated with PCOS[10]. Excess insulin stimulates the ovaries to produce androgens, leading to anovulation. Key indicators include elevated gonadotropin-releasing hormone (GnRH) and luteinizing hormone (LH) levels, with unchanged follicle-stimulating hormone (FSH) levels. Follicular maturation arrest is a primary sign, which can be treated by increasing FSH levels[11].

PCOS may begin as a primary defect during puberty, particularly in those with a family history of the disorder. Elevated prolactin is seen in about 25% of PCOS patients. Treatment aims to lower androgen and insulin levels, raising sex hormone-binding globulin (SHBG), which helps manage symptoms. Thecal cells in PCOS patients produce higher levels of progesterone, testosterone, and 17-hydroxyprogesterone[12]. Genetic changes, such as increased expression of cytochrome P450 (CYP) 11A, 3-HSD2, and CYP17, are also seen in PCOS cells. Obesity, while common in PCOS, is not required for diagnosis. PCOS is linked to an inflammatory state, also seen in conditions like obesity, type 2 diabetes, and cardiovascular disease[13].

**Metformin :**

Millions of people use the well-known medication metformin to treat a range of illnesses, such as obesity, cancer, polycystic ovarian syndro(PCOS),gestationa] diabetes mellitus (GDM), type 2 diabetes, prediabetes, and others[14].For patients who are overweight, metformin is typically prescribed as a first-line treatment for type 2 diabetes mellitus. Metformin's antihyperglycemic effect is thought to be primarily caused by inhibiting gluconeogenesis and increasing glucose utilization, which reduces the amount of glucose produced by the liver[15].The induction of skeletal muscle glucose uptake and the inhibition of hepatic glucose production are dependent on metformin's activation of AMP-activated protein kinase (AMPK)[16].

**Mechanism of Action :**

Women with PCOS exhibit normal insulin molecules and receptors, but they experience post-receptor insulin resistance, impairing the intracellular effects after insulin binds. As a result, they produce higher insulin levels, which directly impact the ovaries and stimulate the liver to release insulin-like growth factor 1 (IGF-1). Elevated insulin and IGF-1 levels lead to increased testosterone production in the ovaries, inhibiting the growth of ovarian follicles and preventing ovulation. This results in the accumulation of small follicles under 10 mm that do not mature[17].

**Dosage And Duration :** Metformin's useful dosage range for controlling hyperglycemia in people with type 2 diabetes is normally 500–2000 mg/day; dosages below this range are usually not associated with meaningful responses. Individualised dosage plans must take into account the patient's effectiveness and tolerance, while staying within the maximum suggested dosage ranges of 2000 mg for children over 10 years old and 2550 mg for adults.Individuals now using immediate-release metformin have the option to convert to extended-release at a dose of up to 2000 mg per day. Furthermore, those with renal impairment require dose modifications[18].

**Table 2 :**

| Category | Immediate-Release Metformin | Extended-Release Metformin |
|---|---|---|
| **Initial Dose** | 500 mg daily or 850 mg daily | 500 mg daily or 1000 mg daily |
| **Titration Dose** | 500 mg weekly or 850 mg every 2 weeks | 500 mg weekly |
| **Maximum Dose** | 2550 mg daily | 2000 mg daily |
| **Geriatric Use** | With caution: start at the low end of the dosing range; assess renal function | With caution: start at the low end of the dosing range; assess renal function |
| **Pediatric Use** | >10 years old: 500 mg weekly | >10 years old: 500 mg weekly |
| **Maximum Pediatric Dose** | Not yet established | 2000 mg daily |

**Potential side effect and Serious side effect :**

Metformin is typically safe and well-tolerated, however up to 30% of individuals may experience gastrointestinal problems like nausea, vomiting, and diarrhoea. Chest discomfort, headaches, sweating, hypoglycemia, weakness, and rhinitis are among less frequent adverse effects. Long-term usage, particularly in individuals with anaemia or peripheral neuropathy, may lower vitamin B12 levels, necessitating monitoring and potentially supplementation.For lactic acidosis, a rare but dangerous disease that affects roughly 1 in 30,000 people, metformin has a black box warning. Malaise, respiratory discomfort, and increased lactate levels are among the symptoms. Hepatic or renal impairment, advanced age, surgery, hypoxia, and drunkenness are risk factors for lactic acidosis. Patients are cautioned against consuming excessive amounts of alcohol since lactic acidosis might cause serious problems such include mortality, hypotension, and hypothermia**.**

**Precautions :**

- **Kidney and Liver Function :**

Since metformin is mostly eliminated by the kidneys, it should not be administered to anyone who have severe liver or renal impairment. Decreased kidney function may lead to a hazardous medication build-up, which raises the possibility of lactic acidosis—a uncommon but dangerous illness.

- **Lactic Acidosis Risk :**

Risk factors for lactic acidosis include severe infections, dehydration, and kidney disease. Lactic acidosis is an uncommon but potentially fatal illness. Patients who develop symptoms including muscle soreness, trouble breathing, or extreme weariness should stop taking metformin and visit a doctor.

- **Drug Interactions :**

Metformin may interact with a number of drugs, such as SSRIs, iodine-based contrast agents, and several diabetes treatments, which may raise the risk of problems and side effects.

- **Alcohol Consumption :**

Limiting alcohol intake and avoiding binge drinking or heavy use is advised because alcohol can raise the risk of lactic acidosis when on metformin.

- **Pregnancy and Contraception :**

Pregnancy and Contraception: In women with PCOS, metformin can aid in ovulation induction, potentially improving fertility. Effective contraception should be utilised if becoming pregnant is not wanted, and people should discuss their alternatives with their healthcare professional.

- **Surgery and Imaging Procedures :**

Because metformin can raise the risk of kidney problems, patients may need to temporarily cease taking it before undergoing surgery or undergoing contrast-agent-based imaging procedures.

## Storage :

Metformin should be kept out of direct sunlight and extremely cold or hot conditions, between 20°C and 25°C (68°F and 77°F). To avoid deterioration, it must be stored in a dry environment away from areas with high humidity. To prevent contamination and ensure correct labelling, it is recommended to keep metformin in its original, firmly sealed container. To avoid unintentional ingestion, it should also be kept out of children's reach.

## Overdose :

Out of 2872 cases (1.9%), 56 self-reported metformin overdoses were studied. Of these, 56.4% of patients experienced hyperlactatemia, and 17.9% had metformin-associated lactic acidosis (MALA), which was more common when paracetamol was also used[19]. Thankfully, no one lost their life. Supportive care, gastrointestinal cleaning (such as gastric lavage), alkalinisation, and emergency haemodialysis for severe instances are the treatments for metformin overdose[20].

## Monitoring :

- **Metformin as an ovulation induction agent :**

Women with PCOS who experience anovulatory infertility can benefit from using metformin. Metformin significantly enhances clinical pregnancy rates when compared to placebo, according to a Cochrane analysis of seven RCTs including 702 women (Peto OR 2.31). Live birth outcomes were only evaluated in three RCTs with 115 women, and because to the underpowered analysis, there was no discernible effect (Peto OR 1.80)[21].

- **Metformin versus aromatic inhibitors :**

Although there is growing evidence that letrozole may result in more live births than clomiphene, there aren't many RCTs comparing the two medications[28].

- **Metformin versus gonadotrophin injection therapy as a second line of treatment for women with anovulatory PCOS:**

There is a lack of reliable data comparing the efficacy of metformin with laparoscopic ovarian drilling or injection therapy. It is fair to provide metformin to all women who are resistant to clomiphene and other medications until a pregnancy is confirmed, as it may improve responses in these women. Metformin could be taken continuously during pregnancy due to its reassuring safety profile. It is advised that metformin be taken into consideration prior to more intrusive procedures, and additional investigation is required to see how it interacts with these treatments.

- **Metformin versus Clomiphene :**

For women with PCOS who have irregular menstruation, Clomiphene has historically been the primary line of treatment, especially for those who are fat or overweight. But for obese women, lifestyle changes are prioritised because even a small amount of weight loss might increase the likelihood of getting pregnant[22]. Despite variations in findings amongst several trials, a meta-analysis of non-obese women (BMI <30-32) revealed no discernible difference in pregnancy or live birth rates between metformin and clomiphene[23].

It has been demonstrated that clomiphene works better in obese women[24]. Metformin has benefits over clomiphene, including no negative endometrial effects, no increased risk of multiple pregnancies, and less long-term ovarian hazards, even though its efficacy varies among non-obese women[25].This means that for non-obese women with anovulatory PCOS, metformin might be a good first-line treatment. If metformin doesn't work, alternative options should be explored[26]. Accumulating data also suggests that women with lower BMI may respond more favourably to metformin, casting doubt on earlier beliefs on the medication's effectiveness in treating obesity[27].

- **Effectiveness of metformin for women with PCOS and repeat pregnancy loss remains :**

There is growing evidence that quitting metformin suddenly after a pregnancy is diagnosed may raise the chance of miscarrying the baby. The majority of experts support the latter theory in the continuing discussion over whether PCOS alone or in conjunction with obesity is the primary cause of recurrent pregnancy loss[29]. Metformin may help pregnant women with PCOS and recurrent miscarriages have better pregnancy outcomes, according to early observational data, although RCTs have not supported this theory[30].

- **Metformin for women with PCOS experiencing hyperandrogenic symptoms:**

Metformin's utility for PCOS women experiencing hyperandrogenic symptoms has been assessed outside of reproductive indications[31]. Metformin and the combined oral contraceptive pill (OCP) did not significantly vary in terms of hirsutism and acne, according to a comprehensive evaluation of six RCTs. When it came to lowering blood testosterone levels and enhancing menstrual patterns, metformin was less successful than OCP. Furthermore, metformin was linked to reduced rates of severe non-gastrointestinal side effects necessitating medication discontinuation but a higher frequency of gastrointestinal adverse effects[31].

- **Metformin for PCOS-afflicted women to maintain long-term health:**

Exercise and nutritional modifications are crucial lifestyle therapies for long-term health improvement in overweight or obese PCOS women. It was shown that metformin was superior to the combination oral contraceptive pill (OCP) in lowering fasting insulin and preventing triglyceride levels from rising; however, there was insufficient data to determine how it affected fasting glucose or cholesterol[31]. There was a dearth of information regarding the effectiveness of metformin or OCP in preventing diabetes, cardiovascular disease, or endometrial cancer. Metformin, on the other hand, may help lower the risk of endometrial cancer in anovulatory women by restoring ovulation, which makes it a viable treatment choice for individuals who are unable to utiliseOCP[32].

## Metformin Pharmacological Drug Interaction :

Metformin is a cation at physiological pH, requiring transporters such as Organic Cation Transporters (OCTs), Multidrug and Toxin Extruders (MATEs), and Plasma Membrane Monoamine Transporters (PMAT) for its absorption, distribution, and excretion[33]. It is excreted unchanged in the urine, so patients with moderate to severe chronic renal impairment (CRI) should avoid metformin due to the risk of accumulation.

Metformin is unlikely to cause many drug-drug interactions (DDIs) because it is not metabolized, but transporters like OCT1, OCT3, OCT2, and MATEs are involved in its absorption and renal excretion. Medications that inhibit these transporters can increase metformin levels in the blood, raising the risk of Metformin-Associated Lactic Acidosis (MALA )a serious condition caused by lactate accumulation due to suppressed glucose production in the liver[34].

Patients should discontinue metformin and seek emergency care if they experience symptoms like severe vomiting or diarrhea, which may indicate MALA[35].

### 1) Interactions with Iodinated Contrast Materials:

ICMs are extensively and effectively used in a variety of procedures, such as urography and angiography. Contrast-induced nephropathy (CIN) would arise from the administration of iodinated contrast media (CM). Therefore, patients on Metformin who have procedures involving Iodinated Contrast Material (ICM) may be at a higher risk of developing a toxic accumulation of Metformin and consequently developing Lactic Acidosis. Patients who have impaired kidney function are at even higher risk, so it is advised that they cease taking Metformin while on ICM[36].

**2) Relationships with substances that suppress acid:**

Blockers of H2 receptors:

**Cimetidine:**
Cimetidine is a broad-spectrum inhibitor of transporters, including Organic Cation Transporter 2 (OCT 2), and a strong inhibitor of Multidrug and Toxin Extruder 1 (MATE1) of proximal tubular epithelial cells. Metformin excretion is decreased when Cimetidine and Metformin are used concurrently, increasing the exposure to Metformin and raising the risk of Metformin Associated Lactic Acidosis (MALA). It is advised to lower the Metformin dosage when Cimetidine is also prescribed[37].

Ronitidine
Because ranitidine may inhibit Multidrug and Toxin Extruder 1 (MATE1), metformin's renal clearance was lowered[38].

Famotidine :
Because it selectively inhibits MATE1, famotidine may be an appropriate H2 blocker for patients taking metformin. This is because famotidine increases the estimated bioavailability of metformin, which enhances its therapeutic efficacy. Furthermore, compared to Cimetidine or Ranitidine, which lessen Metformin's excretion, Famotidine increases the drug's renal clearance[39].

**3) Inhibitors of proton pumps :**

Proton pump inhibitors have the potential to increase plasma metformin exposure by blocking the OCT2 and Multidrug and Toxin Extruder (MATE) transporters. It is advised to keep an eye on the concurrent use of metformin and proton pump inhibitors[40]. The risk of Vitamin B12 deficiency was found to be elevated by the combination of Proton pump inhibitors or H2 receptor blockers and Metformin[41]. the combined effects of metformin and proton pump inhibitors, also known as H2 receptor blockers, that cause malabsorption of vitamin B12. In order to prevent cobalamin deficiency in patients taking metformin and PPIs/H2 receptor blockers, vitamin B12 replacement is advised[42].

**4) Relationship between ranolazine :**

Ranolazine is approved to treat chronic angina. Ranolazine inhibits the release of glucagon by decreasing electrical activity and blocking the sodium channel of pancreatic α cells[43]. The concurrent administration of ranolazine may increase the plasma concentrations of metformin, which may reduce the elimination of metformin by inhibiting the OCT2 transporter. Because of this dose-dependent interaction, patients taking 1000 mg of ranolazine twice daily should not take more than 1700 mg of metformin daily[44].

**5) Relationship to Antimicrobial Agents**

**Trimethoprim:**
Trimethoprim moderately reduces the excretion of Metformin by blocking OCTs and MATEs; however, patients with renal impairment or those on higher doses of Metformin should exercise caution when coadministering both medications[45].

**Cephalexin:**
Cephalexin, a zwitterionic substrate of MATE1, decreases Metformin elimination, which causes accumulation[46].

**Rifampin:**
Rifampin administration may cause an increase in the hepatic uptake of metformin because of increased OCT1 expression[47].

**Dolutegravir:**
Dolutegravir, which inhibits the MATE1 and OCT2 transporters in the renal tubules, is the first-line antiretroviral medication used to treat HIV infection. When metformin and dolutegravir are used together, there's a chance that the drug's side effects—like hypoglycemia and GI intolerance—will worsen. This is because metformin's plasma concentrations will rise as a result of the inhibitory effects on OCT2 and MATE1 transporters. While prescribing Dolutegravir and Metformin concurrently, prescribers may modify the Metformin dosage to avoid intolerable ADRs[48].

**Pyrimethamine:**
Pyrimethamine, an antiparasitic medication, is used to treat cystoisosporiasis and toxoplasmosis. Pyrimethamine inhibits the transporters of MATE and OCT2. When Pyrimethamine and Metformin are administered together, the inhibition of OCT2 and MATE transporters by Pyrimethamine causes a decrease in Metformin's renal clearance, which raises plasma concentrations[49].

**6) Interaction with Beta adrenergic blockers :**

**Atenolol:**
Metoprolol can lower the plasma concentration of metformin by enhancing the drug's uptake in the liver by inducing OCT1, enhancing the drug's uptake in the kidneys by decreasing MATE1 expression, and enhancing the drug's uptake in the thigh muscle by inducing OCT3[50].

**Metoprolol:**
The plasma concentration of Metformin can be decreased by Metoprolol by increasing the hepatic uptake of Metformin through the induction of OCT1, increasing the renal uptake of Metformin By reducing the expression of MATE1 and increasing the uptake of Metformin in thigh muscle through the induction of OCT3[51].

**7) Anticancer Drug Interaction :**

**The Vandetanib:**

Tumor cells in the medulla are treated with venetanib. Since metformin is the substrate of MATE1 and MATE2K transporters, co-administration of vandatetanib, a strong inhibitor of MATE1 and MATE2K transporters, may lead to elevated plasma concentrations of metformin due to decreased elimination. The patients receiving the combination of Vandetanib and Metformin should be monitored carefully for Metformin toxicity[52].

Inhibitors of tyrosine kinase :At clinically relevant concentrations, tyrosine kinase inhibitors like Imatinib, Nilotinib, Gefitinib, and Erlotinib may decrease the removal of Metformin by blocking OCTs and MATEs transporter[53].

## Contraindication :

Current guidelines clearly outline the uses and effectiveness of metformin in type 2 diabetes and continue to extend to other areas of medicine. As an illustration, the UKPDS study found that metformin is linked to a decreased risk of death, and some researchers attempted to use metformin asan anti-aging medication. In addition to having a wide range of applications, metformin is still not recommended in many hypoxemia-related conditions since it can cause lactic acidosis.

**1) Ketoacidosis :**

Insulin therapy should be started in patients with type 2 diabetes who are having severe hyperglycemia and ketoacidosis. Metformin can be started after glycaemic levels have stabilised and there are no contraindications. Metformin is used as a supplement to lower insulin requirements in individuals with type 1 diabetes; however, a randomised controlled trial found that while it improved glycaemic control, it may increase gastrointestinal side effects in people who are overweight. Treatment plans should be customised by clinicians based on the unique needs and preferences of each patient[54].

**2) Cardiac failure :**

Initially, the use of metformin was contraindicated due to concerns of lactic acidosis. Nevertheless, further observational studies and systematic reviews have suggested that people with stable heart failure can safely utilise metformin. Metformin should be stopped in patients who experience congestive heart failure or who have other contraindications. The reviewed literature was diverse, frequently comparing various drugs without providing exact metformin dosages. Overall, individuals with heart failure and type 2 diabetes who received metformin treatment had a 22% decreased death rate[55].

**3) Chronic kidney disease (CKD) :**

Patients with an eGFR of fewer than 30 ml/min/1.73 $m^2$ (stage IV CKD) are limited from using metformin; the dose needs to be changed starting at an eGFR of less than 45 ml/min/1.73 m2 (stage IIIb) [4]. Metformin was found to have neutral effects on the same variables at an eGFR between 30 and 45 ml/min/1.73 m2 and to be associated with a decreased rate of death and serious adverse events at an eGFR between 45 and 60 ml/min/1.73 m2. This information was gathered from a

cohort analysis of a national registry. Despite having a less noticeable effect in stage IV chronic renal disease, biguanide medication is beneficial and reduces the likelihood of adverse drug reactions over a 4-year period of time.

#### 4) Hepatic failure and cirrhosis :

The FDA has issued another warning regarding impaired hepatic function. There is a wide range of liver pathology included in this phrase, thus metformin treatment needs to be customised. Metformin prevented the development of encephalopathy in a retrospective study including cirrhosis patients. Similarly, biguanide medication was continued following a diagnosis of cirrhosis and was linked to better survival in another retrospective analysis. During a 5-year follow-up, the risk of hepatocellular carcinoma was decreased in individuals with cirrhosis secondary to hepatitis C virus infection[56].

#### 5) Inadequate respiration :

The FDA and EMA advise care because individuals with altered blood gas exchange, such as those with asthma, restrictive pulmonary diseases, and chronic obstructive pulmonary disease (COPD), are more likely to experience lactic acidosis. After a COPD exacerbation, metformin was employed in a randomised clinical trial at a rapidly increased dose; however, the glycaemic profile did not improve. This could be the case because there were no incidences of lactic acidosis and the intervention and placebo groups' blood lactate levels were comparable, and because the mean in-hospital glucose was measured and it typically takes metformin 1-2 weeks to reach its maximal hypoglycemic potential[57].

## Special Population :

- **Children:**

  Research has demonstrated that metformin is safe for obese people as young as 7 years old, with no negative side effects. It is now recommended for children over the age of 10[58].

- **Pregnancy:**

Based on the limited information available, metformin does not appear to raise the risk of miscarriage or congenital defects. Meta-analyses of post-marketing research reveal no appreciable effects on the health of mothers or foetuses associated with its use. On the other hand, inadequate glycaemic control may lead to an incorrect correlation between metformin and the increased risk of stillbirth, congenital impairments, and macrosomia[59].

- **Lactation:**

A negligible concentration of metformin is found in human milk. There has been no description of the possible negative impact on the kid or milk production.

- **Elderly:**

Metformin's pharmacokinetics and pharmacodynamics in older persons (65–85 years old) and younger controls were compared in a study, and the results showed that both groups' effects on glucose reduction were comparable. Nonetheless, the elderly population had exposure to and concentrations of metformin roughly twice as high. Because of their lowered eGFR, people over 85 are generally not advised to use metformin[60].

## Conclusion :

In conclusion, polycystic ovarian syndrome is a complicated condition for which, depending on the patient's motivation for seeking treatment, several treatment modalities are needed. It might be challenging to diagnose PCOS in menopausal women and teens. While postmenopausal women do not have a uniform phenotype, hyperandrogenism is a key component of the presentation in adolescence. Other androgen-excess illnesses, mental disorders, obstructive sleep apnea, diabetes, cardiovascular disease, and endometrial cancer risk factors should be ruled out when evaluating women with PCOS. The first-line treatment for irregular menstruation and hirsutism/acne in PCOS is hormonal contraception.Metformin has little to no value in treating hirsutism, acne, or infertility, although it is helpful for metabolic/glycemic disorders and for reducing irregular menstruation. Teens with PCOS can be treated with metformin and hormonal contraception.Although it's unclear if losing weight will improve PCOS in and of itself, patients who are overweight or obese can benefit from lifestyle changes for other reasons.Since metformin is not metabolized or eliminated through urine, the majority of potential medication interactions arise from the inhibition of OCTs and MATEs.As metformin plasma concentrations increase, so does the risk

of Metformin Associated Lactic Acidosis (MALA). Patients experiencing severe vomiting and diarrhoea, which are early indicators of MALA, should cease taking metformin and receive immediate medical assistance. Before prescribing drugs to patients on Metformin, prescribers and pharmacists should be informed of which drugs block the OCT and MATE transporters.

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