Study of Sub-endometrial & Peri-follicular vascularity in cases taking Clomid and/or HMGs or both for induction of ovulation with Correlation to pregnancy rate

A Thesis

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Abstract

180 patients were divided into 3 equal groups. 60 received Clomiphene 50mg twice per day from day 3 for 5 days, 60 received HMG every other day starting from the 3rd day of the cycle and 60 received Clomiphene 50mg twice per day from 3 day for 5 days and HMG daily starting from the 6th day of the cycle. Transvaginal Doppler was used for sub-endometrial and peri-follicular blood when follicles are mature. 21 patients got pregnant (11.7%) and was lowest in clomiphene group but not significant (p = 0.191). Sub-endometrial blood flow was detected in 65% of cases and not associated with pregnancy (p = 0.469) and RI was not significantly different between pregnant and non-pregnant (p = 0.208) and in medications significantly higher in the clomiphene group. Mean perifollicular RI was significantly lower in pregnant group (p = 0.033) and in medications lower in combined group and highest in clomiphene group (p = 0.001).

Keywords: subendometrial blood flow , peri follicular blood flow, Doppler ultrasound, ovulation induction, pregnancy rate

Content

List of tables

List of figures

List of diagrams

INTRODUCTION

Introduction

Infertility is the failure to conceive (regardless of cause) after a period of unprotected intercourse. Reproduction requires the interaction and integrity of the female and male reproductive tracts, which involves (1) the release of a normal pre ovulatory oocyte, (2) the production of adequate spermatozoa, (3) the normal transport of the gametes to the ampullary portion of the fallopian tube (where fertilization occurs), and (4) the subsequent transport of the cleaving embryo into the endometrial cavity for implantation and development. Infertility is caused by male and/or female factors and sometimes certain lifestyle factors have been associated with an increased risk of infertility.

Clomiphene citrate (CC) is the most commonly prescribed agent for ovulation induction for the treatment of sub fertility associated with oligo-ovulation and could be used as a super ovulation regimen for timed intercourse or intrauterine insemination (IUI) cycles, when favorably combined with exogenous gonadotropin or alone. Clomiphene citrate is an anti-estrogenic agent resulting in a 60–85% ovulation rate and 10–20% pregnancy rate per cycle. This disparity seems to be due to the anti-estrogenic mechanism of action of cc which involves lasting estrogen receptor (ER) depletion. Because of its long half-life (2 weeks), cc accumulates in the body and may have a negative effect on the quality and quantity of cervical mucus, endometrial development, which may cause implantation failure, luteal phase defects and significant thinning of the endometrium, which is dose dependent. These adverse effects of cc on the endometrium may explain in part the relatively poor pregnancy rates associated with cc despite the high rate of ovulation. (Ensieh et al. 2008)

Gonadotrophin products utilized in ovarian stimulation are derived from urinary or recombinant sources. Urinary products include human menopausal Gonadotrophin (hMG, highly purified [HP-hMG]), urinary follicle stimulating hormone (u-FSH) and human Chorionic Gonadotrophin (HCG). The recombinant gonadotropin products are recombinant human follicle stimulating hormone (r-hFSH), recombinant human luteinizing hormone (r-hLH) and recombinant human Chorionic Gonadotrophin (r-hCG). In terms of its primary constituents, hMG contains both FSH and LH activity (in the form of LH and HCG, which have short-

and long half-lives, respectively). According to the prevailing hypotheses, the beneficial effect of exogenous LH activity in the form of hCG may result in differences in embryo quality and endometrial receptivity, providing higher live birth rates than r-hFSH in women undergoing ovarian stimulation for ART utilizing a long Gonadotrophin-releasing hormone agonist (GnRH-a) protocol . In contrast, other authors have reported better COS outcomes with r-hFSH in terms of a lower total r-hFSH dose compared with urine-derived Gonadotrophin, and an increased number of follicles, oocytes, embryos and/or pregnancies. (Philippe et al. 2010)

In the menstrual cycle, the endometrium has no adhesive qualities until the implantation window phase, during which for a very short time, the endometrium allows the implantation of gestational sacs. This feature is referred to as endometrial receptivity. Endometrial receptivity has, for a long time, been the major focus in the field of assisted reproduction because the synchronous changes of the endometrium with embryonic development are the basis for embryonic implantation. Reference 8

Angiogenesis plays a critical role in various female reproductive processes such as development of a dominant follicle, formation of a corpus luteum, growth of endometrium, implantation and development of the placenta). It is possible that blood flow towards the peri-implantation endometrium may have effects on the miscarriage and live birth following assisted reproduction treatment (ART), in addition to its role in implantation. (Ernest et al. 2006; Ernest et al. 2007)

Successful implantation depends on a close interaction between the blastocyst and the receptive endometrium. Ultrasound examination of the endometrium allows a noninvasive evaluation of endometrial receptivity. Different ultrasound parameters have been used in evaluation, including endometrial thickness, endometrial pattern, and endometrial volume. A good blood supply towards the endometrium is usually considered as an essential requirement for implantation. It is assessed by Doppler ultrasound. (Merce et al. 2007a; Merce et al. 2007b; Dechaud et al. 2008).

Angiogenesis also result in the processes of ovarian folliculogenesis, corpus luteum formation, and endometrial development. In the ovary, primordial and preantral follicles have no special vascular supply of their own and derive their blood supply from the stromal blood vessels. However, the subsequent growth of the primary follicles leads to the development of a vascular network in the theca layer with increased follicular blood flow. Ovarian Peri-follicular blood flow assessment using Doppler ultrasound has been demonstrated to be a good marker of oocyte competence, embryo viability, and subsequent implantation potential with a number of studies showing a higher pregnancy rate if embryos resulting from the fertilization of eggs from better perfused follicles. (Costello et al 2006; O'leary et al 2009)

Aim of the study

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The aim of this study is to compare the Sub-endometrial & Peri-follicular vascularity in cases taking Clomid and/or HMGs or both for induction of ovulation with Correlation to pregnancy rate.

Review of literature - Physiology of ovulation

Physiology of Folliculogenesis and ovulation

The major function of the female gonad is the differentiation and release of the mature oocyte for fertilization and successful propagation of the species. Additionally, the ovary produces steroids that allow the development of female secondary sexual characteristics and support pregnancy. In mammalian ovaries the individual follicles consist of an innermost oocyte, surrounding granulosa cells, and outer layers of thecal cells. The fate of each follicle is controlled by endocrine as well as paracrine factors. The follicles develop through primordial, primary, and secondary stages before acquiring an antral cavity. At the antral stage, most follicles undergo atretic degeneration, whereas a few of them, under the cyclic gonadotropin stimulation that occurs after puberty, reach the preovulatory stage. These Graafian follicles are the major source of the cyclic secretion of ovarian estrogens in women of reproductive age. In response to preovulatory gonadotropin surges during each reproductive cycle, the dominant Graafian follicle ovulates to release the mature oocyte for fertilization, whereas the remaining theca and granulosa cells undergo transformation to become the corpus luteum. The pool of oocytes in the mammalian ovary becomes fixed early in life; thus, ovarian senescence is linked to the dwindling supply and eventual exhaustion of the pool of primordial follicles (Fair T et al. 2003).

Initial recruitment

During initial recruitment, intraovarian and/or other unknown factors stimulate some primordial follicles to initiate growth, whereas the rest of the follicles remain quiescent for months or years. Alternately, initial recruitment may be due to a release from inhibitory stimuli that maintain the resting follicles in stasis. Initial recruitment is believed to be a continuous process that starts just after follicle formation, long before pubertal onset. After initial recruitment, oocyte growth is a prominent feature of the growing follicles, but these oocytes remain arrested in the prophase of meiosis. For those follicles not recruited, the default pathway is to remain dormant (McGee et al. 2000).

It has been established that FSH is the principal hormone that promotes follicle maturation, especially at more advanced stages of development. Although receptors of FSH are expressed in the granulosa cells of preantral follicles, evidence has been provided that in humans this hormone is not required for follicle maturation up to the antral stage. A logical explanation is that primordial follicles are located in an avascular part of the ovary, and therefore, they can be easily reached by locally produced but not by systemic factors. (Van Wezel et al. 1996).

Follicular maturation to the preovulatory stage is the culmination of a lengthy process in which the maturation of dormant primordial follicles is initiated as the granulosa cells begin to proliferate and form preantral follicles. Granulosa cell division continues and the number of granulosa cell layers increase as the preantral follicle grows. After the preantral follicle attains six-seven granulosa cell layers, the theca internal layer becomes pronounced and the formation of the antral cavity begins. It has been estimated that the duration of time required for the growth of a follicle from the primordial stage to the large preantral stage takes in excess of 150 days. Thus, a follicle which ovulates in any given menstrual cycle will actually have begun to grow at least five menstrual cycles earlier. (Zeleznik 2004)

During antrum development, the follicles acquire capillary networks, located in the theca interna and externa. The blood vessels increase in number and size as follicular development proceeds but do not penetrate the basal membrane. Ovarian activity is characterized by alternating phases of growth and regression that involve both follicular and luteal structures. This dynamic situation is paralleled by a continuous rearrangement of the blood vessel network that evolves in relation to the needs of the tissues and their different levels of activity. This process, which adjusts local blood supply to the specific needs of a tissue, defined as angiogenesis, is triggered by the local production of specific angiogenic factors. In response to these stimuli, endothelial cells from pre-existing vessels will proliferate and develop new capillaries toward the site of production of the factor. Although it is now well-recognized that follicular