The IVF problem patient: pre-existing diseases in infertile patients

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The IVF patient with medical problems
Questions to answer

• Is IVF safe?
• Is pregnancy safe?
  – For the mother?
  – For the child?
• Will the disorder reduce chance of pregnancy?

Common health disorders of young women leading to subfertility

• Cancer and late effects
• Endocrinopathies
  – Diabetes
  – Thyroid disorders
• Thrombophilias
• Autoimmune disorders
• Renal failure
• Obesity
Late Effects of cancer treatment

- 1:950 people aged 16 - 35 is a long term cancer survivor
- Improving survival rates are increasing this number every year
- Multi disciplinary approach to cover wide variety of complications of treatment
  - Cardiovascular/ CNS
  - Late recurrence/ second primary cancer
  - Reproductive health

Medical aspects of ‘late effects’

- 4% (6x background risk) develop secondary malignancy, up to 25 years post treatment
- Common second malignancies include osteosarcoma & leukaemias
- Mostly a consequence of older regimes of treatment
- Effects of therapy
  - Anthracyclines on CVS
  - Mediastinal damage from radiation/ BMT
  - Renal effects of chemotherapy
  - Growth failure/ precocious puberty
  - Endocrinopathies including thyrox/ adrenal/ leptin and bone effects
  - GVH disease after transplant

Chemotherapy

Risk of gonadal damage according to treatment used

- High risk
  - Cyclophosphamide
  - Ifosfamide
  - Chlorambucil
  - Melphalan
  - Busulfan
  - Nitrogen mustard
  - Procarbazine
  - Nitrosoureas

- Moderate risk
  - Cisplatinum
  - Adriamycin
  - Actinomycin

- Low risk
  - Methotrexate
  - Vincristine
  - Vindesine
  - Bleomycin
Radiotherapy

- Effect determined by dose and fractionation
- **Males**
  - Permanent azoospermia in most males treated with > 4Gy
  - Effects on testosterone production less pronounced
- **Females**
  - Primordial follicles are radiosensitive - risks of POF increase with dose
  - Uterine effects include loss of elasticity, reduction in blood flow and failure of endometrial growth

Fertility after cancer treatment

- Will fertility be affected?
- Can we preserve fertility before cancer treatment?
- Will fertility recover after cancer treatment?

Will fertility be affected?

- Incidence of permanent ovarian failure after cyclophosphamide chemotherapy
  - Age <20: 13%
  - Age 20-30: 50%
  - Age >30: 100%
- Rates will be higher after high dose ‘rescue’ chemotherapy, after pelvic radiotherapy or after conditioning chemotherapy pre-stem cell transplant
- Newer chemotherapy regimes for most breast cancers are less gonadotoxic (e.g. ABVD - adriamycin, bleomycin, vinblastine, dacarbazine)

Presli et al, 2004
Likelihood of preserving natural fertility?

- Depends on treatment given and age at treatment
- Even patients treated with high dose chemo/radiotherapy occasionally maintain gameteogenesis and fertility
- Possibility of late resumption of ovulation

Storing fertility

- Cryopreservation of
  - Embryos
  - Gametes
  - Ovarian tissue

Possible drawbacks to superovulation in young women with cancer

- Delay in initiating cancer treatment
  - GnRH antagonist controlled superovulation
- Risk of elevation of oestradiol concentration
  - Most breast cancers in young women are ER positive
  - Aromatase inhibitors
  - Tamoxifen
  - Low dose FSH
  - Is transient elevation of plasma oestradiol concentration harmful?

Casper 2004, Oktay 2003
Pregnancy after cancer treatment

- Children born from cryopreserved embryos appear healthy
- Low chance of long term damage to uterine function after chemotherapy
- Severe effects of abdominal radiotherapy
  - Miscarriage
  - Premature birth
  - Low birthweight
  - Effect is maximal if given pre-pubertally
- Risk of long term damage to DNA after chemo- or radiotherapy - unknown

Common endocrinopathies

Diabetes mellitus

- Women with type 1 diabetes are less fertile and offspring have increased risk of congenital malformation (6.9%)
- Tight pre-IVF control of blood glucose can reduce risk of malformation and normalise response to gonadotropins
  - Metformin
  - Insulin
- Single embryo transfer to reduce risk of pregnancy complications
- Close liaison with diabetic physician and specialist obstetrician

Thyroid disorders

- Androgen & estrogen metabolism are altered by thyroid hormone deficiency and excess
- Frequent chronic anovulation
- Also subfertility in cycling women with thyrotoxicosis
- Restoration of normal thyroid function (or adequate replacement) is mandatory before pregnancy
- Patients on adequate thyroxine replacement respond normally to gonadotropins
- Careful follow up during pregnancy

Laven 2005

Connective tissue disorders

Systemic lupus erythematosus

- Chronic inflammatory multisystem disorder
- May affect 1.5% of women
- Multiple immunologic abnormalities
- Remission/ exacerbation
- Hypertension, renal and skin manifestations
- Alkylating immunosuppressants, NSAIDs, antimalarials, glucocorticoids
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- Offer IVF if
  - Normal creatinine
  - Normal BP
  - Remission for 12 months
- Superovulation may induce flare in symptoms
- Pregnancy complications
  - Placental infarction/pre-eclampsia
  - Fetal death, prematurity
  - Fetal abnormality, neonatal lupus, heart block

Guballa 2000, Huong 2003

Thrombo-embolic disorders

- History of DVT/PE pre-IVF
- Thrombophilia diagnosed during investigation of recurrent miscarriage/subfertility
- Family history
- Smokers
- Hyperhomocysteinemia
- Superovulation with raised plasma oestrogens may produce a hypercoagulable state although studies during IVF are reassuring
- Significant activation of clotting cascade after hCG, worsened by OHSS

Coagulopathy in OHSS

- 0.8% OHSS cases develop VTE
- Arterial and venous thrombotic complications
  - CVA
  - Myocardial infarction
  - Death
- Low dose gonadotropins & modest target for superovulation
- Coasting, cycle cancellation, ‘freeze all’ if over response
- Aspirin, low MW heparin, compression stockings
- Adequate but not over hydration

Macklon 2005

Renal failure and infertility

- Anovulation common in chronic renal failure
- Restoration of normal cycles is often seen after transplantation
- No increase in abnormalities after exposure to cyclosporin from conception
- Some (reassuring) data for tacrolimus and Neoral

US National Transplant Pregnancy Register, 1997

IVF in the renal transplant patient

- Offer IVF if
  - stable transplant with normal serum creatinine (1.4mg/dl)
  - at least two years post transplant
  - CyA +/- prednisolone
- Transvaginal oocyte collection is possible in the presence of a pelvic kidney
- Avoid OHSS - risk of impairment of transplant function
- Single embryo transfer

Pregnancy in the renal transplant patient

• Increased risk of
  – miscarriage
  – hypertension/ pre-eclampsia (45 - 70%)
  – IUGR/ prem
    • 44% neonates had bw >2500g
  – premature delivery/ stillbirth
• Recurrent UTI in >10%
• Severe hydronephrosis in 10% but no increased risk of graft rejection

Pezeshki 2005

The obese infertile patient

WHO Classification:

Normal weight : BMI 19-24.9 kg/m²

Pre-obese or overweight: BMI 25-29.9 kg/m

Obese: BMI ≥ 30 kg/m².

Prevalence of overweight and obesity in schoolchildren aged 10 - 16 years

Int Soc Stud Obesity survey 2001 - 2
Medical and reproductive disorders commonly associated with obesity

**Disorders worsened by obesity**
- Type II DM
- Cholestasis
- Hypertension
- Hypercholesterolaemia
- CHD
- Asthma
- Osteoarthritis
- Thromboembolism

**Reproductive disorders associated with obesity**
- Menstrual irregularity
- Anovulation
- Subfertility
- Miscarriage

Disorders worsened by obesity

Reproductive disorders associated with obesity

Adverse obstetric and perinatal outcomes associated with obesity

**Obstetric factors**
- Maternal hypertension/ PET
- Impaired glucose tolerance and gestational diabetes
- Venous thromboembolism
- Macrosomia and shoulder dystocia
- Intrauterine death
- Increased Caecean section rate and associated surgical complications
- Wound infection and dehiscence
- Postnatal respiratory complications

**Perinatal factors**
- Neural tube defect
- Omphalocele
- Cardiac defects
- Ophthalmic defects
- Oesophageal and upper GI defects
- Limb defects

Obstetric factors Perinatal factors


Obesity and infertility

**Multiple endocrine and metabolic disturbances (+/- PCOS)**

**Adverse effect on IVF cycle**
- increased FSH requirement
- longer stimulation period
- fewer oocytes and embryos

**Effects on**
- ovulation
- follicle growth and endocrinology
- endometrial growth and implantation
- embryo development

**Increased risks of**
- miscarriage
- pregnancy complications
- problems at/ after delivery

Normal BMI | Overweight | Obese | P value
---|---|---|---
N (%)| 165 (58.7) | 76 (27) | 40 (14.2) |  
Total dose of FSH (IU)| 1647 (± 40) | 1811 (± 54) | 1951 (± 89) | <0.01
Days of stimulation| 11.2 | 11.0 | 12.0 | NS
Peak E2 concentrations (pmol/l)| 7149 (±767) | 5334.1 (±539.2) | 6914 (±628) | NS
Cancellation rate n (%)| 8 (5) | 8 (10.5) | 5 (12.5) | NS
Number of oocytes collected| 8.1 (± 0.41) | 8.1 (± 0.54) | 9 (± 6) | NS
Oocytes inseminated| 6.9 (±0.35) | 6.6 (±0.5) | 7.2(±0.54) | NS
Fertilisation rate % (± SEM)| 69.4 (±2.2) | 73 (±2.5) | 78 (± 3.6) | NS
Embryo grade 2 (±0.6) | 1.9 (± 0.09) | 2.3 (± 1.4) | <0.02
Embryos discarded| 4.5 (±0.3) | 4.0 (±0.4) | 6.4 (±0.7) | <0.007
Utilisation rate| 49.1 (±2.85) | 50.34 (±4.27) | 31.14 (±3.93) | <0.01
Clinical pregnancy rate n (%)| 56 (34) | 25 (33) | 8 (20) | NS

Age < 35

**Impact of weight loss and exercise on ovulation and pregnancy**

**Benefits of diet and exercise in obese PCOS**

- Hypocaloric diet (even before weight loss) reduces insulin resistance
- Reduction in saturated fat intake alters lipid profile
- Exercise reduces insulin resistance
- Exercise without a hypo caloric diet does not produce much weight loss
Consequences of ovarian ageing

Age at first birth 1980 - 2002
Do weight loss programmes work?

- Weight loss programmes have poor results (only 15% maintain normal weight, when reached, for > 6 months)
- Audit - Jessop Hospital for Women showed only 6% of women reached target weight in 4 years despite access to dietician
- Pharmacological interventions are only sporadically effective (metformin, orlistat)
- Bariatric surgery shows promise but carries risk

Age related decline in ovarian reserve and impact of diet/exercise on body mass

![Graph showing ovarian reserve and weight over female age range](image)

Should we offer ART to obese women?

No

- Risks to mother and baby are too high
- 78/261 deaths in 2000-2002 Confidential Enquiry were obese - 25% had BMI>35
- Why not just wait until they lose weight?
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**Yes**
- Careful antenatal and intrapartum care can lead to good outcome in most cases
- Obese women should be informed of their increased medical risk but should make their own decisions
- Non-infertile obese women conceive frequently, and no Governmental licence is required
- Weight loss programmes have poor results

Obese-ism?

Denial of access to treatment on grounds of obesity may transgress Article 12 (The right to marry and found a family) and Article 14 (prohibition of discrimination) of the Human Rights Act

Conclusion

- Modern medicine frequently offers ‘cure’ or long term remission to young women with medical disorders
- These patients wish as normal a life as possible
- Many will want to start a family
- Management of infertility in the medically complex patient demands:
  - Careful pre-treatment optimisation of health
  - Multidisciplinary team approach
  - Hospital based IVF
  - Consideration of risk as well as benefit