ASSOCIATION OF BREAST SURGERY

Association of Breast Surgery Summary Statement

INVESTIGATION AND MANAGEMENT OF GYNAECOMASTIA IN PRIMARY & SECONDARY CARE

PURPOSE

These guidelines are for the assessment, referral, and investigation of men with breast symptoms consistent with gynaecomastia, and cover the process from primary care to the specialist clinics of the Breast Unit and Endocrinology. They take into account the *Best Practice Diagnostic Guidelines for Patients Presenting with Breast Symptoms* from 2010.

BACKGROUND

Gynaecomastia is the enlargement of the male breast due to hyperplasia of the glandular tissue driven by alterations in male oestrogen:testosterone ratios. Pseudogynaecomastia is bilateral breast enlargement entirely due to adipose tissue. It does not require investigation or treatment.

Male breast cancer accounts for about 0.6% of all breast cancer: there almost 400 cases annually in the UK (c.f. 55,000 in women).

Benign gynaecomastia can be secondary to multiple medical and recreational drugs, as well as many chronic medical conditions.

- **Physiological**
  1. Neonatal: due to placental oestrogen transfer
  2. Pubertal: pubertal oestrogen production begins prior to testosterone production due to early maturation of aromatase (catalyzes conversion of androgens to oestrogens). Regression occurs in 90% of cases
  3. Senile: Age 70+. Up to 65% of men. Due to the reduction in testosterone relative to oestrogen

- **Drug induced** – 10-20% of gynaecomastia is due to prescribed drugs
  1. Oestrogen containing drugs eg. Bicalutamide, Buserelin, Goserelin
  2. Androgen receptor blocking drugs e.g. Cyproterone acetate, spironolactone, flutamide
  3. Androgen production inhibiting e.g. Finasteride, ketoconazole, dutasteride
  4. A list of medications that can cause gynaecomastia can be found in Appendix A

- **Drug induced** – recreational drugs such as marijuana, amphetamines, heroin, methadone

- **Pathological**
  1. Adrenal or testicular tumours <3% of gynaecomastia
     a. Oestrogen or androgen producing tumours
     b. Aromatase producing tumours
     c. hCG producing tumours

  2. **Endocrine**
     a. Primary hypogonadism [10% of gynaecomastia]
     b. Secondary hypogonadism
     c. Prolactinoma

   d. Thyrotoxicosis
   e. Acromegaly
   f. Androgen insensitivity

3. Systemic illness
   a. Liver cirrhosis
   b. Renal failure
   c. Malnutrition
   d. Obesity
   e. HIV

INVESTIGATIONS RECOMMENDED TO BE DONE IN PRIMARY CARE

Before Referring

1. History to include:
   - Prescribed medications
   - Recreational drug use
   - Current and previous alcohol consumption

2. Chest wall examination – bilateral breasts

Do Not Investigate

- Adolescents with physiological pubertal gynaecomastia
- Elderly men with senile gynaecomastia
- Men with a drug related cause (prescribed medication or recreational drug use)
- Men with obvious breast cancer
- Men with fatty pseudogynaecomastia

Do Investigate

- Eccentric hard masses
- Rapid enlargement
- Recent onset in lean men >20 years
- Persistent painful gynaecomastia
- Massive gynaecomastia in adolescents
- Persistent gynaecomastia in adolescents, duration > 18-24 months

WHAT INVESTIGATIONS?

Blood tests

- 9am Testosterone, Thyroid Function Tests, Liver Function Tests, α-Fetoprotein, β-Human Chorionic Gonadotrophin
- If Testosterone is abnormal: Luteinizing Hormone, Follicle Stimulating Hormone, Sex Hormone Binding Gloubulin, albumin, oestradiol, prolactin
- Testicular Ultrasound Scan if any of the following abnormal blood results are noted: raised βHCG, raised α-Fetoprotein

GPs - WHEN AND WHERE TO REFER

Abnormal endocrine (hormonal) blood results

- Refer to Medical Endocrinology clinic

Abnormal βHCG or αFP blood results or abnormal finding on testicular USS

- Refer to Urology Clinic urgently

SUMMARY STATEMENT:
MANAGEMENT OF GYNAECOMASTIA IN PRIMARY & SECONDARY CARE

Referral directly to the Breast Unit

In the presence of the following clinical scenarios, a referral directly to the local breast unit may be considered.

1. Clinical suspicion of malignancy
    - >50 year old man with unilateral firm sub-areolar mass with or without nipple discharge or with associated skin change
    - Bloody nipple discharge
    - Unilateral ulceration of the nipple
    - Urgent referral is appropriate
2. Unilateral lump with
    - No obvious physiological or drug cause
    - Increased risk - family history
    - Genetic conditions e.g. Klinfelter's Syndrome
3. Persistent painful gynaecomastia (>6 months) with normal blood tests

GYNAECOMASTIA IN THE BREAST UNIT

Gynaecomastia does not require all aspects of triple assessment

1. History:
    - Drug history
    - Alcohol history
    - Recreational drug use
    - Steroid use
    - Family history

2. Clinical examination:
    - Chest, bilateral
    - Nodal areas: axillae and supraclavicular fossae

3. Imaging
    - Bilateral pseudogynaecomastia: No imaging
    - Bilateral gynaecomastia P2: No imaging
    - Unilateral lump <25 P2: No imaging
    - Unilateral lump <25 P3+: USS +/- mammogram

4. Pathology
    - Biopsy only if one or more of the following: P3+, M3+, U3+

HORMONAL TREATMENT

The patient must be informed that this treatment is off-licence. It is most effective for recent onset gynaecomastia, i.e. before gynaecomastia becomes fibrotic, and alleviates mastalgia, not always regression of the mass.

- Tamoxifen 10mg PO OD: 3-9 months.
- Anastrozole 1mg PO OD: 3 months.

SURGICAL REMOVAL

- Dependent on local CCG guidelines

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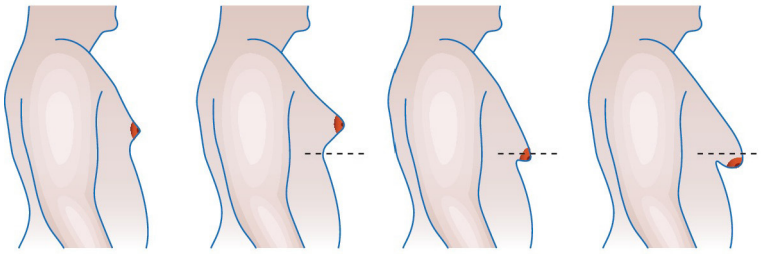
APPENDIX 1

Simon classification for gynaecomastia



Grade 1
Small enlargement, no skin excess

Grade 2a
Moderate enlargement, no excess skin

Grade 2b
Moderate enlargement, with extra skin

Grade 3
Marked enlargement, with extra skin

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APPENDIX 2

(taken from Thiruchelvam P, Walker JN, Rose K, Lewis J, Al-Mufti R. BMJ 2016;354:i4833)

DRUGS KNOWN TO CAUSE GYNAECOMASTIA	
Antiandrogens	bicalutamide, flutamide, finasteride, dutasteride (AA)
Antihypertensive	spironolactone (AA)
Antiretrovirals	protease inhibitors (saquinavir, indinavir, nelfinavir, ritonavir, lopinavir), reverse transcriptase inhibitors (stavudine, zidovudine, lamivudine) (UM)
Environmental exposures	phenothrin (antiparasitical)
Exogenous hormones	oestrogens (E), prednisone (male teenagers), human chorionic gonadotrophin (E)
Gastrointestinal drugs	H_2 histamine receptor blockers (cimetidine) (AA), proton pump inhibitors (eg, omeprazole) (AA)
Analgesics	opioid drugs (RA)
Antifungals	ketoconazole (prolonged oral use) (AA)
Antihypertensives	calcium channel blockers (amlodipine, diltiazem, felodipine, nifedipine, verapamil) (UM)
Antipsychotics (1st gen)	haloperidol (IP), olanzapine, paliperidone (high doses), risperidone (high doses), ziprasidone
Antiretrovirals	efavirenz (UM)
Chemotherapy drugs	methotrexate, alkylating agents–eg, cyclophosphamide, melphalan (AA); carmustine, etoposide, cytarabine, bleomycin, cisplatin (AA), vincristine (AA), procarbazine
Exogenous hormones	androgens (misuse by athletes) (E)
Cardiovascular drugs	phytoestrogens (soya based products, high quantity) (E)
Recreational/illicit drugs	marijuana, amphetamines (UM), heroin (UM), methadone (UM), alcohol
Herbals	lavender, tea tree oil, dong quai (female ginseng), Tribulus terrestris, soy protein (300mg/day), Urtica dioica (common nettle)

DRUGS RARELY CAUSING GYNAECOMASTIA

Amiodarone (um)
Aripiprazole, atorvastatin (um)
Captopril (um), cetirizine, clonidine, cyproterone acetate (ishbg)
Dasatinib, diazepam (ishbg), digoxin (e), domperidone, entecavir, fenofibrate (um)
Fluoxetine (um)
Gabapentin (aa)
Imatinib (aa)
Lisinopril, loratadine (aa)
Metronidazole (aa), misoprostol (um)
Paroxetine (um), penicillamine (aa), phthalates (um), pravastatin (um), pregabalin (aa)
Ranitidine (aa), rosuvastatin (um)|
Sulindac, sulpiride, sunitinib (um)
Theophylline (um)
Venlafaxine (um)

Codes	AA	Antiandrogenic
	RA	Reduced androgens
	E	Oestrogenic
	IAM	Increased androgen metabolism
	ISHBG	Increased concentration of sex hormone binding globulin
	IP	Increased prolactin
	UM	Unknown mechanism