LAPAROSCOPY AND INFERTILITY MANAGEMENT

RAHR, XXVII ANNUAL CONFERENCE
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OBJECTIVES

- To review common indication, extension of laparoscopic surgery and prognosis

  - Diagnosis of infertility
  - Pelvic Adhesive Disease
  - Tubal Factor Infertility
  - Endometriosis
  - Uterine fibroids
  - Chronic anovulation PCOS
  - Mullerian anomalies
DIAGNOSTIC LAPAROSCOPY

Indicated for evaluation of peritoneum, tubes and ovaries

- Initial testing results are inconclusive or abnormal
- Suspected pelvic endometriosis
- During hysteroscopic adhesiolysis for Asherman syndrome and uterine septoplasty for partial or complete uterine septum

Gold standard evaluation for tubal and peritoneal factors

Normal pelvic anatomy

Chromopertubation with Methylene Blue
PELVIC ADHESIVE DISEASE
Goal is to restore anatomy

Pros and cons must be evaluated

Mild to moderate disease has low risk of surgical complications

Severe disease involving bowel, bladder and ureters have high risk of surgical complications and extent of surgery might need to be limited to avoid complications
INFERTILITY – TUBAL FACTOR

35% of all causes of infertility

Site
- Unilateral and Bilateral occlusion

Location
- Proximal end
- Midportion and diffuse
- Distal end tubal occlusion
Laparoscopic tubal patency assessment with Chromopertubation after completion of Hysteroscopic tubal cannulation for Bilateral proximal tubal occlusion

Surgical treatment in selected cases

No other infertility factors
Women of younger <35 yrs
LAPAROSCOPY: TUBAL FACTOR INFERTILITY

- **DISTAL tubal occlusion**
- Hydro – or Hematosalpinx – dilated by fluid obstructed tube

- Unilateral hydrosalpinges – excision with confirmation of patency of contralateral site

- Bilateral large hydrosalpinges – bilateral excision with proximal end of 1.5-2 cm

- Hysteroscopic proximal occlusion by intratubal devices is inferior to laparoscopic salpingectomy in treatment of bilateral hydrosalpinges prior to IVF

Reconstructive microsurgery for distal tubal occlusion

Salpingo-ovariolysis

Salpingoneostomy

Fimbrioplasty: to free agglutinated fimbriae

Fimbrioplasty: correction of prefimbrial phimosis
The degree of damage is graded I-IV with one being the least and IV the worst.

**Spontaneous pregnancy rates**

<table>
<thead>
<tr>
<th>Disease Stage</th>
<th>Surgery</th>
<th>No Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild stage I</td>
<td>67%</td>
<td>24%</td>
</tr>
<tr>
<td>Moderate stage II</td>
<td>41%</td>
<td>10%</td>
</tr>
<tr>
<td>Stage III</td>
<td>12%</td>
<td>3%</td>
</tr>
<tr>
<td>Stage IV</td>
<td>0%</td>
<td>Surgery not offered</td>
</tr>
</tbody>
</table>
LAPAROSCOPY: TUBAL ANASTOMOSIS

- Conventional or Robotic assisted laparoscopic anastomosis after tubal sterilization
Four quadrant suturing technique
The overall pregnancy rate was 85.1% with intrauterine pregnancy 82.6% and 2.5% ectopic.
The pregnancy rate was significantly reduced in patients over 40 years old (53%) compared with patients younger 40 years of 90%

Repair done at the interstitial–ampulla site yielded a significantly higher ectopic pregnancy rate (20.0%) compared with other anastomosis sites

In spite of heterogeneity among the available studies, current evidence suggests that laparoscopic excision or ablation either by electrocautery or laser improves pregnancy rates both by natural and assisted conception.

Goals
- Destruction of endometriotic implants
- Division adhesions to free fallopian tubes, ovaries with restoration of normal anatomy
- Remove ovarian endometriotic cysts

ASRM classification depends on size, site and depth of lesion and point scores were given depending upon severity.

- Stage I (minimal)
- Stage II (mild)
- Stage III (moderate)
- Stage IV (severe)
LAPAROSCOPY: ENDOMETRIOSIS

Active forms of endometriosis - importance of surgical destruction

Inactive forms of endometriosis – healed lesions
**LAPAROSCOPY: ENDOMETRIOSIS**

**Endometrioma ("chocolate cyst")**

The ESHRE 2014 Guideline, in infertile women ovarian endometrioma of > 3cm, laparoscopic ovarian cystectomy results in a better pregnancy rate than drainage alone.

Excision of endometriomas: opening of the cyst (using scissors or electrosurgical or laser energy), the cyst wall is then excised or “stripped away” by applying contraction.

Recurrence rates for endometrioma are reported from 11 to 32% within 1-5 years after excision. The recurrence rate is higher in patients with advanced endometriosis at surgery and in younger patients.

Assisted Reproductive Techniques should be considered if conception has not occurred by 12 months after surgery.

*Soga K, et al., Front Biosci (Elite Ed). 2013 Jan 1;8:676-83.*

LAPAROSCOPY: ENDOMETRIOSIS

- Laparoscopic ablation of endometriotic implants in Stage I-II increased the cumulative pregnancy rate of spontaneous pregnancy.
  - In a five year follow-up of women after laparoscopic surgery, a 65% pregnancy rate, with 23% of women conceiving in the first twelve months.

- Three high quality prospective cohort-studies showed overall spontaneous pregnancy rates of 52–69% for Stage III/IV after laparoscopic surgery, which are much higher than the crude spontaneous pregnancy rates of 33% (moderate) and 0% (severe) after expectant management reported in a study by Vercellini et al.

- Extensive laparoscopic endometriosis ablation in women with Stage III-IV endometriosis and repeated IVF implantation failures improved the IVF outcomes. Performing salpingectomy during surgery demonstrated improvement in delivery rates after surgery. As well 9% spontaneous conception was reported.

LAPAROSCOPIC MYOMECTOMY

Prognostic factor, Symptomatic Intramural fibroids $\geq 5.0 \text{ cm}$ appears to justify myomectomy: decrease implantation, women with fibroid related menorrhagia twice likely to be infertile and double risk of SAB

Conventional or Robotic assisted laparoscopy criteria: a single intramural or subserosal fibroid $\leq 15 \text{ cm}$ or three or fewer fibroids of $\leq 5 \text{ cm}$ whereas, others believe in an individual choice based on pathological findings and surgical skill

Vasopressin is injected into the area over the fibroid, or myoma. An incision is made in the uterine wall over the fibroid. The fibroid is removed. The incision site is closed with sutures.
LAPAROSCOPIC MYOMECTOMY

- 44-62% of infertile women conceive after myomectomy
- 80% of all pregnancies occurred within first year after surgery
- Life birth rate after myomectomy was 42% vs 11% of nonsurgical controls

- Pregnancy loss after myomectomy significantly decreases.
  - In a review of 1941 patients who underwent myomectomy, the spontaneous abortion rate improved from 41% prior to surgery to 19% following myomectomy

- Laparoscopic myomectomy associated with 50% reduction of pelvic adhesions compare to laparotomy, much shorted blood loss and postoperative recovery period

Third line treatment of chronic anovulation in PCOS

As effective as gonadotropins for live birth rates, but without the risks of OHSS and multiple pregnancies.

Improves ovarian responsiveness to successive ovulation induction agents.

Spontaneous ovulation rate of 90% and pregnancy rate of 70% at 12-months after laparoscopic treatment

Treatment effect significantly diminished after 1 year

LAPAROSCOPY: MULLERIAN ANOMALIES

- Confirm suspected anomaly
- Class II: Unicornuate uterus with rudimentary horn
  - No endometrial cavity – no intervention
  - Endometrial cavity present in noncommunicating horn - laparoscopic resection to prevent or treat
    - Endometriosis
    - Ectopic pregnancy
    - Infertility

MRI: unicornuate uterus with left rudimentary horn

HSG: left unicornuate uterus

Left rudimentary horn pregnancy
OPERATIVE LAPAROSCOPY: NONCOMMUNICATING RUDIMENTARY HORN

Right noncommunicating rudimentary horn with hematosalpix

Laparoscopic excision

MRI

Laparoscopy

Hematosalpix
UNEXPLAINED INFERTILITY

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**UNEXPLAINED INFERTILITY**

Infertility in the absence of definable cause despite a evaluation for a couple’s failure to achieve pregnancy after 12 months in women younger 35, or after 6 months in 35 and older.

Initial work up constant with normal male factor, regular ovulation, appropriate ovarian reserve, uterine factor, and tubal factors.

According to the ASRM guidelines, laparoscopy should be performed in women with unexplained infertility in selected cases.

The treatment for unexplained infertility is therefore, by definition, empiric because it does not address a specific defect or functional impairment.

AGE-SPECIFIC SOCIETAL FERTILITY SHIFT

By single year of age

Births per 1,000 women

1968
1998
2008

Age (years)
AGE AND FERTILITY
UNEXPLAINED INFERTILITY

- **The principal treatments**
  - Expectant observation with timed intercourse and lifestyle changes
  - Ovulation Induction with Clomiphene Citrate and Letrozole and intrauterine insemination (IUI)
  - Controlled Ovarian Hyperstimulation (COS) with IUI
  - In Vitro Fertilization (IVF)

  - Although expectant management is associated with the lowest cost, it results in the lowest cycle fecundity rates. An option for a couple with young female partner with excellent ovarian reserve.

  - Despite high cost IVF-ICSI is the treatment of choice when less successful treatment modalities have failed and for older female patients or concerning ovarian reserve.

- The optimal treatment strategy needs to be based on individual patient characteristics such as age, treatment efficacy, side-effect profile such as multiple pregnancy, and cost considerations.
UNEXPLAINED INFERTILITY

- Management needs to be individualized based on age, infertility history, treatment history, costs, and risks/benefit ratio.

- **Lifestyle Changes**
  - Epidemiological studies indicate cigarette smoking, abnormal body mass index (BMI), and excessive caffeine and alcohol consumption reduce fertility potential.
  
  - Women with unexplained infertility should be counseled about weight optimization, reduction of caffeine intake to no more than 250 mg/d, and reduction of alcohol to no more than 4 drinks per week.

FERTILITY OPTIMIZATION

Folate
Protects genes during rapid cell division which increases likelihood of a healthy embryo (via methylation of DNA); Deficiency raises homocysteine which damages reproductive cells. [1-3]

Vitamin B₉ & B₁₂
Both are needed to convert toxic homocysteine to a benign form. Low homocysteine levels linked to a better chance of pregnancy. [4,5]

Vitamin C
Increases serum progesterone levels; Induces ovulation in some women; Enhances effect of the fertility drug clomiphene. [6,7,8]

Vitamin D
Higher levels linked to better success rates of IVF (in vitro fertilization); Influences production of the sex hormones estradiol and progesterone. [9,10]

Vitamin E
Protects reproductive cells (follicles); May improve endometrial response (ability of fertilized egg to implant into uterine wall properly) during IVF. [11,12,13]

Minerals
Several enzymes needed to protect a woman’s reproductive organs (such as superoxide dismutase) are dependent on the trace elements zinc, copper and magnesium. [14]

Antioxidant Status
Reproductive cells, including embryos, are very susceptible to damage from oxidative stress due to the rapid rate of growth; Low antioxidant status can cause infertility or miscarriage. [15]

Cysteine
N-acetyl cysteine can improve ovulation and pregnancy rates in women with infertility due to PCOS (polycystic ovary syndrome) that do not respond to fertility drugs; Improves viability of endometrial cells in vitro; Precursor to glutathione. [16,17]

Glutathione
Protects eggs (fertilized or not) from damage by reactive oxygen species; Protective action of follicle stimulating hormone on embryonic development is due largely to glutathione synthesis. [18,19]

Selenium
Deficiency implicated in miscarriage and infertility; In one trial, 100% of infertile women achieved pregnancy after supplementation. [20]

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UNEXPLAINED INFERTILITY

- **Expectant Management**
  - Studies of couples with unexplained infertility who are followed without any treatment report a broad variation in cumulative pregnancy rates.
  
  - A retrospective review of 45 studies by Guzick and colleagues found an average cycle fecundity of 1.3% to 4.1% in the untreated groups.
  
  - In a recent study, couples with unexplained infertility on a waiting list for IVF in the Netherlands had a 10% to 15% cumulative chance of pregnancy over a 12-month period.
  
  - Spontaneous conception rate increased to 35% during the next 2 years of attempt. Moreover, the rate could reach 80% in younger couples during the following 3 years of unprotected intercourse.
  
  - Spontaneous pregnancy drastically declines with infertility duration of more than 3 years and in women over 30 years of age.
  
  - There are several mathematical models such as Hunault's prognostic model to estimate the rate of spontaneous pregnancy.
  
  - When the chance of spontaneous conception for a couple is acceptable, no further fertility treatment is needed and the best plan for them would be expectant management.
**UNEXPLAINED INFERTILITY AND ENDOMETRIOSIS**

- **Minimal - Mild Pelvic endometriosis** found during laparoscopy 50-80% of patients with unexplained infertility

- Laparoscopic vaporization of endometriosis improves spontaneous pregnancy rates in these women

- Expectant management after laparoscopy in young patients

- Medical treatment with Letrozole OI+IUI x 3-4 cycles, if unsuccessful - IVF

UNEXPLAINED INFERTILITY

IUI involves the placement of washed sperm into the uterine cavity around the time of ovulation.

▪ If IUI performed in natural cycle without ovulation induction with oral agents, or injectable gonadotropins conceptions was reported in 4.1% of the IUI cycles and 2.4% of the timed intercourse cycles.

▪ Ovulation Induction with Clomiphene Citrate and Letrozole paired with IUI is superior to timed intercourse.
  ▪ A Cochrane review on this topic confirmed that IUI with ovulation induction increased the live birth rate compared with IUI alone.

▪ Controlled Ovarian Stimulation - Gonadotropins ovulation timed with IUI is superior then timed intercourse.
  ▪ A meta-analysis of 27 studies involving 2939 cycles revealed that the pregnancy rate per cycle was 8% with gonadotropin treatment alone and 18% with gonadotropin treatment combined with IUI.

▪ Aboulghar and colleagues performed an observational prospective study to determine the optimum number of COH/IUI cycles. They found that by 3 cycles of COH/IUI resulted in a cycle fecundity of 16.4% and a cumulative pregnancy rate of 39.2%.

▪ 3 further trials of COH/IUI in a cycle fecundity of 5.6%, significantly lower than that in the first 3 attempts.

▪ A historical comparison group with 3 failed cycles of COH/IUI who underwent 1 cycle of IVF at the same center resulted in a cycle fecundity of 36.6% per cycle, suggesting that patients should be offered IVF if they fail to conceive after 3 trials of COH and IUI.
Comparison of Different Treatments for Unexplained Infertility

- **Letrozole, Gonadotropins, or Clomiphene Citrate for Unexplained Infertility.**

- Couples with unexplained infertility in a multicenter, randomized trial. Ovulatory women 18 to 40 years of age with at least one patent fallopian tube were randomly assigned to **ovarian stimulation (up to four cycles)** with Gonadotropin, Clomiphene Citrate, or Letrozole.

  - Clinical pregnancies occurred in 1. Gonadotropin 35.5%, 2. Clomiphene 28.3%, and 3. Letrozole 22.4% of cycles.
  - Live birth occurred 1. --- 32.2%, 2. --- 23.3%, and 3. --- 18.7% of cycles.

- The multiple gestation rate with Letrozole was lower than in other groups and the highest was in gonadotropin group.

- All multiple gestations in the clomiphene and letrozole groups were twins.
- Gonadotropin treatment resulted in high number of twin gestations and 10 triplet gestations.

**CONCLUSIONS:** OI with Letrozole resulted in a significantly lower frequency of multiple gestation, Similar Life birth to Clomiphene Citrate and Lower frequency of live birth when compared with Gonadotropins.

Comparison of Different Treatments for Unexplained Infertility

A randomized clinical trial to evaluate optimal treatment for unexplained infertility: Fast Track and Standard Treatment Trial, (FASTT). Female age -18 to 39 yrs.

- 503 couples were randomized to receive either a conventional treatment regimen of 3 cycles of clomiphene/IUI, 3 cycles of FSH/IUI, and up to 6 cycles of IVF or to receive an accelerated treatment course of 3 cycles of clomiphene citrate/IUI and then up to 6 cycles of IVF.

- Per cycle pregnancy rates for CC/IUI, FSH/IUI, and IVF were 7.6%, 9.8%, and 30.7%, respectively.
- Cumulative pregnancy rates
  - In the conventional arm, 18.5% of the women became clinically pregnant after clomiphene citrate/IUI, 25.3% after FSH/IUI cycles and 64% after IVF.
  - In the accelerated arm, 20.7% became pregnant after clomiphene citrate/IUI and 68.4% in an IVF cycle.

Conclusion: Median time to pregnancy was 8 and 11 months in the accelerated and conventional arms, respectively. Average charges per delivery were $9,800 lower in the accelerated arm compared to conventional treatment. The observed incremental difference was a savings of $2,624 per couple for accelerated treatment.

A Randomized Clinical Trial to Determine Optimal Infertility Treatment in Older Couples: The Forty and Over Treatment Trial (FORT-T).

- Randomized to treatment with 2 cycles of Clomiphene Citrate (CC) and IUI, follicle stimulating hormone (FSH)/IUI, or immediate IVF, followed by IVF if not pregnant.
  - 154 couples were randomized to receive CC/IUI (N=51), FSH/IUI (N=52), or immediate IVF (N=51); 140 (90.9%) couples initiated treatment.
  - Cumulative clinical pregnancy rates
    - CC/IUI, FSH/IUI, or immediate IVF were 21.6%, 17.3%, and 49.0%, respectively.
    - After all treatment, 71.4% (110/154) of couples conceived a clinical pregnancy and 46.1% delivered at least one live-born baby.
    - 84.2% of all live born infants resulting from treatment were achieved from IVF.
    - There were 36% fewer treatment cycles in the IVF arm compared to either COH/IUI arm.

In older women with unexplained infertility demonstrated superior pregnancy rates with fewer treatment cycles in the IVF group.

SUMMARY

- The guideline of National Institute for Health and Care Excellence (NICE)
  - The age of women and infertility duration are important factors in offering specific therapy to a couple.
  - Yong women with short duration of infertility benefit form from expectant management followed up by OI with Letrozole or Clomiphene Citrate with IUI.
  - COH/IUI (3-4 cycles) are effective in women under 35, but COH/IUI increase the risk of multiple gestations.
  - COH/IUI is ineffective for couples with long duration of infertility and older women.
  - Couples over 35 and couples and young female patients with long duration of unexplained infertility are best helped with IVF-ICSI
    - Failed fertilization is reported in 8.4%-22.7% of conventional IVF cycles for couples with unexplained infertility
    - It is common practice to offer routine ICSI for these couples. Several studies suggested split IVF/ICSI would be the best option for these couples since its cumulative pregnancy rates are higher than conventional IVF and its cost effective.
  - Through doing more research on reproductive biology and increasing our knowledge of gametogenesis, fertilization, embryo development, implantation and fetus-uterus crosstalk, more effective treatment options in future for infertile couples specially the ones with unexplained infertility would be provided.

FERTILITY PRESERVATION AND OVARIAN CANCER

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FERTILITY PRESERVATION AND CANCER

Integral part of multidisciplinary approach in medical care of reproductive age women with malignancies

High demand in the past decade
• Cancer treatment leads to loss of fertility in young women
• Significant increase in Cancer Survivor population as the result of early diagnosis, effective Tx and high life expectancy
FERTILITY PRESERVATION AND OVARIAN CANCER

- **Borderline ovarian tumors**
  - Good candidates for fertility preservation is commonly only require unilateral oophorectomy or cystectomy
  - Slow growing, Low recurrence and high survival rate

- **Epithelial Ovarian cancer**
  - **Good Candidates**
    - Stage IA
    - Stage IC Grade 1-2, favorable histologic type: serous, mucinous, endometrioid
  - **Ineligible**
    - Stage >IC
    - Grade 3
    - Unfavorable histological type: clear cell
    - Poor survival

Nam et al., Gynecol Obst Invest 2013, 76,(1):14-24
FERTILITY PRESERVATION AND OVARIAN CANCER

- Fertility Preservation methods
  - Fertility sparing surgery with uterine preservation and unilateral salpingo-oophorectomy in patients with good prognosis
  - IVF with embryo freezing
  - Ovarian stimulation with oocyte cryopreservation
  - In selected cases ovarian tissue freezing and in vitro maturation of the oocytes

- Nam, et al 2013 - 918 patients
  - Recurrence 109 (11.9%)
  - Death 48 (5.2%)

- Obstetrical
  - 177 women had 242 pregnancies
  - 214 term births (88%) and 1 preterm delivery (0.4%)
  - SAB 25/242 (10%)
  - No congenital anomalies were detected in children born

Nam et al., Gynecol Obst Invest 2013, 76,(1):14-24
A 34 yo G0 female with an 8-cm left ovarian multicystic mass, underwent laparoscopic oophorectomy and intraoperative pathology showed low malignant potential borderline ovarian tumor, stage IC.
- Gyn oncologist recommended to remove remaining ovary after fertility preservation with embryo freezing.

**Fertility preservation:**
- Emergent IVF, “random start” ovarian stimulation, antagonist protocol
  - 18 oocytes with 12 fertilized and cryopreserved at 2 pronuclear stage (2PN)
- Genetic counseling was completed
- Future procreation: culturing 2PN to blastocyst stage with trophectoderm biopsy with aneuploidy screening and single embryo transfer.
CLINICAL CASE #2
OVARIAN CANCER IN MARRIED FEMALE

- A 32 yo G0 female with history of irregular menses and inability to conceive for 14 months was found with complex adnexal mass, underwent unilateral laparoscopic oophorectomy and staging procedure by gyn oncologist for low malignant potential borderline ovarian tumor, stage IC.
  - Gyn oncologist recommended to remove remaining ovary after fertility preservation

Fertility preservation:
- Emergent IVF, “random start” ovarian stimulation, antagonist protocol
  - 8 oocytes with 5 fertilized and cryopreserved at 2 pronuclear stage (2PN)
  - Patient had ovary removed 2 weeks after egg retrieval
  - Thawing 100% survival, 2 good quality blastocysts transferred in FET protocol no conception, no frozen embryos remaining.

- Genetic counseling and testing was consistent with sporadic tumor
- Future procreation: Donor oocyte cycle, couple is considering using “My Egg Bank” for frozen eggs purchasing.
A 21 yo G0 single female was referred after oophorectomy and diagnosis serous papillary ovarian cancer, Grade 2, stage IB. ER positive receptors.

- Gyn oncologist recommended to remove remaining ovary after fertility preservation
- Reviewed with oncologist to use Letrozole to keep E2 level low

**Fertility preservation:**
- Emergent IVF, “random start” ovarian stimulation, antagonist protocol + Letrozole
- 10 days of stimulation, Pick E2 level 380 pg/ml, 12 oocytes retrieved and cryopreserved.
- Letrozole was stopped after 7 days post retrieval.

- Genetic counseling and testing was consistent with sporadic tumor
- She underwent remaining ovary removal few weeks post retrieval.
- Future procreation: oocyte thawing, fertilization and ET.
FERTILITY PRESERVATION AND OVARIAN CANCER

- Review options of genetic screening for hereditary associated ovarian malignancies and potential embryo screening if tested positive
- Considerations of back to back stimulation when possible for higher yield of oocytes since usually only single ovary is available.
- Discuss possibility of use of donor oocytes or gestational carrier

- Medicolegal considerations
  - Couples commonly split after dealing with cancer and embryos may not be utilized
  - Offer oocyte cryopreservation along with embryo freezing to married women
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WHAT INDICATIONS FOR IVF IN WOMEN WITH PCOS?

- Chronic anovulation with NO response to 1\textsuperscript{st} or 2\textsuperscript{nd} line of treatment

- Multifactorial infertility – male factor, endometriosis, tubal factor and advanced maternal age

- Indications for PGD or PGS
IVF CHALLENGES IN PCOS WOMEN

- Hyper response with early cycle cancelation
- High risk for moderate and severe OHSS
- Egg immaturity, lower fertilization and lower embryo quality
- Higher first trimester losses
Preconception counseling with identification the risk factors for reproductive failure and correct or improvement them prior to ovarian stimulation.

It is imperative to recognize different phenotypical types and the presence of centripetal fat distribution, the degree of which may vary according to ethnicity and geographical area.

Testing thyroid function, glucose metabolism and evaluation for pre diabetes and diabetes
# PREVALENCE OF PCOS PHENOTYPES

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>General</th>
<th>Clinical</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenotype A</td>
<td>19% (13%–27%)</td>
<td>50% (46%–54%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Phenotype B</td>
<td>25% (15%–37%)</td>
<td>13% (11%–17%)</td>
<td>0.026</td>
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<tr>
<td>Phenotype C</td>
<td>34% (25%–46%)</td>
<td>14% (12%–16%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Phenotype D</td>
<td>19% (14%–25%)</td>
<td>17% (13%–22%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

*P* values indicate statistical significance:
P<0.001 | NS

LIFE STYLE OPTIMIZATION

- Regulation of 3 meals, small portions, and food choices: high-fiber carbs, foods high in protein, polysaturated fats, and avoidance of deprivation dieting.
- Exercise daily or at least 3-4 times a week - regulates metabolism, a mood boost, increases endorphins, physical preparedness for pregnancy
- Start on Folic Acid supplementation
- Antioxidants and Vit D supplementation
- Inositol (Myo-inositol) tends to be deficient in women with PCOS and daily supplementation improves metabolism, egg quality, prevents gestational diabetes.

PREPARATION FOR IVF

- **Metformin administration before and during IVF** reduce the incidence of severe OHSS.

- **OCP** for 2-3 months prior to IVF to suppress ovarian androgen production, particularly. It is an effective approach in the androgenic type of PCOS with secondary amenorrhea.

- **Laparoscopic ovarian drilling** in those with prior failures to respond to ovarian stimulation, IVF cancellation for severe OHSS, androgenic type PCOS with large stromal component on TVUS despite OCPs suppression.

LAPAROSCOPIC OVARIAN DRILLING

- If properly done is very effective in reduction of stromal component along with cortex preservation
- Improves ovarian responsiveness to successive ovulation stimulation and reduces risk of severe OHSS
- Treatment effect significantly diminished after 1 year

Stimulation protocol: GnRH antagonist protocol is recommended.

- A Cochrane review of 29 RCTs showed a significantly lower incidence of OHSS in GnRH antagonist cycles than in GnRH agonist cycles (OR 0.43; 95% CI 0.33 to 0.57).
- No Differences in pregnancy rate or live births were between the two protocols.

The dose and choice of Gonadotropins

- Initial dosing should be carefully individualized. Low starting dose of gonadotropin 150 IU of rFSH with return for assessment after 4 days of stimulation and careful monitoring of these patients during stimulation.

Dose and choice of trigger

- In antagonist cycle use of Lupron trigger decrease risk of severe OHSS; reported dose varies from 1 mg to 4 mg with or without low dose of HCG addition.
- Pregnancy rates are not affected when using gonadotropin- GnRH agonists in GnRH antagonist protocols.
- The use of either rLH or HCG trigger does not influence the incidence of OHSS. Commonly reduced dose of HCG is recommended.

COASTING – discontinuation of gonadotropins reduces the incidence of severe OHSS. Coasting in a GnRH agonist or GnRH antagonist cycle for up to 3 days does not adversely affect pregnancy rates.

Cabergoline, a selective dopamine agonist, has been introduced as a secondary prevention strategy reduction of risk of OHSS.

- Cabergoline’s mechanism of action is partial inhibition of the phosphorylation of its associated receptor, the VEGF receptor 2 which plays the key role in pathophysiology of capillary permeability in OHSS.
- Oral Cabergoline is started on the trigger day at 0.5 mg daily for 7 days. It does not affect IVF pregnancy rates.

Scheduled oral Protein intake starting on day of trigger. Patients are provided with the OHSS instructions about symptoms and prevention and incremental increase in protein intake frequency and dose if symptoms increased or persist.

PREVENTION OF OHSS IN IVF CYCLE

- **Freeze all, with embryo transfer in frozen cycle** effective prevention of severe OHSS
  - Initial cycle planning as freeze all or decide at or shortly after retrieval
  - Higher pregnancy rates in frozen cycle reported

- **Cycle cancellation** before administration of HCG is an effective strategy for the prevention of OHSS, but the emotional and financial burden it imposes on patients should be considered prior to cancellation discussion and should be used as the last resort.
IVF CYCLE MANAGEMENT

- Elective single embryo transfer on in fresh cycle if no OHSS or only mild OHSS symptoms.

- Luteal phase support - Progesterone, rather than human chorionic gonadotropin, should be used. In Antagonist cycles with Agonist trigger, addition of estrogen recommended.

- Late onset OHSS is more common and may last for 2-3 weeks from onset of pregnancy, requires monitoring and supportive measures. May have self limited mild-moderate elevation of LFTs noted.