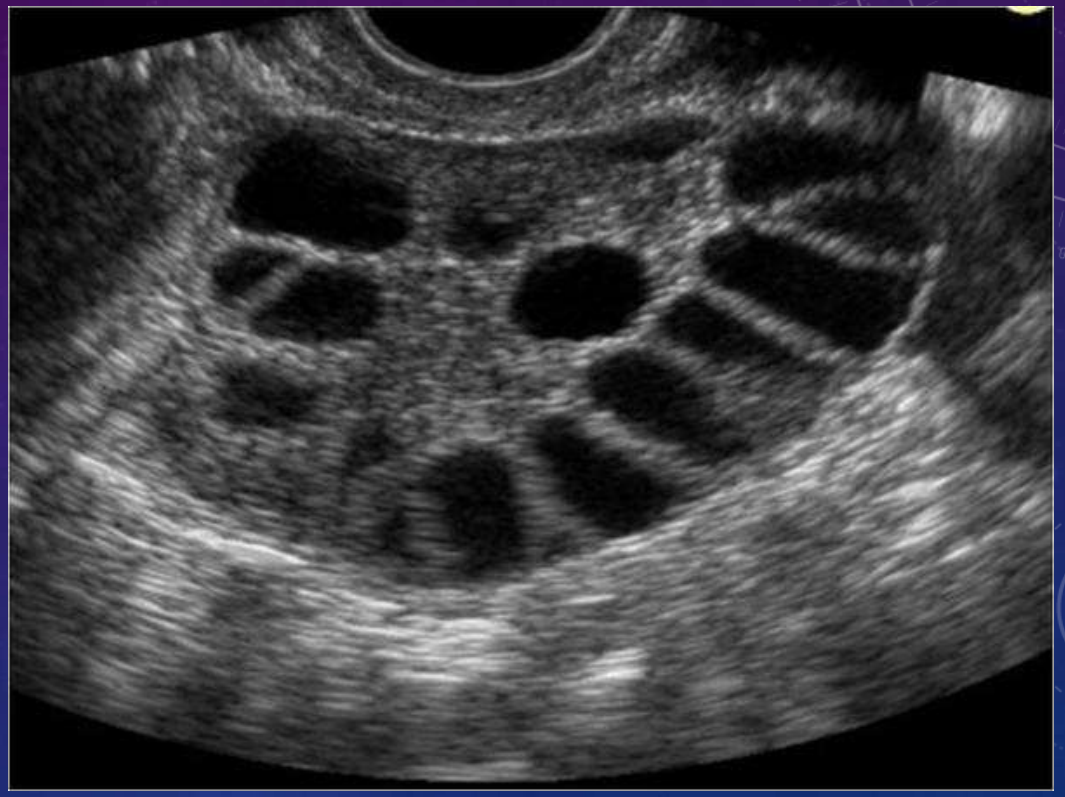
PCOS: WHAT THE FAMILY DOCTOR NEEDS TO KNOW



- Agnieszka Majdan, MD
- Endocrinologist, Jewish General Hospital

FACULTY/PRESENTER DISCLOSURE

- **Faculty: Agnieszka Majdan, MD MA FRCPC**

- **Relationships with commercial interests:**
  - **Grants/Research Support:** CIHR
  - **Speakers Bureau/Honoraria:** AstraZeneca, NovoNordisk, Merck, Janssen,, EliLilly, Sanofi
  - **Consulting Fees:** AstraZeneca, NovoNordisk, Merck, Janssen, EliLilly, Sanofi

Not relevant to today's presentation

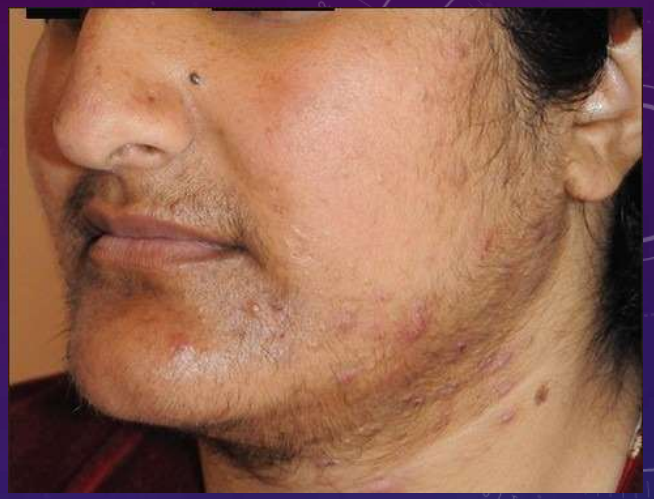
CASE

- Ms M, 24 year old woman complaining of facial hair

  - Problem onset shortly after puberty, progressively worsening; issues with acne in the past (used Accutane), now better
  - Menarche age 14, since then menses irregular, every 3-6 months, has had no menses since 6 months now
  - Has tried laser treatment with some success but "hair keeps coming back"
  - Soon to be married, but not planning pregnancy in the short term
- Exam: Vitals normal, BMI 29; terminal hairs on the chin, sideburns, chest, abdomen, upper thighs

CASE

- How do you evaluate her?
- Does she have PCOS?
- What do you advise?



PLAN OF PRESENTATION

- Pathogenesis of PCOS
- Clinical manifestations
- Diagnosis—work up
  - Adults
  - Adolescents
- Management
- When to refer

PCOS

- PCOS is the most common female endocrinopathy, affecting 6-12% of young women
- Heterogenous disorder

- Pathophysiology and etiology debated
  - Role of insulin resistance, inflammation, ovary, androgens, hypothalamus in pathogenesis
- Central features: reproductive, metabolic and psychological
- Genetic contribution: PCOS represents a complex genetic trait
- Onset typically in teenage years

DIAGNOSIS

When to suspect the dx

- Woman of reproductive age with irregular menses **and** sx of hyperandrogenism
  - Women with oligomenorrhea alone
  - Women with hyperandrogenism
  - Women with PCO on US without clinical features of PCOS do **not** have it

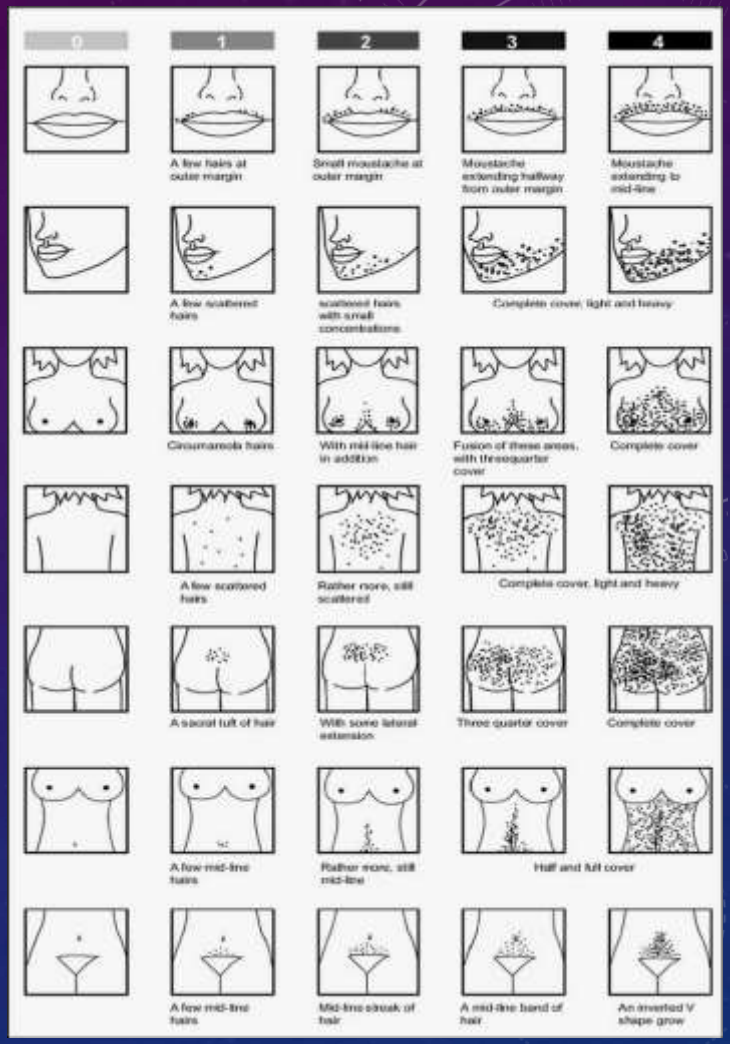
DIAGNOSIS CONT'D

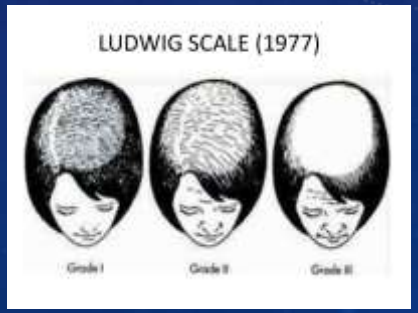
- Rotterdam criteria 2003
  - Two of the three are required:

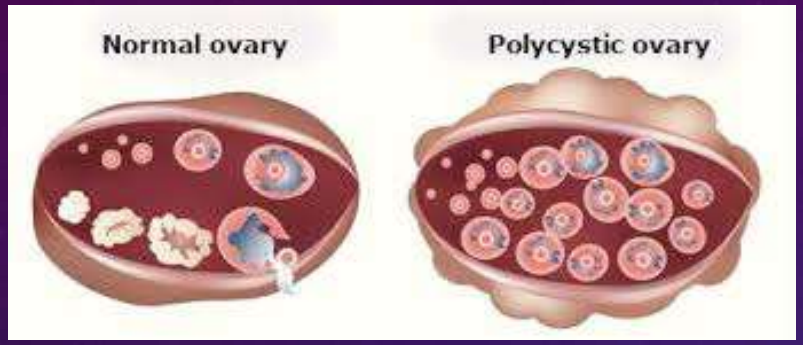
- Oligo- and/or anovulation
- Clinical and/or biochemical signs of hyperandrogenism
- Polycystic ovaries (by ultrasound)

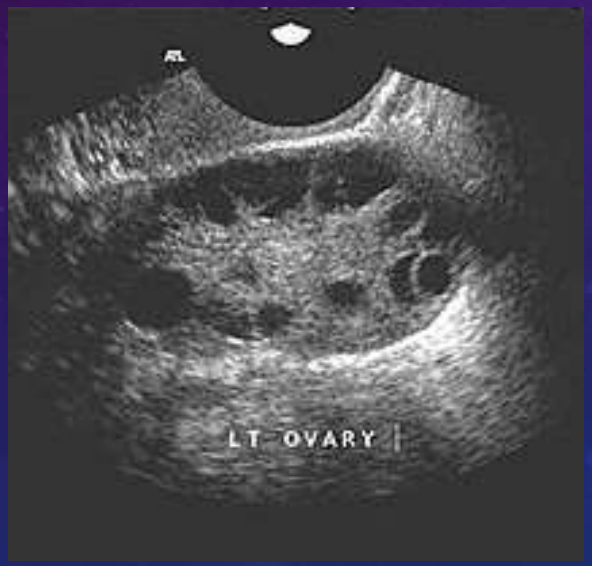
- Once other conditions mimicking PCOS have been ruled out

- Oligo or anovulation
  - Not easy to define since not every bleeding episode is preceded by ovulation
    - <8 menses/year
    - <21 or >45 day cycles or any cycle >90 days
    - Random progesterone <10 nmol/L; midluteal (day 20) progesterone <16
- Hyperandrogenism
  - Total Testo >2 nmol/L
  - May use free/bioavailable Testo
  - Acne or androgenetic alopecia or hirsutism
    - Extreme ethnic variability in body hair amount
    - Ferriman-Gallwey score >6
      - Low threshold for acne or hirsutism in East Asian or Native Canadian woman women
    - Ludwig score for alopecia





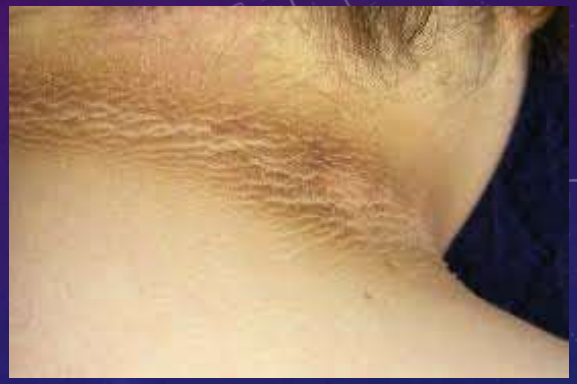




- PCOM
  - Transvaginal US if possible
  - >12 small (<9mm) preantral follicles in peripheral distribution is classic
  - Nonspecific, patter may be seen in N
- Antimullerian hormone
  - Not suitable as diagnostic test

FREQUENT CLINICAL FEATURES OF PCOS

- Metabolic issues
  - Obesity/overweight in 50-85%
  - Insulin resistance
  - Increased risk for Type 2 diabetes
  - Dyslipidemia
  - Metabolic syndrome
  - Cardiovascular risk
  - NAFLD
  - OSA
- Mood disorders
  - Body image, disordered eating, depressive and anxiety sx
- Endometrial cancer

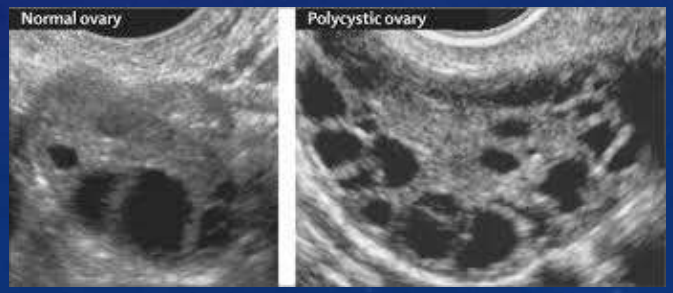


DIAGNOSIS

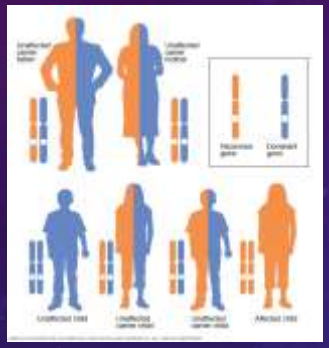
- Differential diagnosis of PCOS

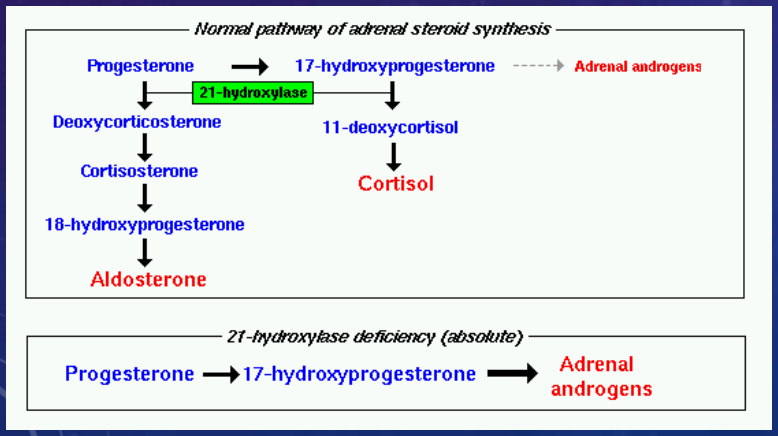
  - Hypothyroidism
  - Hyperprolactinemia
  - Pregnancy
  - Hypothalamic amenorrhea
  - Non-classic Congenital Adrenal Hyperplasia (NCCAH)

  - Hypercortisolism/acromegaly
  - Adrenal/ovarian virilizing tumours



NON-CLASSIC CAH





Very similar clinical presentation

- Common in Eastern-European Jewish population (1:30), Hispanic, Italian or Slavic
- Milder form (heterozygote) of a more severe type of autosomal recessive genetic disorder leading to elevated levels of androgens and aldosterone deficiency
- Most commonly affected enzyme is 21-hydroxylase
    - Important to identify since may have child with more severe “classic” CAH

Screening

- Morning (8AM) follicular-phase 17-hydroxyprogesterone of >6nmol/L
    - Needs to be confirmed with 250ug ACTH stim
        - normal is <43nmol/L

ANDROGEN-SECRETING TUMORS

- Recent-onset, progressive hirsutism, often virilization, older woman
  - Frontal balding, severe acne, clitoromegaly, deepening of voice
  - Typically seen in post-menopausal women
  - Total T is typically >7nmol/L
  - DHEAS typically >22um/L

DIAGNOSIS CON'T

- Watch out in adolescents!
  - Dx should not be made in first 2 years after menarche
  - Need evidence of hyperandrogenism
    - Oligo or amenorrhea with PCO morphology alone is insufficient
  - If evidence of virilisation, need more complete work-up

SUGGESTED INITIAL WORK UP

- History
  - Onset typically in teenage years, slow progression
- Physical exam
  - Skin—alopecia, hirsutism, acne, acanthosis nigricans, skin tags, striae
  - Body weight, BMI, abdominal circumference
  - BP
- Blood test (early follicular phase if possible) before 9am
  - Fasting total testosterone
    - ULN <2.1 nmol/L in women
    - Bioavailable testosterone, DHEAS are optional
  - Prolactin
  - 17-OH progesterone
    - ULN <6nmol/L
  - TSH, FSH/estradiol, BhCG
- Transvaginal US
  - Not necessary if clinical criteria met

Careful! Don't bother getting testo while woman is taking OCPs or metformin or spironolactone…

ONCE DIAGNOSIS MADE…

- Cardiometabolic assessment
  - Fasting glucose, HbA1c, lipids
- NAFLD?
- Mood disorders?
- OSA?

MANAGEMENT

Diagnosis and Treatment of Polycystic Ovary Syndrome: An Endocrine Society Clinical Practice Guideline

Human Reproduction, Vol.33, No.9 pp. 1602–1618, 2018
Advanced Access publication on July 19, 2018 doi:10.1093/humrep/dey256

human reproduction ESHRE PAGES

Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome†‡

Helena J. Teede[1,2,3,*], Marie L. Misso[1,2,3], Michael F. Costello[4], Anuja Dokras[5], Joop Laven[6], Lisa Moran[1,2,3], Terhi Piltonen[7], and Robert J. Norman[1,2,8], on behalf of the International PCOS Network[§]

- Treatment is tailored to the patient's goals:
  - symptoms of androgen excess
  - endometrial protection
  - desire for fertility or contraception
  - addressing metabolic disturbances
- No cure, rather, suppression of symptoms

- Patient education is paramount

HOLISTIC MANAGEMENT

1st line in overweight/obese women: lifestyle with sustained weight loss

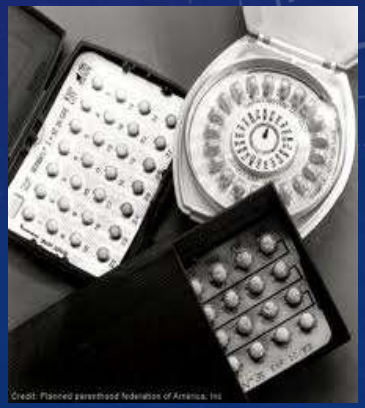
- Particularly effective for adolescents and young women
- As little as a 5% reduction in body weight can help restore ovulation
- Diet
  - Generally healthy eating
  - Tailored to patient preference: reduced carbohydrate, low calorie, IF, WW etc
- Physical activity
- Pharmacotherapy
  - Data on metformin, orlistat, liraglutide ; Contrave?
- Bariatric surgery

Graff 2016, IJCP; Sweatt 2015, FASEB

ANDROGEN EXCESS/OLIGOMENORRHEA

1st line: estrogen-progestin hormonal contraceptive (HC)

- Must rule out contra-indications as risk of thromboembolism may be increased in PCOS
  - HCs further increase the risk
- Endocrine Society 2013 unacceptable risk factors:
  - Age 35 and smoker
  - BP >140/90
  - Dyslipidemia
  - Known vascular disease
  - Diabetes mellitus >20y



CHOICE OF HC

- Inhibition of LH secretion, increase in SHBG (less free androgen), anti-proliferative action of progestin on endometrium
  - Endocrine Society: no preference of type of HC
  - International PCOS Network: 35ug ethinyloestradiol/cyproterone should not be 1st line
- Progestin with minimal androgenicity (cyproterone acetate, drospirenone, desogestrel, norethindrone) clinically most effective
- HCs with more androgenic activity (norgestimate, levonorgestrel) perhaps less optimal choice

- Low-androgenic HC: Diane-35, Yasmin, Yaz, Marvelon, Loestrin, Micronor
- Androgenic: Ortho-Cyclen, Tri-Cyclen, Linessa, Seasonique, Alesse

WHAT ABOUT RISKS OF DROSPIRENONE??

. BJOG 2013;120:801–811.

Table 3. Rates of VTE in comparative studies examining the thrombotic effects of drospirenone-containing oral contraceptive pills

Study	DRSP *n**	Comparator *n*	DRSP users		Comparator		Effect measure	Point estimate	95% CI
			IR†	95% CI	IR†	95% CI			
Drospirenone- versus levonorgestrel-containing OCPs									
Dinger 2007[24]	16 534	26 341	91	59–33	80	52–117	HR	3.3	0.9–10
Dinger 2010[9]	NR‡	NR	NR	NR	NR	NR	OR	1.0	0.5–1.8
Parkin 2011[7]	NR§	NR	23.0	13.4–36.9	9.1	6.6, 12.2	OR	3.3	1.4–7.6
Jick 2011[8]	NR‖	NR	30.8	25.6–36.8	9.6	9.6, 15.9	OR	2.4	1.7–3.4
Lidegaard 2011[22]	NR	NR	93	NR	75	NR	RR	2.12¶	1.68–2.66
FDA 2011 (all users)[11]	142 166	198 839	102.2**	NR	6.64**	NR	RR	1.45	1.15–1.83
FDA 2011 (new users)[11]	NR	NR	136.7**	NR	92.1**	NR	RR	1.57	1.13–2.18
Gronich 2011 (all users)[23]	73 629	21 546††	86‡‡	NR	69‡‡	NR	RR	1.65	1.02–2.65
Gronich 2011 (new users)[23]	NR	NR	NR	NR	NR	NR	RR	1.67	0.98–2.86
LASS 2011[10]	NR	NR	107	81–139	92	69, 120	HR	1.1	0.8–1.7
Drospirenone-containing OCPs versus other OCP users									
Seeger 2007[26]	22 429	44 858	130	80–200	NR	NR	RR	0.9	0.5–1.6
Leppee 2012[27]	NR	NR	NR§§	NR	NR‖‖	NR	Incidence RR	6.4	NR
Drospirenone-containing OCPs versus non-users of OCPs									
Lidegaard 2009[25]	NR	NR	28.3	NR	54.7	NR	RR	4.0	3.3–4.9
Vlieg 2009[28]	NR¶¶	NR	NR	NR	NR	NR	OR	6.3	2.9–13.7
Lidegaard 2011[22]	NR	NR	93	NR	37	NR	RR	4.47	3.91–5.11***

CI, confidence interval; Comparator *n*, sample size of the comparison group, those unexposed to drospirenone-containing OCPs; DRSP, drospirenone; DRSP *n*, sample size of the group of patients on drospirenone-containing OCPs; FDA, Food and Drug Administration; HR, hazard ratio; IR, incidence rate; LASS, Long-term Active Surveillance Study; NR, not reported; OCP, oral contraceptive pill; OR, odds ratio; RR, rate ratio; VTE, venous thromboembolism.

*Patients were given OCPs containing drospirenone and ethinyl estradiol (EE) in combination.

†Incidence rate per 100 000 women-years.

‡Report on 25 VTE cases exposed to drospirenone, 84 controls exposed to drospirenone, 60 VTE cases unexposed to drospirenone, 197 controls unexposed to drospirenone.

§Report on 17 VTE cases exposed to drospirenone, 26 controls exposed to drospirenone, 44 VTE cases unexposed to drospirenone, 189 controls unexposed to drospirenone.

‖Report on 121 VTE cases exposed to drospirenone, 313 controls exposed to drospirenone, 65 VTE cases unexposed to drospirenone, 368 controls unexposed to drospirenone.

¶Rate ratio (RR) presented is that for confirmed VTEs; among non-confirmed VTEs, the RR is 1.78 (95% CI 1.21–2.60).

**Age- and site-adjusted incidence rate.

††Comparator group includes women taking levonorgestrel/EE and norgestrel/EE.

‡‡Crude incidence rate.

§§Incidence rate: 43.8 per 100 000 women.

‖‖Incidence rate: 6.8 per 100 000 women.

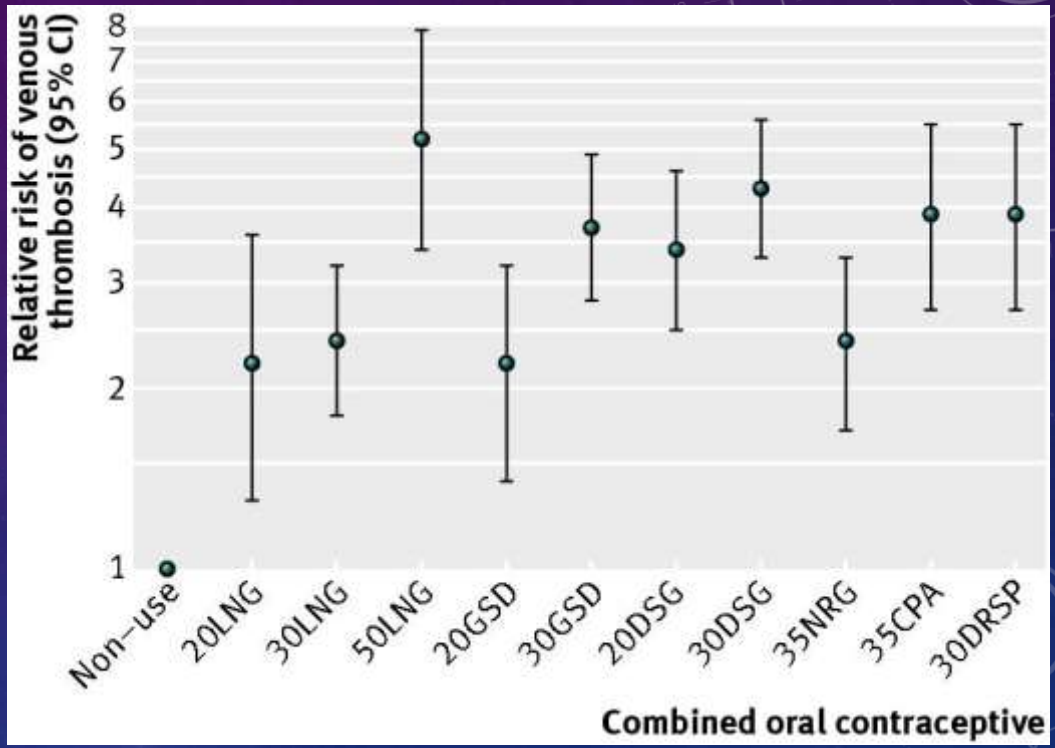
¶¶Report on 19 VTE cases exposed to drospirenone, 14 controls exposed to drospirenone, 421 VTE cases unexposed to drospirenone, 1102 controls unexposed to drospirenone.

***RR presented is for 30–40 μg EE; for 20 μg EE, the RR is 4.84 (95% CI 3.19–5.11).

THROMBOSIS RISK OF HC

- Increases with dose of ethinylestradiol
- Varies with type of progestogen:
  - Levonorgestrel LNG
    - Alesse
  - Gestodene GSD
  - Desogestrel DSG
    - Apri, Mircette, Marvelon
  - Norgestimate NRG
    - Ortho Tri-Cyclen
  - Cyproterone acetate CPA
    - Diane 35
  - Drospirenone DRSP
    - Yasmin, Yaz

Figure 4. Network meta-analysis, per contraceptive plotted on a logarithmic scale. Dots (lines)=overall relative risk (95% confidence interval) of venous thrombosis; non-use=reference group.



deBastos et al, Cochrane Library 2014

WHAT ABOUT THE RISKS OF DROSPIRENONE AND CYPROTERONE ACETATE?

- More recent analyses have shown inconsistent results (eg, Larivee et al BJOG 2017)

- ACOG position statement 2010 regarding VTE risk
  - Baseline population risk 4-5 women/10,000 woman-years
  - Risk associated with pregnancy 29/10,000 woman-years
  - Immediate postpartum 300-400/10,000 woman-years
  - Available HCs 9-10/10,000 woman-years (highest in first few months)

- "Comparable venous thromboembolism rates with drospirenone-containing oral contraceptives and other products".

Estrogen and Progestin Hormone Doses in Combined Birth Control Pills

Estrogen level ethinyl estradiol (micrograms)	Pill Brand Name	Progestin	Dose (mg)
15 mcgm	NuvaRing®	etonogestrel	0.120
20 mcgm	Alesse®; Levlite®; Aviane	levonorgestrel	0.10
	Loestrin 1/20® Fe; Microgestin Fe	norethindrone acetate	1.00
	Mircette®; Kariva	desogestrel	0.15
	YAZ	drospirenone	3.0
	Ortho Evra® (patch)	norelgestromin (norgestimate metabolite)	0.15
25 mcgm	Ortho Tri-Cyclen Lo (triphasic)	norgestimate	0.18/0.215/0.25
	Cyclessa (triphasic)	desogestrel	0.100/0.125/0.150
phasic 20/30/35 mcgm	Estrostep® Fe	norethindrone acetate	1.0/1.0/1.0
30 mcgm	Levlen®; Levora®; Nordette®	levonorgestrel	0.15
	Seosonale® (continuous pill)	levonorgestrel	0.15
	Lo/Ovral®; Low-Ogestrel-28	norgestrel	0.30
	Desogen®; Ortho-Cept®; Apri	desogestrel	0.15
	Loestrin® 1.5/30; Microgestin Fe 1.5/30	norethindrone acetate	1.50
	Yasmin®	drospirenone	3.0
phasic 30/40/30 mcgm	Triphasil®; Tri-Levlen®; Trivora®	levonorgestrel	0.05/0.075/0.125
35 mcgm	Ortho-Cyclen®	norgestimate	0.25
	Ovcon-35®	norethindrone	0.40
	Brevicon®; Modicon®; Necon 0.5/35; Nelova 0.5/35; NEE 0.5/35	norethindrone	0.50
	Necon 1/35®; Nelova 1/35; NEE 1/35; Genora 1/35; Norcept-E 1/35; Norethin 1/35E®; Norinyl® 1/35; Ortho-Novum® 1/35	norethindrone	1.00
	Demulen® 1/35; Zovia®	ethynodiol diacetate	1.00
	Ortho-Novum® 10/11; Jenest®; Necon 10/11; NEE 10/11 (biphasic)	norethindrone	0.50/1.00
	Ortho-Tri-Cyclen® (triphasic)	norgestimate	0.18/0.215/0.25
	Ortho-Novum® 7/7/7 (triphasic)	norethindrone	0.50/0.75/1.00
	Tri-Norinyl® (triphasic)	norethindrone	0.50/1.00/0.50
50 mcgm	Necon® 1/50; Norinyl® 1/50; Ortho-Novum® 1/50; Ovcon-50®	norethindrone	1.00
	Ovral®	norgestrel	0.50
	Demulen® 1/50; Zovia® 1/50E	ethynodiol diacetate	1.00

ANDROGEN EXCESS

- If response to OC suboptimal after six months, may add anti-androgen:
  - Off-label use
    - Spironolactone (Aldactone) 50-100mg BID
    - Cyproterone acetate (Androcur)
      - with OCP 2mg QD or alone, 12.5-100mgQD 10 days each cycle
    - Finasteride (Proscar; 5-alpha reductase inhibitor)
      - Finasteride 1mg QD
- If unable or unwilling to take pill, may take anti-androgen alone (but with reliable contraception!)
- Keep in mind topical treatments:
  - Laser hair removal, eflornithine cream (Vaniqa), antibiotics, isotretinoin (Accutane) for acne

ENDOMETRIAL PROTECTION

- Anovuatory cycles: "unopposed estrogen"
- Increased risk of endometrial hyperplasia and cancer (3x*)
  - Especially in obese patients
- Endocrine Society: no screening of asymptomatic women
- SOGC guidelines: no clear guidelines re. need for endometrial biopsy
  - Consider endometrial biopsy in women over 40 with "prolonged" amenorrhea
- Prevention:
  - Dual- HC
  - If OCP is contraindicated or not needed, progestin only tx
    - Intermittent progestin therapy:
      - Medroxyprogesterone acetate (Provera) 10mg QD x7 days every two months
    - Cyclic tx with progestin-only pill
      - Micronor
    - Levonorgestrel-releasing IUD
    - Expect less effect on androgenic sx

*Haoula HumReprod 2012

INSULIN SENSITISERS, OTHER TREATMENTS

- Endocrine Society: metformin only for women with DM or pre-diabetes
  - May be used in all women as second-line if OC not tolerated or contra-indicated
  - Excellent safety profile
  - Likely good choice in adolescents with insulin resistance
- Inositols
  - Endocrine Scociety: no evidence of benefit
- Statins
  - No role for hyperandrogenism/anovulation
  - Only for women with indications

CONCEPTION ENHANCEMENT

- PCOS is the most common cause of anovulatory infertility
  - Ovulation: regular cycles; day 20 progesterone >16nmol/L or random progesterone >10
- In absence of anovulation, risk of infertility is uncertain
- Remember to evaluate the couple!
  - Consider other causes of infertility…
- Endocrine Society/SOGC--First line: lifestyle
  - Significant weight loss (5-10%) may result in normalization of androgen levels and spontaneous ovulation and may enhance other approaches
- Metformin
  - Used in context of insulin resistance/pre-diabetes
  - Less effective than letrozole
  - No evidence for use during pregnancy
- Gonadotropin therapy
- Pulsatile GnRH
- IVF

OVULATION INDUCTION

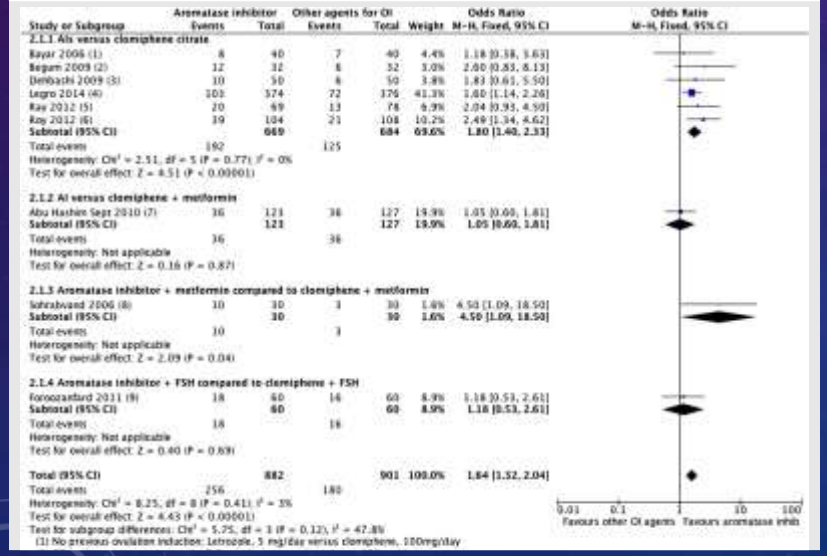
Table 2

Variable	Letrozole (n 98)	Clomiphene citrate (n 1
No. of ovulatory cycles	196/294 (66.6)	216/318 (67.9)
No. of pregnancy	43 (43.8)	28 (26.4)
Pregnancy rate per cycle	43/294 (14.6)	28/318 (8.8)
No. of miscarriage	4 (4.08)	7 (7.42)
Live birth	39 (39.7)	21(19.8)

S – Significant, (P<0.05), NS- Not-significant (P>0.05), Figures in parenthesis are in percentage

Comparison of ovulatory cycle, conception, and pregnancy outcome in clomiphe letrozole group based on n (%)

FIGURE 1



- Clomiphene citrate (Clomid)
  - Unavailable on the market
- Letrozole** (aromatase-inhibitor)
  - Enhances ovulation by blocking estrogen-mediated negative feedback on FSH release; stimulates follicle recruitment and growth
  - More effective than clomiphene was
  - Letrozole 2.5-7.5mg QD day 3-8
    - Exclude pregnancy first!
  - Also effective for obese women
  - No evidence for metformin add-on (Hurley 2017 Fert Ster)

***off label

J Hum Reprod Sci. 2012 Jan-Apr; 5(1): 20–25
Franik 2015 Fert Ster

PREGNANCY WITH PCOS

- Increased risk of gestational diabetes, preterm delivery, pre-eclampsia
  - ? Increased risk of miscarriage
  - Need to check pre-conceptual glucose, BMI, and BP
  - Need for early screening for GDM?

CARDIOVASCULAR HEALTH

- Best approach: lifestyle with weight loss!
  - Should exceed 5% of initial body weight
  - Caloric restriction key; macronutrient composition of diet less important
  - Bariatric surgery an option
- Insulin-lowering medications
  - Metformin
    - Metformin can be used 2nd line in all women if OC contraindicated or ineffective
- Lipid and blood pressure lowering
  - Statins, BP medications in selected cases only; GDM… Long-term risk of T2DM…

LONG TERM FOLLOW-UP

- Patients will need to be followed longitudinally since their needs may change with time (hair/acne→ desiring fertility)
- If normal glucose at baseline, need to be rechecked every 2 y
- If abnormal at baseline, follow up as needed >1/year

CASE

- Overweight woman with PCOS
  - Most bothered by hirsutism
  - No plans for pregnancy short-term
    - Lifestyle
    - OCP would be appropriate
    - May add-on anti-androgen if needed after 6 months
  - If desires pregnancy
    - Lifestyle
    - Referral to specialty clinic
    - Consider letrozole
    - May try metformin given benign s/e profile

WHEN TO REFER….

- Any time you are uncomfortable!
  - Appropriate for GP to diagnose PCOS and to initiate tx and to follow
- Difficulty with diagnosis or differential
- To initiate second-line anti-androgen tx
- To initiate ovulation-enhancing tx

QUESTIONS??