The primary care management of perimenopausal depression

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Background
Psychological symptoms of anxiety, depression and cognitive challenges are often the earliest signs of perimenopause and can affect up to 80% of women. Neurochemical and neurocircuitry changes triggered by fluctuating gonadal hormones affect mood, cognition and behaviour in susceptible women. Perimenopausal depression is an important syndrome occurring in this period. Notably, this condition is often not responsive to conventional antidepressant management.

Objective
The aim of this article is to provide primary healthcare practitioners with evidence-based guidance to recognise and treat perimenopausal depression.

Discussion
Perimenopausal depression is a distinct subtype of major depression with a hormonal aetiology. Accurate diagnosis requires awareness of symptom patterns, history, the use of tools such as the Meno-D scale and possibly a diagnostic trial of menopause hormone therapy (MHT). Treatment is best tailored to the individual and includes lifestyle support, MHT, trauma-informed psychotherapy and psychotropic medications when appropriate. General practitioners play a critical part in diagnosis, management and ongoing support.

PERIMENOPAUSAL DEPRESSION refers to the specific pattern of depressive symptoms that can emerge during the menopause transition[1] and is a distinct subtype of major depressive disorder (MDD) with a hormonal aetiology.[2] It is not recognised in psychiatry classification systems.

Psychological symptoms are often early signs of perimenopause and are caused by neurochemical and neurocircuitry changes due to gonadal hormone fluctuations in the central nervous system (CNS).[3]

Hormonal mood disorders

Women are born with a finite ovarian reserve that is typically depleted between the ages of 40 and 55 years. Menopause is defined as the cessation of menstrual periods for 12 consecutive months. The next phase is postmenopause, characterised by low levels of estradiol and progesterone.

Perimenopause may begin 10 years earlier than menopause, with fluctuating estradiol, declining progesterone, more anovulatory cycles and gradual testosterone decline. This hormonal 'zone of chaos' can profoundly affect the brain and trigger new or recurrent mental illness, especially in women sensitive to hormones (Figure 1).

Women are at increased risk of perimenopausal depression if they have a history of hormone-related mood disorders[4] such as postnatal depression (PND), which affects 15% of women,[5] or premenstrual dysphoric disorder (PMDD; occurs in 5–8% of women).[6] Mood-related side effects occur in 20–30% of women using hormonal contraception.[7]

Neuroscience of hormonal mood disorders

Estradiol, progesterone and testosterone regulate key neurotransmitters: serotonin, dopamine, glutamate and γ-aminobutyric acid (GABA), which influence mood and cognition.

Estradiol has a brain-activating effect by modulating glutamate, serotonin and dopamine, driving energy, mood and cognitive functioning. Progesterone and its metabolite allopregnanolone are calming, modulating GABA[8] to promote sleep and reduce anxiety. Emerging evidence supports testosterone's role in mood and cognition.[9]

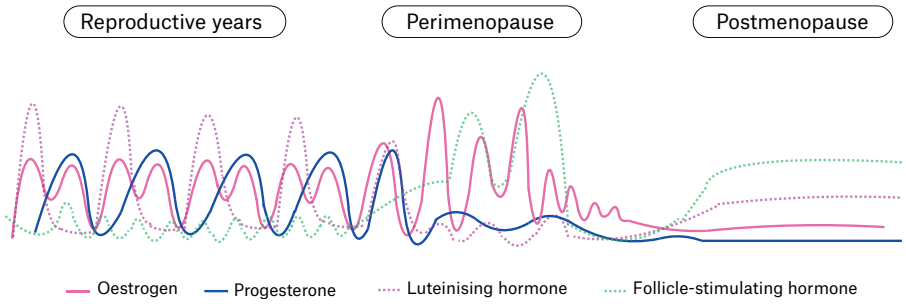

Figure 1. Schematic of gonadal hormone fluctuations in mid to later life in women.

Gonadal hormones enhance synaptic plasticity,[10] playing a key part in neurocircuitry development, which is essential for learning and higher cognition.[10]

Hormonal fluctuations disrupt serotonin and dopamine receptor expression, which are critical for maintaining mood stability.[11,12] Reduced brain oestrogen may lead to cognitive decline and emotional dysregulation in menopausal women.[13]

Symptoms and risk factors for perimenopausal depression

Perimenopausal depression is unlike MDD, which is characterised by persistent low mood. The early symptoms of perimenopausal depression include fluctuating anxiety and agitation, followed by intermittent anhedonia, low libido, social withdrawal, cognitive issues ('brain fog') and episodic rage.[2,14] Physical symptoms include weight gain, joint pain, fatigue and low energy.[14] Symptoms can vary dramatically from week to week. The treatment for perimenopausal depression needs to be different from MDD treatment and requires the consideration of hormone therapy.[1,2]

Risk factors include a history of mood disorders, prior hormonal mood disorders (PMDD, PND),[5,6] early or surgical menopause[15] or primary ovarian insufficiency,[16] neurodivergence (attention deficit hyperactivity disorder [ADHD] and/or autism – more often undiagnosed in females),[17] childhood trauma[18] and living with family violence.[19]

Diagnosing perimenopausal depression

Perimenopausal depression is difficult to diagnose and is frequently identified retrospectively, after the onset of hot flushes and amenorrhoea. Hence, perimenopausal mental ill health is often incorrectly diagnosed, inappropriately treated or missed altogether.[20]

There are no definitive biological tests to objectively diagnose perimenopause or perimenopausal depression. Estradiol and progesterone levels are usually normal in perimenopause, and follicle-stimulating hormone rises following consistent non-ovulation, which occurs late in the menopause transition.[11]

To assist clinicians and women to understand, diagnose and quantify perimenopausal depression, the Meno-D rating scale was developed (Appendix 1, available online only).[21]

The Meno-D is an interviewer- or self-rated scale assessing 12 typical symptoms: low energy, paranoid thinking, irritability, self-esteem, isolation, anxiety, somatic symptoms, sleep disturbance, weight, sexual interest, memory and concentration, scored from 0 (not present) to 4 (severe).

The total score (out of 48) assists in categorising severity and guiding management of perimenopause depression:

- 20–24 = mild; treatment optional, ongoing monitoring required
- 25–32 = moderate; treatment indicated
- >32 = severe; urgent treatment required.

The Meno-D is easily accessible and available in multiple languages, and it can also be used to monitor progress with treatment.

Excluding other mood disorders

Perimenopausal depression can resemble bipolar type 2, unipolar depression, undiagnosed ADHD or complex post-traumatic stress disorder, and it may also co-exist with them.[20] Differentiation requires thorough assessment. Organic causes and substance use, including alcohol, can mimic or compound symptoms.

Treatment for perimenopausal depression

Hormone therapy should be the first-line treatment for new-onset perimenopausal depression (Figure 2). It is more effective than antidepressants, which carry significant side effects and withdrawal risks.[22] Women in this stage often respond poorly to antidepressants.[23]

Many women and healthcare professionals are still concerned about the 2001 Women's Health Initiative (WHI) study that sensationally implied that menopause hormone therapy (MHT) caused breast cancer and strokes.[24] Reappraisal of WHI data showed a decreased incidence of breast cancer with oestrogen treatment alone, and the small breast cancer risk was associated with medroxyprogesterone in the combination MHT arm.[25] The Australian Menopause Society (AMS) provides further information.[26]

Body-identical hormones, especially transdermal estradiol plus micronised progesterone, are safe for most women, with no evidence of increased breast cancer risk[27,28] or venous thromboembolism.[29]

The goal of MHT in perimenopausal depression is to stabilise fluctuating gonadal hormone levels.[3]

MHT oestrogen

Estradiol is lipophilic, allowing it to cross the blood–brain barrier and improve mood and cognition.[3] Conjugated oestrogens and hemihydrate salts cross less effectively, making 17β-estradiol a more potent option for depression. If using hemihydrate gel (eg Estrogel [Besins Healthcare Australia, Sydney, New South Wales, Australia]), higher doses may be needed for mental health benefits.[30] The AMS dose equivalent guide is an important resource.[26] As an activating hormone, estradiol is best taken in the morning.

MHT progesterone

Continuous combined regimens, when appropriate, help stabilise hormonal fluctuations.

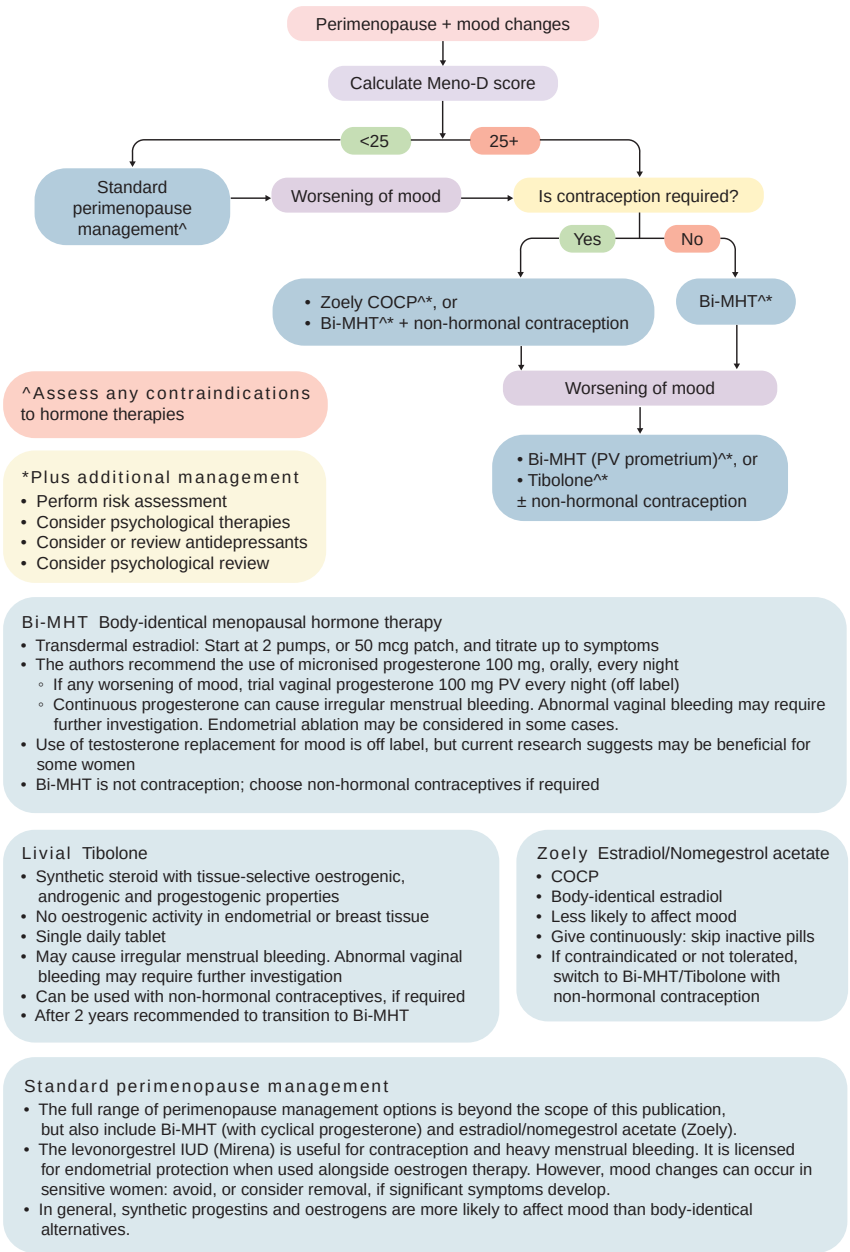

Figure 2. Perimenopausal hormone treatment decision tree.

Bi-MHT, body-identical menopausal hormone therapy; COCP, combined oral contraceptive pill; IUD, intrauterine device; Meno-D, Menopause Depression Rating Scale; PV, vaginally.

Micronised progesterone is the safest option and improves sleep and mood,[31] so it may additionally benefit women with a hormonal intrauterine device (IUD) or post hysterectomy.

Some women are susceptible to progestins, which cause increased depression and anxiety.[32] The older progestins (medroxyprogesterone, dydrogesterone, levonorgestrel, norethisterone) tend to worsen mental illness in sensitive women. It is important to note that this heightened sensitivity can also occur with the levonorgestrel IUD.[32]

While more common with synthetic progestins, micronised progesterone can also worsen anxiety or depression. If so, using micronised progesterone vaginally can reduce CNS exposure.[33]

Testosterone

Although testosterone is licensed for postmenopausal hypoactive sexual desire disorder, emerging evidence suggests benefits for transdermal testosterone treatment in mood and cognition in perimenopause.[9] Testosterone treatment with AndroFeme 1 (Lawley Pharmaceuticals, West Leederville, Western Australia, Australia) 0.5 mL daily takes up to 3–6 months to have an effect and needs monitoring.[34]

Other hormone therapies

For women requiring contraception, the combined oral contraceptive pill Zoely (Theramex, London, UK; currently not on the Pharmaceutical Benefits Scheme), containing nomegestrol and estradiol, is mood neutral.[7] Unless problematic intermittent bleeding occurs, it can be taken without the placebo pills for three cycles to stabilise gonadal hormones.

For women aged in their late 40s and early 50s with perimenopausal depression, tibolone is a useful activating synthetic steroid with oestrogenic, progestogenic and androgenic effects. While it can lead to intermenstrual bleeding, tibolone can treat perimenopausal depression.[35]

If tibolone impact ceases or declines, then standard MHT for women aged in their mid-50s onwards is an important perimenopausal depression treatment.

Antidepressants

Women already taking antidepressants who develop worsening mental illness at midlife should continue their current antidepressants. Where suicidal ideation is present, consider prompt psychiatrist referral.[2]

The Therapeutic Goods Administration currently approves no medications for perimenopausal depression; MHT, contraceptives and antidepressants are used off-label.

Over-the-counter medications

Many women use over-the-counter or naturopathic hormone products. It is essential to discuss these openly, considering

ingredients, poor evidence for efficacy, costs and potential interactions.

Non-pharmacological intervention

Psychotherapy may be needed for coexisting stressors, especially trauma-targeted therapy such as eye movement desensitisation and reprocessing[36] for women with early life trauma experiencing resurgence of symptoms at perimenopause.

Partners and family also need assistance and education to support the woman through menopause transition.

Healthy lifestyle advice about nutrition, exercise, social connection, meditation, cognitive therapies, smoking cessation, alcohol and other drug use such as cannabis minimisation should accompany treatments for perimenopausal depression.

Approach in primary care

The key, as always, is listening. Up to 80% of women experience psychological symptoms, including resurgence of trauma-related symptoms, in perimenopause, so maintaining broad clinical awareness is critical.

It is important for GPs to watch for women aged in their early 40s with new-onset mental illness or relapse of previously stable mood disorders. Other red flags include mood fluctuations, history of hormonal mood symptoms or coexisting menopause symptoms.

The new Medicare Benefits Schedule menopause and perimenopause health assessment item number (695)[37] and the 45–49 health assessment item numbers (703–707) can be used; these allow the involvement of a practice nurse.

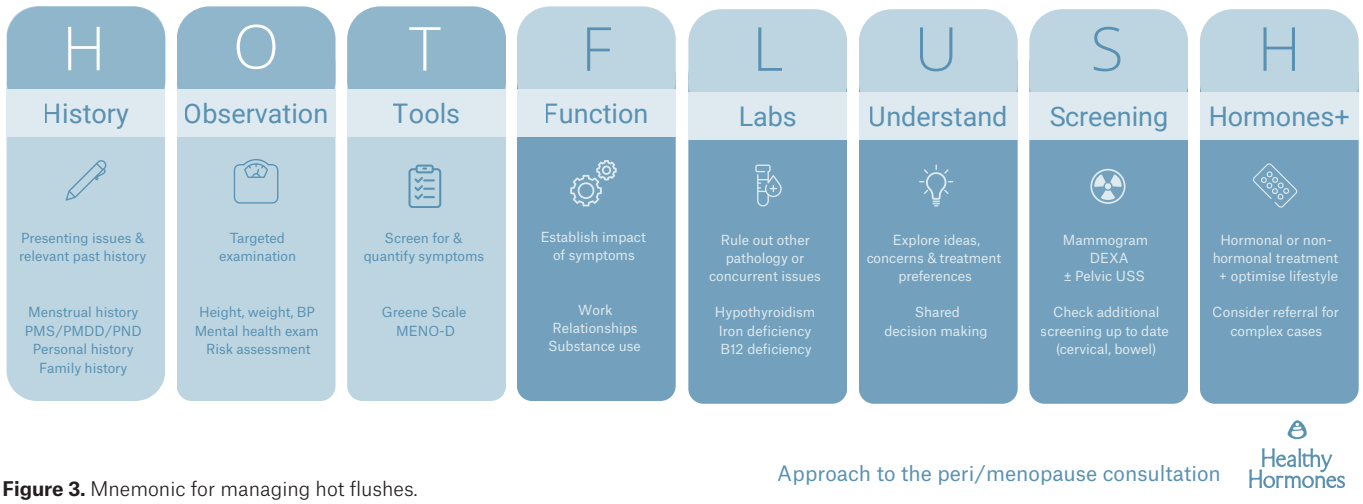

Figure 3. Mnemonic for managing hot flushes.

BP, blood pressure; DEXA, dual-energy X-ray absorptiometry; PMDD, premenstrual dysphoric disorder; PMS, premenstrual syndrome; PND, postnatal depression; USS, ultrasound scan.

Table 1. Key clinical resources for perimenopause care

Organisation	Description	Website
Healthy Hormones	A free, general practitioner–led community for health professionals, offering menopause resources, webinars, courses, events, networking and a forum for case discussions. A separate public platform supports patients.	www.healthyhormones.au or download the app on Apple App Store (https://apps.apple.com/us/app/healthy-hormones/id6749656733) or Google Play (https://play.google.com/store/apps/details?id=au.healthyhormones.community)
Australasian Menopause Society	Evidence-based resources for health professionals and the public regarding menopause and midlife, with an annual scientific meeting.	www.menopause.org.au
Jean Hailes for Women's Health	A not-for-profit organisation providing education, research and clinical resources on women's health across the life course.	www.jeanhailes.org.au
International Menopause Society	A multidisciplinary organisation supporting health professionals worldwide through evidence-based guidelines, position statements, educational resources and biennial congresses.	www.imsociety.org
HER Centre Australia	An Australian initiative dedicated to advancing research, education and clinical care in reproductive and hormonal health. It provides evidence-based resources and training for health professionals.	www.monash.edu/medicine/her-centre

The Healthy Hormones HOT FLUSH acronym offers a practical guide (Figure 3) to approaching perimenopause consultations.

Complex cases often require collaboration with psychologists, psychiatrists and menopause specialists. Perimenopausal depression is associated with suicide,[38] hence the condition needs early identification and appropriate treatment. Reputable resources about menopause are available for clinicians and non-clinicians (Table 1).

Conclusion

GPs are the specialists in whole-person care – and perimenopausal depression demands exactly that. Driven by hormonal fluctuations, perimenopausal depression is a distinct, biologically based condition that remains under-recognised. With greater awareness, appropriate screening (eg Meno-D rating scale) and hormone-based treatment, GPs can improve outcomes for women in midlife facing work, caregiving and family demands. Ongoing education and collaboration support best practice in this complex life stage.

Key points

- Perimenopause changes begin in the brain in a woman's early 40s.
- Perimenopausal depression is different in quality to MDD.
- MHT is effective in treating perimenopausal depression, either alone or in combination with antidepressants plus lifestyle interventions.
- A holistic, collaborative approach is needed to assist women who want help with menopause transition challenges.

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Appendix 1

This appendix is unedited and published as supplied by the author.

MENO-D

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A rating scale to detect depression in menopause

The Meno- D can be completed as a self-report scale or completed by a clinician. The general reference point for each item is the individual's pre-menopausal level or state.

Name: _____ **Date:** _____

A - Low Energy

Over the last 2 weeks have you noticed reduced energy levels?

Prompt questions:
Did you feel more tired after activity than normal? Did your activity decrease because you were tired? Did you feel tired most of the time despite decreasing your activity? Did you continually feel tired so that even small tasks like brushing your hair felt draining?

(Circle appropriate answer)

0	No change in energy, feel active all day
1	More tired after activity than previously
2	Decreased activity because of tiredness
3	Feel tired most of the time despite resting, decreased activity
4	Continually feeling exhausted, even small tasks such as brushing hair feels draining

B - Paranoid Thinking

Over the last 2 weeks have you experienced paranoid thinking?

Prompt questions:
Have you been feeling guilty? Have you been worried that others think badly of you? Have you been suspicious that others think badly of you? Have you been convinced that others have a low opinion of you or are trying to replace you?

(Circle appropriate answer)

0	No paranoid thinking
1	Increasing worry that others think badly of you
2	Suspicious that people at work or home think badly of you
3	Convinced that others have a low opinion of you and are trying to replace you
4	Convinced that others are actively planning to hurt you in many ways

C - Irritability

Over the last 2 weeks have you felt more irritable?

Prompt questions:
Have you felt more irritable than usual? Have you snapped at anyone or been short with anyone over small incidents? Have you felt real rage and had major outbursts about minor incidents?

(Circle appropriate answer)

0	No irritability
1	Mild irritability
2	Increased irritable response to minor incidents
3	Anger expressed by 'snapping', verbal outbursts over minor incidents
4	Rage, major verbal outbursts over minor incidents

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D - Self Esteem

Over the last 2 weeks has your self-esteem been lowered?

Prompt questions:
Have you felt worse about yourself than usual? Have you felt worthless and made negative comments about yourself? Have you believed that the world would be better off without you? Have you harmed yourself in any way? Have you experienced suicidal thoughts? Have you attempted suicide?

(Circle appropriate answer)

0	Good self-esteem or no change in self-esteem
1	Slight decrease in self-esteem
2	Poor self esteem with no reality base
3	Very poor self-esteem in all life-domains
4	No self-worth at all to the point of believing that the world would be better off without you. *(NB – this rating must then lead to further questions about suicide planning, actions and deliberate self-harm)*

E - Isolation

Over the last 2 weeks have you withdrawn socially?

Prompt questions:
Have you socialised as normal? Have you had less of an interest in socialising? Have you become socially withdrawn? Have you felt isolated, even when with others?

(Circle appropriate answer)

0	Socialise normally
1	Decreased socialising
2	Disinterested in socialising
3	Social and occupational withdrawal
4	Feeling isolated, 'in a bubble' even when with others

F - Anxiety

Over the last 2 weeks have you experienced heightened levels of anxiety?

Prompt questions:
Have you felt especially anxious or nervous when in public? Have you felt highly anxious when completing new tasks? Have you felt highly anxious when completing tasks that are routine or familiar to you? Have you had panic attacks and felt extremely anxious when doing normal everyday things?

(Circle appropriate answer)

0	No new anxiety
1	Increased anxiety when in public
2	Highly anxious when doing new tasks
3	Heightened anxiety when doing routine and familiar tasks
4	Panic attacks, highly anxious when doing ordinary and familiar tasks

G - Somatic Symptoms

Over the last 2 weeks have you experienced physical symptoms?

Prompt questions:
Have you had any physical complaints? (eg. increased physical pain with little exertion, frequent headaches or joint and muscle pain that limited activity) Have you experienced severe and debilitating aches and pains that prevented you from engaging in activity?

(Circle appropriate answer)

0	No physical symptoms
1	Increased muscle aches, joint pains on exercise
2	Increased back, leg and joint pains with little exertion
3	Frequent headaches, muscle and/or joint pains limiting activity
4	Severe aches and pains requiring pain relief and preventing activity

H - Sleep Disturbance

Over the last 2 weeks have you experienced sleep disturbance?

Prompt questions:
How has your sleep been? Has your sleep been broken briefly but you could get back to sleep easily? Has your sleep been broken several times each night and you found it hard to get back to sleep? Have you been waking up more than 2 or 3 times per night due to hot flushes, sweating? Have you on most nights been sleeping for only 2 hours or less due to sweating, hot flushes and night chills?

(Circle appropriate answer)

0	No sleep problems
1	Sleep broken by brief waking once or twice a night, but easily fall back to sleep
2	Sleep broken by waking several times a night, but easily fall back to sleep
3	Waking up three or more times per night due to hot flashes and sweating, plus difficulty returning to sleep
4	Sleeping two or less hours per night consistently. Sweating, hot flashes, feeling hot then cold, interrupting sleep all night

I - Weight

Have you gained weight (in comparison to pre-menopause weight)?

Prompt questions:
Has your weight changed at all? Have you gained a moderate amount of weight despite no change in diet or exercise? Have you continued to gain weight despite engaging in strict dieting or increased exercise? Have you had a major weight gain of 6kg or more?

(Circle appropriate answer)

0	No change in weight
1	Mild weight gain (1-2kg)
2	Moderate weight gain despite no change in diet or exercise (3-6kg)
3	Continuing weight gain and abdominal fat deposition, despite dietary restriction and increasing exercise
4	Major weight gain (>6kg) with abdominal, breast, hip and thigh fat deposition

J - Sexual Interest

Over the last 2 weeks have you experienced a reduced libido?

Prompt questions:
Have you had decreased libido? Has your libido diminished significantly? Have you had discomfort with sexual activity in addition to a decreased libido? Have you lost all interest in sexual activity?

(Circle appropriate answer)

0	No change in libido
1	Mild decrease in libido
2	Diminished libido
3	Decreased libido and discomfort with sexual activity
4	Loss of interest in all sexual activity

K - Memory

Over the last 2 weeks have you noticed any memory-related difficulties?

Prompt questions:
Have you had mild problems remembering simple things like names and numbers? Did you need to make lists in order to function at work or at home? Did memory problems lead to dysfunction or impairment in any way?

(Circle appropriate answer)

0	No memory problems
1	Mild problems remembering names and numbers
2	Need to make lists to function at work and/or home
3	Impaired memory leading to dysfunction
4	Severe loss of memory leading to inability to function

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L - Concentration

Over the last 2 weeks have you experienced problems concentrating?

Prompt questions:
Did you have difficulty reading or holding a conversation? How severe were these problems? Were you unable to focus on any task for a suitable period of time?

(Circle appropriate answer)

0	No concentration difficulties
1	Mild problems with concentrating on reading
2	Mild problems with concentrating on reading and watching TV/Films
3	Marked problems with concentrating on reading and watching TV/Films
4	Unable to focus on any tasks

SCORING

Points are indicated as the numerical value of each possible symptom area (A-L) – then the total is added.

The minimum score is 0 and the maximum is 48 points.

Between 20-24 points is considered to denote mild perimenopausal depression, needing onward monitoring.

Between 24-32 points suggests moderate perimenopausal depression needing treatment.

At 32 points and above, the woman is considered to have severe perimenopausal depression needing treatment.