The Global Aware Group
Appropriate Care For Women With Androgen Excess

Global AWARE Group Frequently Asked Questions (FAQs) resource

Objective:

The aim of this resource is to provide accessible information regarding the diagnosis and appropriate treatment of androgen excess. This is in the form of a bank of frequently asked questions and answers (FAQs). The document should act as a supplementary educational resource to support healthcare professionals teaching and learning.

The resource will also act as a directory to share with the user where they can find any relevant further information in existing educational materials developed by the Global AWARE Group.

Audience:

Local consultants, secondary care specialists, primary care physicians, pharmacists

Description:

This FAQ document provides a set of questions and answers to be used to answer common questions regarding the diagnosis and appropriate treatment of androgen excess. They have been developed by the Global AWARE Group members in order to share their experiences from clinical practice.

Each question will have two answers; a **short answer** that is a quick, simple and direct and a **long answer** that is more detailed and comprehensive.

These questions and answers have been developed so that their use is flexible.

The AWARE group is a panel of independent physicians with an expert interest in androgen excess in women. Formation of the AWARE group and its ongoing work is supported and funded by Bayer AG.

How can the FAQs be used?

- By healthcare professionals, as a resource to gain a more detailed understanding of the subject through the longer answers
- For incorporation into country's local AWARE materials (e.g. select a few key FAQs to use on the back page of a booklet)
- To use as a tool to support discussions led by healthcare professionals during workshop sessions, or educational meetings
- To share as content on digital social media channels to help engage a wider audience

For example, the question could be shared alone on Twitter channels, with a link to 'Find out more' and redirect where to access further materials:

Or both the question and answer could be included on platforms such as a closed Facebook group on androgen excess:

Note: use of content on social media will depend on individual country regulations

The Global Aware Group
Appropriate Care For Women With Androgen Excess

Frequently Asked Questions

Note: to navigate quickly through the document to the desired question and answer, use the contents directory below. Simply place your cursor over the question you wish to know the answer to and 'Ctrl + Click'.

Defining androgen excess

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6. Is it possible to diagnose polycystic ovary syndrome (PCOS) **without** observing ovarian morphology (e.g. cystic ovaries)? [1]

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13. What role do lifestyle factors play in the management of polycystic ovary syndrome (PCOS)? [1, 2]

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15. Is there any risk of cancer with hormonal anti-androgen treatment? [1, 2]

The Global Aware Group
Appropriate Care For Women With Androgen Excess

Frequently Asked Questions

Defining androgen excess

1. What is the difference between clinical and biochemical androgen excess? [1, 2]

Short answer:

Women with androgen excess can have either clinical or biochemical hyperandrogenism, or both. **Clinical hyperandrogenism** is an increased sensitivity of receptors in the skin to androgens in the blood. **Biochemical hyperandrogenism** women have increased androgen levels in the blood.

Longer answer:

Androgen excess can be categorised into either clinical or biochemical hyperandrogenism. The main difference is that women either have an increased sensitivity to androgens or there are too many circulating androgens being produced. It is worth noting however, that androgen excess can also present as both clinical and biochemical hyperandrogenism. Some women may have excessive production and/or secretion of androgens *as well as* increased sensitivity of the pilosebaceous unit to androgens.

Clinical hyperandrogenism is an increased sensitivity of the pilosebaceous unit in the skin (includes hair follicle and sebaceous gland) to circulating androgens. Women may have normal serum androgen levels. In **biochemical hyperandrogenism** women have increased androgen levels, either due to excessive production, or secretion of androgens (of adrenal or ovarian origin).

Clinical hyperandrogenism commonly presents as skin symptoms such as hirsutism or acne, whereas in addition to these symptoms, biochemical hyperandrogenism can also lead to more systemic symptoms of menstrual irregularity or infertility as well as longer term health risks such as metabolic syndrome and increased cardiovascular risk.

Find further FREE educational materials from 'The Global AWARE Group' on the European Menopause & Andropause Society website: https://www.emas-online.org/nonemaseducationalmaterials/

References

1. Fauser BCJM, et al. Consensus on women's health aspects of polycystic ovary syndrome (PCOS): the Amsterdam ESHRE/ASRM-sponsored 3rd PCOS consensus workshop group. Fertil Steril 2012;97:28–38
2. Legro RS, et al. Diagnosis and treatment of polycystic ovary syndrome: An endocrine society clinical practice guideline. J Clin Endocrinol Metab 2013;98:4565–4592

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The Global Aware Group
Appropriate Care For Women With Androgen Excess

Recognition and diagnosis of androgen excess

2. How does androgen excess manifest clinically? [1, 2]

Short answer:

Androgen excess does not present with one 'main' distinctive symptom, instead there are a **combination of skin and menstrual symptoms** that may be present individually or all together, including seborrhea, acne, hirsutism, alopecia and menstrual irregularity.

Longer answer:

There are a combination of skin and menstrual symptoms which can appear individually or in combination.

Skin symptoms include hirsutism, acne, seborrhea and alopecia. The presentation of all four hyperandrogenic skin symptoms is known as **SAHA syndrome**: **S**eborrhea, **A**cne, **H**irsutism and **A**lopecia**.**[3, 4] This can be present in 20% of women affected by hyperandrogenism.

Although hirsutism is one of the most common markers of androgen excess (present in 80% of women with androgen excess), women may often use self-care to manage hair growth (e.g. make-up, shaving, waxing) this makes identifying androgen excess in these women more challenging. [1, 5] Skin symptoms can commonly be trivialised and mistaken for a cosmetic problem. Women with hirsutism caused by androgen excess experience high levels of psychosocial distress, 75% of women report anxiety, 30% report depression and 29% report both anxiety and depression.[6]

Presenting symptoms at all life stages can include quality of life impairment and clinical hyperandrogenic symptoms. In the clinic it is common for younger women to present with acne caused by androgen excess or menstrual irregularity. However it may become more common in mid-life for women to present with ovulatory dysfunction or fertility issues.

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References

1. Yildiz B. Diagnosis of hyperandrogenism: clinical criteria. Best Pract Res Clin Endocrinol Metab. 2006;20(2):167-176
2. Ozdemir S, et al. Specific dermatologic features of the polycystic ovary syndrome and its association with biochemical markers of the metabolic syndrome and hyperandrogenism. Acta Obstet Gynecol Scand 2010;89:199–204
3. Orfanos CE, Adler YD, Zouboulis CC. The SAHA Syndome. Horm Res. 2000;54:251-8
4. Fauser BCJM, et al. Consensus on women's health aspects of polycystic ovary syndrome (PCOS): the Amsterdam ESHRE/ASRM-Sponsored 3rd PCOS Consensus Workshop Group. Fertil Steril 2012;97:28–38
5. Sirmans SM, Pate KA. Epidemiology, diagnosis, and management of polycystic ovary syndrome. Clin Epidemiol 2014;6:1–13
6. Lipton MG, et al. Women living with facial hair: the psychological and behavioural burden. J Psychosom Res. 2006. 61(2):161-8

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3. How useful for diagnosis is a family history of polycystic ovary syndrome (PCOS) or acne caused by androgen excess?

Short answer:

Family history is important as it can be linked to some of the symptoms of androgen excess, such as acne or hirsutism and can also be a risk factor for the development PCOS.[1]

Longer answer:

Taking a patients' family history can help to inform the diagnosis of androgen excess or PCOS. For example; 50% of women with hirsutism have a positive family history of hirsutism.

It has also been shown that family history can increase the risk of developing acne and can influence the timing and onset of severity.[2, 3]

Further to this, women who are predisposed to developing elements of the metabolic syndrome such as obesity and type 2 diabetes may also be more likely to develop PCOS. It must be remembered however that PCOS is a common, complex genetic disorder and therefore multiple genes and their interaction with the environment contribute to phenotypic expression.[4]

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References

1. Azziz R, Carmina E, Sawaya ME. Idiopathic hirsutism. Endocr Rev 2000;21:347–362
2. Nast A, et al. European evidence-based (S3) guidelines for the treatment of acne. J Eur Acad Dermatol Venereol 2012;26(Suppl 1):1–29
3. NHS choices. Acne – causes. Accessed at: http://www.nhs.uk/Conditions/Acne/Pages/Causes.aspx
4. Azziz R, et al. The Androgen Excess and PCOS Society criteria for the polycystic ovary syndrome: the complete task force report. Fertil Steril. 2009;91:456–488.

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4. How do I recognise acne that is likely to be caused by androgen excess? [1, 2, 3, 4]

Short answer:

Acne caused by androgen excess predominantly presents along the jaw and chin as papulo-pustular acne. Androgens play an important role in mechanisms of androgenic acne development.

Longer answer:

Acne can be found in various areas of the body, where there are dense populations of sebaceous follicles such as the face, upper chest and back. The distribution of acne can often be related to its cause. Acne that is caused by raised androgen levels, or increased sensitivity to androgens in women with androgen excess, is often found in areas where the pilosebaceous unit (hair follicle and sebaceous gland) are already more sensitive to androgens, for example the jaw and chin. This male-pattern distribution is also where you may also find hirsutism, as a result of androgen excess.

Raised androgen levels causes increased sebum production, leading to altered keratinization and blockage of sebaceous glands as well as bacterial colonization by *Propionibacterium acnes.* These both lead to comedone rupture and inflammation and altogether contribute to acne development.

In women with polycystic ovary syndrome (PCOS) a disorder of androgen excess, it is estimated that androgen excess causes approximately 15% of acne.[5] There are, therefore many other causes of acne including hormonal influences such as menstrual cycle influence or non-hormonal such as medication cosmetics or lifestyle choices such as smoking and poor diet.

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2. Dréno B, et al. Profile of patients with mild-to-moderate acne in Europe: a survey. Eur J Dermatol. 2016; 26(2): 177-84
3. Yildiz B. Diagnosis of hyperandrogenism: clinical criteria. Best Pract Res Clin Endocrinol Metab. 2006;20(2):167-176
4. Dréno B, et al. Adult female acne: a new paradigm. JEADV. 2013;27:1063-1070
5. Bitzer J, et al. The use of CPA/EE in hyperandrogenic skin symptoms – A review. Eur J Contracept Reprod Health Care. 2017;22:172-182

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5. Which hormonal tests are recommended in the diagnosis of **a)** androgen excess and **b)** polycystic ovary syndrome (PCOS)? [1, 2]

Short answer:

Use of laboratory tests is guided by local protocol or availability in clinical practice. Serum 17-hydroxyprogesterone (OHP), 24h urinary free cortisol and DHEA-S can all be used to exclude other hyperandrogenic conditions and therefore confirm a diagnosis of androgen excess.

Longer answer:

As well as the above tests, it is important to evaluate amenorrhea and exclude pregnancy with serum or urine human chorionic gonadotrophin (HCG) tests. Ultrasound can be useful to confirm ovarian morphology in PCOS, however absence of ovarian morphology **does not** exclude a diagnosis of PCOS.

Further tests that may also be helpful include:

- Anti-Mullerian hormone (AMH) 4h urinary free cortisol
- Sex hormone binding globulin (SHBG)
- Serum free IGF-1

A full metabolic assessment should be carried out following confirmation of PCOS.

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References

1. Goodman NF, et al. American Association of Clinical Endocrinologists, America College of Endocrinology and Androgen Excess and PCOS Society Disease State Clinical Review: Guide to the best practice in the evaluation and treatment of polycystic ovary syndrome - part 1. Endocrine Pract 2015;21(11):1291–1300
2. Fauser BCJM, et al. Consensus on women's health aspects of polycystic ovary syndrome (PCOS): the Amsterdam ESHRE/ASRM-Sponsored 3rd PCOS Consensus Workshop Group. Fertil Steril 2012;97:28–38

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6. Is it possible to diagnose polycystic ovary syndrome (PCOS) **without** observing ovarian morphology (e.g. cystic ovaries)? [1]

Short answer:

According to the Rotterdam criteria, women that have clinical androgen excess, also known as biochemical hyperandrogenism, as well as irregular menses can be diagnosed with PCOS without having polycystic ovary morphology.

Longer answer:

According to the Rotterdam criteria (and following exclusion of androgen excess, related disorders, and endocrine causes such as hyperprolactinemia), PCOS can be defined by the presence of at least **two** of the following:

- Hyperandrogenism (either clinical or biochemical)
- Irregular menses (ovulatory dysfunction)
- Polycystic ovary morphology

There are four main phenotypic presentations of this, as detailed in the below table. Women with phenotype B can be diagnosed with PCOS due to biochemical hyperandrogenism and irregular menses resulting in ovulatory dysfunction.

Parameter	Phenotype			
	A	B	C	D
Hyperandrogenism	✓	✓	✓	X
Ovulatory dysfunction	✓	✓	X	✓
Polycystic ovary morphology	✓	X	✓	✓

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References

1. Lizneva D, et al. Criteria, prevalence, and phenotypes of polycystic ovary syndrome. Fertil Steril 2016;106(1)6-15

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7. When should I refer my patients? [1]

Short answer:

Women should be referred immediately if any red-flags suggestive of androgen-secreting tumor or malignancy are encountered. This includes sudden, severe virilisation.

Longer answer:

Red flags for referral include:

- Sudden, rapid onset of hair growth, severe hirsutism, obvious signs of virilisation, or palpable abdominal or pelvic mass
- Further investigations reveal elevated 17-hydroxyprogesterone levels/serum total testosterone >4 nanomol/L
- Irregular bleeding and other suspicions of malignancy

Any of the above requires further investigation as they can be indicative of androgen-secreting tumors. These tumors may be adrenal or ovarian in origin and although they are rare, more than 50% of these are malignant.

If women who are seeking acne treatment have suspected nodular acne or scarring this should always be referred to a dermatologist.

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References

1. Bode D, et al. Hirsutism in women. Am Fam Physician. 2012 15;85(4):373-80

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Impact of androgen excess

8. What are the long-term health risks of androgen excess? [1, 2, 3]

Short answer:

Androgen excess due to elevated androgen levels (biochemical hyperandrogenism) is linked to many long-term medical problems such as insulin resistance, type 2 diabetes, cardiovascular disease and infertility.

Longer answer:

The long-term health risks linked to androgen excess due to elevated androgen levels (biochemical hyperandrogenism) are found particularly in women with polycystic ovary syndrome (PCOS). Multiple long-term health risks are associated with women with PCOS. For example:

Women who have PCOS have a greater cardiovascular risk if there is also:

- Obesity
- Smoking
- Hypertension
- Dyslipdemia
- Subclinical vascular disease
- Impaired glucose tolerance
- Family history of premature cardiovascular disease

The risk is increased further if women have type 2 diabetes, overt vascular, renal or cardiovascular disease or metabolic syndrome.

As well as this, the risk of reproductive issues is increased in women with PCOS. This can include greater risk of:

- Infertility
- Adverse pregnancy outcomes including risk of miscarriage
- Endometrial hyperplasia/cancer

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References

1. Sirmans SM, Pate KA. Epidemiology, diagnosis, and management of polycystic ovary syndrome. Clin Epidemiol 2014;6:1–13
2. Fauser BCJM, et al. Consensus on women's health aspects of polycystic ovary syndrome (PCOS): the Amsterdam ESHRE/ASRM-Sponsored 3rd PCOS Consensus Workshop Group. Fertil Steril 2012;97:28–38
3. Legro RS, et al. Diagnosis and Treatment of Polycystic Ovary Syndrome: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2013;98:4565–92

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Treatment of androgen excess

9. How can androgen excess be treated?

Short answer:

Treatment of androgen excess takes a holistic approach with a focus on the impact on women's life and their individual needs and goals of treatment. [1, 2, 3]

Longer answer: [4, 5]

Treatment of androgen excess can involve a variety of methods, but it focuses on the most bothersome symptoms for the woman and her own treatment goals. This may require specific conversations and counselling advice to take place to help explain the treatment options available. For example, if skin symptoms are most bothersome, these should be treated as a priority, if it is menstrual irregularity, cycle regulation should be the focus. .

It must be recognised that a woman's treatment goals may change throughout herr life and this should always be assessed. For women who have elevated androgen levels, treatment should work to also manage and reduce long-term health risks.

Three main treatment areas for androgen excess include:

- **Lifestyle management** to help reduce the risk of long-term metabolic consequences in women with elevated androgen levels. This may involve improving diet or increasing exercise to help weight loss.
- **Topical or cosmetic options** to target bothersome skin symptoms such as acne, hirsutism, and seborrhea. This can include topical retinoids, antibiotics such as tetracyclines, benzoyl peroxide and azaleic acid. However it can also involve shaving, waxing or laser hair removal.
- **Pharmacological treatment** to help reduce the level of circulating androgens and control their effect at tissue level. This can include antiandrogens in combination with estrogen and spironolactone, finasteride, metformin and GnRH analogues.

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References

1. Legro RS, et al. Diagnosis and Treatment of Polycystic Ovary Syndrome: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2013;98:4565–92
2. Goodman NF, et al. American Association of Clinical Endocrinologists, America College of Endocrinology and Androgen Excess and PCOS Society Disease State Clinical Review: Guide to the best practice in the evaluation and treatment of polycystic ovary syndrome - part 1. Endocrine Pract 2015;21(11):1291–1300
3. Fauser BCJM, et al. Consensus on women's health aspects of polycystic ovary syndrome (PCOS): the Amsterdam ESHRE/ASRM-Sponsored 3rd PCOS Consensus Workshop Group. Fertil Steril 2012;97:28–38
4. Lizneva D, et al. Criteria, prevalence, and phenotypes of polycystic ovary syndrome. Fertil Steril 2016;106(1)6-15
5. Moran LJ, et al. Lifestyle changes in women with polycystic ovary syndrome. Cochrane Database of Systemic Reviews 2011 16;(2):CD007506.

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10. How long should treatment of androgen excess last? [1, 2]

Short answer:

The management and treatment of androgen excess is life-long. Pharmacological treatment with anti-androgens can continue unless contraindicated or in women who are attempting to conceive. Lifestyle management and topical or cosmetic options can also be used where recommended and chosen as part of an individual's treatment plan.

Longer answer:

Management of androgen excess is life-long. However, treatment should always be dependent on the individual needs and goals of treatment for each woman. There are various options for treatment as detailed in question 9. However, it is important for each option to be properly discussed to allow informed treatment decisions.

At the time of writing, there is no specific treatment for polycystic ovary syndrome, however, it has been shown that losing a moderate amount of weight such as 10% in women with PCOS can improve insulin resistance as well as androgenic and reproductive outcomes.

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References

1. Moran LJ, et al. Lifestyle changes in women with polycystic ovary syndrome. Cochrane Database of Systemic Reviews 2011 16;(2):CD007506.
2. Goodman NF, et al. American Association of Clinical Endocrinologists, America College of Endocrinology and Androgen Excess and PCOS Society Disease State Clinical Review: Guide to the best practice in the evaluation and treatment of polycystic ovary syndrome - part 1. Endocrine Pract 2015;21(11):1291–1300

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11. Can I treat androgen excess with any combined hormonal contraceptive (CHC)? [1, 2, 3, 4]

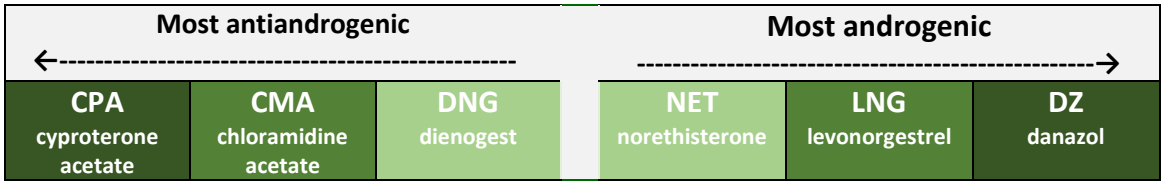
Short answer:

It is important to select the correct combined hormonal treatments. Some progestogens used in CHCs are androgenic (rather than anti-androgenic) and can therefore increase the levels of circulating androgens and worsen symptoms for women with androgen excess.

Long answer:

Anti-androgenic progestogens are a group of female hormones that inhibit the effect of androgens, but another group of progestogens that are androgenic can have the opposite effect. The strength of this effect varies depending upon which progestin is used. When selecting a combined hormonal treatment for androgen excess, it is therefore important to identify and select the appropriate progestogen that inhibits androgen activity and does not worsen symptoms.

Different progestogens also have different anti-androgenic potentials:



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1. Sirmans SM, Pate KA. Epidemiology, diagnosis, and management of polycystic ovary syndrome. Clin Epidemiol 2014;6:1–13
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4. Ruan X, et al. Use of CPA/EE in polycystic ovary syndrome: Rationale and practical aspects. Eur J Contracept Reprod Health Care. 2017;22(3):183-190

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12. Which patients should not receive hormonal anti-androgen treatment? [1]

Short answer:

Women who have contraindications for combined estrogen/progesterone combinations, such as a history of venous thrombotic events, should not receive hormonal anti-androgen treatment for androgen excess.

Long answer:

Combined estrogen, progesterone treatments are contraindicated in women at risk of venous thromboembolism or who may be trying to conceive. Further contraindications as outlined in the WHO MEC include:

- Presence or a history of venous or arterial thrombotic/thromboembolic events or of a cerebrovascular accident
- Presence or history of prodromi of a thrombosis
- History of migraine with focal neurological symptoms
- Diabetes mellitus with vascular involvement
- Known or suspected sex-steroid influenced malignancies
- Severe hepatic disease or tumour
- Known or suspected pregnancy
- Lactation

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References

1. World Health Organization. Medical eligibility criteria for contraceptive use. 5th ed. Geneva: WHO; 2015

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13. What role do lifestyle factors play in the management of polycystic ovary syndrome (PCOS)? [1, 2]

Short answer:

Evidence shows that a healthy lifestyle such as following a balanced diet and regular exercise to reduce body weight can reduce hair growth in hirsutism and also improve insulin resistance in women who have PCOS.

Long answer:

At the time of writing, there is no specific treatment for polycystic ovary syndrome, however, it has been shown that losing a moderate amount of weight such as 10% in women with PCOS can improve insulin resistance as well as androgenic and reproductive outcomes.

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1. Moran LJ, et al. Lifestyle changes in women with polycystic ovary syndrome. Cochrane Database of Systemic Reviews 2011 16;(2):CD007506.
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14. What is the risk of venous thromboembolism (VTE) with combined hormonal ethinylestradiol/progestogen anti-androgen treatment? [1, 2, 3, 4]

Short answer:

Use of an estrogen/progestogen combination is associated with an increased risk for VTE (usually seen as deep vein thrombosis and pulmonary embolism).

Long answer:

The use of an estrogen/progestogen treatment such as cyproterone acetate / ethinylestradiol (CPA/EE) carries an increased risk of VTE (venous thromboembolism) and ATE (arterial thromboembolism). This risk is highest during the first year of use as well as when restarting treatment or switching from an oral contraceptive. It must be noted that only 1-2% of these cases are fatal and the VTE risk remains lower than that during pregnancy and childbirth.

Observational studies of VTE risk with CPA/EE compared to LNG-containing and combined oral contraceptives (low-estrogen <0.05mg) yield varying findings:

- Some studies reported a greater VTE risk, comparable to so-called 3rd generation COCs
- Other studies showed no differences in VTE risk
- Studies that addressed the issue of confounding or duration of use concluded that the VTE risk is not significantly higher

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2. Rosendaal FR. Risk factors for venous thrombotic disease. Thromb Haemost. 1999; 82(2):610-9
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4. Heit JA, Venous thromboembolism: disease burden, outcomes and risk factors. J Thromb Haemost. 2005;3(8):1611-7

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15. Is there any risk of cancer with hormonal anti-androgen treatment? [1, 2]

Short answer:

It has been shown that combined hormonal anti-androgenic therapy is linked to a small increase in risk of developing breast cancer. However **absolute increase in risk is small** and it has also been linked to a reduction in long-term risk of endometrial hyperplasia and endometrial cancer.

Long answer:

Although an increase in the risk of breast cancer has been reported among women who currently or recently used hormonal contraceptives, in comparison to women who had never used hormonal contraceptives, this is usually higher in those who are currently or who have recently been treatment users. Absolute increase in risk remains small and it should be noted that the use of some hormonal anti-androgen treatments such as cyproterone acetate / ethinylestradiol (CPA/EE) is associated with a reduction in long-term risk of endometrial hyperplasia and endometrial cancer.

Note: Absolute risk increase refers to the likelihood that the women will develop breast cancer in their lifetime. A small absolute risk means women's risk is not greatly different to that if they did not use anti-androgenic therapy.

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1. Mørch, et al. 2017. Contemporary Hormonal Contraception and the Risk of Breast Cancer. N Engl J Med 2017; 377:2228-2239
2. Ruan X, et al. Use of CPA/EE in polycystic ovary syndrome: Rationale and practical aspects. Eur J Contracept Reprod Health Care. 2017;22(3):183-190

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