East Kent Hospitals University NHS Foundation Trust

# East Kent Hospitals University NHS Foundation Trust

# MENOPAUSE AND HORMONE REPLACEMENT THERAPY (HRT): BIOCHEMICAL INVESTIGATION

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| Version: | 3.0 |
| Ratified by: | Clinical Biochemistry Senior Staff Group and Clinical Support Services Care Group |
| Date ratified: | October 2022 |
| Name of originator/author: | Edward Kearney/Ellen Bealing/Edmund Lamb |
| Director responsible for implementation: | Dr Edmund Lamb (Clinical Director) |
| Date issued: | October 2022 |
| Review date: | October 2024 |
| Target audience: | Clinical staff (medical, nursing and scientific), Trust wide and primary care |

## Version Control Schedule

| Version | Date | Author | Status | Comment |
|---|---|---|---|---|
| 1.0 | 1st February 2017 | Mr Edward Kearney | | |
| 2.0 | 10th March 2021 | Ellen Bealing | | Review updated NG23; no relevant changes.<br>Review FSRH guideline for contraception; changes highlighted.<br>Added endocrine society guideline advice about chemotherapy, highlighted. |
| 3.0 | 22nd June 2022 | Edmund Lamb | | Review British Menopause Society 2020 HRT guideline and Joint Menopause Practice Guideline 2022.<br>Consultation with Obstetrics and Gynaecology consultants and GPs in primary care (se section 7). |
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## Consultation and Ratification Schedule

| Name and Title of Individual | Date Consulted |
|---|---|
| Drs Louise Lea, Consultant Obstetrician and Gynaecologist | July 2022 |
| Dr Ike Okorocha, Consultant Obstetrician and Gynaecologist | July 2022 |
| Dr Joanna Lambourne, Consultant Obstetrician and Gynaecologist | July 2022 |
| Dr Celia Timms, GP, Ivy Court Surgery | August 2022 |
| Dr Tracey Eastbrook, GP, Balmoral Surgery | August 2022 |
| Dr Cecily Fahey, GP, New Dover Road Surgery | August 2022 |
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| Name of Committee | Date Reviewed |
|---|---|
| Ratification by senior clinical staff in clinical biochemistry through Q-Pulse | August/September 2022 |
| Pathology Management and Governance Committee (PMGC) | September 2022 |
| Clinical Support Services Quality and Risk meeting | October 2022 |
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**Contents**

# 1. Introduction, Background and Purpose

This document gives guidance on what biochemical tests to use when investigating women for menopausal status and when managing women on hormone replacement therapy (HRT).

Menopause is diagnosed retrospectively after 12 months of amenorrhoea. For most women, the 40s and 50s are a time when they move from normal ovulatory menstrual cycles to the cessation of ovulation and menstruation. During this time, intermittent ovulation and anovulation occur; there may be a rise in follicle-stimulating hormone (FSH) concentration and women will experience shortening and/or lengthening of their menstrual cycle. A raised FSH is not diagnostic of menopause but indicates a lack of ovarian response at a point in time. Nevertheless, an FSH concentration in excess of 27 IU/L (see footnote) is consistent with menopause. Luteinising hormone (LH) concentrations observed in both postmenopausal and premenopausal women overlap significantly and LH measurement adds no value to the investigation of menopause and may be misleading. Oestradiol (E2) is an unreliable indicator of menopausal status and should not be used in menopausal testing. This guidance provides recommendations for the most effective biochemical investigation of the menopause and management of HRT. This document gives guidance that is consistent with that developed by NICE (NG23).

*Footnote:*
After examining the evidence for a cut-off NICE did not publish a value for FSH for establishing menopause as they found no study of sufficient quality to justify a recommendation. The cut-off value for FSH >27 IU/L used here is that which pertains to the East Kent method for FSH measurement, obtained from Abbott Laboratories who studied 34 postmenopausal women where the mean was 59.7 IU/L, range (central 95%) 26.7 - 133.4 IU/L.

# 2. Definitions

Menopause is defined as the time when there has been no menstrual periods for 12 consecutive months and no other biological or physiological cause can be identified.

# 3. Scope

All staff involved in requesting or interpreting blood reproductive hormone concentrations should adhere to this guidance. Clinical biochemistry will only process tests where clear and appropriate clinical details are provided in accordance with the above guidance. The laboratory is always happy to discuss cases on an individual patient basis.

# 4. Guidance

**Investigating menopausal status**
It may be useful to assess menopausal status to guide the introduction of HRT or the cessation of contraception.

*Women under 40 years:*
Use FSH to diagnose menopause (premature ovarian insufficiency) in women with secondary amenorrhoea. Women should have serum FSH concentration measurement on at least two occasions four to six weeks apart (Menopause Practice Standards 2022). Do not use oestradiol, progesterone or LH to diagnose menopause.

*Women aged between 40-45 years:*
Use FSH to diagnose menopause in women who have menopausal symptoms and a change in their menstrual cycle. Women should have serum FSH concentration measurement on at least two occasions four to six weeks apart (Menopause Practice Standards 2022). Do not use oestradiol, progesterone or LH to diagnose menopause.

*Women over 45 years:*
NICE recommend no biochemical testing is ***routinely*** necessary to diagnose the menopause in women aged over 45 y (see https://cks.nice.org.uk/topics/menopause/). There are some exceptions to this:

1. Aged over 45 y with atypical symptoms
2. Aged over 50 y of age using progestogen-only contraception (see below).

The diagnosis of menopause is based on at least 12 months amenorrhoea in women who are not using hormonal contraception. However, there are some exceptions to this recommendation: women with amenorrhoea due to previous surgery, progesterone-only contraception or chemotherapy-induced menopause (see below).

**Contraception and menopausal testing**
**1.** In general, women age 40-49 y need to continue to use contraception for 2 years after their last period. Women of 50 y and above need to continue to use contraception for 1 year after their last period. All women ≥55 y can cease contraception as spontaneous conception after this age is extremely rare, even if still experiencing menstrual bleeding (FSRH Guideline 2017).

**2**. Women ≥45 y using combined hormone contraceptive (CHC), high-dose progestogen or HRT: FSH is an unreliable indicator of menopausal status in women on these hormonal contraceptives as these drugs will suppress FSH (FSRH Guideline 2017).

**3.** Isolated FSH results can be misleading and should not be used as a basis for providing advice about stopping contraception; ovulation may still occur with risk of pregnancy, particularly in younger women with a diagnosis of premature ovarian insufficiency. For this reason, the FSRH suggests restricting measurement of serum FSH for advice about stopping contraception to women >50 y using POC who are amenorrhoeic (FSRH Guideline 2017).

**4**. If a woman >50 y with amenorrhoea using progestogen-only contraception (POC, including Depo-medroxyprogesterone acetate (DMPA), progestogen-only pill, progestogen-only implant and levonorgestrel intrauterine systems (LNG-IUS, Mirena™)) wishes to stop contraception before age 55 y, serum FSH can be measured to check menopausal status (FSRH Guideline 2017). If FSH is in premenopausal range then contraceptive method should be continued and FSH measured again 1 year later. If FSH concentration is in post-menopausal range then contraception can be discontinued after 1 more year. (Note: the FSRH states that a single post-menopausal range serum FSH indicates a degree of ovarian insufficiency, but not necessarily sterility. The British Menopause Society (BMS) recommends checking for an elevated FSH level on two blood samples taken 4–6 weeks apart.)

**Chemotherapy**
Chemotherapy may induce menopause and it is clinically useful to establish whether this has occurred, irrespective of a woman's age. In this situation, FSH alone should be measured. Note that ovarian function may resume after 12 months of amenorrhoea, depending on the age of the woman and the dose of treatment.

**Hormone replacement therapy (HRT)**
It is not usually necessary to measure any reproductive hormones in women on HRT and there is a lack of clear evidence-based guidance in this area. The following guidance is for local use in East Kent.

*Oestradiol:*

- The 2020 British Menopause Society guideline does not specifically recommend oestradiol measurement or propose a therapeutic target.
- Oestradiol measurements should not be requested in women receiving oral HRT as results are difficult to interpret, and vary depending on oestrogen type. Due to hepatic metabolism, most oral oestrogens will not be detected by the laboratory method for measuring serum oestradiol.
- Serum oestradiol measurement may be used to check concentration before the next implant due to the risk of tachyphylaxis.
- In women receiving transdermal oestrogen treatment, serum oestradiol measurement may be useful in:
  (i) high risk cases (e.g. those with a history of breast cancer or a BRCA gene);
  (ii) clinical non-responders to treatment (e.g. to help clarify whether due to poor compliance, potential drug interactions, altered absorption or inadequate dose); and
  (iii) in women with premature ovarian insufficiency who are receiving oestradiol to ensure physiological concentrations are achieved (Menopause Practice Standards 2022).
- The local proposed therapeutic range is 200-400 pmol/L.
- Clinicians should be aware of the high uncertainty of measurement of lower concentrations of oestradiol. For example, at a concentration of 200 pmol/L the true result will lie between 150 pmol/L and 250 pmol/L.

*Testosterone:*

- Assessment of serum testosterone concentration is unlikely to be beneficial in making the diagnosis of hormone dependent low sexual desire, as there is poor correlation between circulating levels and clinical symptoms (Menopause Practice Standards 2022).
- Testosterone measurement should only be requested in women in whom testosterone HRT is being proposed due to decreased libido (BMS 2020 guideline). Testosterone concentrations should be checked before commencing treatment to exclude high baseline levels.
- Serum testosterone concentration should be re-assessed ideally within 3-4 months of starting treatment to ensure levels are kept within the female physiological threshold (Menopause Practice Standards 2022)

*SHBG:*

The Joint Menopause Practice Standards (2022) do not support the use of SHBG to calculate free androgen index in patients receiving testosterone HRT. Monitoring of such patients should ensure that total testosterone is maintained within the female reference range.

*FSH:*

There is no role for FSH testing in HRT monitoring. FSH may be supressed in some women receiving HRT.

*Dehydroepiandostenedione sulphate (DHEAS):*

Analysis of DHEAS is not indicated for assessment of menopause/HRT monitoring.

## 5. Consultation and Approval

East Kent Hospitals University NHS Foundation Trust is the key stakeholder for this guidance. This document was initially prepared in consultation with Miss Choy Lee, Consultant Obstetrician and Gynaecologist. Guidance relating to biochemical testing in the setting of HRT has been reviewed by Drs Louise Lea, Ike Okorocha and Joanna Lambourne, Consultant Obstetrician and Gynaecologists, and by Drs Celia Timms (GP, Ivy Court Surgery), T Eastbrook (GP, Balmoral Surgery). Copies of correspondence may be found on the shared drive.

## 6. Review and Revision Arrangements

Two years from implementation date, by author.

## 7. Training

Clinical scientists in Clinical Biochemistry will be trained as part of their duty biochemist competency training. Dissemination will be electronic on Q-Pulse and TrustNet and on the pathology microguide app, with the latter serving as an educational tool for requesting clinicians. Education will also be provided through feedback on laboratory reports and through occasional GP protected learning time events. The guidance was presented and discussed at the Canterbury and Ashford primary care protected learning time event on 4th October 2022.

## 8. Document Control including Archiving Arrangements

This document will be available on Q Pulse and in the Clinical Biochemistry page of TrustNet/Healthcare Professionals. The guidance will also be available on the pathology Microguide app. Implementation will be through the Care Groups by appropriate clinical leads and by proactive dissemination to primary care partners. Archive of this document will be through Q-Pulse.

## 9. Monitoring

Within the Trust, compliance with this guidance must rest with the requesting Care groups. Compliance will be assessed by retrospective audit.

## 10. References and Associated Documents

1. NICE. Menopause: diagnosis and management, NICE guideline [NG23]: December 2019 https://www.nice.org.uk/guidance/ng23

2. Faculty of Sexual and Reproductive Healthcare. FSRH Clinical Guideline: Contraception for Women Aged over 40 Years (August 2017, amended September 2019) Faculty of Sexual and Reproductive Healthcare Clinical Guidance https://www.fsrh.org/documents/fsrh-guidance-contraception-for-women-aged-over-40-years-2017/

3. Stuenkel *et al.* Treatment of Symptoms of the Menopause: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab, November 2015, 100(11):3975–4011

4. Hamoda H *et al*. The British Menopause Society & Women's Health Concern 2020 recommendations on hormone replacement therapy in menopausal women. Post Reproductive Health 2020, Vol. 26(4) 181–208

5. Hamoda H *et al*. Menopause Practice Standards. Produced by the British Menopause Society, Royal College of Obstetricians and Gynaecologists, Society for Endocrinology, Faculty of Sexual and Reproductive Health, Faculty of Pharmaceutical Medicine and the Royal Pharmaceutical Society. Clinical Endocrinology 2022; in press. PMID: 35713204 DOI: 10.1111/cen.14789.