

# INFERTILITY TREATMENT FOR POLYCYSTIC OVARIAN SYNDROME: WHEN CLOMIPHENE DOESN'T WORK

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Many women suffering from infertility fail to release an egg each month. This state of *chronic anovulation* is characterized by irregular menstrual cycles and may be accompanied by obesity or hirsutism (increased hair growth). The condition is known as *polycystic ovarian syndrome* (PCOS) and despite its' name, has little to do with ovarian cysts. There are other hormonal imbalances, such as hypothyroidism, hyperprolactinemia, and hyperinsulinemia, associated with anovulation but PCOS is by far, the most common. In treating infertile couples suffering from PCOS, the first option is the use of an ovulation drug called clomiphene citrate. Clomiphene citrate can be taken by mouth and is initially started at 50 mg (1 tablet) a day and increased incrementally to at least a dose of 150 mg a day in an effort to induce ovulation. With standard clomiphene citrate treatment, 75% of patients suffering from PCOS will resume ovulation. The 25% of patients who do not ovulate with standard dosages of clomiphene citrate are usually referred to as "clomiphene - resistant". The following discussion will outline the treatment options available for clomiphene - resistant patients.

## WEIGHT LOSS

Obesity is known to contribute to infertility and may increase a pregnant woman's risk for complications during pregnancy and delivery. In addition, obesity can lead to high blood pressure, high cholesterol, diabetes, cancer and heart disease. Women with PCOS often present with excessive weight.

Being overweight is defined by a body mass index (BMI) over 25 kg/m<sup>2</sup> while obesity is defined by a BMI over 30 kg/m<sup>2</sup>. The table on this page can be used to calculate your BMI. To use the table, find your height (in inches) in the left hand column, and then move across the row to your weight (in pounds). The number at the top of the column is the BMI for your height and weight.

It is vitally important for overweight women with PCOS to lose weight. There is simply no other therapy that offers as much benefit as sustained weight loss. While studies have demonstrated that women can resume regular menstrual periods and achieve pregnancy after losing as little as 5% of their starting body weight, most women, especially those who have a BMI greater than 28, will need to set a goal of 10-15% weight loss. The weight goal must be maintained for at least 6 months in order to see an improvement in PCOS symptoms.

Many programs are available to assist women in weight loss, including the Lifestyle class offered through Fertility Associates of Memphis. After hormonal causes of excess weight are ruled out, a daily evaluation of calorie intake and exercise output will assist in achieving the weight goal.

BMI (kg/m <sup>2</sup> )	19	20	21	22	23	24	25	26	27	28	29	30	35	40	
	< NORMAL					>< OVERWEIGHT					>< OBESITY				
Height (in.)	Weight (lb.)														
58	91	96	100	105	110	115	119	124	129	134	138	143	167	191	
59	94	99	104	109	114	119	124	128	133	138	143	148	173	198	
60	97	102	107	112	118	123	128	133	138	143	148	153	179	204	
61	100	106	111	116	122	127	132	137	143	148	153	158	185	211	
62	104	109	115	120	126	131	136	142	147	153	158	164	191	218	
63	107	113	118	124	130	135	141	146	152	158	163	169	197	225	
64	110	116	122	128	134	140	145	151	157	163	169	174	204	232	
65	114	120	126	132	138	144	150	156	162	168	174	180	210	240	
66	118	124	130	136	142	148	155	161	167	173	179	186	216	247	
67	121	127	134	140	146	153	159	166	172	178	185	191	223	255	
68	125	131	138	144	151	158	164	171	177	184	190	197	230	262	
69	128	135	142	149	155	162	169	176	182	189	196	203	236	270	
70	132	139	146	153	160	167	174	181	188	195	202	207	243	278	

## **INSULIN SENSITIZERS**

Women with PCOS demonstrate resistance to the action of the insulin hormone that aids the cells throughout the body to take in glucose for nutrition. Therefore, the body has to make more insulin in order to nourish the cells and keep blood glucose levels stable. If the body fails to produce enough insulin, then diabetes will develop. It is documented that PCOS women have nearly a four-fold increase in risk of developing diabetes by age 40 than women who do not have PCOS.

A consequence of resistance to insulin action is a high level of insulin that constantly circulates throughout the body. At the ovary, it is believed that high insulin is the primary reason why PCOS women fail to ovulate. It is reasonable to deduce that if the body can be made to be more sensitive to insulin, then insulin levels could drop and ovulation would resume. Recent studies have confirmed that treatment to raise insulin sensitivity and lower circulating insulin in PCOS patients results in dramatically improved ovulation and pregnancy rates. Furthermore, insulin sensitization lowers the level of androgens (male hormone), which is responsible for hirsutism and acne in many PCOS women. The most commonly used medication is metformin (Glucophage®) and is approved for the treatment of type II diabetes. Fertility Associates of Memphis has recently published a trial in which another diabetes treatment, rosiglitazone (Avandia®), was able to induce ovulation in over 75% of women previously resistant to clomiphene alone.

Insulin sensitization therapy may not just offer the short-term benefit of ovulation induction. It appears that resistance to insulin may not just be associated with PCOS and diabetes but also high cholesterol and heart disease. Recently, a large, federally funded study demonstrated that long-term (more than 4 years) treatment with metformin in people at risk for diabetes could lower their risk of actually developing diabetes by 40% as compared to placebo. It also drastically reduced their cholesterol and risk of cardiovascular disease. Side effects vary from stomach upset and diarrhea with metformin to swollen fingers and feet with rosiglitazone. Tests to monitor your liver and kidney function will be done while taking insulin sensitizers. Your physician will review the individual risks with you.

## **AROMATASE INHIBITORS**

Clomiphene works by blocking the estrogen receptors in the brain and causing it to induce ovulation in the ovary. The same effect can be accomplished with aromatase inhibitors, a group of medications primarily indicated in the treatment of breast cancer. Aromatase inhibitors do not block the estrogen receptors like clomiphene in the brain but inhibit overall production of estrogen temporarily achieving the same effect. Because there is no blockage of the estrogen receptor, the effect is much shorter in duration and there is less detrimental effect on the growth of the endometrial (uterine) lining and the changes in the cervical mucus so common with clomiphene.

The aromatase inhibitor most commonly used is called letrozole (Femara®). It is prescribed in a similar fashion as clomiphene with a five-day course right after her menses. In one study, the investigators had good success with a one-time dose. Ovulation is typically around day 14-16. Due to its mechanism of action, letrozole is a good choice for women with an ovulatory response to clomiphene but is either not achieving pregnancy or is known to have endometrial or cervical mucus development issues. Most people have very few side effects with letrozole. Mild nausea can be controlled by taking the pill with food at night. Uncommonly, women experience tiredness, headaches, muscular aches, or hot flashes. You should contact your physician if you have any side effects.

## **GONADOTROPIN THERAPY**

Gonadotropin therapy is typically the next step for clomiphene - resistant patients. This is medication given by injections typically taken for 8-12 days. Gonadotropins induce the production of multiple eggs that are then released (ovulated) on a specific schedule. Because we can time the moment of ovulation, gonadotropin therapy is often combined with intrauterine insemination (IUI) using the husband's sperm. Gonadotropins are very successful with as many as 90% of patients, previously resistant to clomiphene, successfully ovulating. Careful monitoring of therapy using blood hormone tests and vaginal ultrasounds is necessary. Risks of therapy include a high (1 in 4) probability of twins and a 1-2% chance of triplets (or higher). Rarely, patients may be at risk for ovarian hyperstimulation syndrome (OHSS), which is a serious condition that affects not only the ovaries, but the liver, kidneys and circulatory systems as well. Again, with proper monitoring, the risk of OHSS is largely preventable. A complete description of the gonadotropin therapy, including the risks and cost involved, is available as a separate handout.

## **SURGICAL THERAPY WITH LAPAROSCOPIC OVARIAN DRILLING**

Before 1970, the popular therapy for PCOS was described as ovarian wedge resection. This involved a major operation with a large incision where approximately one quarter to one third of the ovary was taken out in a pie fashion and the ovary was sewn closed. The theory involves the ovary as the source of increased androgen production that is inhibiting ovulation. When a portion of the ovary is removed, many patients would begin to ovulate. However, the effect was temporary and the anovulation would often return within months. Furthermore, the surgery often induced scar tissue that would damage the

nearby fallopian tubes. With the development of clomiphene citrate, the classic ovarian wedge resection was, for most purposes, abandoned.

With the advent of laparoscopy and outpatient surgery, this concept has been revisited. The theory is essentially the same, which is destroying part of the ovarian tissue that is responsible for the increased androgens. However, today, it can be performed as an outpatient basis through the laparoscope, a lighted telescope inserted into the abdomen through one or two small incision sites in the lower abdomen. Numerous (usually 20 or more) 'punctures' are made in the ovary with the use of laser or electrical energy. With or without added clomiphene, ovulation resumes in approximately 20-50% of patients. As with the original procedure, the effect is temporary with anovulation returning after several months. However, surgery through the laparoscope was less likely to form dense scar tissue around the tubes and recovery time was much shorter than the larger operation. Still scar tissue can occur and ovarian drilling is considered only when other techniques have failed.

## **CONCLUSIONS**

Most infertile women with anovulation and PCOS will respond to clomiphene. For those that do not, there are several treatment options available and all have their advantages as well as disadvantages. If you are overweight, then a plan to achieve sustained weight loss is of paramount importance. Using one or more of the treatments reviewed above, most clomiphene – resistant women will be able to ovulate and hopefully, conceive.

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