The Global Aware Group

Appropriate Care For Women With Androgen Excess

Case study 1: Diagnosis and treatment of hirsutism

September 2016 **G.MKT.WH.09.2016.0274**

Introduction

- This case study forms part of a training programme aimed at improving knowledge and skills in the appropriate treatment and care of women with androgen excess.

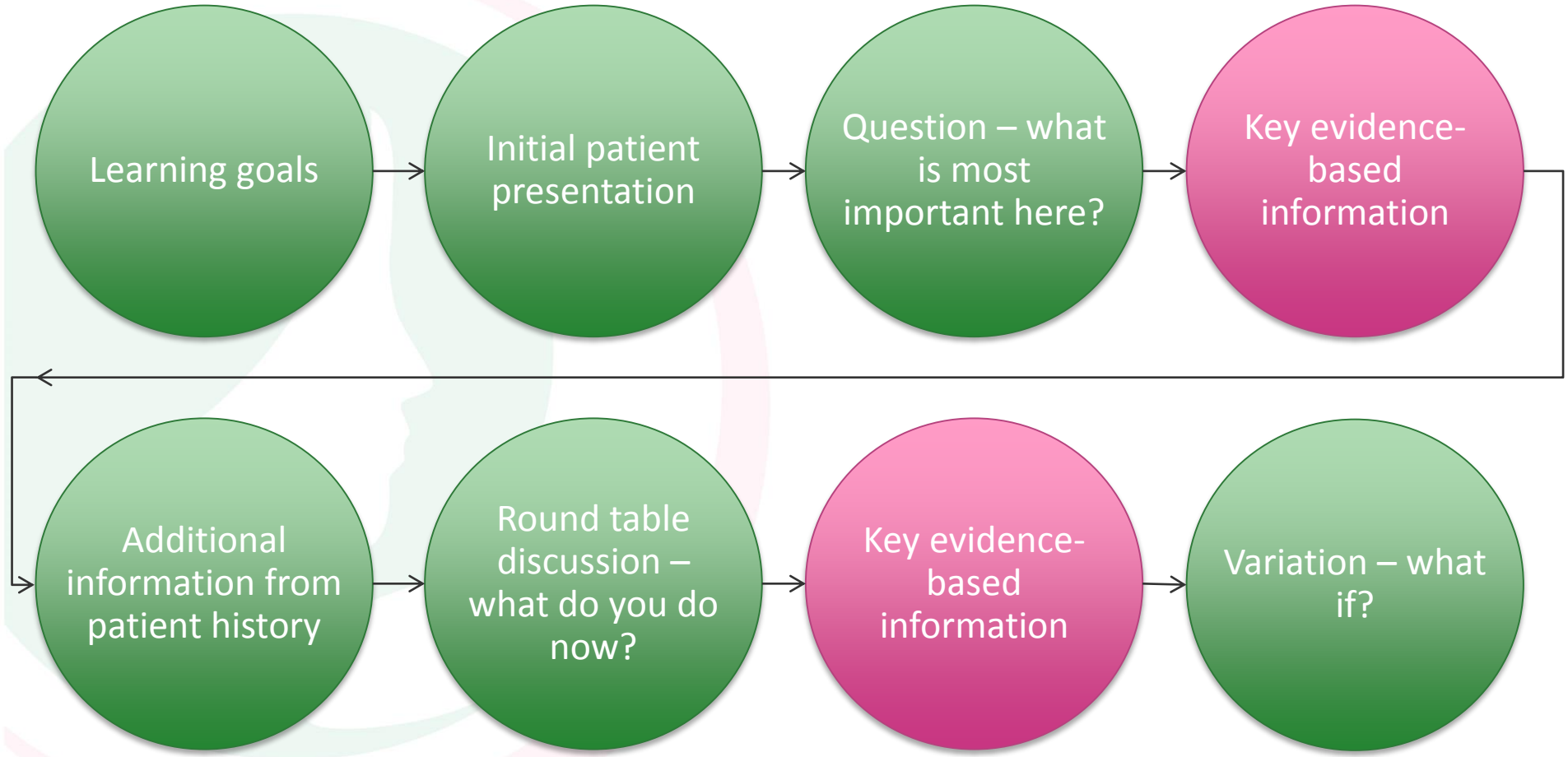
- The content has been developed by the Global AWARE (Appropriate Care for Women With Androgen Excess) Group, an independent panel of physicians with expert interest in the treatment of androgen excess in women, formed in 2015

- Formation of the AWARE group and the group's meetings were supported by Bayer Pharma AG

How to use these case studies

- Progress through each fictional case study is facilitated by:
  - A detailed description of the patient
  - Interactive questions
  - Table discussions
  - Key learning points
- The number of slides used in the workshop can be adapted according to the time available and/or the relative experience of the workshop participants
- All slides are supported by:
  - Guidance notes to assist in the facilitation of participant discussion
  - Fully referenced notes that expand on slide content where relevant
  - A summary of additional resources that participants may wish to access independently

Generalised structure of each case



Opportunities for discussion are guided by two symbols

This symbol indicates an opportunity for participants to consider and discuss their response to a specific question as a whole group

This symbol indicates an opportunity for participants to consider their response to a specific question using smaller group discussion

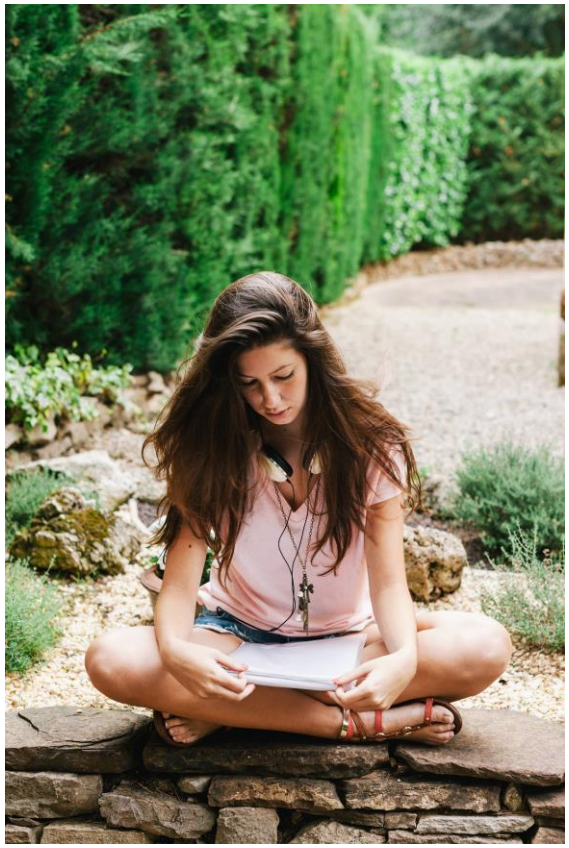
Learning goals

After completing this case study, you should have greater insights into:

- How to reach a diagnosis of hirsutism
- The mechanism behind the presence of excess facial and body hair
- Management options for excess facial and body hair
- Making shared management decisions
- What if? How diagnosis and management may be affected if some of the factors of case presentation were to change

Your patient: Lucia

- 20 year old, nulliparous, nulligravid woman
- Presents with unwanted facial and body hair which appeared at menarche (13 years)
- She has tried shaving and depilation and even laser therapy for her face but now wants to try other options
- She tells you that her mother has the same problem
- She also tells you that the presence of facial hair is making her self-conscious and depressed



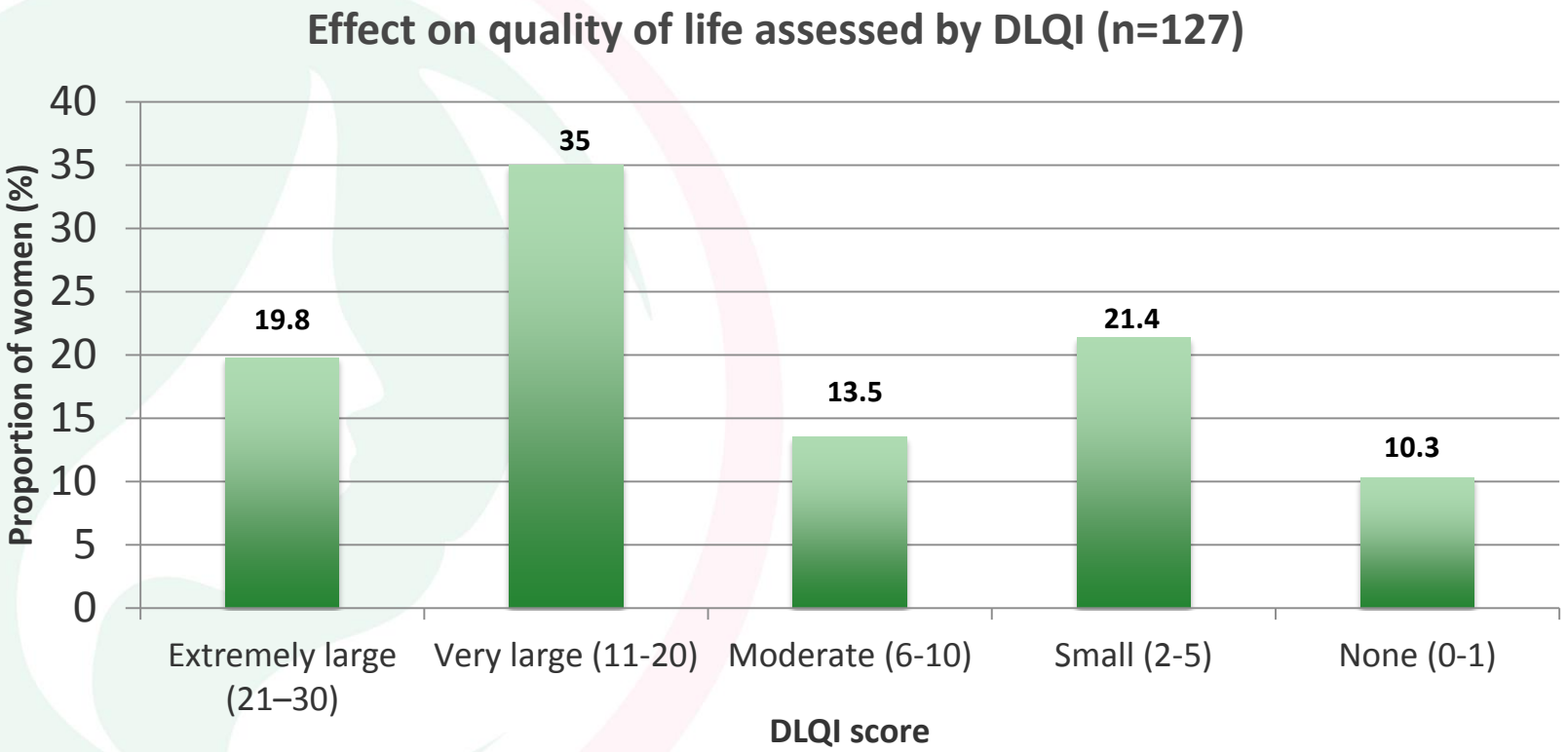
Hirsutism occurs in approximately 5 - 15% of women of reproductive age[1*]

- Hirsutism is the presence of excess body or facial terminal (coarse) hair growth in females in a male-like pattern[2]
- It reflects the interaction between circulating and local androgen concentrations and the sensitivity of the hair follicle to these androgens[3]
- Reported prevalence varies according to ethnicity, for example, women in far-East Asia present less frequently[2]

*Depending on criteria for definition

1. Yildiz B, et al. Hum Reprod Update 2010;16(1):51–64; 2. Escobar-Morreale HF, et al. Hum Reprod Update 2012;18(2):146–170.; 3. Neithardt AB, Barnes RB. Semin Reprod Med 2003;21:285–293

Hirsutism can significantly and negatively impact on quality of life[1]



DLQI: Dermatology Quality of Life Index

1. Palmetun Ekbäck, M, et al. Dermatology 2013;227:278–284

Interactive question

- How would you assess the extent and severity of Lucia's unwanted hair?
  - Subjective assessment?
  - Validated objective assessment?
  - How would you manage assessment when a patient clearly uses cosmetic treatments?

The modified Ferriman-Gallwey (mF-G) scoring system is commonly used to assess severity of hirsutism in clinical trials[1]

- The mF-G system uses 9 body areas to assess hair growth[2]
  - Each area has its own specified definition of the four-point scale[2]
- Photographic depictions of the mF-G scoring system can help in assessing women for excess terminal hair growth[1]

Link below to Yildiz[1] paper illustrates both mF-G and photographic depictions:
http://humupd.oxfordjournals.org/content/16/1/51.full.pdf+html

Asking the patient how frequently she has to shave, wax or seek cosmetic intervention, may provide a useful indication of the scale of the problem for the patient

1. Yildiz B, et al. Hum Reprod Update 2010;16(1):51–64; 2. Hatch R, et al. Am J Obstet Gynecol 1981;140:815–830

Lucia's mF-G score (12) indicates the presence of hirsutism

- Lucia has hair growth around the chin, breast and abdomen
- In the majority of women, an mFG score of 6–8 signifies hirsutism[1]
- Hirsutism can be an important sign of underlying androgen excess, primarily PCOS, irrespective of ethnicity[1-3]
- Other symptoms include acne, seborrhea, alopecia and ovulatory dysfunction[4]

1. Yildiz B, et al. Human Reprod Update 2010;16(1):51–64; 2. Neithardt AB, Barnes RB. Semin Reprod Med 2003;21:285–293.
3. Azziz R. Obstet Gynecol 2003;101:995–1007; 4. Escobar-Morreale HF, et al; Hum Reprod Update 2012;18(2):146–170.

Round table discussion

- Are there any other symptoms that might be relevant to diagnosis, for example, menstrual dysfunction?
  - What about medication use?
  - Any family history of hirsutism?
- What other tests might you carry out at this stage?

- **Please discuss this question together for five minutes**
- **Identify areas where you agree and areas where you had different opinions**
- **Nominate one group member to provide feedback on your discussions**

Any woman presenting with hirsutism requires assessment of ovulatory function[1]

- Ultrasound and testing of serum androgen levels may help with identifying the hirsutism etiology and differential diagnosis[1]

Ultrasound	• Ovarian morphology
Laboratory tests	• Sex hormone binding globulin (SHBG) +/- prolactin • 17-OH (adrenal) +/- DHEA-S • Testosterone specific for ovarian involvement • Follicle stimulating hormone (FSH) • Luteneising hormone (LH)

17-OH: 17-Hydroxyprogesterone
DHEAS: Dehydroepiandrosterone sulfate

1. Escobar-Morreale HF, et al. Hum Reprod Update 2012;18(2):146–170.

Hirsutism can be caused by ovarian or adrenal dysfunction[1,2]

Etiology	Frequency (%)[1]	Clinical clues[1,2]
Polycystic ovary syndrome (PCOS)	71	Irregular menses; normal/mildly elevated androgen levels; polycystic ovaries (on ultrasound); central obesity; infertility, insulin resistance; acanthosis nigrans
Idiopathic hyperandrogenism	15	Normal menses; normal ovaries (on ultrasound); elevated androgen levels
Idiopathic hirsutism	10	Normal menses; normal ovaries (on ultrasound); normal androgen levels
Non-classic congenital adrenal hyperplasia (NCCAH)	3	Family history; high-risk ethnic group; classic onset at birth; non-classic late onset; elevated 17-hydroxyprogesterone level before and after corticotropin stimulation test
Androgen-secreting tumors	0.3	Rapid onset of hirsutism; progression despite treatment; virilization; palpable abdominal or pelvic mass; early morning total testosterone >200 ng/dL

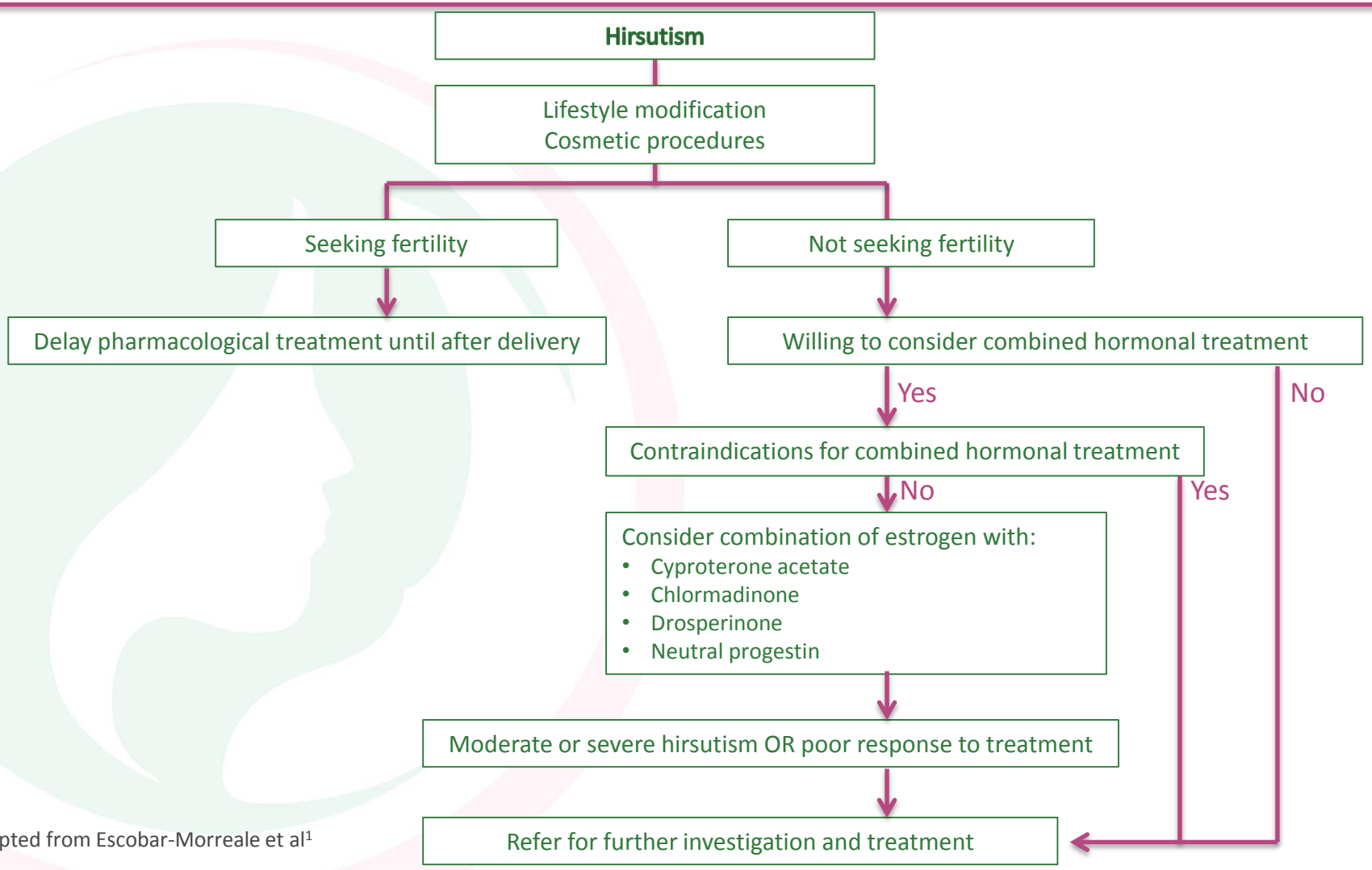
1. Bode D, et al. Am Fam Physician 2012;85(4):373–380; 2. Escobar-Morreale HF, et al. Hum Reprod Update 2012;18(2):146–170; 2.

Interactive question

- Lucia's ultrasound is normal and no other tests or investigations are indicated, therefore you discuss treatment options

- What treatment would you consider and why?
- What would be important information for Lucia when recommending treatment?

Selecting treatment options for hirsutism



Adapted from Escobar-Morreale et al[1]

1. Escobar-Morreale HF, et al. Hum Reprod Update 2012;18(2):146–170

Hormonal therapy is the pharmacological treatment of choice for hirsutism[1]

As Lucia is not overweight and has already tried cosmetic procedures, you discuss the use of combined hormonal treatment

- Use of combined hormonal treatment results in a decrease in serum androgen levels and subjective improvement in hirsutism[1]
- Low-dose combined oral contraceptives, containing neutral (or low androgenicity) progestogens such as desogestrel or gestodene, or an antiandrogen such as cyproterone acetate, chlormadinone acetate or drospirenone are the treatment of choice for hirsutism[1]

1. Escobar-Morreale HF, et al. Hum Reprod Update 2012;18(2):146–170.

CPA/EE is a licensed, highly effective treatment for hirsutism[1*,2]

- A review of the safety and efficacy of CPA/EE in the treatment of hyperandrogenic skin symptoms described:[1*]
  - Significant reduction in hirsutism score between 6 and 12 months after starting treatment
  - Greatest improvements in hirsutism scores with CPA/EE at 12 months
  - Reduction in frequency of shaving or hot wax treatment
  - Treatment to be well tolerated, with a side effect profile similar to that seen with combined oral contraceptives (COCs)

*Please see national approval documentation for Diane-35 for specific license indication in your country

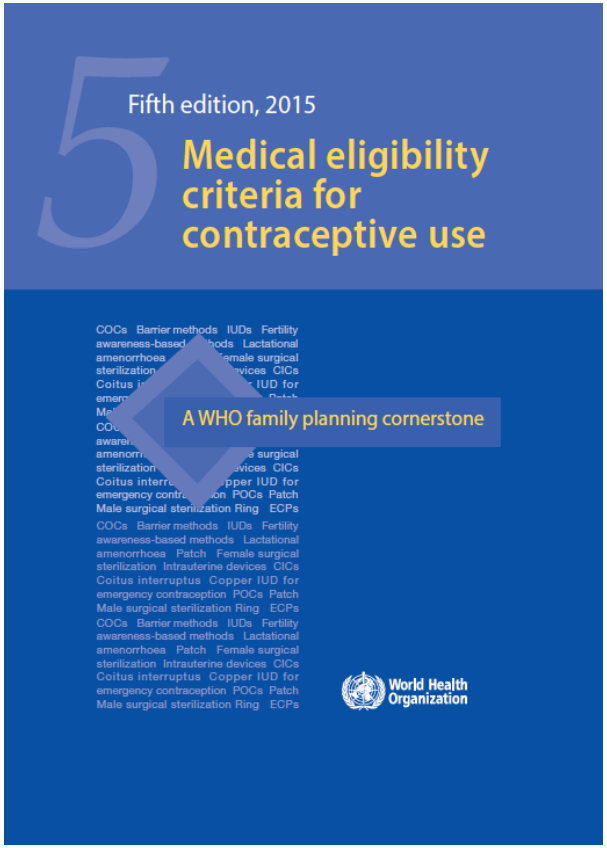
1. Diane-35® Summary of Product Characteristics; 2. J Bitzer, et al. The use of CPA/EE in hyperandrogenic skin symptoms – A review. [In preparation]

Interactive question

- What would be important information for Lucia when recommending treatment?
  - Contraindications?
  - Treatment duration and timing of anticipated outcomes?

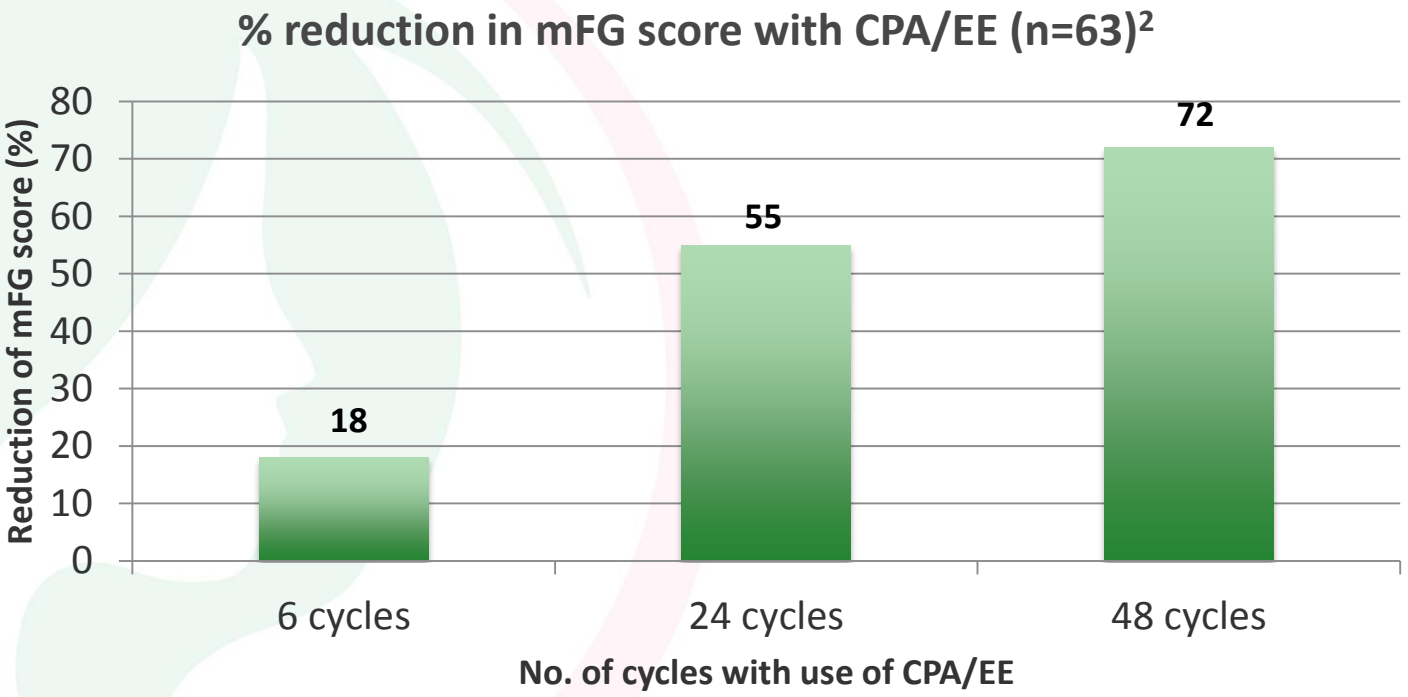
Factors to consider before prescribing combined hormonal treatment

- Patients must be carefully screened before using any estrogen/progestogen combinations for potential contraindications
- WHO MEC provides guidance on contraindications when prescribing combined hormonal treatment[1]



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

Hirsutism is a long-term condition requiring long-term follow-up[1]



CPA/EE; 2mg cyproterone acetate/0.035mg ethinylestradiol

1. Escobar-Morreale HF, et al. Hum Reprod Update 2012;18(2):146–170; 2. Falsetti L, et al. Am J Clin Dermatol 2000;1(2):89–99.

The following slides contain variations to the case

These may be used in workshops where:

- there is additional time available for case discussion
- the participants are more experienced in the management of hyperandrogenic skin symptoms and interested in a more challenging discussion

Table discussion

- How would your diagnosis and investigation of Lucia's hirsutism change if she told you that her menses were sometimes irregular?

- **Please discuss this question together for five minutes**
- **Identify areas where you agree and areas where you had different opinions**
- **Nominate one group member to provide feedback on your discussions**

Presence of menstrual dysfunction and hyperandrogenic skin symptoms can indicate polycystic ovary syndrome (PCOS)

- PCOS is a common disorder affecting 6–21% of women*[1]
- The Rotterdam criteria define PCOS by the presence of two of the following after exclusion of other androgen excess or related disorders:[2]
  - irregular menses
  - hyperandrogenism (either clinical or biochemical)
  - polycystic ovary morphology, after excluding other endocrine causes such as hyperprolactinemia
- In addition to hirsutism, other symptoms evident within the syndrome include central obesity, infertility, insulin resistance, and acanthosis nigrans[3]

* when assessed using the Rotterdam criteria[2]

1. Lizneva D, et al. Fertil Steril 2016;106(1):6–15. 2. Rotterdam ESHRE/ASRM-sponsored PCOS consensus workshop group. Hum Reprod 2004;19:41–47; 3. Escobar-Morreale HF, et al. Hum Reprod Update 2012;18(2):146–170.

It would be appropriate to consider further investigation for PCOS

- In addition to testing for serum androgen levels and ovarian morphology, metabolic assessment is also recommended.[1]

Additional tests to confirm PCOS	
Metabolic assessment	• Assessment of waist circumference and BMI. • Complete lipid profile, including total cholesterol, low-density lipoprotein (LDL)-cholesterol, non-high-density lipoprotein (HDL)-cholesterol, HDL-cholesterol and triglycerides • Oral glucose tolerance test • Blood pressure

1. Escobar-Morreale HF, et al. Hum Reprod Update 2012;18(2):146–170

Table discussion

- How would your management of Lucia's hirsutism change if she was 47 years old with sudden symptoms of hirsutism?

- **Please discuss this question together for five minutes**
- **Identify areas where you agree and areas where you had different opinions**
- **Nominate one group member to provide feedback on your discussions**

Rapid onset of hirsutism could indicate the presence of an androgen-secreting tumour[1]

- Androgen-secreting tumors are rare (<1%) causes of hirsutism[1]
- Rapid onset of hirsutism, virilization or a palpable abdominal or pelvic mass all raise suspicion for an androgen-secreting tumor[1]
- Referral for abdominal CT or MRI scan and ovarian ultrasound is indicated[1]

CT: computerized tomography
MRI: magnetic resonance imaging

1. Escobar-Morreale HF, et al. Hum Reprod Update 2012;18(2):146–170.

When to refer a patient with unwanted body hair[1]

- Women with clinical features of androgen-secreting tumor
  - Sudden, rapid onset of hair growth
  - Severe hirsutism
  - Obvious signs of virilization
  - Palpable abdominal or pelvic mass
- Women in whom further investigations reveal:
  - Serum total testosterone >4 nanomol/L
  - Elevated 17-hydroxyprogesterone levels

1. NICE Clinical Knowledge Summaries. Accessed at: http://cks.nice.org.uk/hirsutism#!scenario

Useful sources of information

Resource	Source
Dermatology Quality of Life Index (DLQI)	Finlay AK, Khan GK. Dermatology Life Quality Index (DLQI)—a simple practical measure for routine clinical use. Clin Exp Dermatol 1994;19(3):210–216.
Modified Ferriman-Gallwey (mF-G) scoring	Hatch R, et al. Hirsutism: implications, etiology, and management. Am J Obstet Gynecol 1981;140:815–830.
Visual scoring of hirsutism	Yildiz B, et al. Visually scoring hirsutism. Hum Reprod Update 2010;16(1):51–64.
Consensus statement on diagnosis and management of hirsutism	Escobar-Morreale HF, et al. Epidemiology, diagnosis and management of hirsutism: a consensus statement by the Androgen Excess and Polycystic Ovary Syndrome Society. Hum Reprod Update 2012;18(2):146–170.
Guidance on contraindications when prescribing combined hormonal treatment	World Health Organization. Medical eligibility criteria for contraceptive use. 5th ed. Geneva: WHO; 2015

Review of learning goals: Lucia

After completing this case study, you should have greater insights into:

- How to reach a diagnosis of hirsutism
- The mechanism behind the presence of excess facial and body hair
- Management options for excess facial and body hair
- Making shared management decisions
- What if? How diagnosis and management may be affected if some of the factors of case presentation were to change

The Global Aware Group

Appropriate Care For Women With Androgen Excess

Case study 2: Diagnosis and treatment of acne

September 2016 **G.MKT.WH.09.2016.0274**

Introduction

- This case study forms part of a training programme aimed at improving knowledge and skills in the appropriate treatment and care of women with androgen excess.

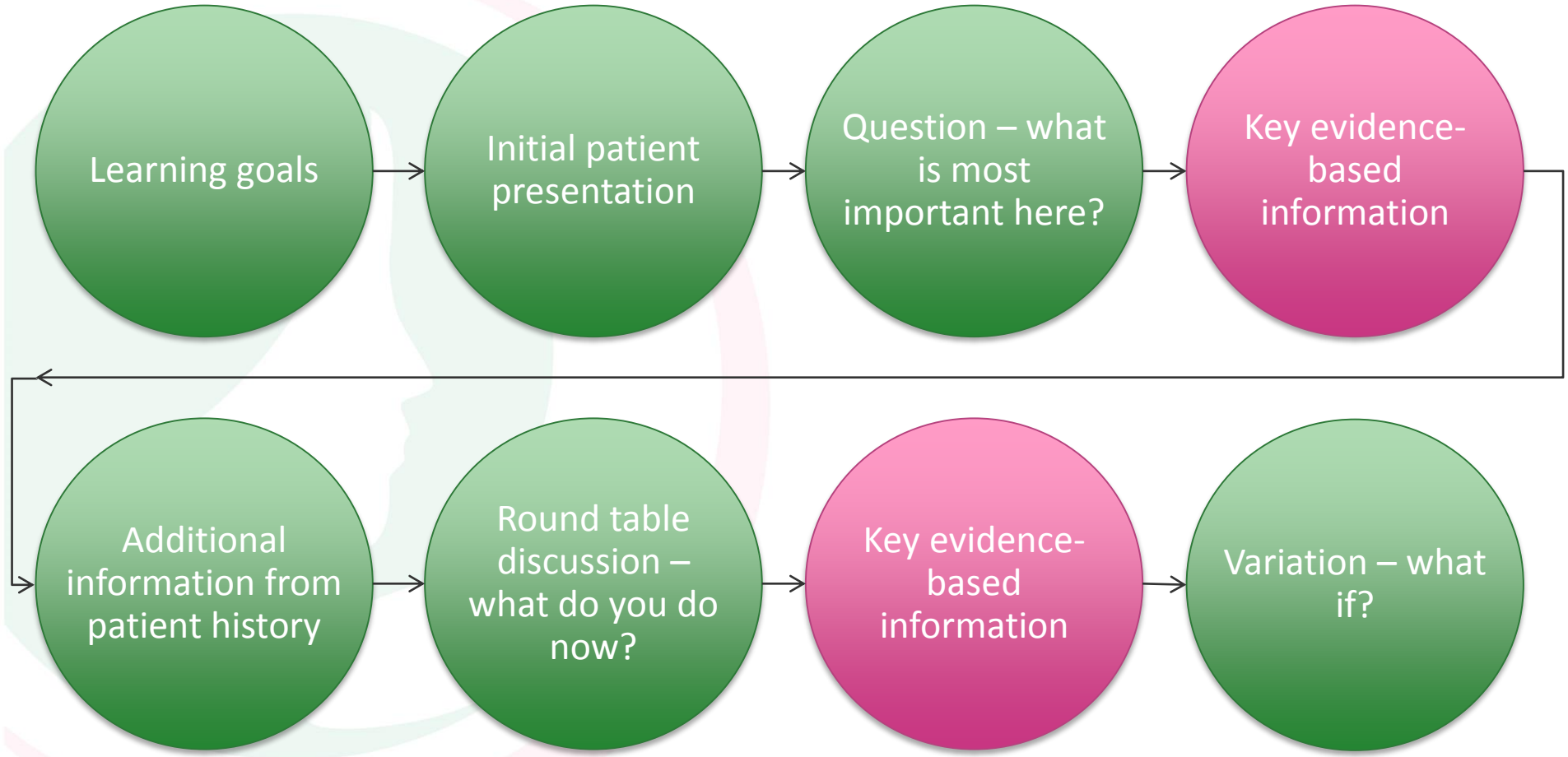
- The content has been developed by the Global AWARE (Appropriate Care for Women With Androgen Excess) Group, an independent panel of physicians with expert interest in the treatment of androgen excess in women, formed in 2015

- Formation of the AWARE group and the group's meetings were supported by Bayer Pharma AG

How to use these case studies

- Progress through each fictional case study is facilitated by:
  - A detailed description of the patient
  - Interactive questions
  - Table discussions
  - Key learning points
- The number of slides used in the workshop can be adapted according to the time available and/or the relative experience of the workshop participants
- All slides are supported by:
  - Guidance notes to assist in the facilitation of participant discussion
  - Fully referenced notes that expand on slide content where relevant
  - A summary of additional resources that participants may wish to access independently

Generalised structure of each case



Opportunities for discussion are guided by two symbols

This symbol indicates an opportunity for participants to consider and discuss their response to a specific question as a whole group

This symbol indicates an opportunity for participants to consider their response to a specific question using smaller group discussion

Learning goals

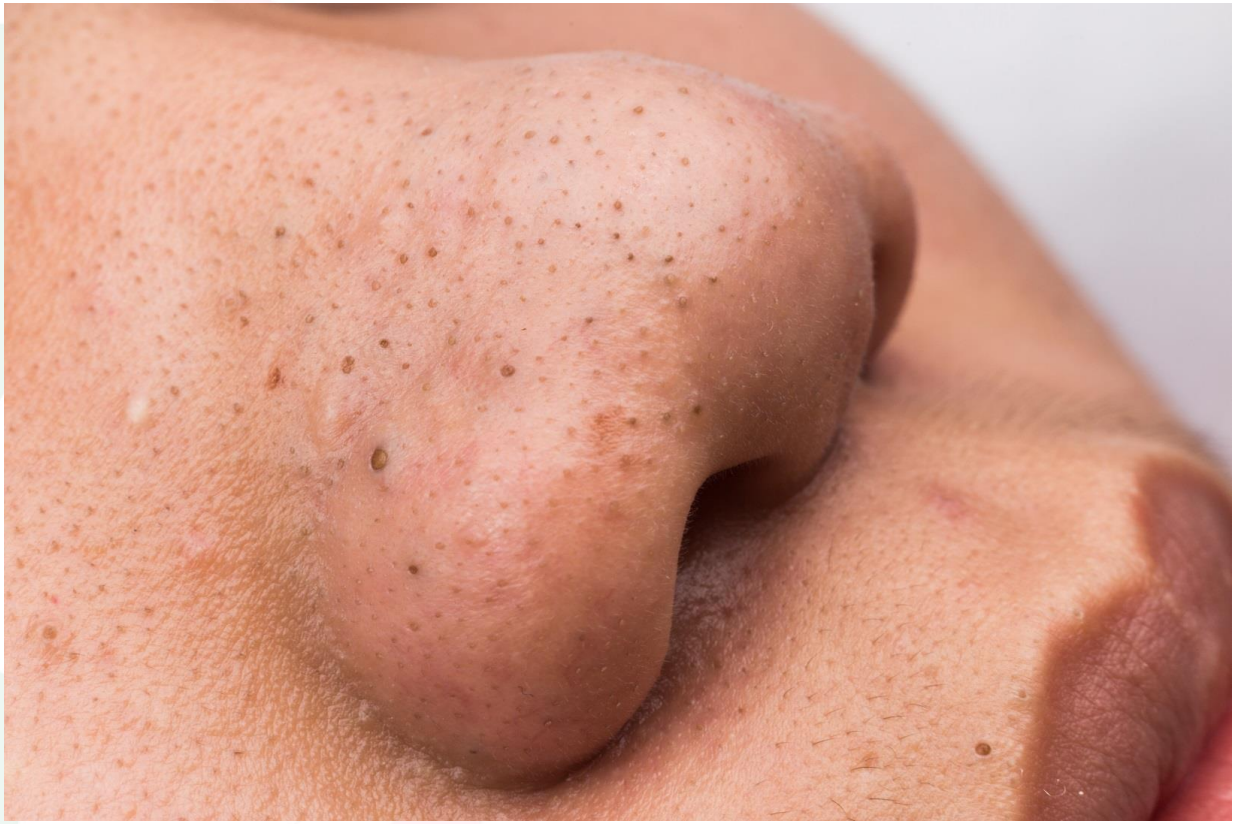
After completing this case study, you should have greater insights into:

- Recognizing acne that can be treated with combined hormonal treatment
- The high prevalence and impact of acne
- Identifying androgen excess as a causative factor
- Managing acne with combined hormonal treatment
- Making shared management decisions
- What if? How diagnosis and management may be affected if some of the factors of case presentation were to change

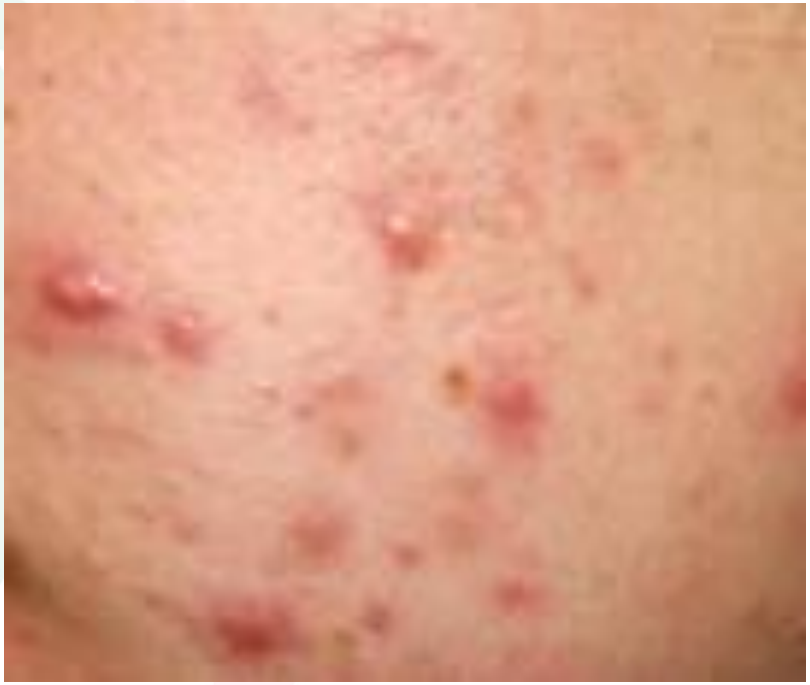
Acne quick quiz

- We are going to present you with images of a number of female patients with acne

Would you treat or refer this patient?



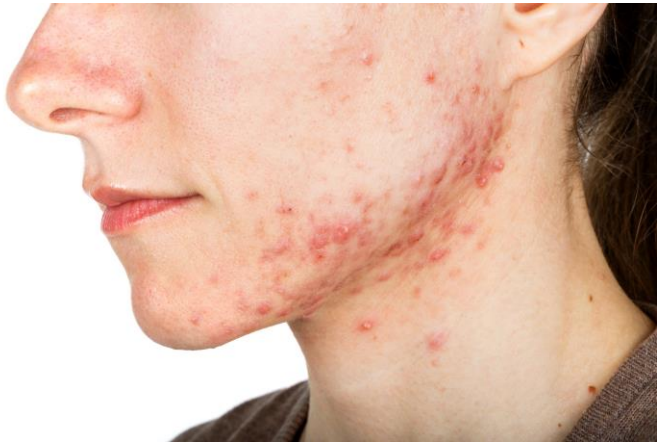
What about this patient? Treat or refer?



And finally…

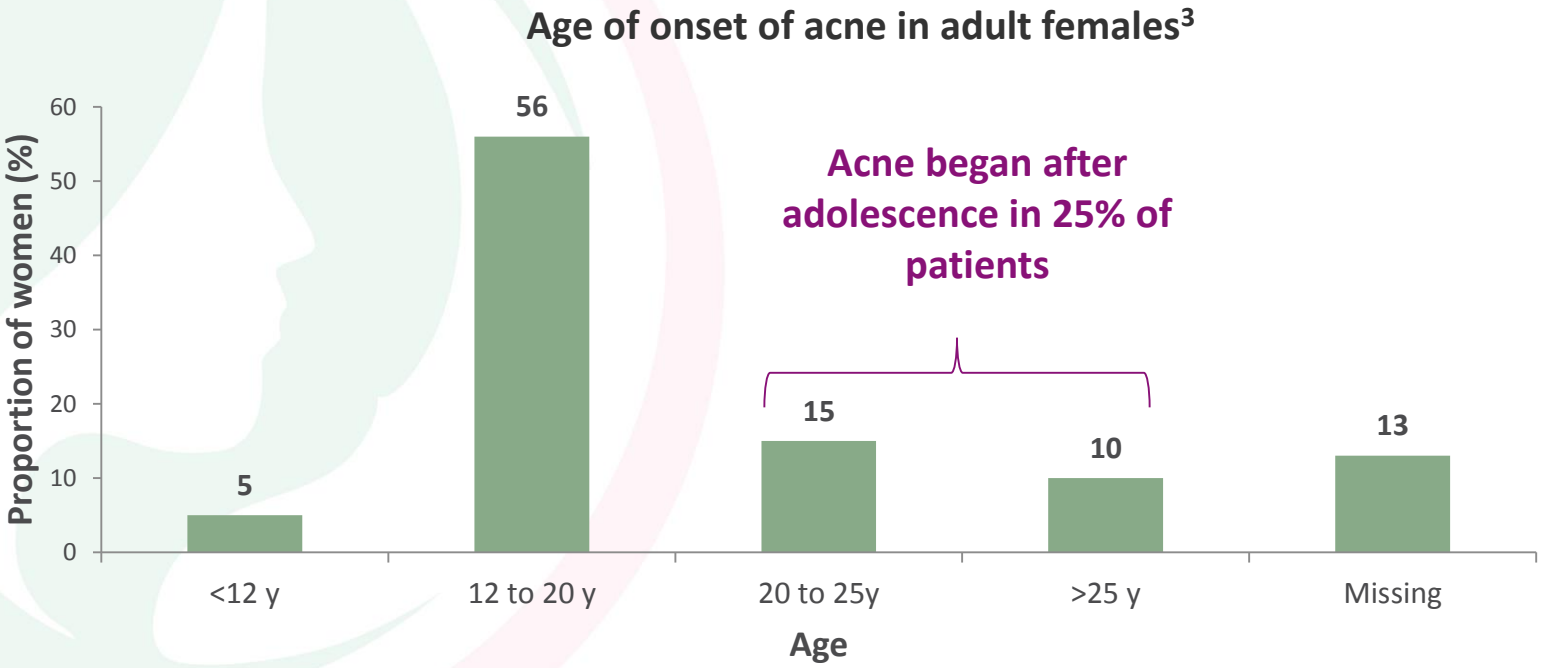
Your patient, Camila

- 19 years old
- Presents with moderate acne that has failed to improve with topical antibiotic treatment
- She tells you that her acne became much worse a year ago
- She also tells you that she is too embarrassed to go out with her friends because she feels miserable about her skin
- She is taking a combined oral contraceptive (COC)



Acne is an extremely common, chronic skin condition[1,2]

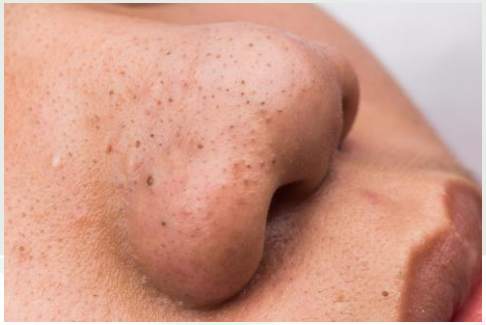
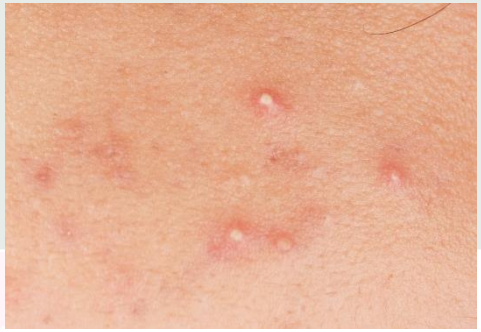
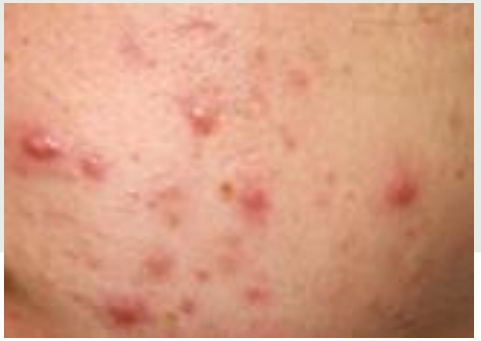
- Prevalence of acne peaks in the teenage years, affecting between 50% and 95% adolescents, depending on how it is assessed[1-3]



1. Zhara Ghodsi S, et al. J Invest Dermatol 2009;129,:2136–2141; 2. Yeung CK, et al. Acta Derm Venereol 2002;82:104–107; 3. Dréno B, et al. J Eur Acad Dermatol Venereol 2014;29:1096-106.

Acne involves multiple pathophysiological factors[1,2]

- Characterised by:
  - increased sebum production and altered keratinisation[1]
  - inflammation and bacterial colonisation by *propionibacterium acnes* of hair follicles on the face, neck, chest and back[2]

Comedonal acne	Papulo-pustular acne	Nodular acne
Presence of open (blackheads) and closed comedones (whiteheads).	Presence of non-inflammatory and inflammatory lesions that may be either superficial (papules and pustules ≤5 mm in diameter) or develop into deep pustules or nodules in more severe disease.	Presence of small nodules (firm, inflamed lesions >5 mm diameter) that are painful by palpation. Large nodules (>1 cm diameter) may extend over large areas and can result in painful lesions, exudative sinus tracts and tissue destruction.
		

1. Gollnick H, Zouboulis CC. Deutsches Arzt Int 2014;111(17):301–312. 2. Shen Y. Acta Derm Venereol 2012; 92: 40–44

Table discussion

- How might impact on quality of life (QoL) affect your decision to treat acne?
  - Would you formally assess the impact of acne on Camila's QoL?
  - What tool might you use?

- **Please discuss this question together for five minutes**
- **Identify areas where you agree and areas where you had different opinions**
- **Nominate one group member to provide feedback on your discussions**

Acne has a significant impact on quality of life[1-4]

- Acne can have an adverse effect on quality of life[1-3]
- Clinically important depression and anxiety have been reported in 18% and 44% of acne patients, respectively[4]
- Psychosocial impact may not always correlate with disease severity but it may influence treatment decisions,[5,6] for example, the need to refer to a dermatologist

A number of tools are available to measure impact of acne on QoL
[see "Additional Resources" at the end of the presentation]

1. Aktan S, et al. Int J Dermatol 2000;39:354–357; 2. Koo JY, Smith LL. Pediatr Dermatol 1991;8:185–188; 3. Stern RS. J Am Acad Dermatol 2000;43:1042–1048; 4. Kellett SC, Gawkrodger DJ. Br J Dermatol 1999;140:273–282. 5. Nast A, et al. J Eur Acad Dermatol Venereol 2012;26(Suppl 1):1–29; 6. Webster GF. BMJ 2002;325(7362):475–479.

A detailed medical history reveals…

- Camila has extensive papulo-pustular acne involving both non-inflammatory and inflammatory lesions
- Her acne had been present for over a year
- She was prescribed topical antibiotics three months ago
- There are no other skin problems such as hirsutism or alopecia present
- Menarche at 12 years, history of irregular periods
- Her periods are regular now she is taking a COC
- Her BMI is 20.4 (weight 55kg; height 156cm)
- She is taking no other medications

Interactive question

- What other factors might you consider at this point?
  - Did Camila use the topical acne treatment properly?
  - Is there a potential trigger for her acne, for example, her method of contraception?

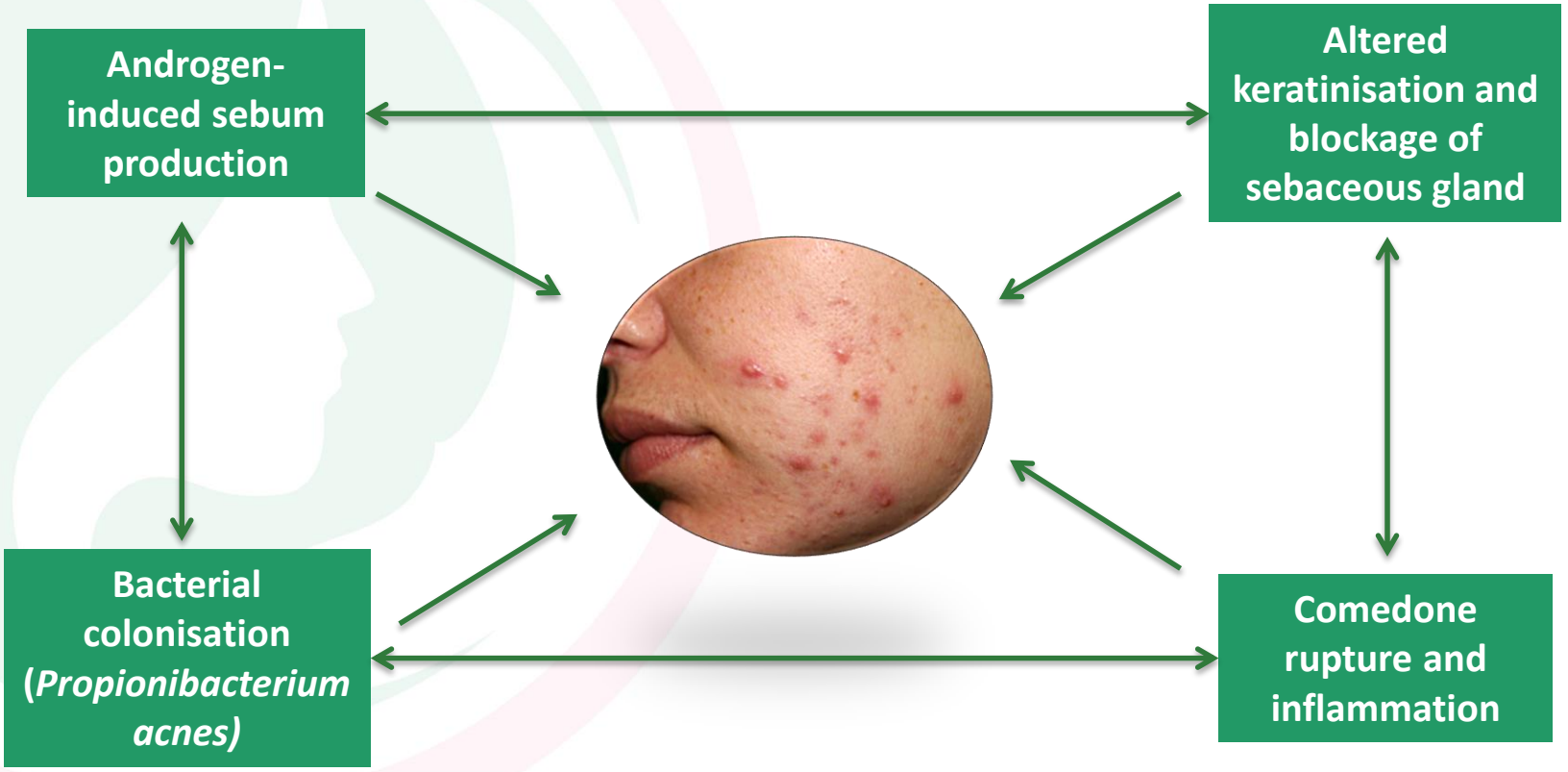
Lack of compliance is an important cause of treatment failure[1,2]

- When recommending treatment, compliance can be maximized by enhancing patient knowledge of the following:[1-3]
  - ✓ Mode of action
  - ✓ Regimen details
  - ✓ Duration of treatment
  - ✓ Expected time before first visible benefit seen
  - ✓ Potential side effects

1. Dréno B, et al. J Eur Acad Dermatol Venereol 2013;27(9):1063–70; 2. Nast A, et al. J Eur Acad Dermatol Venereol 2012;26(Suppl 1):1–29; 3. Webster, GF. BMJ 2002;325(7362):475–479

Androgens play an important role in the pathophysiological processes leading to acne

- Androgens affect the hair follicles and the accompanying sebaceous glands (pilosebaceous unit)[1]



1. Zouboulis CC, et al. Horm Metab Res 2007;39:85–95.

You think that Camila's acne may be linked to her use of an androgenic COC

- Some oral contraceptives may contain an androgenic progestogen which can exacerbate common pre-existing conditions such as acne and hirsutism[1]
  - Androgenic progestogens increase circulating androgen levels and therefore increase sebum production
  - This can be a particular problem with progesterone-only pill (POP) use
- This effect can be eliminated or improved by use of combined oral preparations with low androgenic activity[1]

Camila has stressed a need for continuing contraception and asks about options other than her current COC

1. Darney PD. Int J Fertil Womens Med 1997;Suppl 1:158-69

You decide to switch Camila to an antiandrogenic progestogen/EE combination

Decreasing antiandrogenic effect[1-2]

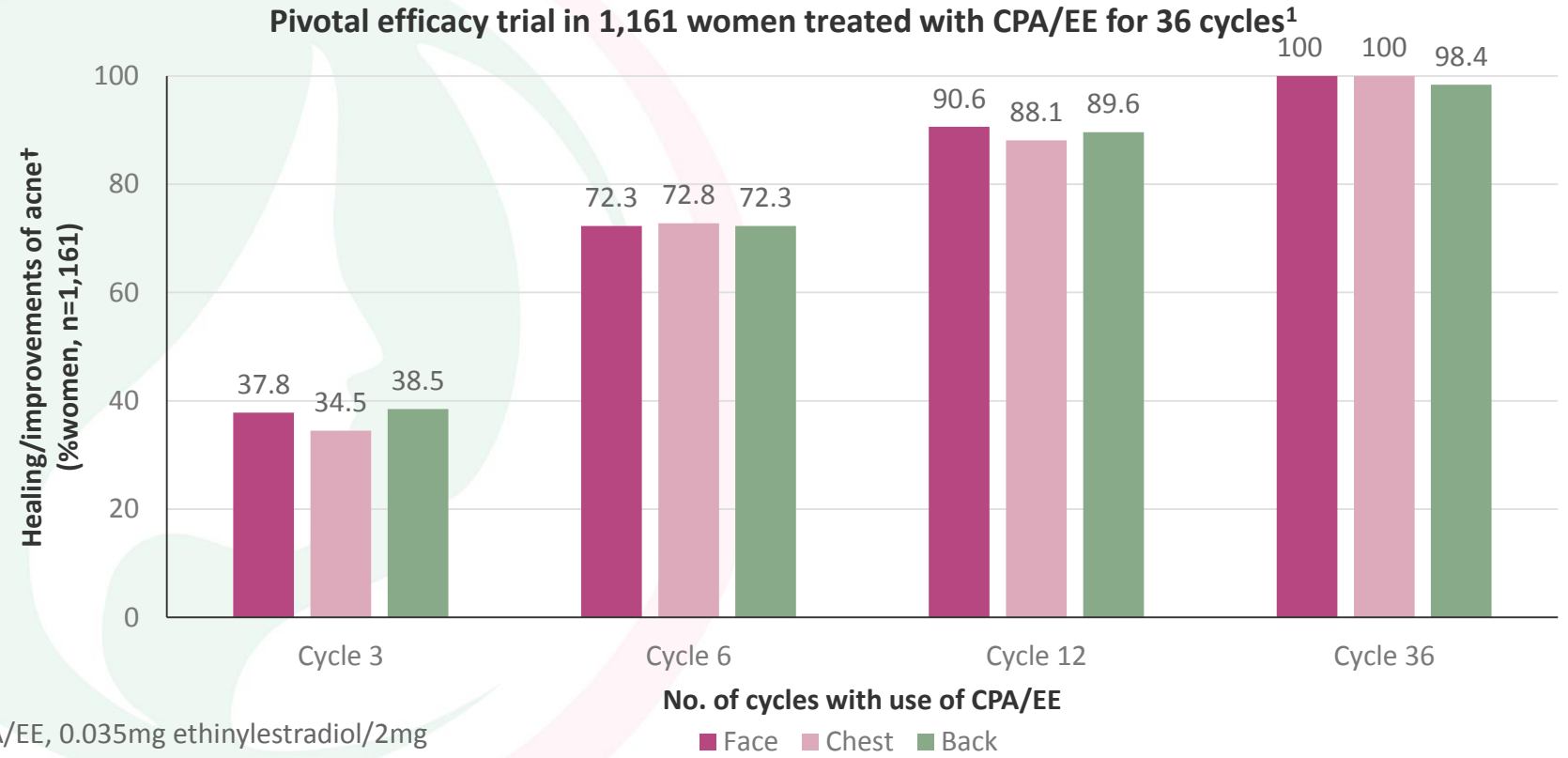
Progestogen	Mode of Action	In combination with EE
Cyproterone acetate (CPA)	Inhibits the activity of 5-alpha-reductase[1] and androgen synthesis in the skin and decreases androgen blood concentration through an antigonadotrophic effect.[2*]	Available in combination with EE for the treatment of acne when alternative treatments, such as topical therapy and antibiotic treatment, have failed.[2*] CPA/EE has the greatest antiandrogenic potential.[3-4] As CPA/EE acts as a hormonal contraceptive, women should not take it in combination with other hormonal contraceptives as concomitant use with another hormonal contraceptive will expose women to a higher dose of estrogen and increased risk of thromboembolism.[2]
Chlormadinone acetate (CMA)	Inhibits the activity of 5-alpha-reductase in the skin and reduces ovarian and adrenal androgen production via its antigonadotropic effect.	Available in combination with EE as a combined oral contraceptive
Dienogest (DNG)	Possesses strong progestational effects and moderate antiandrogenic and antigonadotrophic effects.	Available in combination with EE as a combined oral contraceptive
Drosperinone (DRSP)	Blocks ovarian steroid production, reduces adrenal androgen synthesis and blocks peripheral androgen receptors in the skin.	Available in combination with EE as a combined oral contraceptive

*Please see national approval documentation for Diane-35 for specific license indication in your country

1. Fang S, Liao S. Mol Pharmacol. 1969;5:428-31. 2. Diane-35® Summary of Product Characteristics; 3. Sitruk-Ware R. Hum Reprod Update 2006;12:169–178; 4. Zouboulis CC, et al. Horm Metab Res 2007;39:85–95

CPA/EE is licensed for the treatment of moderate to severe acne when alternative topical or systemic treatments have failed[1*]

- Healing or improvements in the face, chest and back are seen in >88% of patients at 12 months[2]



CPA/EE, 0.035mg ethinylestradiol/2mg cyproterone acetate

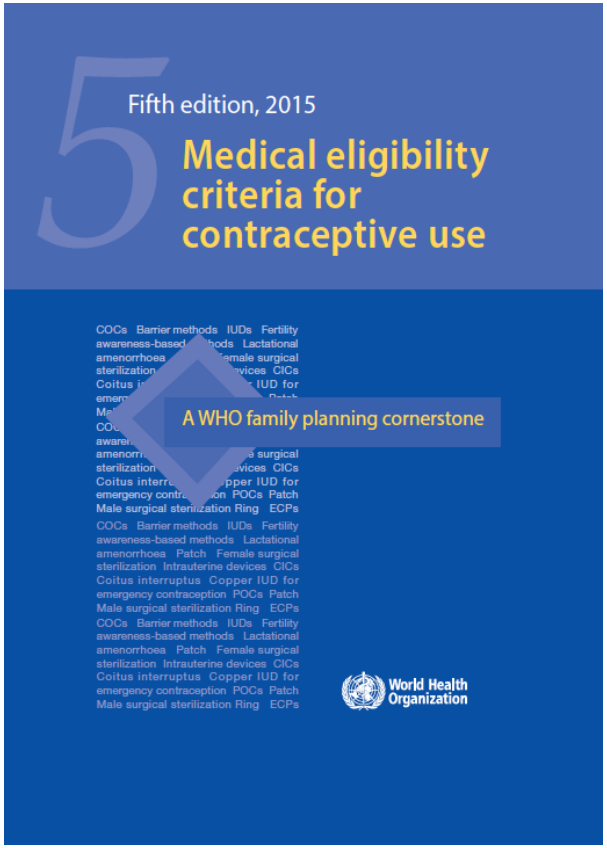
*Please see national approval documentation for Diane-35 for specific license indication in your country

†Symptom severity was assessed and graded subjectively

1. . Diane-35® Summary of Product Characteristics; 2. Aydinlik S, et al. Clin Trials J 1990;27(6):392–402.

Factors to consider before prescribing combined hormonal treatment

- WHO MEC provides guidance on contraindications when prescribing combined hormonal treatment[1]



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

The following slides contain variations to the case

These may be used in workshops where:

- there is additional time available for case discussion
- the participants are more experienced in the management of hyperandrogenic skin symptoms and interested in a more challenging discussion

Variation: Table discussion

- How would your diagnosis and investigation of Camila's acne change if details of her medical history and physical examination changed?
- For example, Camila is not using any contraception and has irregular menses, a BMI of 29 and a family history of diabetes

- **Please discuss this question together for five minutes**
- **Identify areas where you agree and areas where you had different opinions**
- **Nominate one group member to provide feedback on your discussions**

Presence of menstrual dysfunction and hyperandrogenic skin symptoms can indicate polycystic ovary syndrome (PCOS)

- PCOS is a common disorder affecting 6–21% of women*[1]
- The Rotterdam criteria define PCOS by the presence of two of the following after exclusion of other androgen excess or related disorders:[2]
  - irregular menses
  - hyperandrogenism (either clinical or biochemical)
  - polycystic ovary morphology, after excluding other endocrine causes such as hyperprolactinemia
- Hyperandrogenic symptoms such as acne affect approximately 15% of women with PCOS[3]
- In addition to acne, other symptoms evident within the syndrome include hirsutism, central obesity, infertility, insulin resistance, and acanthosis nigrans[4]

* when assessed using the Rotterdam criteria[2]

1. Lizneva D, et al. Fertil Steril 2016;106(1):6–15. 2. Rotterdam ESHRE/ASRM-sponsored PCOS consensus workshop group. Hum Reprod 2004;19:41–47; 3. Azziz R, et al. J Clin Endocrinol Metab 2004; 89(2):453–462; 4. Escobar-Morreale HF, et al. Hum Reprod Update 2012;18(2):146–170.

It would be appropriate to consider further investigation for PCOS[1-3]

Ultrasound	• Ovarian morphology		
Laboratory tests	Tests to exclude other disorders*	Essential tests to confirm PCOS	Additional tests that may be useful
	• Serum thyroid stimulating hormone (TSH) • Serum prolactin • Serum or urine human chorionic gonadotropin (HCG) • DHEA-S • Serum free IGF-1 • 24-h urinary free cortisol	• Serum testosterone • Serum 17-hydroxyprogesterone (OHP)	• Anti-Mullerian hormone (AMH) • Sex hormone binding globulin (SHBG)
Metabolic assessment (following confirmation of PCOS)	• Waist circumference and BMI. • Complete lipid profile, including total cholesterol, low-density lipoprotein (LDL)-cholesterol, non-high-density lipoprotein (HDL)-cholesterol, HDL-cholesterol and triglycerides • Oral glucose tolerance test • Blood pressure		

* Thyroid disease, hyperprolactinemia, nonclassical congenital adrenal hyperplasia, pregnancy, adrenal or ovarian tumors, acromegaly and Cushing syndrome

1. Legro RS, et al. J Clin Endocrinol Metab 2013;98:4565–4592. 2. Goodman NF, et al. Endocrine Pract 2015;21(11):1291–1300; 3. Fauser BCJM, et al. Fertil Steril 2012;97:28–38.

Additional resources

Resource	Source
Dermatology Quality of Life Index (DLQI)	Finlay AK, Khan GK. Dermatology Life Quality Index (DLQI)—a simple practical measure for routine clinical use. Clin Exp Dermatol 1994;19(3):210–216.
Specific acne measures:	
Acne Disability Index (ADI)[3]	Motley RJ, Finlay AY. How much disability is caused by acne? Clin Exp Dermatol 1989;14:194-198.
Cardiff Acne Disability Index (CADI)[4]	Motley RJ, Finlay AY. Practical use of a disability index in the routine management of acne. Clin Exp Dermatol 1992;17:1-3.
Acne-Specific Quality of Life (Acne-QOL) questionnaire[5]	Girman CJ, et al. Evaluating health-related quality of life in patients with facial acne: development of a self-administered questionnaire for clinical trials. Qual Life Res 1996;5(5)481-90.
Acne-QOL[6]	Tan J, et al. Condensation and validation of a 4-item index of the Acne-QoL. Qual Life Res 2006;15(7):1203-10.
European evidence-based guidelines for the treatment of acne.	Nast A, Dréno B, Bettoli V, et al. European evidence-based (S3) guidelines for the treatment of acne. J Eur Acad Dermatol Venereol 2012;26(Suppl 1): 1–29.
Guidance on contraindications when prescribing combined hormonal treatment	World Health Organization. Medical eligibility criteria for contraceptive use. 5th ed. Geneva: WHO; 2015.

Review of learning goals: Camila

After completing this case study, you should have greater insights into:

- Recognizing acne that can be treated with combined hormonal treatment
- The high prevalence and impact of acne
- Identifying androgen excess as a causative factor
- Managing acne with combined hormonal treatment
- Making shared management decisions
- What if? How diagnosis and management may be affected if some of the factors of case presentation were to change

The Global Aware Group

Appropriate Care For Women With Androgen Excess

Case study 3: Diagnosis and treatment of androgenic symptoms of PCOS

September 2016 **G.MKT.WH.09.2016.0274**

Introduction

- This case study forms part of a training programme aimed at improving knowledge and skills in the appropriate treatment and care of women with androgen excess.

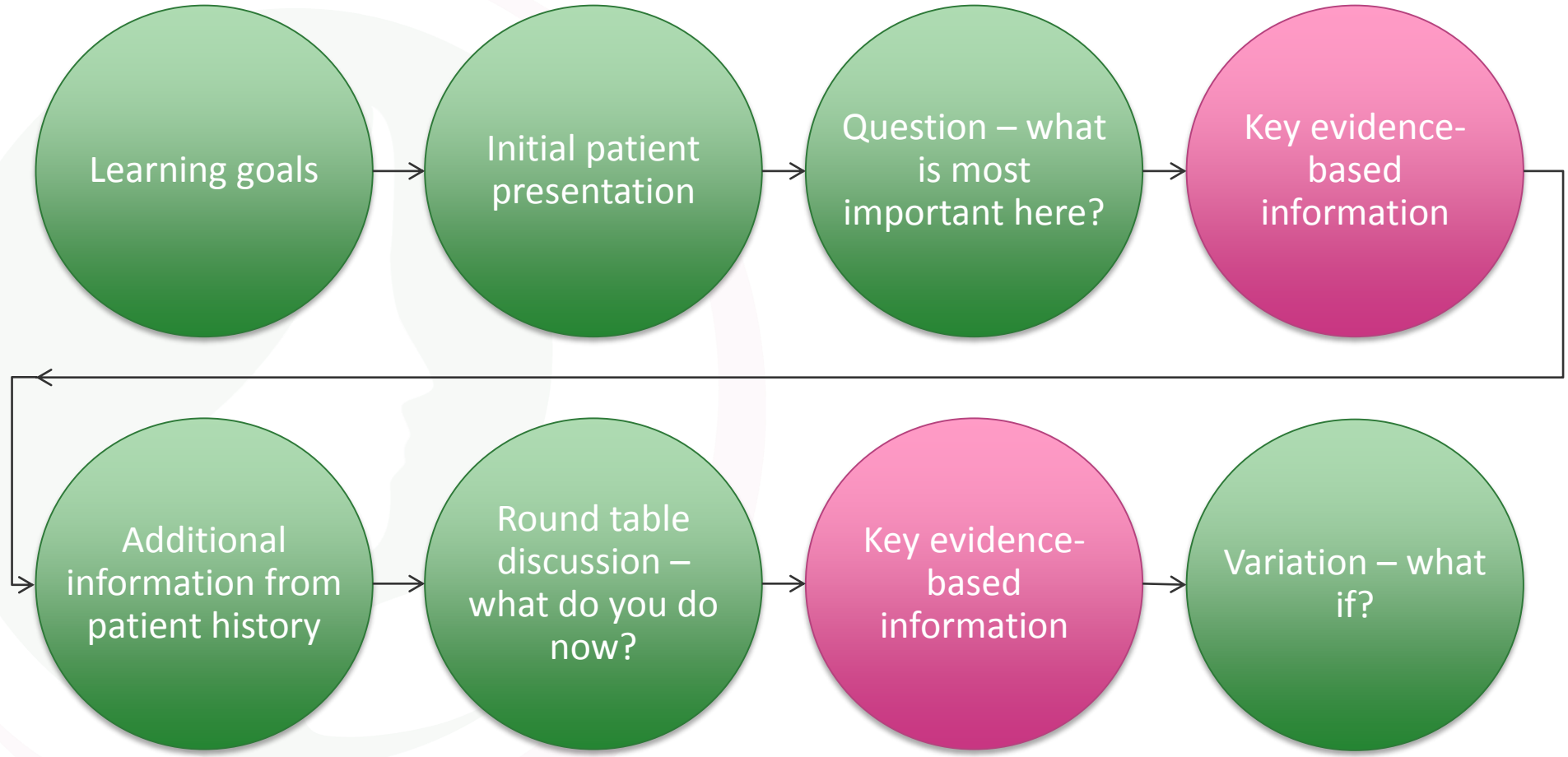
- The content has been developed by the Global AWARE (Appropriate Care for Women With Androgen Excess) Group, an independent panel of physicians with expert interest in the treatment of androgen excess in women, formed in 2015

- Formation of the AWARE group and the group's meetings were supported by Bayer Pharma AG

How to use these case studies

- Progress through each fictional case study is facilitated by:
  - A detailed description of the patient
  - Interactive questions
  - Table discussions
  - Key learning points
- The number of slides used in the workshop can be adapted according to the time available and/or the relative experience of the workshop participants
- All slides are supported by:
  - Guidance notes to assist in the facilitation of participant discussion
  - Fully referenced notes that expand on slide content where relevant
  - A summary of additional resources that participants may wish to access independently

Generalised structure of each case



Opportunities for discussion are guided by two symbols

This symbol indicates an opportunity for participants to consider and discuss their response to a specific question as a whole group

This symbol indicates an opportunity for participants to consider their response to a specific question using smaller group discussion

Learning goals

After completing this case study, you should have greater insights into:

- Symptoms of PCOS
- The prevalence and impact of PCOS
- Confirming a diagnosis of PCOS
- Identifying the correct PCOS phenotype
- Appropriate treatment options for androgenic symptoms of PCOS
- Making shared management decisions
- What if? How diagnosis and management may be affected if some of the factors of case presentation were to change

Your patient: Meili

- Meili is 31 years old with irregular periods
- She recently stopped using hormonal contraception (6 months ago)
- She isn't taking any medication currently but has tried acupuncture for the bleeding problems in the past
- Meili mentions that she and her partner would like to have a baby at some point in the future but she read somewhere that irregular periods may prevent her from getting pregnant

Table discussion

- What are the potential causes of Meili's irregular bleeding?
  - Underlying endocrine problem?
  - Endometrial proliferation?
  - Medication use?

- **Please discuss this question together for five minutes**
- **Identify areas where you agree <u>and</u> areas where you had different opinions**
- **Nominate one group member to provide feedback on your discussions**

Irregular bleeding in women of reproductive age can have different etiology[1]

- Causes include:[1]
  - Endometrial hyperplasia
  - Thyroid dysfunction
  - Prolactinaemia
  - Polycystic ovary syndrome
- Some medications can also cause irregular bleeding, for example, anticonvulsants, antipsychotics

1. Munro MG, et al. Int J Gynecol Obstet 2011;113: 3–13

A detailed medical history reveals…

- Medical history
  - Menarche at 13 years
  - Regular visits to laser epilation for unwanted facial hair
  - Oligomenorrhea to begin with, then irregular cycles
  - Family history of cardiovascular disease and diabetes
  - Mother had hysterectomy at age 48 (she does not know why, potentially due to some sort of cancer)

The physical examination reveals…

- Waist-to-hip ratio: 0.91
- BMI: 28.7 (weight: 85 kg; height: 172 cm)
- She mentions that she gained quite a lot of weight in the last few months
- Gyn status: Speculum and bimanual examination without pathological findings
- Skin: Hair growth around the chin, breast and abdomen

Polycystic ovary syndrome (PCOS) is a common cause of menstrual dysfunction[1]

- PCOS is the cause of:[1]
  - 85% of cases of oligomenorrhea
  - 30–40% of cases of amenorrhea
- Other common presenting symptoms of PCOS include:[1,2]
  - Hyperandrogenic skin symptoms such as hirsutism, acne or alopecia
  - Clinical elements of the metabolic syndrome
  - Infertility

1. Sirmans SM, Pate KA. Clin Epidemiol. 2012;6:1–13; 2. Androgen Excess and PCOS Society Education Committee. Accessed at: http://www.ae-society.org/pdf/handouts/pcos.pdf

Interactive question

- You suspect Meili may have polycystic ovary syndrome, what other test and investigations might you consider?
  - Serum androgens?
  - Ultrasound?
  - What conditions, if any, would you be looking to exclude?

Presence of menstrual dysfunction and hyperandrogenic skin symptoms can indicate polycystic ovary syndrome (PCOS)

- PCOS is a common disorder affecting 6–21% of women*[1]

- The Rotterdam criteria define PCOS by the presence of two of the following after exclusion of other androgen excess or related disorders:[2]
  - irregular menses
  - hyperandrogenism (either clinical or biochemical)
  - polycystic ovary morphology, after excluding other endocrine causes such as hyperprolactinemia

- Geographic location and ethnic origin contribute to the variability in primary presentation of PCOS[3]

* When assessed using the Rotterdam criteria[2]

1. Lizneva D, et al. Fertil Steril 2016;106(1):6–15; 2. Rotterdam ESHRE/ASRM-sponsored PCOS consensus workshop group. Hum Reprod 2004;19:41–47; 3. Mueck A, et al. [In preparation].

It would be appropriate to consider further investigation to confirm a diagnosis of PCOS[1-3]

Ultrasound	• Ovarian morphology		
Laboratory tests	Tests to exclude other disorders*	Essential tests to confirm PCOS	Additional tests that may be useful
	• Serum thyroid stimulating hormone (TSH) • Serum prolactin • Serum or urine human chorionic gonadotropin (HCG) • DHEA-S • Serum free IGF-1 • 24-h urinary free cortisol	• Serum testosterone • Serum 17-hydroxyprogesterone (OHP)	• Anti-Mullerian hormone (AMH) • Sex hormone binding globulin (SHBG)
Metabolic assessment (following confirmation of PCOS)	• Waist circumference and BMI. • Complete lipid profile, including total cholesterol, low-density lipoprotein (LDL)-cholesterol, non-high-density lipoprotein (HDL)-cholesterol, HDL-cholesterol and triglycerides • Oral glucose tolerance test (OGTT) • Blood pressure		

* Thyroid disease, hyperprolactinemia, nonclassical congenital adrenal hyperplasia, pregnancy, adrenal or ovarian tumors, acromegaly and Cushing syndrome

1. Legro RS, et al. J Clin Endocrinol Metab 2013;98:4565–4592. 2. Goodman NF, et al. Endocrine Pract 2015;21(11):1291–1300; 3. Fauser BCJM, et al. Fertil Steril 2012;97:28–38.

Your findings confirm a diagnosis of PCOS

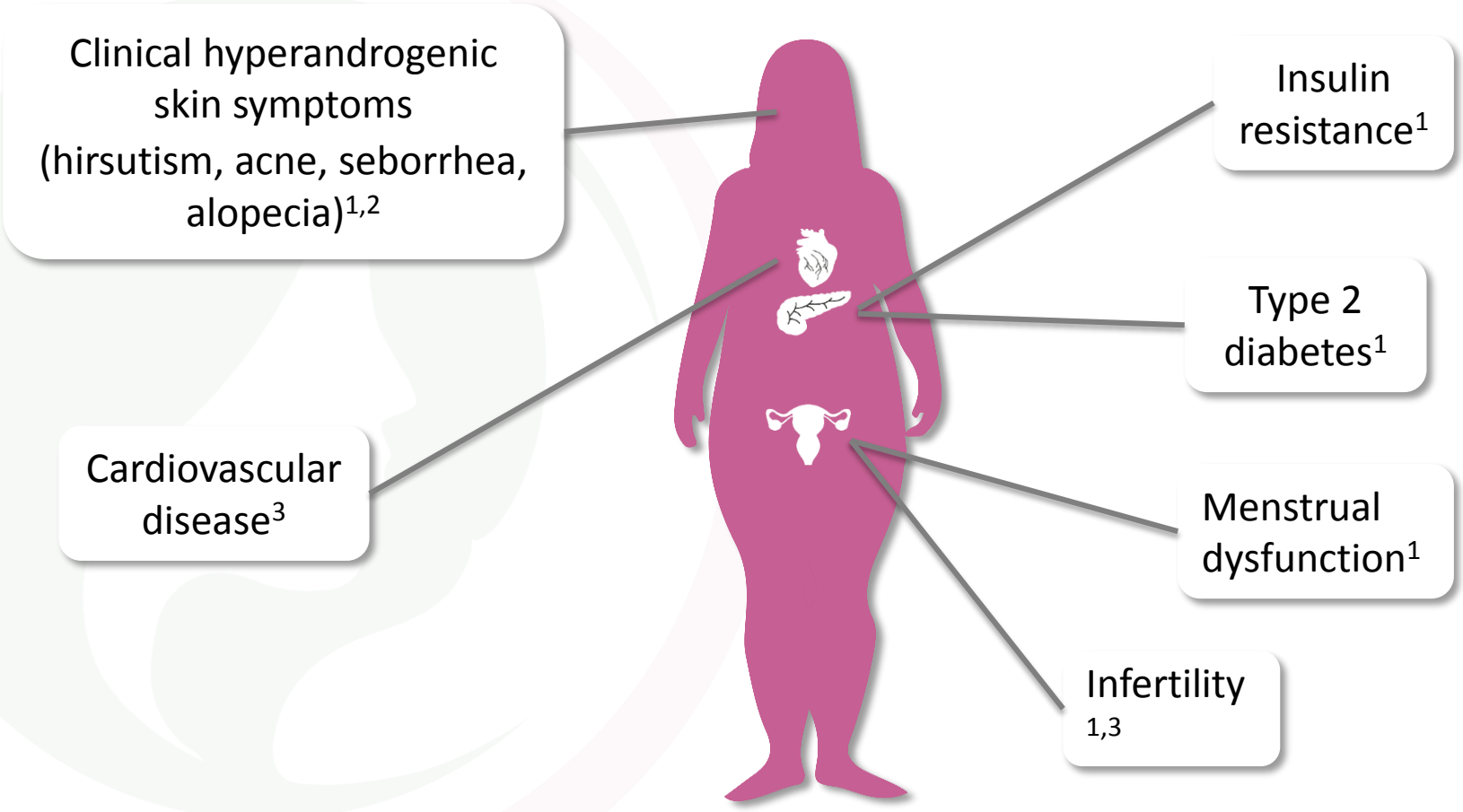
Laboratory

- Essential tests
  - Total testosterone increased
  - 17-OHP normal
- Additional tests you decide to carry out in accordance with department practice
  - DHEA-S, SHBG, and OGTT all normal
  - FSH normal, LH increased, FSH/LH ratio inversed
  - Estradiol slightly elevated
- Ultrasound
  - 8 follicles at the periphery of the left ovary (max DM 10 mm)
  - 8 follicles at the periphery of the right ovary (max DM 13 mm)
  - No indication of endometrial hyperplasia

Interactive question

- Are there any long-term health risks of PCOS?
  - Are they reproductive?
  - Are they metabolic?
  - Are they cardiovascular?

PCOS has an impact on multiple systems within the woman's body[1-3]



1. Sirmans SM, Pate KA. Clin Epidemiol 2014;6:1–13; 2. Fauser BCJM, et al. Fertil Steril 2012;97:28–38; 3. Legro RS, et al. J Clin Endocrinol Metab 2013;98:4565–4592.

PCOS is associated with multiple long-term health risks[1-3]

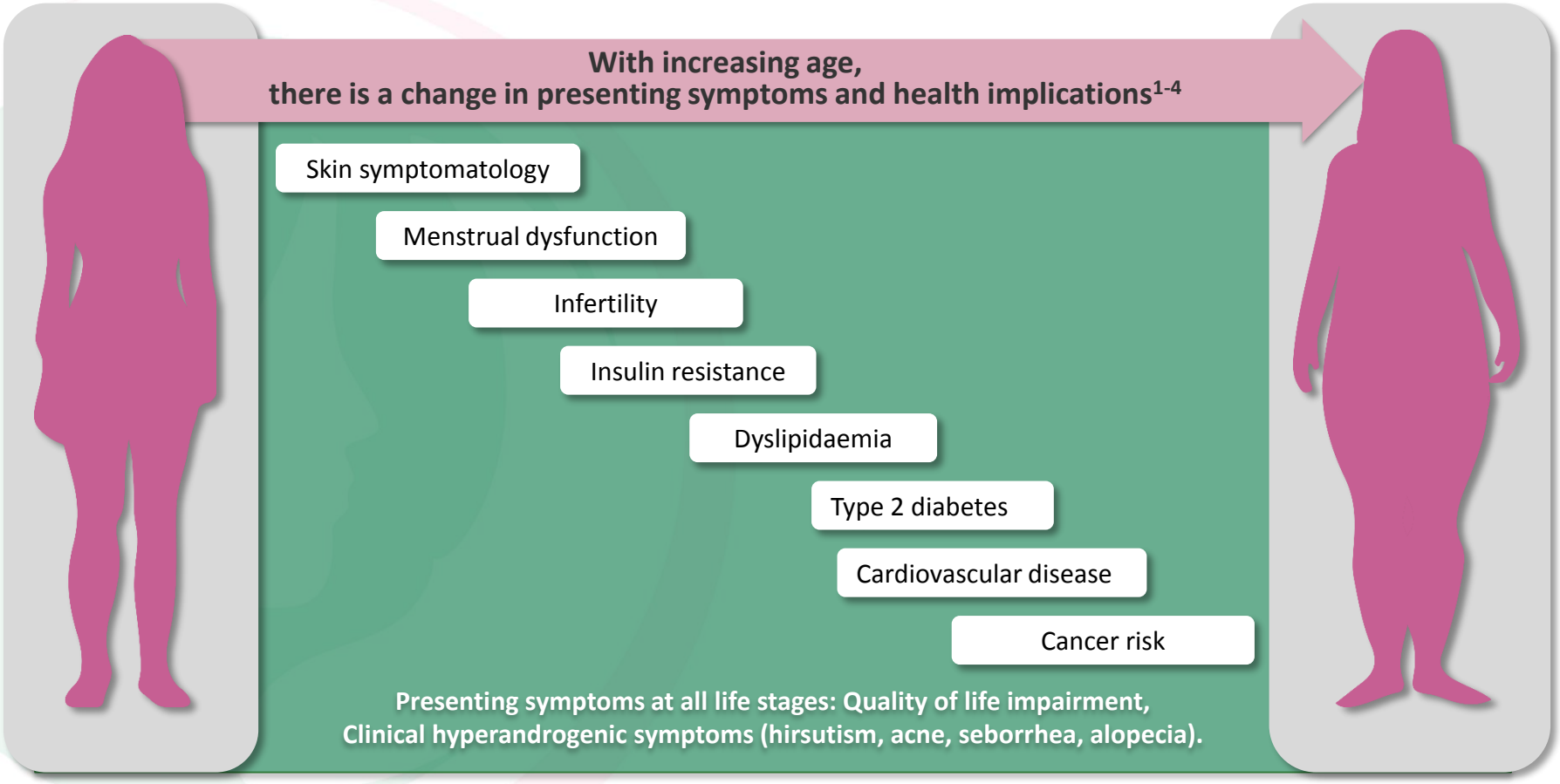
Cardiovascular risk stratification in women with PCOS[1]
At risk – PCOS women with any of the following risk factors
Obesity Cigarette smoking Hypertension Dyslipidemia Subclinical vascular disease Impaired glucose tolerance Family history of premature cardiovascular disease
At high risk – PCOS women with
Metabolic syndrome Type 2 diabetes Overt vascular, renal or cardiovascular disease

Reproductive risk in women with PCOS
Infertility[1,2]
Adverse pregnancy outcomes including risk of miscarriage[2]
Endometrial hyperplasia/cancer[2,3]

- The reproductive and metabolic implications of PCOS, including likelihood of serious cardiovascular morbidity in later life call for prompt diagnosis and management

1. Legro RS, et al. J Clin Endocrinol Metab 2013;98:4565–4592; 2. Sirmans SM, Pate KA. Clin Epidemiol 2012;6:1–13. 3. Fauser BCJM, et al. Fertil Steril 2012;97:28–38.

Primary presentation of PCOS may also vary with age[1-4]



1. Sirmans SM, Pate KA. Clin Epidemiol 2014;6:1–13; 2. Legro RS, et al. J Clin Endocrinol Metab 2013;98:4565–4592.; 3. Fauser BCJM, et al. Fertil Steril 2012;97:28–38; 4. Lizneva D, et al. Fertil Steril 2016;106(1):6–15.

A phenotypic approach to defining PCOS helps to identify those women at greatest risk of metabolic dysfunction[1]

- Those with 'classic' PCOS phenotypes i.e. A and B are at greatest risk of metabolic dysfunction[1]

Parameter	Phenotype A	Phenotype B	Phenotype C	Phenotype D
PCOS features	HA/OD/PCOM	HA/OD	HA/PCOM	OD/PCOM
Hyperandrogenism (HA)	+	+	+	–
Ovulatory dysfunction (OD)	+	+	–	+
Polycystic ovarian morphology (PCOM)	+	–	+	+

1. Lizneva D, et al. Fertil Steril 2016;106(1):6–15

Table discussion

- How would you manage Meili's PCOS?
- What are the pharmacological options?
- What other factors do you need to consider?

- **Please discuss this question together for five minutes**
- **Identify areas where you agree and areas where you had different opinions**
- **Nominate one group member to provide feedback on your discussions**

Management of androgenic symptoms of PCOS

- Pharmacological treatment of PCOS is aimed at reducing the level of circulating androgens and controlling their effect at tissue level[1]
  - Address dermatological symptoms such as hirsutism and acne
  - Reduce the risk of long-term metabolic consequences

- Lifestyle modification i.e. maintaining a healthy diet and exercise and achievement of weight reduction[2]
  - Observational studies show that moderate weight loss (5 to 10%) in women with PCOS can improve insulin resistance as well as androgenic and reproductive outcomes

1. Goodman NF, et al. Endocrine Pract 2015;21(11):1291–300; 2. Moran LJ, et al. Cochrane Database Syst Rev 2011;16(2):CD007506. doi: 10.1002/14651858.CD007506.pub2

Rationale for antiandrogen therapy

- A combination of EE with a progestogen that possesses antiandrogenic activity is regarded as the most appropriate choice for treatment of PCOS[1]
- Androgen-related effects of EE/progestogen combinations include[2]:
  - Increase in sex hormone-binding globulin (SHBG) production and so decrease circulating free androgen levels
  - Reduction in ovarian androgen synthesis
  - Decrease in adrenal androgen synthesis
  - Reduce dihydrotestosterone binding to androgen receptors
- Antiandrogenic potential of EE/progestogen combinations varies according to the dose and type of progestogens used[3]

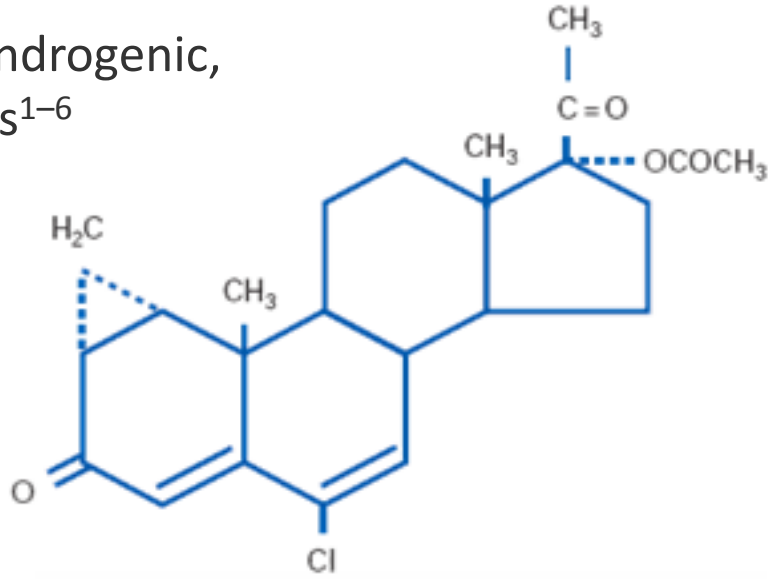
1. Yildiz BO. Semin Reprod Med 2008;26:111–120; 2. Sirmans SM, Pate KA. Clin Epidemiol 2014;6:1–13; 3. Buzney E, et al. J Am Acad Dermatol 2014;71:859.e1-15

You discuss treatment options with Meili

- She is keen to resolve the irregular periods and the hirsutism
- You recommend
  - CPA/EE for the androgenic symptoms
  - a review in 6 months to discuss progress and re-evaluate her priorities (resolution of androgenic symptoms vs. desire for pregnancy)
  - a weight loss programme
- You discuss the cardiovascular risks associated with EE/progestogen treatment

CPA is a steroidal antiandrogen

CPA is a steroid compound with potent antiandrogenic, progestogenic and antigonadotropic activities[1–6]



Antigonadotropic properties:

- Exerts negative feedback on the hypothalamo-pituitary-ovarian axis, decreasing ovarian testosterone synthesis and free testosterone in the circulation[1]
- Inhibition of gonadotropin secretion results in suppression of ovulation[2]

Antiandrogen:

- Inhibits 5α-reductase, reducing DHT levels and thereby blocking downstream initiation of androgenic effects in target cells[3]
- A competitive antagonist at the nuclear androgen receptor[1]

Potent progestogen:

- Leads to alterations of the cervical mucus and transformation of the endometrium[4, 5]
- The strong progestational action of CPA also contributes to dependable contraceptive protection[6]

CPA, cyproterone acetate; DHT, dihydrotestosterone

1. Neumann. Exp Clin Endocrinol 1994;102:1-32; 2. Spona & Huber. Gynecol Obstet Invest 1987;23:184-93; 3. Fang & Liao. Mol Pharmacol 1969;5:428-31. 4. Fedele et al. Contraception 1987;35:497-505; 5. Neumann. Postgrad Med J 1978;54 Suppl 2:11-24. 6. Aydinlik et al. Clin Trials J 1990;27:392-402

Treatment of androgenic skin symptoms with CPA/EE in women with PCOS is most effective as long-term therapy[1]

Acne‡

- **100% efficacy** after 12–24 treatment cycles[1]

Mild Hirsutism#

- **Completely resolved** following 36 treatment cycles[1]

Severe Hirsutism#

- Only **18.2% still had severe hirsutism** following 60 treatment cycles[1]

‡Acne was measured according to the number of lesions and their spread across the face, back and chest
Hirsutism was evaluated using the modified Ferriman-Gallwey score

1. Falsetti L, et al. Hum Reprod. 2001;16(1):36-42.

Metabolic effects of CPA/EE in women with PCOS

- Clinical studies confirm an effect of CPA/EE on lipid metabolism[1]
  - Changes are generally within normal limits and of little clinical relevance
- Effects of CPA/EE on insulin resistance remain inconsistent[2,3]
  - There is a need for caution when using CPA/EE in obese women due to effect of high BMI on insulin resistance
- More research is needed into metabolic changes in women affected by hyperandrogenism, particularly in those with PCOS[1]

1. Bitzer J, et al. [In preparation]; 2. Meyer C, et al. Diabetes Care 2007;30(3):471–478; 3. Bhattacharya SM, Jhan A. Fertility and sterility 2012; 98(4): 1053-59

Addressing cardiovascular safety with EE/progestogen combinations

Use of estrogen/progestogen combinations is associated with an increased risk for VTE (DVT or PE)[1,2]

The use of CPA/EE carries an increased risk of VTE/ATE compared with no use

Highest during the 1st year of use	Highest when restarting or switching from another OC

However, the risk of VTE during COC use remains lower than that during pregnancy and childbirth[3,4]

ATE, Arterial thromboembolism; **COC**, Combined oral contraceptive; **DVT**, Deep vein thrombosis; **PE**, Pulmonary embolism; **OC**, Oral contraceptive; **VTE**, Venous thromboembolism; **CPA/EE**, 0.035mg ethinylestradiol/2mg cyproterone acetate

1. OC class label: www.ema.europa.eu. 2. Rosendaal MD. Lancet 1999;353:1167–1173. 3. Dinger JC *et al.* Contraception 2007;75(5):344–354.4. Heit *et al.* Ann Intern Med 2005;143(10):697–706

Addressing cardiovascular safety with EE/progestogen combinations (continued)

Due to its labeled indication, CPA/EE may channel use towards women with an inherently higher cardiovascular risk[1,2]

Observational studies of **VTE risk with CPA/EE** compared to LNG-containing and other COCs (low-estrogen <0.05mg) yield varying findings

Some studies reported a greater VTE risk, **comparable** to so-called 3rd generation COCs[3–5]

Other studies showed **no differences** in VTE risk[1,6,7]

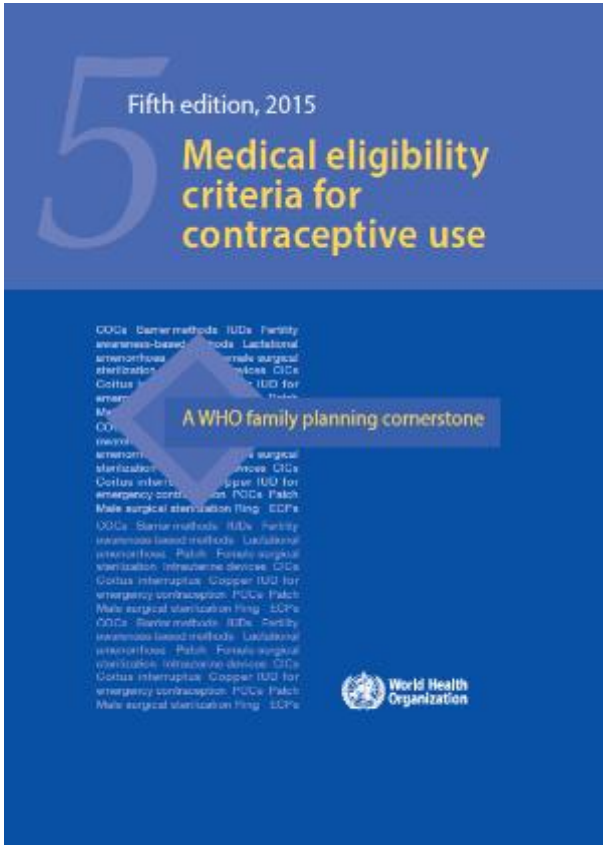
Studies that addressed the issue of confounding or duration of use concluded that the VTE risk is **not significantly higher**[1,7]

COC, Combined oral contraceptive; **LNG**, Levonorgestrel; **PCOS**, Polycystic ovary syndrome; **VTE**, Venous thromboembolism; **CPA/EE**, 0.035mg ethinylestradiol/2mg cyproterone acetate.

1. Seaman HE *et al*. Pharmacoepidemiol Drug Saf 2004;13(7):427–436. 2. Bird ST *et al*. J Thromb Haemost 2013;11(6):1059–1068. 3. Vasilakis-Scaramozza C *et al*. Lancet 2001;358(9291):1427–1429. 4. Seaman HE *et al*. Hum Reprod 2003;18(3):522–526. 5. Lidegaard Ø *et al*. Acta Obstet Gynecol Scand 2013;92(10):1135–1142. 6. Lidegaard Ø *et al*. J Obstet Gynaecol Can 2003;25(7):575–577. 7. EURAS 2007.

Factors to consider before prescribing combined hormonal treatment

- WHO MEC provides guidance on contraindications when prescribing combined hormonal treatment[1]



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

The following slides contain variations to the case

These may be used in workshops where:

- there is additional time available for case discussion
- the participants are more experienced in the management of hyperandrogenic skin symptoms and interested in a more challenging discussion

Variation: Table discussion

- When carrying out investigations into the potential cause of Meili's menstrual dysfunction, you find she is anovulatory
- What would you recommend with regards to treatment?
- Would her eventual desire for pregnancy impact on your decision?

- **Please discuss this question together for five minutes**
- **Identify areas where you agree and areas where you had different opinions**
- **Nominate one group member to provide feedback on your discussions**

Ovulation induction in PCOS

- Polycystic ovary syndrome is the most common cause (70%) of anovulatory subfertility[1]
- Chronic anovulation can increase the risk of endometrial hyperplasia and carcinoma[2]
- Clomifene citrate is the drug of first choice for ovulation induction in women with PCOS[3] - it induces ovulation in 70% of women with PCOS[1]
- Weight loss may have a beneficial effect on reproductive outcomes in women with PCOS[4]

1. Hamilton-Fairley D, Taylor A. Anovulation. BMJ 2003; 327: 546-9; 2. Sirmans SM, Pate KA. Clin Epidemiol 2014;6:1–13; 3. Homburg R. Reprod Biol Endocrinol 2003;1:109; 4. Legro RS, et al. J Clin Endocrinol Metab 2013;98:4565–4592

When to refer a patient with infertility

- In women with PCOS, referral for assisted reproduction techniques may be needed for women who still have difficulty in conceiving despite attempts at ovulation induction[1]

1. Homburg R. Reprod Biol Endocrinol 2003;1:109.

Review of learning goals: Meili

After completing this case study, you should have greater insights into:

- Symptoms of PCOS
- The prevalence and impact of PCOS
- Confirming a diagnosis of PCOS
- Identifying the correct PCOS phenotype
- Appropriate treatment options for androgenic symptoms of PCOS
- Making shared management decisions
- What if? How diagnosis and management may be affected if some of the factors of case presentation were to change