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Navigating Perimenopause

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Learning Objectives

- Focus our conversation today on the early perimenopause transition
- Define Perimenopause
- Review Perimenopause Physiology
- Review the many, many, many, many, many, many symptoms of perimenopause
- Review testing options, recommendations, and pitfalls
- Learn options for hormone therapy in the early perimenopause transition when patients are still cycling
- Review alternative approaches when hormone therapy is not the best option
- Review a case that follows an early perimenopause patient over 4 years
- Stay flexible in the treatment of patients in the early perimenopause transition when everything is everywhere and happening all at once.

What is Perimenopause?

What is Perimenopause?

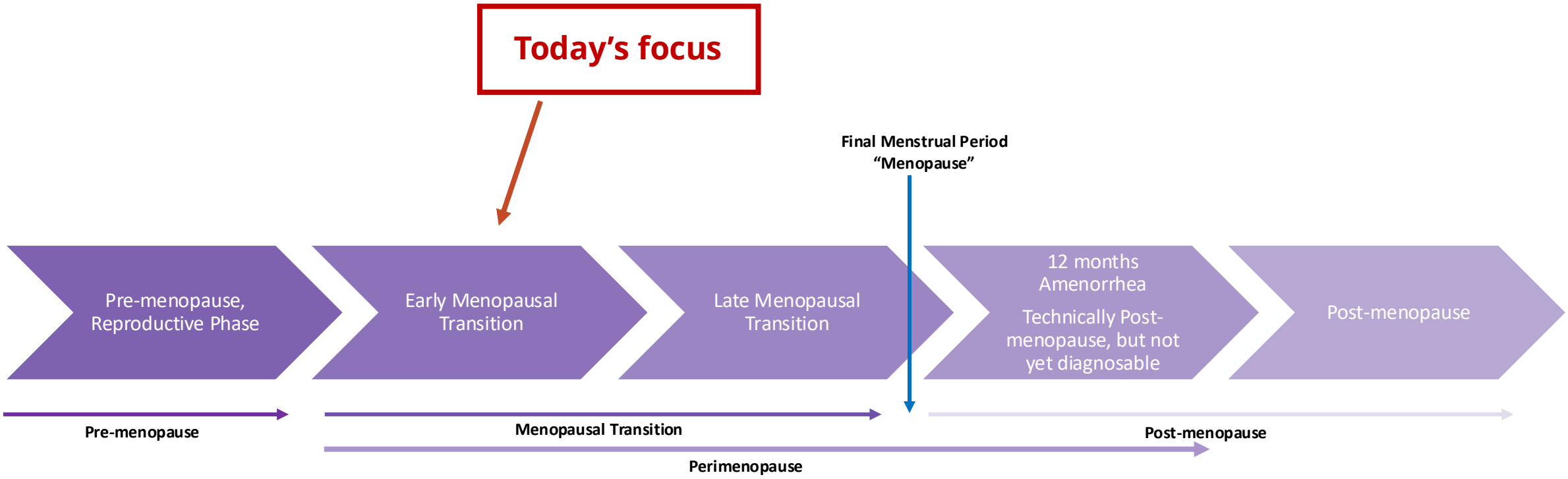
If MENOPAUSE is…

- The cessation of the monthly hormone cycle and fertility in women. Average age of menopause is 51 (**range 40-58**).
- One year after cycles cease, the patient is considered **postmenopausal**.
- Due to ovarian activity fluctuation, menopause is not confirmed until cycles have **ceased for 12 full months**.

Then, PERIMENOPAUSE is…

- **The hormonal changes that happen in the 2-8 years prior to menopause**. Changes are gradual, and patients are often symptomatic.
- Perimenopause is also sometimes called the **“**menopausal transition”.

What is Perimenopause?



Harlow SD, et al. J Clin Endocrinol Met. 2012;97(4):1159-1168.

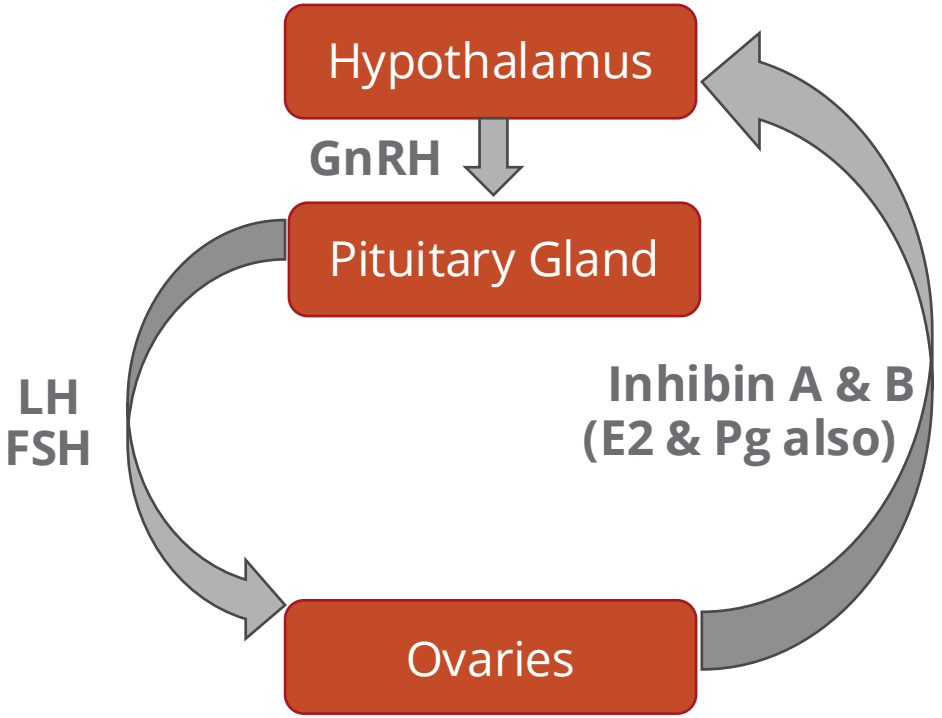
Perimenopause Physiology

Reproductive Physiology

During the reproductive stage the hypothalamic-pituitary-ovarian (HPO) axis has EXCELLENT communication.

- The pituitary releases follicle-stimulating hormone (FSH) to stimulate the development of ovarian follicles.
- It also releases luteinizing hormone (LH) to stimulate ovarian production of testosterone, and FSH to stimulate ovarian production of estradiol.
- The hypothalamus and pituitary receive feedback from estradiol (E2), progesterone (Pg), and other ovarian signals (like inhibin A & B) which help maintain the correct cascade of hormones, signals, and events for fertility and normal menstrual cycles in women.

HPO Axis Signaling



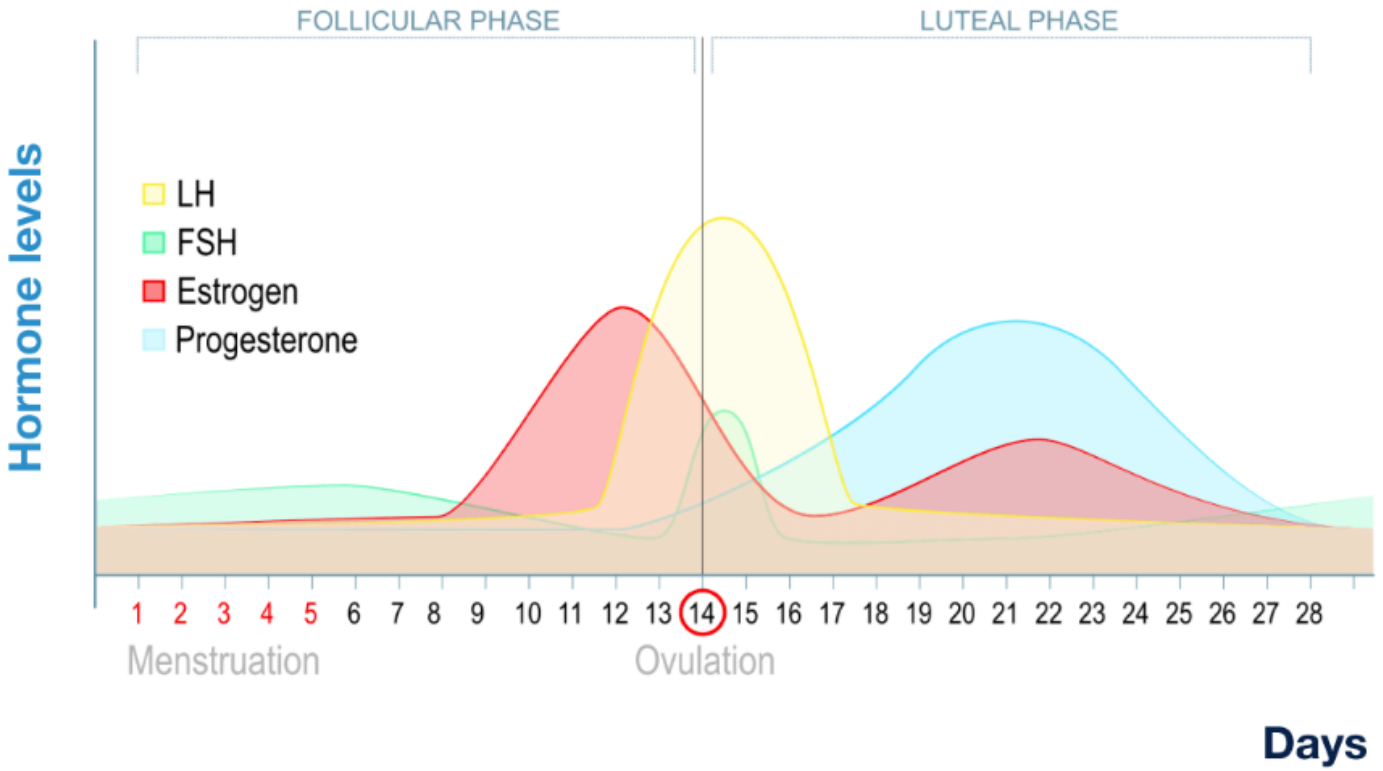
Casper R. In: Post T, editor. UpToDate. Waltham, MA 2023.

Reproductive Physiology

This excellent communication supports a healthy menstrual cycle.

- Cycles are regular.
- Ovulation occurs ~2 weeks before the next menses.
- Estrogen and progesterone levels fluctuate appropriately and are predictable.

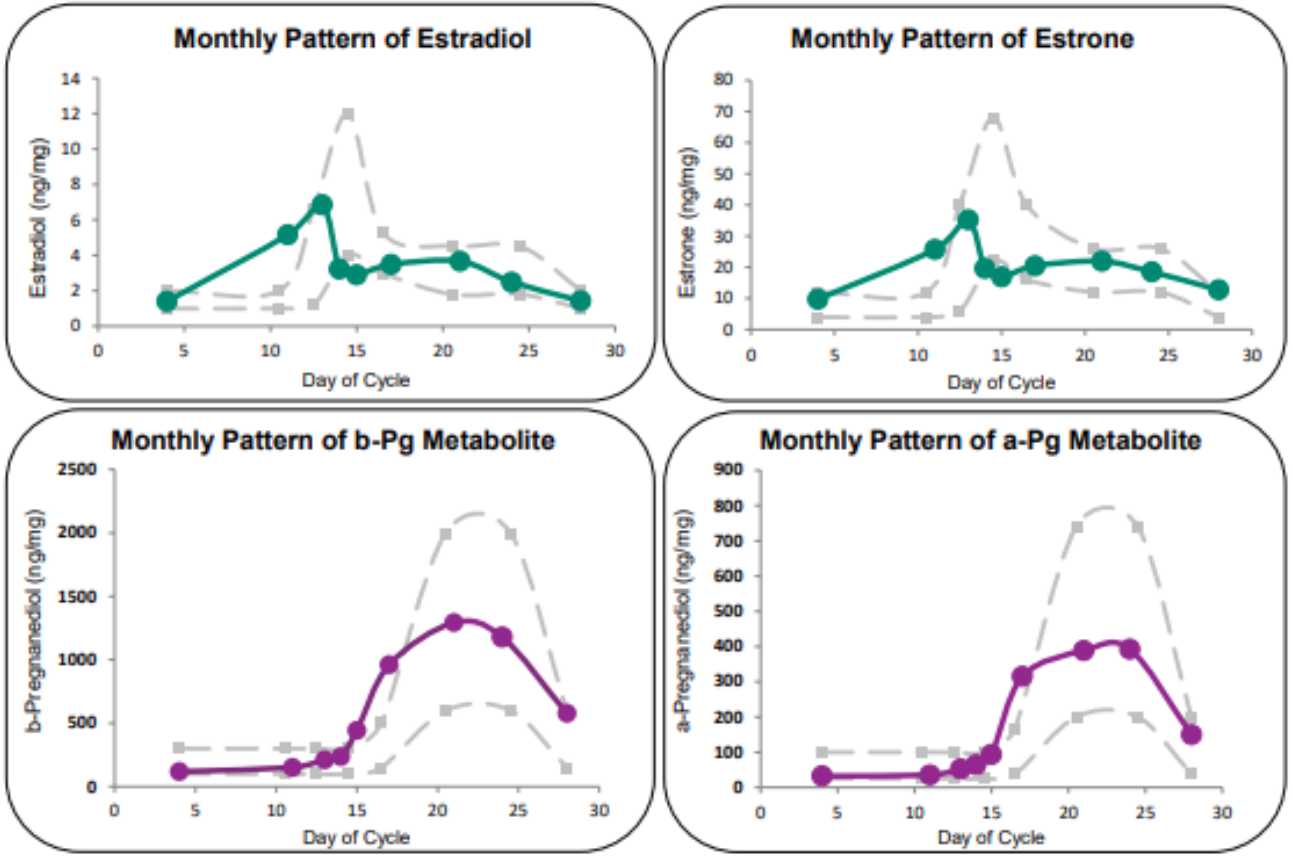
The Ovarian Hormone Cycle:



Info Adapted from:
Hale GE, et al. J Clin Endocrinol Metab. 2007;92(8):3060-3067.
Harlow SD, et al. J Clin Endocrinol Metab. 2012;97(4):1159-1168.

Excellent HPO axis communication – DUTCH Cycle Mapping example

- 36 yo female
- 28-day cycle
- Estrogen ovulatory surge at appropriate time in cycle around day 14 (~2 weeks before next menses)
- Progesterone metabolites rise in the luteal phase, confirming ovulation has taken place
  - Remember that women make a baseline of progesterone from the adrenal glands throughout the month, but the bulk of their progesterone is made by the corpus luteum cells in the ovary following ovulation.



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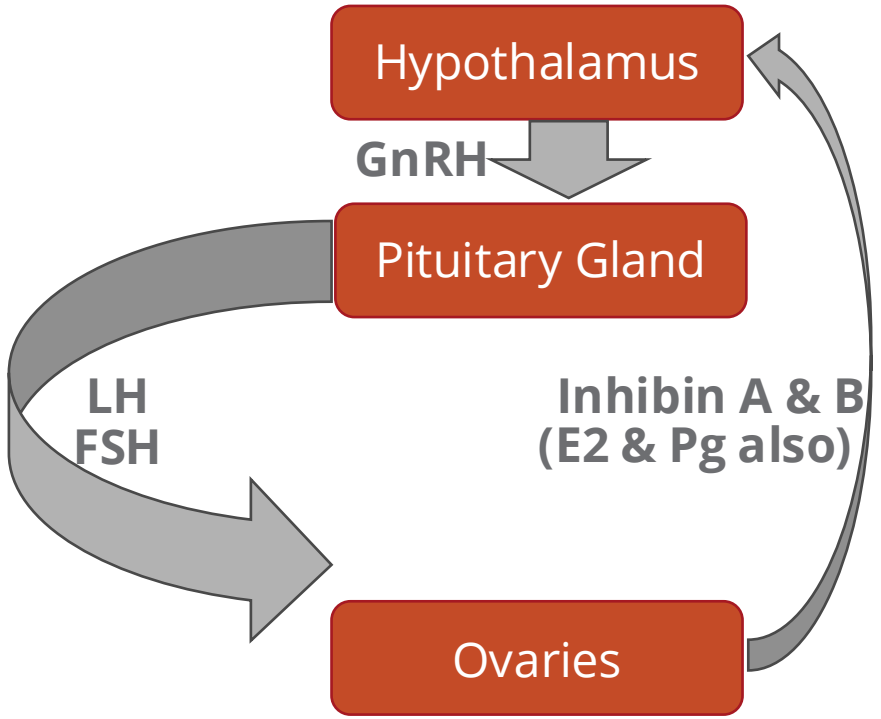
Perimenopause Physiology

During perimenopause, the hypothalamic-pituitary-ovarian (HPO) axis has DECLINING communication.

- Lower ovarian reserve (lower number of eggs available for maturation in the ovaries) leads to lower hormonal feedback (inhibin A & B, estradiol, progesterone) from the ovary to the brain.
- The brain responds to this lower ovarian feedback by surging its pituitary hormones (FSH and LH). The brain is "yelling" at the ovaries to make hormones.
- This can result in **(sometimes) high estradiol, irregular cycles, and low progesterone**.

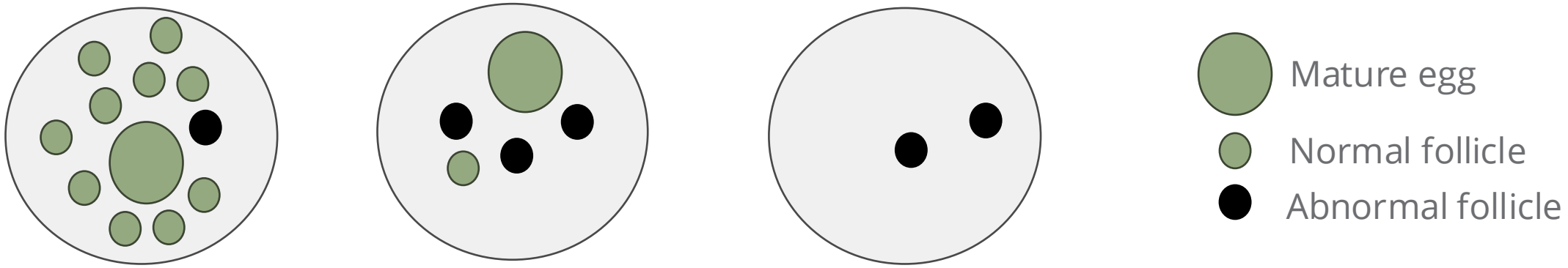
HPO Axis Signaling



Casper R. In: Post T, editor. UpToDate. Waltham, MA 2023.

Perimenopause Physiology

- A decline in follicle number, decline in follicle size at maturation, and decline in follicle sensitivity to FSH leads to **increased FSH signaling from pituitary.**
- In turn, there is irregular, high and low E2 excretion from maturing follicles.
- Leading to increasing cycle irregularity, unpredictable ovulation, and anovulatory cycles.
- Even if ovulation occurs, there may be a decline in progesterone production.
- Patients experience increasing stretches of time with low hormone levels.



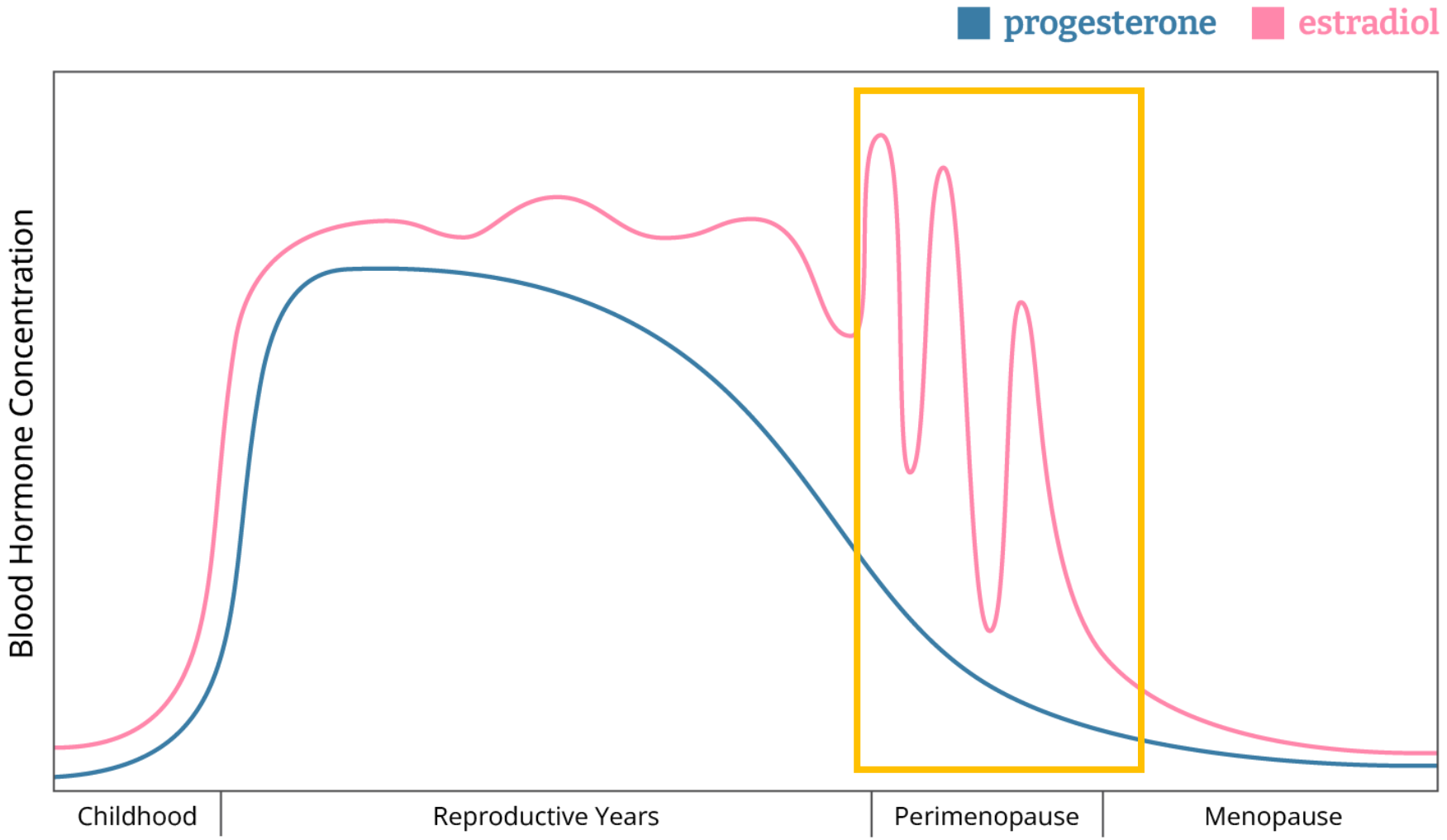
Reproductive phase ovary

Early perimenopausal phase ovary

Late perimenopausal phase or early menopause ovary

Allshouse A, et al. 2018;45(4):613-628.

Perimenopause Physiology



Perimenopause Symptomatology

Perimenopause Symptomatology

Symptoms that are related to relative **progesterone deficiency** (estrogen dominance) or frankly low progesterone, and anovulation:

Heavy menses

Short menstrual cycle interval

Emotional lability

Anxiety

Aggression, irritability, anger

Insomnia

Sundstrom-Poromaa I, et al. Front Neuroendocrinol. 2020;59:100856.

Perimenopause Symptomatology

Symptoms that are related to **estrogen deficiency** occurring in the later stages of the menopausal transition:

- Hot flashes
- Long menstrual cycle interval
- Vaginal dryness
- Dyspareunia
- Depression
- Brain fog
- Insomnia

Sundstrom-Poromaa I, et al. Front Neuroendocrinol. 2020;59:100856.

Perimenopause Symptomatology

	Early Menopausal Transition	Late Menopausal Transition
Overall	More likely to have estrogen dominant symptoms, such as heavy menses, breast tenderness, emotional lability, and short menstrual cycle intervals.	More likely to have estrogen deficiency symptoms, such as hot flashes, vaginal dryness, dyspareunia, depression, brain fog, insomnia, and long menstrual cycle intervals.
Menstrual Cycle Length	Variable. Persistent ≥ 7-day difference in length of consecutive cycles. Example of 6 consecutive menstrual cycle lengths: 20 days, 32 days, 37 days, 19 days, 24 days, 43 days, etc.	Interval of amenorrhea of ≥ 60 days. Example of 6 consecutive menstrual cycle lengths: 61 days, 45 days, 92 days, 90 days, 180 days, FMP.
Mood swings	More likely to feel increased anxiety, irritability, tearfulness, and emotional lability.	More likely to feel low mood and depression.
Heavy menses	More likely in early menopause transition.	Occurs less frequently as estrogen and progesterone decline.
Breast tenderness	More likely in early menopause transition.	Occurs less frequently than in early menopause transition.

Coslov N, et al. Menopause. 2021;28(9):1012-1025.

Perimenopause Symptomatology

	Early Menopausal Transition	Late Menopausal Transition
Brain fog*	Brain fog occasionally.	Brain fog daily.
Insomnia	Sleep issues a few times weekly.	Sleep issues more frequently, even daily. Waking early in the morning becomes a prominent feature.
Musculoskeletal pain & stiffness	Musculoskeletal pain and stiffness may be variable with fluctuating levels of estrogen.	Musculoskeletal pain and stiffness increases with declining estrogen.
Hot flashes	More likely to report "cold flashes", cold sweats, occurring once or twice a week. New AMY study shows this is an important symptom to identify perimenopause, even if menses hasn't changed	Hot flashes and night sweats occurring daily or multiple times a day.
Vaginal dryness		Vaginal dryness tends to come about in the late menopausal transition; occurs with low estrogen.

*Cognitive function decline or "brain fog"

Coslov N, et al. Menopause. 2021;28(9):1012-1025.
Islam, Rakibul M et al. The Lancet Diabetes & Endocrinology. 2025; 13(9): 765 – 776.

Perimenopause Symptomatology

Perimenopausal symptoms may be related to:

- Hormone changes
- Other causes such as aging, lifestyle, diet, disease processes, etc.
- For example:
  - **Heavy menses** may be the result of an undiagnosed uterine pathology such as **endometrial cancer**
  - **Weight gain** can be caused by hypothyroidism
  - **Brain fog** can be caused by low blood sugar and not eating enough
  - **Musculoskeletal pain and stiffness** can be caused by dehydration or over-training

Thoroughly investigate every complaint and do appropriate work-up.

Sundstrom-Poromaa I, et al. Front Neuroendocrinol. 2020;59:100856.

Perimenopause Symptomatology

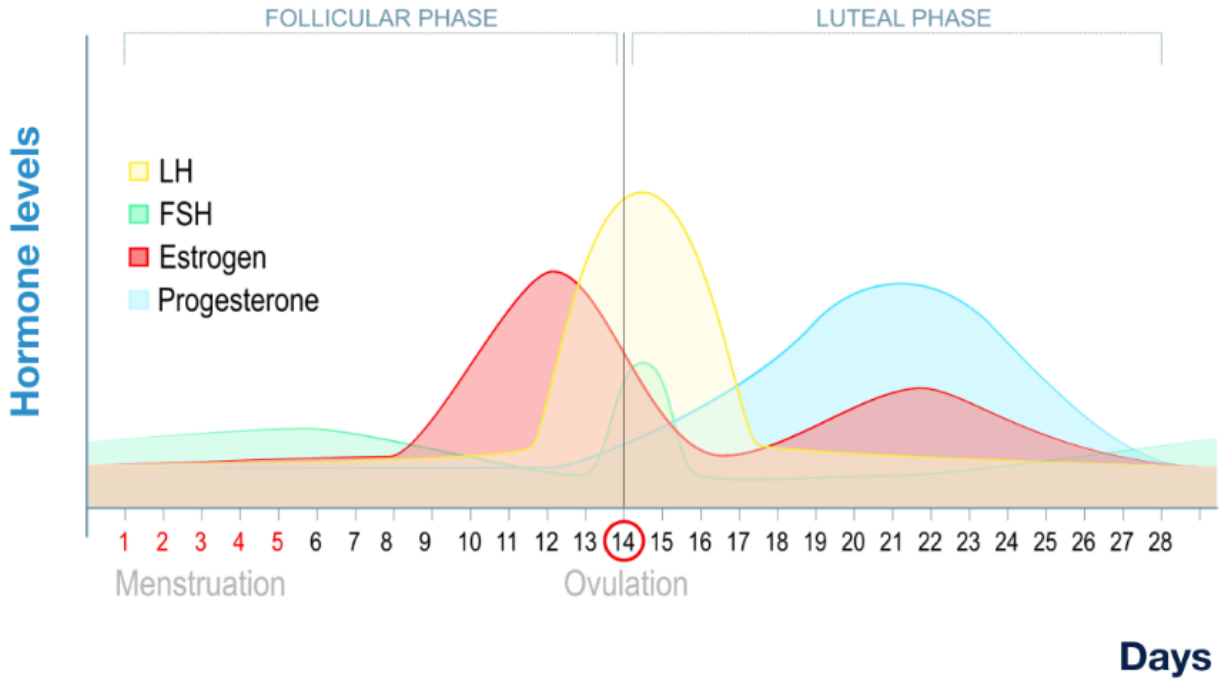
Underlying health conditions can also contribute to perimenopause symptoms:

	Inflammation	Insulin Resistance	Stress/High Cortisol	Poor Underlying Cardiovascular Health	Sedentary Lifestyle
Heavy Menses	✓	✓			
Breast Tenderness	✓	✓			
Brain fog*	✓	✓	✓	✓	✓
Mood swings	✓	✓	✓	✓	✓
Insomnia	✓	✓	✓		
Musculoskeletal pain	✓	✓	✓	✓	✓
Hot flashes	✓	✓	✓	✓	✓
Vaginal dryness			✓		

*Cognitive function decline or “brain fog”

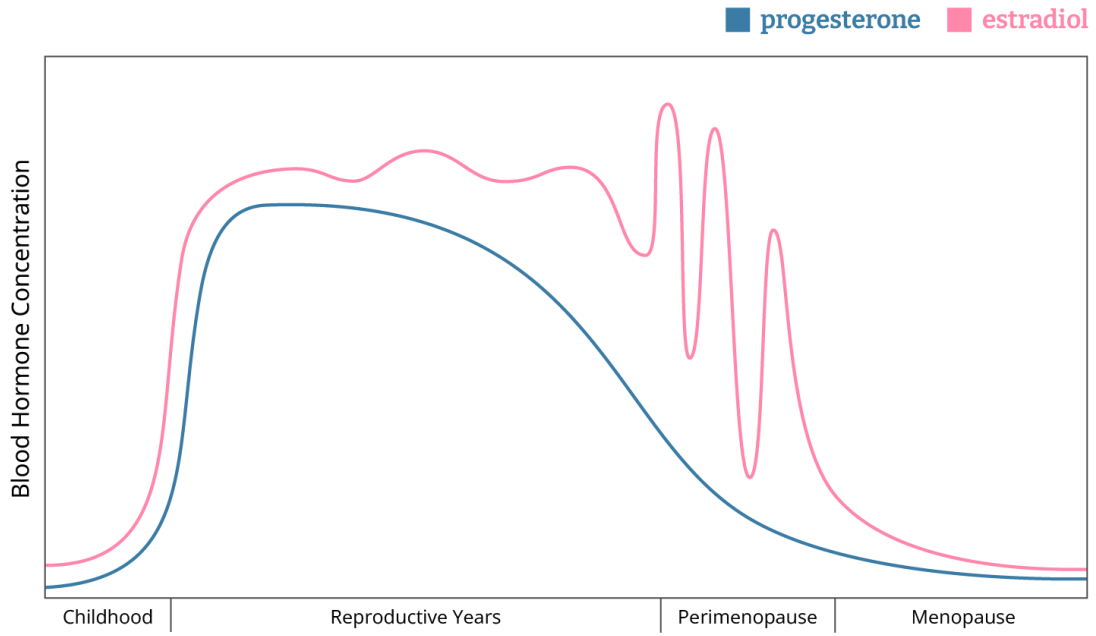
Testing in Perimenopause - If hormones are so erratic during perimenopause, why even test?

Perimenopause Lab Testing



Hormones change a lot throughout a regular menstrual cycle

Hormones change a lot in perimenopause



Perimenopause Lab Testing

Medical associations do not recommend hormone lab testing in perimenopause.

- Lab testing in perimenopause is **notoriously challenging**, especially in the early menopausal transition when one menstrual cycle may not look like another.
- A thorough history is often adequate for identifying the stage she may be in.
- Most importantly: **There is no lab test that predicts the course of perimenopause or timing of menopause onset.**

However:

- Testing may be **reassuring to the patient.**
- Testing may help the provider decide on **hormone therapy types and dosing**
- **Certain situations may require testing**:
  - Early menopause/premature ovarian insufficiency
  - Infertility (and fertility is desired). If a patient with perimenopause symptoms desires pregnancy, quick assessment of AMH and referral as needed to reproductive endocrinology is recommended.
  - Concerning symptoms - abnormal bleeding, pain, genitourinary syndromes
  - When symptoms are cyclical, moderate to severe, and a lifestyle cause is not obvious.

Hale GE, et al. J Clin Endocrinol Met. 2007;92(8):3060-3067.

Perimenopause Lab Testing – beyond sex hormones

Lab assessments of ovarian age include:

- **Antral follicle Count (AFC)** via ultrasound (declines with age) – performed on cycle day 2-5
- **Anti-mullerian hormone (AMH)** via serum (declines along with AFC) – test on any day
  - AMH below 1 warrants referral to reproductive endocrinology for patients desiring fertility
- **Cycle day 1-5 FSH + E2**:
  - Essential to test together because of their tight relationship.
    - Earlier in perimenopause when follicles may still be sensitive to FSH, increasing perimenopausal FSH levels can cause follicles to overproduce E2. This high E2 early in the cycle can suppress FSH back into the normal range.
    - As women go through perimenopause, their follicles become less sensitive to FSH, and you are more likely to see high FSH and low estrogen on testing.
  - **Remember: Increasing FSH indicates ovarian aging.**
- **Inhibin A and B** via serum (declines with ovarian aging) – used in gynecologic oncology and infertility settings

Perimenopause Lab Testing

Table for reference:

Stage	Serum Estradiol LC-MS/MS	Progesterone (ovulatory)	FSH	Inhibin B	AMH
Mid-reproductive	In range for cycle phase	In range	< 10 IU/L	< 153 pg/ml	1-3.5 ng/ml
Late reproductive	In range for cycle phase	In range	> 10 IU/L	< 35 pg/ml	< 1 ng/ml
Early menopausal transition	In range for cycle phase, above or below range also common	In range, but lower than previously	> 10 IU/L	< 30 pg/ml	< 0.5 ng/ml
Late menopausal transition	In range for cycle phase, above or below range also common	May be in or below range during some ovulatory cycles	> 15 IU/L	<20 pg/ml	< 0.5 ng/ml
Post menopause	In the post-menopausal range	In the post-menopausal range	> 25 IU/L, confirmed with serum testing 4 weeks apart	< 10 pg/ml	< 0.5 ng/ml

Lab results are not diagnostic of peri- or post-menopause status.
Ranges can vary by lab.

Hale GE, et al. J Clin Endocrinol Met. 2007;92(8):3060-3067.
Harlow SD, et al. J Clin Endocrinol Met. 2012;97(4):1159-1168.
Miro F, et al. Menopause. 2005;12(3):281-290.

Collection Timing in Perimenopause

Perimenopause Lab Testing - DUTCH Cycle Mapping

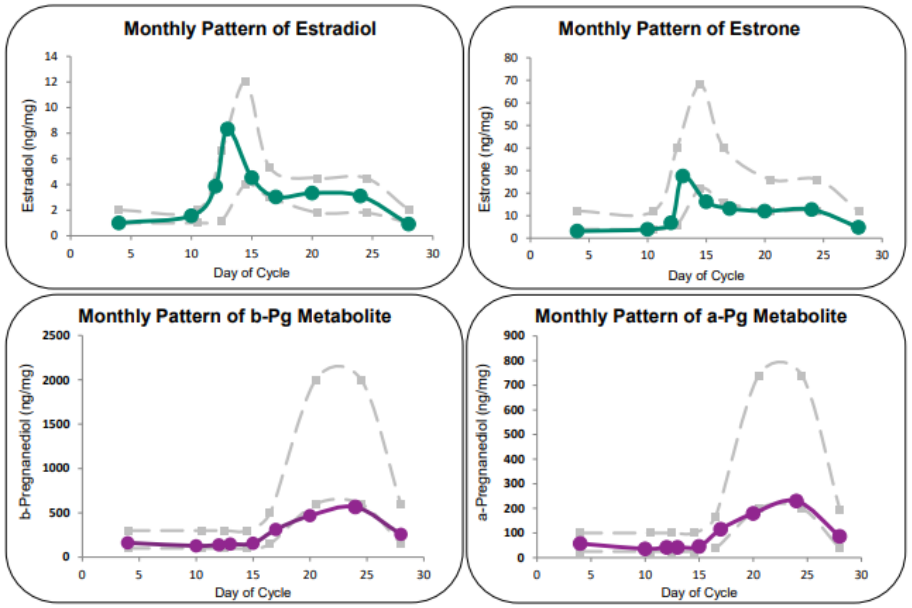
Cycle Mapping Results

dutchtest CYCLE MAPPING

Name: Cycle Map Case
Provider: Precision Analytical
Accession # 972341

D.O.B. 1/1/1990
Collection Dates
12/6-12/27-2020

Estrogen (E) patterns can be seen below in green. Progesterone (Pg) patterns can be seen below in purple. Normal ranges are within the gray dashed lines. See page 2 for more information.



All values given in ng/mg creatinine

Measurement	1	2	3	4	5	6	7	8	9
Day(s) of Cycle	4	10	12	13	15	17	20	24	28

The days listed above were used for measurements. Two samples are used and listed for long cycles or patients without a normal cycle.

Estradiol (E2)	1.00	1.56	3.86	8.33	4.53	3.03	3.33	3.10	0.91
Estrone (E1)	3.1	3.9	6.8	27.5	16.2	13.2	12.0	12.7	4.8
a-Pregnanediol	57	35	41	42	45	115	179	230	86
b-Pregnanediol	162	127	138	147	157	312	467	**565**	256
b-Pregnanediol/E2 Ratio	161	81	36	18	35	103	140	182	282
Creatinine	1.00	1.75	1.90	1.65	2.41	1.23	1.11	0.87	0.86

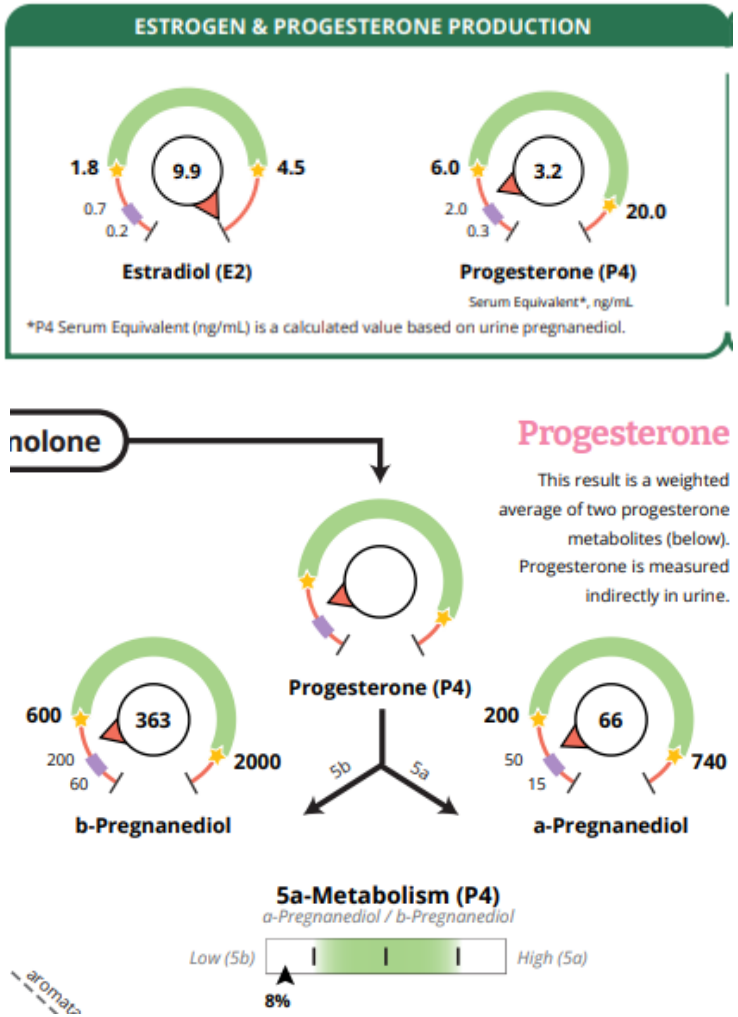
DUTCH Cycle Mapping

- Shows E2 and progesterone metabolites over one cycle, rather than just a single day.
- Ideal when **cycles are unpredictable** and it is difficult to time a one-day test.
  - Patient collects each morning for an entire cycle
- DUTCH dried urine estrogen and progesterone (metabolites) parallel serum LC-MS/MS.
- Consider combining a DUTCH Cycle Mapping Test with cycle day 2-3 labs – FSH, Estradiol, AMH as a starting point for assessing perimenopausal patients with irregular cycles.

Perimenopause Lab Testing - DUTCH Complete or DUTCH Plus

- **DUTCH Complete or DUTCH Plus testing on a single day of the menstrual cycle in patients with irregular cycles can result in collection outside of the luteal phase peak.**
- **DUTCH report dials are designed for the luteal phase peak when Progesterone is highest, and Estradiol is also rising, but is not at its highest point of the entire menstrual cycle.**
- Collection might take place during the Follicular or the Ovulatory phase of the cycle, rather than the intended Luteal phase.
- **If this happens, not all is lost!**
- The table at the bottom of page 3 gives you normal ranges for estradiol, estrone, and the progesterone metabolites during the follicular and ovulatory phases of the cycle.
- This seems obvious, but we have this conversation often with providers. If the levels look off, take a step back and assess cycle timing.
- We have many resources online for calculating collection timing, but sometimes the best laid plans don't work out and that's OK!

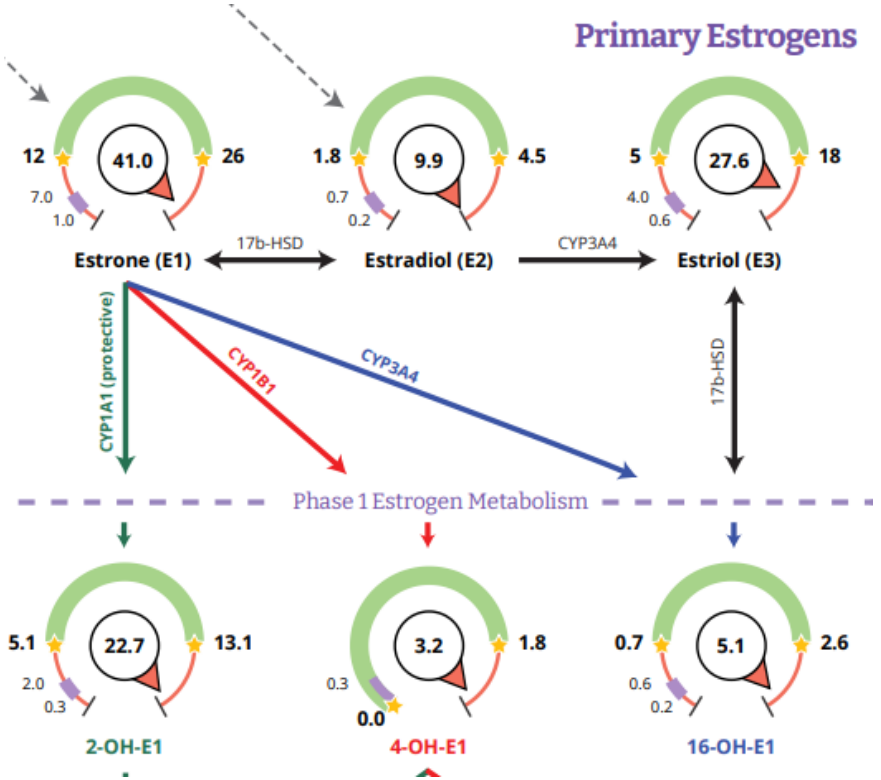
Perimenopause Lab Testing - Ovulatory Phase Collection



Are these results accurate???

YES. DUTCH test results are always accurate.

You simply need to know WHEN in the cycle collection took place to accurately interpret results.



DUTCH Ovulatory Phase Collection

Sex Hormones & Metabolites

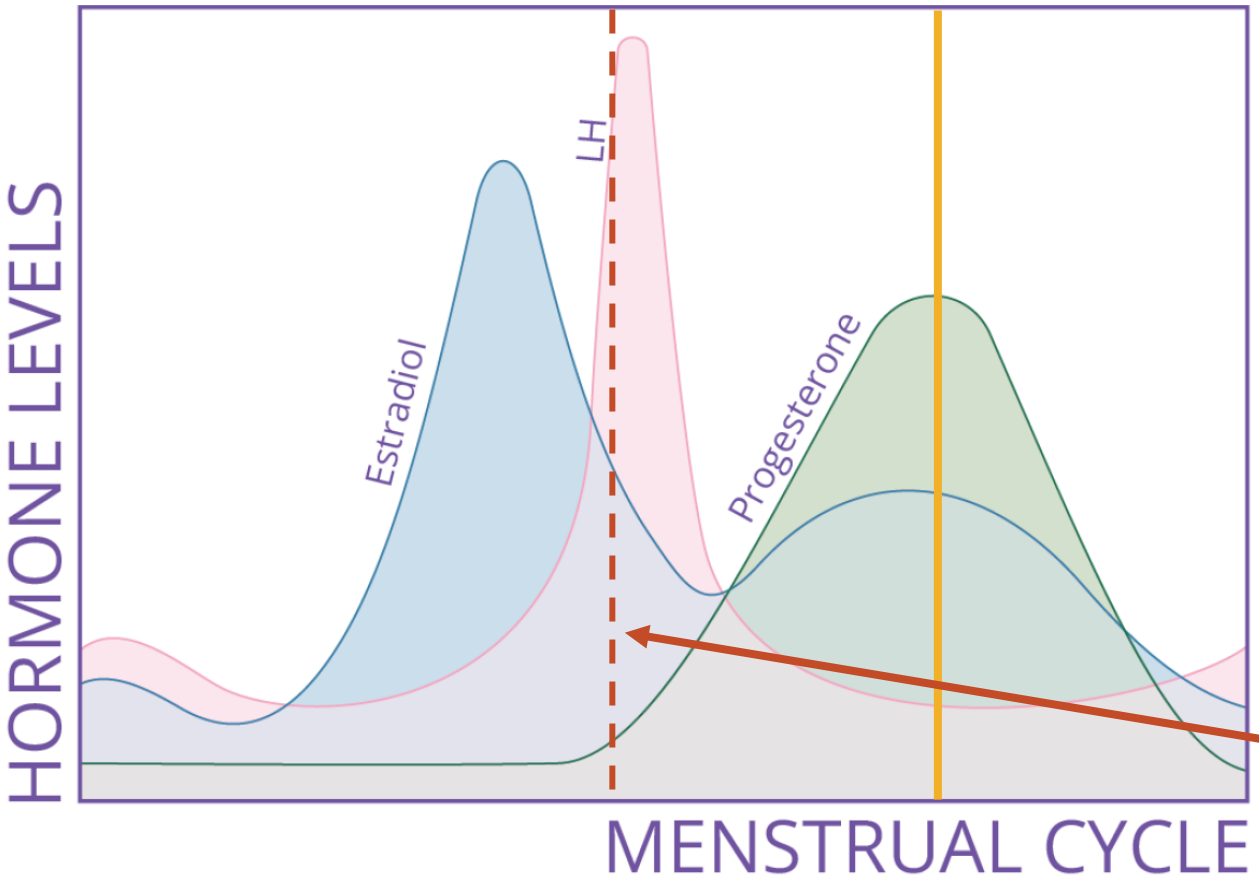
TEST		RESULT	UNITS	LUTEAL*	POSTMENOPAUSAL
Progesterone Metabolites (Urine)					
b-Pregnanediol	Below luteal range	362.5	ng/mg	600 - 2000	60 - 200
a-Pregnanediol	Below luteal range	65.6	ng/mg	200 - 740	15 - 50
Estrogens and Metabolites (Urine)					
Estrone (E1)	Above luteal range	40.96	ng/mg	12 - 26	1.0 - 7.0
Estradiol (E2)	Above luteal range	9.91	ng/mg	1.8 - 4.5	0.2 - 0.7
Estriol (E3)	Above luteal range	27.6	ng/mg	5 - 18	0.6 - 4.0
2-OH-E1	Above luteal range	22.69	ng/mg	5.1 - 13.1	0.3 - 2.0
4-OH-E1	Above luteal range	3.21	ng/mg	0 - 1.8	0 - 0.3
16-OH-E1	Above luteal range	5.12	ng/mg	0.7 - 2.6	0.2 - 0.6
2-Methoxy-E1	Above luteal range	15.80	ng/mg	2.5 - 6.5	0.3 - 1.4
2-OH-E2	Above luteal range	3.41	ng/mg	0 - 3.1	0 - 0.52
4-OH-E2	Above luteal range	1.04	ng/mg	0 - 0.52	0 - 0.12
Total Estrogen	Above range	129.7	ng/mg	35 - 70	3.5 - 15
Metabolite Ratios (Urine)					
2-OH / 16-OH-E1 Balance	Within range	4.43	ratio	2.69 - 11.83	
2-OH / 4-OH-E1 Balance	Within range	7.07	ratio	5.4 - 12.62	
2-Methoxy / 2-OH Balance	Above range	0.70	ratio	0.39 - 0.67	
Androgens and Metabolites (Urine)				**Range**	
DHEA-S	Within range	54.0	ng/mg	20 - 750	
Androsterone	Above range	1969.8	ng/mg	200 - 1650	
Etiocholanolone	Above range	1673.1	ng/mg	200 - 1000	
Testosterone	Above range	17.00	ng/mg	2.3 - 14	
5a-DHT	Within range	5.7	ng/mg	0 - 6.6	
5a-Androstanediol	Within range	29.4	ng/mg	6 - 30	
5b-Androstanediol	Within range	53.8	ng/mg	12 - 75	
Epi-Testosterone	Above range	19.0	ng/mg	2.3 - 14	

* The Luteal Range represents the expected premenopausal luteal range, collected menstrual cycle days 19-22 of a 28-day cycle. If your patient noted taking oral progesterone, the reference range represents the expected range on 100 - 200 mg of oral micronized progesterone (OMP). The ranges in the table below represent ranges in other times of the cycle your patient may have collected, such as follicular or ovulatory phases.

ADDITIONAL NORMAL RANGES	FOLLICULAR	OVULATORY	ON ORAL PG
b-Pregnanediol	100 - 300	100 - 300	2000 - 9000
a-Pregnanediol	25 - 100	25 - 100	580 - 3000
Estrone (E1)	4.0 - 12.0	22 - 68	N/A
Estradiol (E2)	1.0 - 2.0	4.0 - 12.0	N/A

- Estrone and Estradiol are both HIGH BUT
  - Estrone is in the normal range for the ovulatory phase
  - Estradiol is in the normal range for the ovulatory phase
- Progesterone metabolites are LOW BUT
  - A-Pregnanediol falls into the normal range for the ovulatory phase
  - B-pregnanediol is JUST above the normal range for the ovulatory phase, but does not get into the luteal range that confirms ovulation.
- The patient has normal hormone levels for the ovulatory phase of the cycle.
- This is helpful and actionable information, but we cannot confirm ovulation has occurred because collection happened too early in the cycle.

Collection Timing – Ovulatory Phase Collection



Remember – knowing WHERE in the cycle the patient collected gives you plenty of good information!

Only the estrogens and progesterone metabolites that change significantly throughout the cycle.

We can estimate that this ovulation phase collection was done around this time in the cycle

Perimenopause Lab Testing

Estradiol (E2) Reference Ranges:

Phase	Serum E2 (Immunoassay)	Serum Ultrasensitive E2 (LC-MS/MS)	DUTCH Urine E2 (LC-MS/MS)
Follicular Phase	19-144 pg/mL	39-375 pg/ml	1.0-2.0 ng/mg
Mid-cycle/Ovulatory	64-357 pg/mL		4.0-12.0 ng/mg
Luteal Phase	56-214 pg/mL	48-440 pg/mL	1.8-4.5 ng/mg
Post menopause*	< 30 pg/mL	<10 pg/mL	0.2-0.7 ng/mg

Progesterone (P) Reference Ranges:

Phase	Serum Progesterone (Immunoassay)	DUTCH Urine b-Pregnanediol (LC-MS/MS)
Follicular Phase	<1 ng/mL	100-300 ng/mg
Luteal Phase	2.6-21.5 ng/mL	600-2000 ng/mg
Post menopause	< 0.5 ng/mL	60-200 ng/mg

Serum ranges from Quest Labs Estradiol and Progesterone immunoassays. Lab-specific ranges may vary.
LC-MS/MS for E2 is recommended in postmenopausal women.

Perimenopause Case

The Perimenopause Case Workflow

1. Thorough history intake.
2. Lab testing, with consideration to timing within the menstrual cycle.
   a) **Early follicular:** cycle days 2-3
   b) **Midluteal:** 5-7 days after ovulation and 4-10 days before the next period

Early Follicular
Blood Draw
- FSH
- E2 (LC-MS/MS)
- AMH (optional)
- Inhibin B (optional)

Midluteal
Blood Draw
- E2 (LC-MS/MS)
- Progesterone

Urine
- DUTCH Complete or Plus

OR

Early Follicular
Blood Draw
- FSH
- E2 (LC-MS/MS)
- AMH (optional)
- Inhibin B (optional)

Entire Cycle
Urine
- DUTCH Cycle Mapping
- Pair with DUTCH Complete or Plus (optional)

Lab testing in perimenopause **must be done with reference to timing of the menstrual cycle**. Keep in mind that hormones in women of reproductive age, including in perimenopause, are a **moving target.**

The Perimenopause Workflow

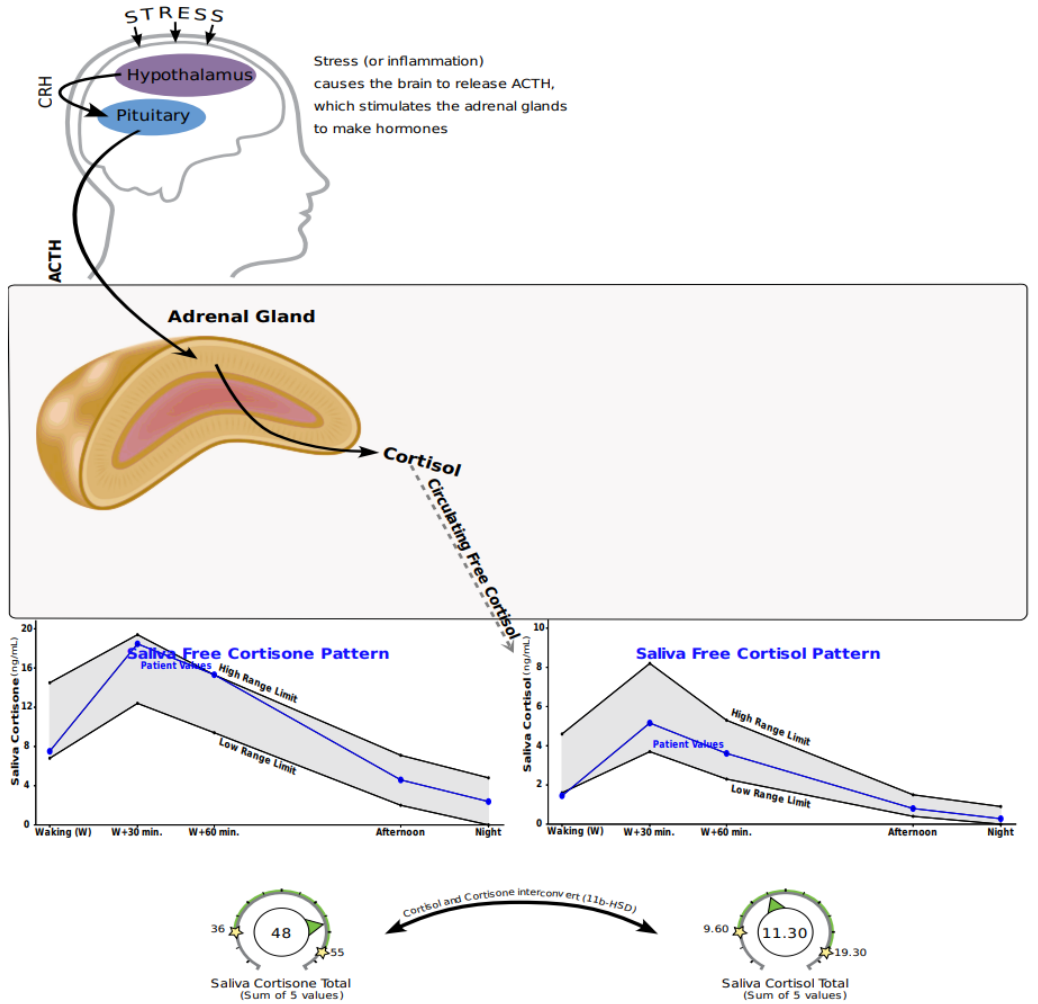
3. At the first visit, provide appropriate lifestyle approaches for most bothersome symptoms. Addition of hormone therapy at this time is appropriate for some patients.
4. At follow-up, review symptoms and severity with lifestyle changes (and HT, if used). Review lab workup and consider additional treatments, including hormone therapy (HT).

HT may be indicated in perimenopause for moderate to severe symptoms that do not improve with lifestyle changes.

Early Perimenopause Case – Beth 45 yo female – Aug 2022

- Initiated care 8/2022 at 45 yo
- HPI: Short 21-day menstrual cycles for the past 3 years, low libido, fatigue worse AM
- Plan: labs, DUTCH CAR
  - WAIT to run full DUTCH panel until we have assessed thyroid function

- Serum Labs, day 16:
  - Estradiol 82, Progesterone 12.2, Testosterone 7, DHEAS 182,
  - TSH 17.79 HIGH, FT4 0.64 LOW, TPO 181 HIGH.
  - All other labs WNL incl Vit D, Lipids



Early Perimenopause Case – Beth 45 yo female – Aug 2022 to March 2023

- Plan:
  - Elevated TSH - Switch from 60mg NP Thyroid to 150mcg Levothyroxine + 5mcg Liothyronine
  - Low-normal waking salivary cortisol/cortisone - Adaptogen tincture in the AM
  - Wait to initiate treatment of hormones until TSH normalizes
  - Continue good whole foods diet

- Follow-up 12/2022
  - Repeat TSH 1.5
    - Thyroid normalized
  - Energy and libido improved, stop Adaptogen tincture
  - Cycles remain 21 days in length
    - Patient desires to try IUD with gynecologist

- Follow-up 3/2023
  - Short 21-day menstrual cycles persist.
  - Did not tolerate Mirena IUD with Gynecologist – “bled constantly”
  - Not ready to try hormone therapy
  - **Start Women’s Phase I by Vitanica – 2 po qd**

Early Menopausal Transition – Non-HRT Support

Changes in progesterone levels can be naturally supported with:

- Anxiolytics (calming support) and GABA support – l-theanine, passionflower, GABA
- Ovulation support – Vitex agnus-castus, Ashwaganda, Maca

Changes in estrogen levels can be naturally supported with:

- Follicular phytoestrogen support – Black cohosh, Maca, Ground flax, Dong quai
- Androgen support – DHEA, Maca, Tribulus, Shatavari

Both estrogen and progesterone levels are supported with:

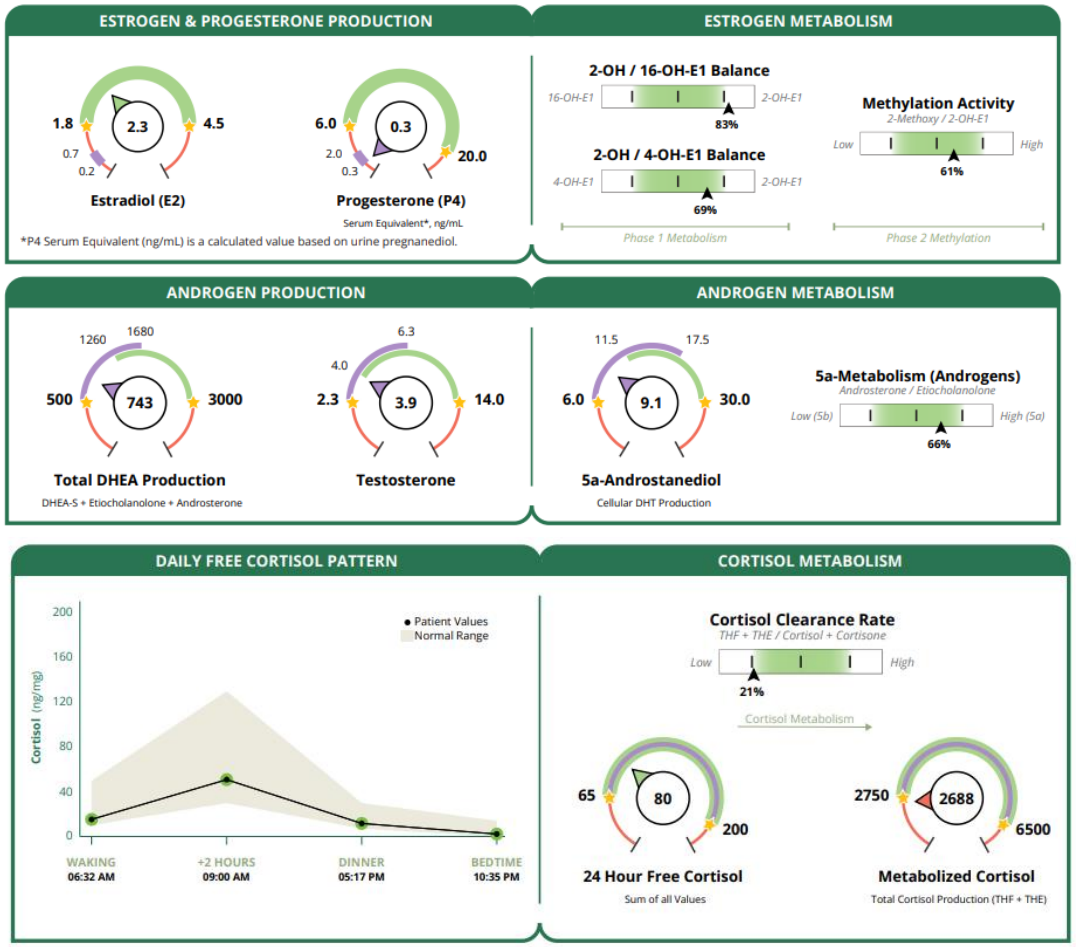
- Stress reduction/modulation
- Sleep hygiene – dark, cool, quiet room. Minimize blue light, wake in the AM with eyeballs on sunlight
- Anti-inflammatory, low glycemic index diet
- Regular exercise, including weight-bearing exercise

Early Perimenopause Case – Beth 47 yo female – October 2024

- Follow-up 10/2024
  - Did great for over a year with 23-day cycles.
  - Ran out of Women's Phase I supplement in July when they moved. Noticed return of **fatigue, poor sleep**.
  - Developed **frozen shoulder** in late July, better with **steroid injection**
  - In August started 26-day cycles, **bleeding heavy with clots** lasting up to 2.5 weeks
  - **Denies hot flashes and night sweats**

  - PLAN: order labs including hormones, thyroid and iron, order TVUS and DUTCH Complete

Early Perimenopause Case – Beth 47 yo female – Nov 2024



- 11/2024
  - TVUS WNL
  - Day 2 labs: FSH 7.2 WNL
  - Day 16 Labs: Ferritin 5 LOW, TSH 4.6 HIGH, Estradiol 114, Progesterone <0.5, Testosterone 16, DHEAS 71
  - DUTCH shows **anovulatory cycle**, **estrogen dominant**, Androgens low normal, Cortisol low, CCR low normal
  - Plan: Treat thyroid, replete iron, start Progesterone 100mg (OMP)
  - What about the estrogen-dominance?

Early Menopausal Transition – Estrogen Dominance

Treat estrogen-dominance? Reduce high estrogen?

Reducing high estrogens can be tricky in perimenopause due to ***fluctuations*** and unpredictable progression into a low estrogen phase.

However, a few things to consider:

- **Diindolylmethane (DIM)** can reduce circulating parent estrogens (E1, E2) via increased phase I metabolism through the 2-OH pathway.
- Estrogens metabolized into the 2-OH estrogen catechols are associated with reduced long-term risk of breast cancer according to observational studies.
- When used in estrogen dominant conditions, DIM has been found to anecdotally reduce heavy menses, breast tenderness, and bloating.
- **Typical dosing 50-500 mg daily.**

Hall DC. Applied nutritional science reports. 2001;1:1-8.
Newman M, et al. BMC Complement Altern Med. 2024;24(405):1-10..

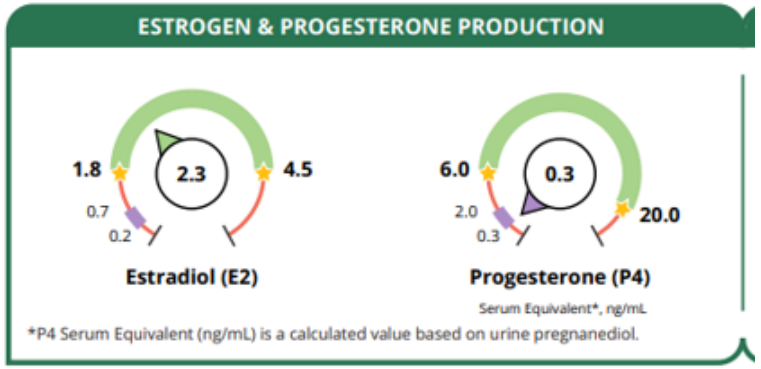
Early Menopausal Transition – Estrogen Dominance

When prescribing DIM in perimenopause:

- Watch for signs of low estrogen:
  - Increasing vasomotor symptoms “hot flashes”
  - Vaginal dryness – new onset or worsening
  - Headaches or worsening migraines
- If using DIM, which can be potent, starting at the low end of dosing range and increase to tolerance.
- Your patient will tell you if it’s too much ☺
  - “So, I started getting hot flashes about 3 weeks into my new treatment!”

Should we give Beth DIM?

- No… while she is estrogen dominant, her estrogen is not high.
- Start by supporting her progesterone



Hall DC. Applied nutritional science reports. 2001;1:1-8.
Newman M, et al. BMC Complement Altern Med. 2024;24(405):1-10..

Early Menopausal Transition HRT - Progesterone

Oral micronized progesterone (OMP) provides the following benefits:

- **Endometrial decidualization** (stabilizes endometrial growth; reduces heavy bleeding, hyperplasia, and the risk of endometrial cancer – all of which increase in perimenopause).
- Reduces estrogen receptors and receptor functionality, **limiting the effects of high estrogens.**
- Provides feedback to the hypothalamic-pituitary complex to **suppress FSH**, reducing the excess FSH seen with ovarian aging.
- Promotes **diuresis**, reducing a feeling of "bloating" which is a common complaint in perimenopause. (Note that **too much** OMP can **cause** bloating.)
- As part of first-pass metabolism, oral progesterone is converted to its metabolites, one of which (5 alpha-pregnanediol) is a potent GABA-A agonist in the brain, which can **relieve anxiety and irritability, and help with sleep**. This is why OMP is taken at bedtime.

Memi E, et al. 2024;25(4):751-772.

Early Menopausal Transition HRT - Progesterone

Positive evidence for OMP-only therapy for perimenopause and early menopause symptoms:

Symptom	Citation
Heavy menstrual bleeding	Saarikoski S, et al. Maturitas. 1990;12(2):89-97.
Endometrial hyperplasia prevention with luteal phase defect	Stanosz S, et al. J Clin Endocrinol Metab. 2014;99(12):E2472-E2476.
Abnormal uterine bleeding due to ovulatory disorders (AUB-O)	Pinkerton JV. Menopause. 2011;18(4):453-461.
Cyclic mastalgia, abdominal bloating	Wyatt K, et al. BMJ. 2001;323(7316):776-776.
Vasomotor symptoms (Hot flashes, night sweats)	Hitchcock CL, et al. Menopause. 2012;19(8):886-893.
Insomnia	Hitchcock CL, et al. Menopause. 2012;19(8):886-893.

Progesterone therapy common side effects: Breast tenderness, mood swings, bloating, constipation, headaches, increased appetite, fluid retention, drowsiness, dizziness (especially OMP)

Memi E, et al. 2024;25(4):751-772.
NAMS. Menopause. 2022;29(7):767-794.

Early Menopausal Transition HRT - Progesterone

Oral micronized progesterone (OMP) dosing considerations:

- Progesterone dosing in perimenopause may be **higher** than after menopause because baseline E2 is often higher.
- **Common perimenopausal OMP dose range 100-400 mg.**
- Cyclic use of progesterone, such as days 14-26 of a 28-day cycle, is common in this phase because estrogen is still cycling.
- Continuous dosing may be optimal in the late menopausal transition, when estrogens are erratic, and cycles are very irregular.
- Cyclical dosing may be required during the early menopausal transition in order to allow menstruation to happen. Removing the OMP for a few days allows for a **"withdrawal bleed"**, where endometrial shedding occurs due to the progesterone "break". Continuous progesterone may obscure hormone fluctuations by stabilizing the endometrium, possibly inhibiting menstrual bleeding and obscuring outward signs of hormone cycles. **In my experience, these patients often start spotting constantly until you allow a withdrawal bleed.**

Casper R. Post T, editor. UpToDate. Waltham, MA 2023.
de Villiers TJ, et al. Climacteric. 2016;19(4):313-315.
Shifren JL, et al. Menopause. 2014;21(10):1038-1062.
NAMS Advisory Panel. Menopause. 2022;29(7):767-794.

Early Menopausal Transition HRT - Progesterone

OMP dosing considerations based on stage:

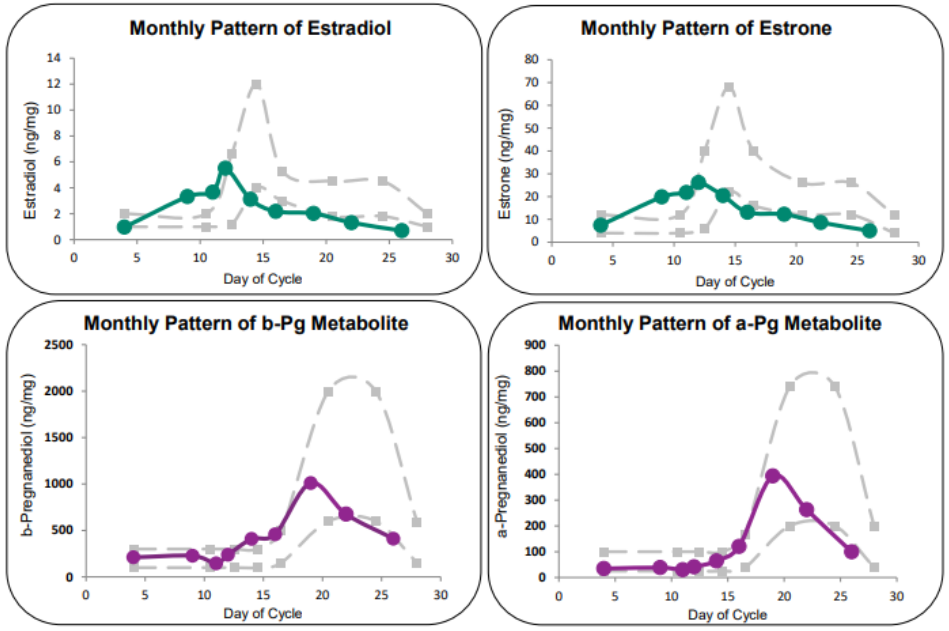
Phase	OMP Dosing Consideration	Use
Perimenopause, regular cycles (may be shorter or longer than previously)	100-400 mg	Nightly starting about 12 days and ending 2 days before expected menstruation.
Perimenopause, irregular cycles with little predictability	100-400 mg	Nightly for 12-14 days per calendar month OR continuously.
Perimenopause, no cycle for < 12 months	100-200 mg	Nightly for 12-14 days per calendar month OR continuously (higher doses are acceptable if desired).
Menopause, No menstrual bleeding for > 12 months	100-200 mg	Nightly for 12-14 days per calendar month OR continuously (higher doses are acceptable if desired).

Note:

If estrogen therapy is added and the patient has a uterus, OMP 100 mg must be used continuously for adequate protection against endometrial hyperplasia. Also, OMP 200 mg nightly for 12-14 days or continuously may be more protective than OMP 100 continuously for endometrial hyperplasia if the patient has a uterus and is taking a high estrogen dose.

Memi E, et al. Rev Endocr Metab Disord. 2024;25(4):751-772.

Early Perimenopause Case – Beth 48 yo female – Jan & March 2025



All values given in ng/mg creatinine

Measurement	1	2	3	4	5	6	7	8	9
Day(s) of Cycle	4	9	11	12	14	16	19	22	26

The days listed above were used for measurements. Two samples are used and listed for long cycles or patients without a normal cycle.

Estradiol (E2)	0.97	3.33	3.66	5.51	3.12	2.18	2.03	1.31	0.70
Estrone (E1)	7.4	19.8	21.8	26.1	20.4	13.1	12.2	8.6	5.0
a-Pregnanediol	34	38	30	41	64	120	393	263	99
b-Pregnanediol	210	228	146	237	408	458	**1010**	675	411
b-Pregnanediol/E2 Ratio	217	68	40	43	131	210	498	513	591
Creatinine		0.52	0.68	0.70	0.66	0.86	0.81	0.84	0.78

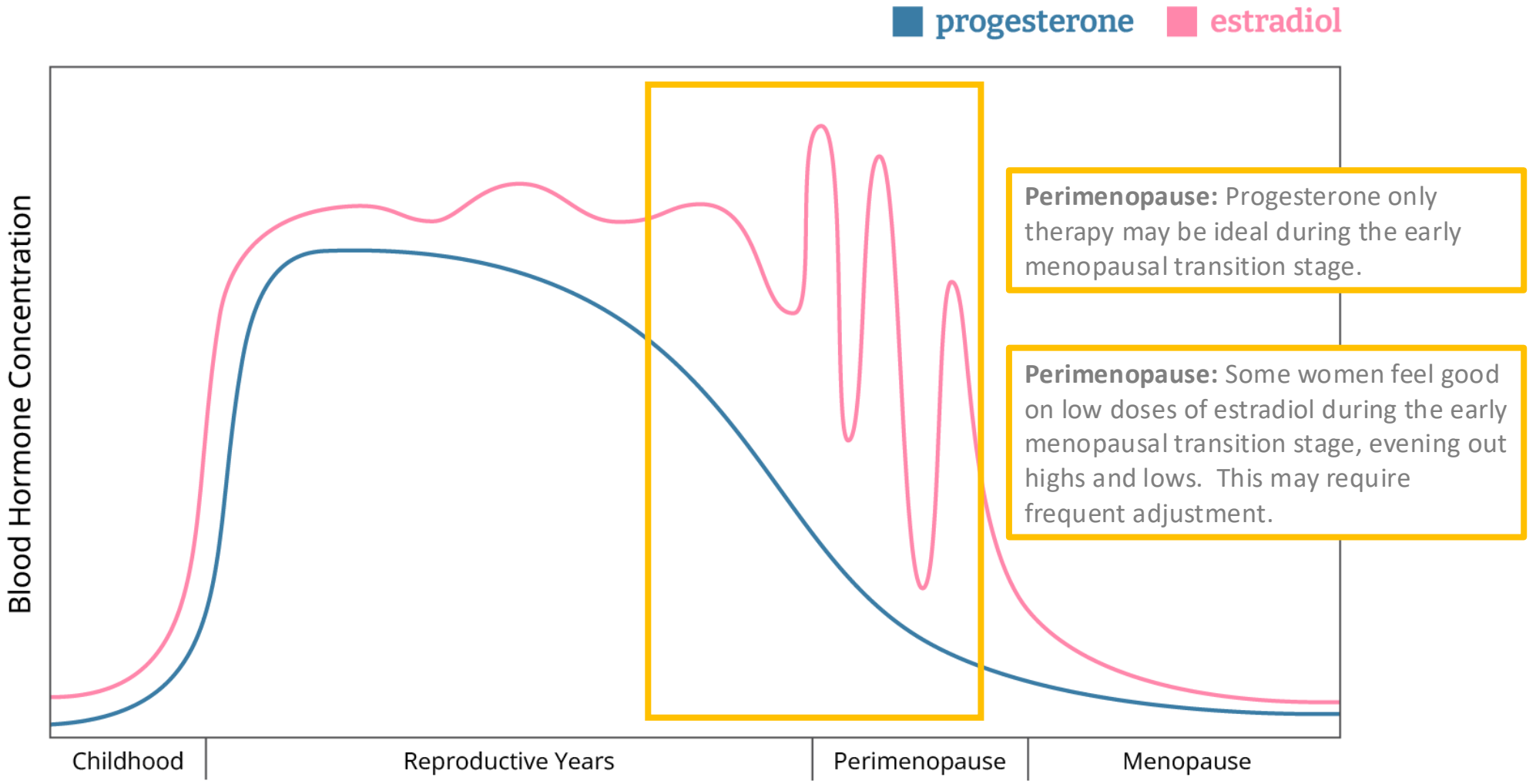
- Follow-up 1/2025
  - Thyroid stabilized
  - OMP 100mg caused **"uncontrollable crying all day long"** so discontinued after only 5 days of use
  - Resumed Women's Phase 1 by Vitanica – 2 po qd
  - Order DUTCH Cycle Mapping
- 3/2025
  - Taking Women's Phase I by Vitanica daily
  - Short average 21-day menstrual cycles, "otherwise great!"
  - Did not tolerate OMP, but doing great back on herbal support
  - Cycle Map from Feb 2025 on herbal support shows patient has regular cycle with evidence of ovulation

Early Perimenopause Case – Beth 49 yo female – Nov 2025 – 8 months later

- 11/2025
  - Fatigue and poor sleep
  - Intercourse now painful due to dryness
  - Still taking Women's Phase I and getting 21 day cycles but has had two 28-day cycles in the last 6 months
  - Nails breaking, hip pain, plantar fasciitis.
    - Both mother and older sister report their hip pain improved with HRT.
  - Tried Progesterone again and did not tolerate – weepy
  - Tried DHEA 15mg which helped for a month or two, no longer helping
  - Day 16 Labs: Ferritin 43, TSH 1.5, Estradiol 52, Progesterone 2.0, Testosterone 22, DHEAS 153
  - Day 3 Labs: FSH 18, Estradiol 55

- Plan: Initiate HRT
  - Start **Estradiol patch 0.025mg** - apply 1 patch twice weekly
  - Start Progesterone 100mg - insert one **vaginally** (upper 1/3 of vaginal vault) 12-14 days per month. DO NOT use during menses.
  - Start Vaginal Estradiol Cream 0.01% - apply nightly for 7 nights, then 1-2 times weekly thereafter.
    - May not need this with the systemic estrogen from the patch.
  - WAIT to stop Women's Phase I, but can probably go off this if tolerating hormone therapy
  - Labs and DUTCH Complete in 3 months

Early Menopausal Transition HRT



Early Menopausal Transition HRT - Estrogen

Bioidentical E2:

- **TD E2** is a **standard route of administration (ROA)** due to its **low-risk** profile, ease of access, and **effectiveness** at controlling vasomotor symptoms (VMS) and genitourinary syndrome of menopause (GSM), along with its benefits for bone mineral density (BMD).
- **Oral E2** is the most common prescription but may not be appropriate for some patients with increased cardiovascular disease (CVD) risk, such as smokers or patients with high venous thromboembolism (VTE) risk.
- **Vaginal E2** can be used ***in low doses*** for ***localized effects*** for vulvovaginal atrophy (VVA) and GSM with a high safety profile. Location of vaginal application influences therapy outcomes.
- **Choosing starting dose** can be as simple as starting at the lowest dose and working up, or may involve starting at a higher dose if symptoms are moderate to severe, especially if the patient already has a healthy lifestyle.
- **If the patient has a uterus, she must be on progesterone once she starts E2 for endometrial protection.**

Cagnacci A, et al. Medicina. 2019;55(9):602.
NAMS. Menopause. 2022;29(7):767-794.

Early Menopausal Transition HRT – Endometrial protection

Oral or vaginal bioidentical micronized progesterone

- The synthetic progestin, medroxyprogesterone acetate (MPA) carries increased breast cancer risk and is more thrombogenic than bioidentical progesterone.
- Levonorgestrel is a progestin that is used in the Climera Pro patch, and is approved for endometrial protection against uterine cancer in women on estradiol therapy with an intact uterus.
- **Oral micronized progesterone (OMP)** is the only ROA for bioidentical progesterone that has FDA-approval for endometrial protection, however, **vaginal micronized progesterone (VMP)** can be used for endometrial protection if the patient finds side effects of the oral to be intolerable.
- **Transdermal progesterone is not appropriate if the patient has a uterus and is using estrogen therapy (ET) as it does not reach the endometrium to balance the proliferative effects of E2.**
- However, some perimenopausal patients report benefits such as better sleep, better mood, reduced hot flashes. Early perimenopause is a **clinical gray area** and TD progesterone may be supportive at this time (if not using concurrent estrogen therapy).
  Consider switching to OMP if uterine symptoms dominate (heavy menses).

Leonetti HB, et al. Obstet Gynecol. 1999;94(2):225-228.
Leonetti HB, et al. Fert Sterility. 2003;79(1):221-222.
Stute P, et al. Climacteric. 2016;19(4):316-328.
Vashisht A, et al. Gynecol Endocrinol. 2005;21(2):101-105.
Wren BG, et al. Cliimacteric. 2000;3(3):155-160.

Hormone Therapy (HT) – Estrogen and Progesterone

Estrogen therapy is FDA-approved for:

- Bothersome vasomotor symptoms (hot flashes, night sweats)
- Prevention of osteoporosis/osteopenia
- Vulvovaginal atrophy (VVA)
- Premature hypoestrogenism (POI, iatrogenic menopause)

Other noted areas that ET may impact:

- Cardiovascular protection
- Sleep
- Dementia in some populations
- Muscle mass and weight management
- Mood disorders
- Skin elasticity
- Joint pain
- Quality of life

OMP is FDA-approved for:

- Prevention of endometrial hyperplasia in non-hysterectomized postmenopausal women who are using ET.

Other noted areas that progesterone therapy may impact:

- Bone mineral density (BMD)
- Mood and sleep disorders due to progesterone's alpha metabolite modulation of GABA(A) receptors
- VMS (e.g., hot flashes)
- Potential neurobiological (brain protective) effects

Shifren JL, et al. Menopause. 2014;21(10):1038-1062.

Hormone Therapy (HT) – Estrogen and Progesterone

- **Contraindications are based on long term use in postmenopausal patients**. These should be reviewed with every patient before initiating HT.
- **Research on the long-term outcomes in perimenopausal patients is not available**, however, perimenopausal women are younger and often healthier than menopausal patients and represent a population in which E2 therapy for bothersome VMS is safe and effective.

For more discussion of HT safety, please review our online **Introduction to HRT course**, especially module 2 which focuses on E2 therapy**.**

Beyond Hormone Therapy (HT)

Not all perimenopause symptoms are directly related to hormone changes.

- **Each symptom should be investigated** for a root cause before treating with HT alone.
- Many symptoms can be improved with **lifestyle changes**. Common strategies that support multiple perimenopausal symptoms:
  - Quit smoking
  - Weight loss if appropriate
  - Reduce or eliminate alcohol consumption
  - Optimize hydration
  - Movement (yoga, weightlifting, etc.)
  - Mindfulness based stress management
  - The Mediterranean diet
    - Low-glycemic, anti-inflammatory, high in isoflavones, omega-3s & PUFAs
- **Non-hormonal medications** may be ideal for controlling some symptoms (e.g., SSRIs for perimenopausal depression, progestin IUD for heavy menses, anti-inflammatories for musculoskeletal pain, etc.)

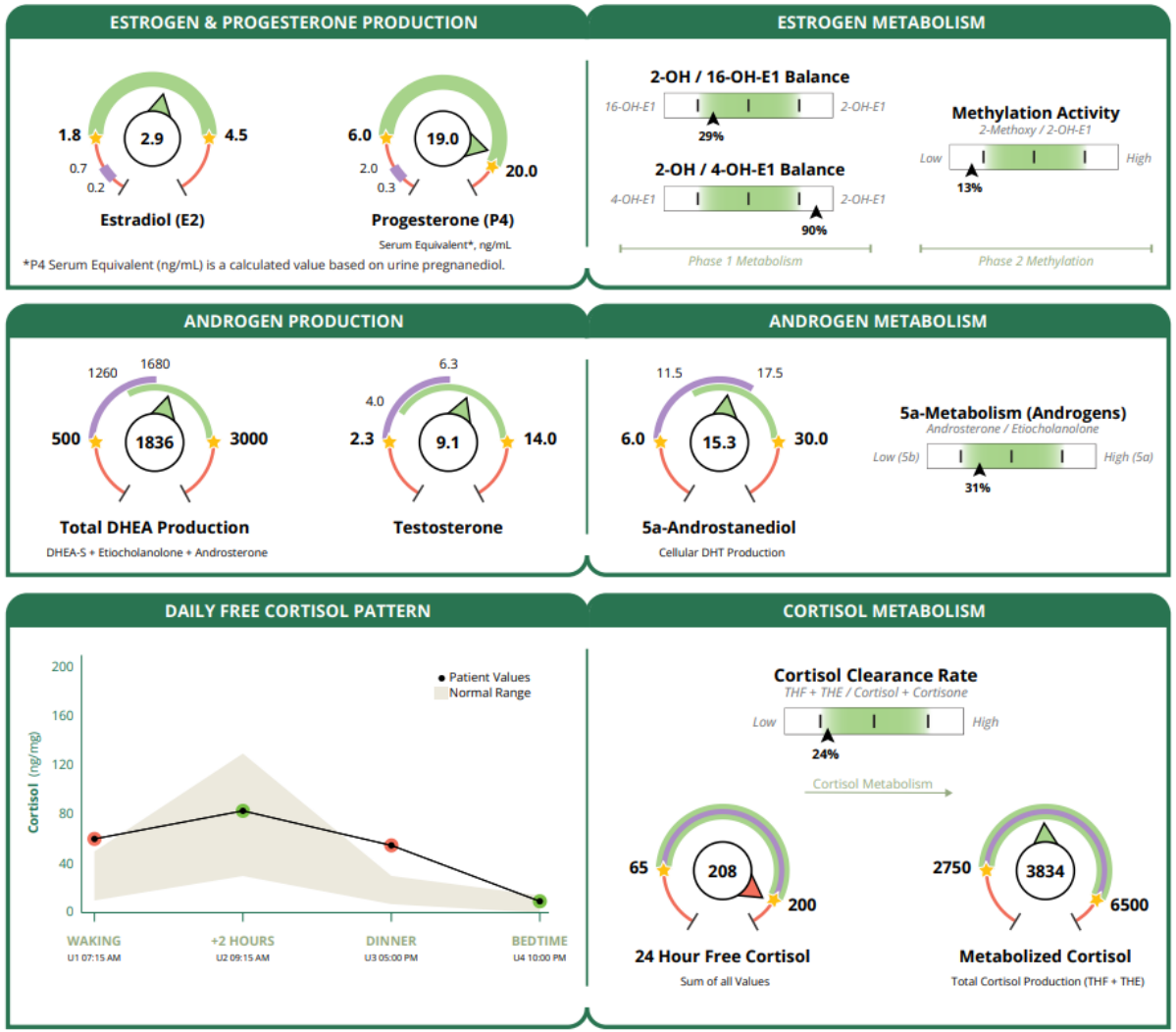
If not using HT in perimenopause, you may need to support these areas separately:

Estrogen's Actions

- **Brain:** Mood, cognition, memory, and focus, thermoregulation, sleep, energy
- **Hair (scalp) growth**
- **Skin:** Elasticity, collagen, repair, moisture
- **Muscle mass**
- **Nervous system:** Parasympathetic balance
- **Joint health**
- **Bone density:** Inhibits bone resorption, increases vitamin D
- **Breast health:** Stimulates breast cell growth
- **Liver function:** Maintains healthy cholesterol, triglycerides
- **Weight management:** Increases metabolic rate, **Insulin sensitivity**
- **Uterine health**
- **Genitourinary system:** Elasticity, acidity, microflora, moisture, lubrication
- **Cardiovascular:** Clotting homeostasis, vasodilation, lowers blood pressure, endothelial function, lowers LDL and increases HDL, lowers homocysteine

Early Perimenopause Case – Beth 49 yo female

- Most recent visit 3/2026
  - Energy “pretty good” but experiencing brain fog. Wakes feeling anxious.
  - Cycles were 28 days upon initiating Estradiol patch and vaginal Progesterone!
  - Pain with intercourse, hip pain, plantar fasciitis and frozen shoulder all resolved
  - Continues 1 capsule of Women’s Phase 1.
  - Feeling good on hormones, wants to address her gut health.
    - Experiencing abnormal loose stools, no change in whole foods diet, eating 3 meals per day
  - Day 22 Labs: Estradiol 176, Progesterone 17.8, Testosterone 21, DHEAS 121

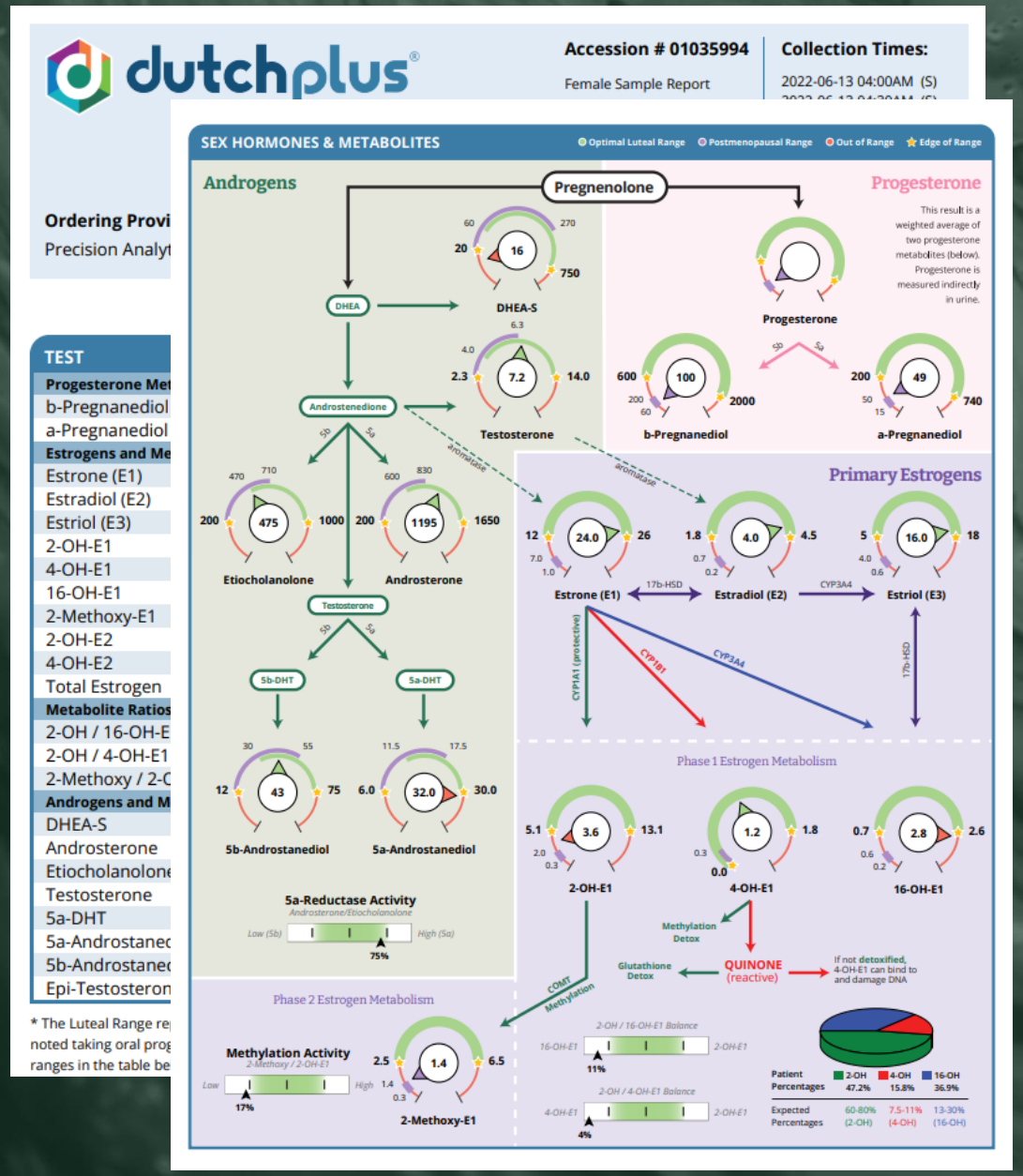


Early Perimenopause Case – Beth 49 yo female

- Plan
  - Continue Estradiol 0.025mg patch twice weekly
  - Continue Prometrium 100mg insert 1 vaginally 12-14 days per month
  - Continue vaginal estradiol cream 1-2 times weekly
  - Continue Women's Phase I 1 capsule per day
  - Order functional stool testing to assess gut health, estrobolome
  - Add heaping spoonful of ground flax seeds daily
  - Add Bacopa Complex for brain fog
  - Add L-theanine to support sleep

Early Perimenopause Case - Take-Aways

- Take-aways
  - Stay flexible, creative and safe
  - Patients who do not tolerate hormones may respond well to herbal therapy
  - Patient who at first do not need hormones and do well on herbs, may eventually need hormones, possibly both
  - Use labs and DUTCH testing to guide next steps and teach patients
  - Remember that you can use panels individually. While seeing the whole picture is often ideal, taking it one step at a time is also OK and can be therapeutic for patients. Use all of our tools!

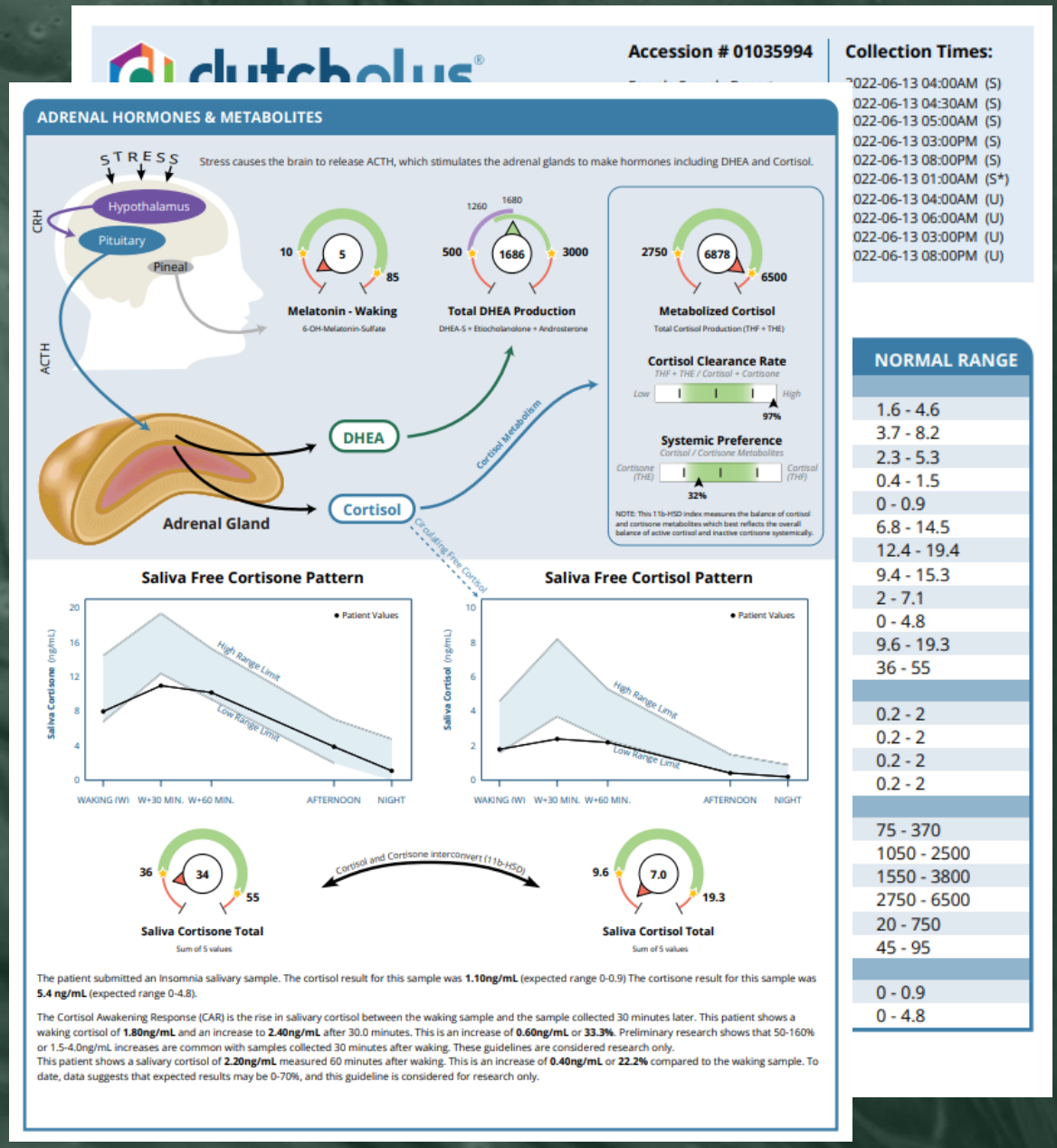


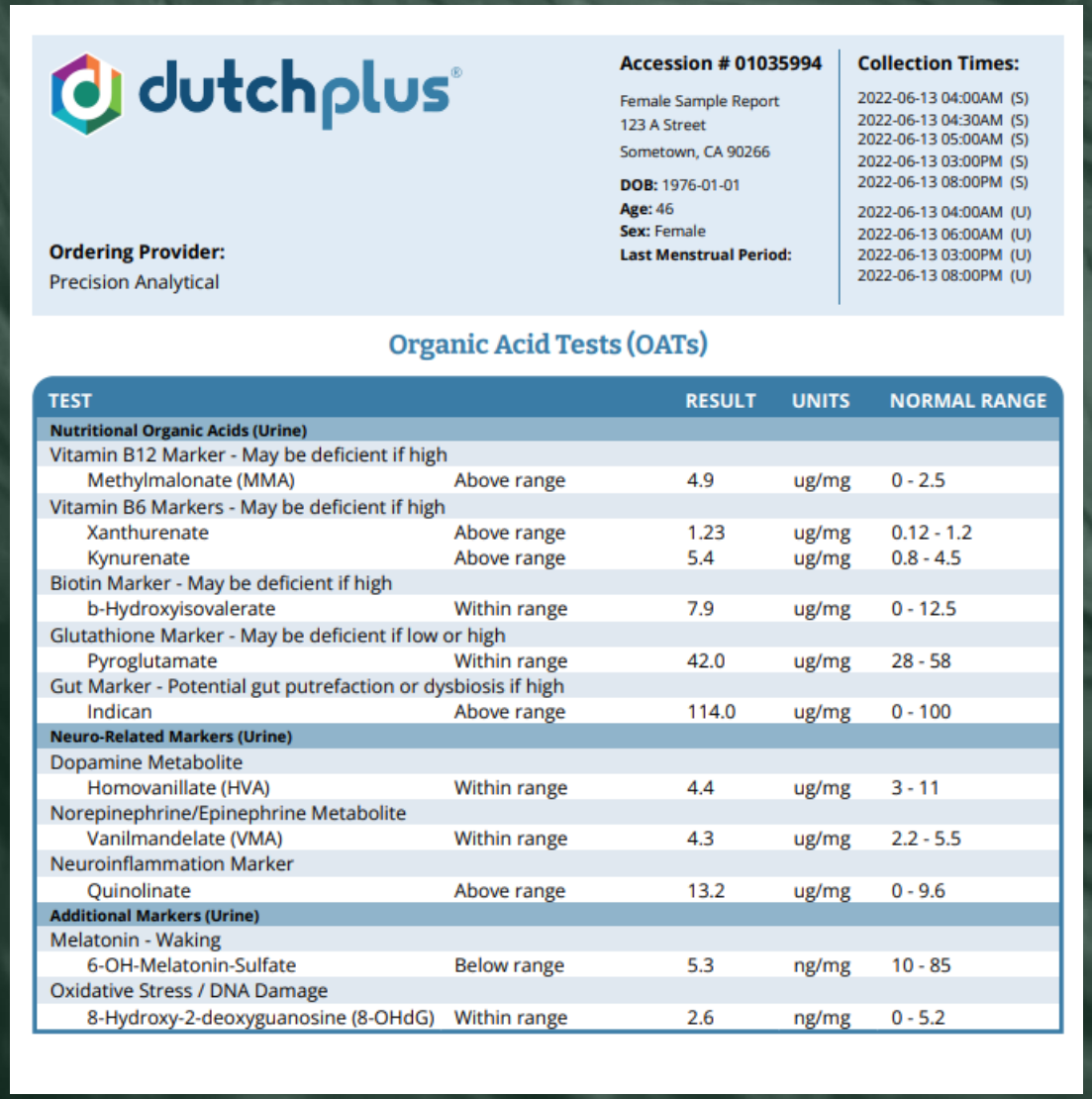
Sex Hormones Panel

- Estrogens
  - Phase 1 & 2 Metabolism Ratios
- Progesterone
- Androgens

Adrenal Panel

- Free Cortisol
- Metabolized Cortisol
- DHEA





dutchplus®

Accession # 01035994

Female Sample Report
123 A Street
Sometown, CA 90266

DOB: 1976-01-01
Age: 46
Sex: Female
Last Menstrual Period:

Collection Times:

2022-06-13 04:00AM (S)
2022-06-13 04:30AM (S)
2022-06-13 05:00AM (S)
2022-06-13 03:00PM (S)
2022-06-13 08:00PM (S)

2022-06-13 04:00AM (U)
2022-06-13 06:00AM (U)
2022-06-13 03:00PM (U)
2022-06-13 08:00PM (U)

Ordering Provider:
Precision Analytical

Organic Acid Tests (OATs)

TEST		RESULT	UNITS	NORMAL RANGE
Nutritional Organic Acids (Urine)				
Vitamin B12 Marker - May be deficient if high				
Methylmalonate (MMA)	Above range	4.9	ug/mg	0 - 2.5
Vitamin B6 Markers - May be deficient if high				
Xanthurenate	Above range	1.23	ug/mg	0.12 - 1.2
Kynurenate	Above range	5.4	ug/mg	0.8 - 4.5
Biotin Marker - May be deficient if high				
b-Hydroxyisovalerate	Within range	7.9	ug/mg	0 - 12.5
Glutathione Marker - May be deficient if low or high				
Pyroglutamate	Within range	42.0	ug/mg	28 - 58
Gut Marker - Potential gut putrefaction or dysbiosis if high				
Indican	Above range	114.0	ug/mg	0 - 100
Neuro-Related Markers (Urine)				
Dopamine Metabolite				
Homovanillate (HVA)	Within range	4.4	ug/mg	3 - 11
Norepinephrine/Epinephrine Metabolite				
Vanilmandelate (VMA)	Within range	4.3	ug/mg	2.2 - 5.5
Neuroinflammation Marker				
Quinolinate	Above range	13.2	ug/mg	0 - 9.6
Additional Markers (Urine)				
Melatonin - Waking				
6-OH-Melatonin-Sulfate	Below range	5.3	ng/mg	10 - 85
Oxidative Stress / DNA Damage				
8-Hydroxy-2-deoxyguanosine (8-OHdG)	Within range	2.6	ng/mg	0 - 5.2

Organic Acids Panel

- Key Deficiencies
- Dysbiosis
- Inflammation
- Oxidative Stress
- Melatonin

DUTCH Course: Foundations of Menopausal Hormone Replacement Therapy

Become proficient in hormone prescribing and monitoring!

Learn how to help your perimenopausal patients with lifestyle, diet, supplement, and hormone therapy considerations!

Thank You!

McKenzie Mescon, ND, FMCP-M

May 27, 2026

Navigating Perimenopause

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