

BARTS ENDOCRINE E-PROTOCOLS REPRODUCTIVE ENDOCRINOLOGY

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FEMALE REPRODUCTIVE ENDOCRINOLOGY

SCREENING FOR OVULATION

INDICATION

To confirm ovulation in a woman with menstrual periods who presents with infertility.

[LH and FSH rise for approximately 48 hours ("surge") at the onset of the ovulatory phase.

Progesterone production rises in the ovulatory phase to maximum during the luteal phase.]

CONTRAINDICATIONS

None specific

PRECAUTIONS

Test not feasible in a patient without a menstrual cycle

PREPARATION

Confirm menstruation. Exclude other causes of infertility (hyperprolactinaemia, chromosomal problems, thyroid dysfunction, PCOS, premature ovarian failure and structural /gynaecological causes).

PROCEDURE

Blood sample on day 21 of the cycle for progesterone. As cycle length sometimes variable, better to take blood on days 18, 21 and 24 (mark day of cycle on form).

INTERPRETATION

Progesterone >30 nmol/l between days 18 -24 = adequate luteal phase that cycle.

SENSITIVITY AND SPECIFICITY

Sensitivity 86% and specificity 83%

REFERENCES

Sverdloff R.S. et al., Endo. Metab. Clin. N. Amer. 17, 301-332 (1988).

Jordon J. Et al., Fertil Steril.62:54-62 (1994)

The Practice Committee of the American Society of Reproductive Medicine. Fertil. Steril. 82, s1 (2004)

PROGESTERONE CHALLENGE

INDICATION

To induce bleeding in amenorrhoea and to differentiate between causes of amenorrhoea.

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Authors: MD, CS, SLC, ABG

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CONTRAINDICATIONS

Patients with previous reactions to progestogens

PRECAUTIONS

Exclude pregnancy as cause of amenorrhoea

PREPARATION

None specific

PROCEDURE

Medroxyprogesterone acetate 10 mg po daily for 5 - 10 days (depending on response)

INTERPRETATION

1) If patient has bleeding within one week of stopping progesterone, then she has:

sufficient oestrogen to stimulate endometrial growth and normal outflow tract

These women are at risk for endometrial hyperplasia from unopposed estrogen.

Treat with cyclic progesterone (≥ 4 times per year), or COCP if preferred.

2) If patient has no bleeding, then she has: Oestrogen deficiency (ovarian failure or hypogonadotrophic hypogonadism) or outflow tract obstruction. COCP can be used to induce menstruation if no outflow obstruction and no contraindication. Consider US/S pelvis if anovulatory state is longstanding to rule out significant hyperplasia.

SENSITIVITY AND SPECIFICITY

Progesterone challenge test in patients with endometrial pathology for detection of endometrial proliferation activity: sensitivity 76%, specificity 100%

REFERENCES

Macia M et al, Int.J.Gyn.Obs. 1993 Feb:40(2):145-9

CLOMIPHENE TEST

INDICATION

Demonstration of the capacity for ovulation to be induced in a woman with anovulation.

CONTRAINDICATIONS

Pregnancy

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Do not carry out test if body weight <50kg

PRECAUTIONS

Arrange by fertility clinic to enable follicle tracking by ultrasound

Rarely causes abdominal bloating. Small risk of multiple pregnancy.

Rarely, ovarian hyperstimulation with cardiovascular collapse, ascites and pleural effusions.

PREPARATION

Explain timing: first day of period = day 0). Women without cycles start test at arbitrary time.

PROCEDURE

Start clomiphene on day 0 of cycle and give 2-3mg/kg in divided doses (reasonable start dose is 50mg tds).

Take bloods at D0, D4, D7 and D10

measuring LH, FSH, progesterone and oestradiol and follicle tracking.

If the test is unsuccessful over 2 cycles, repeat using higher doses of clomiphene

INTERPRETATION

LH and FSH rise, probably as a consequence of an anti-oestrogen stimulating GnRH.

This leads to follicular maturation, oestrogen production, LH release, and ovulation.

Positive result:

- rise in LH (to >20 U/l).
- rise in FSH (to >10 U/l).
- rise in progesterone to >30 nmol/l.

SENSITIVITY AND SPECIFICITY

Poorly defined. Note: Within a general infertile population, abnormal CCT were found in 3% of women younger than 30, 7% in women aged 30-34, 10% in women aged 35-39 and 26% aged 40 or older. An abnormal test predicts lower pregnancy rate with conception rate in 43% of women with normal results and 9% in those with abnormal results.

REFERENCE

Sverdloff R.S. et al., Endo. Metab. Clin N. Amer. 17, 301-332 (1988).

Scott Rt et al., Obstet Gynecol. 1993 Oct;82(4Pt1):539-44

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POLYCYSTIC OVARIAN SYNDROME

DIAGNOSIS

Variable criteria from different sources

Need a pattern rather than a single diagnostic test

NIH–NICHD criteria: Both hyperandrogenism and chronic anovulation

Rotterdam criteria: Two of the following conditions: hyperandrogenism; chronic anovulation; polycystic ovaries on ultrasound

Androgen Excess Society criteria: Hyperandrogenism and ovarian dysfunction (including infrequent or irregular ovulation or anovulation) and/or polycystic ovaries.

CLINICAL FEATURES TO RECORD

Menarche

Thelarche

Adrenarche

Current / previous menstrual cycles – range of cycle length and duration of bleeding

Current and previous menstrual cycle / range of duration of bleeding and range of interval from first day of bleed to first day of the next.

Onset, progression and location of hirsutism

Measures used to remove hair and frequency

Greasy skin and acne

Fertility history

Temporal recession / clitoromegaly (virilisation signs)

BIOCHEMICAL SUPPORTING EVIDENCE

Raised LH:FSH ratio, elevated androgens, mildly elevated prolactin, low SHBG Exclude significant hyperprolactinemia, non-classical congenital adrenal hyperplasia (SST with 17-OHP), thyroid dysfunction, androgen-secreting tumours, Cushing's syndrome first (LDDST with androgens) and consider acromegaly

TREATMENT

There is no curative treatment

Identify the most troublesome symptom(s) to manage

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1) HYPERANDROGENAEMIA

(HIRSUTISM, ALOPECIA, ACNE)

Oral contraceptive pill

Dianette anti-androgenic because: increases SHBG, competes for 5-alpha -reductase and decreases adrenal androgen production. (In contrast, OCP's with levonorgestrel are androgenic)

Indications: Desire for regular bleeds

Contraindications: Obesity, thromboembolic disease, history of breast cancer, smoker

Antiandrogens

Cyproterone acetate (50mg day 1-10 of cycle), spironolactone, flutamide, finasteride.

Potentially teratogenic, use with reliable contraception.

Vaniqa cream

Apply to face. Slow to take effect (up to 4 months). May cause local irritation.

Skin laser therapy

Best for dark hair on fair skin. Rarely available via NHS (try Royal Free hospital)

Regaine (minoxidil)

Effective for androgenic alopecia but effects wear off if stopped.

Available over the counter (2% solution), not NHS.

2) OLIGOMENORRHOEA

Oral contraceptive pill

See notes above

Metformin

Moderately effective at restoring cycles.

Intermittent progestagens

Medroxyprogesterone acetate 10 mg od for 5-10 days, 3-4 times per year.

3) SUBFERTILITY

Full assessment of patient and partner to identify all contributing factor

Metformin

Moderately effective in restoring ovulatory cycles, but the live birth rate compared to clomiphene is poor. Not licensed for PCOS.

Clomiphene citrate

Via fertility unit for follicle tracking.

Outcomes better than metformin in obtaining conception and live births in most, but not all, head-to-head trials.

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Prednisolone in reversed circadian rhythm

2.5mg on rising and 5mg on retiring will effectively suppress ACTH and hence ACTH-dependent androgens. This prednisolone should not be enteric-coated as it is poorly and variably absorbed and may not cause adequate suppression.

May work when all else fails but note that patients becomes steroid-dependent and will need the usual counselling regarding steroid card, sick day rules etc (see adrenal protocols).

The treatment is usually associated with a return of menstrual cyclicity. Acne often improves but prednisolone alone improves hirsutism in only 25%.

4) METABOLIC DYSFUNCTION

Document BMI and advise accordingly

Screen for type 2 Diabetes and check lipid profile

Estimate insulin resistance using HOMA-IR model:

$\frac{\text{Fasting glucose (mmol/L)} \times \text{Fasting Insulin } (\mu\text{U/ml})}{22.5} = \text{IR}$

IR > 2.5 suggestive of insulin resistance

Difficult to use this model for estimation in several circumstances including puberty

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FEMALE HRT

INDICATIONS

Absence of ovarian function (eg Turner's syndrome etc)

Premature ovarian failure (autoimmune, iatrogenic ,idiopathic etc)

Secondary ovarian failure (hypogonadotropic hypogonadism, pituitary disease)

Relief of severe menopausal symptoms

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CONTRAINDICATIONS

Oestrogen-driven malignancy
Genetic cancer prone syndrome with
History of thromboembolic disease

PRECAUTIONS

Oestrogen treatment can lead to nausea, headaches, breast tenderness, weight gain and hypertension – these may be avoided by changing the preparation type

There is an increased risk of thromboembolic disease and breast cancer depending on dose, preparation and circumstances under which the replacement is prescribed

Aim to stop after 7-10 years post natural time of menopause

PRINCIPLES AND PREPARATIONS

- The ovary makes oestrogen, progesterone and some testosterone.
- HRT describes oestrogen replacement in women whose own oestrogen levels are low
- Progesterone must be given to all women receiving oestrogen who have a uterus – oestrogen alone can cause endometrial cancer and this is prevented by progesterone administration
- The principle of administration of HRT is for oestrogen to be administered continuously; progesterone can be given through part of the cycle, the removal of progesterone leading to a withdrawal bleed. Alternatively progesterone can be given (in older women) continuously for 'period-free' HRT ('Continuous combined HRT.')
- The combination of oestrogen and progesterone may be pre-ordained within the preparation or 'bespoke' by prescribing the two hormones separately. Familiarise yourself with the available combinations but be aware of the types and doses of the component hormones which they contain and the cyclical dose variation
- Oestrogens vary by source, by route of administration and by potency
- Progestogens vary by source and chemical structure (first / second / third generation), by route of administration, thrombogenic potential and androgenic quality
- Tibolone (Livial) is a synthetic steroid with oestrogenic, progestational and androgenic properties, first marketed in 1991 for post-menopausal vasomotor symptoms. Tibolone is now also licensed for the prevention of osteoporosis - however, at present, there are no data on whether tibolone prevents fractures. You may wish to use this first line for HRT in post-menopausal women as it is free of withdrawal bleeds and particularly as the risk of thromboembolism may be lower than traditional HRT. There may be an increased stroke risk

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especially if there are other prior risk factors in which case avoid. RCT by Cummings SR et al also suggestive of reduction in breast cancer (although there may be a small increase in endometrial cancer)

REFERENCES

Cummings SR et al. The effects of tibolone in older postmenopausal women. N Engl J Med. 2008 Aug 14;359(7):697-78.

Oestrogen subtypes

Type	Route	Dose equivalence
Conjugated equine oestrogen	oral	0.625mg standard (1.25mg available)
Oestradiol valerate	oral	2mg standard (1mg and 4mg also available)
Oestrogen patch	transdermal	50mcg is equivalent (doses of 25-100mcg per 24h available)
Synthetic oestrogens eg Ethinyl oestradiol (in COCP) Greater effect on liver function	oral	20mcg is equivalent to above Most COCP contain 30mcg Some COCP contain more
Oestrogen implants	Subcut implant	Dose as BNF
Local oestrogen	vaginal	Dose not absorbed systemically Application in gel / on pessary for local symptom relief only

Progesterone subtypes

Type	Examples	Dose equivalence / Notes
First generation	Norethindrone acetate Ethinodiol diacetate MPA	Less androgenic than 1 st gen; more than 3 rd gen Oral or im. Oral doses 2.5-10mg for days 1-10
Second generation	Levonorgestrel Norgestrel Norethisterone	Dose 1-2.5mg pper day for part of cycle
Third generation (thrombogenic)	Desogestrel Norgestimate Gestodene	Less androgenic, less metabolic impact Less androgenic

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MALE REPRODUCTIVE ENDOCRINOLOGY

SEMEN ANALYSIS

Parameter	Normal Value
Volume	>2.0ml
Viscosity	Normal
Morphology	'Normal' (no strict criteria for this)
pH	7.2-8.1
Sperm concentration (million/ml)	>20
Motility	Total >50%, >25% rapid progressive
Vitality (% live/% dead)	>50%
MAR IgG (direct sperm antibody)	Negative
Nucleated / round cells (million/ml)	<1
Leucocytes per μ l	<25-75

HUMAN CHORIONIC GONADOTROPHIN TEST (hCG stimulation)

INDICATIONS

Differential diagnosis of male hypogonadism, looking at Leydig cell function.

CONTRAINDICATIONS / PRECAUTIONS

None

PROCEDURE

hCG 2000 units IM on days 0 and 2 / Paediatric dose < 2 years, 1000 units daily for 3 days. Samples for testosterone on days 0, 2 and 4.

INTERPRETATION

Normal response is for testosterone to rise to outside the normal range. This shows that a testis is present, which may be intraabdominal if none palpable.

In gonadotrophin deficiency, without primary testicular abnormality, the low basal testosterone value should triple after hCG.

SENSITIVITY AND SPECIFICITY

Most studies done in children so the values would not apply to our patients

REFERENCES

Tzvetkova P et al., Systems Biol Reprod Med. Jan 1997;39:163-71

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TESTOSTERONE REPLACEMENT

Testosterone therapy is used for male patients with hypogonadism. Therapy is usually started when the serum testosterone level is less than 9 nmol/l (normal range: 9-35 nmol/l). However, meta-analyses have shown positive results in some patients with a serum testosterone <12 nmol/L (the 'grey zone')

There are a number of preparations that are available for use. These include testosterone injection, implant, oral tablets and transdermal patches.

General side effects include prostatic disorders, gynaecomastia, mood disorders, hypertension, dizziness and changes to laboratory tests (polycythaemia and lipid changes).

Careful and regular monitoring of the prostate gland and breast must be performed at least once yearly and twice yearly in elderly patients and at-risk (with clinical and familial factors).

Prior to testosterone initiation, all patients must undergo a detailed examination in order to exclude a risk of pre-existing prostate cancer (do not prescribe if total serum PSA > 4 ng/ml). Contraindications include:

- Cancer patients at risk of hypercalcaemia due to bone metastases.
- Hypertension (relative contraindication only)
- Epilepsy
- Migraine

Testosterone injection (Sustanon and testosterone enanthate)

Injection intramuscularly 2-4 weekly.

Variable testosterone levels which may be clinically apparent. Aim to keep peak (7 days after injection) and trough (prior to next injection) within the reference range. NB Arachis oil excipient – relevant for patients with peanut allergy

Long-acting testosterone formulation for injection (nebido)

By deep intramuscular injection

Initial injection 1g then second injection after 6 weeks for more rapid achievement of steady state.

Injections thereafter every 10-14 weeks dictated by serum testosterone and clinical status

Testosterone implants (pellets implanted every 6 months)

Insertion by trained individual. Pellets may be extruded after insertion.

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Oral testosterone undecanoate

Short half life therefore tds administration

Erratic testosterone levels (monitor DHT rather than testosterone)

Disproportionately high DHT levels (theoretically greater risk of polycythaemia and raised PSA)

Transdermal patches (andropatch)

Stable levels but high incidence of skin irritation and may be fiddly to use

Testogel and Testim (and tostran)

Transdermal testosterone gel applied to skin.

Well tolerated although sachets fiddly and instructions to wait before showering.

50mg of testosterone applied once daily. Maximum of 100mg per day can be used. Only 9-14% of the dose is bioavailable and therefore 50mg/day gel will deliver 5mg/day testosterone.

The patient himself should administer the application, onto clean, dry, healthy skin over both shoulders or both arms or abdomen.

These gels can be transferred to other persons by close skin to skin contact, resulting in increased testosterone serum levels and possible adverse effects. The doctor must inform the patient carefully about the risk of testosterone transfer and about safety instructions as set out in the Summary of Product Characteristics (SPC). Testim comes in a more convenient 'tube' packaging but has a distinctive odour.

Tostran available in metred-dose delivery bottle and higher concentration (therefore smaller volume of application)

FERTILITY INDUCTION IN HYPOGONADOTROPHIC HYPOGONADISM

INDICATION

Induction of spermatogenesis in patients with hypogonadotrophic hypogonadism, by replacing LH and FSH

CONTRAINDICATIONS

Untreated cause of infertility in partner

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PRECAUTIONS

Discontinue testosterone replacement

Couples must be warned that medical therapy can take months to years to reach maximal effect and so must be counselled about other options [assisted reproduction /adoption.]

PROCEDURE (Variants of regime in use: discuss with individual consultant)

- Document testosterone level and sperm count at outset
- Prescribe hCG (Pregnyl) 1500iu subcutaneously twice per week for 6 months. hCG has the action of pituitary LH. LH stimulates the Leydig cells to make testosterone. If levels exceed the upper limit of normal (30nmol/l), the dose can be halved. .
- Different sperm induction regimes are in current use: discuss with individual consultant.
- One option is to prescribe 6 months of LH action (via Pregnyl) alone, adding in FSH only if sperm count still < 10 million / ml after 6 months.
- After 6 months prescribe Menopur 150 units subcutaneously three times a week. Menopur contains 75u LH and 75u FSH. The aim of this is for the FSH component to hopefully induce spermatogenesis. The LH component of Menopur is not an issue in sperm induction and therefore, no adjustment of the Pregnyl dose is necessary
- Some consultants prefer to prescribe FSH concurrently with LH from the outset of therapy.
- If FSH action inactive at a dose of 150 units subcutaneously 3 times a week, increase to 300 units three times a week (some consultants prescribe 300 units three times a week as the starting dose)
- For FSH action, an alternative to menopur is follitropin-alfa or Gonal-F. This may be more readily available although is more expensive. The dose is equivalent.
- Check testosterone levels and semen analysis at 3 months and 6 months after starting therapy. The dose of both Pregnyl and Menopur can be halved if testosterone levels exceed 30nmol/l.
- Note that patients (especially with acquired diseases like NFPA) get pregnant very early on in this regimen (ie with very poor sperm counts).
- If successful induction of spermatogenesis occurs consider sperm freezing at 6 months.
- The maximal duration of treatment is debated although on average conception occurs 2-3 years of gonadotrophin therapy and therapy should probably not be further continued.
- Preparations of high-purity synthetic FSH are available, but these are needed for stimulation of follicles in females, where LH will of course cause problems. These high-purity preparations are more expensive, and are not required in males, where LH is given anyway, provided that menopur is available

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