

Polycystic Ovary Syndrome (PCOS) Symptoms, Causes & Treatments - A Review

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Abstract: Polycystic ovary syndrome [PCOS] is one of the most common endocrinopathy of women at reproductive age. Association between PCOS and type-1 endometrial cancer has often been reported. The prolonged an ovulation with consequent continued secretion of oestrogen unstopped by progesterone may enhance the development and growth of this into malignancy, particularly in young women. Hypersecretion of luteinizing hormone [LH], chronic hyperinsulinemia and increased insulin-like growth factor [IGF] levels may represent risk factors for endometrial cancer. Although, data analysis is carried out to calculate an estimate the risk of endometrial cancer in women with PCOS. Anecdotal cases of low-grade endometrial stromal sarcoma and carcinosarcoma have been reported in association with prolonged unopposed oestrogen stimulation, and in particular with PCOS. A few studies have addressed the possibility of an association between PCOS and epithelial ovarian cancer risk. Women with PCOS produce higher-than-normal amounts of male hormones. This hormone imbalance causes them to skip menstrual periods and makes it harder for them to get pregnant. Nowadays almost maximum of woman are suffering from this fatal syndrome which shows various risk factors in their later pregnancy period. Till now research is going on for this syndrome.

Keywords: androgenetic alopecia; cyproterone acetate; drospirenone; polycystic ovary syndrome; spironolactone, MAPK/ERK/p38 signaling pathway; metformin; clomiphene citrate.

1. Introduction

Polycystic ovary syndrome (PCOS) is an endocrine disorder that affects at least 7% of infertile women. Polycystic ovary syndrome (PCOS) affects more than 10% of women at reproductive age and is one of the most common endocrinal disorders in this age group. PCOS is a heterogeneous disease with neuroendocrine findings and characterized by menstrual irregularity and hyperandrogenism, with or without presence of polycystic ovarian morphology. PCOS presents with a broad spectrum of phenotypes. Insulin resistance is not universal in PCOS. However, certain phenotypes are associated with insulin resistance and an increased long-term risk of developing metabolic syndrome (MBS) and cardiovascular disease which are compounded by concurrent obesity. Metabolic syndrome is comprised of a combination of the following states: increased insulin resistance, dyslipidemia, cardiovascular diseases, and increased abdominal obesity. Women with polycystic ovary syndrome (PCOS) have an increased risk of developing metabolic syndrome over the course of their lives. Metabolic syndrome increases risk of major cardiovascular events, morbidity, quality of life, and overall health care costs. Though metabolic syndrome in women with PCOS is an area of great concern, there is no effective individual medical therapeutic to adequately treat this issue. Clomiphene Citrate (CC) is recommended as first line treatment for induction of ovulation in patients with PCOS by virtue of its efficacy, safety, and ease of administration. Alternatives for CC-resistant patients include gonadotrophin therapy (better with low-dose step-up protocol) and laparoscopic ovarian diathermy. Recently, recombinant FSH (rFSH) has been introduced in clinical practice and it seems more effective than urinary FSH as demonstrated by a significantly higher number of follicles recruited and embryos obtained with a shorter treatment period. The addition of GnRH-agonist to the stimulation protocol for women affected by PCOS could reduce premature

luteinization and increase cycle fecundity. Other drugs under investigation are metformin and cabergoline. The primary goal of the treatment of hirsutism is central or peripheral androgen suppression using 3 groups of drugs: inhibitors of androgen production (oral contraceptives, GnRH analogues), peripheral androgen blockers like cyproterone acetate, flutamide, finasteride and spironolactone, and insulin-sensitizing agent like metformin. Work-out too could also improve not only menstrual cycle and infertility, but also insulin resistance and its adverse metabolic consequences.

2. Common Symptoms for PCOS Patients

Some women start seeing symptoms around the time of their first period. Others only discover they have PCOS after they've gained a lot of weight or they've had trouble getting pregnant. PCOS is a problem with hormones that affects women during their child bearing ages 15 to 44. Up to 70% of women with PCOS hadn't been diagnosed. PCOS affects a woman's ovaries, the reproductive organs that produce estrogen and progesterone hormones that regulate the menstrual cycle. The ovaries also produce a small amount of male hormones called androgens. The ovaries release eggs to be fertilized by a man's sperm. The release of an egg each month is called ovulation. Follicle-stimulating hormone (FSH) and luteinizing hormone (LH) control ovulation. FSH stimulates the ovary to produce a follicle a sac that contains an egg and then LH triggers the ovary to release a mature egg. PCOS is a 'syndrome' or group of symptoms that affects the ovaries and ovulation. Its three main features are:

- Cysts in the ovaries
- High levels of male hormones
- Irregular or skipped periods

In PCOS, many small, fluid-filled sacs grow inside the ovaries. The word "polycystic" means "numerous cysts". These sacs are actually follicles, each one containing an

immature egg. The eggs never mature enough to trigger ovulation. The lack of ovulation alters levels of oestrogen, progesterone, FSH, and LH. Estrogen and progesterone levels are lower than usual, while androgen levels are higher than usual. Extra male hormones disrupt the menstrual cycle, so women with PCOS get fewer periods than usual. (Mol et al. 2019)

2.1 Other Symptoms

- a) **Improper periods:** A lack of ovulation prevents the uterine lining from shedding every month. Some women with PCOS get fewer than eight periods a year.
- b) **Heavy flow:** The uterine lining builds up for a longer period of time, so the periods you do get can be heavier than normal.
- c) **Growth of hair:** More than 75% of women with this condition grow hair on their face and body including on their back, belly, and chest. Excess hair growth is called *hirsutism*.
- d) **Acne:** Male hormones can make the skin oilier than usual and cause breakouts on areas like the face, chest, and upper back.
- e) **Darkening of the skin:** Dark patches of skin can form in body creases like those on the neck, in the groin, and under the breasts.
- f) **Headaches:** Hormone changes can trigger out headaches in few women.

PCOS affects body by following ways:

Having higher than normal androgen levels can affect your fertility and other aspects of your health.

Infertility

To get pregnant, woman have to ovulate. Women who don't ovulate regularly don't release as many eggs to be fertilized. PCOS is one of the leading causes of infertility in women.

Insulin-sensitizing agents, including metformin, rosiglitazone, and pioglitazone, have been effective in improving fertility and ovulation in women with PCOS. There are conflict in the literature regarding whether metformin, clomiphene, or a combination of the two agents works for improving rate of pregnancy in women with PCOS. A recent study confirmed that six months of metformin therapy was more effective than six months of clomiphene therapy for improving fertility in anovulatory, non-obese women with PCOS. A large random trial of more than 600 women found that clomiphene is better working than metformin in achieving live birth in infertile women with PCOS. An other study too showed no benefit from combining drugs like metformin and clomiphene. Although two analysis suggested that the combination is much better than using clomiphene alone. Finally, two systematic reviews found challenging results: one suggests metformin does not affect ovulation or pregnancy rates, and the other suggests metformin does. (Nestler et al. 2016)

Weight gain

More than 70% of women with PCOS suffers from obesity. High insulin levels boost the production of male hormones named androgen. High androgen levels lead to symptoms such as excess hair growth, acne, improper

periods and obese. The weight gain is triggered only due to male hormones (androgen), it's typically in the abdomen which causes men tend to carry weight.

Abdominal fat is the massive kind of fat in our body. That's why it's associated with an increased risk of heart disease and other health conditions. (Smith et al. 2019)

Metabolic syndrome

Both obesity and PCOS increases risk for high b.p (blood pressure) level, low HDL (good cholesterol), and high LDL (bad cholesterol). These factors are metabolic syndrome, and they increase the risk for diabetes, and angina pectoris.

Sleep apnea

This condition causes repeated pauses in breathing during the night, which hampers sleep. Sleep apnea is more common in women who are overweight if they have PCOS. The risk for sleep apnea is 5 to 10 times higher in obese women with PCOS than in those without PCOS. (Fothergill et al. 2019)

Cancer

Medical management for abnormal vaginal bleeding or endometrial hyperplasia consists of estrogen-progestin oral contraceptives, cyclic or continuous progestin or a levonorgestrel-releasing intrauterine device named Mirena. Lifestyle modification with caloric restriction and exercise is appropriate to treat obesity as a concomitant risk factor for developing endometrial disease. An increased risk of ovarian cancer may also exist in some women with PCOS. There are strong data to suggest that oral contraceptive use is protective against ovarian cancer and increases with the duration of therapy. The mechanism of this protection may be through suppression of gonadotropin secretion rather than the prevention of "incessant ovulation". There is no apparent association of PCOS with breast cancer, although the high prevalence of metabolic dysfunction from obesity is a common denominator for both conditions. Recent data suggest that the use of metformin may be protective for both endometrial and breast cancer. There are insufficient data to evaluate any association between PCOS and vaginal, vulvar and cervical cancer or uterine leiomyosarcoma. (Lisa M et al. 2019)

Insulin resistance

Up to 70 percent of women with PCOS have insulin resistance, meaning that their cells can't use insulin properly. Insulin is a hormone the pancreas produces to help the body use sugar from foods for energy. When cells can't use insulin properly, the body's demand for insulin increases. The pancreas makes more insulin to compensate. Extra insulin triggers the ovaries to produce more male hormones obesity is a major cause of insulin resistance. Both obesity and insulin resistance can increase your risk for type 2 diabetes.

Inflammation

Women with PCOS often have increased levels of inflammation in their body. Being overweight can also contribute to inflammation. Studies have linked excess inflammation to higher androgen levels.

PCOS diagnosis

Doctors typically diagnose PCOS in women who have at least two of these three symptoms .

- High androgen levels
- Irregular menstrual cycles
- Cysts in the ovaries

Your doctor should also ask whether you've had symptoms like acne, face and body hair growth, and weight gain. A pelvic exam can look for any problems with your ovaries or other parts of your reproductive tract. During this test, your doctor inserts gloved fingers into your vagina and checks for any growths in your ovaries or uterus.

Blood tests check for higher-than-normal levels of male hormones. You might also have blood tests to check your cholesterol, insulin, and triglyceride levels to evaluate your risk for related conditions like heart disease and diabetes. An ultrasound uses sound waves to look for abnormal follicles and other problems with your ovaries and uterus.

Common medical treatments:

Birth control pills and other medicines can help regulate the menstrual cycle and treat PCOS symptoms like hair growth and acne. Drugs used in the treatment of polycystic ovarian syndrome (PCOS) include metformin (off-label use), spironolactone, eflornithine (topical cream to treat hirsutism), and oral contraceptives. Oral contraceptives containing a combination of estrogen and progestin increase sex hormone-binding globulin (SHBG) levels and thereby reduce the free testosterone level. Luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels are also suppressed. This restores cyclic exposure of the endometrium to estrogen-progestin, with the resumption of menstrual periods and decreased hirsutism. However, the use of oral contraceptives may be associated with an increased risk of thrombosis and metabolic abnormalities.

An oral contraceptive containing ethinyl estradiol and a progestin with minimal androgenic activity, such as norgestimate, norethindrone, or desogestrel, should be selected. Drospirenone-ethinyl estradiol combined with drospirenone (Yasmin) has a progestin that acts as an antiandrogen and thus may add antiandrogenic effects.

Birth control

Taking estrogen and progestin daily can restore a normal hormone balance, regulate ovulation, relieve symptoms like excess hair growth, and protect against endometrial cancer. These hormones come in a pill, patch, or vaginal ring.

Metformin

Metformin improves insulin resistance (diagnosed by elevated fasting glucose or fasting glucose/insulin ratios) in patients with PCOS; other useful agents include rosiglitazone and pioglitazone.

Metformin (Glucophage, Fortmet) is a drug used to treat type II diabetes. It also treats PCOS by improving insulin levels. One study found that taking metformin while making changes to diet and exercise improves weight loss, lowers blood sugar, and restores a normal menstrual cycle better

than changes to diet and exercise alone. Impaired progesterone (P4) signaling is linked to endometrial dysfunction and infertility in women with polycystic ovary syndrome (PCOS). Here, we report for the first time that elevated expression of progesterone receptor (PGR) isoforms A and B parallels increased estrogen receptor (ER) expression in PCOS-like rat uteri. The aberrant PGR-targeted gene expression in PCOS-like rats before and after implantation overlaps with dysregulated expression of *Fkbp52* and *Ncoa2*, two genes that contribute to the development of uterine P4 resistance. *In vivo* and *in vitro* studies of the effects of metformin on the regulation of the uterine P4 signaling pathway under PCOS conditions showed that metformin directly inhibits the expression of PGR and ER along with the regulation of several genes that are targeted dependently or independently of PGR-mediated uterine implantation. Functionally, metformin treatment corrected the abnormal expression of cell-specific PGR and ER and some PGR-target genes in PCOS-like rats with implantation. Additionally, we documented how metformin contributes to the regulation of the PGR-associated MAPK/ERK/p38 signaling pathway in the PCOS-like rat uterus. Our data provide novel insights into how metformin therapy regulates uterine P4 signaling molecules under PCOS conditions. (N.P. Johnson et al. 2014)

Letrozole

This breast cancer treatment can work to stimulate the ovaries. Letrozole is an aromatase inhibitor used to induce ovulation in patients with irregular menses or no menses at all. Letrozole works to induce ovulation by blocking estrogen production, leading to increases in follicle-stimulating hormone (FSH) release.

Letrozole plays very important role in the treatment of infertility women with PCOS. However, its efficacy is still inconsistent, especially when compared with clomiphene.

Previous systematic review and meta-analysis reported that letrozole could significantly enhance the live birth and pregnancy rates in patients with PCOS. However, the other meta-analysis did not find positive efficacy of letrozole when compared with clomiphene. The results of the present study are consistent with the previous studies. The results of this retrospective study showed that no significant differences of adverse events were detected between 2 groups. In addition, patients in the Letrozole group did not exert better outcomes in primary endpoint of live birth, birth weight, and infant gender; and also in secondary endpoints of the number of women with conception, pregnancy, pregnancy loss, pregnancy loss in first trimester, and ovulation, compared with subjects in the clomiphene group. Additionally, no significant differences in adverse events were found between 2 groups. It indicated that letrozole and clomiphene have similar efficacy and safety in treating infertility women with PCOS. This retrospective study had several following limitations. First of all, the sample size was still relative small, which may affect the results of this study. Then, this retrospective study had its own intrinsic limitation, which may impact its results. Thirdly, this study did not include comprehensive endpoints, such as quality of life in infertility women with PCOS, because it just analyzed the outcome data based on the completed cases only. Fourth, this study did not utilize randomization and blinding, which

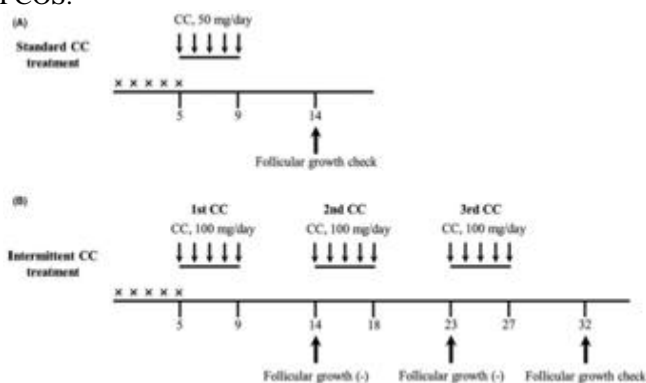
may increase the risk of case selection. Therefore, the future studies should avoid all these limitations. (Hui-juan Guanget al. 2018)

Spironolactone

This medication blocks the effects of androgen on the skin. Spironolactone can cause birth defect, so effective contraception is required while taking this medication. It isn't recommended if you're pregnant or planning to become pregnant. Androgens such as testosterone are responsible for hair growth on the face, chest, and stomach that some young women with PCOS have. Androgens can also cause acne. Spironolactone works by lowering the level of androgens, which lessens hair growth and improves acne. (Ganie et al. 2013)

Clomiphene

Clomiphene is a fertility drug that can help women with PCOS get pregnant. However it increases the risk for twins and other multiple births. Clomiphene citrate (CC) has been used as a first-line treatment for anovulatory polycystic ovary syndrome (PCOS). However, some patients with PCOS are resistant to standard CC treatment. In this study, a new CC treatment protocol was developed, named "intermittent CC treatment" (ICT) and its efficacy was investigated on the induction of follicular growth in patients with PCOS who were resistant to standard CC treatment. Patients with PCOS who are receiving low-dose FSH treatment, it is difficult to predict when the follicles will respond to FSH and when follicular growth will start. As a result, the long-term administration of FSH is needed. Another problem is that the response to FSH is different among treatment cycles, even in the same patient. This suggests that there is a window that follicles can respond to gonadotropin and start follicular growth and that the window appears at random times during the treatment cycles. As long-term FSH treatment can keep the serum FSH levels high, this regimen should be able to find this window, even if it appears at random times. Based on this hypothesis, alternative treatments that can maintain high serum FSH levels are also promising for the induction of follicular growth in CC-resistant patients with PCOS. Thus, this study developed a new CC treatment protocol, named "intermittent CC treatment" (ICT). It was hypothesized that maintaining high serum FSH levels by repeating the administration of CC would effectively induce follicular growth in CC-resistant patients. This study was undertaken to investigate whether ICT is a useful treatment method for the induction of follicular growth in CC-resistant patients with PCOS.



Treatment regimens with standard clomiphene citrate (CC) treatment and intermittent CC treatment (ICT). Standard CC treatment: Patients with polycystic ovary syndrome (PCOS) were given 50 mg of CC daily for 5 days, starting on the menstrual cycle day (MCD) 5. Follicular growth was checked on MCD 14. If follicular growth was not observed by the standard CC treatment, they underwent ICT. ICT: The patients who were resistant to the standard CC treatment were given 100 mg of CC daily for 5 days (MCD 5-MCD 9) of the next menstrual cycle (first CC). The follicular growth was checked on MCD 14. If follicular growth was not observed, the patients were regarded as non-responders to the first CC and were given a further 100 mg/day of CC daily for 5 days (MCD 14-MCD 18) (second CC). The follicular growth was checked on MCD 23. If follicular growth still was not observed, the patients were regarded as non-responders to the second CC and were given a further 100 mg/day of CC daily for 5 days (MCD 23-MCD 27) (third CC). If follicular growth still was not observed on MCD 32, they were regarded as non-responders to the third CC.

3. Result

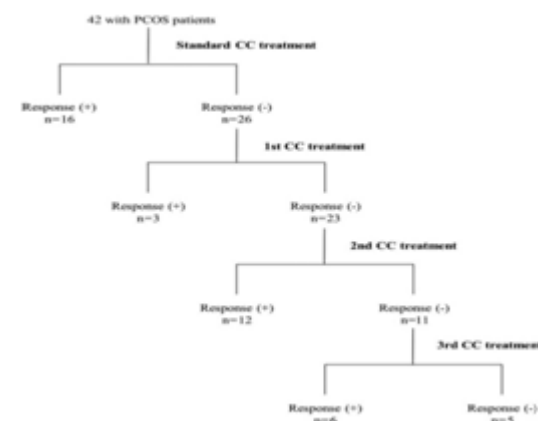


Figure aside shows the effects of CC on the induction of follicular growth in patients with PCOS. Of the 42 patients, 26 (61.9%) did not show follicular growth by the standard CC treatment. They were diagnosed with CC-resistant PCOS and underwent ICT, in which the first CC was effective for three out of 26 (11.5%) patients. The remaining 23 patients underwent the second CC, and of these, 12 (52.2%) patients responded. The remaining 11 underwent the third CC, and of these, six (54.5%) patients responded. In total, ICT was effective for 21 out of the 26 (80.8%) CC-resistant patients with PCOS. On the day of the HCG injection, a single mature follicle was observed in 18 patients, whereas double mature follicles were observed in three patients, who underwent the second CC. Three of the 21 patients became pregnant by ICT during the study cycle. No case of OHSS or multiple pregnancies was observed.

Effects of intermittent clomiphene citrate (CC) treatment (ICT) for standard CC-resistant patients with polycystic ovary syndrome (PCOS). The 42 patients with PCOS received a standard CC treatment. A response meant that follicular growth was observed 5 days after the last day of CC administration, but 26 patients were resistant

to the standard CC treatment and underwent ICT (first CC, second CC, and third CC)

Drospirenone

Drospirenone, in conjunction with EE, acts to suppress gonadotropins. This is achieved through inhibition of ovulation as described above. Drospirenone has a bioavailability of 76% with approximately 20% excreted through the feces, and 45% through the renal system. The half-life of drospirenone is 30 hours, which is slightly longer than the half-life of EE (24 hours). Drospirenone differs from other progestins currently available in other COC compounds, as it exhibits both mineralocorticoid effects and antiandrogenic effects. Part of the novel nature of drospirenone stems from it being structurally and functionally analogous to spironolactone. Spironolactone is an aldosterone antagonist, and a potassium-sparing diuretic. Because of this structural and functional similarity with spironolactone, drospirenone also exhibits anti-mineralocorticoid activity. This property counteracts the estrogen stimulated activity of the renin-angiotensin-aldosterone system, which can influence the regulation of water and electrolyte balance. Because of the possibility that potassium levels may increase, drospirenone should not be used in patients with kidney, liver or adrenal disease. In addition, any patient on other medications that can raise potassium levels (such as ACE inhibitors, angiotensin II receptor antagonists, NSAIDs, potassium-sparing diuretics, and heparin) should be cautioned. This anti-mineralocorticoid activity may also contribute to less water retention as well as less breast swelling and tenderness in women using this form or progestin compared to others. Preclinical studies in animals and in vivo have shown that drospirenone has no androgenic, estrogenic, glucocorticoid or anti-glucocorticoid activity (product monograph). Preclinical studies have shown anti-androgenic activity. Due to its anti-androgen effect, drospirenone can also be used as adjunct treatment for hirsutism, and may be a progestin of choice in women who complain of excessive hair growth. (Ruchi Mathur et al. 2008)

Hair removal medicines

A few treatments can help get rid of unwanted hair or stop it from growing. Eflornithine (Vaniqa) cream is a prescription drug that slows hair growth. Laser hair removal and electrolysis can get rid of unwanted hair on your face and body.

Electrolysis

A tiny needle is inserted into each hair follicle. The needle emits a pulse of electric current to damage and eventually destroy the follicle.

Surgery

Surgery can be an option to improve fertility if other treatments don't work. Ovarian drilling is a procedure that makes tiny holes in the ovary with a laser or thin heated needle to restore normal ovulation. There are two types of surgical interventions used to treat PCOS: **Laparoscopic ovarian drilling** and **Ovarian wedge resection**.

1) Laparoscopic ovarian drilling:

In 1935, Stein and Leventhal described an association among polycystic ovaries, oligo-anovulation, and hirsutism, which was called polycystic ovary syndrome (PCOS). PCOS is defined using the Rotterdam criteria. PCOS affects 12% of women of reproductive age and is the first cause of infertility due to anovulation. The first-line treatment for PCOS-related infertility is medical, using clomiphene citrate (CC). CC induces ovulation in 75% of women. Hyperandrogenism, obesity, high ovarian volume, and an ovulation are predictive factors for the failure of CC. In CC-resistant infertility, there is no standard for management. Aromatase inhibitor has been shown to be effective in restoring ovulation and pregnancy instead of the CC. Although it has not proved its efficiency for CC-resistant infertility compared with placebo (OR 3.17, 95% CI 0.12–83.17) or with ovarian drilling (OR 1.19, 95% CI 0.76–1.86). The two principal options available are a medical treatment by gonadotropin or a surgical management by ovarian drilling. There is no significant difference in birth rate between these two options. Ovarian drilling leads to a lower risk of multiple pregnancies (OR 0.21, CI 95% 0.08–0.58) and avoids hyperstimulation syndrome. Medical treatment requires biological and ultrasound follow-ups, which can be extended over a long period due to the low-dose protocol used. A laparoscopic or transvaginal hydrolaparoscopic drilling involves surgery and anesthesia. The duration during which the ovarian drilling allows to restore an ovulation and thus to obtain a spontaneous pregnancy in case of isolated PCOS is unknown. Published data on the efficacy of recurrent ovarian drillings are scarce. Long-term efficacy, allowing more than one pregnancy through the recovery of spontaneous ovulation, may be a significant advantage over the medical treatment. The possibility of repeating this surgery after a couple of months or years should also be assessed. (Duleba et al. 2002)

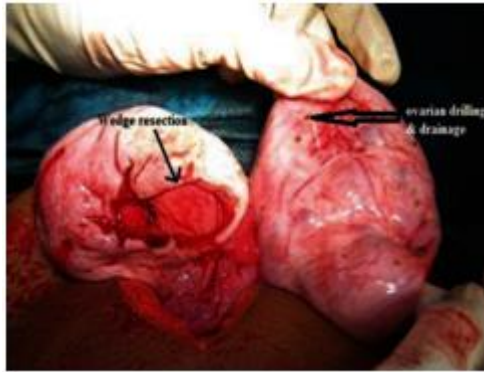
Completion of an ovarian drilling operation



2) Ovarian wedge resection

In this procedure removal of wedge shaped segment of each part of ovary. Then using a special microsurgical techniques, then sewing back the edges of the ovary together in such a way as to prevent scar tissue formation. The procedure requires approx 1 hour and is performed on an outpatient basis, typically requiring patients to be away from work no more than 6 to 7 days. The surgery is performed in the pre-ovulatory or, 'pre-peak' phase of the cycle. The procedure is performed to treat a recognized disease, polycystic ovarian syndrome, it's typically covered by most insurance plans. As with any surgical procedure, there are inherent risks and one should be well informed of those risks before proceed. If a

patient with documented polycystic ovarian syndrome is not responding to ovulation inducing medications, robotic laparoscopic ovarian wedge resection may offer the best opportunity to achieve pregnancy.(Mulazim et al. 2003)



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