Effect of Oral Contraceptive Pill Pretreatment on Ongoing Pregnancy Rates in Patients of IVF (A randomized Controlled Trial)

Thesis

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Ahmed Mahmoud Abdel-rahim

Contents

List of Abbreviations

BMI	:	Body mass index
CD	:	Cycle day
COCs	:	Combined oral contraceptives
COH	:	Controlled ovarian hyperstimulation
COH-ET	:	Controlled ovarian hyperstimulation-embryo transfer
COX-1	:	Cyclooxygenases
DMPA	:	Depomedroxyprogesterone Acetate
E2	:	Estradiol
ECM	:	Extracellular matrix
EVT	:	Extravillous trophoblast cells
FDA	:	Food and Drug Administration
FSH	:	Follicle stimulating hormone
GnRH	:	Gonadotropin releasing hormone
hCG	:	Human chorionic gonadotropin
IGF1	:	Growth factor 1
IL6	:	Interleukin 6
IL6-R	:	IL6 receptor
IVF	:	In-vitro fertilization
LH	:	Luteinizing hormone
LIF	:	Leukemia inhibitory factor
P	:	Progesterone
PCOS	:	Polycystic ovarian syndrome
PD	:	Post-treatment day
PGs	:	Prostaglandins
POPs	:	Progestin only pills
RCTs	:	Randomized controlled trials
TGF-b	:	Transforming growth factor-b
WHO	:	World Health Organization
WMD	:	Weighted mean difference

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Introduction

Pituitary suppression with oral contraceptives (OCs) and gonadotropin releasing hormone agonist (GnRH-a) before ovarian hyperstimulation has frequently been used in vitro fertilization (IVF) treatment. Previous studies have suggested that combined use of oral contraceptives and GnRH-a may improve the IVF outcome ***(Damario et al., 1997).***

Oral contraceptives can normalize the leutinizing hormone(LH)/ follicle stimulating hormone (FSH) ratio and reduce ovarian androgen concentrations ***(Suikkari et al., 1991).***

Pituitary suppression with oral contraceptives before ovarian hyperstimulation has been reported to circumvent the initial gonadotropin flare response ***(Benadiva et al., 1988).***

Anovulation induced by oral contraceptives, showing bilateral ovarian quiescence, has also been reported to reduce miscarriage rate in the following pregnancy ***(Clifford et al., 1996)***.

Oral contraceptives were suggested to reduce the incidence of functional ovarian cyst formation, shorten the time required to achieve pituitary suppression and decrease gonadotropin requirements ***(Biljan et al., 1998).***

The use of oral contraceptives prior to controlled ovarian hyperstimulation (COH) was suggested to allow for convenient cycle scheduling as well as for ovulation suppression so that subsequent GnRH-a treatment cannot stimulate residual corpus luteum function ***(Barmat et al., 2005).***

On the other hand, some studies showed that pre treatment with a combined OCP resulted in fewer clinical pregnancies, more days of gonadotrophin therapy and a higher amount of gonadotrophins needed due to pituitary oversuppresion. Also it was found to increase risk of poor response in patients with low ovarian reserve. This is mainly important with regard to the financial aspect of the IVF/ICSI treatment. A limitation of this review is that most included studies were of small number and poor quality ***(Smulders et al., 2010)***.

So far, most of published studies in this subject were either of low number of cases ***(Damario et al., 1997,*** 99 cases); ***(Suikkari et al., 1991,*** *7 cases*); ***(Clifford et al., 1996,*** 106 cases); ***(Barmat et al., 2005,*** 80 cases) or not properly randomized ***(Damario et al., 1997***); ***(Suikkari et al., 1991***); ***(Barmat et al., 2005***) and all of them include cases of PCOS.

Aim of the Work

To determine the effect of use of oral contraceptives in pretreatment during IVF cycle on ongoing clinical pregnancy rate, duration of induction of ovulation and total induction dosage.

1. Research hypothesis: (null hypothesis)
   The use of oral contraceptives in pretreatment during IVF cycle does not affect clinical pregnancy rate.
2. Research question:
   Does oral contraceptives in pretreatment during IVF cycle affect clinical pregnancy rate?
3. Primary outcome:
   Clinical pregnancy rate/embryos transferred
4. Secondary outcomes:
   Duration of induction of ovulation.
   Number of ampoules used for induction of ovulation.
   Number of oocytes retrieved.
   Number of good quality embryos.

Chapter I

Hormone contraceptives controversies and clarifications

Recently, there has been some controversy, and serious questions have been raised by sincere individuals who are concerned that hormone contraceptives may have an abortifacient mechanism of action. we affirm that all life is created by God and that human life is initiated at conception. Fertilization, not implantation, marks the beginning of human life. Disruption of the fertilized egg represents abortion. (***Michalas, S. et al., 1996)***.

The hormone contraceptives include four basic types: combination oral contraceptives (COCs), injectables (Depoprovera), progestin only pills (minipill, or POPs), and implants (Norplant). In this paper, they will, where convenient, be collectively referred to as the "pill." Most hormone contraceptives are noted to work by 3 methods of action:

1) Primarily, they inhibit ovulation by suppression of the pituitary/ovarian axis, mediated through suppression of gonadotrophin releasing hormone from the hypothalamus.

2) Secondarily, they inhibit transport of sperm through the cervix by thickening the cervical mucous.

3) They cause changes in the uterine lining (endometrium) which have historically been assumed to decrease the possibility of implantation, should fertilization occur. This presumption is commonly known as the "hostile endometrium" theory.

A thorough review of the medical literature uncovers ample data to support the first two methods of action, which are contraceptive actions. (Appropriate references will be found in the sections discussing each type of hormone contraceptive.) However, there is no direct evidence in the literature to support the third proposed method of action. This conclusion is shared by the respected Gynecologic Endocrinology textbook authors Yen and Jaffe. ***(Yen SSC and Jaffe, 1991).***

Normal physiology

It is helpful at this point to review the basic physiology of the normal ovulatory cycle. Specific endocrinologic details are best found in a text of gynecologic endocrinology. However, in general, after a young woman completes puberty, the levels of estrogen rise and fall twice during each normal menstrual cycle. The pituitary gland releases follicle stimulating hormone (FSH), which causes new, ovum-containing follicles (eggs) to develop in the ovaries during the first half (or follicular phase) of the menstrual cycle. The follicle steadily increases estrogen production, which reaches a peak about one day prior to ovulation. The surge of estrogen stimulates her pituitary gland to secrete another essential hormone, luteinizing hormone (LH), which in turn serves to trigger ovulation (egg release).Ultrasound can be used to assess the growth and development of the ovarian follicle (cyst around the egg cell) and can indicate the degree of readiness for ovulation Ritchie ***(Ritchie, 1985).***

During an ovulatory cycle the usual cyst size varies from 20 to 28 mm. Non-ovulating follicles rarely exceed 14 mm in diameter. Ovulation is associated with complete emptying of the follicular contents in 1 to 45 minutes. After ovulation, the follicle which has released the egg becomes

filled with another type of cell, a luteal cell. The luteal cells proliferate under the influence of pituitary luteinizing hormone, (LH), and secrete ever increasing quantities of both estrogen and progesterone. ***(Speroff, Glass, and Kase 1994)***

The follicle (now a corpus luteum) most commonly appears as a smaller, irregular cyst which, if conception has NOT occurred, diminishes in size and ceases to function 2 weeks after ovulation. With subsequent decrease of luteal estrogen and progesterone, the uterine lining (endometrium) is then shed as the menstrual period. However, if conception HAS occurred, the embryo begins, by the time it implants, to secrete another chemical messenger, hCG (human chorionic gonadotropin), which acts like LH to rejuvenate and stimulate the corpus luteum to continue its function until the placenta takes over hormone production 2 months later. The corpus luteum produces, in the six days after ovulation, 10 to 20 times the levels of both estrogen and progesterone seen in a non-ovulatory "pill" cycle. (Preovulatory pill cycle has estradiol level of 25 pg/ml, preovulatory normal cycle has estradiol level of about 40 pg/ml.) During an ovulatory cycle, estradiol reaches a peak of 400 pg/ml during the day before ovulation-a ten to 16 fold increase-and peaks again at 275 pg/ml by day 6 after ovulation, which is the day of implantation. Progesterone values rise from a preovulatory 0.5 ng/ml to a peak of 10 ng/ml by implantation day-a twenty fold rise. These high levels act on the lining in theseseven days to prepare it for implantation and support of the arriving (via the fallopian tube) living embryo. Corpus luteum function continues until 8 to 10 weeks from ovulation, at which time (noted above) the placenta assumes the burden of producing these hormones to support the growing pregnancy ***(Brenner et al.,1977.)***

In the extensive literature we have reviewed, no writer has addressed this very significant question: In a menstrual cycle on the "pill" in which ovulation occurs, what is the histology of the endometrium six days after ovulation (the time of implantation)? Certainly the hormone milieu and endometrial histology will be different from a menstrual cycle on the "pill" in which ovulation does not occur(i.e.,the typical atrophic, or "hostile," endometrium). The FSH-LH-estradiol surge the day before ovulation, and the resulting corpus luteum formation, with its ten to twentyfold estradiol and progesterone output, should produce significant changes in the endometrium. In a normal menstrual cycle, on the day of ovulation the uterine lining (proliferative endometrium) is not receptive to implantation. Seven days of follicle and corpus luteum hormone output transform it to "receptive." The same follicle and corpus luteum hormone output, when ovulation occurs in a "pill" cycle, should have a similar salutary effect on the pill-primed endometrium. It is highly probable that the so-called "hostile to implantation" endometrium– heralded (without proof) from the beginning by the "pill" producing companies, echoed (without investigation) by 2 generations of scientific writers, and now adopted (as a scientific fact) by some sincere prolife advocates– simply does not exist six days after ovulation in a pill cycle. What is currently known about the endometrial response to corpus luteum hormones suggests this conclusion. Research regarding endometrial histology on the sixth day after escape ovulation in "on pill" cycles would add useful information to the current discussion ***(Crosignani et al. 1996)***.

Zanatu reports on two women with prolonged infertility (8 to 14 months) after Depo-Provera injections: "We successfully induced ovulation with the sequential adminstration of clomiphene citrate and human chorionic

gonadotropin, and pregnancy immediately followed." This suggests that once ovulation has occurred, the burst of natural estrogen and progesterone from the corpus luteum simply override even the most potent hormone contraceptive, producing a receptive endometrium, and resulting in a normal implantation and ongoing pregnancy ***(Zanartu, 1997)***.

The abortifacient theory proponents propose a second line of evidence that they feel strongly suggests the "pill" is associated with an early abortifacient effect. This refers to an increased risk per pregnancy of tubal pregnancy. The lack of a corresponding increase in intrauterine pregnancy is suggested as evidence of a contraimplantation effect of the "pill." One writer states that "All published data show that the extrauterine ratio of pregnancies is increased for women on BCPs . . ." Our own review of the literature has shown this increased ectopic rate to be true of progestin only pills (POPs) and Norplant. However, we have found absolutely no data in the literature that supports an increased ectopic to intrauterine pregnancy ratio for women using combined oral contraceptives (COCs) or Depoprovera. Comments and references accompany our discussion of these individual agents below. ***(Larimore, 1999)***

Two additional lines of reasoning have more recently been offered by abortifacient theory proponents. The first has to do with integrins, an endometrial polypeptide which is felt by some to be associated with endometrial receptivity. These integrins are "conspicuously absent in patients with luteal phase deficiency, endometriosis, and unexplained infertility….In most OC users, the normal patterns of expression of integrins is grossly altered." This is felt by the proponent to be evidence of potential abortifacient action at the endometrial level. The problem with this theory is that it

deals with endometrium in pill cycles that are not ovulatory. As noted previously, an entirely different hormone milieu exists for seven days to prepare the endometrium for implantation in an "on pill" ovulatory cycle, just as it does in a normal (or "non-pill") ovulatory cycle. We are aware of no studies dealing with integrins in an ovulatory pill cycle ***(Mol et al. 1995)***.

The second line of reasoning has to do with endometrial thickness in a pill cycle. This position notes from the medical literature that "Recent MRI studies show that pill users have endometrial linings that are 40-60% thinner than women not on the pill," and, "ten recent IVF studies confirm that "endometrial thickness is related to the functional receptivity of the endometrium." We do not dispute these quotations from the literature. However, as is the case in the previous paragraph, they simply do not apply to endometrial thickness or receptivity in an ovulatory pill cycle, nor do they purport so to apply ***(Speroff, et al., 1994).***

Definition of Abortifacient

Abortion, when used as a medical term, refers to the loss of a pregnancy less than 20 weeks gestational age, regardless of whether the termination is intentional or spontaneous. Spontaneous abortions are commonly known as miscarriages. There are literally hundreds of factors that have been implicated in the loss of human pregnancies. For example, aging of the woman, alcohol, infections, RU486, cocaine, genetic disorders, uterine structural anomalies, methotrexate, some prostaglandins and trauma have all been shown to contribute to abortions. There are many more factors that may contribute to fetal loss, but have not been proven to do so. Implicated factors include almost any environmental substance known to man, including impurities