ENDOCRINE LATE EFFECTS

Endocrine consequences of treatment are very common after a wide range of treatments for most childhood and adult cancers. They can be extremely debilitating and can include loss of fertility, impact on sexual function, fatigue, hot flushes, cardiovascular/metabolic disorders, bone disease and hypothyroidism. These conditions often present with vague symptoms or are preventable with appropriate management from health care professionals.

These one-page guides were created through a collaboration of Endocrinologists, GPs and Oncologists. The guides are endorsed by the Royal College of Physicians and the Royal College of Radiologists. The topics cover: pituitary insufficiency, ovarian insufficiency, testicular insufficiency, bone health, thyroid problems and hot flushes when HRT is contraindicated. These guides highlight the treatments that can cause endocrine late effects, the symptoms and give important information on the management and when to refer to a specialist.

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Bone problems and osteoporosis

Any cancer patient may be at risk of poor bone health. The following are additional risk factors:

- Post-menopausal women and men >50 yrs
- Low BMI (<19 kg/m2)
- Immobility
- Current smoking
- Alcohol >3 units/day
- History of parental hip fracture
- History of rheumatoid arthritis, inflammatory bowel disease or diabetes
- Falls risk (peripheral neuropathy, cachexia, sarcopenia)

Cancers at high risk of bone problems, osteoporosis and fragility fractures

- Haematological malignancies (lymphoma, leukaemia, myeloma)
- Gastric cancer

Treatments which may be followed by bone complications

- Glucocorticoid (GC) therapy
- High dose methotrexate (cumulative dose >40,000 mg/m2)
- Chemotherapy – predominantly alkylating agents (eg cyclophosphamide and chlorambucil), platinum compounds and specific chemotherapies (eg ifosfamide)
- Ovarian suppression therapy or androgen deprivation therapy (ADT)
- Aromatase inhibitors (AI), and tamoxifen in pre-menopausal women
- Haematopoietic stem cell transplant (HSCT)
- Total body irradiation (TBI)
- Radiotherapy to cancers of the brain, nasopharynx, orbit and surrounding tissues, including proton therapy
- Gonadal radiotherapy
- Focal radiotherapy involving bones >40 Gy (pelvis/rib)
- Brachytherapy

Symptoms of bone problems and osteoporosis

- Often asymptomatic
- Fragility fracture may present with pain
- Severe vitamin D deficiency may cause pain and proximal weakness
- Pelvic pain following pelvic radiotherapy may indicate insufficiency fractures

Potential actions

- At end of treatment (and ideally at start of treatment), all patients should be assessed for fracture risk by FRAX/ Qfracture

FRAX does not take any cancer treatments into consideration, so clinical judgement required

- All patients at increased risk due to treatment should undergo a DXA scan 1 year after end of treatment
- All patients taking GCs, AI therapy or ADT should follow current international algorithms (see refs)
- Patients who have a low BMD (T score <-1, Z-score <-2) should have screens for secondary causes of low bone mass, including blood tests for calcium, vitamin D, PTH, ALP and LFTs, coeliac screen, serum and urine electrophoresis, assessment of gonadal status (oestradiol, 9am testosterone, LH and FSH)
- All patients with pelvic pain following pelvic radiotherapy should have MRI scan of pelvis to look for insufficiency fractures
- If clinical suspicion/high risk of vertebral fracture, should perform DXA or lateral thoracic/lumbar radiography

Treatment

- **Low bone mass/osteopenia** (a T-score <-1 and >-2.5, or a Z-score <-2 in those <40 years old)
- Lifestyle advice (smoking, alcohol intake, weight bearing exercise for 30 mins x5 a week)
- Recommend intake of calcium: 700-1000mg/day (supplements if diet insufficient) and ensure vitamin D >50 nmol/l (800IU once daily if replacement required)
- Manage secondary causes, eg treat hypogonadism (premenopausal women and men) if no contraindications
- Osteoporosis (T-score ≤-2.5, fragility fracture or Z-score <-2 with history of fragility fractures) Follow FRAX and NOGG guidelines
- For AI and ADT follow guidelines
- Follow-up DXA scans should be determined by BMD and clinical risk

Important points

- Low threshold for referral to metabolic bone clinic, particularly in young patients, hypogonadism and insufficiency fractures
- Presence of new fragility fracture (particularly vertebral fracture) is high risk of further fracture
- Withdrawal of denosumab treatment has been associated with rebound vertebral fractures – if denosumb to be stopped liaise with specialist
- If suspected radiation induced fracture, refer to rheumatology or metabolic bone clinic (or fracture clinic if unstable fracture on x-ray)
- DXA scan cannot distinguish between osteoporosis and severe vitamin D deficiency; DXA should only be performed in those who are vitamin D replete

Ref for aromatase inhibitors
J Bone Oncol. 2017 Mar 23;7:1-12. doi: 10.1016/j.jbo.2017.03.001.

Ref for androgen deprivation therapy
Oncotarget. 2017 May 18;8(43): 75646-75663. doi: 10.18632/ oncotarget.17980.

Ref for NOGG guidelines
https://link.springer.com/ article/10.1007/s11657-017-0324-5

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Hot flushes and HRT/testosterone replacement contraindicated

Cancers whose treatment can cause hot flushes and HRT/testosterone replacement may be contraindicated

- Breast cancer
- Prostate cancer
- Ovarian/endometrial cancer

Treatments which may be followed by hot flushes and HRT/testosterone replacement contraindicated

Androgen deprivation treatments (ADT)

- Luteinising hormone (LH) blockers (eg goserelin, leuprorelin, decapeptyl) for prostate cancer, which block LH production in the pituitary gland, thereby stopping the testicles from producing testosterone
- Anti-androgens (flutamide, bicalutamide) which block testosterone receptors on prostate cancer cells
- Gonadotrophin releasing hormone (GnRH) receptor blocker (degarelix), which acts at the hypothalamus to stop the pituitary from producing LH

Hormone treatments for breast cancer

- Tamoxifen (stops oestrogen reaching the cancer cells)
- Aromatase inhibitors (eg exemestane, anastrozole, letrozole), which work in post-menopausal women by stopping the body converting androgens into oestrogen
- LH blockers (goserelin)

Symptoms of hot flushes

- Hot flushes may range from a sensation of rising heat (particularly in the face), through to drenching sweats and panic attacks
- Cancer treatments may induce permanent or temporary ovarian/testicular insufficiency
- During hormonal treatment for prostate cancer men experience tiredness, impotence, breast tenderness, weight gain, memory disturbance, mood changes

Men may be at risk of **heart disease or diabetes** if ADT treatment is for more than 6 months

- Consider bone health – *see Bone problems and osteoporosis guide*

History detailing

- Type of cancer: is it hormone sensitive, or was ovarian/testicular insufficiency induced by treatment (surgery or chemotherapy)?
- What are the patient's risk factors – osteoporosis, cardiovascular risks?
- Are there any risks if HRT treatment given, eg risks of recurrence or blocking cancer treatment effects? (see below)
- Ask about erectile dysfunction or vaginal dryness, and lack of libido, sexual dysfunction, dyspareunia, psychological concerns, fertility issues, as patients may not otherwise disclose these concerns

Non-pharmaceutical management for men and women

- Stress clearly identified as a trigger for flushing in some patients and CBD and acupuncture may usefully reduce this
- Consider practical interventions such as reducing spicy foods, caffeine, alcohol, and sleeping in or wearing natural fibres like cotton

Treatment in women

Risks of HRT

Women with breast cancer who are treated with HRT are three times more likely to have cancer recurrence

Ovarian and Endometrial Cancer

- Some ovarian/endometrial cancers (particularly low grade) have oestrogen receptors and can be treated with tamoxifen and aromatase inhibitors
- Please ask oncologist for advice on risk of using HRT if patient receiving active treatment for these cancers
- Following successful curative cancer treatment there is no contraindication for HRT

Topical low dose vaginal oestrogen is considered an acceptable treatment for patients using aromatase inhibitors with dyspareunia and vaginal dryness who have already tried simple lubricants

Alternatives to HRT

- Drug options: clonidine (25–75mcg orally twice daily or via patch), venlafaxine (37.5–75mg daily)
- Weak SSRIs such as citalopram (10–20mg once daily) or gabapentin (300mg three times daily) have also been shown to be beneficial

There is a theoretical concern that Paroxetine/Fluoxetine may interfere with Tamoxifen metabolism, use alternatives where possible

Treatment in men with prostate cancer on ADT

- NICE recommends medroxyprogesterone 20 mg per day to be offered initially for 10 weeks
- If medroxyprogesterone not effective, then consider change to cyproterone acetate, with a 50mg starting dose, and if necessary, upward titration within the range 50–150mg/day in 1 to 3 divided doses
- Consult with oncologist if testosterone remains low, symptoms debilitating and ADT completed (testosterone replacement may be suggested)

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Ovarian insufficiency

Primary ovarian insufficiency (POI) when the ovary is damaged
Secondary ovarian insufficiency is when damage occurs to the pituitary/hypothalamus

Cancers which may be followed by ovarian insufficiency

- Cancers of the brain, nasopharynx, orbit and surrounding tissues
- Ovarian/gynaecological cancer
- Haematological malignancies
- Colorectal/anal cancer
- Breast cancer
- Pancreatic cancer
- Bladder cancer

Treatments which may be followed by ovarian insufficiency

- Chemotherapy – predominantly alkylating agents (eg cyclophosphamide and chlorambucil), platinum compounds and specific chemotherapies (eg ifosfamide)
- Surgery – bilateral oophorectomy, pituitary, hypothalamus
- Radiotherapy (including proton beam) – ovarian, abdominal, pelvic, brain, head, orbits, nasopharynx, pituitary, hypothalamus
- Total body irradiation

Symptoms of oestrogen insufficiency

- Amenorrhoea and oligomenorrhoea
- Fertility problems
- Osteoporosis/fragility fracture
- Hot flushes, night sweats, palpations
- Vaginal dryness
- Reduced libido/pain during sex
- Problems with memory and concentration
- Joint stiffness, aches, and pains
- Recurrent UTI

History detailing

- If pre-menopausal: are they menstruating and is it a regular menstrual cycle?
- If young adult, have periods started, completed puberty, and have they grown to an appropriate height?
- Are they experiencing hot flushes?
- Any dyspareunia or vaginal dryness?
- Any post coital bleeding?
- Any psychological issues or sexual problems?
- Are there any fertility issues or concerns?

Oligo/amenorrhoea

- Can be primary when the ovary is damaged (high LH/FSH) or secondary when damage is to the pituitary/hypothalamus (low normal LH/FSH). Both have low oestradiol (<100pmol/L)

Blood tests for:

- LH, FSH, oestradiol (day 1–5 if menstruating)
- Consider exclusion of other causes of amenorrhoea eg PCOS, elevated prolactin

Potential actions:

- If under 50 years of age, in the absence of contraindications start oestrogen replacement
- Contraindications include
  - breast, endometrial cancer, and presence of BRCA mutations
  - thrombophilia

- **If unsure seek specialist advice**
- **If young adult, refer to endocrinology**
- **If secondary ovarian insufficiency refer to endocrinology** as further pituitary surveillance needed.
- Tamoxifen causes amenorrhoea but pregnancy can still occur and LH/FSH not a robust indicator of ovarian function.
- Contraception is recommended in premenopausal women

Oestrogen replacement

- Consider HRT first line (more physiological) unless contraception required then COCP or HRT with alternative method of contraception.
- Oestradiol is important for the prevention of menopausal symptoms and bone protection.

Usual risks of HRT do not apply to young women (there is currently no data in this age group).

- Women with a uterus must have progestogen (cyclical, continuous, or impregnated IUCD) together with oestrogen replacement

Vaginal dryness

- Consider treatments such as topical oestrogen, Replens, dermol 500 wash in the standard way

Cervical smears may be challenging and painful **seek specialist advice as required**

Hot flushes

Blood tests for:

- LH, FSH, oestradiol
- Oestrogen replacement if under 50 years of age if not contraindicated
- If oestrogen replacement contraindicated or not wanted, *please review Hot flushes and HRT/testosterone replacement contraindicated guide*

Fertility

- If seeking fertility, or wish to review options for future fertility in context of ovarian insufficiency then **refer to local fertility services**
- If sexually active advise the patient to use contraception even if no periods as there's still a small chance of returning ovarian function and unplanned pregnancy
- Discuss risks of STI if sexually active

Pregnancy

- If the patient becomes pregnant then **refer to obstetrics**
- High risk pregnancies if previous:
  - Pelvic/chest radiotherapy
  - Chemotherapy eg bleomycin, busulphan, carmustine, lomustine can cause restrictive lung defects
  - Anthracyclines and chest radiotherapy can cause cardiac decompensation

Psychological issues

- Ask if any concerns regarding mood, quality of life, sexual dysfunction
- If concerns **refer to mental health and well being services or specialist psychosexual counselling**

Osteoporosis/fragility problems

- *See Bone problems and osteoporosis guide*

If you would like further information on menopause management in ovarian insufficiency please review NICE guidelines **www.nice.org.uk/guidance/ng23**

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Pituitary insufficiency

If a patient has undergone surgery or radiotherapy which may have affected the pituitary or hypothalamus, refer to endocrinology for assessment/pituitary surveillance.

Cancers which may be followed by pituitary insufficiency

- Brain tumours either close to or involving the hypothalamus or pituitary
- Cancers of nasopharynx, orbit and surrounding tissues
- Haematological malignancies
- Brain tumours or metastatic cancer treated with dexamethasone for 4 weeks or longer
- Brain metastases (most frequently lung, breast, kidney, melanoma and bowel)

Treatments which may be followed by pituitary insufficiency

- Neurosurgery either close to or involving the hypothalamus or pituitary
- Radiotherapy (including proton beam) to cancers of nasopharynx, orbit and surrounding tissues
- Total body irradiation
- New cancer treatments: biological therapies, immunotherapies
- Dexamethasone for 4 weeks or longer

Symptoms of pituitary insufficiency

- Fatigue, weakness, depression
- Anorexia and weight loss
- Sexual dysfunction: reduced libido, erectile dysfunction, irregular or lack of periods, vaginal dryness, hot flushes
- Fertility problems
- Symptoms of hypothyroidism

Patients at risk of hypopituitarism should be under the care of an endocrinologist

Blood tests

- Do 9am cortisol in patients not on dexamethsone or other glucocorticoid

If 9am cortisol less than 100nmol/L, start hydrocortisone at a dose of 15 mg in the morning and 5 mg at 3pm; this will mean patient is protected; refer urgently to endocrinology

If 9am cortisol between 100 and 350nmol/L, patient needs further urgent assessment; refer urgently to endocrinology

- Check TFTs. fT4 below normal range with low/normal or mildly elevated TSH suggests secondary hypothyroidism. (state on blood request '?secondary hypothyroidism due to pituitary insufficiency')

Do not start levothyroxine until cortisol status is known, as this may precipitate an adrenal crisis

- In men, check 9am testosterone and SHBG; if testosterone low and LH and FSH are not raised, this suggests secondary hypogonadism; *please refer to Testicular insufficiency guide*
- In premenopausal women with absent menstrual cycle, check LH, FSH and oestradiol; if oestradiol low and LH and FSH not raised, this suggests secondary hypogonadism; *please refer to endocrinology*
- In postmenopausal women, check FSH; if FSH is low/normal, this suggests hypopituitarism

Important points

Consider hypophysitis if evidence of hypopituitarism during and after use of immunotherapies

- Headache, cognitive problems and neurological symptoms may indicate recurrence, second tumour or consequence of cranial irradiation
- New acute neurological symptoms, suspicion of CVA, VP shunt blockage (headache, symptoms suggestive of infection). **Refer to neuro-oncology/ neurosurgery urgently**
- Patients treated with total body irradiation or cranial/head radiotherapy may develop asymptomatic hypopituitarism; regular screening is required for growth hormone (GH) deficiency and secondary hypogonadism, hypothyroidism and hypoadrenalism
- Patients with hypopituitarism are at risk of cardiovascular disease, diabetes and hyperlipidiaemia
- Hypopituitarism following radiation may evolve over many years; most deficiencies occur within 10 years but can occur later; ongoing follow up is required
- Ensure patients with secondary adrenal insufficiency have a MedicAlert card and are aware of sick day rules; refer to Pituitary Foundation for further information

Thirst and polyuria can be suggestive of diabetes insipidus

- Exclude diabetes mellitus and hypercalcaemia
- Diabetes insipidus is not associated with cranial irradiation or any other cancer therapy, so may suggest tumour or metastases affecting the hypothalamus or pituitary
- Cognitive dysfunction and memory issues can occur at a young age after cranial irradiation

Consider referring to local services for neuro-pyschometric testing, or to community services if employment or benefits support is needed

Ref for emergency management of adrenal insufficiency www.endocrineconnections.com/content/5/5/G1.full.pdf+html?sid=7089eafb-d130-40ac-9da8-2957e880db19

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Testicular insufficiency

Primary testicular insufficiency is when the testes are damaged
Secondary testicular insufficiency is when damage occurs to the pituitary/hypothalamus

Cancers which may be followed by testicular insufficiency

- Cancers of the brain, nasopharynx, orbit and surrounding tissues
- Testicular cancer
- Colorectal/anal cancer
- Prostate cancer
- Bladder cancer
- Haematological malignancies

Treatments which may be followed by testicular insufficiency

- Chemotherapy – predominantly alkylating agents (eg cyclophosphamide and chlorambucil), platinum compounds and specific chemotherapies (eg ifosfamide)
- Surgery – bilateral orchidectomy, pituitary, hypothalamus
- Radiotherapy (including proton beam) – testicular, abdominal, pelvic, brain, orbits, nasopharynx, pituitary, hypothalamus
- Total body irradiation

Symptoms of testosterone insufficiency

- Reduced libido
- Erectile dysfunction
- Fertility problems
- Reduced frequency of shaving
- Reduced muscle bulk
- Osteoporosis/fragility fracture
- Hot flushes, night sweats, palpitations
- Problems with memory and concentration

History detailing

- If an adult, do they have any issues with libido, erectile function, lack of shaving?
- If a young adult, have they progressed through puberty and grown to an appropriate height?
- Any psychological issues or sexual problems?
- Are there any fertility issues or concerns?
- Are they experiencing hot flushes?

Bloods tests for testosterone insufficiency

- LH, FSH, 9am testosterone, sex hormone binding globulin (SHBG) (to calculate free testosterone, which may be helpful, for example, in obese patients)
- Exclude other causes of low testosterone, eg elevated prolactin
- Testicular insufficiency is primary when the testes are damaged (high LH/FSH), or secondary when damage is to the pituitary/hypothalamus (low normal LH/FSH); both have low testosterone
- High FSH and normal testosterone can indicate sertoli cell damage, which only affects sperm production (no effect on testosterone)

Do not check testicular function at the time of significant intercurrent illness, or whilst a patient is undergoing active cancer-related treatment

Potential actions

If blood tests show low 9am testosterone (on two occasions), refer to endocrinology

Testosterone replacement

- Testosterone can be replaced with testosterone gel, short acting or long-acting injections
- Monitor annual testosterone level, FBC (due to risk of secondary polycythaemia) and prostate/PSA screening

Fertility

- Elevated FSH in presence of normal testosterone may indicate sertoli cell damage and fertility issues
- Fertility should be discussed with the patient at risk or with evidence of testicular insufficiency and before starting testosterone replacement
- If semen stored prior to cancer therapy, advise the patient to contact the storage facility to arrange a check of current fertility status and confirm they have up-to-date details and consent
- If patient interested in knowing their fertility status, arrange semen analysis with appropriate counselling
- If patient seeking fertility, or wishes to review options for future fertility, then

Refer to local fertility services with expertise in male factor infertility

- Psychological support may be needed to discuss abnormalities in semen analysis and loss of fertility
- If sexually active, advise the patient to use contraception
- Discuss risks of STI if sexually active

Sexual function

- Patients who have undergone surgery to spinal cord, sympathetic nerves or pelvis
- Radiotherapy to testes or pelvis
- Patients who are hypogonadal

Psychological issues

- Ask if any concerns regarding mood, quality of life or sexual dysfunction; if appropriate, refer to mental health and well being services or specialist psychosexual counselling

Osteoporosis/fragility problems

- *See Bone problems and osteoporosis guide*

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Thyroid problems

Cancers which may be followed by thyroid problems

- Brain/head and neck cancers
- Pituitary tumours
- Thyroid cancer
- Breast cancer
- Haematological malignancies

Treatments which may be followed by thyroid problems

- Surgery leading to thyroid removal
- Head and neck, mediastinal, cervical spine radiotherapy (including proton beam)
- Bone marrow transplant with or without total body irradiation
- Therapeutic MIGB
- New cancer treatments: biological therapies, immunotherapies

Symptoms of thyroid problems

- Fatigue
- Weight loss or weight gain
- Heat or cold intolerance
- Diarrhoea or constipation
- Anxiety, tremors, sweating
- Dry hair or skin
- Hair loss
- Menstrual disturbance
- Neck lump

History detailing

- Symptoms of thyroid overactivity?
- Symptoms of thyroid underactivity?
- Neck swelling or neck lump?

Hypothyroidism

- Is primary when the thyroid is damaged (high TSH, low/normal fT4)
- Is secondary when there is hypothalamic-pituitary damage (low fT4, low/normal or mildly elevated TSH)

If the patient is at risk of secondary hypothyroidism an fT4 level must be requested

Blood tests for:

- TSH, fT4
- Autoantibodies (TPO antibody) if considering an autoimmune cause
- 9am cortisol to confirm adequate level before commencing replacement if at risk of hypopituitarism (*see pituitary insufficiency section*)
- No need for imaging for hypothyroidism

Potential actions

Primary hypothyroidism

- Repeat TFT as thyroid disease may evolve if thyroiditis
- Consider levothyroxine replacement if clinical or subclinical hypothyroidism (TSH >7 with normal T4)
- Start with a low dose (50mcg)
- Primary hypothyroidism – titrate up to normalise TSH

Secondary hypothyroidism

- TSH is not a valid marker of thyroid status and should be ignored; titrate using fT4, aiming for middle of fT4 normal range
- Caution if at risk of cardiac dysfunction, eg prior anthracyclines or mediastinal radiotherapy

Hyperthyroidism

Blood tests for:

- TSH, fT4
- TSH-receptor antibody

Potential actions

- Consider repeating if investigations and clinical signs are suggestive of thyroiditis

Refer to secondary care for further investigations and antithyroid therapy

- May require beta blockade for symptom control

Secondary thyroid nodule/cancer surveillance

- Childhood/young adult cancer survivors who received mediastinal/neck radiotherapy should be advised to see their GP urgently if develop a neck mass
- For patients presenting with a new thyroid or neck mass refer urgently to neck or thyroid lump service as per local protocols
- Annual neck examination by palpation for patients who have undergone radiotherapy which may have treated the neck
- Use of thyroid ultrasound in surveillance is contentious Please seek local thyroid specialist advice' See ref **www.ighg.org/guidelines/topics/thyroid-cancer/recommendations**

Pregnancy and the thyroid

- Where preconception planning feasible, optimise thyroid function prior to a pregnancy
- If the patient becomes pregnant, manage levothyroxine replacement as for all patients with thyroid dysfunction in pregnancy

Refer early to appropriate antenatal/obstetric services

- Refer to cardiology if at risk of cardiac dysfunction, eg prior anthracyclines or mediastinal radiotherapy

Accompanying notes
Breast cancer screening is recommended for women over 25 who received mediastinal irradiation; refer to local breast screening services

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