**Infertility Clinical Guideline**  
**Polycystic Ovary Syndrome**

**Purpose:** To provide a consistent process for determining the optimal course of treatment for patients with suspected or confirmed Polycystic Ovary Syndrome (PCOS) as the underlying etiology of infertility.

**Goal:** To assist staff in understanding the clinical signs and impact of PCOS and provide a clinical rationale and approach to treating PCOS-related infertility.

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| **Polycystic ovary syndrome (PCOS) is a very heterogeneous disorder that may include different phenotypes (Rotterdam workshop)**  
  - hyperandrogenism, chronic anovulation, and polycystic ovaries  
  - hyperandrogenism and chronic anovulation but normal ovaries  
  - hyperandrogenism and polycystic ovaries but ovulatory cycles  
  - chronic anovulation and polycystic ovaries but no clinical or biochemical hyperandrogenism  
  - 62.8% of patients may be anovulatory, but 28.8% may have normal ovulatory cycles  
| **Laboratory parameters may include some or all of the following: (Guastella)**  
  - Elevated luteinizing hormone (LH)  
  - Elevated LH/FSH (Follicle Stimulating Hormone) ratio  
  - Elevated Testosterone  
  - Elevated DHEAS  
    - Should be used with caution as a marker of adrenal androgen secretion (Azziz)  
  - Decreased SHBG (sex hormone binding globulin)  
    - The measurement of SHBG and total testosterone, from which can be calculated free Testosterone, has a high predictive value for PCOS  
  - Sonographic findings of polycystic ovaries should not be considered the sin qua non for PCOS  
    - 20%-30% of healthy young women may demonstrate these findings.  
| **Obesity (central adiposity) is common in women with PCOS and is linked to failure or delayed response to the various infertility treatments.**  
  - Dyslipidemia, which may involve elevations in triglycerides and LDL and total cholesterol and low levels of HDL cholesterol occur frequently  
  - 70% of PCOS patients exhibit an abnormal lipid profile  
  - Weight loss can be associated with the resumption of spontaneous ovulation  
| **Insulin Resistance is common in women with PCOS – 50%-70%**  
  - Body mass index, hirsutism and total testosterone are predictors of insulin resistance |
The incidence of type 2 diabetes is increased (Svendson).

There are serious long-term cardiovascular sequelae, including atherosclerosis and other vessel changes with an increased risk for stroke and coronary artery disease (Rizzo).

Metformin appears to lower the fasting insulin level, but it does not appear to result in consistent significant changes in BMI or waist-to-hip ratio (Lord, Tang, Palomba).

Metformin does not significantly increase ovulatory frequency and should not be the first line drug for ovulation induction (Swanton).

Metformin does not decrease the risk of miscarriage.

- Ovulation Induction is often required to achieve pregnancy (Messinis)
  - 75% of women taking Clomiphene will ovulate, but only 22% may conceive per ovulatory cycle.

- Gonadotropins may be utilized
  - Women with PCOS are prone to hyper-respond and are at risk for multiple gestation and ovarian hyperstimulation syndrome.
  - 70% of women may be expected to ovulate, but only 20% may conceive per cycle.

- In vitro fertilization should be considered for PCOS patients who fail to conceive with clomiphene
  - There appears to be no benefit in metformin co-treatment before and during IVF in women with PCO without any other features of PCOS.

Client Target Population

This guideline applies to all women with signs or symptoms of PCOS attempting to achieve conception.

Diagnosis

- Diagnosis should be based upon the clinical history and physical examination.
- Laboratory testing may include measurements of SHBG, total Testosterone, FSH, LH.
  - Exclude late onset congenital adrenal hyperplasia, Cushing’s syndrome and virilizing tumors, when clinically indicated.
- Tests for insulin resistance are highly variable and may include homeostatic model assessments (HOMA) or QUICKI if available. Otherwise, a 2 hour oral glucose tolerance test with insulin measurements is the preferred method of assessment. Identification of insulin resistance should lead to specific therapy.
  - A simple glucose to insulin ratio <4.5 predicts insulin resistance but is less reliable due to the large range of variability in insulin levels among different ethnicities.
- Sonographic examination may reveal multiple follicular cysts bilaterally.
- When clinically appropriate, patients may be screened for Cushing’s syndrome, congenital adrenal hyperplasia, and androgen secreting neoplasms.

Treatment

- Before any intervention is initiated, preconception counseling should be provided emphasizing the importance of lifestyle modification, especially weight reduction and exercise in overweight women, smoking cessation, and control of alcohol consumption.
- Weight loss should be recommended as the first line therapy in obese women.
Clomiphene Citrate is the treatment of first choice for induction of ovulation in anovulatory women with PCOS
- Dosing should begin at 50 mg/day and may be increased up to 200 mg/day based only upon ovulatory response or lack thereof.
  - The addition of metformin may be beneficial for women demonstrating resistance to clomiphene
- Gonadotropin dosing should reflect the risk of hyper-response (Farhi)
  - Initial dosing should start with 37.5 IU to 75 IU
  - Either step-up (increasing the dose based upon response) or step-down (decreasing the dose based upon response) protocols are acceptable (Andoh)
  - Cycle cancellation is advised when there are >2 follicles larger than 14 mm in diameter and/or when the estradiol level is ≥ 2500 pg/ml (Dickey)
In vitro fertilization should be recommended for all clomiphene resistant patients
- The use of antagonist protocols can minimize the risk of ovarian hyperstimulation syndrome
- Women with PCOS may be excellent candidates for eSET and frozen embryo transfer cycles
  - High oocyte yield can be expected
  - A frozen transfer cycle may be beneficial in providing a uterine environment that is more conducive to implantation, given the likely high estrogen levels during a fresh stimulation cycle

**Best Practices**
- Promote weight reduction
- Provide preconception counseling, including a discussion of risks for multiple gestation with ovulation induction
- Clomiphene citrate is the agent of first choice for ovulation induction
- Gonadotropins may be used cautiously for ovulation induction in the face of resistance to clomiphene
- IVF is the treatment of choice for failed ovulation induction
- PCOS patients should be ideal candidates for elective single embryo transfer
- Consideration should be given to promoting a frozen embryo transfer cycle in lieu of a fresh transfer given the expected high levels of estrogen in PCOS and possible altered uterine environment that may be detrimental to implantation

**Medical Director Escalation**
- Medical director to review cases of >3 failed gonadotropin cycles where additional cycles are recommended

**Case Example**
A 28 year old member presents with irregular periods, a BMI > 28 and mild hirsutism. She states that she and her husband have been unable to conceive which she suspects is due to the fact that she believes she does not ovulate. Her history is otherwise unremarkable. A preliminary evaluation reveals mildly elevated total testosterone levels. The Semen analysis is normal. An evaluation of tubal patency is not performed given a lack of risk factors for tubal disease. The glucose to insulin ratio is abnormal, suggesting insulin resistance. After the patient is counseled about the
risks of insulin resistance, and after appropriate baseline screening of hepatic and renal function, she is started on metformin. Simultaneously, she begins a regimen of clomiphene 50 mg. Her periods remain irregular despite an increase in dosage to 150 mg. An attempt at ovulation induction with Gonal F 75 IU results in a hyper-response and the cycle is canceled. She is advised to pursue IVF. eSET is highly recommended given her age and the likelihood of retrieving a large quantity of oocytes. Further discussion addresses the benefit of freezing all good quality blastocysts for a subsequent frozen embryo transfer cycle. The member would like to minimize the risk of a multiple gestation while increasing her chance for conception. An IVF cycle, utilizing an antagonist protocol and no more than Gonal F 150 IU/day, results in the retrieval of 22 oocytes. Ultimately, 8 high quality embryos are frozen. The member awaits the transfer of a single thawed embryo within the next 2 months.

Bibliography


Guastella E, Longo RA, Carmina E: Clinical and endocrine characteristics of the main polycystic ovary syndrome phenotypes. Fertil Steril 2010; 94: 2197-2201


The Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group: Consensus on infertility treatment related to polycystic ovary syndrome. Fertil Steril 2008; 89: 505-522

Revision History

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<thead>
<tr>
<th>Version</th>
<th>Date</th>
<th>Description of Change</th>
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<td>07/11/2011</td>
<td>Converted from training document to job aid format -ekb</td>
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<td>2.0</td>
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<td>Reformatted revised content from Dr. Dlugi – ekb</td>
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<tr>
<td>3.0</td>
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