A Review on new drugs for treatment of Polycystic Ovarian Syndrome

Mohammed J Manna [1], Murtadha S Jabur [2], Atheer S. Alsabah [3], Luma Saad Baqir [1]

1. College of Dentistry, Mustansiriyah University, Iraq; mohammedalmanna@uomustansiriyah.edu.iq.
2. College of Pharmacy, National University for Science and Technology, Iraq.
3. College of Pharmacy, Al-Bayan University, Iraq.

Abstract : Polycystic ovary syndrome(PCOS) is a most common prevalent endocrine disorder in females at reproductive period. Metabolic pathophysiology and sequelae associated with this syndrome range from insulin resistance to it is complication such as obesity, infertility , diabetes , and cardiovascular diseases . Insulin resistance plays a potential role in this pathophysiology , this makes counteract this resistance as the first –line treatment in PCOS .So various clinical trials have tried to control clinical and biochemical aspects of this disorder. Although traditional insulin sensitizing drugs such as metformin and pioglitazone and Antiandrogens have been used for treatment metabolic and clinical aspects of PCOS , however their efficacy is not significant in terms of obesity and cardiovascular risk reduction compared with more recent insulin sensitizers such as incretin mimetics (glucagon like peptide -1 agonists and Dipeptidyl peptidase- 4 inhibitors) , sodium glucose cotransporter -2 inhibitors and other miscellaneous treatment including statins , melatonin and vitamin D3.This current pharmacological advances and potential therapeutic strategies giving patients and clinicians more choices.

Keywords : polycystic ovarian syndrome , glucagon like peptide -1 agonists and Dipeptidyl peptidase 4 inhibitors , sodium glucose cotransporter -2 inhibitors , anti-androgens , ovulation inducers , statins , melatonin and vitamin D3.

مراجعة عن الادوية الجديدة لمعالجة متلازمة تكيس المبيض

محمد جبار مانع[1] , مرتضى صالح جبر[2] , اثير صباح الصباح[3] , لمى سعد باقر[1]

1. كلية طب الاسنان – الجامعة المستنصرية / بغداد – العراق
2. كلية الصيدلة – الجامعة الوطنية للعلوم والتكنولوجيا / ذي قار – العراق
3. كلية الصيدلة – جامعة البيان / بغداد - العراق

:الخلاصة

متلازمة تكيس المبيض هي احد اغلب الاضطرابات الهرمونية شيوعا بين النساء في فترة النضج. حيث ان الامراضية الايضية وما يتعلق بها من تبعات سلبية لهذه المتلازمة تشمل مقاومة الانسولين ومضاعفاتها مثل السمنة والعقم ووداء السكري والامراض القلبية الوعائية. وتلعب مقاومة الانسولين دورا مضاعفا في هذه الامراضية ممايجعل التصدي لهذه المقاومة هو الخط الاول في معالجة متلازمة تكيس المبيض. وعليه فأن عدة محاولات سريرية جربت للسيطرة على الجوانب السريرية والكيميائية الحياتية لهذا الاضطراب. وبالرغم من استخدام الادوية التقليدية المحفزة لفعالية الانسولين مثل الميتفورمين والبايوكليتازون ومضادات الاندروجين لمعالجة الجوانب السريرية والايضية لمتلازمة تكيس المبايض الا ان فعاليتها لم تكن ذات قيمة على نطاق السمنة وتقليل الخطورة القلبية الوعائية مقارنة بمحفزات فعالية الانسولين الحديثة مثل محفزات الانكرتين ومثبطات نواقل الصوديوم والكلوكوز والادوية المتفرقة الاخرى كالستاتينات والميلاتونين وفيتامين د3. حيث ان التطورات الدوائية والستراتيجيات العلاجية المتضاعفة تعطي للمرضى والاخصائيين خيارات اكثر.

3.الكلمات المفتاحية: متلازمة تكيس المبيض ,مثبطات نواقل الصوديوم والكلوكوز ,مضادات الاندروجين , الستاتينات ,الميلاتونين ,فيتامين د

Introduction

Poly cystic ovarian syndrome (PCOS) was firstly described by Stein and Leventhal in 1935 [1]. It is one of the most common and important endocrinological abnormality in female through reproductive periods [2]. With prevalence of 10-15% depending on diagnostic criteria [3]. It is the main cause of infertility and ovulatory failure in female during reproductive periods [4]. According to Rotterdam's criteria of PCOS diagnosis it should be two out of three: First, oligo- or anovulation , second , clinical or biochemical hyperandrogenism, third, ultrasonographic polycystic ovary [5]. On the other hand, there is a great risk of metabolic disorders related to PCOS including hyperlipidemia , obesity , insulin resistance , diabetes , hepatic and cardiovascular diseases and even endometrial carcinoma [6 ,7,8 ,9].

There are a lot of theories that have been implicated to explain the pathophysiology of PCOS ; all these theories focus on increased estrogen levels with subsequent hyperandrogenism that can causes hirsutism , acne , menstrual irregularities and infertility [10]. Data also suggest that insulin resistance exaggerates the effects of luteinizing hormone (LH) on ovarian theca cells that induces androgen release [11]. On the other hand , studies showed that hypersecretion of gonadotropin releasing hormone (GnRH) from hypothalamus can generate excess LH with subsequent hyperandrogenism of ovary that in turn produces more androgens [10]. Another explanation for PCOS is related to that higher levels of insulin in blood (hyperinsulinemia) that will subsided secretion of sex hormone binding globulin (SHBG) from liver ; this decline in level of SHBG will increases free testosterone resulting in hyperandrogenism [12]. The most important complication in female with PCOS are fertility , menstrual irregularities and dermatological related diseases [13]. There here been different reviews in the past validates drug treatment on PCOS ; however almost of these reviews investigates drug effect on biological markers rather than clinical features that these results may be conflicting.

Pharmacological interventions

Treatment of female patient with PCOS is based on the identification and management of clinical features. These features could be androgen related features such as hirsutism , menstrual irregularities , alopecia androgenitca , and anovulation. In addition , feature may be related to metabolic insulin resistance such as obesity, Acanthosis nigricans and other features. Furthermore , evaluation the effect of these medication on biochemical parameters.

Oral contraceptive

Although traditional combined oral contraceptive (OCPs) can help to regulate menstrual cycle , however , they may aggravate insulin resistance , metabolic and coagulation risk , in addition to OCPs doesn't improve features of hyperandrogenism [14]. On the other hand , the choice of OCPs in female patient with PCOS is very mandatory since most of progestins based contraceptive possess androgenic effects [10]. An essential consideration for the progestin component is the potency of androgencity of the progestin [15]. Furthermore , OCPs are associated with metabolic detrimental effect through worsening the triglyceride and glucose hemostasis [16] .

Interestingly , cyproterone acetate is relatively new drug combined with ethinylestradiol has been evaluated in clinical studies for control features of hyperandrogenism such as hirsutism , acne , seborrhea , and alopecia and other conditions related to hyperandrogenism in PCOS [17]. In addition this combination may increases fertility and improve pregnancy outcome [16]. Moreover , cyproterone acetate based OCPs also improves biochemical hyperandrogenism and reduces long term risks of PCOS complications such as metabolic potentials and endometrial carcinoma [18,19]. Furthermore , Sanjeewani Fonseka *etal* study at 2020 showed that cyproterone acetate base OCPs treatment produced significant reduction in hair density and it can be considered an effective medication for treatment PCOS [20].Unfortunately this combination is associated with increased risk of venous thromboembolism as compared with non-user females [21, 22]. However , newer OCPs that have less potential androgencity such as desogestrel , norethindrone and norgestimate ; these agents and the newest OCPs that contain a combination of dropirenone (non-androgenic progestin) and ethinylestradiol are ideal contraceptive for female with PCOS [10]. On the other hand , the newest OCPs have the ability to reduce hyperandrogenic features in PCOS patients in addition to it is contraceptive effect [23]. Also this combination have negative effect on glucose and lipid metabolisms [16]. Surprising that dropirenone /ethinylestradiol increases risk of venous thromboembolism just risk of PCOS itself [24].

Anti –androgens

Antiandrogens (spironolactone ,flutamide , finasteride and cyproterone) are usually prescribed for treatment of hyperandrogenism features through their systemic decreasing effect of androgens levels [16]. These medications are effectively used for treatment PCOS patients because their ability to reduce hirsutism , hair loss and other androgen related conditions [25]. Elenis E *et al* study at 2021 , showed that early initiation of Anti-androgens therapy could prevent infertility and promote conception in PCOS female [26].

Spironolactone as anti-androgen acts primarily as androgen antagonist [27].It is effective treatment for PCOS , however it may be associated with menstrual irregularities and

feminization of male fetus in pregnant patients , so that spironolactone is mostly use in combination with OCPs [16].

Flutamide is a nonsteroidal anti-androgens , it is lack progestinic effect is very novel drug for treatment PCOS associate with hirsutism [28].However , it is associated with increased risk of hepatotoxicity [16].

Finasteride is a 5 –alpha reductase inhibitor that inhibits conversion of testosterone into dihydrotestosterone [29]. Diri H *et al* study at 2017, showed that Finasteride can reduce both hair loss and hirsutism scores and also can decrease feature of hyperandrogenism in POCS [30]. Moreover , finasteride significantly reduces insulin resistance parameters including Body Mass Index (BMI) , HOMA –IR of both insulin and glucose [30] . In addition , using finasteride in combination with spironolactone can lead to decrease hirsutism score as compared with spironolactone alone [31].Furthermore , addition of finasteride to cyproterone acetate /ethinylestradiol result in significant reduction in fasting glucose [32]. H. Diri *et al* study at 2017, has also showed that addition of Finasteride to metformin resulting in synergistic effect through reducing both insulin resistance and hyperandrogenism [30]. However , on the other hand , Rui Oliveira-Soares *et al* study showed that finasteride treatment has been associated with increased of incidence of menstrual cycle irregularities in patient with PCOS [33].

Cyproterone acetate is a progestin with anti-androgencity properties that act by inhibiting the binding of testosterone to its receptors [10]. Chunjing Cao *et al* study at 2021 , showed that cyproterone can effectively improve the symptoms of secretion of sex hormone , blood glucose level, and lipid disorder in patients with PCOS [34].

Insulin sensitizers

Insulin resistance and hyperinsulinemia are widely known to contribute to the high levels of androgens in PCOS[35].Insulin sensitizers such as metformin , thiazolidinedione , Glucagon like peptide -1 (GLP -1) agonist , Dipeptidyl peptidase 4 (DPP-4) inhibitors and sodium glucose co –transporter- 2 (SGLT2) inhibitors have been investigated in treatment of PCOS through decreasing insulin resistance [36, 37 , 38 ,39 , 40].

Metformin

Metformin is a biguanide compound acts through inhibition production of hepatic glucose , decreasing intestinal glucose absorption and also increasing insulin sensitivity in skeletal muscles and adipose tissues [10]. A recent studies showed that metformin improve fertility , pregnancy , and increased ovulation outcome in female with PCOS as compared with placebo group [41]. Studies also showed that metformin can improve clinical pregnancy outcome and decrease risk of ovary hyper stimulation syndrome (OHSS) in female with PCOS subjected to in

vitro fertilization (IVF) [42]. On the other hand , metformin associated with decrease weight in patients with PCOS [43]. However , metformin treatment is associated with a lot of side effects including gastrointestinal , peripheral neuropathy , vitamin B12 deficiency , Megaloplastic anemia [44].

Thiazolidinedione

Pioglitazone is a thiazolidinedione drug acts through activation of peroxisome proliferator-activated receptors γ (PPAR- γ) [2]. It acts by modulation of peripheral glucose uptake , adipogenesis and also regulation of insulin sensitivity [45].Also pioglitazone have beneficial effects on hyperlipidemia and potential to improve cardiovascular risk [46] . Rana *et al* study at 2020 , showed that pioglitazone treatment for 3 consecutive cycle produce 44% success in ovulation and 20% improve in pregnancy rate [37]. On the other hand , Yifeng Xu *et al study* at 2017, showed that pioglitazone improve menstrual cycle and also induce ovulation in PCOS female better than metformin in long term use [47].Furthermore , Rana *et al* study at 2021 ,showed that pioglitazone improve both plasma glucose levels and insulin resistance in addition to decrease LH in obese PCOS female [48] .However , pioglitazone is associated with many side effect such as pedal edema , increased weight , osteoporosis and hemolytic anemia [46].

Newer insulin sensitizer

Glucagon like peptide -1 agonists

Glucagon like peptide -1 (GLP-1) agonists are group of antidiabetic medications that elicit pharmacological effect similar to incretins which are GIT hormone that have the ability to modulate insulin release in response to meals [49]. Glucagon like peptide -1 (GLP-1) agonists are class of antidiabetic agents that have similar effects of incretins analogue [50] Two GLP-1 agonists exenatide and liraglutide have been evaluated in treatment of PCOS . Krzysztof *et al* study at 2022 , showed that Liraglutide .can be used for decrease insulin resistance , metabolic dysregulation with subsequent CVD risk in female with PCOS [51].Moreover, this group of medications has the ability to improve metabolic functions and ovulatory profiles [51]. On the other hand , Georgios S *et al* study at 2020 , showed that liraglutide significantly decrease body weight , BMI , and abdominal circumference and also this drug has the ability to reduce serum testosterone and improve SHBG in obese patients females with PCOS [52].Similarly Mojca *et al* study at 2022 , showed that liraglutide was superior on metformin in reducing body weight and weight circumference [53].Moreover , study by Nylander M *et al* at 2017 , showed that liraglutide has the ability to decrease body weight , serum androgens and improve fertility

and ovulation in PCOS female [54]. Furthermore , Han y *et al* study at 2019 , showed that liraglutide is more effective than metformin in weight reduction and improvement insulin sensitivity with less GIT side effect [55]. On the other hand , Rui *et al* at 2021 study showed that exenatide is superior to metformin in reduce body weight , BMI , waist circumference and also improve glucose and insulin level in female patient with PCOS [40].

Dipeptidyl peptidase 4 (DPP-4) inhibitors

Are new class of antidiabetic medications that may aid to control blood sugar by increasing the concentration incretin that increases insulin action ,so that these agents may have new tendency to be used in PCOS[56]. There are at least three DDP-4 inhibitors ; sitagliptin , linagliptin , and valdigliptin have been investigated in treatment of PCOS , these agents have the ability to improve function of Beta cells of pancreas and also improve glucose tolerance [57]. Simona F *et al* at 2018, showed in study that sitagliptin was improved both beta cells function and HOMA test outcome [58]. On the other hand , Sura S *et al* study at 2019 -2020 , found that DDP-4 inhibitors can help PCOS patients to decreasing insulin resistance , HBA1c , and androgen levels [59].Moreover , Mohammed *et al* at 2020 ,study showed that combination DPP-4 inhibitors and metformin was superior to monotherapy for control glucose tolerance and insulin resistance and moreover body weight and androgen index outcomes [38].Furthermore , Tao et al at 2018 showed in their study that combination of metformin and DDP-4 inhibitors was effective in weight reduction and improvement of lipid profile and inhibition of inflammatory mediators in polycystic ovary [60].

Sodium glucose cotransporter -2 inhibitors

Although traditional insulin sensitizers such as metformin and thiazolidinedione can improve metabolic function and insulin actions however , there is no dedicated study on metformin confirms its activity on weight reduction superior to placebo [61].On the other hand , although incretins primarily GLP-1 agonists have the potential role in overcome metabolic dysfunction in PCOS ; however their use was limited due to there is no oral dosage form available [62]. Also DDP -4 inhibitors have been limited use since they lack cardioprotective protection [62]. Therefore , there is still demand for new effective medications offering solutions against this challenges and be more effective and less side effect .

Sodium glucose cotransporter -2 (SGLT-2) inhibitors are a class of antidiabetic drugs that have unique mechanism through decreasing blood glucose levels by glycosuria in addition to its natriursis effect, so these agents cause decrease renal glucose reabsorption in renal proximal tubules [39]. There are four drugs of SGLT-2 inhibitors including dapagliflozin , empagliflozin , dapagliflozin and licogliflozin have been evaluated in PCOS .

Studies showed that SGLT-2 inhibitors have document cardioprotective effect which is mandatory for increased risk of cardiac disorders in PCOS [63]. On the other hand , study by Javed Z *et al* at 2019, on 19 female with PCOS found that empagliflozin reduce body weight , BMI , WHR , fat and metabolic rate mass compared to metformin , however it has non-significant effect on androgen and other biochemical hormones [64].However , newest SGLT-2 inhibitor licogliflozin have been shown to reduce testosterone precursors androstenedione and Dehydroepiandrosterone (DHEA) [65].Moreover , Tan S *et al* at 2021, study showed that licogliflozin decreases hyperinsulinemia and hyperandrogenism in female with PCOS [66]. Moreover , Verma S, McMurray J at 2018 , found that these group of drugs have the ability to improve metabolic function in patients with diabetes including lipid profile and serum uric acid which are in value for female with polycystic ovary [67]. Also studies suggests that SGLT-2 inhibitors have potential role in preserving function of beta cells of pancreas through promoting glucose secretion and reducing insulin secretion indirectly [68].

Ovulation inducers

Induction of ovulation is the cornerstone for treatment female with PCOS associated with anovulation and fertility [69].Clomiphene citrate is a selective estrogen receptor modulator act on hypothalamus antagonistic effect on estrogen receptors level to gonadotropin release [70].

Tamoxifen is another estrogen receptor modulator with less adverse effect profile and comparable outcomes to clomiphene citrate [71]. On the other hand , letrozole has been used for induction of ovulation by inhibiting conversion of androgen into estrogen [72].Studies showed that all these drugs (clomiphene , tamoxifen , and letrozole) are associated with comparable efficacies on ovulation , endometrial thickness and fertility outcome ;However , this study showed that letrozole has highest pregnancy rate is comparable with clomiphene and tamoxifen , although this difference is not significant [69]. On the other hand Sarah and Suhair at 2019 study showed that letrozole in PCOS patients result in significant therapeutic outcome than clomiphene citrate in the induction of ovulation , however letrozole was associated with higher incidence of pregnancy rate than clomiphene citrate [73]. Furthermore Akihisa T *et al* at 2018 , showed in study that intermittent use of clomiphene citrate was more effective in about 80% compared with 54% in traditional use of clomiphene in PCOS [74].

Miscellaneous emerging medications in PCOS

Statins

Statins are a 3 –hydroxy3-methyl glutamate co enzyme A (HMG –CoA) reductase inhibitors that considered first line treatment for hyperlipidemia [75]. Statins recently considered as potential drugs that can improve the metabolic dysfunction and reproductive function in female with PCOS [76]. Seyam E *et al* at 2018 , study showed that statins treatment

in patients with PCOS resulting in significant reduction in androgens including testosterone and DEHEA [77]. Moreover , Yang *et al* study at 2019, yield similar data [78]. Furthermore , study by Jianguo *et al* at 2021 , showed that statins therapy can reduce androgen levels and also improve dermatological manifestations of hyperandrogenism in polycystic female [79].

Angiotensin converting enzyme inhibitors (ACE inhibitor)

Rennin angiotensin system (RAA) plays an essential role in reproductive female including oocyte maturization , ovulation , in addition to corpus luteum formation ad steroidogenesis [80]. Furthermore , elevated levels of Ag II are suspected to be involved in the pathophysiology of oxidative stress , insulin resistance , obesity , ad other clinical and biochemical features of PCOS[81] . Ramaglingam *et al* study at 2017 , showed that patients with insulin resistance have high levels of circulating ACE and this explain partly by increased reactive oxygen species in those patients [81]. On the other hand, lone et al study at 2020 , showed there is a polymorphism in ACE gene associated with increased risk of PCOS [82]. Nevertheless , studies showed that lisinopril can modify PCOS , possibly by inhibition of systemic and ovarian production of plasminogen activator inhibitor-1 (PAI-1) [83]. Fatemeh Yari *et al* study at 2017 , showed that using of captopril in very low dose in PCOS patients having DD genotype is potential treatment [84].

Vitamin D3

Recent clinical researches have shown that vitamin D3 deficiency is common parameter in patients with PCOS and that deficiency may be associated with endocrine and metabolic dysfunction in those patients [85]. Moreover , it has been demonstrated that vitamin D3 deficiency is higher incidence in females with PCOS [86].Chen –YM *et al* study at 2020 , demonstrated that vitamin D3 supplement can be effective for control insulin resistance , hyperandrogenism and lipid metabolism in patients with PCOS [87]. \

Melatonin

Melatonin is the primary hormone that is secreted by the pineal gland , act mainly to regulate circadian rhythms, reproductive function, and the sleep cycle [88]. Spinedi E *et al* study at 2018 , showed that high levels of melatonin is essential for folliculogenesis and ovulation, on the other hand, reduced follicular melatonin levels may be responsible for ovulatory dysfunction PCOS [89] . It had also been suggested that melatonin has an anti-androgenic effect by decreasing of testosterone production [90]. Also, melatonin has beneficial effects on metabolic parameters, including blood glucose, lipid profile , and insulin resistance [91]. Shabani A, *et al* study at 2019 , showed that melatonin treatment for three weeks in PCOS females had beneficial effects on insulin sensitivity , homeostasis model of assessment-insulin resistance (HOMA-IR), total lipid profile including - low-density lipoprotein (LDL) levels

[92].Moreover , it has been approved that melatonin concentration in female with PCOS can reflect the link with serum LH/FSH ratio , whereas higher melatonin level is associated with reduced LH/FSH ratio [93]. Tagliaferri V *et al* study at 2018, showed that six months treatment with melatonin for a 40 females patients with PCOS improves hyperandrogenism and menstrual cycle irregularities [94].

Conclusions

Polycystic ovarian syndrome is a common disorders of endocrine system in female of reproductive period . Different risk factors have been evaluated in PCOS , including obesity , insulin resistance , hyperlipidemia . insulin resistance is mandatory factor that play crucial role the pathophysiology of this disorder. Different studies suggest the use of newer medication for treatment metabolic and biochemical changes associated with PCOS.

In this review almost all studies that use hormonal contraceptive were associated with improve quality of life and premature development of PCOS- related complications , in addition to their activity for regulation of menstrual cycle . However , traditional contraceptives are associated with androgenic profile that may not counteract hyperandrogenism –related PCOS. So that newer contraceptive were emerged such as combination of cyproterone acetate ethinylestradiol that can abolish features of hyperandrogenism such as hirsutism , acne , seborrhea , and alopecia and other conditions related to hyperandrogenism in PCOS . In addition this combination may increases fertility and improve pregnancy outcome .However , Unfortunately this combination is associated with increased risk of venous thromboembolism. Newer OCPs that have less potential androgencity such as desogestrel , norethindrone and norgestimate ; these agents and the newest OCPs that contain a combination of dropirenone (non-androgenic progestin) and ethinylestradiol are ideal contraceptive for female with PCOS. On the other hand , this combinations have negative effect on glucose and lipid metabolisms .Surprising that dropirenone /ethinylestradiol increases risk of venous thromboembolism just risk of PCOS itself.

Antiandrogens (spironolactone ,flutamide , finasteride and cyproterone) are effectively used for treatment PCOS patients because their ability to reduce hirsutism , hair loss and other androgen related conditions .Spironolactone however it may be associated with menstrual irregularities and feminization of male fetus in pregnant patients , so that spironolactone is mostly use in combination with OCPs . On the other hand , flutamide is associated with increased risk of hepatotoxicity .Finasteride can reduce both hair loss and hirsutism scores and also can decrease feature of hyperandrogenism in POCS . In addition , using finasteride in combination with spironolactone can lead to decrease hirsutism score as compared with

spironolactone alone . However , finasteride treatment has been associated with increased of incidence of menstrual cycle irregularities .Nevertheless cyproterone acetate can effectively improve the symptoms of secretion of sex hormone , blood glucose level, and lipid disorder in patients with PCOS .

Studies showed that traditional insulin sensitizer such as metformin and pioglitazone have the ability to improve ovulation and pregnancy rate and also can reduce incidence of ovarian hyperstimulation syndrome . However , these agents are associated with a lot of side effects as well as their efficacy is not significant in terms of obesity and cardiovascular risk reduction compared with more recent insulin sensitizers.Reviewed studies also showed that newer GLP-1 agonist such as liraglutide and exenatide are associated with more significant reduce body weight , insulin resistance , and increase of ovulation rate as compared with metformin ; however these agents are only available in parenteral route that not preferred by part of patients. Other studies that conducted in evaluation of DDP 4 inhibitors such as sitagliptin were significant in reduction of IR , body weight , androgen levels and pro-inflammatory cytokines as compared with metformin ; however these agents lack cardioprotective effects related to PCOS. Although traditional insulin sensitizers such as metformin and thiazolidinedione can improve metabolic function and insulin actions however , there is no dedicated study on metformin confirms its activity on weight reduction superior to placebo [61].On the other hand , although incretins primarily GLP-1 agonists have the potential role in overcome metabolic dysfunction in PCOS ; however their use was limited due to there is no oral dosage form available [62]. Also DDP -4 inhibitors have been limited use since they lack cardioprotective protection [62]. Therefore , there is still demand for new effective medications offering solutions against this challenges and be more effective and less side effect .

Studies showed that SGLT-2 inhibitors such as empagliflozin have document cardioprotective and also have the ability to reduce body weight , BMI , WHR , fat and metabolic rate mass compared to metformin , however it has non-significant effect on androgen and other biochemical hormones .Nevertheless newest SGLT-2 inhibitor licogliflozin have been shown to reduce testosterone precursors androstenedione and Dehydroepiandrosterone (DHEA) .

Induction of ovulation is the cornerstone for treatment female with PCOS associated with anovulation and fertility . Studies showed that all these drugs (clomiphene , tamoxifen , and letrozole) are associated with comparable efficacies on ovulation , endometrial thickness and fertility outcome ;However , studies showed that letrozole has highest pregnancy rate is comparable with clomiphene and tamoxifen .some studies showed that clomiphene citrate is more effective when given intermittently. Although different medications has been used in management of PCOS there is still resistant cases that may get beneficial outcome by using

other new miscellaneous agent such as statins , melatonin and vitamin D 3 ; these agents showed some benefit by improve both biochemical and clinical manifestations of PCOS that at least can be used as adjuvants in management of PCOS in selected patients.

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