**Assisted Reproductive Technologies ART**

* All technique involving direct manipulation of oocyte/sperm outside the body.
* **Major Assisted Reproductive Technologies :**
  1. In vitro fertilization and embryo transfer (IVF-ET)
  2. Direct intra-peritoneal insemination (DIPI)

Not used nowadays

* 1. Gamete intra-fallopian transfer (GIFT)
  2. Zygote intra-fallopian transfer (ZIFT)
  3. Intracytoplasmic sperm injection (ICSI)
* **Indications of ART :**
  1. Tubal factor infertility “main indication”
  2. Endometriosis
  3. Male factor infertility
  4. Unexplained infertility
* **Typical ART cycle (steps) :**
  1. Controlled ovarian stimulation
  2. Monitoring (growth of follicle) with Transvaginal ultrasound and Serum E2 (estradiol)
  3. Prevention of premature LH surge and Ovulation
  4. Oocyte maturing with HCG
  5. Oocyte retrieval
  6. Fertilization by IVF/ICSI
  7. Invitro embryo culture
  8. Luteal support
  9. Transfer of fresh embryo/cryopreseve of excess
  10. First trimester pregnancy monitoring
* Ovarian stimulation regimens : (most commonly method used is injections in 99.9% of centers)
* **We have 2 protocols for ovarian stimulation :**
  1. Long protocol “most common”
  2. Short protocol “in patients who don’t respond to long protocol”
* **Long protocol :**
  1. On day 21 of cycle previous to the treatment cycle Give long acting GnRH agonist (Deycapeptyl ,for down regulation of pituitary gland to prevent spontaneous ”endogenous” LH surge that will cause ovulation ) one injection will be effective for one month .
  2. After 1 week ( on day 28) period will occur , on 2nd day of period we must check if the down regulation was successful or not by 2 ways :
     + Vaginal US to see if there are follicles or not (if no follicles this means successful down regulation, Endometrium 8-9mm good )
     + Estrogen (17 beta-estradiol) level must be low, if both conditions are present continue to next step.
  3. On 3rd day of period Give injectable ovulation induction agents (menopausal or recombinant FSH ) daily .
  4. After 1 week check if she is responding or not (normal responding → continue same dose , over responding → decrease dose or under responding→ increase dose ) to avoid ovarian hyperstimulation syndrome.
  5. Continue dose and repeat US day after day to measure size of follicles , until we have at least 3 follicles measuring at least 17 mm in size.
  6. Give HCG to trigger ovulation and release of the egg (release of egg should occur 40 hours after HCG is given) .
  7. Oocyte retrieval should be done at day 13 of cycle, 36 hours after HCG (not beyond to avoid rupture and release of egg) , under sedation or GA by vaginal approach under US guidance ,All follicles >10mm aspirated
     + Complications:
       - haemorrhage
       - pelvic infection
       - rupture of a cyst
       - laceration of sacral vein
       - lumbosacral osteomyelitis
  8. Eggs are picked from the specimen that was drawn .
  9. give progesterone at day of Oocyte retrieval to maintain lueteal phase to support implantation .
  10. Insemination by 2 methods :
      1. Conventional IVF :
         + If husband has good number of sperms , wash and clean them then put 50,000-100,000 motile sperms in each test tube , and put one egg (after removing cumulus oophorus) in each , then wait for spontaneous fertilization to occur
      2. ICSI (intra-cytoplasmic sperm injection ) :
         + If failed IVF , Teratospermia , Asthenospermia , severe oligo or azospermia we inject one sperm in the cytoplasm of the egg and wait for fertilization.
  11. Fertilization normally takes 12 hours to occur
  12. 5-6 days after fertilization the blastocyst will form , so we do embryo transfer by transvaginal approach (same as in IUI) , embryo transfer can also be done at day 3 after fertilization at this stage we call it 8 cell stage not blastocyst , maximum 2 embryos transferred .
  13. Wait for implantation .
  14. Do pregnancy test After 2 weeks of embryo transfer .
* GnRH agonist can be given as injections or nasal spray .
* **Advantage of blastocyst culture :**
  + True viability assessment
  + Developmental potential
  + Synchronize the stage of development
  + Reduce risk of expulsion
  + Allows Preimplantation Genetic Diagnosis :
    - Single cell is taken from each embryo and tested using PCR or FISH techniques
    - Aneuploidy or Structural abnormalities (translocations, inversions)
    - Inherited gene disorder
      1. Cystic fibrosis
      2. Thalassemia
      3. Haemophelia
      4. Duchnemuscular dystrophy
  + Few embryo can be transformed
* **Short protocol :**
  1. On day 1 of period start giving daily injections of low dose GnRH agonist .
  2. On day 3 of period start giving GnRH antagonist .
  3. At day 12 of period stop GnRH agonist , and give HCG .
  4. After 40 hours we stop GnRH agonist injections and do egg retrieval .
  5. 5-6 days after egg retrieval do embryo transfer .
  6. After 2 weeks of egg retrieval do serum pregnancy test .
* **Embryo cryopreservation :**
  + Improves cumulative pregnancy/retrieval
  + OHSS is avoided
  + Principle : embryos are sealed in vials and cooled -30°C to -110◦C , thawing process is reversed
  + All stage of Embryo can be frozen
  + For indefinite
  + Embryo survival 50-90%
  + Better for zygote than cleavage stage and blastocyst
  + Overall success 15-20%
* Success rate of IVF in young age group is 40% , but decreases with increasing age (in older ages the eggs will be of bad quality so chance of pregnancy is low) .
* Multiple pregnancy :
  + 35% of ART are multiple pregnancy majority are twins 30.7% , and 4.3% are triplets
* **Ovarian Hyperstimulation Syndrome OHSS :**
  + It is a syndrome characterized by variable degree of ovarian enlargement and/or ascites, pleural effusion, oliguria, hemoconcentration, thromboemolism, and electrolyte disturbances which may be life threatening.
  + OHSS is the main cause of maternal death in IVF , 1 in every 32,000 IVF patient .
  + Commonly as an iatrogenic complication of ovulation induction mainly “injectable” as HMG, FSH, rFSH.
  + Rarely may complicate normal pregnancy.
  + Incidence**:** -Mild OHSS; 8 – 23%. - Severe OHSS: 3.5-8% in IVF stimulated cycles .
* **Risk factors of OHSS :** 
  + 1. Patient characters: OHSS common with:
       - Younger cases.
       - Cases with lower body weight.
       - Anovulatory cases with menstrual disorders, normal endogenous GnH, and estrogen.
       - Previous history of OHSS.
    2. PCO: about 50% of OHSS cases have PCO,
    3. Pure FSH: OHSS is reported to be lower than HMG (FSH+LH) in these cases.
    4. Clomid: usually mild degree occurs in 13.5%.
    5. Luteal phase support: risk increased with HCG and decreased with progesterone.
    6. Pregnancy : 3-4 times more risk for OHSS (due to high HCG)
* **Pathogenesis of OHSS :**
  + - Increased capillary permeability specially from the enlarged ovaries → extravasation of fluid into the abdominal cavity → Ascites , pleural effusion , Hypotension, → decrease intravascular compartment → oligouria, Hemoconcentration ,Decreased renal perfusion → sodium and water retentions and thromboembolism **.**
    - **N.B**: Renal failure may occur in the final stage due to sever volume depletion.
* **Classification** :

|  |  |  |  |
| --- | --- | --- | --- |
| **Grade** | **Ovary** | **Clinical** | **Lab. Blood** |
| **1.Mild** | 5-I0cm | -Abdominal Distension  -GIT upset  -Minimal pain  -no hemoconcentraction or ascites | -PCV < 45  - WBC < 15.000/cc  -Normal renal function |
| **2.Moderate** | 10-12 cm | -Moderate ascites  -no hemoconcentraction | -PCV < 45  - WBC < 15.000/cc  -Normal renal function |
| **3.Sever** | > 12cm | -Marked ascites  -Dyspnea  -Hypovolemia  -Mild Thromboembolism  - hemoconcentraction | -PCV > 45  - WLC > 15.999/cc  -Impaired renal function |
| **4.Critical** | MARKED | -Tense ascites  -Hydrothorax  -Sever Thrombocmbolism  -Adult respiratory distress syndrome  -Life threatening  - hemoconcentraction | -PCV > 55  -WLC > 25000/mm3,  -serum creatinine> 1.6 mg/dl  -creatinine clearance < 50 ml/min. |

* + Hemoconcentration is defined as : PCV > 45 , or WBC > 15,000
* **Complications of OHSS :**
  1. Thromboembolic complications.
  2. Liver dysfunction: liver enzymes are elevated in 15% and persist for 2 months after.
  3. Respiratory complications: adult respiratory distress syndrome ARDS
  4. Renal complications: renal failure due to hypoperfusion.
  5. Adnexal torsion: due to enlargement, however laparoscopic unwinding is successful.
  6. Internal hemorrhage.
  7. Miscarriage rate: Increased from 30% to 50% in OHSS stimulated cycles. (which is good to ↓ HCG)
* **Prediction of OHSS :**
  + By continues monitoring of E2 (estradiol) plasma level + U/S folliculometry .
  + combination for Predicting OHSS and in Determining the optimum time and safety for giving hCG.
* **Prevention of OHSS :**
  1. Withhold HCG administration.
  2. Luteal phase support: use of progesterone, no HCG.
  3. Follicular aspiration: it was suggested that aspiration of the follicles is protective against OHSS.
  4. Cryopreservation of embryo with subsequent replacement in non stimulated or natural cycle.
  5. Intravenous albumin administration
  6. Hydroxyethyl-starch: Large molecule, long 1/2 life.
  7. Immunoglobulin: IgG, IgA gammglobuins have low level in patient with severe OHSS. When given IV reduce the severity.
  8. Corticosteroids
  9. Cabergolin
* **Treatment :**
  1. Mild cases: can be treated with analgesia in outpatient clinic ,Spontaneous recovery within 2-3 Wk (conservative measures and follow up)
  2. Moderate and severe cases: General treatment
     1. Hospitalization and reassurance.
     2. Observations; (ICU)
* **Medical treatment :**
  1. Circulation and electrolytes:
     1. Preserve the intravascular volume and renal perfusion.
     2. Done using colloid plasma expanders or human albumin, (effect is temporary)
     3. Sodium and water restriction (non effective).
  2. Symptomatic treatment:
     1. Analgesia: paracetamol and opioids, avoid volteren(because it may lead to renal damage).
     2. Antiemetics: metoclopramid.
  3. Prevent Thromboembolism through Anticoagulant therapy (LMW heparin)
  4. Antihistamines: was suggested to cause stabilization of capillary membrane.
  5. Dopamine: in oliguric cases to improve perfusion and avoid renal failure.
  6. Ascites : Aspiration of ascetic fluid or pleural effusion
     + By Paracentesis or transvaginal aspiration under U/S guidance.
     + Advantages:
       - Improvement of respiration, and Decrease abdominal discomfort .
       - Increase venous return and COP.
       - Increase urine output and createnine clearance reflecting improving renal functions.
* **Avoid : X X X**
  1. Anti-PG : eg. Volteren → disturb renal function.
  2. Danazol: ineffective.
  3. Diuretics: used only in pulmonary edema (Diuretics cause more ↓ in intravascular compartment and more hemoconcentration →thromboembolism ).
* **Surgical treatment**: (Indications of surgery in severe OHSS)
  1. Signs of intraperitoneal Hemorrhage and/or rupture of ovarian cyst.
  2. Adnexal torsion.
  + Laparotomy: should always be avoided and if deemed necessary, measures are done to preserve (Ovary)

* **Notes :**

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Check pictures in the slide

* + Rate of ectopic in normal pregnancy is 1% , but in IVF is 5% .
  + Rate of OHSS is 5 % in IVF .