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Recent advances in emerging PCOS therapies

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Abstract

Polycystic ovary syndrome is a prevalent endocrinopathy involving androgen excess, and anovulatory infertility. The disorder is also associated with many comorbidities such as obesity and hyperinsulinemia, and an increased risk of cardiovascular complications. Reproductive, endocrine, and metabolic symptoms are highly variable, with heterogenous phenotypes adding complexity to clinical management of symptoms. This review highlights recent findings regarding emerging therapies for treating polycystic ovary syndrome, including i) pharmacological agents to target androgen excess, ii) modulation of kisspeptin signalling to target central neuroendocrine dysregulation, and iii) novel insulin sensitisers to combat peripheral metabolic dysfunction.

Addresses

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Introduction

Polycystic ovary syndrome (PCOS) is a complex endocrine disorder that is a leading cause of infertility in reproductive aged women [1,2], and with an increasing incidence globally [3]. The most widely accepted guidelines for a clinical diagnosis of PCOS requires the presence of a minimum of two out of three principal features: physical or biochemical signs of androgen excess, ovulatory disfunction, and polycystic ovarian morphology [4]. However, a range of comorbidities are also associated with the disorder, including obesity, insulin resistance, type 2 diabetes, and cardiovascular conditions [5–8], contributing to heterogenous phenotypes. Currently, there is no cure for PCOS, with therapies centred on the management of symptoms, and/or assisted fertility. This review will provide a brief summary of PCOS pathophysiology, and current standard treatments for PCOS, followed by an overview of recent findings regarding novel and emerging therapeutic strategies in PCOS management. In particular, focussing on pharmacological targeting of androgen excess, central neuroendocrine dysfunction, and peripheral metabolic pathophysiology.

Pathophysiology of PCOS

Primary neuroendocrine dysfunction may play a role in the etiology of some forms of PCOS [9]. Neuroendocrine regulation of fertility is controlled by the gonadotropin releasing hormone (GnRH) neurons. The release of GnRH peptide in a pulsatile pattern stimulates secretion of the gonadotropins luteinising hormone (LH), and follicle stimulation hormone (FSH) from the anterior pituitary. LH and FSH act in synergy at the ovary to drive folliculogenesis, steroidogenesis, and ovulation in normal menstrual cycle physiology. With PCOS, however, there is an increased pulse frequency of GnRH, and GnRH secretion, which biases pituitary secretion of LH over FSH. This disrupted gonadotropin profile impairs normal maturation of the ovarian follicle and ovulation, leading to thecal cell hyperplasia and increased ovarian androgen production [10]. In turn, the hyperandrogenic ovarian state disrupts gonadal steroid hormone negative feedback acting back on the hypothalamus, with ovarian oestradiol and progesterone less effective to lower LH pulse frequency in patients with PCOS, and further exacerbating elevated GnRH-mediated LH release. Insulin resistance and hyperinsulinemia are also common in PCOS, independent of BMI [5], and deficits in insulin action can exacerbate ovarian androgen production. Together, these pathologic processes create a self-perpetuating loop of impaired HPG axis function in PCOS.

Current recommended treatments for PCOS

Current PCOS therapies are symptom-driven, and also depend on whether fertility treatment is being sought. For women with PCOS that are not seeking assistance with fertility, combined oral contraceptive pills (OCs) comprised of oestrogens and progestins are commonly prescribed to treat menstrual irregularities and physical manifestations of hyperandrogenism (hirsutism, acne, and androgen-related alopecia) [4]. OCs have several anti-androgenic effects. Oestrogens and progestins reduce gonadotrophin release from the pituitary, and reduce androgen production downstream in the ovaries,

ultimately decreasing levels and bioavailability of testosterone. Where cosmetic procedures and OCs are suboptimal for treating hyperandrogenism, additional anti-androgen medications may be used. These either block the androgen receptor (AR) or modulate the androgen biosynthesis pathway (e.g. spironolactone, finasteride). For metabolic features of PCOS, weight loss and dietary techniques alone or in combination with oral insulin sensitisers (e.g. metformin) are recommended [4].

For women with PCOS seeking fertility treatment, an alternate approach is necessary, as OCs prevent ovulation, and anti-androgens are detrimental for a male fetus. Instead, weight loss techniques and ovulation induction agents are typically advised. Letrozole is a first-line pharmacological intervention to induce ovulation. Letrozole prevents the aromatase-induced conversion of androgens to oestrogens and this, in turn, increases the secretion of FSH, presumably due to reduced negative feedback, to stimulate follicular maturation [11]. A selective oestrogen receptor modulator clomiphene citrate is also used for ovulation induction, often in combination with metformin, but may increase endometrial cancer risk [12]. Women with PCOS undergoing fertility treatment with either letrozole or clomiphene citrate are at an increased risk of ovarian hyperstimulation syndrome (OHSS), a serious side effect that impacts the ovarian vasculature and which, in some cases, can require hospitalisation.

Novel and emerging strategies for treatment of PCOS

While current treatment strategies for the endocrine, metabolic, and reproductive features of PCOS are effective, there is still a need for improvement. First, many current therapies are associated with adverse side-effects, for example, weight gain associated with the use of OCs, gastrointestinal issues linked to metformin, and increased risk for OHSS in fertility treatments. Second, hormone treatments are not always appropriate, for instance in individuals where oestrogen-therapy is contraindicated, such as breast cancer, venous thromboembolism, and stroke. Fortunately, there are a number of novel treatments for PCOS management that are showing potential in preclinical animal models, and in early clinical studies (summarised in Table 1).

New treatments targeting androgen excess

Hyperandrogenism contributes to the central pathogenesis of PCOS and underlies many of the troubling overt symptoms for PCOS patients. Consistent with this, animal models that recapitulate the metabolic and reproductive features of PCOS are typically generated by prenatal or peripubertal exposure to excess androgens [13]. Therapeutic reduction of androgens, or AR blockade, are therefore important strategies in PCOS treatment. Early timing of anti-androgen treatment might also be critical for improving fertility outcomes. A retrospective population-based study in Sweden found women with PCOS who had early intervention with anti-androgen treatment (before 18 years) had an improved fertility rate compared to those with later interventions [14]. Further, studies in mice indicate that excess androgens may have long-term impacts on follicle and oocyte quality that can continue to impair fertility, even after restoration of hyperandrogenism [15].

Direct AR antagonists can cross-react with GABA-A receptors in the brain, increasing the risk of seizures [16]. To circumvent this risk, peripherally selective second generation AR antagonists have limited capacity to cross the blood brain barrier, and could be a viable tool for PCOS therapy. Indeed, a clinical trial found peripherally selective AR antagonist bicalutamide (Casodex) in combination with OCs was more effective in treating hirsutism in women with PCOS than treatment with OCs and placebo [17]. Darolutamide (ODM-201, Nubeqa) is another AR antagonist with low blood-brain barrier penetrance [18], which has recently gained approval in several countries for treatment of some prostate cancers, however no trials testing darolutamide as a treatment in PCOS are currently underway. While peripheral AR antagonists may be beneficial for cosmetic hyperandrogenism-related PCOS symptoms in women, use of direct AR blockers is unfortunately not viable for patients seeking fertility treatment, due to fetal risks. Further, animal models indicate the central reproductive and metabolic deficits of PCOS arise from androgen actions in the brain, and not the periphery [19].

While the ovaries are likely the predominant source of excess androgens in PCOS, adrenal androgens may also be important. For example, studies have shown that up to 50% of women with PCOS have elevated dehydroepiandrosterone sulphate (DHEAS) - a marker of adrenal androgen production [20]. Also, women with congenital adrenal hyperplasia display many PCOS-like features, including polycystic appearance of the ovary [21]. One of the functions of adrenal androgens is to mediate the stress response via the hypothalamic-pituitary-adrenal (HPA) axis. In response to stress, hypothalamic corticotropin-releasing hormone (CRH) activates the CRH receptor CRHR1, and adrenocorticotropic hormone release from the pituitary, which in turn stimulates adrenal release of cortisol and androgens. It is unclear if HPA hyperactivity, or adrenal androgen production, contributes to hyperandrogenism in PCOS. However, a rodent study found disrupted hypothalamic *Crh* and *Crhr1* expression in a prenatally androgenised mouse model of PCOS [22]. Further, a recent study reported adrenal androgen production in adolescents with PCOS correlated with hirsutism severity [23]. Interestingly, a modulator of CRH signalling is currently being explored

Table 1

Novel and emerging strategies for treatment of PCOS.

Type	Class	Name	Therapeutic target	Study type	Outcome	Ref.
Androgen modulator	AR antagonist	Bicalutamide	Hyperandrogenism	Human, phase 3 double blind RCT	Improved reduction of hirsutism when combined with OC	[17]
	CRHR1 antagonist	Tildacerfont	Hyperandrogenism	Human, phase 2, RCT	Recruiting in progress ClinicalTrials.gov Identifier: NCT05370521	
	Sex steroid transporter protein	SHBG	Hyperandrogenism	Human GWAS	Higher SHBG levels may protect from PCOS comorbidities	[27]
			Hyperandrogenism, comorbidities	Human genetic association studies	Potential causal link between low SHBG and PCOS	[26]
Incretin/incretin modulator	GLP-1 receptor agonists	Semaglutide	IR, Hyperandrogenism, obesity	Human, meta-analysis of published RCT	Reduced BMI, improved HOMA-IR compared with metformin, side-effects of headache and nausea	[55]
		Exenatide	IR, obesity	Human, Randomised single blind comparative study	Improved HOMA-IR, insulin sensitivity, blood glucose either alone or in combination with SGLT2 inhibitor	[50]
		Liraglutide	Hyperandrogenism, obesity	Human, RCT	Reduced free androgens and body weight in comparison to placebo	[53]
	DPP-4 inhibitors	Sitagliptin	Hyperandrogenism	Rat, DHEA model of PCOS	Reduced T	[58]
		Sitagliptin & metformin	IR	Rat, HCG & Insulin model of PCOS with IR	Improved HOMA-IR	[59]
		Sitagliptin	IR, obesity	Human, double blind crossover study	Improved blood glucose in GTT, decreased visceral fat	[60]
Insulin sensitiser	SGLT 2 inhibitors	Empagliflozin	IR	Human Phase 4 randomised open-label trial	Weight loss, no change in HOMA-IR	[49]
		Canagliflozin	IR	Human, prospective randomised open-label trial	Weight loss, improved HOMA-IR, improved menstrual cyclicity, reduced uric acid, reduced DHEA-S.	[48]
	SGLT1/2 inhibitor	Licogliflozin (LIK066)	IR, hyperandrogenism	Human, RCT	Reduced hyperinsulinaemia, improved HOMA-IR, reduced hyperandrogenaemia	[51]
	Mitochondrial-derived peptide	Humanin	IR	Rat, DHEA model of PCOS Human, in vitro	Decreased body weight, serum oestradiol/DHEA,	[46]

(*continued on next page*)

Table 1. (*continued*)

Type	Class	Name	Therapeutic target	Study type	Outcome	Ref.
					& restored ovarian morphology in PCOS-like rat, improved oxidative stress in cell line	
			IR	Rat, DHEA model of PCOS	Beneficial effects on IR, Improved HOMA-IR	[45]
Neuroendocrine modulator	GnRH receptor antagonist	Cetrorelix	GnRH hyperactivity	Mouse - AMH model of PCOS	Increased LH concentration and pulsatility, restored estrous cyclicity and ovarian morphology	[29]
	Kisspeptin receptor agonist	MVT-602	GnRH hyperactivity	Human, crossover RCT & Human in vitro, Mouse in vitro,	Induced sustained LH peak in healthy women and women with PCOS, increased Kiss1R signalling in Kiss1R transfected HEK293 cells, increased GnRH neuron firing in mouse brain slices	[35]
	NK3R antagonist	Fezolinetant	GnRH hyperactivity	Human - Phase 2a, RCT	Reduced serum LH, LH:FSH, reduced T	[39]
	Kappa receptor agonist – peripherally restricted	Difelikefalin	GnRH hyperactivity	Mouse – PNA model of PCOS	Reduced LH and T, improved estrous cycling, improved ovarian morphology	[42]

Abbreviations: AMH, Anti-mullerian hormone; AR, Androgen receptor; CRHR1, Corticotropin releasing hormone receptor 1; DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone sulphate; dipeptidyl peptidase-4, DPP-4; FSH, follicle-stimulating hormone; GnRH, gonadotropin releasing hormone; GTT, Glucose tolerance test; HCG, Human Chorionic Gonadotrophin; HOMA-IR, homeostatic model assessment of insulin resistance; IR, Insulin resistance; LH, luteinising hormone; NK3R, Neurokinin 3 Receptor; PCOS, Polycystic ovary syndrome; PNA, Prenatal androgen; OC, Oral contraceptives; RCT, Randomised Controlled Trial; SHBG, Sex Hormone Binding Globulin; SGLT, Sodium glucose co-transporter; T, testosterone.

as a potential PCOS therapy. Tildacerfont is a non-steroidal, oral CRHR1 antagonist which inhibits pituitary ACTH to limit the production of adrenal androgens. A phase 2, randomised clinical trial examining the safety and efficacy of tildacerfont in women with PCOS who have elevated adrenal androgens is currently recruiting (NCT05370521), with initial outcomes expected before mid-2023.

An alternate method for targeting androgen excess is to reduce androgen bioavailability. Sex hormone-binding globulin (SHBG) is a sex hormone transporter with high affinity for testosterone, that directly modulates the clearance and bioavailability of sex steroids in the blood and target tissues. Growing evidence indicates SHBG could be a promising diagnostic biomarker for PCOS, and a potential therapeutic target. Lower SHBG levels are associated with PCOS [24], and recent genetic association studies indicate this may be a causal link [25,26]. Of interest, a recent GWAS study found women with higher SHBG to have a reduced incidence of PCOS comorbidities [27], which suggests that therapeutically increasing SBHG levels in women with PCOS could have a protective effect.

Clinical targeting of neuroendocrine dysfunction

Direct modulation of GnRH with GnRH antagonists is utilised in fertility treatments to decrease GnRH-mediated release of LH and FSH in controlled ovarian stimulation. In women with PCOS however, OSS risk is high, and GnRH antagonists often result in the production of an increased number, but decreased quality of oocytes [28]. Outside of fertility treatment, there is a lack of clinical evidence that GnRH antagonists would be of benefit for PCOS therapy. However, an investigation in a PCOS mouse model generated by prenatal exposure to anti-Mullerian hormone shows some promise. Intermittent treatment with the GnRH antagonist cetrorelix rescued reproductive and neuroendocrine PCOS-like features in this mouse model [29]. Other novel neuroendocrine PCOS treatments are aimed at reducing GnRH pulsatility by targetting upstream inputs within the GnRH neuronal network that are sensitive to oestrogen, progesterone, and androgens produced by the ovary. The best known therapeutic target to achieve this is a hypothalamic population of neurons that co-express the neuropeptides kisspeptin, neurokinin B, and dynorphin, known as 'KNDy' neurons, and which are recognised as key for GnRH pulse generation (Figure 1.) [30,31]. Kisspeptin and neurokinin B have stimulatory actions on GnRH secretion, whereas dynorphin is inhibitory. Loss of function gene mutations in KISS1R, the kisspeptin receptor, and *TAC3* or *TACR3* (encoding neurokinin B and its receptor, respectively) result in hypogonadal hypogonadism [32–34].

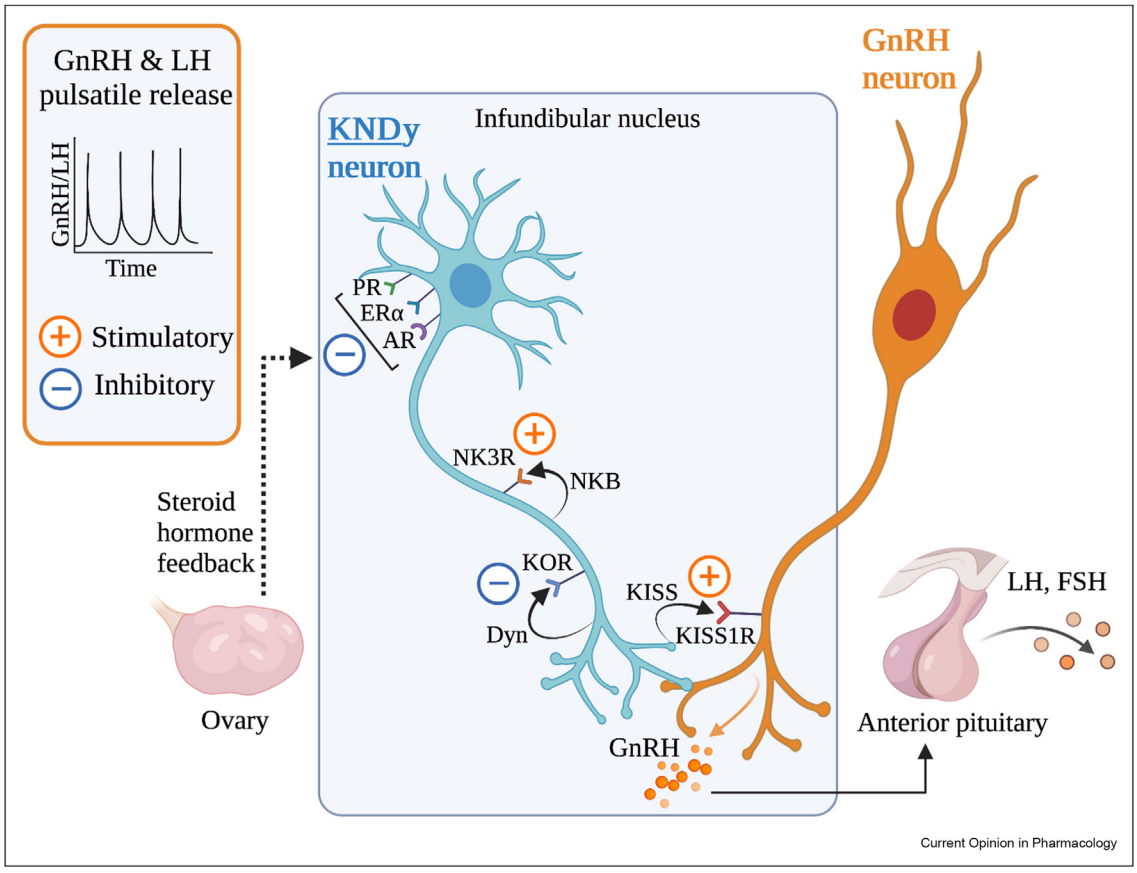
Modulation of kisspeptin

A kisspeptin receptor agonist, MVT-602, has recently been investigated as a novel therapeutic strategy for fertility treatment in PCOS. In a clinical trial, MVT-602 administration was found to produce a markedly prolonged increase of LH levels in healthy control women in comparison with native kisspeptin (KP54) (time of peak LH: 21–22 h vs. 4.7 h, respectively), and a single injection of MVT-602 also increased LH levels in women with PCOS [35]. In parallel with the clinical trial, the authors performed *in vitro* studies that similarly showed an extended duration of action of MVT-602. A Kiss1R transfected HEK-293 cell line treated with MVT-602 had increased levels of a downstream signal of kisspeptin, inositol monophosphate, in comparison to kisspeptin-54 treatment. In addition, electrophysiological recordings from GnRH neurons in mouse brain slices showed MVT-602 induced a rapid GnRH firing rate over a prolonged period in comparison to native kisspeptin. While this clinical trial consisted of a small sample size (six women with PCOS, six with HA, and nine healthy controls), the results of this pilot study show promise for the development of novel modulators of kisspeptin signalling in assisted fertility treatments.

Modulation of neurokinin B

An alternative strategy to block KNDy-mediated stimulation of GnRH secretion is modulation of neurokinin B activity via its cognate neurokinin 3 receptor (NK3R). Results from Phase 2 clinical studies demonstrate that oral administration of the NK3r antagonist MLE4901 can reduce LH pulse frequency, and serum levels of LH and testosterone in women with PCOS [36,37]. In a chronic dihydrotestosterone (DHT)-treated mouse model of PCOS, MLE4901 was found to reverse PCOS-metabolic traits including decreasing adiposity, although reproductive deficits were not ameliorated in this model [38]. Although MLE4901 has since been discontinued due to a rare hepatotoxic side effect, another NK3r antagonist fezolinetant (ESN364) developed for the treatment of vasomotor symptoms in postmenopausal women has shown promise in treating PCOS in early clinical trials. A recent Phase 2a, randomized, double-blind, placebo-controlled study found that oral administration of fezolinetant for 12 weeks significantly reduced serum LH and testosterone in women with PCOS [39]. Importantly, fezolinetant is structurally unrelated to MLE4901, and has shown no adverse hepatic effects [40]. A Phase 3 long-term safety study has also recently been completed, and although at the time of writing the results have not been published, a New Drug Application (NDA) for fezolinetant has been submitted to the U.S. Food and Drug Administration (FDA).

Figure 1



Neuroendocrine control of fertility

Modulation of dynorphin

Targeting the dynorphin receptor kappa opioid to enhance dynorphin-mediated inhibition of kisspeptin secretion is another potential avenue for restraining GnRH pulsatility in PCOS. Indeed, there is some evidence from animal models that modulating these receptors can impact LH pulsatility [41,42]. Kappa opioid receptors are expressed in the arcuate nucleus by KNDy neurons, as well as non-KNDy neurons, therefore it is unknown whether the antagonist effects on LH pulsatility are mediated directly via KNDy neurons or their afferents. However, loss of non- KNDy expressing KOR cells in the arcuate nucleus has been shown to increase LH pulse frequency in ovariectomised rats [43]. Interestingly, kappa receptor modulation may additionally exert effects on body weight, with emerging evidence implicating kappa opioid receptors in metabolism [44].

Treatments targeting insulin resistance

Hyperinsulinemia and insulin resistance is common in PCOS, both in obese and non-obese women. Further, insulin excess contributes to hyperandrogenism by exasperating ovarian androgen production, as well as reducing SHBG to increase bioavailability of testosterone. A lack of protection from cardiovascular risks by metformin, as well as adverse gastrointestinal side effects, has motivated the search for alternative insulin sensitising agents for managing insulin resistance in PCOS, including hHumanin analogues, sSodium glucose co-transporter inhibitors, and incretin mimetics.

Humanin

Humanin is a mitochondrial-derived peptide with protective effects under stress conditions in a number of cell types including neurons, leukocytes and gonadal cells. A recent study found decreased expression of humanin in ovarian follicular fluid and granulosa cells of PCOS patients with insulin resistance, but not in patients with PCOS without insulin resistance [45]. In the same study, they found supplementation of DHEA-induced PCOS-like rats with a humanin analog improved plasma fasting glucose and insulin in a dose-dependent manner [45]. Other work by this group also showed that humanin supplementation in a DHEA-induced rat model of PCOS could decrease PCOS-associated body weight gain and restore ovarian morphology [46]. The DHEA-induced rat model of PCOS has some limitations however [13], and a recent commentary highlighting this

work cautions that further studies on humanin analogs in additional animal models of PCOS are needed [47].

Sodium glucose co-transporters (SGLT1, SGLT2)

SGLT2 inhibitors are a recent class of anti-diabetic drug used in the treatment of type 2 diabetes. They primarily act to improve blood glucose by inhibiting renal glucose absorption, and increase urinary glucose excretion, but can also cause weight loss and increase insulin sensitivity, presenting a promising alternative to insulin sensitising drugs in the treatment of PCOS co-morbidities. While data are limited, recent clinical trials comparing the efficacy of SGLT2 inhibitors in overweight/obese patients with PCOS indicates substantial benefits over standard metformin treatment, with significantly reduced body weight [48,49], decreased serum DHEAS, and fewer medication-related adverse effects [48]. Similarly, women with PCOS who received 24 weeks treatment of the SGLT2 inhibitor dapagliflozin had reduced body weight, fasting glucose, and blood pressure, but also lowered serum total testosterone and free androgens, and increased SHGB levels [50].

Whereas SGLT2 regulates glucose uptake in the kidney, a different transporter type SGLT1, mediates glucose uptake in the intestine. A recent short-term (2 week) Phase 2 trial on a dual SGLT1/2 inhibitor licogliflozin (LIK066) in women with PCOS found this dual treatment significantly reduced serum insulin and androgen levels in comparison to treatment with placebo [51]. Although these early trials are limited by small sample size, and direct comparisons are difficult due to discrepancies in the controls used and differences in trial duration, results of a recent meta-analysis of SGLT2 studies support a positive association of SGLT2 inhibitors on metabolic parameters in PCOS [52]. Although not yet approved for use in PCOS, preliminary results from these clinical trials suggest that SGLT2 inhibitors show promise as a new potential therapy for PCOS.

Incretin mimetics

Incretins are hormones which are produced in the gut in response to food, stimulating glucose-dependent insulin release, and include glucose-dependent insulinotropic peptide (GIP), and glucagon-like peptide 1 (GLP-1). There is inconsistent data regarding whether incretin hormone levels are altered in PCOS, however incretin mimetics such as the GLP-1 receptor (GLP-1R) analogs have shown promise in PCOS treatment. For example, a clinical trial found the GLP-1R agonist Liraglutide reduced free androgens and body weight, and improved insulin sensitivity in comparison to placebo, in hyperandrogenic PCOS women [53]. Similarly, the GLP-1R agonist Semaglutide had improved effects over metformin on insulin resistance and weight loss in overweight and obese patients with PCOS [54,55]. In addition to effects in peripheral tissues, there is some evidence GLP-1R analogues modulate GnRH release. For example, GLP-1 neurons from the brain stem directly innervate a subset of GnRH neurons in mouse hypothalamus, and optogenetic stimulation of the GLP-1 afferents decreases the firing rate of GnRH neurons [56]. Further, a study in female rats found the proestrous LH surge is increased after intracerebroventricular or subcutaneous administration of GLP-1, and decreased by treatment with a GLP-1R analogue [57]. Interestingly, combined treatment of GLP-1R analogs with SGLT2 inhibitors may improve metabolic outcomes. For example, obese women with PCOS treated with GLP-1R agonist exenatide in combination with a SGLT2 inhibitor dapagliflozin, had significantly improved weight loss, mean blood glucose, insulin sensitivity and secretion over either treatment alone, or combined dapagliflozin/metformin treatment [50]. Despite showing promise in PCOS therapy, use of GLP-1R analogs may be limited by the fact they are administered by injection, and are associated with gastrointestinal side effects.

Incretins are rapidly inactivated by the enzyme dipeptidyl peptidase 4 (DPP4), and DPP-4 inhibitors are an anti-diabetic medicine shown to increase GLP-1 and GIP. Rodent models of PCOS show the DPP-4 inhibitor sitagliptin can improve insulin resistance, and reduce testosterone [58,59]. Clinical studies on DPP-4 inhibitors in PCOS are limited, but a recent study indicated sitagliptin could reduce visceral adiposity and improve insulin-glucose signalling in women with PCOS [60].

Conclusion

There are a number of promising new therapies for PCOS emerging, which comprise a range of pharmacological strategies to target androgen excess, central neuroendocrine dysfunction, and/or metabolic pathophysiology (see Table 1). While there are no current AR antagonists approved for the treatment of PCOS, there is growing interest in the potential of therapeutic modulation of SHBG to manage hyperandrogenism. Recent evidence from clinical studies indicates that modulators of the KNDy neuronal network that target the central neuroendocrine pathophysiology of PCOS may also be incredibly useful therapeutic tools. Similarly, humanin, SGLT2 inhibitors, and incretin mimetics, show promise in mitigating metabolic dysregulation in PCOS. These emerging PCOS therapies have the potential to improve patient outcomes in the future, beyond currently available strategies. However, further clinical investigations are needed to verify their efficacy and safety, particularly over the long term, and across PCOS phenotypes.

CRediT author statement

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

Papers of particular interest, published within the period of review, have been highlighted as:

* of special interest
** of outstanding interest

1. Bozdag G, *et al.*: **The prevalence and phenotypic features of polycystic ovary syndrome: a systematic review and meta-analysis**. *Hum Reprod* 2016, **31**:2841–2855.
2. Lizneva D, *et al.*: **Criteria, prevalence, and phenotypes of polycystic ovary syndrome**. *Fertil Steril* 2016, **106**:6–15.
3. Safiri S, *et al.*: **Prevalence, incidence and years lived with disability due to polycystic ovary syndrome in 204 countries and territories, 1990-2019**. *Hum Reprod* 2022, **37**:1919–1931.
4. Teede HJ, *et al.*: **Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome**. *Fertil Steril* 2018, **110**:364–379.
5. Cassar S, *et al.*: **Insulin resistance in polycystic ovary syndrome: a systematic review and meta-analysis of euglycaemic-hyperinsulinaemic clamp studies**. *Hum Reprod* 2016, **31**:2619–2631.
6. Lim SS, *et al.*: **Overweight, obesity and central obesity in women with polycystic ovary syndrome: a systematic review and meta-analysis**. *Hum Reprod Update* 2012, **18**:618–637.
7. Wekker V, *et al.*: **Long-term cardiometabolic disease risk in women with PCOS: a systematic review and meta-analysis**. *Hum Reprod Update* 2020, **26**:942–960.
8. Aziz M, *et al.*: **Polycystic ovary syndrome: cardiovascular risk factors according to specific phenotypes**. *Acta Obstet Gynecol Scand* 2015, **94**:1082–1089.
9. McCartney CR, *et al.*: **The role of gonadotropin-releasing hormone neurons in polycystic ovary syndrome**. *J Neuroendocrinol* 2022, **34**, e13093.
10. McCartney CR, Campbell RE: **Abnormal GnRH pulsatility in polycystic ovary syndrome: recent insights**. *Curr Opin Endocr Metab Res* 2020, **12**:78–84.
11. Elizur SE, Tulandi T: **Drugs in infertility and fetal safety**. *Fertil Steril* 2008, **89**:1595–1602.
12. Brinton LA, *et al.*: **Fertility drugs and endometrial cancer risk: results from an extended follow-up of a large infertility cohort**. *Hum Reprod* 2013, **28**:2813–2821.
13. Stener-Victorin E, *et al.*: **Animal models to understand the etiology and pathophysiology of polycystic ovary syndrome**. *Endocr Rev* 2020, **41**.
14. Elenis E, *et al.*: **Early initiation of anti-androgen treatment is associated with increased probability of spontaneous conception leading to childbirth in women with polycystic ovary syndrome: a population-based multiregistry cohort study in Sweden**. *Hum Reprod* 2021, **36**:1427–1435.
15. Bertoldo MJ, *et al.*: **A hyperandrogenic environment causes intrinsic defects that are detrimental to follicular dynamics in a PCOS mouse model**. *Endocrinology* 2019, **160**:699–715.
16. Henderson LP: **Steroid modulation of GABAA receptor-mediated transmission in the hypothalamus: effects on reproductive function**. *Neuropharmacology* 2007, **52**:1439–1453.
17. Moretti C, *et al.*: **Combined oral contraception and Bicalutamide in polycystic ovary syndrome and severe hirsutism: a double-blind randomized controlled trial**. *J Clin Endocrinol Metab* 2018, **103**:824–838.
18. Fizazi K, Smith MR, Tombal B: **Clinical development of Darolutamide: a novel androgen receptor antagonist for the treatment of prostate cancer**. *Clin Genitourin Cancer* 2018, **16**:332–340.
19. Caldwell ASL, *et al.*: **Neuroendocrine androgen action is a key extraovarian mediator in the development of polycystic ovary syndrome**. *Proc Natl Acad Sci U S A* 2017, **114**:E3334–E3343.
20. Goodarzi MO, Carmina E, Azziz R: **DHEA, DHEAS and PCOS**. *J Steroid Biochem Mol Biol* 2015, **145**:213–225.
21. Guarnotta V, *et al.*: **Clinical and hormonal characteristics in heterozygote carriers of congenital adrenal hyperplasia**. *J Steroid Biochem Mol Biol* 2020, **198**, 105554.
22. Manti M, *et al.*: **Maternal androgen excess and obesity induce sexually dimorphic anxiety-like behavior in the offspring**. *Faseb J* 2018, **32**:4158–4171.
23. Taylor AE, *et al.*: **11-Oxyandrogens in adolescents with polycystic ovary syndrome**. *J Endocr Soc* 2022, **6**:bvac037.
24. Deswal R, Yadav A, Dang AS: **Sex hormone binding globulin - an important biomarker for predicting PCOS risk: a systematic review and meta-analysis**. *Syst Biol Reprod Med* 2018, **64**:12–24.
25. Wang C, *et al.*: **Mendelian randomization analyses for PCOS: evidence, opportunities, and challenges**. *Trends Genet* 2022, **38**:468–482.
26. Zhang Y, *et al.*: **Polycystic ovary syndrome susceptibility loci inform disease etiological heterogeneity**. *J Clin Med* 2021, **10**.
27. * Ruth KS, *et al.*: **Using human genetics to understand the disease impacts of testosterone in men and women**. *Nat Med* 2020, **26**:252 [+].

This study investigates genetic determinates of high testosterone levels, and the associated disease risk. It involves a genome-wide association study (GWAS) and Mendelian randomization analysis on a dataset of >425,000 women and men from the UK Biobank study. This work demonstrates a causal effect of elevated testosterone levels on PCOS risk (OR 1.51; 95% CI 1.33–1.72 per 1 SD higher levels of bioavailable testosterone). This is an important finding as it suggests elevated testosterone is in itself causative of PCOS etiology, and not merely a consequence of ovarian dysfunction or impaired insulin signalling. A second important finding is that SHBG may a have a protective effect on comorbid disease risk in PCOS.

28. Lambalk CB, *et al.*: **GnRH antagonist versus long agonist protocols in IVF: a systematic review and meta-analysis accounting for patient type**. *Hum Reprod Update* 2017, **23**:560–579.
29. Tata B, *et al.*: **Elevated prenatal anti-Mullerian hormone reprograms the fetus and induces polycystic ovary syndrome in adulthood**. *Nat Med* 2018, **24**:834–846.
30. Navarro VM: **New insights into the control of pulsatile GnRH release: the role of Kiss1/neurokinin B neurons**. *Front Endocrinol* 2012, **3**:48.
31. Clarkson J, *et al.*: **Definition of the hypothalamic GnRH pulse generator in mice**. *Proc Natl Acad Sci U S A* 2017, **114**:E10216–E10223.
32. de Roux N, *et al.*: **Hypogonadotropic hypogonadism due to loss of function of the KiSS1-derived peptide receptor GPR54**. *Proc Natl Acad Sci U S A* 2003, **100**:10972–10976.

33. Seminara SB, *et al.*: **The GPR54 gene as a regulator of puberty**. *N Engl J Med* 2003, **349**:1614–1627.

34. Topaloglu AK, *et al.*: **TAC3 and TACR3 mutations in familial hypogonadotropic hypogonadism reveal a key role for Neurokinin B in the central control of reproduction**. *Nat Genet* 2009, **41**:354–358.

35. * Abbara A, *et al.*: **Kisspeptin receptor agonist has therapeutic potential for female reproductive disorders**. *J Clin Invest* 2020, **130**:6739–6753.
This study uses a human cell line transfected with the kisspeptin receptor, to demonstrate that a novel Kiss1R agonist, MVT-602, mediates Kiss1R-mediated signalling more potently than native Kisspeptin-54. In parallel, clinical studies are performed to demonstrate that MVT-602 elicits a more prolonged and sustained effect on LH increase than Kisspeptin54 in healthy women, and also increases LH in women with PCOS and women with hypogonadotropic hypogonadism. The prolonged actions of MVT-602 on LH levels shows promise as a fertility treatment for healthy women, as well as those with reproductive disorders.

36. George JT, *et al.*: **Neurokinin B receptor antagonism in women with polycystic ovary syndrome: a randomized, placebo-controlled trial**. *J Clin Endocrinol Metab* 2016, **101**:4313–4321.

37. Skorupskaite K, *et al.*: **Kisspeptin and neurokinin B interactions in modulating gonadotropin secretion in women with polycystic ovary syndrome**. *Hum Reprod* 2020, **35**:1421–1431.

38. Sucquart IE, *et al.*: **Neurokinin 3 receptor antagonism ameliorates key metabolic features in a hyperandrogenic PCOS mouse model**. *Endocrinology* 2021, **162**.

39. ** Fraser GL, *et al.*: **Randomized controlled trial of neurokinin 3 receptor antagonist fezolinetant for treatment of polycystic ovary syndrome**. *J Clin Endocrinol Metab* 2021, **106**:e3519–e3532.
This study investigates the effects of a neurokinin 3 receptor antagonist Fezolinetant in treating hyperandrogenism in women with PCOS. Study participants received once-daily oral administration of either 60 mg, 180 mg Fezolinetant, or placebo for 12 weeks. Fezolinetant showed a significant dose-dependent reduction in total testosterone and LH levels in comparison to placebo, and improved LH:FSH in women with PCOS to a range comparable to the early to mid-follicular stage in healthy women. This is the first study to show that an NK3r antagonist can induce a sustained reduction in hyperandrogenimia, and improve the LH to FSH profile in women with PCOS.

40. Modi M, Dhillo WS: **Neurokinin 3 receptor antagonism: a novel treatment for menopausal hot flushes**. *Neuroendocrinology* 2019, **109**:242–248.

41. Goodman RL, *et al.*: **Kisspeptin, neurokinin B, and dynorphin act in the arcuate nucleus to control activity of the GnRH pulse generator in ewes**. *Endocrinology* 2013, **154**:4259–4269.

42. McCarthy EA, *et al.*: **Inhibiting Kiss1 neurons with kappa opioid receptor agonists to treat polycystic ovary syndrome and vasomotor symptoms**. *J Clin Endocrinol Metab* 2022, **107**:e328–e347.

43. Dai M, *et al.*: **Reduction of arcuate kappa-opioid receptor-expressing cells increased luteinizing hormone pulse frequency in female rats**. *Endocr J* 2021, **68**:933–941.

44. Romero-Pico A, *et al.*: **Kappa-opioid receptor blockade ameliorates obesity caused by estrogen withdrawal via promotion of energy expenditure through mTOR pathway**. *Int J Mol Sci* 2022, **23**.

45. Wang Y, *et al.*: **Humanin alleviates insulin resistance in polycystic ovary syndrome: a human and rat model-based study**. *Endocrinology* 2021, **162**.

46. Wang Y, *et al.*: **Humanin regulates oxidative stress in the ovaries of polycystic ovary syndrome patients via the Keap1/Nrf2 pathway**. *Mol Hum Reprod* 2021, **27**.

47. Rodriguez Paris V, Walters KA: **Humanin: a potential treatment for PCOS?** *Endocrinology* 2021, **162**.

48. Cai M, *et al.*: **Efficacy of canagliflozin versus metformin in women with polycystic ovary syndrome: a randomized, open-label, noninferiority trial**. *Diabetes Obes Metabol* 2022, **24**:312–320.

49. Javed Z, *et al.*: **Effects of empagliflozin on metabolic parameters in polycystic ovary syndrome: a randomized controlled study**. *Clin Endocrinol* 2019, **90**:805–813.

50. ** Elkind-Hirsch KE, *et al.*: **Exenatide, dapagliflozin, or phentermine/topiramate differentially Affect metabolic profiles in polycystic ovary syndrome**. *J Clin Endocrinol Metab* 2021, **106**:3019–3033.
This 24 week clinical trial compared the efficacy of various weight loss medications in women with PCOS and obesity. Five different treatment groups were included: 1) GLP-1R agonist exenatide, 2) SGLT2 inhibitor dapagliflozin, 3) exenatide/dapagliflozin, 4) metformin/ dapagliflozin, and 5) phentermine topiramate. All drug treatments reduced fasting glucose, testosterone, and free androgens, however the dual exenatide/dapagliflozin treatment resulted in the greatest weight loss, and improvement in insulin secretion-sensitivity index. This report is the first to compare the therapeutic effects of a GLP-1R agonist and an SGLT2 inhibitor both alone and in combination for treating PCOS, and is an important step in developing treatments that can simultaneously lead to weight loss and improve insulin resistance.

51. * Tan S, *et al.*: **Licogliflozin versus placebo in women with polycystic ovary syndrome: a randomized, double-blind, phase 2 trial**. *Diabetes Obes Metabol* 2021, **23**:2595–2599.
This Phase 2, multi-centre clinical study led by Novartis Pharmaceuticals, examined whether the dual SGLT1/2 inhibitor Licogliflozin could improve hyperinsulinemia and hyperandrogenism in women with PCOS. Patients received 50 mg of licogliflozin 3times/day for 2 weeks. Licogliflozin treatment versus placebo significantly lowered hyperinsulinemia (AUC-Insulin by 68%, Max insulin by 74%, HOMA-IR by 30%). There was no significant changes in free testosterone, but a 19% reduction in androstendione, and 24% reduction in DHEAS following Licogliflozin treatment. This is the first study to examine the use of dual SGLT2/1 inhibitors in PCOS therapy.

52. Sinha B, Ghosal S: **A meta-analysis of the effect of Sodium glucose cotransporter-2 inhibitors on metabolic parameters in patients with polycystic ovary syndrome**. *Front Endocrinol* 2022, **13**, 830401.

53. Elkind-Hirsch KE, *et al.*: **Liraglutide 3 mg on weight, body composition, and hormonal and metabolic parameters in women with obesity and polycystic ovary syndrome: a randomized placebo-controlled-phase 3 study**. *Fertil Steril* 2022, **118**:371–381.

54. Cena H, Chiovato L, Nappi RE: **Obesity, polycystic ovary syndrome, and infertility: a new avenue for GLP-1 receptor agonists**. *J Clin Endocrinol Metab* 2020, **105**.

55. Han Y, Li Y, He B: **GLP-1 receptor agonists versus metformin in PCOS: a systematic review and meta-analysis**. *Reprod Biomed Online* 2019, **39**:332–342.

56. Vastagh C, *et al.*: **Networking of glucagon-like peptide-1 axons with GnRH neurons in the basal forebrain of male mice revealed by 3DISCO-based immunocytochemistry and optogenetics**. *Brain Struct Funct* 2021, **226**:105–120.

57. Outeirino-Iglesias V, *et al.*: **GLP-1 increases preovulatory LH source and the number of mature follicles, as well as synchronizing the onset of puberty in female rats**. *Endocrinology* 2015, **156**:4226–4237.

58. Wang F, *et al.*: **Effects of dipeptidyl peptidase-4 inhibitors on transforming growth factor-beta1 signal transduction pathways in the ovarian fibrosis of polycystic ovary syndrome rats**. *J Obstet Gynaecol Res* 2019, **45**:600–608.

59. Wang Q, *et al.*: **Metformin and sitagliptin combination therapy ameliorates polycystic ovary syndrome with insulin resistance through upregulation of lncRNA H19**. *Cell Cycle* 2019, **18**:2538–2549.

60. Devin JK, *et al.*: **Sitagliptin decreases visceral fat and blood glucose in women with polycystic ovarian syndrome**. *J Clin Endocrinol Metab* 2020, **105**.