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Management of polycystic ovary syndrome

- Clinical Specialty: Obstetrics and Gynecology
- Intended Users: Physicians and Students
- JC Objective: To discuss ***evidence-based management of PCOS***

Evidence from Cochrane Library (CDSR) and Database of Abstracts of Reviews of Effects (DARE)

Recommendations

History and Symptom Analysis

1) Chief complaint(s)
   a) Menstrual cycle disturbances resulting from anovulation (e.g., oligomenorrhea, amenorrhea, dysfunctional uterine bleeding)
   b) Infertility
   c) Hyperandrogenism (hirsutism, acne, androgenic alopecia)
   d) Obesity
   e) Miscarriage
2) Review of systems
   a) Constitutional: increase in weight, fatigue or anxiety, temperature intolerance
   b) Skin and hair: male pattern baldness, facial hair growth, acne, hyperpigmentation (axillae, nape of neck, under breasts, or skin flexures), dry skin, brittle hair and nails
   c) Neck: change in neck size, noticing shirt collars feel tighter
   d) Breasts: decrease in breast size, galactorrhea
   e) Cardiovascular: hypertension, chest pain, shortness of breath, exertional dyspnea, exercise intolerance, ankle swelling
   f) Genitourinary: enlarged clitoris
   g) Endocrine: polydipsia, polyphagia, polyuria (Impaired glucose intolerance, Type 2 diabetes mellitus, Gestational diabetes)
   h) Neurological: headache, visual disturbance
3) History of present illness
   a) Menstrual pattern, last normal menstrual period (LNMP)
   b) Onset and duration of signs of androgen excess
   c) Duration of infertility
   d) Amount and duration of body weight changes
   e) Lifestyle habits, such as diet, exercise, smoking, alcohol intake, drug use
4) Past medical history
   a) Growth and sexual development; onset of menarche

b) Past diagnosis of endometrial hyperplasia

5) Medication history: Current medications, including use of exogenous androgens
6) Family history: PCOS, Obesity, Thyroid disease, Infertility, miscarriage, Diabetes, Cardiovascular disease, Dyslipidemia

Physical Examination

1. Vital signs (blood pressure): higher incidence of hypertension
2. Height, weight, body mass index (BMI): 25-30 = overweight; >30 = obese
3. Waist-hip ratio to determine body fat distribution: >0.72 = abnormal
4. Skin exam: assess for signs of hyperandrogenism (hirsutism, acne, androgenic alopecia or male-pattern baldness) and signs of insulin resistance (acanthosis nigricans in the axillae, nape of neck, under breasts, or skin flexures)
5. Neck exam: assess for thyroid enlargement
6. Breast exam: assess for decrease in breast size
7. Cardiovascular: assess for signs of cardiovascular disease (hypertension, abnormal heart sounds, decreased peripheral pulses, lower extremity edema)
8. Abdominal exam: assess for striae (Cushing's syndrome), enlargement, masses
9. Bimanual vaginal exam: for loss of vaginal rugae, clitoromegaly, enlarged uterus or ovaries
10. Neurological exam: assess for visual impairment (pituitary tumor)
11. Psychological exam: depression scale if indicated

Diagnostic Procedures

1) Laboratory tests:
   a) FSH: typically slightly decreased or normal with PCOS;
   b) LH: elevated in 50 to 60% of clients with PCOS
   c) LH/FSH ratio: >2 in PCOS
   d) Prolactin: slightly elevated in some women with PCOS
   e) 24-hour urine free cortisol: mild elevations in PCOS
   f) TSH: to evaluate thyroid disorders, typically normal with PCOS
   g) E2: typically slightly decreased with PCOS
   h) Androgens: to help confirm PCOS and exclude androgen producing tumors
      i) Free androgen index (FAI): typically elevated with PCOS
      ii) Total testosterone: typically normal or slightly elevated with PCOS; moderate elevations (>200ng/dL) concerns for tumor
      iii) SHBG: typically suppressed with PCOS;
      iv) DHEA-S: to evaluate for adrenal disorders, typically normal or slightly elevated with PCOS; concerns with moderate elevations (Cushing's)

i) 17 hydroxyprogesterone: to evaluate for adrenal disorders

j) 2-hour 75 g oral glucose tolerance test (OGTT) if BMI ≥28: to evaluate for glucose intolerance or diabetes mellitus

k) Fasting lipid profile(FLP): to evaluate for hyperlipidemia; may be elevated with PCOS

l) C-reactive protein (CRP), fibrinogen, homocysteine: may be elevated

2) Pelvic ultrasound, **TVUS**: frequently shows ovaries of increased size due to a greater number of follicles (12 or more follicles measuring 2 to 9 mm in diameter) or an increased ovarian volume. Findings may be nonspecific.

3) **Endometrial biopsy**: unopposed estrogen from chronic anovulation (≥6 months) puts PCOS patients at higher risk for endometrial hyperplasia/cancer.

Criteria for Diagnosis: in addition to exclusion of related disorders:

1. Oligo- or anovulation
2. Clinical and/or biochemical signs of hyperandrogenism
3. Polycystic ovaries by TVUS

Differential Diagnoses: all the disorders mentioned in the workup

Management

Patient Education

1) Explain diagnosis. PCOS is a heterogeneous condition

2) Explain risks associated with PCOS.

a) Increased cardiovascular risk due to elevated atherogenic markers (CRP, homocysteine), elevated serum lipids, and hypertension.

b) increased risk for type 2 diabetes (risk is as high as 5 to 10 times that of general population). Age of onset occurs as early as 3rd or 4th decade. 30% of women with PCOS have impaired glucose tolerance.

c) higher risk for endometrial cancer. The main theory involves that of unopposed estrogen stimulation

d) Pregnancy-related risks include infertility, miscarriage, and gestational diabetes. The exact pathogenesis of miscarriage is not clearly defined, and appears to be the result of several interrelated factors, including elevated LH levels, hyperandrogenemia, insulin resistance, and abnormal follicular growth

e) Depression and anxiety are long-term risks due to infertility and negative cosmetic effects.

Non-pharmacological Treatment

1) **structured dietary, exercise, or behavioral intervention**. Lifestyle modification with emphasis on controlled eating patterns (reduced fat intake and increased fiber).

a) Evidence: DECREASED Weight, WHR, Adiposity distribution (waist circumference), Fasting insulin, oral glucose tolerance test, Total testosterone, Clinical hyperandrogenism (hirsutism)

b) No data for ovulatory menstrual cycles, pregnancy outcomes, live birth or

miscarriage, initiation of menses or significant shortening of cycle, change in menstrual bleeding pattern

2) Smoking cessation should also be addressed to reduce cardiovascular risk.
3) Routine screening. All patients should be screened for hypertension, glucose intolerance with 2-hour 75g OGTT, and for dyslipidemia with fasting lipid profile (FLP)
4) Cosmetic therapies. for hirsutism include bleaching, electrolysis, and laser therapy. (effective to some degree but may involve expense, skin irritation and scarring, and long term time commitment)

Pharmacological Treatment

1) **Combined oral contraceptives**:
   a) Mechanisms of action: suppression of LH secretion and increased circulating SHBG.
   b) Treatment is aimed at suppressing hyperandrogenism, restoring menstrual regularity, preventing endometrial hyperplasia, possibly improving lipid levels, and treating acne and hirsutism.
   c) Use of non-androgenic 3rd generation progestins, such as norgestimate or desogestrel, or anti-androgens, such as drospirenone, is recommended..
2) **Medroxyprogesterone acetate**: 10 mg for 7 every (Q) 1 to 3 months. to induce menses, reduce endometrial hyperplasia, and restore menstrual regularity. Therefore prevents the associated risk for endometrial cancer
3) **Clomiphene** and anti-estrogens
   a) **Clomiphene citrate**:
      i) first-line treatment for anovulatory women who wish to conceive. 50 to 100 mg/day for 5 days at beginning of cycle.
      ii) Restores menstrual regularity,
      iii) improves ovulation rate (**NNT 2**) clinical pregnancy rate (**NNT 6**).
      iv) 80% will ovulate in response to treatment, and 50% of those will conceive.
      v) Pregnancy response usually occurs within the first six ovulatory cycles. Prolonged duration of treatment does not increase rate of pregnancy.
      vi) Insufficient evidence that adding another agent can increase ovulation rates.
   b) **Tamoxifen**: 5 to 40 mg/day for 4 days at beginning of cycle. No Placebo RCTs
      i) Clomiphene vs tamoxifen: insufficient evidence
4) **Insulin sensitizers**: to improve insulin sensitivity
   a) **Metformin** versus placebo:
      i) improved ovulation rate. (**NNT 8**).
      ii) improved clinical pregnancy rate. The benefit is confined in the non-obese group
      iii) NO evidence that metformin improves live birth.
      iv) Metformin improves hyperinsulinemia, hyperandrogenism, menstrual cyclicity

b) Metformin versus clomiphene
   i) metformin resulted in a higher clinical pregnancy rate in the non-obese women.
   ii) In obese women with PCOS,
      (1) Clomiphene resulted in a higher clinical pregnancy rate in the obese women
      (2) clomiphene resulted in a higher ovulation rate than metformin
      (3) clomiphene resulted in a higher live birth rate than metformin

c) metformin plus CC versus CC
   i) no evidence that combination improves live birth
   ii) better pregnancy rate
   iii) higher ovulation rate

5) **Exogenous gonadotropins**:
   a) **uFSH** (Metrodin)
   b) **rFSH** (Gonal F and Puregon).
      i) Both uFSH and rFSH are equally effective in inducing ovulation in women who are resistant to clomiphene. Risks of both include multiple pregnancies and OHSS.
      ii) Risks can be reduced by using lower doses. The most frequently used dosing schedules are low dose step up and step down regimens.
   c) Human menopausal gonadotropin (**hMG**). Contains FSH and LH. Has been associated with increased risk of OHSS.
6) Antiandrogens: e.g. **Spironolactone** effective treatment for hirsutism, although birth control is needed as all have teratogenic potential. When used with COC, antiandrogens work synergistically by suppressing androgen levels through different mechanisms.
7) Lipid-lowering medications: **statins**
8) Treat elevated blood pressure with appropriate medications, and add aspirin as appropriate for reduction of cardiovascular risk.

Laparoscopic ovarian drilling

1) LOD (with or without medical ovulation induction) versus gonadotrophins alone,
   a) ***NO evidence of a difference*** in the ovulation rate, clinical pregnancy rate, live birth rate and miscarriage rate in women with clomiphene-resistant PCOS undergoing LOD (with or without medical ovulation induction) compared to gonadotrophin.
   b) The reduction in multiple pregnancy rates in women undergoing LOD
2) Risks: **adhesion formation**, and potential surgical and anesthesia risks. There are ongoing concerns about long-term effects of LOD on ovarian function (**POF**).
3) Insufficient evidence for
   a) unilateral versus bilateral LOD
   b) laser versus diathermy;

References

1. SO: Brown Julie, Farquhar Cindy, Beck James, Boothroyd Clare, Hughes Edward. **Clomiphene and anti-oestrogens for ovulation induction in PCOS**. Cochrane Database of Systematic Reviews: Reviews 2009 Issue 4 John Wiley & Sons, Ltd Chichester, UK DOI: 10.1002/14651858.CD002249.pub4
2. SO: Nugent David, Vanderkerchove Patrick, Hughes Edward, Arnot M, Lilford Richard. **Gonadotrophin therapy for ovulation induction in subfertility associated with polycystic ovary syndrome**. Cochrane Database of Systematic Reviews: Reviews 2000 Issue 3 John Wiley & Sons, Ltd Chichester, UK DOI: 10.1002/14651858.CD000410
3. SO: Tang Thomas, Lord Jonathan M, Norman Robert J, Yasmin Ephia, Balen Adam H. **Insulin-sensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for women with polycystic ovary syndrome, oligo amenorrhoea and subfertility**. Cochrane Database of Systematic Reviews: Reviews 2010 Issue 1 John Wiley & Sons, Ltd Chichester, UK DOI: 10.1002/14651858.CD003053.pub4
4. SO: Farquhar Cindy, Lilford Richard, Marjoribanks Jane, Vanderkerchove Patrick. **Laparoscopic drilling by diathermy or laser for ovulation induction in anovulatory polycystic ovary syndrome**. Cochrane Database of Systematic Reviews: Reviews 2007 Issue 3 John Wiley & Sons, Ltd Chichester, UK DOI: 10.1002/14651858.CD001122.pub3
5. SO: Moran Lisa J, Hutchison Samantha K, Norman Robert J, Teede Helena J. **Lifestyle changes in women with polycystic ovary syndrome**. Cochrane Database of Systematic Reviews: Reviews 2011 Issue 2 John Wiley & Sons, Ltd Chichester, UK DOI: 10.1002/14651858.CD007506.pub2
6. SO: Sinawat Supat, Buppasiri Pranom, Lumbiganon Pisake, Pattanittum Porjai. **Long versus short course treatment with Metformin and Clomiphene Citrate for ovulation induction in women with PCOS**. Cochrane Database of Systematic Reviews: Reviews 2008 Issue 1 John Wiley & Sons, Ltd Chichester, UK DOI: 10.1002/14651858.CD006226.pub2
7. SO: Bayram Neriman, van Wely Madelon, Van der Veen Fulco. **Pulsatile gonadotrophin releasing hormone for ovulation induction in subfertility associated with polycystic ovary syndrome**. Cochrane Database of Systematic Reviews: Reviews 2003 Issue 3 John Wiley & Sons, Ltd Chichester, UK DOI: 10.1002/14651858.CD000412.pub2
8. SO: Bayram Neriman, van Wely Madelon, Van der Veen Fulco. **Recombinant FSH versus urinary gonadotrophins or recombinant FSH for ovulation induction in subfertility associated with polycystic ovary syndrome**. Cochrane Database of Systematic Reviews: Reviews 2001 Issue 2 John Wiley & Sons, Ltd Chichester, UK DOI: 10.1002/14651858.CD002121