Basic treatments/options including ovulation induction & Intra uterine Insemination

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Aims of this talk

- To discuss the basic treatment options available
- To discuss the efficacy and potential complications of these treatments

Evaluation & investigation

- Detailed medical/ surgical history to incorporate 'life-style' issues
- Physical examination including BMI
- Access to timely and comprehensive investigation
- Diagnose and access to appropriate treatment

Other factors

- The duration of the infertility
- The age of the female partner
- 'Life-style' of the couple
- Criteria for NHS treatment

'Fit to Fertile'

Female:	Folic acid	Male: Loose underwear
	BMI < 30	Avoid hot baths
	Alcohol	Weight
	Smoking	Smoking
	Diet	Alcohol
	Exercise	Diet
	Caffeine	Exercise
		Caffeine

Basic treatments

- Expectant management
- Weight loss
- Oral preparations to induce ovulation
- Natural cycle IUI
- IUI with super-ovulation

Expectant Management

- Education and support of the couple
- Reassurance that no disease/ abnormality detected
- Use of ovulation predictor kits/ follicular monitoring during natural cycle

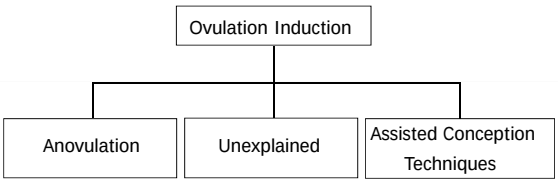
Ovarian stimulation/ovulation induction

'Not an exact science ……..'

'safe, cheap, consistently effective ovulation induction'

(Emmet J. Lamb 1965)

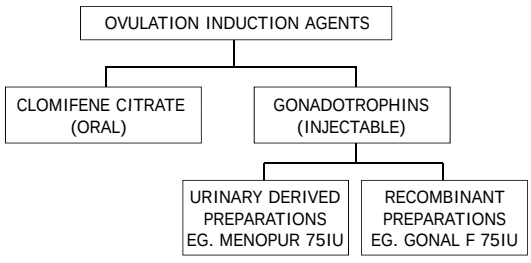
Indications for Ovarian Stimulation



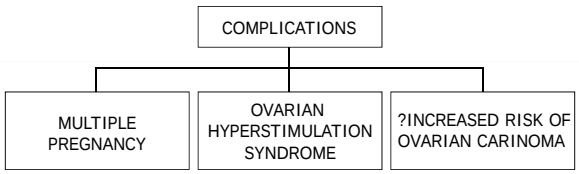
The Challenges

- Effective fertility drugs for precise control over ovarian stimulation
- Tailoring treatments to meet individual needs
- Reducing risk of Multiple pregnancy
- Reducing risk of OHSS
- Poor Responders
- PCOS
- Cost

Ovarian Stimulation



Ovarian Stimulation



Oral preparations

- Clomifene citrate
- Metformin
- Tamoxifen
- Aromatase inhibitor eg: Letrozole

Incidence and classification of Anovulation

- Anovulation accounts for about 21% of female fertility problems
- Management should be directed at determining diagnosis, excluding other fertility problems and initiating ovulation induction therapies
- Aims to achieve repeated uni-follicular ovulation in order to achieve a singleton birth

Incidence and Classification

- WHO Group I/ Hypothalamic or pituitary: Hypogonadotrophic hypogonadism/ Hyperprolactinaemia
- WHO Group II/ PCO
- WHO Group III/ Premature ovarian failure

Polycystic Ovarian Syndrome

- Definition: Presence of 2 out of 3 criteria
  - Oligo- and/ or anovulation
  - Hyperandrogenism (clinical or biochemical)
  - Polycystic ovaries on ultrasound

AFTER EXCLUSION OF OTHER CAUSES

Polycystic Ovarian Syndrome

- High frequency in families suggests an important genetic factor
- Diet has a profound effect of symptoms of PCOS
- Women with PCOS who are obese have an increased risk of insulin resistance, impaired GTT, Type 2 diabetes (assess glucose tolerance in women with PCOS and BMI > 29)

Polycystic Ovarian Syndrome

- Women with BMI > 29 take longer to conceive
- In anovulatory women with BMI > 29, weight loss increases chance of conception (diet and exercise)
- Results of fertility intervention affected by BMI
- High BMI adversely affects pregnancy outcome (increased risk of miscarriage)

Metformin

- Should be used prior to ovulation induction agents

(improvement of ovarian function is rapid due to reduction in circulating androstenedione)

- First line management for the patient with PCOS no benefit in patients with PCO alone

Metformin

- Reduces risk of miscarriage
- Extensive evidence available to support use in all PCOS patients undergoing any form of ovulation induction and controlled ovarian stimulation for ART
- Reduces risk of OHSS
- Higher pregnancy rates

'The use of metformin for women with PCOS undergoing IVF treatment.' Human Reprod. 2006 June (Tang T, Glanville J, Orsi N, Barth JH, Balen, AH.)

Clomifene Citrate

- First clinical trials 1961
- Effective first line choice for WHO classified type II ovulatory failure

'Oral anti-oestrogens and medical adjuncts for sub-fertility associated with anovulation.' Cochrane Database Syst Rev. Jan 2005 (Beck JI, Boothroyd C, Proctor M, Farquhar C, Hughes E.)

- No benefit for ovulatory patients, may reduce chance of pregnancy

(N.I.C.E 2004)

Therefore not recommended for the treatment of Unexplained Fertility

- Ultra-sound monitoring

(N.I.C.E 2004)

Clomifene Citrate

- Induces ovulation in 70-85% of patients, with 40-50% conception rate (The ESHRE Capri workshop 1997)
- Counsel patients regarding the risk of OHSS and multiple pregnancy
- Commence therapy with 50 mgms day 2-6 of spontaneous or withdrawal bleed
- Monitor all cycles with ultrasound
- Discontinue therapy if anovulatory after increasing dose to 150mgms
- Maximum 9-12 cycles of therapy

Tamoxifen

- Equally as effective as Clomifene citrate, suitable alternative

'Comparison of tamoxifen andv clomifene citrate for ovulation induction: a meta-analysis.' Human Reprod. June 2005 (Steiner AZ, Terplan M, Paulson RJ.)

- Alternative to Clomifene citrate resistant patients and those patients that suffer side-effects
- Unlicensed

Aromatase Inhibitors (Letrozole)

- Predicted to become 'the Gold Standard' for ovulation induction
- Decrease in multifollicular development
- Higher pregnancy rate & lower multiple pregnancy rate
- Combined with gonadotrophin in ART, reduced dosage of FSH

'Review: aromatase inhibitors for ovulation induction.'Clin Edocrinol Metab. March 2006 (Casper RF, Mitwally MF.)

More research required

'the greatest hazard of gonadotrophin therapy appears to be the unpredictable sensitivity or if you will overdosage'

(Emmett J. Lamb 1965)

Gonadotrophin Therapy

hMG / Recombinant-derived FSH and LH

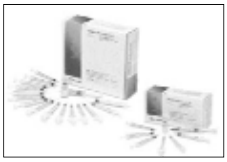
Reduction in the overall therapy cost per baby born in favour of r-FSH v's HP-uFSH in ovulation induction

'r-FSH v's Hp-uFSH in ovulation induction: a prospective, randomised study with cost-minimization analysis.' Reprod Biol Endocrinol. July 2006 (Revelli A, Poso F, Gebbarelli G, Moffa F, Grassi G, Massobrio M.)

Advances

Prefilled pens

Multi-dose system



Gonadotrophin Therapy

Dose Considerations:

- Indication for treatment
- Type of Treatment
- Age of patient
- Baseline FSH
- Cost Implications

Ovarian Stimulation

- Mono/bi-follicular Ovulation Induction
- Super Ovulation Induction
- Controlled Ovarian Stimulation

Intra Uterine Insemination

Rationale:

The introduction of good quality sperm into the uterine cavity 'just' prior to ovulation

Natural cycle IUI

- Promoted as good practice by NICE for treatment of Unexplained infertility
- Efficacy of treatment?

Evidence to suggest no benefit without the use of gonado

trophins

(Hughes EG. The effectiveness of ovulation induction and IUI in the treatment of persistant infertility: a meta-analysis. Human Reproduction 1197 Sept; 13:1865-72)

Super-ovulation +/- IUI

- Aim for mono/bi-follicular stimulation
- Most patients treated easily with 'standard protocol'
- PCOS the 'real challenge'

Super ovulation Induction Regimes

- Standard Protocol
- 'Step-up' low dose Protocol.

(Polson *et al.* 1987; Hamilton-Farley *et al.* 1991; Frands and Hamilton-Farley 1996; White *et al.* 1996)

- 'Step-down' Protocol.

(van Santbrink *et al.* 1995)

- Low dose Protocol with GnRH agonist

'Step-up' protocol using r-FSH more efficient in obtaining monofollicular development and ovulation than 'step-down' protocol

(Christin-Maitre S, Hughes JN; Recombinant FSH Study Group) Hum Reprod. Aug 2003

Super ovulation with IUI

- Patient selection!
- Assess eligibility for NHS treatment
- Treatment implications counselling
- HFEA consent to disclosure
- Assessment of the 'Welfare of the child'

Super ovulation with IUI

- NICE guidelines
- HFEA licensed treatment since 2007
- Conception rate per cycle 15-18%, twin pregnancy rate 10-20%, risk of triplets < 1%
- Ultrasound monitoring of all cycles
- Cancel treatment if more than 3 dominant follicles (14mm)
- Trigger ovulation when follicular diameter at least 18mm
- Insemination of 'washed' highly concentrated sample of motile sperm introduced into the uterine cavity
- Progesterone support in luteal phase?

Complications of ovarian stimulation

- OHSS
- Multiple pregnancy
- Poor response or failure to respond

O.H.S.S.

- Iatrogenic
- Incidence: mild to moderate 10%, severe 0.5-1%

Risk factors:

- Young
- PCOS
- Large number of oocytes
- High estradiol levels
- Conception cycles
- Multiple pregnancy

The Prevention

- Identification of high risk patients eg PCOS
- Care with high risk patients
- Protocols for treatment
- Ultrasound monitoring of all ovulation induction/ stimulation cycles

Poor Responders

Poor responders more of a clinical challenge than OHSS?

- Questions to ask:

How to accurately identify patients prior to any treatment?

Which is the best treatment regime to optomise ovarian response and increased clinical pregnancy rate?

Predicting Ovarian Reserve

Indicators:

- Older patient
- Previous poor response
- Basal FSH
- Inhibin B
- Anti-mullerian hormone

'Inhibin B and anti-mullerian hormone: markers of ovarian response in IVF/ICSI patients?' BJOG. Nov 2004 (Muttukrishna S, Suharjono H, Mc Garrigle H, Sathanandan M.)

Predicting ovarian reserve

- Dynamic Clomid challenge test

'The clomiphene citrate challenge test for the prediction of poor ovarian response and non-pregnancy in patients undergoing IVF.' Fertil Steril. Sep 2006 (Hendricks DJ, Mol BW, Bancsi LF, Te Velde ER, Broekmans FJ.)

- Antral follicle count

'Antral follicle count in the prediction of poor ovarian response and pregnancy after IVF.' Fertil steril. Feb 2005 (Hendricks DJ, Mol BW, Bancsi LF, Te Velde ER, Broekmans FJ.)

- Doppler studies of ovarian stromal blood flow

'Relationship of ovarian blood flow at the baseline ultrasound scan to subsequent follicular response in an IVF program.' Obstet Gynaecol. Nov 1996. (Zaidi J, Barber J, Ktei-Mensah A, Bekir J, Campbell S, Tan SL.)

Poor Responders

- Clear from all research studies, no single test will be able to accurately predict all the patients who will fail to respond to ovarian stimulation, and even utilising multiple tests we will still experience unexpectedly poor response to therapies to induce ovarian stimulation and ovulation induction.

Summary

Although we refer to these treatment options as basic, it is important to remember that the 'basic' principle we want to achieve is, access to 'safe and evidence-based' investigation, diagnosis and treatment of the sub-fertile couple with the intention of the safe delivery a healthy live baby.

Thank you