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Clomiphene Citrate (Clomid, Serophene) was introduced into clinical medicine for the treatment of anovulation in the 1960's. Its introduction represented a major breakthrough in the medical management for ovulation induction. Prior to Clomiphene, patients with PCOS who were anovulatory had few options besides weight loss and surgical wedge resection of the ovaries. While wedge resection was successful, it required a major surgical procedure and was associated with a high incidence of tubal scarring, both of which limited its widespread application. Sufficient weight loss has proven difficult for even the most motivated patients.

Early studies with Clomiphene suggested that up to 80% of patients could respond favorably (by successfully ovulating) and approximately half of those who ovulated achieved pregnancy. Of those who ovulated, 20% ovulated at 100 mg/day and about 10% ovulated by taking 150 mg/day. The remaining 20% ovulated at either 200 or 250 mg/day. The Physician’s Desk Reference (PDR) does not recommend increasing the dose above 100mg/day, however; many physicians consider either 150 or 200 mg/day to be the maximal dose. The question then becomes: What can be done for the patient who fails to ovulate at maximal doses of clomiphene? A corollary to this question is: Does anything predict which patients will respond to clomiphene?

Before tackling the first question, let’s investigate whether the clomiphene resistant patient can be predicted. The World Organization (WHO) classifies anovulatory women into 3 categories. Those for whom the ovaries fail to function properly because of decreased signals from the brain (hypothalamus and pituitary) are in Group I. Typically the pituitary hormone “follicle stimulating hormone (FSH)” is low in these patients. This may be due to excessive exercise, disorders of inadequate weight such as anorexia nervosa, tumors of the hypothalamus or pituitary, or a rare disorder called Kallman’s syndrome. Most patients in Group I will not ovulate in response to clomiphene because the hypothalamic-pituitary axis is not functioning normally. Patients with PCOS are in Group II and clearly can respond to clomiphene in most cases. Patients with intrinsic ovarian failure are in Group III. These patients will have an elevated FSH level and may include premature ovarian failure, prior surgery or radiation, or advancing age. Patients in Group III do not respond to clomiphene because the ovaries have stopped functioning. Therefore patients with a low FSH (Group I) or a high FSH (Group III) will be clomiphene resistant. Both groups are usually detected by a failure to have a period after a progesterone-like medication (Provera, Aygestin, Prometrium) is given. In addition, the hormone prolactin may be elevated in patients with a pituitary tumor or an underactive thyroid gland (hypothyroidism) may be cause clomiphene resistance if not detected.

Another concern has been whether a patient’s weight should be used to select the appropriate dose of clomiphene, or to predict those who might be resistant. It does appear that patients who weigh more, require higher doses of clomiphene, but in any one patient, weight cannot be used to predict the dose that will successfully induce ovulation. In conclusion, prior to initiating clomiphene, all patients should be given progesterone in an attempt in induce a period (after a negative pregnancy test), an FSH level if a period is not induced, and both a thyroid test (TSH) and a prolactin level. Weight loss should be encouraged for those who are overweight, to increase the probability of success, and to lessen complications during pregnancy.

For those patients who do not ovulate after maximal doses of clomiphene, at least 10 different options have been proposed. They are:

1. Extended clomiphene
2. Addition of hCG
3. Addition of dexamethasone
4. Addition of bromocriptine
5. Pretreatment suppression

6. Gonadotropins
7. Sequential clomiphene and gonadotropins
8. Ovarian drilling
9. Aggressive weight loss regimens

Treatments for Patients Resistant to Clomiphene

1.) **Extended Clomiphene**
There are 2 approaches in the literature. 1.) 250 mg for 8 days, then hCG 6 days later or 50 mg for 5 days with increasing doses of 50 mg every 5 days until a follicle develops (monitored by ultrasound). While both of these approaches have been reported to be successful, neither has been validated in large groups of patients.

2.) **Addition of hCG**
Human chorionic gonadotropin (hCG) mimics the LH signal necessary for ovulation. This is thought not to occur in some patients on clomiphene despite adequate follicle development. hCG is given to induce ovulation if a follicle > 20 mm is seen on ultrasound, usually by cycle day 14. hCG given prematurely may actually cause the follicle to undergo atresia (stop growing), so appropriate timing by ultrasound is critical.

3.) **Addition of Dexamethasone**
The adrenal gland can make male hormones, especially DHEAS. If the DHEAS level is elevated, the addition of dexamethasone has been shown to improve the response to clomiphene. Dexamethasone is a synthetic steroid and can worsen the body’s ability to metabolize sugar (promote intolerance) and is not ideal for patients with insulin resistance.

4.) **Addition of Bromocriptine**
If the pituitary gland is making too much prolactin, this will interfere with the hypothalamus and pituitary’s ability to respond to clomiphene. The addition of a medication called bromocriptine will improve the response to clomiphene in these patients.

5.) **Pretreatment suppression**
In theory, high levels of luteinizing hormone (LH) seen in PCOS will stimulate androgen production by the ovary that interferes with ovulation. Oral contraceptive pills (OCP’s) can suppress LH and androgens and can lead to a better response to clomiphene in some subjects. OCP's also lower the chance of ovarian cysts which have been shown to lower the probability of proper ovulatory function. A similar approach has been reported with gonadotropin releasing hormone analogs (GnRH) such as leuprelide (Lupron).

6.) **Insulin sensitizing agents**
PCOS is associated with resistance to the hormone “insulin” that allows the body to take up sugar (glucose). Because of this resistance, high levels of insulin are necessary to keep the blood sugar normal. High levels are thought to cause excess androgen production from the ovary. Medications that lower insulin levels (such as metformin, troglitazone, rosiglitazone, pioglitazone, d-chiro-inositol) are thought to improve the ovary’s ability to ovulate. One study found that the combination of metformin and clomiphene works better than clomiphene alone. These medications have enjoyed widespread use for clomiphene resistance despite a relative paucity of evidence for their efficacy.

7.) **Gonadotropins**
Probably the most common (albeit the most expensive and aggressive) approach to the clomiphene resistant patient is to administer gonadotropins (FSH) by daily injection. FSH is a potent stimulator of follicle growth. The problem is that patients with PCOS may over respond and develop ovarian hyperstimulation syndrome (OHSS). OHSS can be a serious, medically unstable condition requiring hospitalization. Multiple pregnancies (including triplets or more) are also more common with gonadotropins. In order to provoke an appropriate ovarian response, several approaches have been advocated including the “low-slow” approach, the “step down” approach and pretreatment with leuprelide (Lupron) to suppress the pituitary. None of these approaches appear to be superior.
8.) **Addition of gonadotropins to clomiphene**

If gonadotropins are too strong and clomiphene alone is not strong enough, why not try the two drugs together? Protocols utilizing clomiphene on cycle days 5-9, and then gonadotropins (injectable FSH) on days 9-12 have been used successfully for ovulation induction. I have found this combination to be particularly useful in the clomiphene resistant patient.

9.) **Ovarian drilling**

Because the classic wedge resection lead to frequent adhesions of the tubes, the modern version is to perform laparoscopy (minimally invasive surgery) and use electrical energy or a laser to puncture holes in the ovary. The purpose is to reduce the number of cells in the ovary making testosterone, thereby helping the ovary function better. Success rate of 80% for ovulation and 40-60% for pregnancy have been reported, but not exclusively in clomiphene resistant patients. Obviously, since ovarian drilling requires surgery, it is not a frequent first line treatment, but it may be particularly useful in patients unwilling or unable to use gonadotropins.

10.) **Aggressive weight loss regimen**

Studies have shown that weight loss alone can be successful for patients who are overweight and anovulatory. The degree of weight reduction necessary is modest but still appears to be difficult for many patients. The ideal strategy for weight reduction in PCOS patients remains to be determined. Medications for weight reduction also exist, but have not been of proven benefit for patients with PCOS. In summary, there are many options for clomiphene resistant PCOS patients. Each has been shown to be effective, but not universally. Individual patient characteristics and preferences, in consultation with her physician will determine which treatment is most appropriate for her.

**References:**


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