Psychotropics in Women

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- Conflict of Interest: No one offered to pay me
- Caveat: Ringing cellphones are subject to fine
- Disclaimer: I might overshoot my time

Primer

- Perinatal – Pregnancy & Lactation
- Premenstrual Syndrome
- PCOD
- Menopause

Perinatal

Perinatal Depression (Payne, PCNA Jun, '17)

Affect on Mother

- Low maternal weight gain
- Increased rates of substance use
- Increased ambivalence about pregnancy
- Overall worse health status

Untreated antepartum depression is one of the strongest risk factors for PostPartum Dep which has a 20% fatality by suicide – one of the leading causes of peripartum mortality

Affect on Child

- Increased risk of preterm birth
- Low birth weight
- Higher cortisol levels (increased vulnerability to psychopathology)

PDD – increased rates of infantile colic, impaired maternal-infant bonding, interferes with parental behaviour; less infant safety and healthy child development practices, harsh discipline. Negative effects on infant development; IQ, language and behaviour

Pk/Pd changes during pregnancy

The pharmacokinetics and pharmacodynamics changes during pregnancy include

- delayed **gastric emptying**
- decreased albumin levels (decreased drug protein binding)
- increased vascular volume hence reduced serum levels of drugs,
- **enhanced hepatic metabolism** and
- **increased renal clearance**

All these significantly affect drug levels in the body

Babu GN, Desai G, Chandra PS. Antipsychotics in pregnancy and lactation.Indian J Psychiatry 2015;57:303-307

Pk/Pd in fetus

Fetus has

- Low levels of drug binding to plasma proteins,
- **immature hepatic metabolism,**
- A relatively **permeable blood brain barrier** and difficulties in transporting drug metabolites back to the maternal circulation combined with the **reduced ability of the fetus to metabolize drugs**.
- Hence at one end adequate levels of medication have to be maintained in the maternal serum, at the same level it has to be less in the fetal circulation

Safety Of Psy Meds in Pregnancy

The FDA classifies drug safety using the following categories:

A = controlled studies show no risk

B = no evidence of risk in humans

C = risk cannot be ruled out

D = positive evidence of risk

X = contraindicated in pregnancy

- Chance of fetal exposure to psychotropic drugs, especially in the first trimester is high
- There is ample evidence of an increase in teratogenicity with polypharmacy
- Hence planning pregnancy is of foremost importance in preventing the fetal exposure to multiple psychotropics.

Teratogenicity in Pregnancy

- Most cardiovascular malformations reported in infants exposed to **paroxetine were ventricular septal defects** (67% [8/12])

- Other antidepressants, including citalopram (511 exposed infants), escitalopram (152), fluoxetine (1633), fluvoxamine (36), and sertraline (1205), were not associated with an increased risk of malformations

Antidepressants	FDA PREGNANCY CATEGORY
Amitriptyline	C
Escitalopram	C
Fluoxetine	C
Paroxetine	D
Sertraline	C
Bupropion	B

Paroxetine is a definite no

SSRIs in Pregnancy

- Evidence suggests that SSRI exposure in utero does **not have significant** long-term effects on cognition or behavior
- Based on limited information, **mirtazapine, bupropion, and venlafaxine** do not appear to be major teratogens
- Selective serotonin reuptake inhibitors (SSRIs) are **not generally thought to be major teratogens**.
- **Fluoxetine is the most studied in pregnancy**

Safety of Newer Antidepressants in Pregnancy. Pharmacotherapy. 2007;27(4):546-552. ©2007

- Third-trimester exposure to newer antidepressants, including SSRIs and serotonin-norepinephrine reuptake inhibitors (e.g., venlafaxine), has been associated with a **poor neonatal adaptation syndrome.**

- In addition, SSRI use may be associated with an increased risk of **persistent pulmonary hypertension of the newborn.**

- Preliminary evidence suggests that SSRI exposure in utero **does not have significant long-term effects** on cognition or behavior.

- Little or no information is available on duloxetine

Safety of Newer Antidepressants in Pregnancy. Pharmacotherapy. 2007;27(4):546-552. ©2007

- The relative risk of persistent pulmonary hypertension, a potentially life threatening condition, is increased in infants prenatally exposed to SSRI, from 1.2 per 1000 live births in unexposed infants to 3 per 1000 live births in SSRI exposed neonate

- A neonatal maladaptation syndrome in infants exposed to SSRIs during late pregnancy is well known. It includes symptoms such as jitteriness, feeding problems, respiratory distress, hypoglycemia .

Benzodiazepines	FDA PREGNANCY CATEGORY
Alprazolam	D
Chlordiazepoxide	D
Clonazepam	D
Diazepam	D
Lorazepam	D

Antipsychotics	FDA PREGNANCY CATEGORY
Clozapine	B
Olanzapine	**C**
Quetiapine	C
Risperidone	C
Haloperidol	C

Anti Epileptics	FDA PREGNANCY CATEGORY
Carbamazepine	D
Lithium	D
Lamotrigine	**C**
Valproic Acid	D

Lactation

Lactation risk categories are as follows:

L1 = safest;

L2 = safer;

L3 = moderately safe;

L4 = possibly hazardous;

L5 = contraindicated

- Drugs are mainly transferred into breast-milk by passive diffusion and small molecules of very lipid soluble drugs diffuse very rapidly.

- Once in the milk, those drugs which are **lipophilic**, can be **further concentrated in hind-milk** which has a higher fat content than fore-milk.

K. Yoshida et al 2015

- There seem to be no reasons to prevent a mother from breast-feeding her baby if she is taking a TCA.

- Much less is known about the SSRI antidepressants, but if they are particularly indicated, and provided that the infants are carefully monitored, we believe that women should not be discouraged from breast-feeding if they want to

- It is advisable to check by means of routine blood tests that the **infant's hepatic and renal functions are normal before a mother is to breast-feed** if she is receiving psychotropic medication.
- The baby must always be repeatedly and systematically examined and monitored for the possible presence of any adverse effects
- The daily infant fuoxetine doses (mg/kg) were estimated to be **between 3% and 10%** of the maternal dose. Amounts of both fuoxetine and nor¯uoxetine in infants' plasma and urine were below the lower limit of detection (2.0 ng/ml).

Antidepressants	LACTATION RISK CATEGORY
Amitriptyline	**L2**
Escitalopram	L3 in older infants
Fluoxetine	**L2 in older infants** L3 in neonates
Paroxetine	**L2**
Sertraline	**L2**
Bupropion	**L3**

Benzodiazepines	LACTATION RISK CATEGORY
Alprazolam	L3
Chlordiazepoxide	L3
Clonazepam	L3
Diazepam	L3-L4 if used chronically
Lorazepam	L3

Antipsychotics	LACTATION RISK CATEGORY
Clozapine	L3
Olanzapine	**L2**
Quetiapine	L4
Risperidone	L3
Haloperidol	**L2**

Anti Epileptics	LACTATION RISK CATEGORY
Carbamazepine	**L2**
Lithium	L4
Lamotrigine	**L3**
Valproic Acid	L2

FGAs

- High-potency conventional antipsychotic agents such as haloperidol do not appear to increase the risk of teratogenicity
- Low-potency antipsychotic agents such as chlorpromazine have a small, but statistically significant increased risk of nonspecific teratogenic effects with first trimester exposure
- A meta-analytic study of first trimester exposure to low-potency neuroleptics (Trifluperazine, Chlorpromazine) found an increase of **one case of malformation for every 250 pregnancies** in which exposure occurred
- In a survey of more than 50,000 mother-child pairs that identified 142 first trimester exposures and 284 total exposures to chlorpromazine, there was no elevation in the rate of physical malformations with chlorpromazine

SGAs

- Many of these agents, however, induce **maternal hyperglycemia, impaired glucose tolerance, weight gain and increase in birth weight** all of which predispose to unfavorable obstetric outcomes and long-term maternal complications in **Mothers**
- Studies have demonstrated increased risk of low birth weight, while some have shown higher incidence of large for gestational age in **infants** exposed to atypical antipsychotics
- Of the **227** reports of pregnancies, there were **eight reports** of major malformations of unknown typology have been observed.

Newham JJ, Thomas SH, MacRitchie K, McElhatton PR, McAllister-Williams RH. Birth weight of infants after maternal exposure to typical and atypical antipsychotics: Prospective comparison study. Br J Psychiatry 2008;192:333-7.

Littrell KH, Johnson CG, Peabody CD, Hilligoss N. Antipsychotics during pregnancy. Am J Psychiatry 2000;157:1342.

SGAs

Olanzapine is often used

- Various congenital malformations have been reported after its use in pregnancy including four cases of neural tube defects. However, **there was the use of concomitant medication**

Risperidone is also one of the commonly used SGA.

- Reports of congenital anomalies of known typology have been observed, but there are no recurrent patterns of anomalies.

Quetiapine

- Of the 227 reports of pregnancies, there were **eight reports of major malformations** of unknown typology have been observed

Molecule Wise 7/10/2017

- It is important to monitor the women for gestational diabetes who are on typical antipsychotics.
- There is a lack of information on the long-term cognitive and behavioral outcome in the infants exposed to atypical antipsychotics
- However Children with and without histories of neuroleptic exposure showed no differences in behavioral functioning or Intelligence Quotient (IQ) when followed up to 5 years of age

PCOS

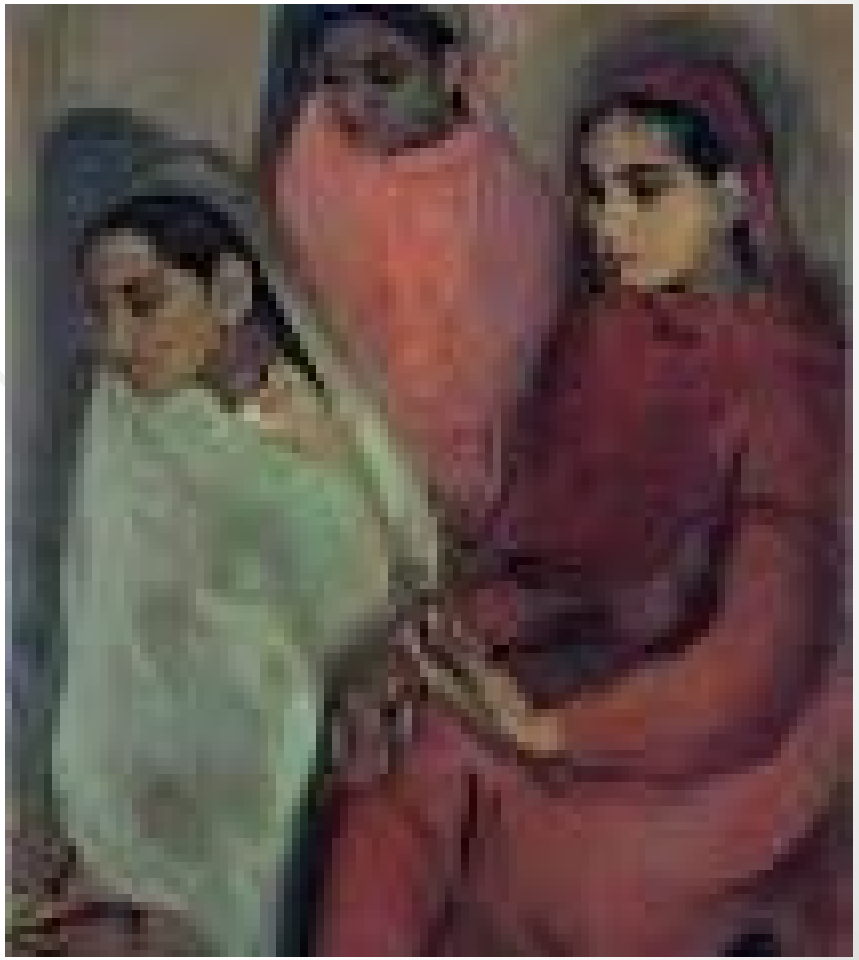


Table 1. Criteria for Diagnosis of PCOS

Clinical finding	*National Institutes of Health criteria, 1990 (must have both of the findings marked below)*	*Rotterdam criteria, 2003 (must have any two of the findings marked below)*	*Androgen Excess and PCOS Society, 2009 (must have A plus either B or C)*
Hyperandrogenism*	X	X	A
Oligomenorrhea	X	X	B
Polycystic ovaries		X	C

PCOS = polycystic ovary syndrome.

**—Clinical or biochemical evidence of excess androgen.*

Information from reference 19.

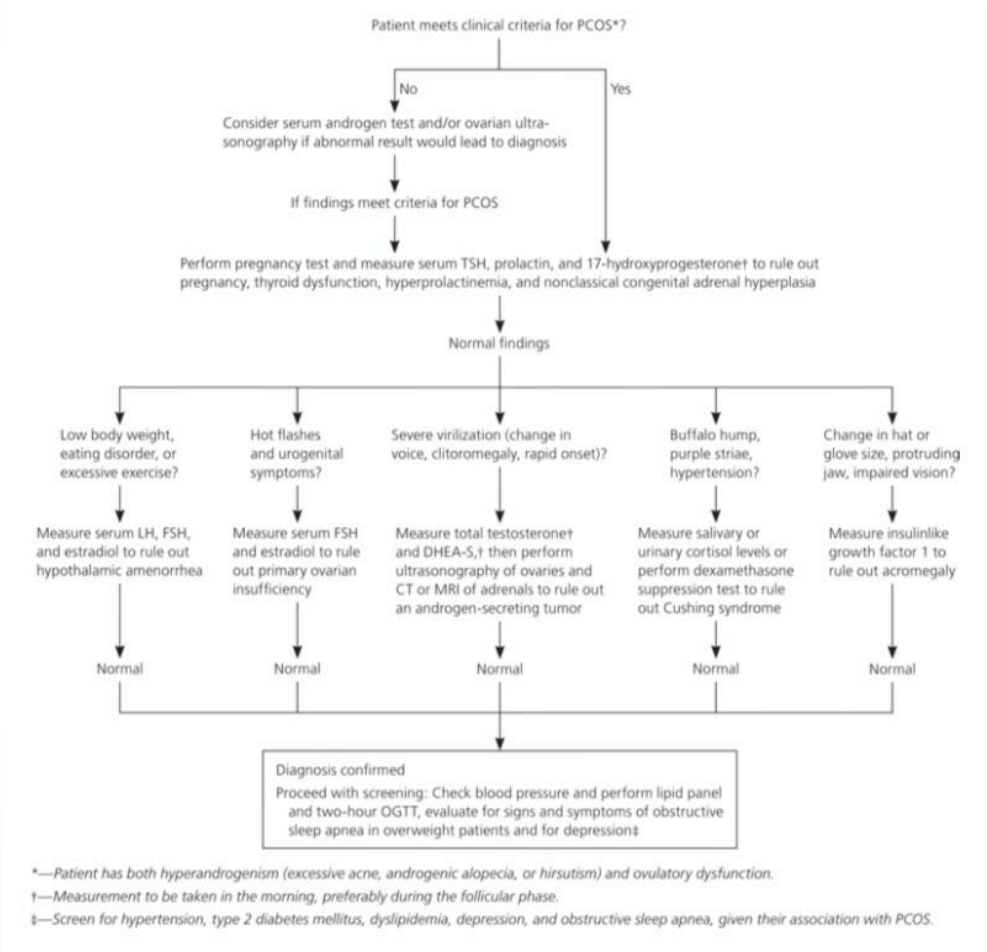

Patient meets clinical criteria for PCOS*?
No
Yes
Consider serum androgen test and/or ovarian ultrasonography if abnormal result would lead to diagnosis
If findings meet criteria for PCOS
Perform pregnancy test and measure serum TSH, prolactin, and 17-hydroxyprogesterone† to rule out pregnancy, thyroid dysfunction, hyperprolactinemia, and nonclassical congenital adrenal hyperplasia
Normal findings
Low body weight, eating disorder, or excessive exercise?
Hot flashes and urogenital symptoms?
Severe virilization (change in voice, clitoromegaly, rapid onset)?
Buffalo hump, purple striae, hypertension?
Change in hat or glove size, protruding jaw, impaired vision?
Measure serum LH, FSH, and estradiol to rule out hypothalamic amenorrhea
Measure serum FSH and estradiol to rule out primary ovarian insufficiency
Measure total testosterone† and DHEA-S,† then perform ultrasonography of ovaries and CT or MRI of adrenals to rule out an androgen-secreting tumor
Measure salivary or urinary cortisol levels or perform dexamethasone suppression test to rule out Cushing syndrome
Measure insulinlike growth factor 1 to rule out acromegaly
Normal
Normal
Normal
Normal
Normal
Diagnosis confirmed
Proceed with screening: Check blood pressure and perform lipid panel and two-hour OGTT, evaluate for signs and symptoms of obstructive sleep apnea in overweight patients and for depression‡
*—Patient has both hyperandrogenism (excessive acne, androgenic alopecia, or hirsutism) and ovulatory dysfunction.
†—Measurement to be taken in the morning, preferably during the follicular phase.
‡—Screen for hypertension, type 2 diabetes mellitus, dyslipidemia, depression, and obstructive sleep apnea, given their association with PCOS.

Table 2. Treatments for Polycystic Ovary Syndrome

Medication or device	*Description*	*Manifestations treated*	*FDA pregnancy category*	*Main adverse effects*	*Typical dosage*	*Cost**
Clomiphene†	Ovulation induction agent, selective estrogen receptor modulator	Infertility (first-line therapy)[19]	X	Multiple pregnancy or ovarian hyperstimulation, thrombo-embolism, visual disturbances	50 to 100 mg daily	$15 for 100 mg daily for 5 days
Eflornithine (Vaniqa)‡§	Inhibits hair growth	Mild hirsutism (second-line therapy)[33]	C	Mild skin irritation	13.9% cream applied to affected area twice daily	$78 (brand) for 1 30-g tube
Finasteride (Proscar)‡	5-alpha-reductase inhibitor	Hirsutism (weak recommendation because of inconsistent study results)[32]	X	Hypersensitivity reaction, decreased libido	5 mg daily	$10 (generic) and $273 (brand)
Flutamide‡	Nonsteroidal antiandrogen used mostly for prostate cancer	Hirsutism (safe and effective according to low- to very low-quality evidence)[32]	D	Liver toxicity, thrombocytopenia, leukopenia, hot flashes	250 mg once or twice daily[32]	$32 for 250 mg daily
Hormonal contraceptives (e.g., pill, patch, vaginal ring)‡‖	See article for details	Menstrual irregularities, hirsutism, acne (first-line therapy)[19,30,32]	X	Nausea, headache, spotting, thrombophlebitis, deep venous thrombosis	Varies	Varies
Letrozole (Femara)‡	Nonsteroidal competitive inhibitor of aromatase; inhibits conversion of adrenal androgens	Infertility (first-line therapy)[19,29]	C	Osteoporosis, thrombo-embolism, MI, hot flashes, arthralgias	2.5 to 7.5 mg daily for 5 days	$8 (generic) and $128 (brand) for 2.5 mg daily for 5 days
Levonorgestrel-releasing intrauterine system (Mirena)‡	Intrauterine device	Endometrial hyperplasia Abnormal uterine bleeding (FDA approved)[31]	X	Amenorrhea, nausea, vomiting; rare complications include the device becoming embedded in the myometrium and uterine perforation	5 years	$815 (not including cost of placement)
Metformin‡	Insulin-sensitizing agent	Insulin resistance (first-line therapy) Menstrual irregularities (second-line therapy added to hormonal contraceptives) Hirsutism (third-line therapy added to hormonal contraceptives and spironolactone)[19]	B	Gastrointestinal upset, lactic acidosis, increase in homocysteine levels	1,500 to 2,250 mg daily	$4 for 1,000 mg twice daily
Spironolactone‡	Antiandrogenic antimineralocorticoid	Hirsutism (second-line therapy added after 6 months of oral contraceptive therapy if not improved)[32,33] Acne (second-line therapy)	C	Hyperkalemia, nausea, breast tenderness	50 mg daily to 100 to 200 mg daily	$15 for 100 mg daily

NOTE: *Thiazolidinediones have been omitted from the table because the Endocrine Society has determined that their risk-benefit ratio is unfavorable.*

FDA = U.S. Food and Drug Administration; MI = myocardial infarction; PCOS = polycystic ovary syndrome.

**—Estimated retail price of one month's treatment (unless otherwise noted) based on information obtained at www.goodrx.com and www.lowestmed.com (accessed May 24, 2015).*

†—FDA approved for female infertility caused by PCOS.

‡—Not FDA approved for treatment of manifestations of PCOS.

§—Not studied specifically in women with PCOS; therefore, effectiveness is unknown.

‖—Based on mostly anecdotal evidence.

Adapted with permission from Radosh L. Drug treatments for polycystic ovary syndrome. Am Fam Physician. 2009;79(8):672-673, with additional information from references 19, and 29 through 33.

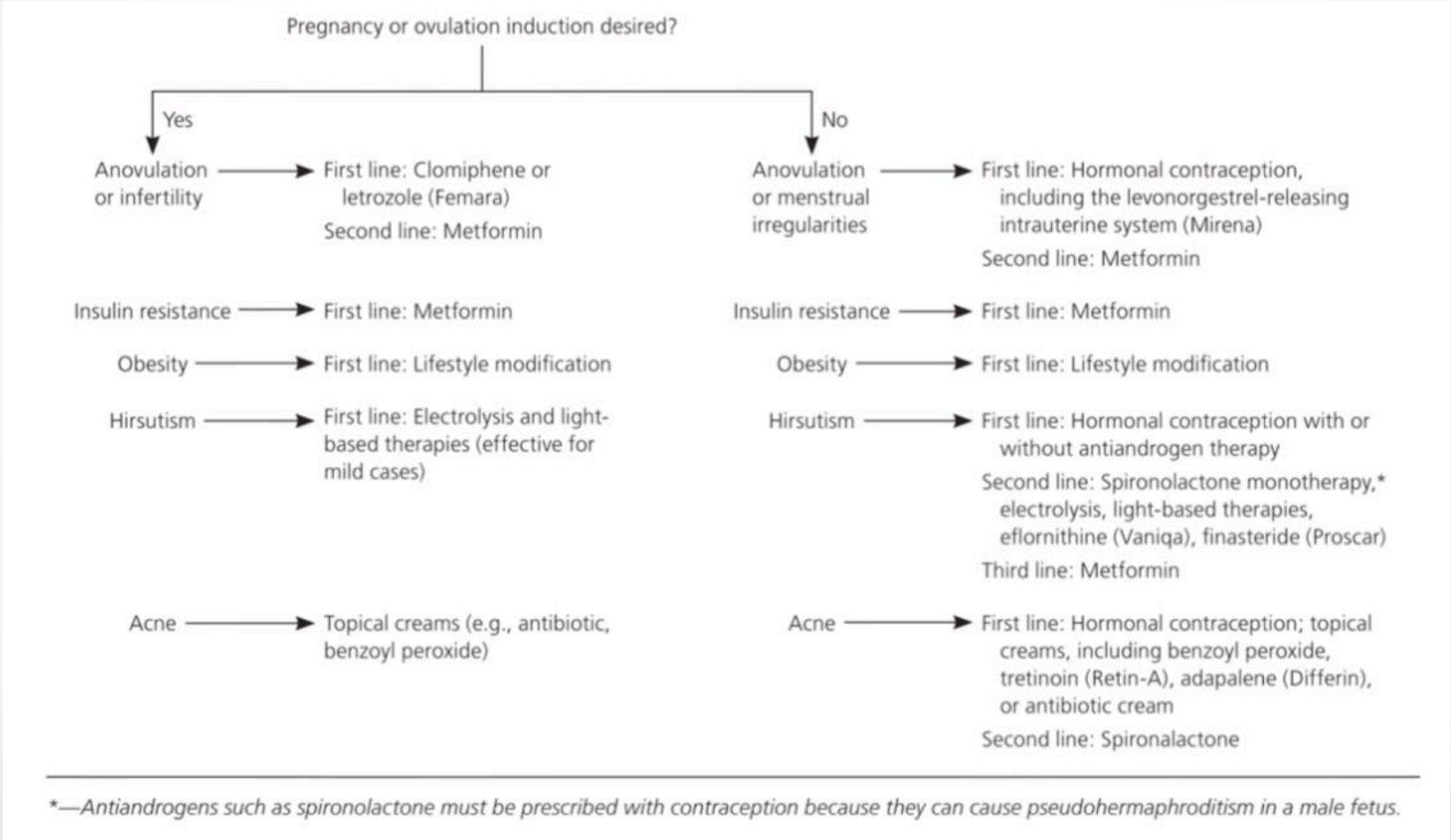

Pregnancy or ovulation induction desired?
Yes
No
Anovulation or infertility
First line: Clomiphene or letrozole (Femara)
Second line: Metformin
Anovulation or menstrual irregularities
First line: Hormonal contraception, including the levonorgestrel-releasing intrauterine system (Mirena)
Second line: Metformin
Insulin resistance
First line: Metformin
Insulin resistance
First line: Metformin
Obesity
First line: Lifestyle modification
Obesity
First line: Lifestyle modification
Hirsutism
First line: Electrolysis and light-based therapies (effective for mild cases)
Hirsutism
First line: Hormonal contraception with or without antiandrogen therapy
Second line: Spironolactone monotherapy,* electrolysis, light-based therapies, eflornithine (Vaniqa), finasteride (Proscar)
Third line: Metformin
Acne
Topical creams (e.g., antibiotic, benzoyl peroxide)
Acne
First line: Hormonal contraception; topical creams, including benzoyl peroxide, tretinoin (Retin-A), adapalene (Differin), or antibiotic cream
Second line: Spironalactone
*—Antiandrogens such as spironolactone must be prescribed with contraception because they can cause pseudohermaphroditism in a male fetus.

Table 2. Treatments for Polycystic Ovary Syndrome

Medication or device	*Description*	*Manifestations treated*	*FDA pregnancy category*
Clomiphene†	Ovulation induction agent, selective estrogen receptor modulator	Infertility (first-line therapy)[19]	X
Eflornithine (Vaniqa)‡§	Inhibits hair growth	Mild hirsutism (second-line therapy)[33]	C
Finasteride (Proscar)‡	5-alpha-reductase inhibitor	Hirsutism (weak recommendation because of inconsistent study results)[32]	X
Flutamide‡	Nonsteroidal antiandrogen used mostly for prostate cancer	Hirsutism (safe and effective according to low- to very low-quality evidence)[32]	D
Hormonal contraceptives (e.g., pill, patch, vaginal ring)‡‖	See article for details	Menstrual irregularities, hirsutism, acne (first-line therapy)[19,30,32]	X
Letrozole (Femara)‡	Nonsteroidal competitive inhibitor of aromatase; inhibits conversion of adrenal androgens	Infertility (first-line therapy)[19,29]	C
Levonorgestrel-releasing intrauterine system (Mirena)‡	Intrauterine device	Endometrial hyperplasia Abnormal uterine bleeding (FDA approved)[31]	X
Metformin‡	Insulin-sensitizing agent	Insulin resistance (first-line therapy) Menstrual irregularities (second-line therapy added to hormonal contraceptives) Hirsutism (third-line therapy added to hormonal contraceptives and spironolactone)[19]	B
Spironolactone‡	Antiandrogenic antimineralocorticoid	Hirsutism (second-line therapy added after 6 months of oral contraceptive therapy if not improved)[32,33] Acne (second-line therapy)	C

Appendix III: Daily Recording of Severity of Problems (DRSP) symptom diary

DAILY RECORD OF SEVERITY OF PROBLEMS

Please print and use as many sheets as you need for at least two FULL months of ratings.

Name or Initials _____

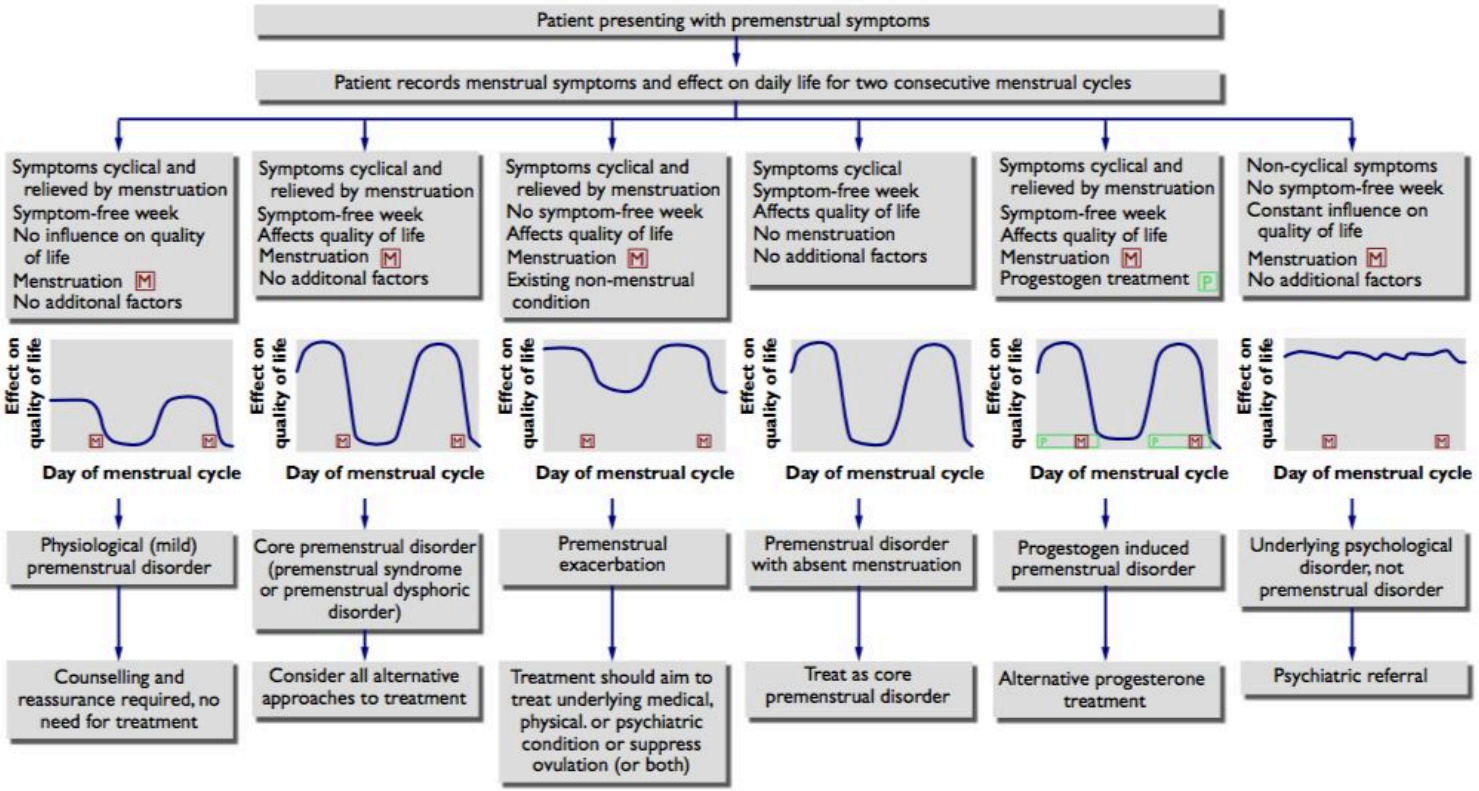
Month/Year _____

Each evening note the degree to which you experienced each of the problems listed below. Put an "x" in the box which corresponds to the severity: 1 - not at all, 2 - minimal, 3 - mild, 4 - moderate, 5 - severe, 6 - extreme.

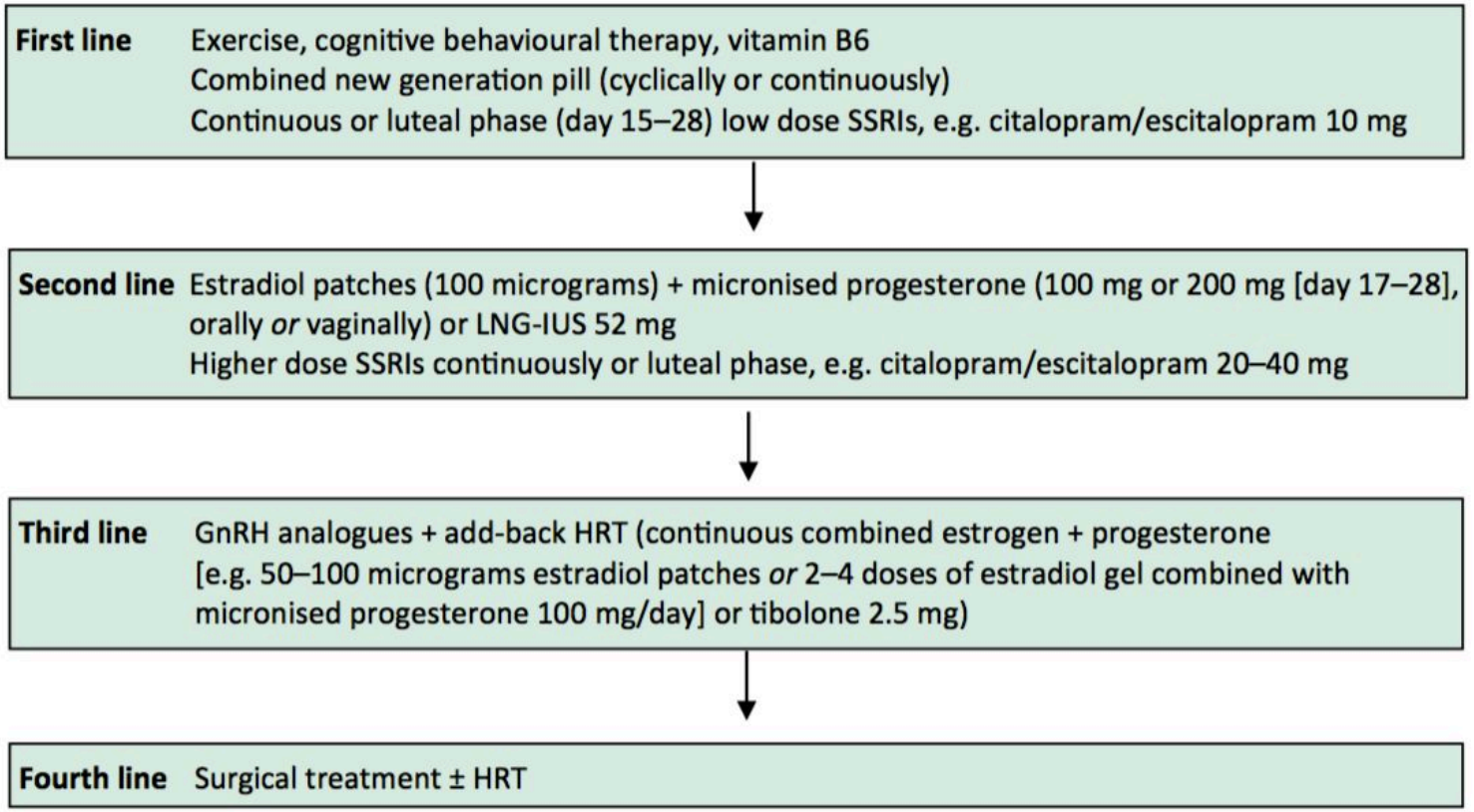
Enter day (Monday-"M", Thursday-"R", etc) >																														
Note spotting by entering "S" >																														
Note menses by entering "M" >																														
Begin rating on correct calendar day >	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
1 Felt depressed, sad, "down" or "blue", or felt hopeless, or felt worthless or guilty	6 5 4 3 2 1																													
2 Felt anxious, tense, "keyed up" or "on edge"	6 5 4 3 2 1																													
3 Had mood swings (i.e. suddenly feeling sad or tearful) or was sensitive to rejection or feelings were easily hurt	6 5 4 3 2 1																													
4 Felt angry or irritable	6 5 4 3 2 1																													
5 Had less interest in usual activities (work, school, friends, hobbies)	6 5 4 3 2 1																													
6 Had difficulty concentrating	6 5 4 3 2 1																													
7 Felt lethargic, tired or fatigued, or had lack of energy	6 5 4 3 2 1																													
8 Had increased appetite or overate, or had cravings for specific foods	6 5 4 3 2 1																													
9 Slept more, took naps, found it hard to get up when intended, or had trouble getting to sleep or staying asleep	6 5 4 3 2 1																													
10 Felt overwhelmed or unable to cope, or felt out of control	6 5 4 3 2 1																													
11 Had breast tenderness, breast swelling, bloated sensation, weight gain, headache, joint or muscle pain, or other physical symptoms	6 5 4 3 2 1																													
At work, school, home or in daily routine, at least one of the problems noted above caused reduction of productivity or inefficiency	6 5 4 3 2 1																													
At least one of the problems noted above caused avoidance of or less participation in hobbies or social activities	6 5 4 3 2 1																													
At least one of the problems noted above interfered with relationships with others	6 5 4 3 2 1																													

Premenstrual Syndrome

Appendix II: Classification of PMS[1]



Appendix IV: How PMS is treated – a decision-making algorithm[132]



Perimenopause

The menopausal transition is often marked by-

1. Somatic symptoms (aches and pains, myalgia, fatigue)
2. Physiologic symptoms (vasomotor symptoms [VMS] of hot flashes and nighttime awakenings)
3. Other symptoms (sleep disturbances, sexual arousal disorders, and urogenital complaints) and
4. Psychological symptoms (irritability, anxiety, low libido).

- Overall, this period may represent a time of higher vulnerability for psychiatric problems and generally poorer quality of life.
- The perimenopausal period is associated with a higher vulnerability for depression, with risk rising from early to late perimenopause and decreasing during postmenopause.
- Women with a history of depression are up to 5 times more likely to have a MDD diagnosis during this time period.

- As is true for MDD in other patient populations, *antidepressants may be considered appropriate first-line therapy for moderate-to-severe depression in perimenopausal women*.
- Antidepressants are generally effective in women across the lifespan, and few studies have prospectively assessed whether menopausal status influences antidepressant efficacy.
- However, there is some evidence of variability in the efficacy of some antidepressants (in particular, the selective serotonin reuptake inhibitors [SSRIs]) when used to treat depression in the context of perimenopausal hormonal changes.

- ERT may be appropriate for women in perimenopause who do not take hormonal contraceptives and are willing to take hormones to improve their menopausal symptoms.
- *The role of hormone replacement therapy in the treatment of mood disorders remains unconfirmed.*

Thank You For Your Kind Audience

- I'm happy to provide references and answer further questions on –
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