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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 thyroid/ adrenal/leptin and bone effects
  - GVH disease after transplant

Chemotherapy

Risk of gonadal damage according to treatment used

- High risk
  - Cyclophosphamide
  - Ifosfamide
  - Chlorambucil
  - Melphelan
  - Busulfan
  - Nitrogen mustard
  - Procarbazine
  - Nitrosureas
- Moderate risk
  - Cisplatinum
  - Adriamycin
  - Actinomycin
- Low risk
  - Methotrexate
  - Vincristine
  - Vinblastine
  - 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 (eg 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 superovulaton
- 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 I 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 liason with diabetic physician and specialist obstetrician

Jonasson 2007, Laven 2005, Dicker 1992

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/ excerbation
- 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

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

Lox 1995, 1998, Biron 1997

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

Khalaf 2000, Pezeshki 2005, Nadalo 2007

Pregnancy in the renal transplant patient

- Increased risk of
  - miscarriage
  - hypertension/ pre-eclampsia (45 - 70%)
  - IUGR/ prom
    - 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

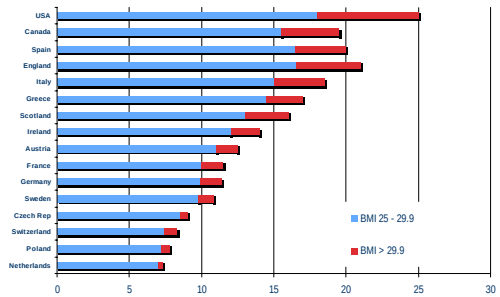
WHO Classification:

Normal weight : BMI 19-24.9 kg/m^2

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

Obese: BMI $\geq$ 30 kg/m^2.

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

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 Caesarean section rate and associated surgical complications
- Wound infection and dehiscience
- Postnatal respiratory complications

Perinatal factors

- Neural tube defect
- Omphalocoele
- Cardiac defects
- Opthalmic defects
- Oesophageal and upper GI defects
- Urogenital defects
- Limb defects

Sebire, 2001; Cedergren, 2004; Linne, 2004, Yu, 2006

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

Spandorfer, 2004, Fedorcsak, 2004, Wittemer, 2000

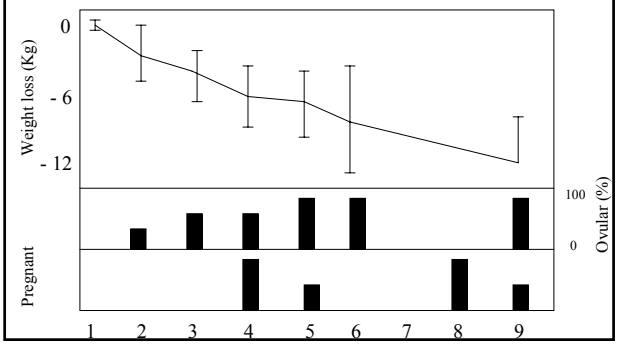
	Normal BMI	Overweight	Obese	P value
n (%)	165 (58.7)	76 (27)	40 (14.2)	
Total dose of FSH (IU)	1647 (± 40)¤	1811 (± 54)¤	1951 (± 89)¤	0.01
Days of stimulation	11.2	11.0	12.0	NS
Peak E2 concentrations (pmol/l)	7149 (±767)	5334.1 (±539.2)	6914 (±628)	NS
Cancellation rate n (%)	8 (5)	8 (10.5)	5 (12.5)	NS
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

¤ Post Hoc test (LSD), p< 0.05

Age < 35

Metwally et al, 2007

Impact of weight loss and exercise on ovulation and pregnancy

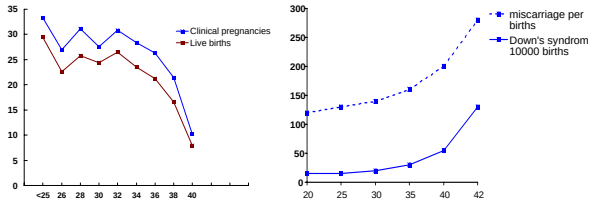


Benefits of diet and exercise in obese PCOS

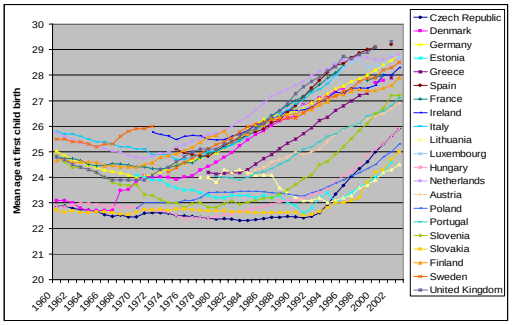
- Hypocaloric diet (even before weight loss) reduces insulin resistance
- Reduction in saturated fat intake alters lipid profile
- Exercise reduces insulin resistance
- Exercise without a hypo caloric diet does not produce much weight loss

But……..

Consequences of ovarian ageing



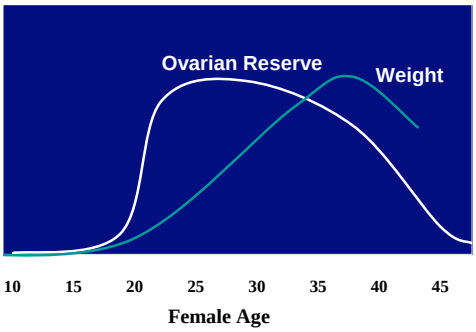
Age at first birth 1980 - 2002



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



Should we offer ART to obese women?

No

- Risks to mother and baby are too high
- 78/261 deaths in 2000 - 02 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