Appendix

Algorithm for Abnormal Uterine Bleeding

Table of Contents

Figures

Boxes

Figure 1. Abnormal Uterine Bleeding Between Menarche and Menopause

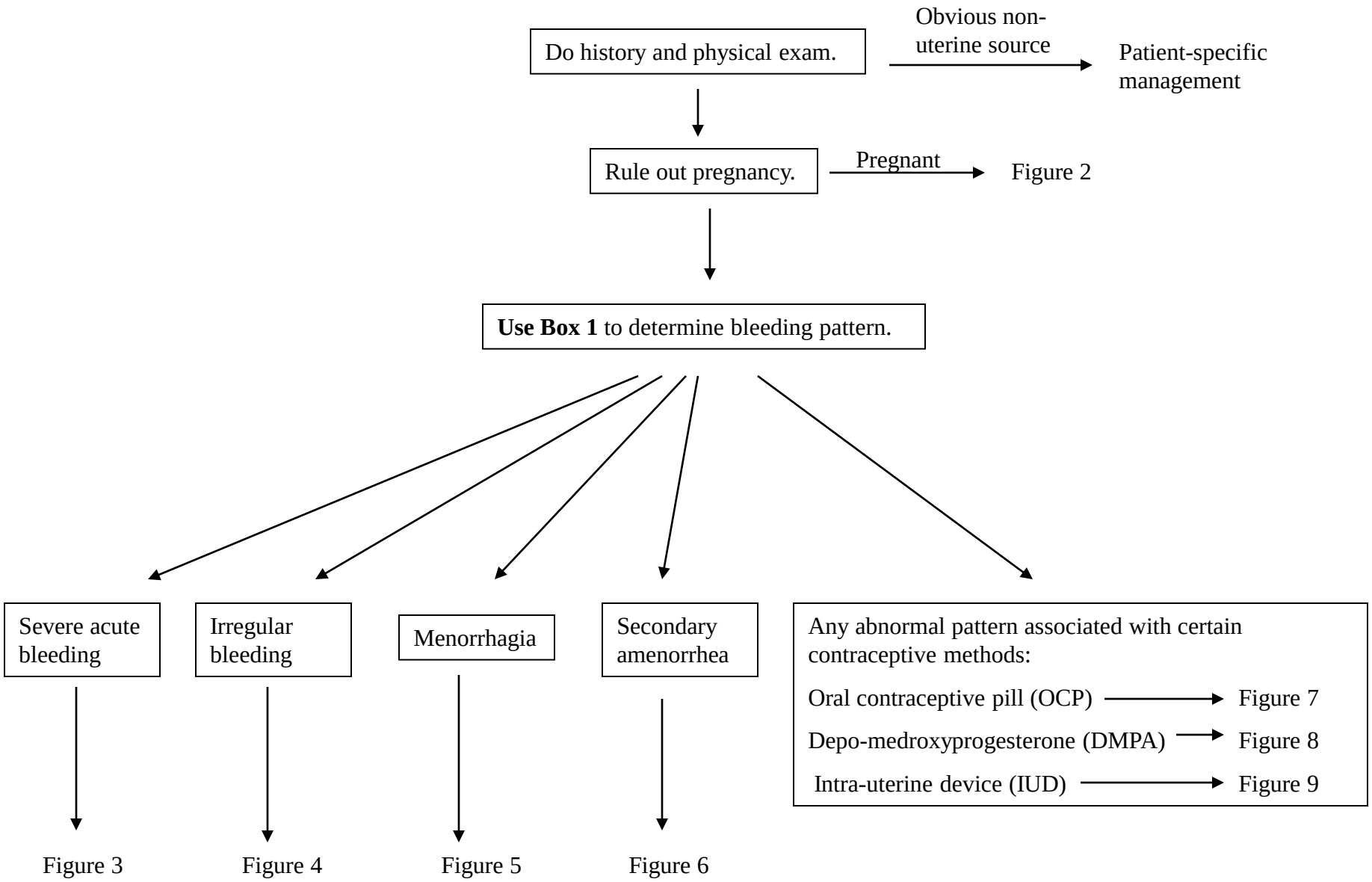


Figure 2. First Trimester Bleeding

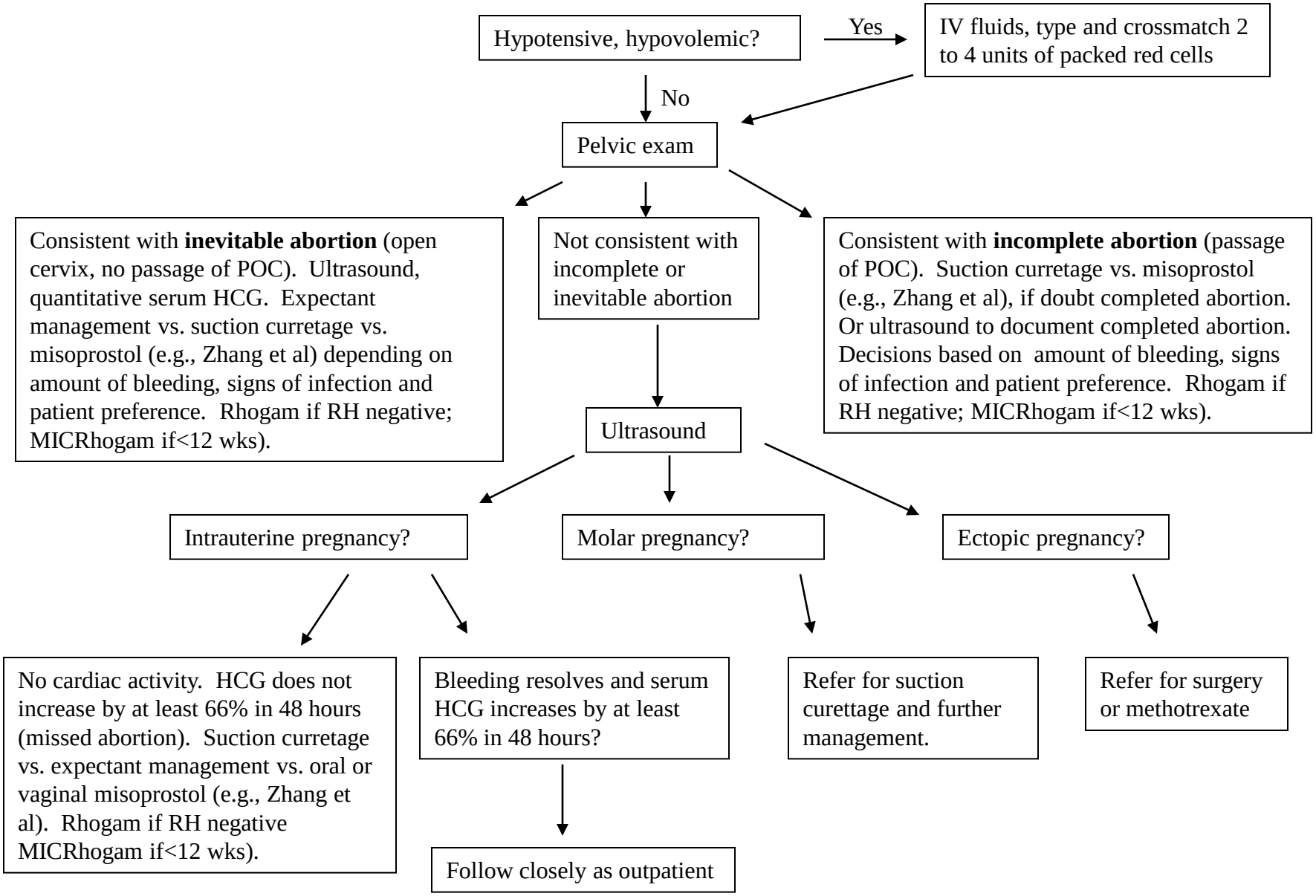


Figure 3. Severe Acute Bleeding in the Nonpregnant Patient

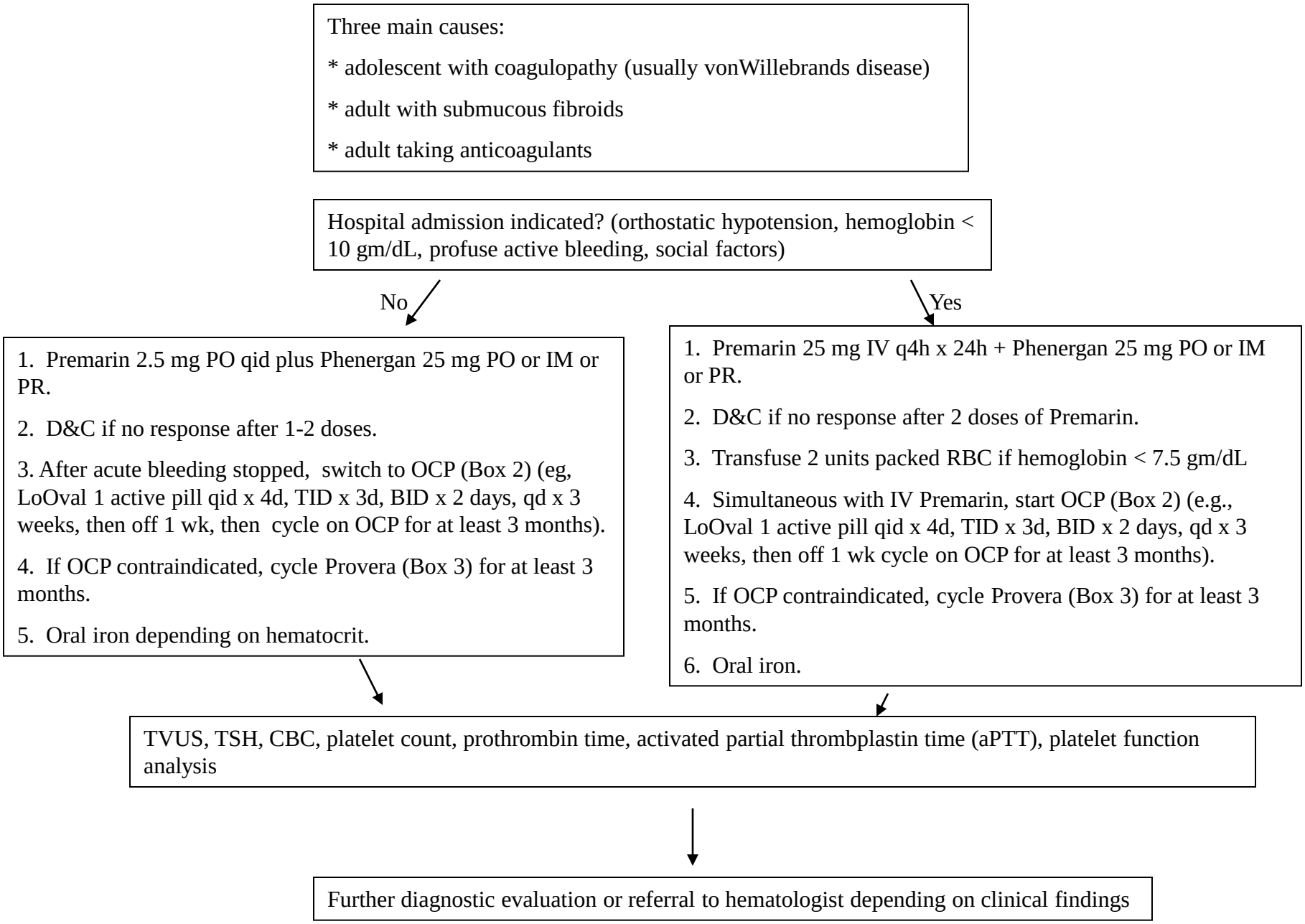


Figure 4. Irregular Bleeding in the Nonpregnant Patient

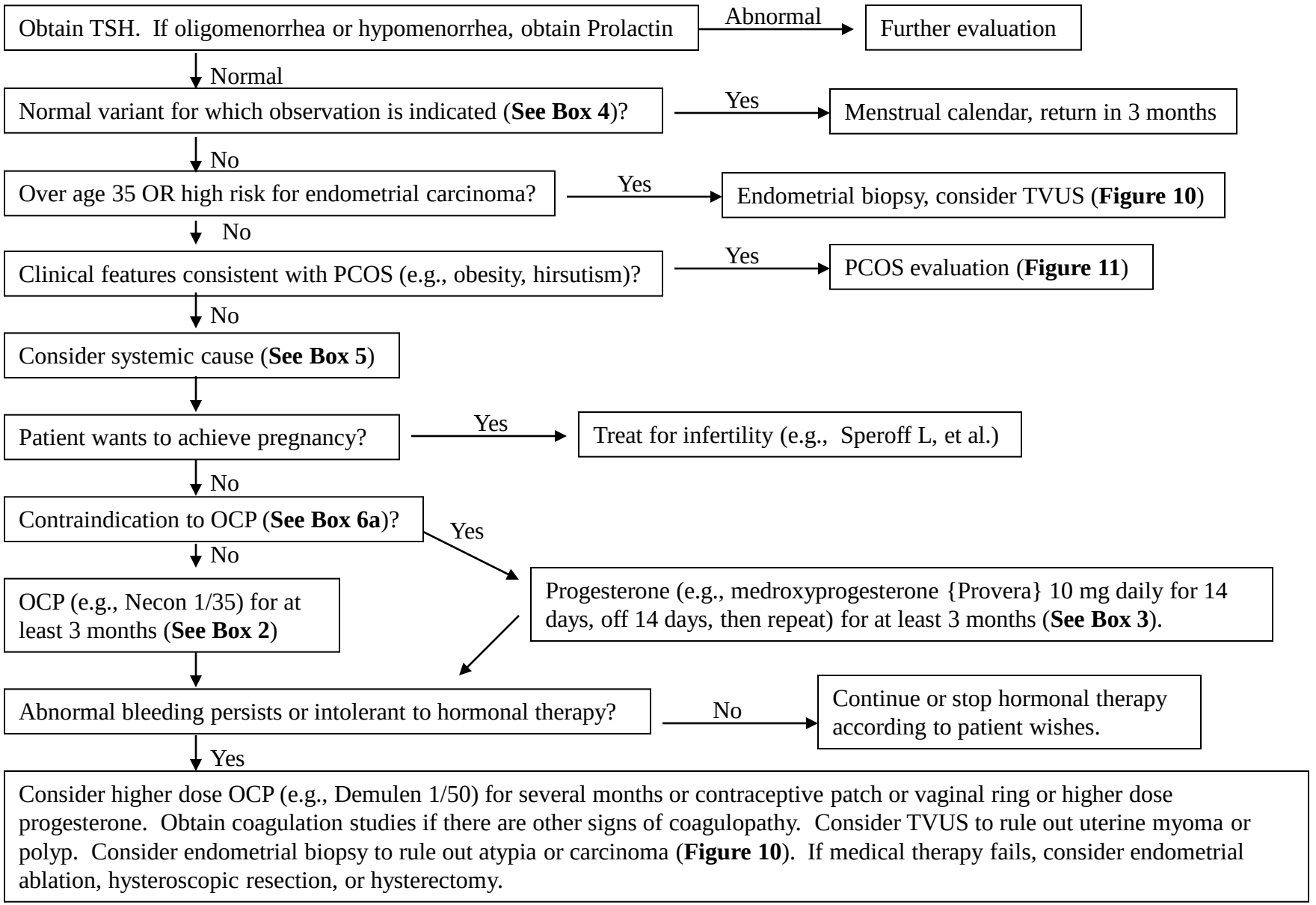


Figure 5. Menorrhagia in the Nonpregnant Patient

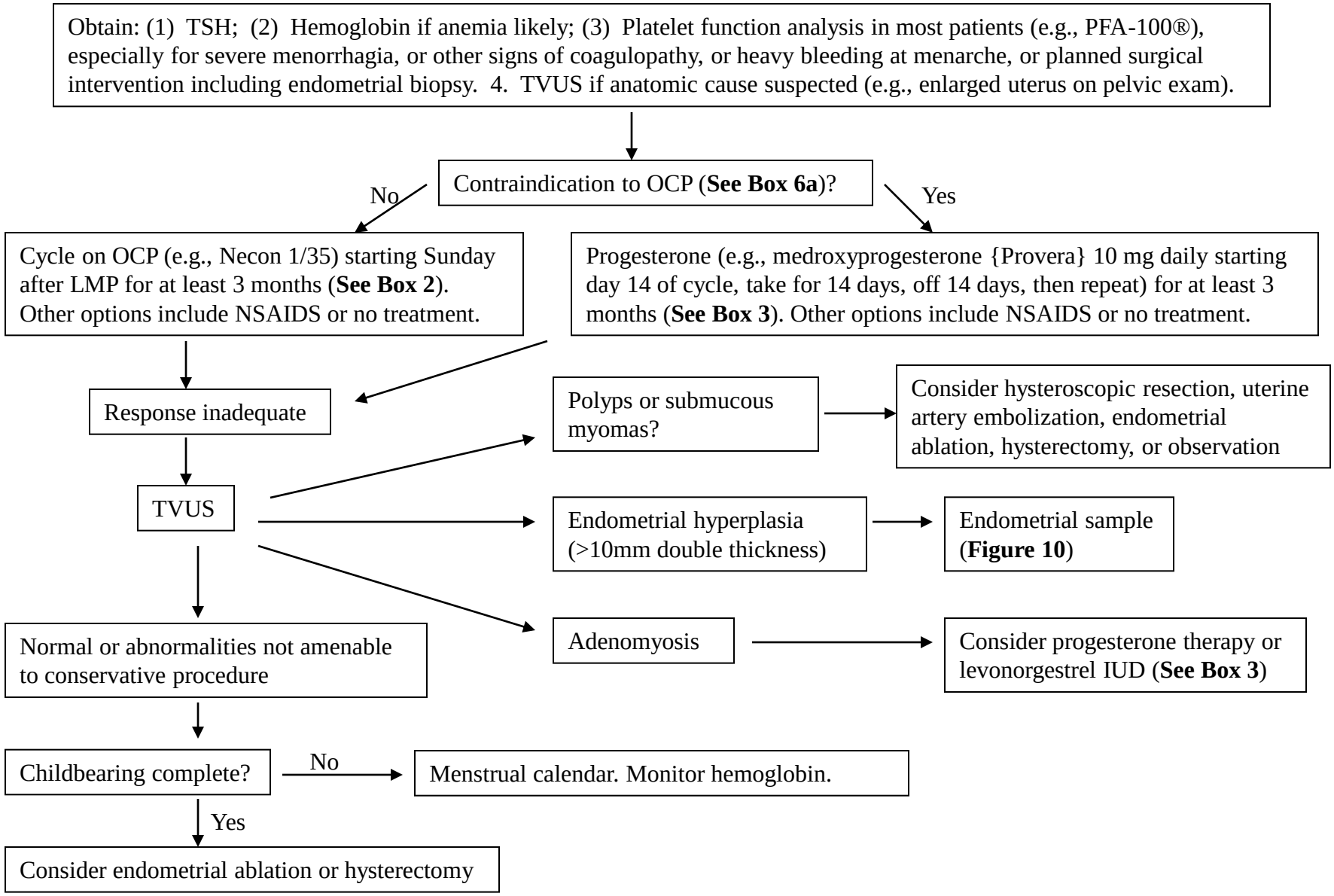


Figure 6. Secondary Amenorrhea

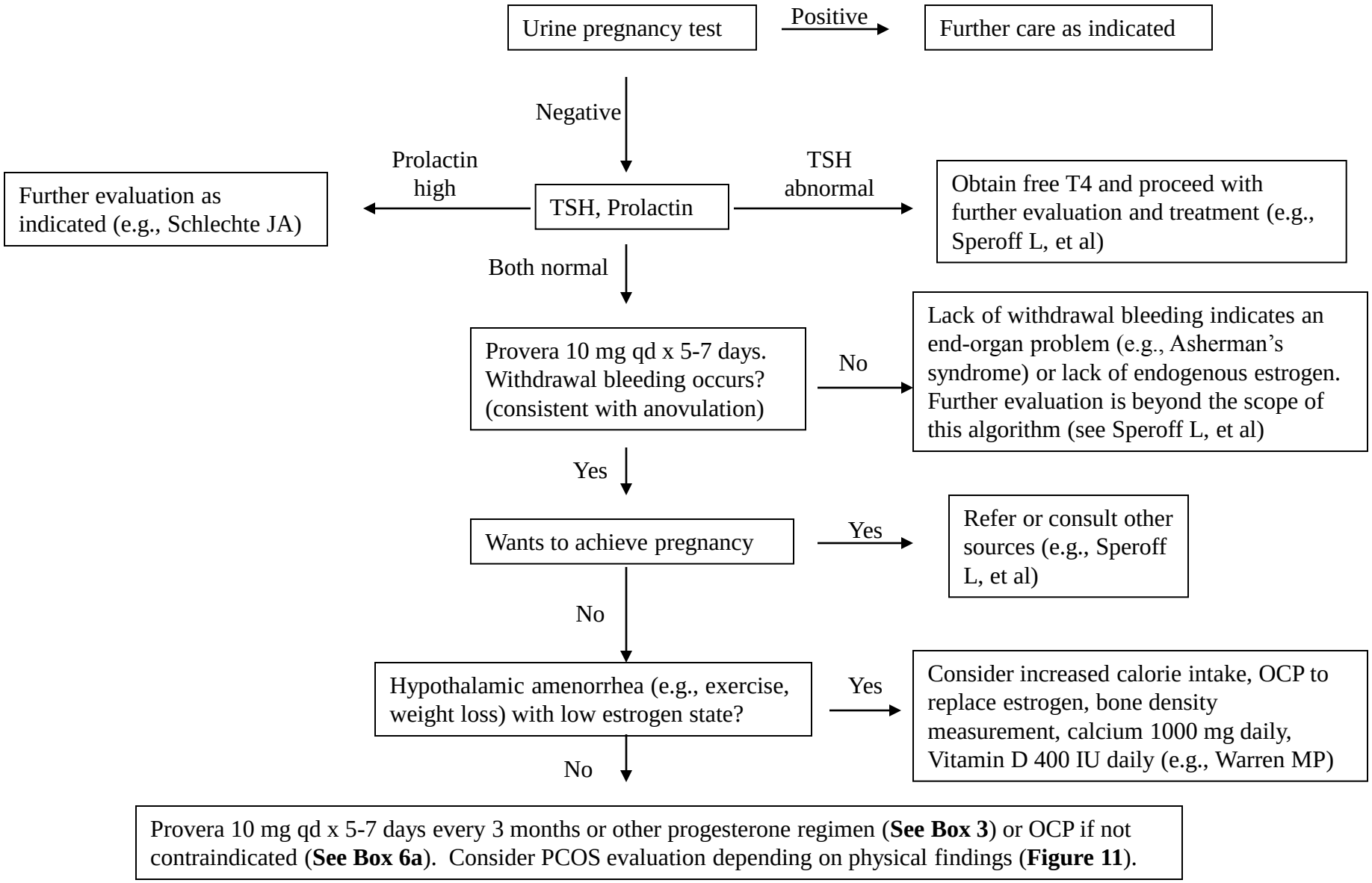


Figure 7. Oral Contraceptive Pill Associated Bleeding

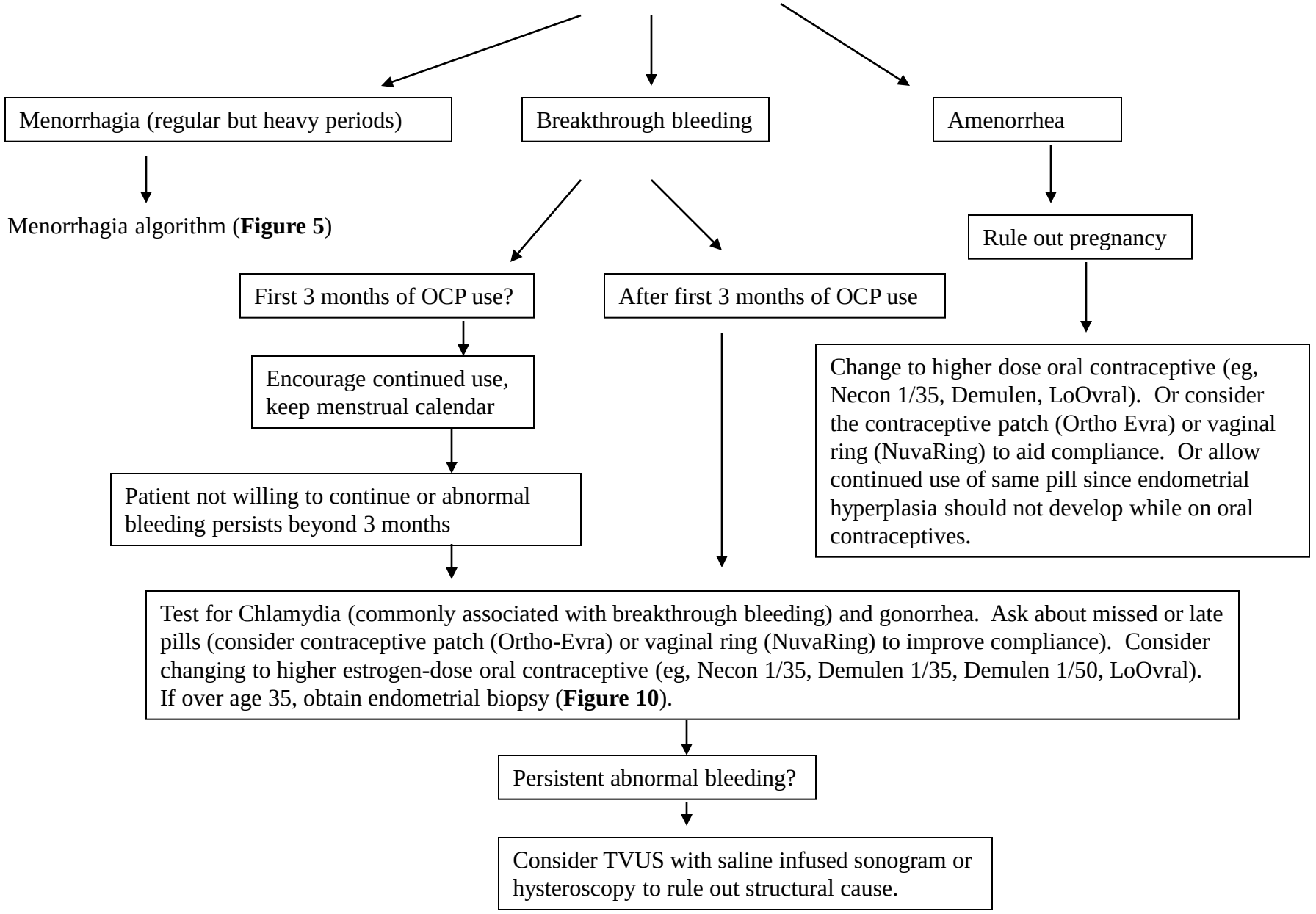


Figure 8. Depo-Medroxyprogesterone or Progesterone-Only Pill Associated Bleeding

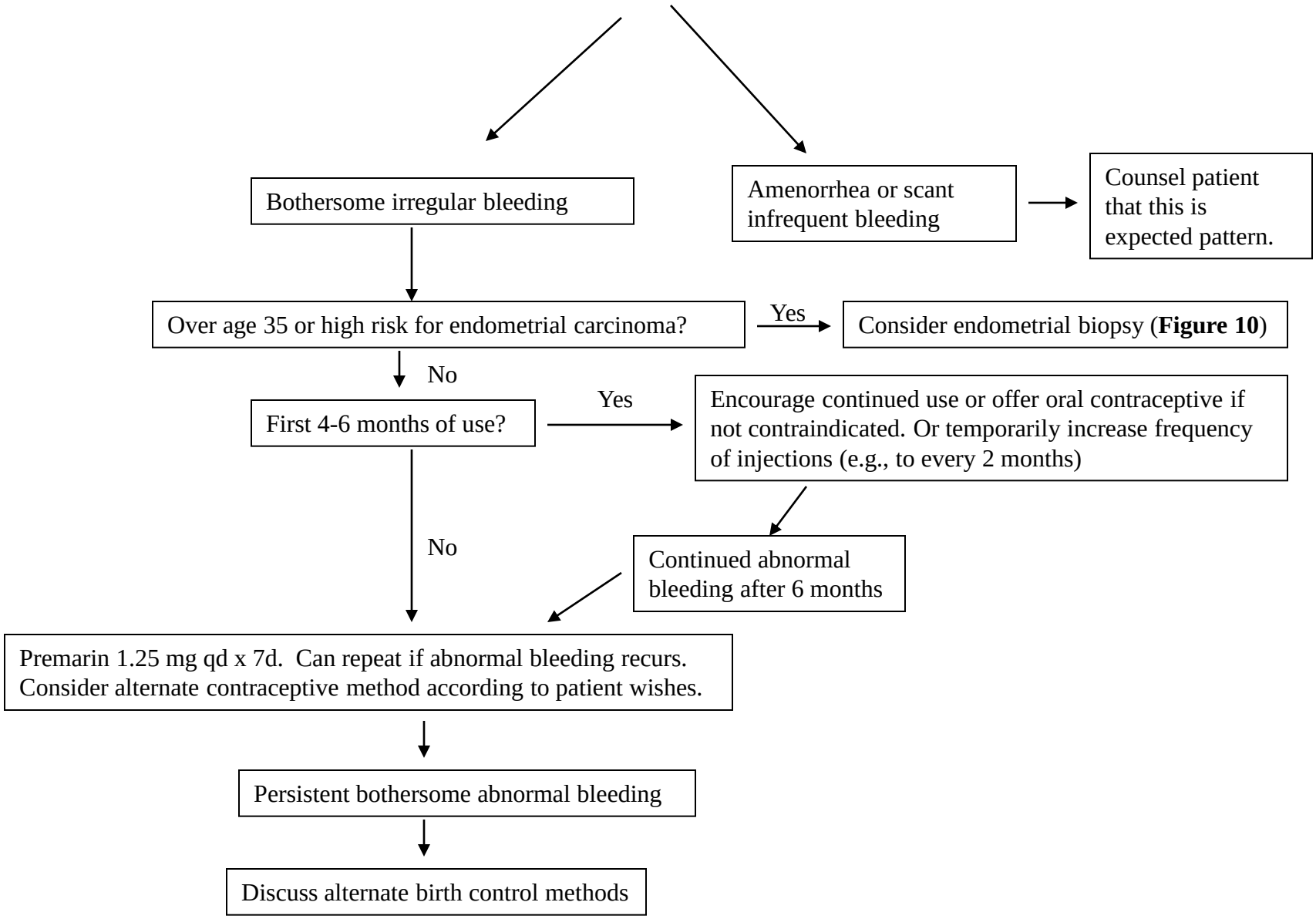


Figure 9. Intrauterine Device Associated Bleeding

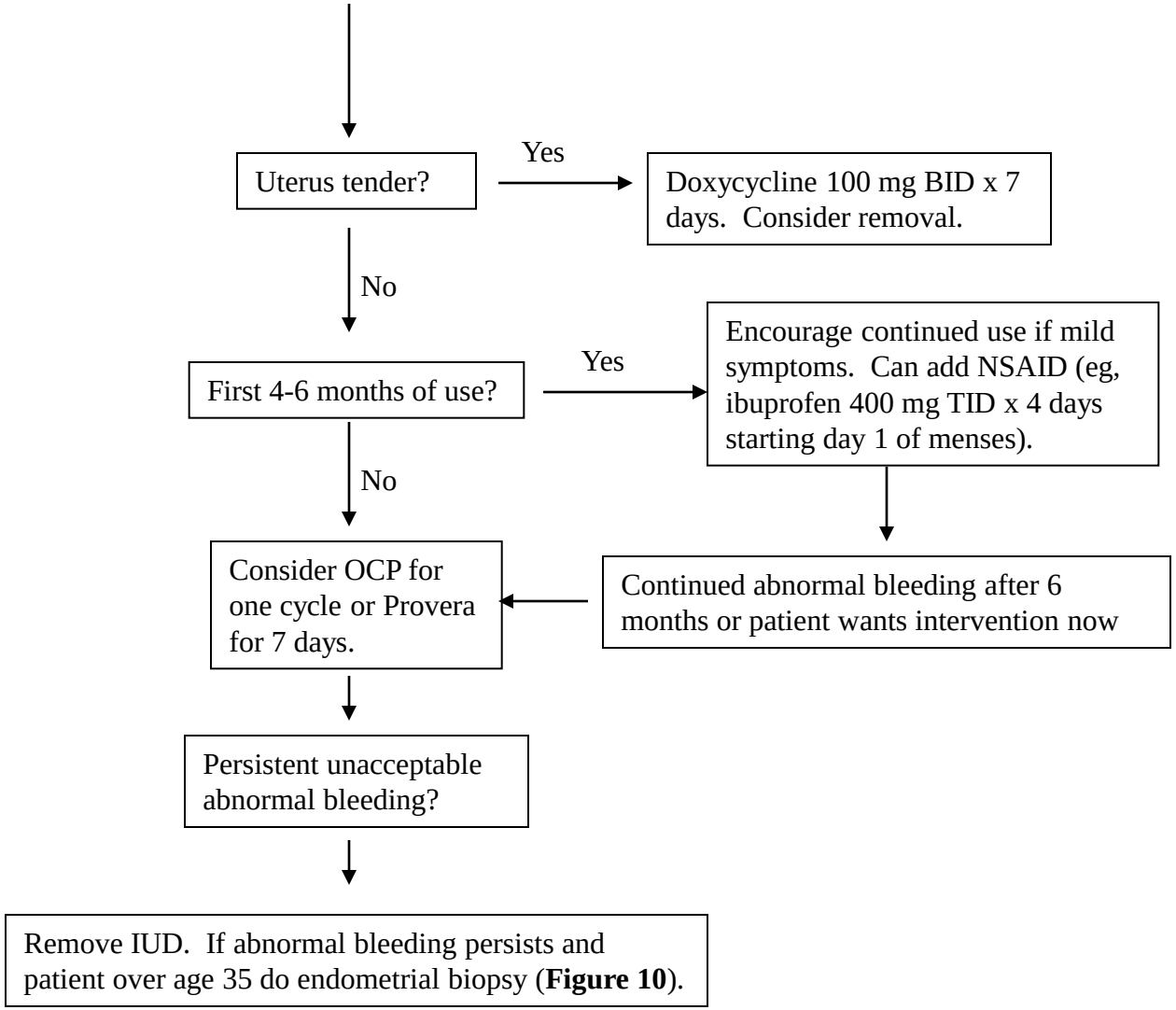


Figure 10. Endometrial Biopsy (Pipelle Aspiration)

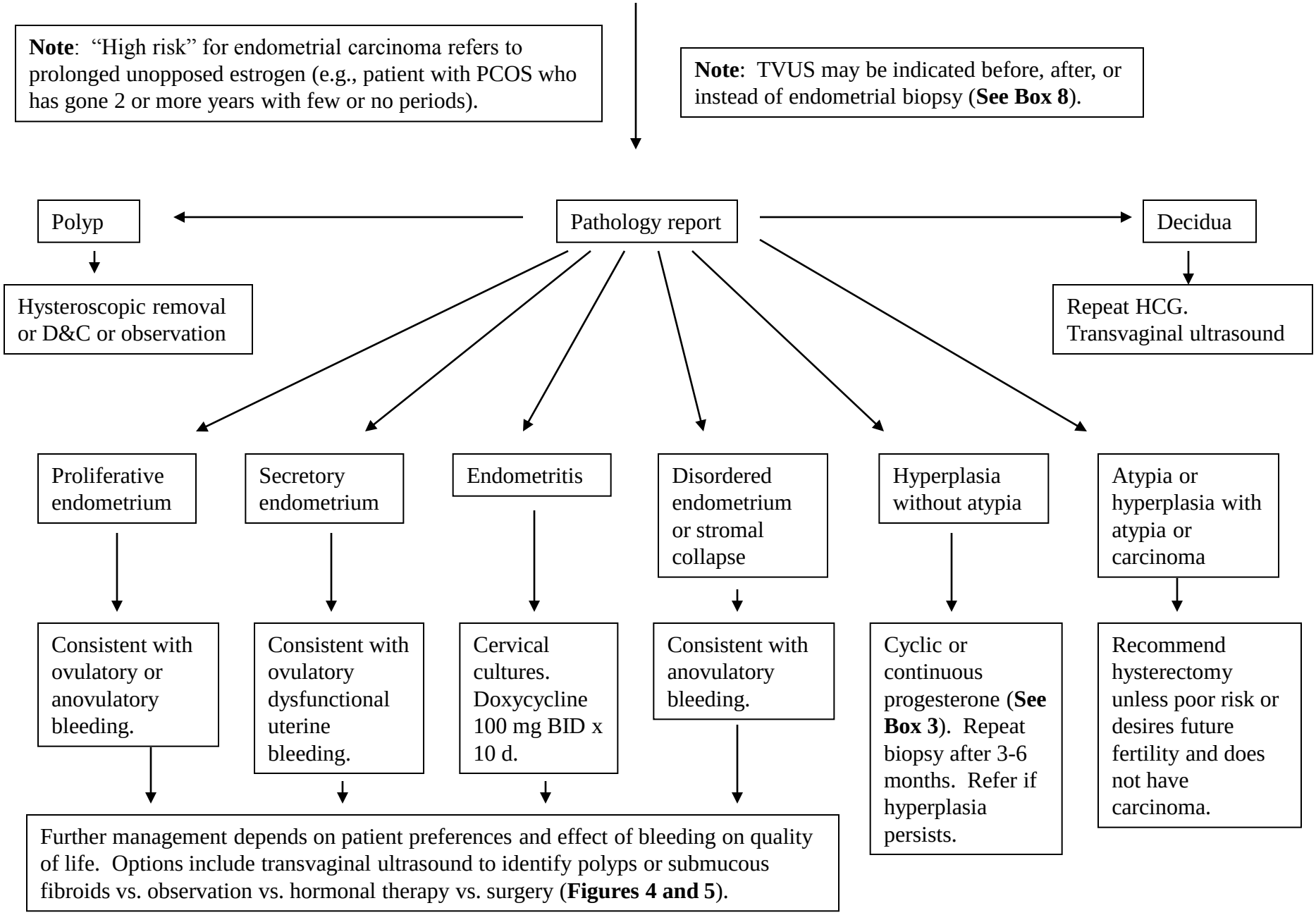
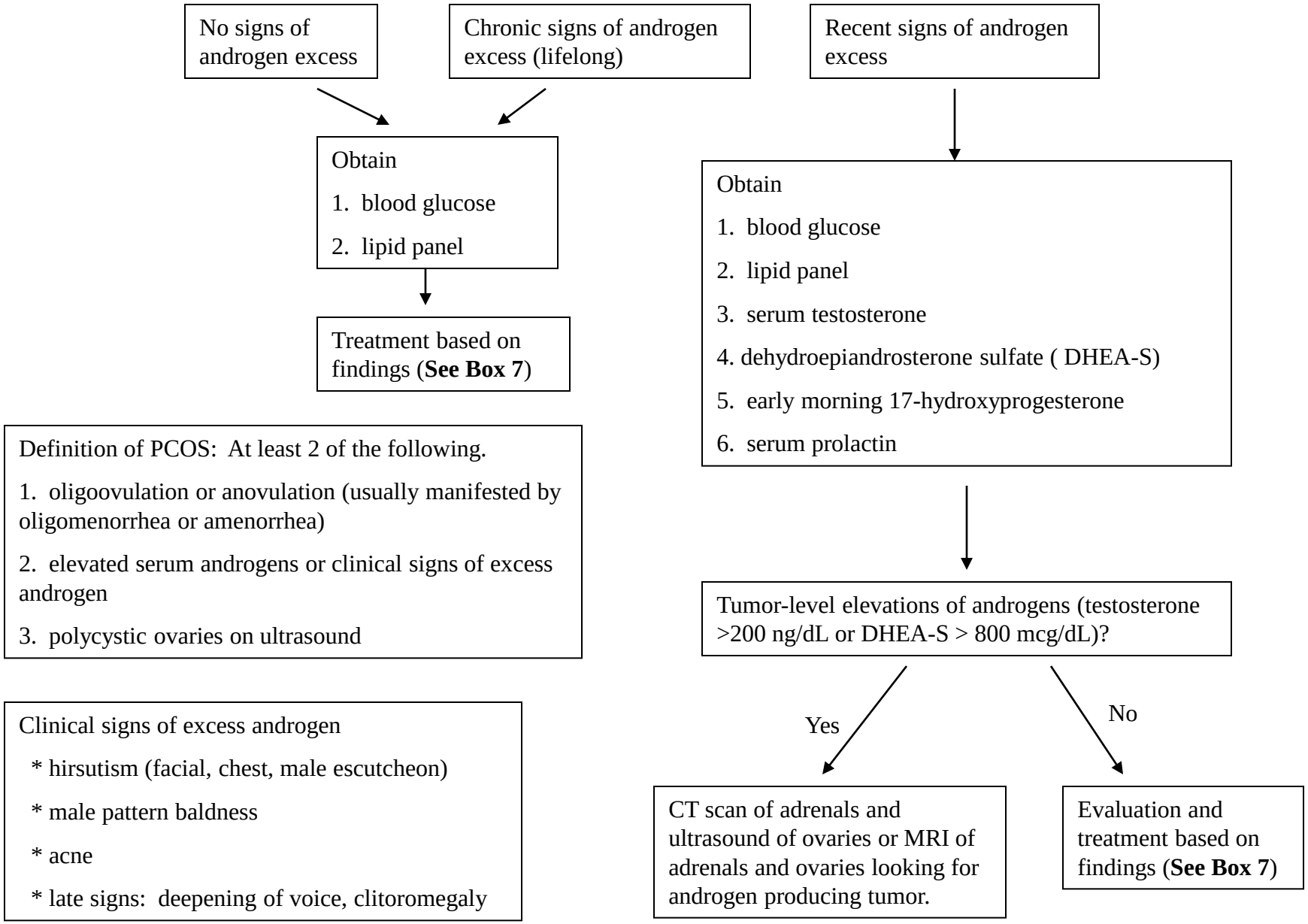


Figure 11. Possible Polycystic Ovary Syndrome



Box 1. Bleeding Pattern Definitions and Criteria

Definition of normal: The normal interval (first day of one period to first day of the next) is 21 to 35 days. The normal duration of bleeding is 1 to 7 days. The amount should be less than 1 pad or tampon per hour.

Severe acute bleeding: The patient presents acutely with bleeding that requires more than one pad/tampon per hour or with vital signs indicating hypovolemia (eg, tachycardia, hypotension, orthostatic hypotension).

Irregular bleeding: Includes oligomenorrhea, prolonged bleeding, intermenstrual bleeding, and other irregular patterns. One common presentation is prolonged bleeding, which follows prolonged absence of menses. Distinguish from secondary amenorrhea (regular menses followed by absent menses).

Menorrhagia: The subjective complaint of heavy but regular bleeding, plus >7 days of bleeding or clots or iron deficiency anemia. Bleeding >12 days should be considered irregular regardless of cyclic pattern.

Secondary amenorrhea: Strictly defined as the absence of periods for a length of time equivalent to at least 3 previous cycle intervals **or** absence of bleeding for 6 months regardless of previous interval. However, earlier evaluation of absent menses is often appropriate and need not be delayed to satisfy the definition.

Box 2. Combination Oral Contraceptive Pill

For women who have difficulty remembering to take the pill or difficulty taking it at the same time every day, consider the contraceptive patch (Ortho Evra) or the vaginal ring (NuvaRing). If the goal is to achieve amenorrhea, the OCP can be given continuously, but is usually withdrawn every 3 to 4 months to allow endometrial shedding and avoid irregular bleeding.

Irregular bleeding

In most women, suspect a thin endometrium and cycle on OCP (e.g., Necon 1/35, or contraceptive patch {Ortho Evra} or vaginal ring {NuvaRing}) for at least 3 months. If PCOS suspected (i.e., thick endometrium), consider starting with one or more cycles of progesterone (Box 3), and then continue cyclic progesterone or switch to OCP depending on the patient's wishes and the need for contraception.

If there is heavy bleeding at the time of the visit, start a moderate estrogen OCP (e.g., LoOvral) one active pill qid x 4d, then one TID x 3d, then one BID x 2 days, then skip one week, then cycle on OCP for at least 3 months.

Menorrhagia

Can start OCP any time but typically on Sunday following first day of menses.

Box 3. Progesterone Therapy

In most cases, use cyclic progesterone, usually medroxyprogesterone (Provera) because of its low cost. If side effects (similar to PMS) are unacceptable, consider micronized progesterone (Prometrium), norethindrone (Aygestin), or megestrol (Megace).

Cyclic progesterone:

Start medroxyprogesterone 10 mg daily for 14 days, then off 14 days, then on 14 days, and so on without regard to bleeding pattern. This regimen has the advantage of simplicity. If bleeding occurs before completing the 14-day course, the patient can double the dose (20 mg) and "reset the clock" (count the first day of bleeding as day #1 and start medroxyprogesterone on day 14) or not reset the clock and continue the schedule without regard to bleeding pattern.

Other options include medroxyprogesterone 10 days per month (e.g., calendar day 1 to 10 or calendar day 16 to 25) regardless of bleeding pattern. Or the "clock can be reset" each month, by counting the first day of bleeding as day 1 and starting medroxyprogesterone on day 14, regardless of calendar date.

If the patient is bleeding at the time of the visit, start medroxyprogesterone now and increase every 2 days as needed to stop the bleeding (20 mg, 30 mg, 40 mg, 60 mg, 80 mg) until bleeding stops or intolerable "premenstrual" side effects develop (e.g., bloating, irritability). Continue for 14 days and then cycle 14 days on, 14 days off, and so on.

Continuous progesterone:

Continuous progesterone may be indicated if the goal is to achieve amenorrhea (e.g., busy professional or athlete, intractable menstrual migraine, catamenial seizures, severe mental retardation). Maintaining amenorrhea is often more difficult than cycling progesterone (ie, there may be unpredictable spotting). Options include

- Oral progesterone: medroxyprogesterone Provera 10-20 mg daily. Or "Minipill" (e.g., norethindrone 0.35 mg daily).

- Depo-medroxyprogesterone (Depo-Provera) 150 mg IM every 13 weeks. Often used in teenagers to improve compliance. Less often used over age 40 due to concerns about osteoporosis.

- Levonorgestrel IUD (Mirena): Effective for 5 years. (Contraindications in **Box 6b**.)

Box 4. Normal Variations

Irregular bleeding within 2 years of menarche (due to immaturity of the hypothalamic-pituitary-ovarian axis). Although anovulatory cycles are expected after menarche, many adolescents will request more than reassurance and may benefit from hormonal therapy (**Figure 4**).

Irregular perimenopausal bleeding. Missed periods or prolonged intervals are expected in perimenopause. Initially, cycle lengths may also decrease, but intervals less than 21 days or other irregular patterns require endometrial biopsy.

Premenstrual spotting. A few days of premenstrual spotting, if it is contiguous with the period, can be a normal variant. The total duration should be less than 8 days.

Postmenstrual spotting. A few days of postmenstrual spotting, if it is contiguous with the period, can be a normal variant. The total duration should be less than 8 days. Postmenstrual spotting can be a sign of endometritis which could be treated with doxycycline 100 mg BID x 7d.

Brief midcycle spotting. Midcycle spotting can occur at the time of ovulation due to the normal dip in serum estrogen levels. However, this is not common and should prompt an endometrial biopsy in women over age 35.

Single early period (<21 days) or occasional missed period. A single early period may not require an endometrial sample even in a woman over age 35 if subsequent periods are regular and no other abnormal bleeding occurs. However, there should be no procrastination if subsequent cycles are abnormal. Also, it would not be wrong to sample even after one early period in a woman over 35 if she is concerned. Early periods and occasional missed periods are common in younger women and may result from mental stress or illness.

Box 5. Evaluation for Systemic Cause of Abnormal Uterine Bleeding

Step 1. If uterus tender, obtain gonorrhea and chlamydia cultures and start doxycycline 100 mg twice daily for 7 days.

Step 2. Determine whether the patient is taking a medication that could cause abnormal uterine bleeding. Examples include phenytoin, antipsychotics [e.g., olanzapine, risperidone], tricyclic antidepressants [e.g., amitriptyline, nortriptylene], and corticosteroids [e.g., prednisone, dexamethasone]). Although these medications can cause abnormal bleeding, further evaluation and treatment are usually completed despite medication use.

Step 3. Determine the presence of advanced systemic disease based on history and physical exam (e.g., liver failure, kidney failure). Abnormal uterine bleeding is a late finding in these diseases. Therefore, with the exception of thyroid disease, laboratory screening in the absence of obvious clinical manifestations is not necessary. Patients with advanced systemic disease may benefit from further management as described in **Figure 4**.

Box 6a. Contraindications to Oral Contraceptives

- Previous thromboembolic event or stroke
- History of estrogen dependent tumor
- Active liver disease
- Pregnancy
- Hypertriglyceridemia
- Over age 35 and smokes >15 cigarettes per day
- Over age 40 is not a contraindication but many physicians favor progesterone therapy in this age group (Box 3).
- Migraine with aura

Box 6b. Contraindications to the IUD

- Pregnancy
- Pelvic inflammatory disease
- Uterine distortion
- Immunocompromise
- History of ectopic pregnancy
- Not mutually monogamous

Box 6c. Contraindications to Nonsteroidal Antiinflammatory Drugs

- Aspirin sensitivty
- Pregnancy
- Caution in renal/hepatic failure, peptic disease

Box 6d. Contraindications Progesterone

- Active liver disease
- Thrombophlebitis
- Pregnancy

Box 7. Treatment of Polycystic Ovary Syndrome

1. Prevention of endometrial hyperplasia. If the patient has amenorrhea, withdraw medroxyprogesterone (Provera 10 mg daily for 7 days), then cycle on OCP (**See Box 2**) unless contraindicated. If the patient is bleeding at the time of the visit, start cyclic medroxyprogesterone (**See Box 3**) followed by the OCP after 2-3 months. If the OCP is contraindicated, continue cyclic medroxyprogesterone. The progestin in the oral contraceptive should have low androgenic activity (e.g., Yasmin, Demulen, Ortho Tri-Cyclen). (e.g., Barbieri and Ehramann, Rosenfield) If the patient has had amenorrhea for over a year, consider endometrial biopsy or TVUS followed by biopsy for endometrial hyperplasia (stripe > 10mm).

2. Hirsutism. Primary treatment is the OCP (e.g., Yasmin). Other options, which include shaving, chemical depilatories, spironolactone, and hydrolysis, are discussed elsewhere (e.g., Baribieri and Ehrmann).

3. Infertility. Options, which include weight loss, metformin, clomiphene citrate, and gonadotropin releasing hormone, are discussed elsewhere (e.g., Speroff).

4. Abnormal uterine bleeding. In general the treatment of abnormal uterine bleeding is the same for women without PCOS (**See Figures 4-6**). However, most women with PCOS have a thick endometrial lining and should receive a 10-14 day course of progesterone (e.g., Provera), followed by withdrawal bleeding, before starting the oral contraceptive pill.

5. Elevated lipids. Follow National Cholesterol Education Program (NCEP) guidelines. (Available at http://www.nhlbi.nih.gov/guidelines/cholesterol/index.htm)

6. Elevated blood sugar. Determine the presence of diabetes or glucose intolerance using established criteria (http://care.diabetesjournals.org/cgi/content/full/28/suppl_1/s37/T2). Obtain oral glucose tolerance test in women with normal fasting glucose but other risk factors for diabetes (obesity, family history, ethnicity). Consider metformin for initial treatment.

7. Overweight. Diet and exercise counseling.

8. **Elevated 17-hydroxyprogesterone**. Evaluate for nonclassic congenital adrenal hyperplasia. (e.g., Ehrmann)

9. **Elevated prolactin**. Evaluate further depending on degree of elevation. (e.g., Schlechte)

Box 8. Endometrial biopsy vs. Transvaginal Ultrasound (TVUS)

TVUS may be indicated before, after, or instead of endometrial biopsy. The two tests are not mutually exclusive and provide different information. TVUS can detect endometrial poylps, uterine myomas, and endometrial hyperplasia. Endometrial biopsy can detect hyperplasia, atypia, and carcinoma. The conservative approach is to do the endometrial biopsy whether or not a TVUS is obtained. However, other factors may enter the decision:

1. TVUS may be indicated if the patient will likely require operative management (e.g., office biopsy would be a technical challenge or fibroids suspected on physical exam or probable need for eventual hysteroscopy or endometrial ablation).

2. Practical considerations. High-quality TVUS is not available in many locations. TVUS is costly and insurance status may influence the order of testing.

3. One option is to first rule out neoplasia with the endometrial biopsy, then start hormonal therapy, and obtain a TVUS only if abnormal bleeding persists despite hormonal therapy.

4. The TVUS is less invasive and less painful than endometrial biopsy. One study reports experience with initial TVUS and no further evaluation if the double-thickness endometrial stripe is < 5 mm (Goldstein, et al).

Box 9. Abbreviations

DHEA-S – dehydroepiandrosterone sulfate

DMPA – depo-medroxyprogesterone (Depo-Provera)

HCG – human chorionic gonadotropin

IUD – intrauterine device

LMP – last menstrual period

OCP – oral contraceptive pill

PCOS – polycystic ovary syndrome

PMS – Premenstrual syndrome

POC – products of conception

TSH – thyroid stimulating hormone

TVUS – transvaginal ultrasound

Box 10. References

1. Barbieri RL, Ehrmann DA. Diagnosis and treatment of polycystic ovary syndrome in adults. Available at UpToDate.com. Accessed on 3/9/05. 2005.

2. Ehrmann DA. Polycystic ovary syndrome. N Engl J Med 2005;352:1223-36.

3. Goldstein SR, Zeltser I, Horan CK, Snyder JR, Schwartz LB. Ultrasonography-based triage for perimenopausal patients with abnormal uterine bleeding. Am J Obstet Gynecol 1997;177(1):102-8.

4. Rosenfield RL. Treatment of polycystic ovary syndrome in adolescents. Available at UpToDate.com. Accessed on 3/9/05. 2005.

5. Schlechte JA. Clinical practice. Prolactinoma. N Engl J Med 2003;349(21):2035-41.

6. Speroff L, Fritz M, Fritz MA. Clinical Gynecologic Endocrinology and Infertility. 7th ed. Baltimore: Lippincott Williams & Wilkins; 2004.

7. Warren MP. Amenorrhea and infertility associated with exercise. Available at UpToDate.com. Accessed on March 11, 2005. 2005.

8. Zhang J, Gilles JM, Barnhart K, Creinin MD, Westhoff C, Frederick MM. A comparison of medical management with misoprostol and surgical management for early pregnancy failure. N Engl J Med 2005;353(8):761-9.