The Comparison between the Compliance of Different Forms and Routes of Progesterone Administration in the Luteal Phase Support in Intracytoplasmic Sperm Injection Cases

Thesis

Submitted for Partial Fulfillment of the Master Degree of
Obstetrics and Gynecology

By

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Nessma Hesham Salem

Contents

List of Abbreviations

ART	**:**	Assisted Reproductive Technology
CC	**:**	Clomiphene Citrate
DG	**:**	Dedrogesterone
ELISA	**:**	Enzyme-linked immunosorbent assay
ET	**:**	Embryo transfer
FSH	**:**	Follicle stimulating hormone
GABA	**:**	γ-amino butyric acid
GIFT	**:**	Gamete intra-Fallopian transfer
GNRH	**:**	Gonadotrophin releasing hormone
HCG	**:**	Human chorionic gonadotrophin
HMG	**:**	Human menopausal gonadotrophin
ICSI	**:**	Intra cytoplasmic sperm injection
IM	**:**	Intramuscular
IVF	**:**	In vitro fertilization
LH	**:**	Luteinizing hormone
LPS	**:**	Luteal Phase Support
NS	**:**	Not significant
PR	**:**	Pregnancy rate
V	**:**	Vaginal
VACTERL	**:**	Vertebral, anal, cardiac, tracheoesophageal, renal, limb deformity)

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"The Comparison between the Compliance of Different Forms and Routes of Progesterone Administration in the Luteal Phase Support in Intracytoplasmic Sperm Injection Cases

Protocol

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Introduction

World-wide, an estimated nine percent of couples meet the definition of infertility with 50-60% of them seeking care. Although there is some controversy about whether the proportion of the population with self-reported infertility is increasing, stable or decreasing, there has clearly been increasing utilization of ART.

ART is any treatment dealing with means of conception other than vaginal coitus, frequently involving handling of gametes or embryos.

Indications for intracytoplasmic sperm injection include severe deficits in semen quality, obstructive and non-obstructive azoospermia. In addition, treatment by ICSI should be considered for couples in whom a previous IVF treatment cycle has resulted in failed or very poor fertilization ***(NICE Clinical Guidelines).***

Progesterone prepares the endometrium for pregnancy by stimulating proliferation in response to human chorionic gonadotropin (hCG), which is produced by the corpus luteum. This occurs in the luteal phase of the menstrual cycle. In assisted reproduction techniques (ART) the progesterone or hCG levels, or both, are low and the natural process is insufficient, so the luteal phase is supported with

either progesterone, hCG or gonadotropin releasing hormone (GnRH) agonists. Luteal phase support improves implantation rate and thus pregnancy rates but the ideal method is still unclear ***(Daya et al., 2004).***

The luteal phase is defined as the period between ovulation and either the establishment of pregnancy or the onset of menstruation two weeks later. Following ovulation, the luteal phase of a natural cycle is characterized by the formation of a corpus luteum, which secretes steroid hormones including progesterone and estradiol (E2). If conception and implantation occur, the developing blastocyst secretes human chorionic gonadotrophin (HCG) ***(Gazvani et al., 2008).***

During assisted reproductive technology (ART) treatment, the use of gonadotropin-releasing hormone (GnRH) agonists and the aspiration of follicular fluid can lead to a relative progesterone deficit and inappropriate preparation of the endometrium for embryo implantation. The use of GnRH agonists in ovarian stimulation, which prevents a premature surge of LH, ultimately leads to suppression of the pituitary gland, thereby blocking the secretion of LH at least 10 days following the last applied GnRH dose ***(Smitz et al., 1988),*** as well as the pulsatile secretion of progesterone ***(Kubik et al., 1986).*** In addition,

high levels of estrogen observed during induced cycles result in an inhibiting effect on the implantation of human embryos ***(Forman et al., 1988).***

The use of pharmaceutical luteal support to reach the physiological ratio of estrogen to progesterone could only be beneficial as defective production of progesterone may impair implantation and pregnancy rates, given the important role of this hormone supplementation in early pregnancy ***(Daya et al., 2008).***

Premature onset of menses was recognized as indicative of a luteal phase deficiency of progesterone production, which was shown to be correctable by exogenous progesterone ***(Kerin et al., 2007).***

Methods of luteal phase support include corpus luteum stimulation to secrete endogenous estrogen and progesterone by serial injections of human chorionic gonadotrophin (hCG) or with exogenous replacement of progesterone ***(Friedler et al., 1999).***

The use of hCG for luteal phase is associated with a marked increase in the risk of ovarian hyperstimulation syndrome (OHSS) therefore progesterone is the preferred choice ***(Pabuccu and Akar, 2005).***

Nowadays the need for luteal support in ART treatment has been universally known. Progesterone can be

administered by oral, intramuscular or vaginal routes. However, the optimal route has not yet been established. Progesterone administered orally demonstrated lower bioavailability due to the first-liver-pass effect ***(Jondet et al., 1993),*** which calls for the use of higher doses that give rise to a fairly large number of side effects such as somnolence and sedation, which are also associated with a lower pregnancy rate ***(Liccardy et al., 1999).***

There is increasing evidence that vaginal and intramuscular progesterones are at least equally effective, considering the rate of biochemical and clinical pregnancies as well as their outcomes ***(Penzias et al., 2003).*** However, through the use of vaginal progesterone, reiterated painful application of intramuscular injections and their complications, such as local soreness, abscesses, and inflammatory reactions, were avoided ***(Penzias et al., 2002).***

Aim of the work

To compare the compliance of different routes and forms of progesterone administration in the luteal phase support in ICSI cases.

Research question:

In women undergoing ICSI and need luteal support, which of the progesterone preparations has the best compliance i.e. acceptability and tolerability from the patients' point of view? And why?

Research hypothesis:

Regarding women undergoing ICSI and needing luteal support, every company claims that its product has the best compliance but we think that patients themselves are the best to decide.

Patients and methods

Protocol outline:

Study design:

Randomized controlled trial.

Study setting:

The study will be conducted at the assisted Reproduction Technology Unit (ARTU) of Ain Shams University Maternity Hospital and a private center.

Study population:

The study will include 80 infertile patients attending the clinic and seeking ICSI.

Ethical points:

A verbal and written consent will be obtained from each patient.

There is no conflict of interests in this study.

All patients' information will be kept private.

Patients will be selected to be included in the study according to the following criteria:

- **Inclusion criteria:**

  Any ICSI case.

- **Exclusion criteria:**
  - Embryos of bad quality.
  - Recurrent ICSI failure.
  - Bad quality endometrium (poor endometrial thickness).

Included women will be followed up for 14 days after randomization into 4 groups:

- **Group 1:** Where vaginal progesterone will be administered in the form of prontogest 400 mg suppositories (Marcryl-Egypt).
- **Group 2:** Where vaginal progesterone administered in the form of crinone 8% gel (Merck Serono), where the opposite end to the thick end is bent until it breaks away and the thick end is squeezed after inserting the applicator in the vagina where the gel is released. Each applicator delivers 1.125 grams of crinone gel containing 90 mg of progesterone.
- **Group 3:** where vaginal progesterone administered in the form of endometrin vaginal tablets 100 mg (Ferring), where the tablet is put into the applicator and inserted in the vagina and released after pushing the plunger.

- **Group 4:** where progesterone in the form of prontogest 400 mg suppositories (Marcryl-Egypt) will be administered rectally.

Outcome measures:

The tolerability and acceptability of the three progesterone preparations will be determined by a questionnaire asking about side effects and given to patients after a period of 14-18 days, in addition to the secondary outcome which is the pregnancy rate.

Sample size justification:

Sample size was calculated using stata program, setting the type-1 error (α) at 0.05 and the power (1-β) at 0.8. Results from a previous study ***(Geber et al., 2007)*** showed that Overall tolerability and acceptability were significantly better in the Crinone group than in the other group (85% Vs 14%). Calculation according to these values produced a minimal sample size of 20 cases per group.

Data Management and Analysis:

The collected data will be revised, coded, tabulated and introduced to a PC using Statistical package for Social Science **(SPSS 15.0.1 for windows; SPSS Inc, Chicago, IL, 2001).** Data will be presented as Mean and Standard