International Federation of Fertility Societies

Global Standards of Infertility Care

Standard 19

Clomiphene and its use in ovulation induction

Guidance for practitioners

Name	Clomiphene / Clomid guidance for its use in infertility management
Version number	19.1/IFFS/Standards
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Date of first release	October 2017
Date approved by IFFS	October 2017
Date of review	October 2020

Introduction

Clomiphene citrate (CC) was originally used to induce ovulation as treatment of anovulatory infertility, but has since been used to treat other causes of infertility. CC is a selective estrogen receptor modulator that exhibits primarily estrogenic antagonist properties as well as estrogenic agonist activity. Currently available preparations of CC contain a mixture of two geometric isomers: enclomiphene and zuclomiphene in a ratio of 3:2. Enclomiphene is the more potent isomer and primarily responsible for the clinical action of the medication. CC induces ovulation by its effects on the hypothalamus and pituitary, inducing enhanced release of GnRH and subsequently gonadotropins (FSH and LH) from the pituitary that stimulate follliculogenesis.

Rationale

Clomiphene citrate is the medication most frequently used to treat infertility. It is an oral medication that is easy to administer, generally well tolerated, is not associated with birth defects, is relatively inexpensive, does not require sophisticated monitoring, has been in use for almost 50 years and has been shown to be effective. CC is typically used as a single agent for ovulation induction in patients with anovulatory infertility. Alternative medications that are used to treat anovulatory infertility include metformin and aromatase inhibitors. In anovulatory or oligo-ovulatory women, treatment is initiated with the lowest dose of CC. However, when the initial dose of CC fails to result in ovulation, alternative dosing and administration schedules may be effective. Some women fail to ovulate in response to CC alone (CC resistance). In these cases, CC may be utilized in combination with adjuvant therapies such as metformin, laparoscopic ovarian diathermy or drilling (LOD), or glucocorticoids. Alternatively, CC resistant patients may undergo treatment with gonadotropins or IVF.

Clomiphene citrate is also used in women who have regular menstrual cycles and unexplained infertility. Proposed protocols include CC with timed intercourse (ASRM, Fertil Steril, 2013, Battacharya 2008, Guzick et al, 1998, Wordsworth 2011), CC with intrauterine insemination (Reindollar F&S 2010, Diamond NEJM 2015), CC Plus gonadotropins (Lu 1996, Ransom 1996, Ron-el 1989) and also CC based IVF protocols as a low cost alternative (Gibreel Cochrane 2012, Zhang 2016, Ferraretti 2015) and as a treatment option for low responders (Karimzdeh 2011, Revelli 2014, Ragni 2015).

Scope of this guidance

This guidance covers the uses of CC in the treatment of anovulatory infertility, including alternatives and adjuvant therapy when CC fails to result in ovulation, as well as risks of CC therapy...

Evidence for this guidance

Pretreatment evaluation

For those women with oligo/anovulation, a complete gynecologic history, physical examination and hormonal evaluation are indicated to identify the underlying etiology. Targeted hormonal testing should evaluate for pregnancy (hCG), thyroid disease (TSH), hyperprolactinemia (prolactin) and primary ovarian insufficiency (FSH and estradiol). as further evaluation and alternative treatment for these conditions is warranted. Other testing for polycystic ovary syndrome, non-classic adrenal hyperplasia, diabetes may be indicated based on history and exam. Assessment of anatomic factors, tubal patency, and male factor screening are also appropriate if history suggests risk or if pregnancy fails to occur after 3-6 ovulatory treatment cycles. Early assessment is also warranted in a woman over 35 years due to age related decline in fertility.

Clomiphene Treatment

CC is an oral medication that is typically administered for 5 consecutive days starting on the 2nd, 3rd, 4th, or 5th day of the menstrual cycle. The goal is to find the lowest effect dose that reliably induces ovulation as higher doses are associated with a greater incidence of side effects and risk of multiple gestation. The initial starting dose of CC is typically 50 mg. Typically in anovulatory women, CC is administered after a progestin induced menstrual bleed to effectively shed the endometrial tissue and prevent starting CC if the patient is in the luteal phase or pregnant. However, CC may be started remote from a spontaneous or progestin induced menstrual bleed if the hormonal profile and ultrasound evaluation confirms ovulation is not imminent or has already occurred. This strategy has been associated with higher pregnancy rates (Diamond 2012, Legro NEJM 2014). Routine baseline physical or ultrasound examinations prior to starting CC at the start of each cycle are unnecessary.(Opsahl 1996.) However, prior to starting CC pregnancy should be excluded.

Treatment with CC in anovulatory PCOS women is associated with an overall ovulation rate of 60-80% and pregnancy rate of 30-40% (Brown Cochrane 2009, Thessaloniki 2008). When compared to placebo, treatment with CC results in a benefit for ovulation (OR 7.47, 95%CI 3.24-17.23) and pregnancy (OR 5.77, 95%CI 1.55-21.48) (Brown Cochrane 2009)..The majority of individuals will ovulate on a 50 mg/day dose (52%), with decreasing response to higher doses in increments of 50 mg (100 mg, 22%; 150 mg

12%, 200 mg, 7%, 250 mg 5%) (Gysler 1982). Lower doses (12.5 mg/day or 25 mg/day) may be necessary in small women and those who demonstrate multifollicular development or sensitivity to CC.(Dodge 1986) Larger doses may be required to induce ovulation in women with PCOS and also correlate with higher BMI (Al-Azemi. 2004). Cumulative conception rates in anovulatory women who ovulate in response to CC 50 mg/day, 100 mg/day, and 150 mg/day at 3 months are 50%, 45%, and 33% respectively, while conception rates at 6 months for those doses are 62%, 66%, and 38% respectively (Imani 1999; Thessaloniki 2008). Success rates are lower in obese individuals with 16% achieving live birth in women with BMI > 35 kg.m2 compared with 28% for women with BMI < 30 kg/m2 (Legro, NEJM 2007).

In individuals who do not respond to a particular dose, response may be improved with increasing the duration of therapy from 5 days to 7-8 days (Lobo 1982). Alternatively, increasing doses of CC may be utilized, increasing in increments of 50 mg and evaluating response before increasing further. Traditionally progestin is administered to induce menses before starting the higher dose of CC again on day 2-6 of the induced menstrual bleed.

"Stair-step" protocol

An alternative dosing schedule for CC resistant patients has been proposed termed the "stair-step" protocol. In this protocol, the higher dose of CC is started without a progestin withdraw bleed, once lack of response has been documented by ultrasound assessment by day 14-21 with or without hormonal confirmation. (Hurst 2009) The advantage is a shorter time to achieve ovulation when increasing doses of CC are required.

Assessing ovulation

It is important to confirm that ovulation is occurring in response to CC. Methods that have been used include basal body temperature chart, urinary LH detection kits, serum progesterone measurement, ultrasound assessment of ovarian follicle size and serum measurement of estradiol, LH, and progesterone. Serial measurement of serum LH and estradiol is the most reliable way to detect ovulation, but require frequent visits and

venipunctures and may be costly (Luciano1990) Basal body temperature assessment is a cost effective way to assess ovulation in response to CC, but is not as reliable as other methods to detect timing of ovulation (Luciano 1990, Guermandi 2001). Urinary LH kits are effective in detecting ovulation and correlate well with serum LH (Luciano 1990). The surge is typically noted 5-12 days after treatment is completed (Opsahl MS 1996). However, in some women with PCOS, endogenous LH levels may be high leading to false positive results. Serum progesterone confirms ovulation by 2 days after the LH surge in approximately 90% of patients (Luciano 1990). Serial transvaginal ultrasound may be used to monitor follicular size and has the advantage to determining the number of developing follicles as well as presumptive ovulation (De Crespigny 1981). Ultrasound alone may not predict the timing of ovulation, however, as follicular size at time of ovulation is variable. The method used to assess ovulation in an individual depends on available resources, access to care, and cost effectiveness.

Addition of hCG ovulation trigger with CC

Ovulation occurs in response to an endogenous LH surge, which triggers oocyte maturation and expulsion of the oocyte from the ovarian follicle. In anovulatory women treated with CC or aromatase inhibitors, ovulation triggers are advocated in lieu of an endogenous LH surge to control the timing of ovulation. If the ovulation trigger is administered too early in the cycle, then the oocyte may not be fully mature. Medications include urinary hCG, recombinant hCG, recombinant LH, and GnRH agonist. Two studies and a systematic review (George 2007, Yilmaz 2006, George Cochrane 2014) have evaluated the effect of exogenous ovulation trigger in anovulatory women treated with CC. There were no differences in live birth rate, ovulation rate, clinical pregnancy rate, or miscarriage rate with or without hCG ovulation trigger.

<u>Alternative therapies to CC</u>

Metformin

Published evidence has suggested that CC is better than metformin for inducing ovulation in some (Legro NEJM 2007; Zain 2009), but not all studies.(Palomba 2005). The largest randomized controlled study demonstrated that CC was superior to metformin for ovulation induction in women with PCOS. (Legro NEJM 2007) This study randomized 626 women with PCOS to CC plus placebo, extended-release metformin plus placebo, or a combination of CC and metformin for up to 6 months. Participants included couples with a normal semen analysis and at least one patent fallopian tube. The dose of CC was increased by 50 mg/day to a maximum dose of 150 mg CC until ovulation was achieved. Couples were instructed to have regular intercourse every 2-3 days and ovulation was monitored by weekly progesterone levels. The live birth rate per group was significantly higher in the CC (22.5%) and CC plus metformin (26.8%) groups compared to metformin alone (7.2%) ($P<0.001$). While the rate of multiple pregnancy was greatest in the CC group (6.0%), the rates of pregnancy loss did not differ significantly among the groups. The rate of live birth was significantly higher in women with BMI < 30 kg/m2 compared to BMI ≥ 35 kg/m2. In another randomized controlled study of 115 women, live birth rates were also better with CC compared to metformin (59% vs 23.7%, P=.002) (Zain 2009)

In contrast one randomized controlled trial evaluating the use of CC or metformin for 6 months to treat anovulation in 100 non-obese women with PCOS. (Palumba 2005) Women were randomized to either metformin 850 mg twice daily or CC 150 mg for 5 days for 6 months duration. When compared to CC, metformin therapy was associated with a significantly higher cumulative pregnancy rate (68.9% vs 34.0%, P<.001), although the ovulation and live birth rate were not significantly different.

A meta-analysis of studies comparing CC and metformin showed CC to have a better live birth rate compared to metformin (Siebert 2012). Another meta-analysis found CC was associated with a better live birth rate than metformin for obese women with PCOS (Tang. Cochrane 2012)

Metformin + CC as primary treatment

Many studies have evaluated the addition of metformin to CC as primary treatment for anovulation in women with PCOS. Studies have shown mixed results with regards to ovulation and pregnancy rates. The largest study evaluated 626 women randomized to CC, or metformin, or both as primary treatment of anovulation in PCOS.(Legro NEJM 2007) When comparing treatment with CC vs CC +metformin, ovulation rates were better with CC+metformin (p=.003), but pregnancy rates, conception rates among those who ovulated, miscarriage rates, and live birth rates were no different in CC vs CC +metformin groups. While many studies have evaluated effect of CC compared to CC+metformin on ovulation and pregnancy rates, results have been variable with some studies showing a benefit and others no benefit. However, a systematic review showed that there was no evidence that metformin in combination with clomiphene improved live birth rates when compared to clomiphene alone (OR 1.16. 95%CI 0.85-1.56) (Tang Cochrane 2012)

Aromatase inhibitors

Aromatase inhibitors stimulate ovulation by down regulating production of estrogen leading to increase in GnRH and FSH which stimulate follicular development in the ovaries. Letrozole, an orally active aromatase inhibitor has been used as an ovulation-inducing agent. In studies letrozole treatment appears to be comparable or superior to CC when used as an ovulation induction agent in women with PCOS. (Bayar 2006; Badawy 2009; Begum 2009; Dehbashi 2009, Ray 2012, Roy 2012, Legro NEJM 2014). The largest randomized double-blind controlled trial involved 750 women with PCOS and evaluated CC and letrozole as first line medications for ovulation induction.(Legro NEJM 2014) Letrozole was associated with a higher cumulative birth rate compared to CC (27.5% vs 19.1%, P=0.007), higher cumulative rate of ovulation (61.7% vs 48.3%, P<0.001), with no differences in pregnancy loss, twin pregnancy, or congenital anomalies. The average BMI in this study population was 35 kg/m2. Live birth rates in women with BMI $\leq$ 30 kg/m2 were no different with CC vs letrozole suggesting letrozole may be more beneficial in obese women. A systematic review was performed including all the studies identified above. Live birth rate was significantly better with letrozole

compared to clomiphene citrate (OR 1.80, 95%CI 1.40-2.33) (Franik Cochrane 2012) Based on these results, letrozole may be superior to CC in women with PCOS.

Clomiphene citrate resistance

Approximately 15-20% of women with PCOS fail to ovulate in response to CC. In these women treatment options include using CC with an additional treatment modality (adjunctive therapy) or an alternative treatment modality.

CC and Metformin

Metformin, an oral biguanide, is an insulin sensitizing medication and has been shown to induce ovulation in women with PCOS (Onalan 2005). The mechanism is postulated to be improvement in insulin sensitivity. Several randomized controlled trials have assessed the addition of metformin to CC treatment compared to CC alone in women who carry the diagnosis of CC resistance. The majority of the studies show a benefit with addition of metformin. In these trials metformin is typically administered one month prior to starting CC, but ranges from 4 days to 3 months. The dose of metformin typically utilized ranged from 1000mg daily to 2000 mg daily. The largest trial randomized 80 women with CC resistance to either CC 150 mg for 5d followed by hCG trigger when the lead follicle reached 20mm and timed intercourse, or the same CC protocol with the addition of metformin 500 mg three times daily starting 12 days before CC and continuing until the lead follicle was 20mm. (Hwu 2005) Adding metformin to CC significantly improved ovulation (42.5% vs 12.5%; P=0.03) and pregnancy rates (15% vs 0%; P=0.026). The second largest trial randomized 56 CC resistant patients to pretreatment with metformin 750 mg twice daily or placebo for one months prior to a CC 100 mg daily x5 days. (Kocak 2002) The rate of ovulation was significantly higher in the CC+metformin group compared to placebo 77.7% vs 14.2%, P<.001). The cumulative pregnancy rate was higher in the CC+metformin group compared to control (P=.04). A meta-analysis revealed that CC +metformin resulted in better ovulation (OR 5.09 95%CI 1.44-17.98) and pregnancy (OR 9.62, 95%CI 2.95-31) compared to CC alone in CC resistant women. (Creanga 2008). A systematic review found CC+metformin resulted in

higher live birth rates when compared to CC alone in women with CC resistance(RR 6.5, 95%CI 1.2-35). (Moll 2007) Based on these data, it is reasonable to add metformin pretreatment to CC regimen in CC resistance patients to improve ovulation and pregnancy rates.

In CC resistant women, treatment with metformin +CC was shown to have similar rates of ovulation and pregnancy rates when compared to aromatase inhibitors and laparoscopic ovarian diathermy (Abu Hashim 2015). However, when compared to gonadotropins, metformin +CC was shown to have a significantly lower ovulation rate (OR 0.25, 95%CI 0.15-0.41, P<.00001) and pregnancy (OR 0.45, 95%CI 0.27-0.75, P=.002). In this study there was no significant difference in multiple pregnancy rates. (Abu Hashim 2015)

Laparoscopic Ovarian Diathermy

Laparoscopic ovarian diathermy or drilling (LOD) involves creating holes in the ovarian cortex using some form of energy. This procedure is a less invasive version of the ovarian wedge resection and is associated with less adhesions, and avoids removal of ovarian tissue. The mechanism for resumption of ovulation with this procedure is poorly understood but may be related to destruction of ovarian stroma with a resulting decrease in androgen production.

Surgical techniques for LOD include laparoscopy and transvaginal hydrolaparoscopy. Energy sources used to create holes in the ovary include monopolar or bipolar energy, CO2 (carbon dioxide), KTP (potassium-titanyl phosphate), argon, and Nd:YAG (neodymium:yttrium-aluminum-garnet) lasers, and harmonic scalpel. All these techniques have similar efficacy (Seow 2008, Fernandez 2011). The number of holes placed per ovary is variable in the literature as is the energy and duration. However, as few as 4 punctures with 40W and depth of 4-5 mm have been shown to be effective. (Seow 2008, Fernandez 2011, Thessaloniki 2008, Abu-Hashim JGOR 2011). Potential ovarian failure is a concern with a large number of punctures and energy used. (Dabirashrafi 1989) Some studies have demonstrated unilateral ovarian diathermy to be

as effective as bilateral. (Fernandez 2011, Sunj 2013) Postoperative adhesions have been reported to variable degrees following LOD.(Fernandez 2011)

Laparoscopic ovarian diathermy has been used to facilitate ovulation induction in CC resistant women. Studies have demonstrated that in CC resistant women, LOD is as effective as gonadotropins and CC+metformin. A meta-analysis of randomized controlled trials and a separate systematic review observed that in CC resistant women, ovulation and pregnancy rates after LOD are similar to those achieved by treatment with gonadotropin therapy, and the risk of multiple pregnancy is significantly lower, 1% versus 16% (Farquhar 2012; Fernandez 2011). The benefits do not appear to be transient, with decreases in LH, testosterone, androstenedione, and PCO-appearing ovaries maintained for over 3 years (Amer 2002). A meta-analysis of several randomized controlled trials has shown that LOD and CC+metformin have no significant difference in ovulation rates (OR 0.88, 95% CI 0.53-1.47, P=0.62), pregnancy rates (OR 0.96, 95%CI 0.60-1.54, P=0.88), and miscarriage rates (OR 0.94, 95% CI 0.39-2.27, P=0.89) (Abu Hashim 2015, Abu Hashim JGOR 2011)). When considering these therapies, the risks and benefits of surgery need to be weighed against the risks and benefits of other therapies.

Clomiphene and Glucocorticoids

In some anovulatory women who fail to ovulate to CC alone, addition of glucocorticoids to the CC treatment regimen may induce ovulation successfully. One prospective, randomized trial involved 64 anovulatory women who had not received clomiphene previously (Daly 1984). Of those receiving clomiphene only, 14/22 ovulated and 8/14 conceived, while of those receiving clomiphene plus dexamethasone, 23/23 ovulated and 17/23 conceived ($p<0.05$). The benefit was most notable in women with DHEA-S serum concentrations of 200µg/dl or greater. Two large trials evaluated clomiphene-resistant anovulatory patients with normal DHEAS levels. Both studies utilized a 10-day course of dexamethasone 2 mg/day administered with start of CC.(Parsanezhad 2002; Elnashar 2006). Both studies demonstrated significantly higher pregnancy rates with CC plus dexamethasone compared to CC alone. Glucocorticoid treatment has important side effects and risks that must be addressed should this regimen be used.

Gonadotropins

Gonadotropins have been used as second line therapy to induce ovulation in those women who failed to ovulate to CC or failed to conceive with CC. Concerns with gonadotropin therapy in women with PCOS and high antral follicle count include multifollicular development and risk of high order multiple gestation and severe ovarian hyperstimulation syndrome (OHSS).(Thessaloniki 2008) In this population, the goal of gonadotropin simulation is monofollicular development, which is different than the gonadotropin stimulation strategy in women with unexplained infertility. The step-up protocol involves starting daily dose of 37.5-75 IU FSH daily, which is only increased by 25-50 IU after 14 days if there is no response (Balen 2013, Hugues 2006). The treatment duration may be long 28-35 days, however there is a low risk of multiple follicular development and multiple gestation. The step-down protocol utilizes a loading dose of FSH of 150 IU daily with a reduction in dose by 37.5 IU every 3 days when follicular development is noted on ultrasound (van Santbrink 1997, Thessaloniki 2008). With both of these protocols serial ultrasound and serum estradiol measurement are necessary in order to adjust the dose of gonadotropins to decrease the risk of multiple gestation and OHSS. It is recommended that ovulation is triggered, typically with hCG, when there is no more than 2 follicles ≥14 mm with the largest of 17mm. If there are more than 2-3 follicles ≥ 14-16mm, then consideration should be made to withhold hCG administration due to the risk of multifetal gestation and OHSS(Thessaloniki 2008)

The low dose stimulation protocols in CC resistant patients result in approximately 70% rate of monofollicular development, pregnancy rate of 20%, with a low incidence of multiple gestation (<6%) and OHSS (<1%).(Thessaloniki 2008) When comparing the available gonadotropin preparations, (i.e. human menopausal gonadotropins [mg], purified urofollitropin [FSH-P], highly purified urofollitropin [FSH-HP], highly purified menotropin [HP-HMG], recombinant FSH [rFSH]) there was no difference in live birth rate, clinical pregnancy rate, miscarriage rate, incidence of multiple gestation, incidence of OHSS and total dose of gonadotropin or number of days of stimulation. (Weiss Cochrane 2015)

IVF

The advantages of IVF in the treatment of infertility in CC resistant women with PCOS include development of a reasonable number of follicles with a reduction in the risk of multifetal gestation due to the ability to perform elective single embryo transfer. Stimulation protocols utilize low doses of FSH and or FSH + hCG with careful monitoring to decrease the risk of OHSS. In women with PCOS other strategies to reduce the risk of OHSS without adversely affecting live birth rates include use of metformin (Palomba 2013, ASRM PC OHSS 2016), use of protocols with GnRH antagonist suppression rather than GnRH agonist protocols (Toftager Hum Reprod 2016, Al-Inany 2011, ASRM OHSS 2016), and use of GnRH agonist to trigger oocyte maturation prior to oocyte retrieval. (Engmann 2008, ASRM PC OHSS 2016).

Risks of clomiphene citrate

Side effects

The most common side effects with CC therapy are mood swings (64-78%) and hot flushes (10-33%) (Blenner 1991, Choi 2005, Legro NEJM 2014). Other non-specific side effects noted in approximately 2-5% of women include breast tenderness, pelvic pain and pressure, nausea and weight gain. These side effects may persist for days after the medication has been completed. Visual disturbances such as scotomata, light sensitivity, and blurred or double vision are uncommon, occurring with a prevalence of < 2%.(Purvin 1995) If these symptoms are encountered then treatment should be stopped and an alternative method of ovulation induction pursued.

Multiple gestation

CC treatment is associated with multiple gestation due to multifollicular development. The risk in anovulatory women is approximately 7% -8% (Schenker 1982; Ahlgren 1976; Legro 2014) and in women treated for unexplained infertility is approximately 2.6% - 7.4% (Badawy 2009; Dankert 2007). The majority of multiple pregnancies resulting from

CC therapy are twin gestations. Triplet and higher-order pregnancies are rare (0.08% - 1.1%) (Reindollar 2010; Reefhuis 2011)

Congenital Anomalies

There is no evidence that CC treatment is associated with an increase in the risk of birth defects (Ahlgren 1976;Correy 1982; Legro NEJM 2007; Legro NEJM 2014)

Cancer

There is no evidence that CC is associated with the development of ovarian (Jensen 2009; Rizzuto 2013; ASRM Fertility Drugs and CA 2016), breast (Terry 2006; Brinton 2005; ASRM Fertilty Drugs and CA 2016) or endometrial cancer (Jensen 2009 Clin Epi ; Brinton 2013 HR, ASRM Fertilty Drugs and CA 2016)

Summary of evidence

In anovulatory women CC has been shown to effectively induce ovulation in the majority of women. CC is more effective than metformin for ovulation induction in women with PCOS and in obese women, letrozole may be more effective than CC. When there is CC resistance, then options include CC plus adjunctive therapies such as metformin, ovarian drilling, glucocorticoids or using gonadotropins for ovulation induction or IVF.

Conclusion

CC treatment is an acceptable treatment option with high quality evidence indicating the benefits of therapy in couples with oligo/anovulatory infertility. CC treatment may also have a role in treatment of unexplained infertility

Recommendation for Practice

1. Women with infertility due to anovulation should have full history, physical, and hormonal evaluation to determine the cause prior to initiating therapy with CC.

2. Prior to initiation of Clomiphene therapy women should be advised of the risks of multiple pregnancy.

3. Therapy with CC should normally be initiated at a dose of 50 mg for 5 days typically starting on day 2, 3, 4, or 5 after a menstrual bleed, and the dose titrated up in 50 mg increments. Normally the dose should not exceed a maximum of 150 mg daily if there is no resulting ovulation.

4. If there is no response to 5 days of therapy, duration of clomiphene may be increased in a subsequent cycle to 7-8 days of therapy

5. In the absence of ovulation in response to CC, a “stair-step” protocol may be utilized whereby a higher dose of CC is initiated without first performing a progestin withdrawal. This potentially shortens the time to determining the ovulatory dose.

6. Ovulation is most accurately assessed by serial measurements of estradiol, LH and progesterone, however acceptable alternatives include ultrasound, urinary LH, serum progesterone and BBT.

7. In women with PCOS, CC should be considered superior to metformin for ovulation induction and pregnancy.

8. Routine addition of metformin to CC does not improve live birth rates.

9. In obese women with PCOS, letrozole may be more effective that CC in achieving ovulation, pregnancy and live birth.

10. In anovulatory women who have CC resistance, the addition of metformin to CC improves ovulation and pregnancy rates.

11. LOD may be used in CC resistant patients, however it has not been shown to be superior to CC +metformin and carries the risk of laparoscopy and ovarian insufficiency.

12. Gonadotropins are a second line protocol to induce monofollicular ovulation in women with PCOS who have failed to respond to CC. Starting doses are lower than those used for controlled ovarian hyperstimulation typically starting at 37.5 to 75 IU daily

13. IVF with eSET is an a treatment option used in CC resistant anovulatory infertility to reduce the risks of multiple pregnancy

14. Common side effects of CC include hot flashes and mood swings. Visual changes and scotomata are rare and should necessitate stopping therapy. Twin gestation in anovulatory women is < 10% with CC and triplets are <1%.

15. With CC there is no increase in the risk of birth defects or subsequent cancer.

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