On-label and off-label drug use in the treatment of female infertility

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Female infertility affects millions of couples worldwide and is estimated to account for one-third of all cases of infertility. The purpose of this article is to review the uses of both off-label treatments and those approved by the US Food and Drug Administration for female infertility, by examining the mechanism of action, the side-effect profile, fetal anomaly risks, and contraindications for the various drugs. (Fertil Steril® 2015;■:■–■. ©2015 by American Society for Reproductive Medicine.)

Key Words: Female infertility, medications for female infertility

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After the discovery and development of a particular drug, it needs to undergo preclinical and clinical research as early steps in the US Food and Drug Administration (FDA) approval process. The drug is then subject to intense FDA review and postmarket safety monitoring. Only a few drugs are FDA approved for anovulation, or for use during an in vitro fertilization (IVF) cycle. Most of the drugs prescribed to treat female infertility are used in an off-label manner. Often, these off-label drugs have been evaluated in the phase I or phase II trials of clinical research but have not been fully assessed in phase III or phase IV trials. This review summarizes the evidence of efficacy, side effects, and risks for the drugs that are most frequently used in off-label treatment of female infertility (Tables 1 and 2).

OVULATION-INDUCTION AGENTS

Clomiphene Citrate

Clomiphene citrate (CC) is a nonsteroidal ovarian stimulant that is FDA approved for ovulation induction for anvoluatory infertility (1). Clomiphene citrate has been widely used alone, and in combination with intrauterine insemination (IUI), for treatment of unexplained subfertility, in an off-label fashion. The mechanism of action is based on its mixed estrogenic and antiestrogenic properties. Clomiphene binds estrogen (E) receptors throughout the reproductive system; however, this binding to nuclear E receptors reduces receptor concentrations by interfering with the normal process of E receptor replacement. Depletion of E receptors at the hypothalamus results in reduced perceived levels of circulating E, which induces compensatory pulsatile gonadotropin-releasing hormone (GnRH) secretion and increases ovarian follicular activity.

Clomiphene is frequently used in an off-label fashion to treat unexplained female infertility by inducing multifollicular response and correcting potential subtle ovulatory dysfunction (2). Clomiphene is not suited for women with hypothalamic anovulation, as an intact hypothalamic-pituitary-ovarian (HPO) axis is required for its mechanism of action (2). In women with anovulatory infertility, such as those with polycystic ovary syndrome (PCOS), approximately 80% ovulate, and approximately 40% conceive.

In couples with unexplained infertility, the evidence for use of CC is murky. One Cochrane review (3) concluded that no studies have provided evidence that CC, either with or without IUI, increases pregnancy rate compared with placebo. Based on this review of 7 trials, the American Society for Reproductive Medicine recommends against using CC alone for treatment of unexplained infertility (4). By contrast, a recent, multicenter trial, conducted through the Reproductive Medicine Network (RMN), compared the live-birth rate in 900 couples with unexplained infertility, who were randomized to conditions using IUI with either gonadotropin, CC, or letrozole. Live birth occurred in 32.2%, 23.3%, and 18.7% of cycles in the 3 conditions, respectively. Those in the gonadotropin arm had a significantly higher rate of multiples, leading the authors to conclude that CC with IUI should be the first line treatment for couples with unexplained infertility (5). Side effects include bloating, abdominal discomfort, ovarian enlargement, vision changes, headaches, hot flashes, and abnormal uterine bleeding (1).

Received November 20, 2014; revised January 6, 2015; accepted January 7, 2015.
R.S.U. has nothing to disclose. K.S.M. has nothing to disclose.
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Fertility and Sterility® Vol. ■, No. ■, ■ 2015 0015-0282/$36.00

http://dx.doi.org/10.1016/j.fertnstert.2015.01.011

TABLE 1

FDA-approved treatments used in female infertility.

Drug generic	Mechanism of action	Excretion and half-life	FDA indication/off-label reproductive use	Main side effects	Pertinent drug interactions	Anomaly risk	Contraindications
CC Clomid (Sanofi-Aventis)	Mixed estrogenic and antiestrogenic properties	Half-life: 5–7 d Renal > biliary excretion	FDA: Ovulation induction in unexplained and anovulatory infertility Off-label: Inducing multifollicular response	Bloating Abdominal discomfort Ovarian enlargement Vision changes Headaches Hot flashes Abnormal uterine bleeding	No known drug interactions	Category X Increased rates of embryo-fetal loss and structural malformations (boney changes, fetal cataracts, cleft palate, metaplastic changes of the reproductive tract) in animals	Known hypersensitivity Women who are pregnant Liver disease or history of liver dysfunction Abnormal uterine bleeding Ovarian cysts or ovarian enlargement Uncontrolled thyroid or adrenal dysfunction Intracranial lesion
Gonadotropins FSH (Bravelle) Follitropin alpha (Gonal-f) Follitropin beta (Follistim) Lutropin alpha (Luveris) LH + FSH (Menopur)	Human gonadotropin analogs	Half-life: 11–38 h Renal excretion	FDA: Ovarian stimulation and ovulation induction in anovulatory women undergoing ART	Bloating Rash Abdominal or pelvic pain Ovarian enlargement Mood swings Fatigue	No known drug interactions	Category X	Known hypersensitivity Primary ovarian failure Uncontrolled thyroid or adrenal dysfunction Intracranial lesion Sex hormone–dependent tumor Abnormal uterine bleeding Ovarian cysts or enlargement (not PCOS) Women who are pregnant
hCG Ovidrel Novarel Profasi Pregnyl	Alpha subunit is analog of LH	Half-life: 29 h Renal excretion	FDA: Final follicular maturation and early luteinization as part of ART; ovulation induction in anovulatory women Off-label: Secretion of progesterone from corpus luteum in luteal phase of ART	Injection-site inflammation GI disturbance Intermenstrual bleeding Body and/or back pain Fever Headache Hot flashes	No known drug interactions	Category X Intrauterine death and impaired parturition	Known hypersensitivity Primary ovarian failure Uncontrolled thyroid or adrenal dysfunction Intracranial lesion Abnormal uterine bleeding Ovarian cyst or enlargement Sex hormone–dependent tumors Women who are pregnant
GnRH antagonists Ganirelix (Merck) (Antagon) Cetrorelix (Cetrotide)	Competitively blocks GnRH receptors on the pituitary gonadotroph	Half-life: 12–16 h Renal > biliary excretion	FDA: Inhibition of pre mature LH surges in women undergoing controlled ovarian hyperstimulation Off-label: Treatment of OHSS	Hot flashes Headache Nausea, vomiting Abdominal discomfort Ovarian enlargement	No known drug interactions	Category X Increased litter reabsorption in animals	Known hypersensitivity to GnRH antagonists, GnRH, or GnRH analogs Known or suspected pregnancy

Usadi. Off-label drugs in female infertility. Fertil Steril 2015.