Different controlled ovarian stimulation protocols and its effect on the oocyte quality and pregnancy outcome in “in-vitro “ fertilization cycles

An Essay
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ABSTRACT

The aim of this study was to evaluate the effectiveness of different controlled protocols of ovarian stimulation which were long, short and microdose protocols as GnRH agonist protocols and multiple dose protocol as a GnRH antagonist protocol in ICSI cycles as regard to the number of mature oocytes, number of embryos transferred, clinical pregnancy rate and cancellation rate.

Ovulation of the normal female is a complex process involving many organs. The hypothalamus pulsatile generator of reproduction, produce & secrete gonadotrophin releasing hormone which evokes the pituitary to release FSH &LH.In response to gonadotrophin stimulation, the ovaries initiate a dynamic process of steroidogenesis, which result in the formation of mature ovum ready to be fertilized. Any defect in this group of complex process results in failure of conceive or infertility which affects up to 14% of couples nowadays.

Key words : stimulation protocols - the oocyte quality - pregnancy outcome - “in-vitro “- fertilization cycles

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LIST OF ABBREVIATIONS

Abs: Antibodies
ACE: Angiotensin converting enzyme
ACTH: adrenal corticotrophin hormone
ART: Assisted reproduction technology
BBT: Basal body temperature
BMI: Body mass index
CC: Clomiphene citrate
CCCT: Clomiphene citrate challenge test
OC_s: Oral Contraceptives
COH: Controlled ovarian hyperstimulation
CT: Computerized tomography
E_2: Estradiol
E.E:Ethenyl estradiol
EP: Ectopic pregnancy
ET: Embryo transfer
FSH: Follicle stimulating hormone
GH: Growth hormone
GIFT: Gamete intrafallopin transfer
GnRH: Gonadotropin releasing hormone
GnRH-a: Gonadotrophin releasing hormone agonist
GRH: Growth hormone releasing hormone
HBV: Hepatitis B virus
HCG: Human chorionic gonadotrophin
HCV: Hepatitis C virus
HIV: Human immunodeficiency virus
HMG: Human menopausal gonadotrophins
HSG: Hysterosalpingography
ICSI: Intracytoplasmic sperm injection
IUI: Intrauterine insemination
IVF: In vitro fertilization
LH: Luteinizing hormone

MBH: Mediobasal hypothalamus
MRI: Magnetic resonance image
OHSS: Ovarian hyperstimulation syndrome
PCOS: Polycystic ovarian syndrome
PCT: Post coital test
PGD: Preimplantation genetic diagnosis
POF:Premature ovarian failure
TRH: Thyrotropin releasing hormone
TSH: Thyroid stimulating hormone
TVS: Transvaginal ultrasound
WHO: World Health Organization
ZIFT: Zygote intrafallopian transfer

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INTRODUCTION

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Infertility affects up to one in seven couples all over the world (***Royal College of Obstetricians and Gynecologists, 2000***). A proportion of these couples may be able to ultimately conceive, but for the majority conception is unlikely without some form of medical intervention (***Collin, 2001***). In vitro fertilization and, more recently, ICSI are now commonly used treatment for infertility attributable to tubal factor, significant endometriosis and male factor and also used to treat persistent unexplained infertility (***Lloyd et al., 2003***).

Before describing strategies, an understanding of the usual controlled ovarian hyperstimulation (COH) protocol is needed for comparison. The protocol involves two steps:

1) Down-regulation of anterior pituitary gland by GnRH agonists.

2) Controlled ovarian hyperstimulation with gonadotropins.

(Pinkas et al., 2000)

The purpose of down-regulation is to temporarily take away the ability of anterior pituitary gland to release the LH surge. When GnRH-a is administrated, it will initially cause an increase in FSH and LH levels followed by suppression or down-regulation in FSH and LH levels. The suppression of endogenous FSH levels means more exogenous FSH must be administrated to achieve a given level of ovarian stimulation. The advantage of GnRH-a and gonadotrophins is that they reduce the necessity to cancel the cycles (***Moghissi, 2000***).

Different GnRH-a regimens have been used but a major distinction is based on the duration of use before the invitation of gonadotrophin therapy. The short or flare regimen is begun during the follicular phase of the treatment cycle,

1 or 2 days before gonadotrophin administration while long down regulation regimen is begun either during the luteal phase of the cycle before treatment or during the follicular phase at the treatment cycle and is continued for at least 10 days before gonadotrophin administration (***Cramer et al., 1999***).

Other investigators who observed that follicular phase flare protocols (microdose protocols) produce clinical results similar to luteal phase protocol (***Leondires et al., 1999***).

In support of these drugs, patients classified as "poor-responders" were reported to have lower cancellation rates, improved cycle quality and pregnancy after using microdose GnRH-a protocol (***Surrey &Schoolcraft, 2000***).

So it has been established that GnRH-a themselves may contribute to low ovarian response. Pituitary over suppression induced by GnRH-a causes an increase in the gonadotrophin requirement for ovarian stimulation and a reduction in the number of oocytes retrieved and fertilized. Pituitary over-suppression could occur after excessive or prolonged doses of GnRH-a administrated according to the long luteal protocol. With the aim of reducing the intensity of pituitary suppression, several schemes have been proposed with lower analogue doses or even interrupting their administration (***Depalo et al., 2001***).

The GnRH antagonists were introduced in recent years as a new alternative for COH cycles in IVF-ET. Either in the form of multiple dose protocol or single dose protocol (***Escudero et al., 2004***).

GnRH antagonists competitively block pituitary gland receptors, including a rapid, reversible suppression of gonadotrophin secretion. Due to their pharmacological mode of action, GnRH antagonists can be administrated at mid-cycle to prevent a premature LH surge while not causing any suppression in the early follicular phase, which is a crucial time for follicular recruitment. This

is particularly important in those patients who have decreased ovarian reserve. ***Nikolettos et al., (2001)*** postulate that the use of antagonist protocol in poor responders may improve the ovarian responsiveness to gonadotrophin stimulation compared with the conventional long GnRH agonist regiment.

As physicians gained greater experience and comfort with GnRH-antagonists regimens, compatible outcomes in pregnancy and implantation rates were achieved (***Williams et al., 2002***).

AIM OF THE WORK

AIM OF THE WORK

The aim of this work to evaluate effectiveness of different controlled ovarian stimulation protocols (GnRH-agonist protocols and GnRH-antagonist protocols) in ICSI cycles as regard to the oocyte number and quality, embryo number and quality and clinical pregnancy rate.

Review of Literature