Issn 1110 -6352

THE EGYPTIAN JOURNAL OF FERTILITY AND STERILITY

Volume 19 Number 1 January 2015

EFSS

EDITOR : MOHAMED YEHIA

The Egyptian Journal Of Fertility And Sterility

The Official Journal of the Egyption Fertility and Sterility Society (**EFSS)**

Instrucions To Authors

SUBMISSION OF PAPERS

Manuscripts should be written in English, typed with double spacing, submitted and, where possible, on a disk. Figures and diagrams should, if possible be used instead of tables. The work shall not be published elsewhere in any language without the written consent of the editor in chief. The articles published in this journal are protected by copyright. Contributors should submit their papers and disk to:

Editor in chief
Prof dr. Mohamed Yahia
Prof. ob & gynecology, Ain Shams University
Email: mysoliman@gmail.com

Asst. Editor:
Prof. Ahmed Badawy,
Prof. ob & gynecology, Mansoura University.
Email: ambadawy@yahoo.com

Preparation of manuscripts

- Papers should be typed double- spaced, on white paper, size A4 (210 x 297 mm). upper, lower, right and left margins should have a minimum of 25 mm.
- The pages should be numbered consecutively, beginning with the title page, each section of the manuscript should commence on a new page, in the following sequence: title page; abstract, synopsis, and key words, main text (ending with acknowledgments); references; tables; and legends for illustrations.

Title page

The title page should contain:

1. The title itself, and subtitle if any.
2. The number(s) of the author(s), first name(s) mentioned and highest academic degree).
3. The number(s) of the department(s) and/ or institution(s) from which the study originated.
4. The name and full address (including telephone and tele-fax numbers) of the "corresponding" author.
5. A "running title" of maximum 40 characters, including word spaces.

Abstract, Synopsis and Key words

- Page 2 of the manuscript. shou'd carry an Abstract not exceeding 250 words. A structured abstract is required for original research articles; excluded are case reports and brief communications. The structured abstract should contain the following headings (each of them beginning a new paragraph): Background and aim: (main question or hypothesis), Methods (Study design, number and type of subjects, treatment, and type of statistical analysis), Results (outcome of study and statistical significance, if appropriate). Conclusions (those directly supported by data, along with any clinical implications).
- The abstract should be followed by 3 - 7 key words or short phrases for Indexing purposes. Key words should be separated by semicolons.

- Synopsis: A ~ummary of the abstract in maximum of 30 words to be printed in the table of contents mainly describing the conclusions.

Main Text

- The text is conventionally divided into sections headed; Introduction, Material and Methods, Results, and Discussion. Lengthy papers may require sub-headings for clarification, particularly in the Results and Discussion sections.
- When reporting research on human beings, the authors must include an assurance that the work was approved by a medical ethics committee and that the subjects gave their informed consent to participate. do not repeat in the text all the data displayed in the tables or illustrations, do not repeat detailed data (numbers) of results in the discussion section. Avoid unqualified statements and conclusions that are not supported by the data.

Acknowledgments

Acknowledgments should only be made to funding institutions and organizations and, if to persons, only to those who have made substantial contributions to the study.

References

- References should be numbered consecutively (Arabic n merals) in the order in which they appear in the text. In the text section, the reference numbers should be given in parentheses. References within tables or legends should be numbered in accordance with the order in which they appear in the text.
- Avoid abstracts as references. Unpublished observations and personal communications -may not be used as refer - ences, but may be cited within parentheses in the text. Only papers published or in press should be numbered and .included in the reference list. Use the form of references adopted in index Medicus i.e., the Vancouver Style

Examples of correct form of references

1- Standard journal article

List all authors when six or less. When seven or more, list only first six and addetal. Toppozada MK, Gaafar AA, Shaala SA. In - vivo inhibition of the human non pregnant uterus by prostaglan din E2. Prostaglandins, 1974; 8: 401 - 406.

2- Books:

(a) Personal author: Speroff L, Glass RH, Kase NO. clinical gynecologic endocrinology and infertility. 4th edition, Baltimore, Williams & Wilkins; 1988: 105

(b) Chapter in book; Wilhelmsson L, Norstrom A, Tjugum 1, Hamberger L. Interaction between prostaglan dins and catecholamines on cervical collagen. In: Toppozada M., Bygdeman '. M., Hafez ESE, Eds. Prostaglandins and fertility regulation. Advances in reproductive health care. Lancaster, England, MTP Press Ltd., 1985 : 75 - 80.

3- Agency publication

National Center for Health Statistics. Acute conditions: incidences and associated disability, United States July 1908 - June 1909. Rockville. MD.: National Center for Health Statistics, 1972.

Tables

Tables should be typed on separate sheets. They should be numbered consecutively (in Roman numerals) and should be provided with a brief title. Vertical and horizontal lines should not be used within the body of the table.

Illustrations

All figures must be clear and submitted either as glossy black and white photographs or as graphic reproductions (Two complete sets); freehand or typewritten lettering is unacceptable. Roentgenograms and similar material should be submitted as photographic prints. Letters, numbers and symbols must be clear and large enough to remain visible after size-reduction for printing.

Each figure should have on its reverse side, lightly written by pencil, the numerical order (Fig. #), the name(s) of the author(s), and the correct orientation, e.g., an arrow pointing to the top. Do not mount it on cardboard, or use clips or tapes.

Photomicrographs must have an internal scale marker (or the magnification factor must be given in the legend). Any symbols, arrows or letters used should be in strong contrast with the background. Previously published illustrations must be acknowledged, giving the original source; with a written permission from the copyright-holder to reproduce the material. No permission is required for documents in the public domain.

For illustrations in colour, colour negatives or positive tran parencies must be supplied . .Legends for illustrations should be typed on a separate page, using Arabic numerals corresponding to the illustrations.

Proofs

Proofs will be sent for the correction of typographic errors only. No change in make-up can be accepted. Proofs not returned within 10 days will be considered approved by the author.

The Egyptian Journal of Fertility and Sterility has no page charges and offers no free reprints. The cost of printing illustrations in colour will be charged to the author(s). Significant changes in the printed proofs will also be charged to authors.

Contents :

Letter from the Editor:

Dear colleagues,

This is the first issue of 2015, I hope that this year will be better than the previous one and bring peace and prosperity to all Egyptians.

We are trying to diversify the type of papers in the magazine as you can find in this issue. We have incorporated a paper about emergency contraception and we definitely need your contributions and we are waiting for your scientific work.

During the past few weeks there was a lot of talk about the 3 parent embryo , with the law passed in England to perform mitochondrial DNA transfer, in order to prevent serious genetic diseases like muscular dystrophy passing from mother to child . The technique replaces faulty mitochondrial DNA in an egg or embryo with healthy DNA from a female donor. Diseases arising from faulty mitochondrial DNA usually affect several organs, and include symptoms like muscle wasting, loss of movement control, diabetes and epilepsy. They can also cause liver failure, heart problems, stroke-like episodes, and - in severe cases - death.

According to a new study published in a leading journal recently, around 2,500 women could benefit from mitochondrial donation in the UK. This would amount to an average of 150 babies born each year.

The study also estimates around 12,400 women in the US would benefit from the procedure should it be introduced, amounting to around 770 or more births a year.The questions that are posed by this emergent procedure from the religious point needs clarification as it is pound to come to our practice soon and we need to be prepared for it .

Yours
Professor Mohamed Yehia
Ain Shams University
Editor in chief

Evaluation of the effect of bacterial colonization in cervical mucus on the outcome of ICSI cycles

Farahat M., Nouh B., Rageh K., Ismael M.S., Fata A., Hablas W., Wafa Y
International Islamic center for population studies and research, Al Azhar University, Cairo, Egypt.

Abstract

Objective: Evaluation the effect of chlamydial infection and microbial flora in cervical mucus at the time of embryo transfer on fertilization and implantation in women undergoing ICSI procedures.

Patients and Methods: 500 infertile women were enrolled in this study. All were recruited from the outpatient clinic of Assisted Reproduction unit in International Islamic Centre for Population Studies and Researches, Al-Azhar University. All participants underwent pituitary down-regulation using either long or short protocol followed by ovarian stimulation, oocytes retrieval, fertilization, and embryos transfer. In the study group, cervical swabs were taken with the first folliculometry and screened for Chlamydia & other bacterial growth; antibiotics were given accordingly for positive cases. During ET, cervical swabs were taken from control group and tested for Chlamydia & other bacterial infection but with no usage of any antimicrobials, pregnancy tests were done two weeks after ET, and the participants were accordingly divided into two subgroups: pregnant group and non-pregnant group.

Results: Overall incidence of pregnancy: 193/500 (38.6 %), and for those who got pregnant, the incidence of Chlamydia alone (in study group) was 8.89 % compared to 8.74% (in control group). Incidence of other bacterial growth (in study group) was 35.56% compared to 30.1% (in control group). Incidence of associated Chlamydia & other bacterial growth (in study group) was 8.89 % compared to 5.83% (in control group)

Conclusion: Chlamydial infection and microbial flora of the cervix detected during ET has no role in the implantation process, and does not affect pregnancy rates significantly in women undergoing ICSI, and antimicrobial has no significant role in improving outcome of pregnancy rate.

Key words: Cervical mucus, bacterial colonization, Chlamydia, ICSI.

Introduction

The hostility or receptivity of the cervix to spermatozoa is dependent to a great degree upon the condition of the cervical mucus, a subject that deserves more attention in the gynecological literature. It is unfortunate that so much stress has been placed on evaluation of tubal patency, determination of ovulation and analysis of semen with relative neglect of the cervical factor. In intracytoplasmic sperm injection (ICSI), embryo transfer (ET) is usually performed 72 hours after oocyte retrieval. For standard ET procedure, transfer is accomplished via transcervical cannulation and injection of embryos into the uterine cavity. [1]

Embryo implantation is the main event that limits the success of ICSI-ET. Despite the presence of satisfactory embryo morphological analysis as well as adequate histological and histochemical endometrial characteristics, overall ICSI –ET pregnancy rates remain poor. This indicates that additional factors might interfere with the normal embryo implantation process. These factors range from culture conditions, hormone stimulation, gamete immaturity or quality of chromosomal abnormality to the possi-

bility of bacterial contamination of the uterine cavity. [2] ICSI-ET procedures involve needle puncture of the vagina for egg retrieval and placement of embryos through the cervix, thus contamination is possible from vaginal-cervical microorganisms particularly because vaginal antiseptics usually are not used during egg retrieval or embryo transfer to avoid injury of the egg or embryos [3]. Prophylactic antibiotics administered to women at time of oocyte retrieval, were claimed to be associated with a reduction in positive microbiology cultures of embryo catheter tips 48 hours later in 78.4% of patients [4]. The minimal inflammation in response to microorganisms that enter the endometrium from the cervix during embryo transfer provides another mechanism that could damage the developing embryo and prevent pregnancy [4].

Regarding the mechanisms that may be responsible for damaging the developing embryo. First, it is conceivable that intense concentrations of microorganisms on the cervix may be associated with subclinical chronic endometritis and therefore poor uterine receptivity. Second, the ET procedure may inoculate cervical microorganisms into the uterine cavity, potentially altering the biochemical or ultrastructural characteristics of the endometrium required for satisfactory embryo implantation and early development. Third, the possible direct contamination of embryos during transcervical embryo transfer may cripple their ability to implant [5].

Subjects and Methods

The aim of this study was to evaluate the effect of bacterial colonization in cervical mucus on the outcome of ICSI cycles.

- Study setting: The study was carried out from February 2012 to June 2013, 500 participants with infertility were enrolled in the study in international Islamic center for population studies and research, Al Azhar University, Cairo, Egypt. All were recruited from the outpatient clinic of Assisted Reproduction unit.
- Research Design: A prospective follow-up study design was used in carrying out the study.
- Study subjects: The study included 500 consecutive patients from those attending the unit with the diagnosis of infertility who were assigned for treatment with intra-cytoplasmic sperm injection (ICSI). The inclusion criteria included women age less or equal to 36 years, whose uteri were morphologically normal as confirmed by HSG and U/S to limit additional factors that may affect the results of the study. Moreover, none of the women included in this study had clinical evidence of vaginitis or cervicitis or has a concurrent use of antibiotics. Each woman participated only once in the study. Ethical committee approval was obtained and all subjects gave their oral consent to be included in the study.
- Study Maneuver: Taking history, abdominal and pelvic examination was also performed. Routine investigations were carried out for all participants according to the protocols applied in the unit. Down regulation and induction of ovulation were initiated for every patient according to the applied protocol. Follicular monitoring and estimation of endometrial thickness were performed using TVS every other day starting six days after initiation of gonadotropins. In study group, cervical swabs were taken with the first folliculometry and screened for Chlamydia and other bacterial growth, antibiotics were given accordingly for positive cases), then after hCG administration and oocytes retrieval, embryo transfer (ET) was done 48-72 hours after oocyte using a standardized technique, with a cook ET catheter. A maximum of four embryos were transferred at a time. No antiseptic solution was used to prepare the cervix for embryo transfer, but this was only washed with normal saline. In the control group, cervical swab was taken and tested for Chlamydia and other bacterial growth but with no any antimicrobials given even in positive cases), luteal phase support was given and patients were scheduled for B-hCG two weeks after ET, and the participants were accordingly divided into two subgroups: a pregnant group , and a non-pregnant group.
- Bacteriological investigation methods:

a. Polymerase chain reaction (PCR): was used for the detection of the Chlamydia trachomatis. PCR involved three steps, namely DNA extraction, amplification, and detection of specific DNA product.

b. Culture: Swabs were cultured on blood agar, chocolate agar and ma ckonky's agar. The plates were incubated aerobically and anaerobically in 5% CO_2 at 37 ^{0}C. Bacteria were isolated for identification by standard laboratory procedures.

Results

All data were collected, tabulated and subjected to statistical analysis. Comparison of the socio-demographic characteristics of the study and control groups, revealed no differences of statistical significance, their age was around 29 years. Their BMI around 26.5, the

mean duration of infertility was respectively 5.8 and 6.1 years, and the mean of FSH level was 6.6 and 6.3 respectively, they were mostly housewives. Concerning the cause of infertility in the two groups, the figure (1), shows no statistically significant difference between study and control in the cause of infertility, it was mainly male factor with 62% to 64%.

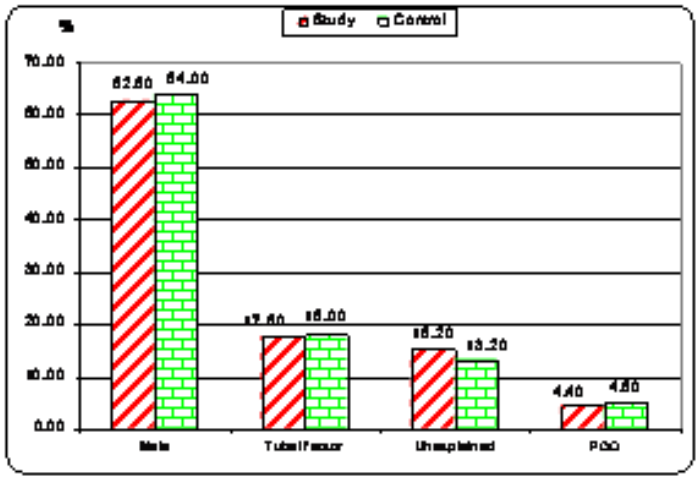

Figure 1: Relation between study and control as regard to cause of infertility.

Regarding the characters of ICSI cycles, there were no statistically significant differences between the two groups in number of administered HMG ampoules (37 to 38 ampoules), duration of stimulation is around 12.5 days, endometrial thickness at time of embryo transfer ranged from 10.5 to 10.9 mm. Nearly, 8 oocytes were retrieved, 4 of them were fertilized and almost 2 embryos were transferred, as shown in figure (2)

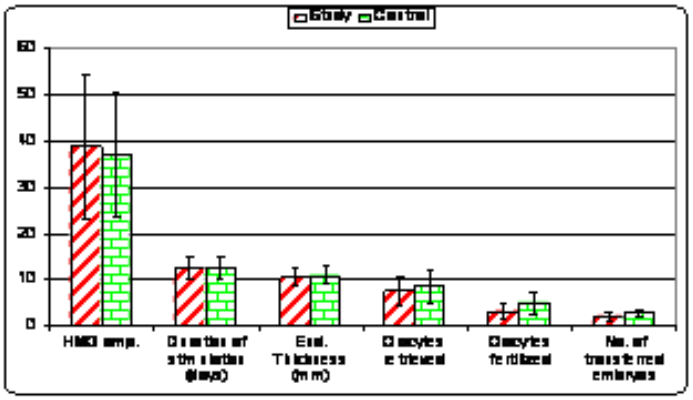

Figure 2: Comparison between study and control as regard characters of ICSI cycle.

Concerning bacterial growth, figure (3) and (4) indicate that the organisms isolated varied from staphylococci, Klebsiella, E-coli, lactobacilli and to less extent anaerobic cocci. However, no differences of statistical significance could be noticed between the study and control group

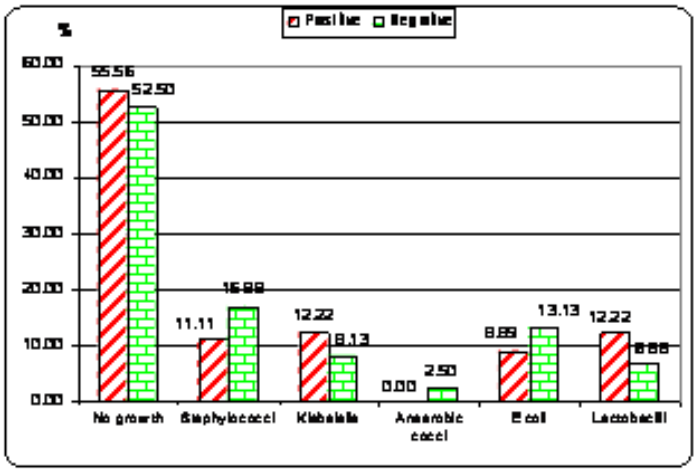

Figure 3: Relation between cultures of bacterial growth as regard to pregnancy test in study group.

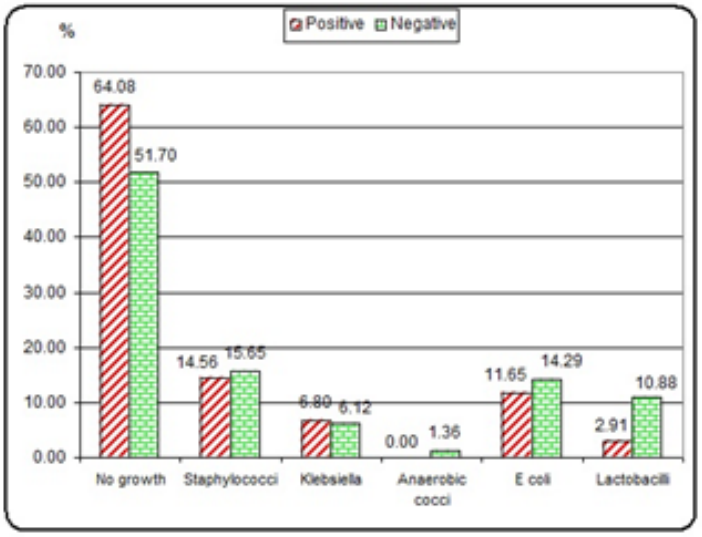

Figure 4: Relation between cultures of bacterial growth as regard to pregnancy test in control group.

The chlamydial growth data were also similar in the two groups. As illustrated in figure (5), no differences of statistical significance could be revealed between them, the positive cases was 17.7% and 14.5% in preg-

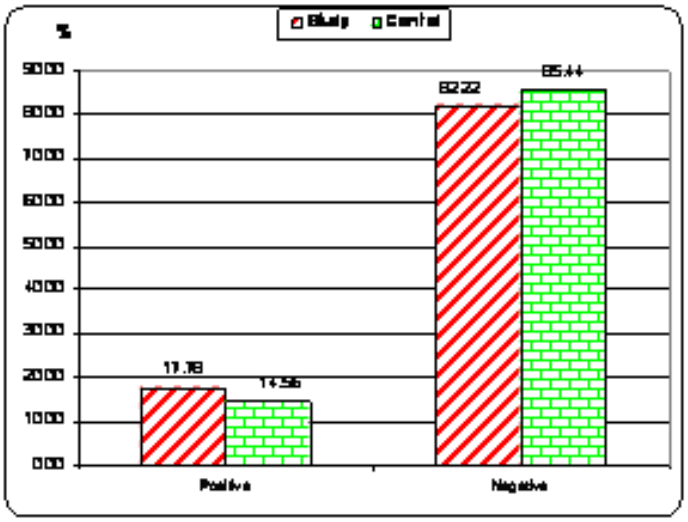

Figure 5: Relation between study and control pregnant cases as regard to Chlamydia.

Comparison of various combinations of bacterial and or chlamydial growth did not show any differences of statistical significance between the pregnant cases in the two groups. Also, figure (6) shows that overall incidence of pregnancy: 193/500 (38.6 %), and for those who got pregnant, the incidence of Chlamydia alone (in study group) is 8.89 % compared to 8.74% (in control group). Incidence of other bacterial growth (in study group) is 35.56% compared to 30.1% (in control group). Incidence of associated Chlamydia & other bacterial growth (in study group) is 8.89 % compared to 5.83% (in control group)

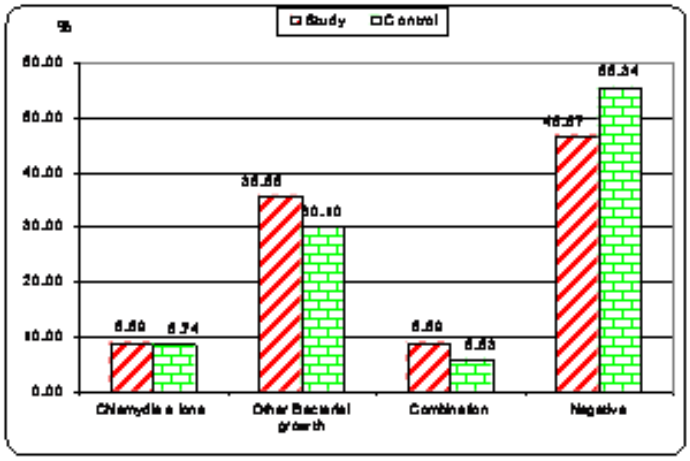

Figure 6: Relation between study and control pregnant cases as regard to combination between positive culture and Chlamydia

Discussion

Embryo implantation is the main event that limits the success of IVF-ET [5]. Genital infections, particularly those caused by sexually transmitted microorganisms, rank among the leading causes of infertility [6]. The fear that genital bacterial contamination may interfere with embryo implantation has been suggested as far back as 1978 [7].Clinical studies have shown that bacterial contamination of the embryo transfer catheter has a significant negative effect on the clinical pregnancy rates [8,9,10].In addition, cervical sterility at the time of ART procedures cannot be achieved with the routine use of vaginal antiseptics since there is evidence these solutions have been shown to have a negative impact on the quality of the oocytes collected and the embryos available for transfer [11].Moreover, there is insufficient evidence about the effects of different antibiotic prophylaxis regimens on ART cycle outcomes [4,12,13]. The influence of the cervical mucus present at time of embryo transfer and its bacterial contamination on the outcome of ICSI cycles has been highly debated due to conflicting results in the medical literature. Some authors have demonstrated diminished pregnancy rates, while others have shown not. In addition, most of studies supported the use of samples of cervical mucus from catheter tips at time of embryo transfer. C. trachomatis is believed to be one of the major causes of cervical factor infertility, as a result of the alterations of the epithelium and mucus composition, and by the presence of inflammatory cells; anyway, the overall impact of cervical disorders on fertility still needs to be assessed [14]. It has been suggested that impaired ovarian function and low ovarian response to ovulation induction are associated with C. trachomatis infection [15]. Earlier studies have shown that pathogenesis of the disease was not only induced by the infectious agent but also due to immune response to infected tissues [14]. Detection of Chlamydia species in the endocervices of women undergoing IVF-ET has been associated with decreased implantation rates [16]. The cervix is usually colonized by other potentially pathogenic microorganisms that can be introduced into the uterine cavity or contaminate embryos during ET [17]. The consequences of this septic milieu on the outcome of embryo implantation are unclear. Egbase P.E., et al, in 1996, has reported poor IVF-ET results in patients with positive microbial growth after catheters used in ETs were cultured. From a pathophysiologic standpoint, at least three mechanisms may be considered for explaining the lower pregnancy rates observed among patients with positive cultures: First, it is conceivable that intense concentrations of microorganisms on the cervix may be associated with subclinical chronic endometritis and, therefore, poor uterine receptivity. Second, the ET procedure may inoculate cervical microorganisms into the uterine cavity potentially altering the biochemical or ultrastructural characteristics of the endometrium required for satisfactory embryo implantation and early development. Third, the possible direct contamination of embryos during transcervical ET may cripple their ability to implant [18].

In light of this controversy, and the need to clearly identify the potential value of bacterial contamination of the cervical mucus and role of antibiotic on the outcome of ICSI cycles, it was decided to perform this study. The vaginal flora contains a large variety of bacterial species, including aerobic and anaerobic organisms, as revealed by modern microbiologic methods [19]. Moreover, the diversity and kinds of organisms that comprise the vaginal microbial community vary among women [20]. Since the lower genital tract is a naturally inhabited with vaginal flora and pathogenic organisms, operative procedures through or adjacent to this field leads to a moderate to high incidence of

infection. Therefore recommendations for antibiotic prophylaxis have been established in many procedures, including vaginal hysterectomy, abdominal hysterectomy, and cesarean section [21]. However, unlike most assisted reproductive techniques, these are major operative procedures that may carry a high morbidity rate from infections. With regards minor operative procedures related to ART, such as during trans-vaginal oocyte retrieval and embryo transfer, there are no clear recommendations by any society (e.g. American society of Reproductive Medicine [ASRM], European Society for Human Reproduction and Embryology [ESHRE], Middle East Fertility Society [MEFS], Mediterranean Society for Reproductive Medicine [MSRM]) or other evidence-based guidelines (e.g. NICE guidelines). However, these procedures have a high possibility of ascending infection from the lower genital tract to the upper genital tract, especially for those procedures that pass through the endocervical canal into the uterine cavity (e.g. intrauterine insemination and embryo transfer). Since these procedures have only small areas of tissue trauma, it is questionable whether or not antibiotic prophylaxis, the use of antibiotics for the prevention of infection, for these procedures protects against ascending infection. Therefore, antibiotic prophylaxis might have a role to prevent infection in these procedures, but this has yet to be officially quantified. In essence, in today's evidence based medical environment, any recommendation must be built on two main questions: (a) whether ascending infections occur as a result of the procedure and (b) whether this results in a decreased pregnancy rate in such cases. Only then can a proper set of guidelines be proposed to answer this clinical query.

The present study aimed to evaluate whether the presence of cervical microorganisms in cervical mucus at embryo transfer has an effect on the success of pregnancy in women undergoing ICSI procedure, and what is the benefit of antimicrobials on the outcome of ICSI cycles. The present study has shown that there were no statistically significant differences between the study group and control group women as regards to their age, duration of infertility, and serum FSH level measured on day 3 of the cycle. This was important in order to be able to compare pregnant versus non-pregnant women as regards the presence of Chlamydia and other organisms, and to investigate the relation between the presence of these microorganisms and the success or failure rates of the process of ICSI. Similarly, there were also no statistically significant differences between the two groups, study group and control group, as regards to the number of retrieved oocytes and the number of transferred embryos. This is again to ensure that both groups had equal chance of success, and of getting pregnant. The present study has demonstrated that there were no statistically significant differences between the two groups of study and control groups as regards to bacterial growth in pregnant cases, despite of antibiotics given to study group according to culture and sensitivity tests. The present study findings have also shown that subjects in the study group, who were positive for Chlamydia and received anti-chlamydial medications, show no statistically significant difference between them and other positive chlamydial cases in control group who did not receive any antichlamydial medications as regard to the pregnancy rate.

Conclusion

The present study reports that chlamydial infection and microbial flora of the cervix detected during ET has no role in the implantation process, and does not affect pregnancy rates significantly in women undergoing ICSI procedure for the treatment of infertility, and antimicrobial has no significant role in improving outcome of pregnancyrate.

The following table will summarize and demonstrate some published studies in relation to our study (arranged in a chronological manner)

Study	Year	Sample size	Maneuver	Conclusion
Lunenfeld E., et al, [22]	1989	200	Chlamydial-specific IgG and IgA antibodies in the serum of 106 patients that have conceived in an in vitro fertilization and embryo transfer (IVF-ET), and in a group of 94 patients that went through the program at the same period of time and did not conceive.	The authors have concluded that their results indicate the possible role of past or chronic active chlamydial infection on the success of an IVF-ET program.
Lessing J.B., et al, [23]	1991	86	The prevalence of specific chlamydial IgG and IgA antibodies have determined in 86 infertile women undergoing in vitro fertilization (IVF). Pregnancy was later achieved by IVF in 13 of 32 seropositive and 19 of 32 seronegative women.	The results have demonstrated that high levels of specific antichlamydial antibodies (IgG and IgA) are not correlated with the outcome of IVF-embryo transfer treatment.

Witkin S.S., et al, [24]	1995	307	Chlamydia trachomatis in the endocervices of 307 asymptomatic culture-negative women undergoing in vitro fertilization (IVF). C. trachomatis was detected by polymerase chain reaction (PCR) in 20 subjects (6.5%)	There were strong correlations between a positive finding and both failure to become pregnant (p=0.013) and spontaneous abortion after embryo transfer (p=0.004).They have concluded that an undetected C. trachomatis infection may be responsible for implantation failure or spontaneous abortion after IVF and embryo transfer.
Egbase P.E., et al,[8]	1996	110	Microbiological cultures were performed on endocervical swabs and embryo transfer catheter tips.	The clinical pregnancy was 57.1 % in the group of patients without growth and 29.6% in the group with positive microbial growth from catheter tips. Concluded that the presence of microorganisms on the cervix, as detected on the catheter used for ET, was associated with poor IVF-ET outcome.
Claman P., et al, [25]	1996	195	To examine IVF-ET outcome in patients with and without serologic evidence of Chlamydia trachomatis infection and chlamydia heat shock protein 60 (CHSP 60) antibodies, these investigators have conducted a retrospective case control study on 195 IVF-ET patients with tubal factor infertility who underwent oocyte pick-up	There are no differences in pregnancy rates or outcomes in patients with and without serologic evidence of previous C. trachomatis infections.
Sharara F.I, et al, [26]	1997	194	These authors have carried out a study to evaluate the impact of elevated serum Chlamydia IgG antibodies (Ab) on in vitro fertilization (IVF) outcome in a large infertility population. 194 women undergoing a total of 316 IVF cycles were evaluated. All couples with positive serum Chlamydia IgG Ab were pretreated with doxycycline, 100 mg twice daily, for 10 days prior to the first IVF cycle. They have found that one hundred seven women (55.2%) had elevated serum Chlamydia IgG Ab. One hundred seventy-two IVF cycles (54.4%) were in patients with elevated Ab as compared to 144 cycles (45.6%) in controls with negative Ab.	Concluded that there was no correlation between IVF outcome and quantitative IgG Ab titers in women with elevated serum Chlamydia Ab.
Fanchin R., et al, [9]	1998	279	The tips of catheters were subjected to quantitative (≥10 colonies = positive culture group; <10 colonies = negative culture group) and qualitative microbial assessment.	The presence of cervical microbial flora (particularly E. coli) at the time of ET, as detected through bacteriologic assessment of ET catheter is associated with decreased IVF-ET success
Liversedge N.H., et al, [27]	1999	301	High vaginal swabs taken at the time of oocyte collection were assessed by Gram staining.	Although the prevalence of bacterial infection was much higher in infertile patients having IVF treatment, compared to others in antenatal and general gynecological populations, no significant effect upon fertilization and implantation rates was found.
Johnson K. [28]	2000	297	In the study, cultures were taken from catheter tips used during the cycles, both at the time of egg retrieval and again at embryo transfer, All patients were then routinely treated prophylactically with ceftriaxone (2 g IV) and metronidazole (1 g IV) at egg retrieval. They later underwent embryo transfer.	Implantation rates were statistically less for those who tested positive on both occasions (9.3%), compared with those who tested negative both times (21.6%) or who tested positive only at egg retrieval (19.3%). %)

Study	Year	Sample size	Maneuver	Conclusion
Moore D. [29]	2000	91	cultures were taken from catheter tips used during the cycles, both at the time of egg retrieval and again at embryo transfer, All patients were then routinely treated prophylactically with 100 mg of doxycycline twice a day for 5 days, starting before embryo transfer	The negative impact on pregnancy rates was only true of one particular bacteria, Streptococcus viridans, which reduced the pregnancy rates to 7%. Most other bacteria seemed to have no effect, being associated with a 37% pregnancy rate, and administration of prophylactic antibiotics, in this case, was ineffective in changing any of the vaginal microbial growth in the patients
Salim R., et al, [10]	2002	204	Bacteriological culture of cervical canal	Failure to conceive in ART is significantly associated with bacterial colonization of the uterine cervix.
Cortinas P., et al, [30]	2004	41	The relationship between presence of anti-Chlamydia trachomatis and anti-HSP60 antibodies in serum and follicular fluid of infertile women has investigated. Serum IgG and follicular fluid IgA to Chlamydia trachomatis and human heat shock protein 60 (HSP60) were determined in 41 women undergoing in vitro fertilization (IVF).	A significant association was found between the presence of bacterial antibodies in serum and IgA anti-HSP60 in follicular fluid. Although the authors have reached to the conclusion that Chlamydia trachomatis infection might be triggering an autoimmune process that could negatively affect the success of IVF, they have not reported the pregnancy rates achieved, and whether it was associated with the levels of these markers.
Meherafza M., et al, [31]	2007	260	After transferring the embryo, about 3cm of the end of catheters were cut and put in selective culture media. After incubating in special conditions by using current bacteriological methods; bacteria were isolated and characterized	The study revealed that microbial flora of the cervix didn't influence in poor ICSI-ET outcome.
Selman H., and Mariani M. [32]	2007	152	During embryo transfer, separate samples were collected for microbial examination from the following sites: the fundus of the vagina, the cervix, the embryo culture medium prior and post-embryo transfer, the tip of the catheter samples were separately cultured to identify any bacteria or yeast present.	the presence of vaginal-cervical contamination at the time of E.T. is associated with significantly decreased pregnancy rate
Aboul Fotouh I., and Al-Inany M.G. [33]	2008	25	Cervical mucus samples were taken immediately prior to embryo transfer and the tips of the post-transfer catheters were examined for bacterial contamination, and their levels were recorded.	The presence of bacterial contamination of catheter tips during embryo transfer is evidently limited and doesn't affect the cycle outcomes.
Abd- Raboh S., et al. [34]	2011	300	A study group of 150 infertile females attending infertility centers for ICSI and a control group of 150 multiparus females attending outpatient clinics for IUD introduction have been included. Endocervical swabs from cases and controls have been examined for chlamydial antigen using immunochromatography. Also sera were examined for IgG and IgM for Chlamydia trachomatis in both groups.	Results: 12 positive cases for serum Ig G in study group (8.0%) and 16 in controls (10.67%) has been revealed. While serum IgM was found in 4 study cases (2.7%), with no positives in the controls. Regarding Chlamydia antigen detection in endocervical swab, there was 6 positive study group cases (4.2%), while no cases were positive in controls. Conclusion: the study reports a very low prevalence rate of Chlamydia trachomatis infection in Egyptian females, which minimizes its role as cause of infertility in Egyptian population and subsequently its impact on success of ICSI is not much expressed. Cultural impact on sexual life style in Egyptian population could justify these findings.

Study	Year	Sample size	Maneuver	Conclusion
Van Oostrum N., et al, [35]	2013	27 studies	This study is a meta-analysis of data on the prevalence of BV in women with infertility, the association between BV and the cause of infertility, and the associations between BV and conception rates and early pregnancy loss following IVF over 27 Systematic literature searches of the electronic databases, PubMed, EMBASE, CINAHL, Cochrane Library and ISI Web of Knowledge.	None of the studies found an association between abnormal vaginal flora and conception rates following IVF treatment.
Our study	2013	500	To evaluate the effect of bacterial colonization in cervical mucus on the outcome of ICSI cycles. 500 participants who underwent ICSI were enrolled in the study, As regard study group 250 cases, cervical swabs were taken with the first folliculometry and screened for Chlamydia and other bacterial growth; antibiotics were given accordingly for positive cases. During ET, cervical swabs were taken from control group 250 cases and tested for Chlamydia and other bacterial infection, but with no usage of any antimicrobials, Pregnancy tests were done two weeks after ET, and the participants were accordingly divided into two subgroups: a pregnant group and non-pregnant group	Our study reports that chlamydial infection and microbial flora of the cervix detected during ET has no role in the implantation process, and doesn't affect pregnancy rates significantly in women undergoing ICSI procedure for the treatment of infertility, and antimicrobial has no significant role in improving outcome of pregnancy rate.

References

1. Elder K. and Dale B. (2011): In vitro Fertilization, 3rd edition. U.K., New York, Australia: Cambridge University Press, P.152.
2. Paulson R.J., Sauer M.V. and Lobo R.A. (1995): Factors Affecting Embryo Implantation after Human Invitro Fertilization. A Hypothesis. Am J Obstet Gynecol; 163:2020-3.
3. Yaron Y., Peyser M., Samuel D., and Lessing J. (1994): Infected Endometriotic Cysts Secondary to Oocyte Aspiration for Invitro Fertilization.Hum Repord; 9:1759-60.
4. Egbase P.E., Sharhan M., and Grudzinskas J.G. (1999): Prophylactic Antibiotics and Endocervical Microbial Inoculation of the Endometrium at Embryo Transfer. Lancet; 354:651-2.
5. Tabibzadeh S. and Babakina A., (1995): the Signals and Molecular Pathways Involved in Implantation. Asymbiotic Interaction between Blastocyst and Endometrium Involving Adhesion and Tissues Invasion. Hum Repord; 10:1579-1602.
6. Faro S. (1991): Chlamydia Trachomatis: Female Pelvic Infection. Am J.Obstet Gynecol; 164:1767-70.
7. Czernobilsky B. (1978): Endometritis and infertility. Fertil Steril. 1978 Aug; 30(2):119-30.
8. Egbase P.E., Al-Sharhan M., Al-Othman S., et al, (1996): Incidence of Microbial Growth from the Tip of the Embryo Transfer Catheter after Embryo Transfer in Relation to Clinical Pregnancy Rate Following in-Vitro Fertilization and Embryo Transfer. Human Reproduction; 11(8): 1687-1689
9. Fanchin R., Harmas A., Benaoudia F., et al, (1998): Microbial Flora of the Cervix Assessed at the Time of Embryo Transfer Adversely Affects Invitro Fertilization Outcome. Fertil Steril; 70;866-70
10. Salim R., Ben-Shlomo I., Olodner R., et al, (2002): Bacterial colonisation of the uterine cervix and success rate in assisted reproduction: results of a prospective study. Human Reproduction 17, 337–340.
11. Van Os H.C, Roozenburg B.J, Janssen-Caspers H.A, et al, (1992): Vaginal disinfection with povidon iodine and the outcome of in-vitro fertilization. Hum Reprod. 1992 Mar; 7(3):349-50.
12. Peikrishvili R, Evrard B., Pouly J.L, and Janny L., (2004): Prophylactic antibiotic therapy (amoxicillin + clavulanic acid) before embryo transfer for IVF is useless. Results of a randomized study. J Gynecol Obstet Biol Reprod (Paris). 2004 Dec; 33(8):713-9.
13. ACOG (2006): American College of Obstetricians and Gynecologists Committee on Practice Bulletins, ACOG Practice Bulletin No. 74. Antibiotic prophylaxis for gynecologic procedures. Obstet Gynecol. 2006 Jul; 108(1):225-34.
14. Paavonen J. and Eggert-Kruse W. (1999): Chlamydia trachomatis: impact on human reproduction. Hum Reprod Update 1999; 5:433–47.
15. Malik M., Rizvi S., Hakim A. and Jain M. (2006): Chlamydia trachomatis in females and Infertility in India. J. Med. 2006; (123): 770 – 5.
16. Witkin S.S., Sultan K.M., Neal G.S., et al, (1994): Unsuspected Chlamydia Trachomatis Infection and IVF Outcome. Am J Obstet Gynecol; Nov

171(5):1208-14.
17. Bartlett J.G., Moon N.E., Goldstein P.R., et al, (1978): Cervical and Vaginal Bacterial Flora: Ecologic Niches in the Female Lower Genital Tract. Am J Obstet Gynecol; 130:658-61.
18. Lessey B.A., Damjanovich L., Coutifaris C., et al, (1992): Integrin Adhesion Molecules in the Human Endometrium. Correlation with the Normal and Abnormal Menstrual cycle.J Clin.Invest; 90:188-95.
19. Zhou X., Bent S.J, Schneider M.G., et al, (2004): Characterization of vaginal microbial communities in adult healthy women using cultivation independent methods. Microbiology, 2004 Aug; 150(Pt 8):2565-73.
20. Heinemann C. and Reid G. (2005): Vaginal microbial diversity among postmenopausal women with and without hormone replacement therapy. Can J Microbiol. 2005 Sep; 51(9):777- 81.
21. ACOG (2003): American College of Obstetricians and Gynecologists Committee. Prophylactic antibiotics in labour and delivery. ACOG Practice Bulletin, clinical management guidelines for obstetrician-gynecologists 2003; Number 47.
22. Lunenfeld E., Shapiro B.S, Sarov B., et al, (1989): The association between chlamydial-specific IgG and IgA antibodies and pregnancy outcome in an in vitro fertilization program. J In Vitro Fert Embryo Transf.; 6(4): 222-7.
23. Lessing J.B, Kletter Y, Amster R, et al, (1991): Success rates in in vitro fertilization treatment and its correlation with high titer antibodies for Chlamydia trachomatis. Isr J Med Sci.; 27(10):546-9.
24. Witkin S.S, Klingman I., and Bongiovanni A.M., (1995): Relationship between an asymptomatic exposure to Chlamydia trachomatis and an autoimmune response to spermatozoa. Hum Reprod 1995;10: 2952–5.
25. Claman P, Amimi M.N, Peeling R.W, et al, (1996): Does serologic evidence of remote Chlamydia trachomatis infection and its heat shock protein (CHSP 60) affect in vitro fertilization-embryo transfer outcome? Fertil Steril.; 65(1):146-9.
26. Sharara F.I, Queenan J.T., Springer R.S., et al, (1997): Elevated serum Chlamydia trachomatis IgG antibodies. What do they mean for IVF pregnancy rates and loss? J Reprod Med.; 42(5): 281-6.
27. Liversedge N.H., Jenkins J.M. and Keay S.D. (1999): Antibiotic Treatment Based on Seminal Cultures from Asymptomatic Male Parteners in IVF is Unnecessary and May be Detrimental. Hum. Repod; 11, 1227-1231.
28. Johnson K., (2000): Normal Vaginal Flora May Hamper IVF Success, OB/GYNNews.(2000),FindArticles.com.30Mar,2011.http://findarticles.com/p/articles/mi_m0CYD/is_1_35/ai_59579586/
29. Moore D.E, Soules M.R, Klein N.A, et al, (2000): Bacteria in the transfer catheter tip influence the live-birth rate after in vitro fertilization. Fertil Steril. 2000 Dec; 74(6):1118-24.
30. Cortinas P, Munoz M.G, Loureiro C.L and Pujol F.H., (2004): Follicular fluid antibodies to Chlamydia trachomatis and human heat shock protein-60 kDa and infertility in women. Arch Med Res; 35(2):121-5.
31. Mehrafza M., Heidarzadeh A., Jafari M., et al, (2007): survey of the effect of cervix microbial flora on outcome of intracytoplasmic sperm injection (ICSI), Journal of Guilan University of medical sciences spring 2007; 16 (61):1-8
32. Selman H. and Mariani M., (2007): Examination of bacterial contamination at the time of embryo transfer and its impact on the IVF/pregnancy outcome, J. Assist. Reprod. Genet (2007) 24: 395-399.
33. Aboul Fotouh I. and Al-Inany M.G. (2008): The levels of bacterial contamination of the embryo transfer catheter relate negatively to the outcome of embryo transfer. Middle East Fertility Society Journal Vol. 13, No. 1, 2008.
34. Abd-Raboh S., Saleh H.A., Hanafy N.H., and Darwish H.B., (2011): The detection of Chlamydia Trachomatis Antigen in cervical secretions and serum antibodies in infertile females undergoing ICSI and its impact on pregnancy success. Life Science Journal. 2011; 8(2):259-263] (ISSN: 1097-8135).
35. Van Oostrum N., Petra D.S., Joris M. and Hans V. (2013): Risks associated with bacterial vaginosis in infertility patients: a systematic review and meta-analysis, Hum. Reprod. (2013).

Intrauterine contraceptive device versus barrier methods for breast cancer women undergoing postoperative chemotherapy: A randomized controlled trial

[1]H. Nabil,[2]M. Hegazy
[1]Department of Obstetrics and Gynecology
[2]Department of surgical Oncology, Oncology center, Mansoura University, Mansoura, Egypt

Abstract

Objective: to compare the effectiveness of intrauterine device and the barrier methods of contraception in the form of male condom during the postoperative chemotherapy period in patients with breast cancer at the reproductive age.

Study design: A randomized controlled clinical study enrolled married patients, aged ≤ 44 yearswith breast cancer scheduled for chemotherapy. Group (A) (n=51) randomly used intrauterine device and group (B) (n=51) used male condom for contraception.

Results: Although patients' menstrual patterns showed no significant differences at the entry to the study, patients in group (A) showed heavier cycles when evaluated after 3m and again after 6m form the onset of the chemotherapy. The duration of bleeding (mean ±SD) was 7.7±1.7 and 5.6±1.3 in group A and B respectively after 3m and significant changes in the cycle length and the duration of bleeding after 6m had occurred. Likewise, the incidence of genital tract infection was higher in the group using intrauterine device while receiving chemotherapy.

Conclusion: While intrauterinecontraceptive device was always considered as the method of choice for most of the malignant patients, this study showed that it is more practical to use the barrier methods at least during the chemotherapy cycles in order to minimize the associated hazards of chemotherapy induced bone marrow depression on the safety of intrauterine device.

Key Words: breast cancer, reproductive age, intrauterine contraceptive device, barrier methods.

Introduction

Breast cancer is the most common malignancy in women, and one in eight women will be diagnosed with breast cancer during her lifetime (1). Itis considered as the second leading cause of cancer mortality among women (2). While breast cancer risk increases with age, approximately 35% of breast cancers occur during the reproductive and premenopausal years (3). Although epidemiologic surveillances found that the absolute risk of breast cancer under the age of 40 is relatively low, reproductive age group women remain a very critical age while managing cancer.Surgical treatment was and continues to be the primary line for all ages but still the postoperative management; an ever-changing field, in young patients, in particular, has attracted recent interest(4). Therefore, chemotherapy is increasingly being considered appropriate for all women under the age of 35 years. However, it poses the particularly difficult problem of fertility preservation, that's why the benefits of chemotherapy need to be weighed against the possible dangers, and therapy should be individualized according to cancer pathology and patient's circumstance (5).

Alterations in menstrual function and fertility may occur in women who receive chemotherapy for breast cancer and some demonstrated that women < 35 years old resume regular cycles 2 years after treatment, with

Dr. Hanan Nabil
Department of OB/GYN,
Mansoura Faculty of Medicine,
Mansoura, Egypt
Tel (+2)01000571004
hanannobil00@yahoo.com
2015

outcomes more variable than for women ≥ 35 years old [6]. Generally, the progress in diagnostic tools, care and treatments of breast cancer, increases the survival rate more than 80% at 5 years for operable stages in young women [7].

While women were previously advisedto postponeconceiving for two to five years after breast cancer diagnosis, newer published data does not demonstrate an alteration in survival with breast cancer to pregnancy intervals longer than 10 months [8].

The strong relation described many years ago between steroid hormones and breast cancer and the high incidence of hormone receptor positive tumors, made the capability of prescribing hormonal contraception for the patients in the reproductive age, a matter of putting the patient into jeopardy [9, 10].

From this aspect, safe, effective and suitablecontraception should be discussed and made available to all women undergoing diagnosis, treatment, and follow up for breast cancer [11].In the current study, we described a protocol for a randomized controlled study to assess the effectiveness and the method related complications while using non-hormonal intrauterine contraceptive device (IUD) or barrier (male condom) contraceptives for patients at the reproductive age with breast cancer and scheduledto receive adjuvant postoperative chemotherapy.

Patients and Methods

Thisrandomized controlled clinical study enrolled patients with hormone-receptor-positive operable invasive primary breast cancer who are scheduled to undergo post mastectomy firstline adjuvant chemotherapy at Oncology center, Mansoura University Hospital, Mansoura, Egypt, in the period from July 2010 to June 2014 and in need to use a proper contraceptive method. Patients who gave a written informed consent after receiving detailed written and verbal information were admitted to the study. Participation was voluntary and could be withdrawn by the patient at any time.The study was authorized by the Department of Obstetrics & Gynecology, Mansoura Faculty of Medicine, Mansoura University and approved by the Institutional Research Ethical Committee.

The study included married patients in the reproductive age as defined by World Health Organization (WHO) (≤ 44 years old) [12].All patients were screened for eligibility during their hospital stay in the oncology center and those who met the inclusion criteria were informed about the study concept and invited by their oncologists to take part in the study. Those patients were diagnosed and treated surgically according to the national guidelines of breast cancer management and subjected to the tumor board where 6 cycles of chemotherapy (Epirubicin, Cyclophosphamide, Fluorouracil and Taxotere) were addressed for each patient. A detailed history, general and pelvic examinations and ultrasound evaluation were carried out for all patients. Exclusion criteria were evident pelvic inflammatory disease (PID) or recent form of it, pre or post-operative history of heavy menstrual bleeding, presence of anomalies of the uterus, distorted uterine cavity by any lesionsas uterine myomas. Diabetic patients were also excluded from the study being at higher risk of genital infection. Patients with active liver disease or dysfunction were also excluded because they carry the risk of bleeding tendency.

By the above rules, 102 women were included in this study and randomized to select IUD or male condom according to a computer-generated random numeric table prepared by an independent statistician with concealment of method option by the use of closed envelopes that were given to a third party (nurse) who assigned patients into 2 equal study arms each one (51); group A (IUD) or group B (male condom). In group (A): we offered cupper T 380A IUD (safe load, DKT Company) for contraception where it is inserted under sterile conditions by a single gynecologist, followed by transvaginal ultrasound for post insertion assessment. Warning signs as missed period, lower abdominal pain, vaginal bleeding or discharge wereinformed to every patient and instructed to seek a medical advice when any occur. Azithromycin (500 mg) a single dose orally was given to all patients in this group as a prophylaxis before insertion of the IUD [13].In the other group (B); patients were instructed in a session including her partner to use the male condom for protected intercourse and informed about the faulty behaviors that may lead to condom breaking, leaking, or slipping off during intercourse that predispose for method failure [14].Data were recorded at preliminary phase of inclusion in the study then at three months and six months intervals. During this follow up periods, at 3 and 6 months, patient's history regarding the menstrual cycle pattern (subjectively assessed by the amount of menstrual blood loss, duration of bleeding and the number of sanitary towels used [15]), development of genital infection whether lower or upper, data of general examination and pelvic examination were recorded.

A "Satisfaction Questionnaire" about the method used was prepared to be fulfilled by both partners during the first visit (after 3 months) and the second visit (after 6 months) and gathered data were subjected to tabulations and analytical studies.

- Are you satisfied with the method of contraception you use?
- Do you prefer to keep using this method?
- Do you want to suggest these IUDs or male condom methods to the others?

Statistical analysis:
Statistical analysis was performed using SPSS for windows version 17.0 (SPSS, Chicago, IL). Continuous data were expressed as mean ± standard deviation (SD). Data were checked for normality and equality of distribution, prior to any analysis being performed. Skewed continuous variables were logarithmically transformed to accomplish a normal distribution. For variables that would not reach a normal distribution by logarithmic transformation, nonparametric tests would be used. Chi square and Student t test were appropriately used and P-values<0.05 were considered to be of statistical significance.

Results

This study included 102 women in the reproductive age divided into two equal groups. Group (A= IUD users, n=51) and Group (B= male condom users, n=51). The socio-demographic data of both groups appeared comparable with no significant difference as shown in **table [1]**. Most of the patients in both groups were with low parity, however nulli-parity was recorded in (11.8%) in group (A) and (9.8%) in groups (B). Family history of breast cancer was evaluated and found to be positive in 17.6% of patients in group (A) and in 13.7% in group (B).Invasive ductal carcinoma was identified as the predominant histological type in both groups. The tumor staging based on TNM staging [16] showed no significant differences between both groups.
Menstrual cycles were regular in most of patients and the amount of bleeding described subjectively by the patients was average in more than 85% of patients in both groups.
Patients' criteria that were evaluated during the first 3 months after starting the chemotherapy are presented in **table [2]**. There is a relative increase in the number of patients with heavy cycles in group (A)(21 out of 51) versus (9 out of 51) in group (B) as well as a significant increase in the duration of bleeding among group (A).The incidence of recurrent lower genital tract infections were much higher in group (A) compared to group (B), meanwhile upper genital tract infections were found also higher in the same group using IUD.
After 3 months more (6 months of starting chemotherapy), all patients were reevaluated and the data are presented in **table [3]**. The cycle pattern showed a significant change as regard the duration and the amount of bleeding and in comparing both groups (p value is 0.001). Lower genital tract infections occurred in 29/51 in group (A) compared to 8/51 in group (B) and upper genital tract infections also remained higher in group (A).
As regard patients' satisfaction, in group (A) less number of patients were satisfied with IUDs comparing the two periods of evaluations (after 3m and after 6m) where 35.3% only were satisfied after 6 months use. On the other hand, the group (B) patients showed high acceptability and satisfaction with the condom use yet rather than their husbands. After completing the courses of chemotherapy, 15 out of 51 patients used IUD asked for changing the method versus only 5 in the group using condoms.

Table (1)
Patients' characteristicsat the start of the study

Characteristics	Group A (IUD user, N=51)	Group B (condom user N=51)	P value
Age (years) Mean ±SD	36.4 ± 4.2	36.2 ± 4.4	0.783
parity Mean ±SD	1.16 ± 0.46	1.16 ± 0 .42	0.855
Nulliparous women	6 (11.8%)	5 (9.8%)	
Occupation: HW EM	HW: 3 (66.7%) EM: 17 (33.3%)	HW: 31 (60.8%) EM: 20 (39.2%)	
Residence: U R	U: 21 (41.2%) R: 30 (58.8%)	U: 20 (39.2%) R: 31 (60.8%)	
Family history of breast cancer	Positive: 9 (17.6%) Negative: 42 (82.4%)	Positive: 7 (13.7%) Negative: 44 (86.3%)	
Age of menarche Mean ±SD	11.6 ± 1.7	11.3 ±1.3	0.200
Cycle rhythm	Regular: 46/51 Irregular: 5/51	Regular: 44/51 Irregular: 7/51	
Cycle length Mean ±SD	31.52 ± 8.37	29.32 ± 6.22	0.167
Cycle duration Mean ±SD	5.30 ± 1.12	5.34 ± 1.09	0.488
Amount of bleeding	Average: 45/51 Heavy: 6/51	Average: 44/51 Heavy: 7/51	
Breast cancer staging at operation	SI: 11 (21.6%)	SI: 15 (29.4%)	
	SII: 35 (68.6%)	SI: 30 (58.8%)	
	SIII: 5 (9.8%)	SII: 6 (11.8%)	
Histo-pathological type	L: 6 (11.8%)	L: 5 (9.8%)	
	D: 45 (88.2%)	D: 46 (90.2%)	

P-values<0.05 were considered to be of statistical significance.
HW: House wife U: Urban
EM: Employer R: Rural
L: Lobular carcinoma D: Ductal carcinoma

Table (2)
Patients' characteristicsafter 3 months of chemotherapy

Variable	Group A (IUD user, N=51)	Group B (condom user n=51)	P value
Failure rate	0	0	
cycle regularity	Regular: 33 (64.7 %) Irregular: 18 (35.3%)	Regular: 36 (70.6 %) Irregular: 15 (29.4 %)	----
Cycle Length	37.78 ±10.81	36.28 ± 8.1	0.09
Duration of bleeding	7.72 ± 1.738	5.6200 ± 1.38343	0.018
Amount of bleeding	Average:30 Heavy: 21	Average: 42 Heavy : 9	----
Lower genital 3tract infection	23/51	11/51	----
Upper genital tract infection	8/51	2/51	----
Patients satisfaction	38/51 (satisfied =74.5%) 13/51 (unsatisfied =25.5%)	45/51 (satisfied =88.2%) 6/51 (unsatisfied =11.3%)	----
Partner satisfaction	47/51 (satisfied =92.2%) 4/51 (unsatisfied =7.8%)	20/51 (satisfied =39.2%) 31/51 (unsatisfied =60.8%)	----
Method discontinuation	0/51	0/51	----

P-values<0.05 were considered to be of statistical significance.

Table (3)
Patients' characteristicsafter 6 months of chemotherapy

Variable	Group A (IUD user. n=51)	Group B (condom user n=51)	P value
Failure rate	0	0	
cycle regularity	Regular: 18 Irregular: 33	Regular: 34 Irregular: 17	----
Cycle Length	40.82 ± 10.71	49.9 ± 10.46	0.001
Duration of bleeding	3.66 ± 1.89	2.48 ± 2.31	0.001
Amount of bleeding	Average: 16 Heavy: 35	Average: 49 Heavy: 2	----
Lower genital tract infection	29/51	8/51	----
Upper genital tract infection	8/51	1 /51	----
Patients satisfaction	18/51 (satisfied =35.3%) 33/51 (unsatisfied =64.3%)	47/51(satisfied =92.2%) 4/51(unsatisfied =7.8%)	----
Partner satisfaction	40/51 (satisfied =78.4%) 11/51(unsatisfied =21.6%)	10/51(satisfied =19.6%) 41/51(unsatisfied =80.4%)	----
Method discontinuation	15/51	5/51	----

P-values<0.05 were considered to be of statistical significance.

Discussion

Based on the mandatory contraception during the post-operative adjuvant chemotherapy in reproductive age group patients with breast cancer, and the multiple different health hazards associating the chemotherapy in those patients, the choice of an ideal practical method of contraception may put the patients and the gynecologist in a great argument. The authors included 102 patients in the current study aiming to find an ideal contraceptive method during the chemotherapy cycles. The Society of Family Planning has issued guidelines about the contraceptive choices for women diagnosed with cancer. Although chemotherapy and radiation therapy can compromise fertility, many women remain fertile and pregnancy cannot be ruled out, even with patients with a severely compromised ovarian reserve [17].

It is well known that cancer increases the risk for thromboembolic disorders, therefore, estrogen/progestin contraception is not recommended during cancer treatment. World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC) recommend that women with active cancer or who have been treated for cancer in the last 6 months should avoid combined hormonal contraceptive methods [18].

Hormones are known to play a role in the development of breast cancer;consequently, the use of combined contraceptive pills or progestin-only pills is not recommended in women undergoing treatment for breast cancer [10].

Furthermore, some reported that in breast cancer survivors, non-hormonal contraceptive methods should be used as first-line options. Hence, in the current study, authors randomly selected whether copper IUD or male condom method and did not refer to any hormonal contraception. The Copper IUD is considered as a hormone-free, long-acting reversible contraceptive and has no restrictions for use in the setting of current breast cancer[11].

Two common expected problems can meet patients receiving chemotherapy and IUD users. As they usually suffer from a state of immune compromisation with different forms of bone marrow suppression [19] including anemia, leucopenia and thrombocytopenia, there is associated increased risk of recurrent infection and higher tendency of bleeding. In the current study, the results support this as patients' examination after the first three months revealed that 21out of 51patients using IUD reported heavy cycles with significant increase in cycle duration meanwhile this may be attributed to the recent location of IUD and the associated hematological disorders occurred with the initiation of chemotherapy. Lower genital tract infections occurred

in 23 cases and upper genital tract infections were found in 8 cases that may be explained by the state of immune suppression and bone marrow affection as well as the endometrial congestion due to device location. Moreover after another 3 months (i.e. 6 months of starting chemotherapy), the above mentioned figures showed significant changes between both studied groups regarding the increase in the duration and the amount of menstrual bleeding in group (A)patients; lower genital tract infections increased to affect 29 patients, meanwhile upper genital tract infections remained unchanged (8 cases). This could be explained again by more immune compromisation, thrombocytopenia and long standing endometrial congestion.

Barrier methods as male or female condoms are always considered as the convenient health hazards free methods of contraception but with a relatively high failure rate [14]. In the current study, it was found that most of patients' partners were not satisfied with this method that reflects the sexual behavior of eastern couples.After explanation of benefits and risks, most of the couples agreed to continuethe same method throughout the chemotherapy treatment cycles.

On the other hand condom users developed lower rates of genital tract infections and less cycle pattern disturbances compared to IUD users while in both groups, failure rates were zero and this was not surprising to the authors as it might reflects the relative less fertile anovulatory cycles present during chemotherapy.

Levonorgestrel Intrauterine system (LNG-IUS) was described by some studies [11] as an alternative method for contraception carrying the benefit of minimal bleeding and least failure rate, depending on the minimal systemic absorption of progesterone, especially in patients receiving tamoxifen that may induce endometrial hyperplasia. A large recent study conducted in Finland [20] found that the Finnish women who used the LNG-IUS for 5 years had an increased rate of breast cancer compared to the general Finnish population.

Tubal sterilization, and in some cases ovariectomy are sometimes used as an irreversible optimum method of contraception in cancer survivors [11]. As a large group of patients with breast cancer diagnosed in their reproductive ages exhibited low parity, didn't complete their families yet, and they always seek for a reversible contraceptive method. Included patients in the current study were randomized for IUDs and barrier methods only.

Despite some recent studies recommend the use of copper IUD, as a highly effective, hormone-free method for women with a history of breast cancer or LNG-IUS to minimize menstrual blood loss in cases with anemia [21] the current study prefers the use of barrier methods (male condom for example) that showed a high efficacy in maintaining less frequent cycles with less bleeding and low incidence of genital tract infections (p value <0.001) specifically while the patients were receiving chemotherapy.

Lastly the authors can state that; all women seeking contraception during the cancer treatment period should be provided with information about relative effectiveness of available contraceptives with their health hazards during such different period of treatment.

Conclusion

Despite the non-hormonal intrauterine contraceptive device was considered a safe effective method of contraception in the middle aged women with breast cancer on chemotherapy, barrier methods (male condom) with the precise use is recommended at least during the early critical post-operative period.

References

1. Siegel R, Naishadham D, Jemal A. Cancer statistics. CA Cancer J Clin, 2012; 62:10–29.
2. Youlden DR, Cramb SM, Dunn NA, Muller JM, Pyke CM, Baade PD. The descriptive epidemiology of female breast cancer: an international comparison of screening, incidence, survival and mortality. Cancer Epidemiol, 2012; 36(3): 237-248
3. National Cancer Institute Surveillance Epidemiology and End Results. SEER state fact sheets. January 19, 2011.National Cancer Institute Surveillance.
4. Cardoso F, LoiblS,Pagani O. The European Society of Breast Cancer Specialists recommendations for the management of young women with breast cancer.Eur J Cancer, 2012; 48(18):3355-3377.
5. Clive S and Dixon JM. The value of adjuvant treatment in young women with breast cancer. Drugs, 2002; 62(1):1-11.
6. Carlson RW, Allred DC, Anderson BO. Breast cancer: clinical practice guidelines in oncology. J Natl Comp CancNetw, 2009; 7:122–192.
7. Hussein A. Assi, E. Khoury K,Dbouk H. Epidemiology and prognosis of breast cancer in young women. Journal of Thoracic diseases, 2013; 5: 1-5
8. De Bree E,Makrigiannakis A, Askoxylakis J. Pregnancy after breast cancer. A comprehensive review. J SurgOncol, 2010; 101:534–542.
9. Kreipe HH1, Ahrens P, Christgen M. Beyond staging, typing and grading. New challenges in breast cancer pathology. Pathologe, 2010; 31(1):54-59.
10. Marchbanks PA, Curtis KM, Mandel MG. Oral contraceptive formulation and risk of breast cancer. Contraception, 2012; 85:342-350.
11. Petra M Casey, Stephanie S Faubion, Kathy L MacLaughlin. Caring for the breast cancer survivor's health and well-being.World J ClinOncol, 2014; 5: 693–704.
12. World Health Organization, Women's Health. Media center. Fact sheet N°334. World Health Organization, 2013.
13. Caddy S, Mark H Yudin, Hakim J. Best practice to minimize risk of infection with intrauterine device insertion. J. ObstetGynaecol Can, 2014; 36(3):266-274.
14. Duerr A, Gallo MF, Warmer L. Assessing male condom failure and incorrect use. Sexually Transmitted Diseases,2011 Jul;38(7):580-586
15. Higham JM, Shaw RW. Clinical association with objective menstrual blood volume. Eur J ObstetGynecolReprodBiol, 1999;82(1):73-76.
16. Sinn HP, Helmchen B and Wittekind CH. TNM classification of breast cancer: changes and comments. Patologe, 2010; 31(5):361-366.
17. PolonskyM. Cancer and Contraception Guideline. Contraception, 2012;86:191-198.
18. Centers for Disease Control and Prevention. United States. Medical eligibility criteria for contraceptive use, 2010; 59: 1–88.
19. Urabe A. Bone Marrow suppression. Nihon Rinsho, 2003; 61(6):949-953.
20. Soini T, Hurskainen R, Grenman S. Cancer Risk in Women Using the Levonorgestrel-Releasing Intrauterine System in Finland. ObstetGynecol, 2014; 124:292-299.
21. Society of Family Planning / Contraception Clinical Guidelines, Cancer and contraception, 2012;86: 191–198.

The role of endometrial scratching and intrauterine injection of HCG for optimizing the outcome of ICSI after implantation failure

Al Khiary M, El Zayat M
Department of Obstetrics and Gynecology, Mansoura University, Mansoura, Egypt
Genetic engineering and Biotechnology Institute, Monofia University, Monofia, Egypt

Abstract

Objective: To evaluate the effect of endometrial scratching plus pre transfer flushing of uterine cavity by HCG on clinical pregnancy and implantation rate in casas with previous implantation failure.
Patients & Methods: The study includes 195 infertile ladies with previous implantation failure. They were randomly divided into three equal groups. All groups would offered ICSI cycle employing either long GnRH agonist or the GnRH antagonist protocol according to patient characteristics. In the first.group, no further intervention was done and in the second group, endometrial scratch during the luteal phase of the immediate preceding cycle was employed, while in the third group endometrial scratch plus pre transfer intrauterine injection of HCG were done.
Results: All variables were expressed as mean + standard deviation In all studied groups, there were no significant difference as regard their age , duration of infertility , body mass index and base line follicle stimulating hormone as well as base line and peak level of estradiol (P values > 0.05 .).The biochemical and the clinical as well as the implantation rates were higher in the endometrial scratch group than in the control group (55.9% Vs 37.7%, 45.8% Vs 31.1% and 34.9% Vs 21.9% respectively with significant difference, P< 0.05) More increase in the same outcome measures were noted when comparing the third group with the first group (60% Vs 37.7%, 50% Vs 31.1% and 38.1 Vs 21.9 % respectively, P values< 0.05). The clinical and implantation rates increase in the third group more than the second group (45.8% Vs 50% and 34.9% Vs 38.1%) with no statistically significant difference, P> 0.05).
Conclusion: We found that adding pretransfer intrauterine injection of HCG to endometrial scratch improves the implantation rate in ICSI cycle.

Key Words: endometrial scratch, intrauterine HCG, ICSI, implantation.

Introduction

Infertility is not only worldwide medical problem but also a psychosocial one as well with incidence about 10 – 15 % (1). Many treatment strategies have been developed, aiming at achieve pregnancy, with In vitro fertilization and Intracytoplasmic sperm injection (IVF / ICSI) came as last step. A large drop is present between embryo transfer and occurrence of pregnancy, with up to 70 % of embryo losses occur at time of implantation, and reducing such high figure represent a great challenge (2). Multiple variables could affect the success of IVF /ICSI, among which is optimum endometrial receptivity which represents the corner stone of successful implantation (3)
Failure of implantation may arise from abnormalities of endometrium, embryo or immune system (4). Needless ,Implantation, to progress in its successful pathway with opposition , attachment and invasion ,need a certain dialogue between receptive endometrium and a healthy good quality embryo (5 , 6) . This dialogue is complex and regulated by interaction between hormonal, growth factors, cytokines and certain gene expression (7). Again, implantation, in its basic mechanism, represents an inflammatory reaction of the endometrium to the embryo. Employing such fact,

Dr. Moustafa Al Khiary, MD
Assistant professor of OB/GYN, Mansoura University
Tel: 0502247154 / 01005086777
Email mostafakhiary@yahoo.com
Mostafaalkhiary @gmail.com

many investigators started to induce or improve such inflammatory response by many ways aiming to improve endometrial receptivity and implantation with subsequently increase the success of IVF / ICSI.
For many years, endometrial scratch before IVF/ICSI was employed to improve endometrial receptivity and implantation with controversial results obtained depending ontiming of doing endometrial injury (8-11). Recently , a systematic review and meta – analysis demonstrated that endometrial injury / scratch during luteal phase of the cycle preceding IVF- ICSI trial is associated with 70% improvement in clinical pregnancy rate (Relative Risk 3.32 , 95% CI 1.72 -3.13) (12). Endometrial injury may act through, firstly, induction of decidualizationas shown in animal study (13). Secondly, release of different cytokines and growth factors which are important in process of implantation as, leukemia inhibitory factor, and interleukin-11 and heparin-banding endothelial growth factor (11).
Moreover, the receptivity of the endometrium is considered as a steroid hormone, estrogen as well as progesterone dependent process and is limited to a certain period of time, implantation window, during which a potentially healthy embryo is allowed to adhere and invade (14). Human Chorionic Gonadotropin (HCG) required for pregnancy maintenance is secreted by the early embryoand through its effects upon inflammatory and endothelial cells responsiveness as well as release of angiogenic factors could have early effective role in regulating implantation (15, 16). Based on these important effects of HCG upon implantation, Mansour et al. (17) was the first to report the work with intrauterine administration of HCG with significant improvement of pregnancy rate in IVF / ICSI cycle.
The aim of this study was to evaluate the effect of flushing the endometrial cavity with HCG, before embryotransfer, in association with endometrial injury, done in the immediate preceding cycle, upon clinical pregnancy and implantation rates of ICSI cycles with previous implantation failure.

Patients and Methods

A total of 195 participants with infertility were included in the study .They were recruited from fertility care unit, Mansoura university hospital and private assisted reproduction clinic during the period from Jan 2012 till Jan 2014. The research protocol was approved by research committee of the university. The inclusion criteria were women age under 40 years, body mass index less than 35, no thrombophilia or immunological disorders or under control , no uterine myoma and within normal uterine cavity by hysteroscopic examination and previous IVF-ICSI trial with implantation failure. Azoospermia and frozen embryo were excluded from the study.
Explanation of the study is offered to all participants and informed written consent is obtained then the participants were randomly allocated into three groups Randomization was carried out through a computer generated number and a sealed envelopes opened by a nurse. . All groups would offered ICSI cycle employing either long GnRH agonist or the GnRH antagonist protocol according to the indication of treatment and patient characteristics. The first group (n=65) with no further intervention was done , women in the second group (n=65) would be subjected to endometrial scratch during luteal phase of the preceding cycle and finally , the third group (n=65) where endometrial scratch was done during luteal phase of the preceding cycle in association with intrauterine injection of HCG just before embryo transfer .
Endometrial scratch, for second and third groups, was done as an office procedure on day 21 – 24 of spontaneous cycle preceding ICSI trial with or without systemic analgesia. Participant laid in lithotomy position with insertion of Cusco speculum then clean ectocervix followed by introduction of Pipelle biopsy catheter(Pipelle de Cornier , Proimed , Neuilly – en –Thelle , France) with gentle endometrial scratch in different directions , rotatory and up and down movements . The routine use of prophylactic antibiotic was not warranted.
After oocytes retrieval, most suitable sperms would be chosen to be injected into most suitable oocytes two to three days later; the embryos were assessed morphologically for quality. In all groups in the third day ,one to three grade A l B quality embryos chosen for transfer under guidance of abdominal ultrasonography with full or partially full urinary bladder The woman laid in lithotomy position with visualization of cervix using Cusco speculum then cleaning of the portio was done followed by partially suction of cervical mucus .using 1 mL syringe then irrigation of the cervix by embryo culture medium . In the first and second groups , soft catheter (Wallace – Smith Medical International Ltd) was loaded by embryos and at mid uterine cavity, the embryos were placed and catheter left in situ for few minutes before withdrawal and then examined . In the third group , employing the procedure described by Mansour et al , 2011(17) , just before embryo transfer , 500 IU of HCG was added to 40 ul tissue culture medium was injected inside uterine cavity using soft catheter which was left in situ for 7 minutes then embryo (s) transfer was (were) done as described before ..
Luteal phase support was carried on as scheduled then quantitative serum assessment of HCG was done two

weeks after embryos transfer followed by ultrasonographic evaluation 2 – 3 weeks later for positive cases. Outcome measures of the study were biochemical as well as clinical pregnancy rate and implantation rate. Biochemical pregnancy was defined as quantitative HCG assay more than 50 mIU l ml 2 weeks after embryo transfer. Clinical pregnancy was defined as presence of at least one intrauterine gestational sac with fetal pole and cardiac pulsation on transvaginalsonography scane at 4 – 6 weeks after embryo transfer. Clinical pregnancy rate was number of clinical pregnancy divided by the number of embryo transfer procedures. Implantation rate was number of gestational sacs on tranvaginal ultrasonography scan at 4- 6 weeks after embryo transfer divided by number of transferred embryos.

Statistical analysis

All statistical analysis were performed using SPSS for windows version 17.0 (SPSS, Inc ,Chicago , Ill ,USA .). Continuous variables were analyzed as mean +standard deviation (SD). Categorical nominal data were expressed as frequency and percentages. One way analysis of variance test (ANOVA) was used to compare between basic characteristics of the three groups. Student t-test, Fisher s exact test were used when appropriate to make a comparison between groups .P <0.05 is considered as significance.

Results

195 women were included in the current study that was carried out during the period of Jan 2012 to Jan 2014 There was no dropped out cases in any step of the study. 15 cases (7.7 %) were cancelled because of risk of ovarian hyperstimulation syndrome (9 cases , 4.6 %) and poor embryos quality (6 cases , 3.1%) . There were as follow, 4 cases in group (1), 6 cases in group (2) and 5 cases in group (3). All variables were expressed as mean and standard deviation. Table (1) shows that there was no significant difference between groups as regard age of the participants , duration of infertility , body mass index (BMI) and base line follicle stimulating hormone (FSH) In addition in comparing base line and peak levels of estradiol in all groups , also , no significant difference was noted .

With separate comparison between each group, endometrial thickness at time of HCG administration and number of oocytes retrieved, were nearly similar with no significant difference. Also , the fertilization rate per retrieved oocyte was 70% , 68% and 71.5% while the number of transferred embryos per cycle were 2.8 , 2.4 and 2.65 with no significant difference , tables, 2- 4 .

As regard the outcome measures , the biochemical and clinical pregnancy as well as the implantation rates were higher in endometrial scratch group than in the control group (55.9%Vs 37.7% , 45.8% Vs 31.1% and 34.9%Vs 21.9% respectively with significant difference p<0.05 .)Table (2). More increase , in the previous outcomes , was found when comparing the third group (endometrial scratch plus HCG injection)with the first control group and he figures were as follow 60% Vs 37.7% , 50%Vs 31.1%% and 38.1% Vs 21.9% respectively table (3) . .

In an attempt to declare the beneficial effect of flushing the endometrium by HCG together with endometrial scratch, we made a comparison of the outcomes between the second and third groups. The clinical pregnancy rate increase from 45.8% in second group to 50% in the third group as well as improvement of implantation rate by about 8% (from 34.9% to 38.1%) .However , this improvement was not to the degree to be significantly different table (4) .

Table (1)

Patients characteristics

Variables	Group(1) n = 61	Group(2) N = 59	Group(3) N =60	P
Age (year)	29.45 ±3.7	30.15 ±4.1	28.95 ±3.3	0.353
Duration of infertility (year)	8.4 ±4.1	7.6 ±3.7	8.15 ±4	0.251
BMI (kg / m)	28.80 ±3.1	30.50 ±4.2	29.30 ±3.4	0.235
FSH (mIU/ml	6.32 ±2.85	6.74 ±3.23	7.15 ±2.54	0.548
Basal estradiol	35.86 ±10.56	38.35 ±11.15	37.15 ±10.40	0.634
(pg / ml)	2850.45 ±925	2785.30 ±885	2710.50 ±845	0.215

Table (2)

Study outcome in group 1 & 2.

Variables	Group(1) n = 61	Group(2) N = 59	P
Endometrial thickness on day of HCG (mm)	10.46 ±4.2	10.14 ±4.05	0.527
Number of oocytes retrieved	13.15 ±5.17	12.35 ±4.35	0.714
Fertilization rate per retrieved oocytes	70% ±15.45	68% ±18.10	0.483
Number of transferred embryos per cycle	2.8 ±0.4	2.4 ±0.5	0.265
Biochemical pregnancy rate	23/61 37.7%	33/59 55.9%	0.050
Clinical pregnancy rate	19/61 31.1%	27/59 45.8%	0.045
Implantation rate	32/146 21.9%	44/126 34.9%	0.035

Table (3)
Study outcome in group 1 & 3.

Variables	Group(1) n = 61	Group(2) N = 60	P
Endometrial thickness at day of HCG (mm)	10.46 ±4.2	10.54 ±4.27	0.74
Number of oocytes retrieved	13.15 ±5.17	12.85 ±4.90	0.437
Fertilization rate per retrieved oocyte	70% ±15.45	71.5% 16.15	0.513
Number of transferred embryos per cycle	2.8 ±0.4	2.65 ±0.44	0.445
Biochemical pregnancy rate	23/61 37.7%	36/60 60%	0.035
Clinical pregnancy rate	19/61 31.1%	30/60 50%	0.030
Implantation rate	32/146 21.9%	60/153 38.1%	0.015

Table (4)
Study outcome in group 2 & 3.

Variables	Group(1) n = 59	Group(2) N = 60	P
Endometrial thickness on day of HCG (mm)	10.14 ±4.05	10.54 ±4.27	0.431
Number of oocytes retrieved	12.35 ±4.35	12.85 ±4.90	0.445
Fertilization rate per retrieved oocytes	68% ±18.10	71.5% ±16.5	0.389
Number of transferred embryos per cycle	2.40 ±0.5	2.65 ±0.44	0.183
Biochemical pregnancy rate	33/59 55.9%	36/60 60%	0.214
Clinical pregnancy rate	27/59 45.8%	30/60 50%	0.158
Implantation rate	44/126 34.9%	60/153 38.1%	0.116

Discussion

Implantation is a multifactorial complex process where interaction between different molecular and hormonal pathways take places .Inspite of great advances in biotechnology of assisted reproduction , there still be a great discrepancy between embryo transfer rate and the resultant low implantation rate with up to 70% of embryos lost .For better implantation and success of ICSI ,it is important to transfer a morphologically good embryo inside uterine cavity with receptive endometrium (18).

HCG is secreted from early embryo before implantation and has appreciative role in further embryonic development. One of key regulator of inflammatory response , endometrial immune tolerance and angiogenesis associated with successful implantation , is embryonic HCG (19 , 16) .Moreover , it was found that embryos with higher secretion of HCG have more potentiality for successful implantation (20) . Also, local endometrial injury was found to increase the clinical pregnancy and implantation rate. This attractive benefit is not fully understood but may be related to induction of inflammatory response with release of proinflammatory growth factors and cytokines that may play a role in successful implantation (11).

Many researches were designed to evaluate the effectiveness of endometrial injury for improving the endometrial receptivity .Endometrial injury , during the luteal phase of the cycleimmediately preceding the ICSI trial ,was employed in the present study where significant improvement of the clinical pregnancy (45.8% Vs 31.1 %) and implantation rates (34.9% Vs 21.9 %) were observed in group (2) in comparison to group (1) . These findings were in agreement with the results shown by Zhou L et al (9), with important difference that we included cases with previous implantation failure only . Also ,in consistent with our results, Suleyman et al (22) , when examined the effect of double endometrial scratch in the immediate preceding luteal phase and in early follicular phase of stimulation cycle , in normoresponder with single embryo transfer , they reported improvement of clinical pregnancy rate (48.2 %) in the intervention group more than control group (29 %) (p =0.025).Furthermore, in cases with previous implantation failure , , less figures , but still statistically significant improvement was found with clinical pregnancy rate (32.7%Vs 13,7%) and implantation rate (13.07 %Vs 7.1 %) They employed two endometrial injuries technique at follicular and luteal phases if the immediate preceding cycle (11 ,21) . On contrary to the previous good results, other author did not find significant difference between the intervention and the control groups in terms of chemical, clinical and implantation rates when offering luteal endometrial scratch (23).

According to the knowledge about the central and well established effect of HCG in regulating implantation , some investigators studied the effect of parenteral HCG administration during luteal phase after frozen – thawed embryo transfer and found no significant difference in clinical pregnancy and implantation rates (24 , 25) . Moreover , few authors evaluated the effect of flushing endometrial cavity with HCG jus t before embryo transfer as Mansour et al (17)who restricted their work to fresh first time cycle onlyand Alvaro S et al (26) who included frozen – thawed embryo as well as previous implantation failure in his study. Both authors found statistically significant improvement in terms of clinical pregnancy and implantation rates, in the intervention and control groups , which were 75% Vs 60% and 41.6% Vs 29.5% in Man-

sour study and 51% clinical pregnancy rate Vs33% in Alvaro S et al study(26) .In the current study, in the third group , with flushing the endometrial cavity with HCG before embryo transfer and preceded endometrial scratch , there were improvement in clinical pregnancy and implantation rates in comparison to first control group(50% Vs31.1 % and 38.1% Vs 21.9% with significant difference p <o.o5) . This is in consistent with the results obtained by Mansour et al (17) and Alvaro S et al (26) It import us to know that our study population was restricted only to cases with previous implantation failure and in the same time frozen – thawed embryos were excluded . The improvement in the third group may be explained partially by the effect of endometrial scratch and partially due to intrauterine injection of HCG before embryo transfer

To explore if there is significant improving effect of HCG endometrial flushing to a previously scratched endometrium , we made a comparison between the second and the third groups .There were increase in clinical pregnancy rate by about 10%(from 45.8% in group (2) to 50% in group (3) and implantation rate from 34.9% in group (2) to 38.1% in group (3) but , unfortunately , the improvement was not statistically significant .These may be explained by the relatively small number of each group , choice of the transferred embryos depending on morphological assessment only without adding metabolic evaluation as well as exclusion of thawed embryos where intrauterine injection of HCG is thought to give good outcome .Also , both procedures may improve the outcomes through sharing some pathways responsible for implantation .

Conclusion

Combined endometrial scratch (in the luteal phase of the immediate preceding cycle) with HCG endometrial flushing (before embryos transfer) is a simple safe and cost – effective procedure and is associated with improvement of ICSI outcomes. It may be, in future, offered as a routine step in all IVF l ICSI cycles. More trials are needed to reproduce the outcomes in a large scale with miscarriage and live birth rates should be added for outcome measures.

Reference

1. Munster K, Helm P. infertility and the seeking of infertility treatment in a representative population. Br J Obstet Gynaecol. 1995 Dec; 102 (12):978-84.
2. DekelN, gnainskyY, Granot I, Mor G .Inflammation and implantation. Am J Reprod Immunol. 2010; 63:17 – 21.
3. 3- Wang H, Dey SK. Roadmap to embryo implantation: clues from mouse models .Nat Rev Genet .2006; 7 (3): 185 – 199.
4. Margalioth EJ , Ben- Chetrit A , Gal M ,Eldar-Geva T .Investigation and treatment of repeated implantation failure following IVF- ET. Hum Reprod. 2006; 21:3036-43.
5. AchacheH, Revel an .Endometrial receptivity markers, the journey to successful embryo implantation .Hum Reprod Updat. 2006; 12: 731 – 46
6. Fukui A ,Funamizu A , Yokota M ,Yamada K , Nakamua R ,Fukuhara R , et al .Uterine and circulating natural Killer cells and their roles in women with recurrent pregnancy loss , implantation failure and pre-eclampsia . JR eprod Immunol 2011; 90: 105 -10.
7. Almog B , Shalom-Paz E , Dufort D , Tulandi T .Promoting implantation by local injury to the endometrium .Fertil Steril .2010 ;94:206 – 209 .
8. Barash A , Dekel N , Fieldusf S ,Segal I , Schechtman E ,GranotI,.Local injury to the endometrium doubles the incidence of successful pregnancies in patients undergoing in vitro fertilization . Fertil Steril .2003; 79: 1317 – 1322.
9. Zhou L, Li R, Wang R, Huang HX, ZhongK.Local injury to the endometrium in controlled ovarian hyperstimulation cycles improves implantation rates. Fertil Steril .2008; 89:1166-1176.
10. Karimazade AM, OskouianH, Ahmadi S, Oskouian L. local injury to the endometrium on the day of oocyte retrieval has a negative impact on implantation in assisted reproductive cycles: a randomized controlled trial .Arch GynecolObestet. 2010; 281:499- 503.
11. Gnainsky Y, Granot I ,Aldo PB ,Barash A , Or Y , Schechtman E et al . Local injury of the endometrium induces an inflammatory response that pro-

motes successful implantation .Fertil Steril. 2010; 94:2030- 2036.
12. PotdarN, Gelbava T, Nardo LG. Endometrial injury to overcome recurrent embryo implantation failure: a systematic review and meta- analysis .Reprod Biomed Online. 2012 Dec; 25 (6):561 – 71.
13. Finn CA, Martin L. Endocrine control of the timing of endometrial sensitivity to a decidual stimulus. Biol Reprod .1972; 7: 82 – 86.
14. Almog B , Shalom- Paz E , Dufort D , Tulandu T .Promoting implantation by local injury to the endometrium . Fertil Steril .2010; 94: 2026 – 2029.
15. Lopata A, Hay D .The potential of early human embryos to form blastocysts, hatches from their zona and secrete HCG in culture. Hum Reprod .1989; 4: 87 -94.
16. Licht P, Fluhr H, Neuwinger J , Wallwiener D , Wild L . Is human chorionic gonadotropin directly involved in the regulation of the human implantation? Mol Cell Endocrinol .2007; 269: 85 – 92.
17. Mansour R, TawabN,Kamal O , El- Faisal Y , Serour A , Aboulghar M , Serour G .Intrauterine injection of human chorionic gonadotropin before embryo transfer significantly improves the implantation and pregnancy rates in invitro fertilization lintracytoplasnic sperm injection :a prospective randomized study . Fertil Steril .2011, 96 (6): 1370 – 1374.
18. Gunby I, Bissonnette F, Librach C, Cowan I .Assisted reproductive technologies (ART) in Canada. 2006, results from the Canadian ART Register .Fertil Steril .2010; 93:2189 – 201.
19. Bourdiec A , Bedard D , Rao CV , Akoum A .Human chorionic gonadotropin regulates endothelial-cell responsiveness to interleukin 1 and amplifies the cytokine – mediated effect on cell proliferation , migration and the release of angiogenic factors . Am J Reprod. Immunol 2013. Published online ahead of print Jan 28, 2013.
20. Xiao – Yan C , Jie I , Diang J , Tao I , Xin – Ru I , Guang- Lun Z .A highly sensitive electrocheiluminescence immunoassay for detecting human embryonic human chorionic gonadotropin in spent embryo culture media during IVF – ET cycle . J Assist Reprod Genet .2013; 30 (3):377 – 382.
21. Narveker SA , Gupta N , Shetty N , Kottur A , Srinivas M , Rao KA .Dose local endometrial injury in the nontransfer cycle improve the IVF –ET outcome in the subsequent cycle in patients with previous unsuccessful IVF ?A randomized controlled pilot study . J Hum ReprodSci.2010; 3:15 – 9.
22. Suleyman G , Cavit K , Mesut A U, Ozkan Y , Ersan O , Esin Y . Endometrial injury may increase the clinical pregnancy rate in normoresponders undergoing long agonist protocol ICSI cycles with single embryo transfer .Euro J Obestet Gynecol Reprod Biol .2014 ; 173 :58 – 62 .
23. Leili S , Shohre M , Ashraf A , Marize A , Parvin F , Zahra R .Local injury to the endometrium does not improve the implantation rate in good responder patients undergoing in – vitro fertilization . Iranian j reprod med .2011; 9 (4): 285 -288.
24. Maryam E, Elham R, Tahereh E. Effect of adding human chorionic gonadotropin to the endometrial preparation protocol in frozen embryo transfer cycle .Int J Fertil Steril .2012 ; 6 (3): 175 – 178 .
25. Ben-Meir A , Aboo – Dia M , Revet A , Eizenman E , Laufer N , Simon A , the benefit of human chorionic gonadotropin supplementation throughout the secretory phase of frozen – thawed embryo transfer cycles . Fertil Steril .2010; 93 (2):351 – 354.
26. Alvaro S , Jorge G , Olga P , Omar C , Guillermo C , Ana PS , Julio FD .Effect of intrauterine injection of human chorionic gonadotropin before embryo transfer on clinical pregnancy rates from in – vitro fertilization cycles : a prospective study .Reprod Biol Endocrinol .2014 ;12 : 9 .

Improving the pregnancy rates by pre-ovulatory saline perturbation before intrauterine insemination: A prospective randomized controlled trial

Khiary M, Ragab A
Departments of Obstetrics and Gynecology,
Mansoura University, Mansoura, Egypt

Abstract

Objective: to evaluate effect of pre ovulatory saline flushing on pregnancy rate in patients with ovulatory dysfunction, unexplained infertility, endometriosis and male sub-fertility.
Patients & Methods: the study involved 246 of infertile couples divided blindly by election into two equal groupseach contain 123; non pertubated group (A) and saline infusion group (B). Controlledovarian hyper-stimulation by Clomiphene Citrate (100 mg on cycle day 3-7) +HMG (75-150 IU) followed by administration of HCG 5000 IU IM. On the pre-ovulatory day; when one or two follicles >17mm by TVS, tubal flushing with 20 ml salinewas carried out in half of the cases (group B).
Results: Patient's demographic data in both groups showed no significant differences, the mean age was 27.8 ± 7.3 and 26.7 ± 8.1 years respectively. The mean weight in Kg ± SD was 77.1 ± 9.9 and 79.8 ± 10.3, the mean height in cm ± SD was 160.5 ± 5.8 and 162.8 ± 7.1 while the duration of infertility in years was 3.4 ± 1.6 and 3.5 ± 1.1 years respectively. The number of follicles reached the maturity in both groups showed no significant difference being 4.43 ± 1.7 and 4.67 ±1 respectively while the overall pregnancy rate was significantly different in both groups (15/123 =12.1% in group A and 29/123 =23.57 % in group B and p-value < 0.001). Abnormal pregnancies were more or less similar in both groups (multiple pregnancy, abortion and ectopic occurred in 4,2 and 1 case of the first while occurred in 5,4 and 1 case of the second group). Finally the live birth rates was 7.3 % (9/123) in group A and 19.5 % (24/123) with a significant difference (p value < 0.005).
Conclusion: adding saline flushing to (COH +IUI) cycles can be used as a cost-effective first line treatment for couples with infertility.

Key Words: tubal hydrotubation, infertility, IUI.

Introduction

Infertility is an important problem worldwide. The frequency of infertile couples is suggested to be in a range of 10 – 15% [1]. In approximately one third of the couples, infertility is caused by a male factor, in another third by female factor and in the rest by combined or unexplained factors. For couples with ovulatory dysfunction, early stages endometriosis, unexplained infertility and male sub-fertility, different therapeutic modalities have been proved efficient with various degree of success in achieving pregnancy. These modalities started by controlled ovarian stimulation and timed coitus passing through ovarian stimulation with intrauterine insemination (IUI) or intrauterine insemination alone and ended by IVF or ICSI .The first two modalities are the first choice infertility treatment for the above possible causes. The pregnancy rate per cycle was high using controlled ovarian stimulation (COS) with IUI rather than COS with timed coitus or IUI with non-stimulated cycle [2] (Cochrane Rev., 2006). In spite of being relatively safe and cost-effective, these modalities have lower pregnancy rate per cycle compared with IVF [3].
Hysterosalpingography (HSG) has been claimed to have therapeutic func-

Dr. Mostafa Khiary, MD
Assistant professor of OB/GYN, Mansoura University
Tel:05022471543_ 01005086777
Email: mostafakhiary@yahoo.com
mostafaalkhiary@gmail.com
2015

tion with increased pregnancy rate which may be related to mechanical or immunological effects [4]. Upon these observation, many authors had employed the technique of tubal flushing with significant increased pregnancy rate in stimulated cycles with IUI in couples with unexplained infertility[5,6] and early stages endometriosis [7,8].Alsooriginal used tubal flushing without IUI in cases with mild tubal disease with high degree of success in achieving pregnancy [4].

Tubal flushing could be done as an outpatient procedure and represent easy, less invasive and cost-effective treatment alternative as well as a good trial of achieving pregnancy while being on the list for IVF. Controlled ovarian hyper-stimulation and intrauterine insemination (COH+IUI) remains the first choice treatment for ovulatory dysfunction, unexplained infertility, endometriosis and male sub-fertility[3].

After completed investigation of infertile couples, COH+IUI is often tried as the first line treatment as this increases the livebirth rate compared to IUI alone[2]. Again; tubal Flushing with lipiodol has been tried in a smallrandomized clinical study on women with endometriosis [7] and evidenced to an innovative treatment for unexplained andendometriosis-related infertility[9] whereas the overall pregnancy rate was 30%at 6 months with no complications[9,10].

In this study, we investigated the effect of pre ovulatory saline flushing on pregnancy rate in patients with ovulatory dysfunction, unexplained infertility, endometriosis and male sub-fertility undergoing intrauterine insemination husband.

Patients and methods

This study was carried out at Fertility Care Unit, Mansoura University Hospital and a private practice setting during the period from June 2011 to October 2013 and comprised of 246 infertile couples undergoing intrauterine insemination (IUI). All patients were diagnosed to have mild male factor, minimal or mild endometriosis or unexplained infertility. All women were <36 years old, normo-ovulatory confirmed by day 21 serum progesterone >5 ng/ml, had patent tubes confirmed by hysterosalpingography and normal laparoscopic findings apart from minimal or mild endometriosis. All semen samples were evaluated according to WHO criteria 2010. The study was approved by the local Institutional Research Ethical Committee and each participant received a brief explanation of the research idea and aim of the work and gave a written consent.

All couples (n=246) were randomly allocated to either study (n=123) or control group (n=123) using computer-generated random table and sealed envelopes.All IUI cycles were preceded by ovarian superovulation with clomiphene citrate 50 mg tablets (Clomid; Hoechst Marion Roussel, Cairo, Egypt, ARE) orally twice daily for5 days starting on the second day of the menstrual cycle and one hMG ampoule 75 IU (Menogon; Ferring Pharmaceuticals, Malmo, Sweden) IM daily for 5 days starting day 5 ofthe cycle. Cycles were monitored by transvaginal ultrasound for the mean follicular volume and thickness of the endometrium on days 10, 12, and 14 of the cycle. Human chorionic gonadotropin 5,000 IU injection was given to induce ovulation when at least one follicle measured 18 mm or more.

All semen samples were collected in the laboratory after 3 to 5 days of sexual abstinence. After liquefaction for 30 minutes at room temperature, volume, pH, sperm count, and progressive motility were evaluated according to the WHO standard criteria. Sperm concentration was performed with a hemocytometer on two separate preparations of the semen sample (dilution1:20 in Ringer's solution). Sperm motility was determined by assessing at least five microscopic fields to classify at least200 spermatozoa (x4,000 magnification). The motility was graded progressive, non-progressive, or immotile. Motile sperm were selected by a swim-up procedure. In all cases,the motile sperm fraction was washed twice by centrifugation, and the sperm pellet was suspended in 0.35 mL of Earle's balanced salt solution (Sigma-Aldrich Co., Ayrshire, United Kingdom) as a capacitating medium in all patients. After swim up preparation ,the IUI was performed with a catheter (The Curve; Medical Systems, Inc., Herts, United Kingdom) 32-36 hours after hCG injection with the total number of motile spermatozoa after preparation more than 5 millions [11]. All patients received 30 mg/day of dydrogesterone (Duphaston; Solvay Pharmaceuticals, Hanover, Germany) after insemination till the day of hCG testing. Serum hCG was determined 2 weeks after hCG injection in the absence of menstruation for diagnosis of pregnancy. The outcome measure was the occurrence of clinical pregnancy with TVS performed two weeks later .

Saline flushing was done on the pre-ovulatory day when one or two follicles>17mm were confirmed by trans-vaginal ultrasound. Tubal flushing with20ml saline by saline flushing procedure was done [12] through cleaning the portio surface with saline swab, inserting and cuffing a foley's catheter (8F) in the cervical canal and finally 20ml saline was injected slowly into the uterine cavity under TVS guidance. The routine use of prophylactic antibiotics was not warranted. After swim-up preparation,

Statistical analysis

All statistical analysis was performed using SPSS for windows version 17.0 (SPSS, Chicago, IL). Continuous data were expressed as mean ± standard deviation (SD). Data were checked for normality and equality of distribution, prior to any analysis being performed. Skewed continuous variables were logarithmically

transformed to attain a normal distribution. For variables that would not attain a normal distribution by logarithmic transformation, nonparametric tests would be used. P-values <0.05 were considered to be of statistical significance.

Result

A total of 246 couples were involved in the study divided blindly into two equal groups each contain 123; non pertubated group (A) and saline infusion group (B). Patient's demographic data in both groups showed no significant differences where the mean age was 27.8 ± 7.3 and 26.7 ± 8.1 years respectively. The mean weight in Kg ± SD was 77.1 ± 9.9 and 79.8 ± 10.3, the mean height in cm ± SD was 160.5 ± 5.8 and 162.8 ± 7.1 while the duration of infertility in years was 3.4 ± 1.6 and 3.5 ± 1.1 years respectively [table 1].

COH and IUI were done for all cases in group A and B, the results obtained and gathered in table [2]. The number of follicles proposed to reach the maturity in both groups showed no significant difference being 4.43 ± 1.7 and 4.67 ±1 respectively. The overall pregnancy rate was significantly different in both groups (15/123 =12.1% in group A and 29/123 =23.57 % in group B and p-value < 0.001). Abnormal pregnancies encountered are more or less similar in both groups as multiple pregnancy, abortion and ectopic occurred in 4,2 and 1 case of the first while occurred in 5,4 and 1 case of the second. Finally the live birth rates registered was 7.3 % (9/123) in group A and 19.5 % (24/123) and there is a significant difference between both (p value < 0.005).

Table (1)

show the demographic data in both groups with no significant difference between them:

Parameter	Group (A): n =123	Group (B): n =123	P value
Mean age (years) ± SD	27.8 ± 7.3	26.7 ± 8.1	0.17
Weight (kg) ± SD	77.1 ± 9.9	79.8 ± 10.3	0.018
Height (cm) ± SD	160.5 ± 5.8	162.8 ± 7.1	0.026
Duration of infertility (years) ± SD	3.4 ± 1.6	3.5 ± 1.1	0.056
Mean motile spermatozoa before IUI ± SD	$6.2 \chi 10^6$ ±1.2	$5.9 \chi 10^6$ ±1.8	0.035

P value showed no significant difference between both groups in any of the variables.

Table (2)

show the number of follicles measuring > 16 mm in both groups, clinical pregnancy rate and fate of this pregnancy.

Parameter	Group (A): N =123	group (B): n = 123	P value
No. of follicles >16 mm	4.43 ± 1.7	4.67 ±1.	0.043
Clinical pregnancy:	15/123 =12.1%	29/123 =23.57 %	< 0.001**
Multiple pregnancy	4	5	0.045
Abortion	2	4	0.034
Ectopic	1	1	
Live birth rate	9/123 (7.3 %)	24/123 (19.5 %)	<0.005*

P value (**) it is highly significant.

Discussion

The present study has approved the treatment concept based on increased fertility after lipiodol flushing and saline infusion sonohysterography where tubal flushing with oil-soluble media (e.g. lipiodol) versus no intervention, was associated with a significant increase in pregnancy rate(OR 3.30, 95% CI 2.00-5.43) as proved by some authors [13]. On the other hand tubal flushing with oil-soluble media was not significantly more effective than tubal flushing with water-soluble media for achieving pregnancy (OR 1.21, 95%CI 0.95-1.54). Here in our research we used only 20 mm3saline perturbation in the expected pre-ovulatory day after COH and injecting 5000 IU HCG.

Saline flushing may be attributed to enhance pregnancy rates by many presumed effects; mechanical effect by opening of loose adhesions around the fimbriae [14] immunological effects; reducing sperm phagocytosis or enhancing the survival rate of spermatozoa [15, 7] or decreasinglevels of toxic peritoneal factors such as cytokines is another proposal effect [16].

The cross talk between embryo and endometrium is found to be enhanced withhigh implantation rates in IVF following endometrial stimulation [17]. Again ,this cross talk between embryo and endometrium after endometrial flushing with embryo culture media the day before embryo transfer increases endometrial receptivity and consequently the pregnancy rates[17] .Such results were achieved in our study where flushing the endometrium and the tubes with non-oil containing fluid "20 mm3 saline" before IUI in 123

casesis found to significantly increases the number of pregnancy and live births rates than in the other non pertubated group "p values were <0.001 and < 0.005 respectively".

On the other hand, Edelstam etal.2001 [18] demonstrated that a balanced salt solution used for pertubation gave the same overall pregnancy rate as this described with lipiodol. Ramazzotto etal.,1985[19] reported no complications with low-dose lignocaine pertubations and was well tolerated, the same results were reached by Edelstam et al., 2008 [5] who studied 130 cycles by using 50 mg C.C.+ IUI techniques in a randomized controlled trial by using 1.73 ml lignocaine hydrochloride in a balanced salt solution in 67 cases and saline perturbation in 63 cases and demonstrated that clinical pregnancies in the pertubated group is highly significant compared with non pertubated group ($P < 0.05$) whatever the mode of pertubation.

Importantly, cervical mucus has been reported to have unfavorable effects on pregnancy rates following IVF or ICSI and so cervical mucus aspiration before IUI appeared to lead to significantly increased pregnancy rates [20]. In our research; the increase in pregnancy rate was doubled in pertubated than non pertubated group; this may encourage us to use this procedure on a large scale being a safe treatment option, well tolerated, an office procedure, and assists in the diagnosis with significant therapeutic effect as well as reducing the need for surgical intervention.

Conclusion

Pre-ovulatory saline hydrotubation is a simple cost effective method that increases significantly pregnancy rates in infertile couples treated by ovarian hyper-stimulation with IUI with negligible or no side effects or contraindications.

References

1. Münster K, Helm P.Infertility and the seeking of infertility treatment in a representative population. Br J ObstetGynaecol. 1995 Dec;102(12):978-84.
2. Verhulst SM1, Cohlen BJ, Hughes E, TeVelde E, Heineman MJ. Intra-uterine insemination for unexplained subfertility. Cochrane Database Syst Rev. 2006 Oct 18;(4):CD001838.
3. Streda R, Stepan J, Zadrobilkova I, Cermakova E.Ovulation induction increases pregnancy rate during intrauterine insemination compared with natural cycles. CeskaGynekol 2007; 72:397-402.
4. PratibhaSaini and Antriksh Kumar . Pretreatment with hydrotubation in infertility management improves pregnancy rates. IVF Unit, Saini IVF and Fertility Research Centre, Chandralok Colony, Rajpur Road, Dehradun, UA 248001, India International Congress Series 09/2004; 1271:11-14. DOI: 10.1016/j.ics.2004.05.167
5. Edelstam G1, Sjösten A, Bjuresten K, Ek I, Wånggren K, Spira J. A new rapid and effective method for treatment of unexplained infertility.Hum Reprod. 2008 Apr;23(4):852-6. doi: 10.1093/humrep/den003.
6. Aboulghar MA1, Mourad LM, Al-Inany HG, Aboulghar MM, Mansour RT, Serour GA. Prospective randomized study for hydrotubation versus no hydrotubation before intrauterine insemination in unexplained infertility. Reprod Biomed Online. 2010 Apr;20(4):543-6. doi: 10.1016/j.rbmo.2010.01.003.
7. Nugent D, Watson AJ, Killick SR, Balen AH and Rutherford AJ (2002) A randomized controlled trial of tubal flushing with lipiodol for unexplained infertility. FertilSteril77, 173–175.
8. Johnson NP1, Kwok R, Stewart AW, Saththianathan M, Hadden WE, Chamley LW.Lipiodol fertility enhancement: two-year follow-up of a randomized trial suggests a transient benefit in endometriosis, but a sustained benefit in unexplained infertility. Hum Reprod. 2007 Nov; 22(11):2857-62. Epub 2007 Sep 21.
9. UzunO, FindikS, DanaciM, KatarD,ErkanL. . Pulmonary and cerebral oil embolism after hysterosalpingography with oil-soluble contrast medium. Respirology2004;9:134-136.
10. Brent K, Hadden W, Weston-Webb M, Johnson NP. After the FLUSH Trial: a prospective study of lipiodol flushing as an innovative treatment for unexplained and endometriosis-related infertility. Aust N Z J ObstetGynaecol 2006;46:293–297.
11. Ombelet W1, Deblaere K, Bosmans E, Cox A, Jacobs P, Janssen M, Nijs M. Semen quality and intrauterine insemination. Reprod Biomed Online. 2003 Oct-Nov;7(4):485-92.

12. BartkowiakR, Kaminski P, Wielgos M, Bobrowska K . The evaluation of uterine cavity with saline infusion sonohysterography and hysteroscopy in infertile patients .NeuroEndocrinol Lett 2006 Aug ; 27 (4) : 523 – 8
13. Luttjeboer F1, Harada T, Hughes E, Johnson N, Lilford R, Mol BW.Tubal flushing for subfertility.Cochrane Database Syst Rev. 2007 Jul 18;(3):CD003718.
14. Rasmussen F, Lindequist S, Larsen C, Justesen P. Therapeutic effect of hysterosalpingography: oil-versus water-soluble contrast media - a randomized prospective study. Radiology 1991; 179:75–9.
15. Edelstam GA, Andersson E, Radestad A, Flam F, Gottlieb C.The effect of lignocaine on sperm phagocytosis in the peritoneal fluid from women with or without endometriosis. Hum Reprod (1998) 13:1353-1345.
16. Agic A, Xu H, Finas D, Banz C, Diedrich K, Hornung D. Is endometriosis associated with systemic subclinical inflammation? GynecolObstet Invest (2006) 62:139-147
17. Kapiteijn K, de Bruijn CS, de Boer E, de Craen AJ, Burger CW, van Leeuwen FE &Helmerhorst FM2006 Does subfertility explain the risk of poor perinatal outcome after IVF and ovarian hyperstimulation? Human Reproduction 21 3228–3234.
18. Edelstam GAB, Sjösten ACE, WernekinkSalamon AC. Pertubation with lignocaine—a possible new treatment for women with endometriosis and impaired fertility, Ups. J Med Sci 2001;106:51-57
19. Ramazzotto LJ, Curro FA, Paterson JA, Tanner P, Coleman M. .Toxicological assessment of lidocaine in the pregnant rat. J Dent Res 1985;64:1214-1218
20. Simsek E, Haydardedeoglu B, Hacivelioglu SO, Cok T, Parlakgumus A, et al. (2008) Effect of cervical mucus aspiration before intrauterine insemination. Int J GynaecolObstet 103: 136-139.

Prednisolone in unexplained implantation failure: a randomized controlled clinical trial of efficacy

Waleed El-refaie, MD,
Mohamed Sayed Abdelhafez, MD,
Department of Obstetrics and Gynecology, Mansoura University, Mansoura, Egypt

Abstract

Objective: To evaluate of the effect of adding prednisolone to improve the outcomes of intracytoplasmic sperm injection (ICSI) in women with previous unexplained implantation failure.

Materials & Methods: This is a randomized controlled study performed in Fertility Care Unit in Mansoura University Hospital and private fertility care centers, Mansoura, Egypt. The study comprised of women undergoing ICSI and has history of one or more implantation failure. All women were randomly divided into two groups; the study group received prednisolone in a dose of 20 mg/day starting from the day of oocyte retrieval while the control group received no treatment. The primary outcome was clinical pregnancy rate and the secondary outcomes were implantation rate and miscarriage rate.

Results: 108 women (53 in the study group and 55 in the control group) subjected to final analysis. There was no significant difference between the study and control groups as regard the clinical pregnancy rate (45.3% vs 32.7%; P = 0.237), implantation rate (22.1% vs 15.2%; P = 0.145) and miscarriage rate (33.3% vs 33.3%; P = 1.000).

Conclusion: Administration of prednisolone in the luteal phase to women with previous unexplained implantation failure does not result in significant increase in clinical pregnancy or implantation rates.

Key Words: ICSI, Implantation failure, Prednisolone.

Introduction

The need for assisted reproductive technology (ART) is increasing, since more than 10% of couples suffer from some form of infertility. The in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) have spread throughout the world, with apparently around 5 million babies born worldwide by 2012. In just over 35 years, the field of IVF/ICSI has grown and its success has improved as measured by the increase in live birth rate per cycle initiated from less than 1% to a rate of more than 33%. For women aged < 35 years, the pregnancy rates using embryos generated from one stimulated cycle were found to be about 50-60% [(1)].

Many factors have been suggested as causes of failure in ICSI cycles such as poor oocyte yield by the ovary, factors related to the laboratory culture and medias and faults during embryo transfer; these factors would decrease the pregnancy rate. However, in practically successful IVF/ICSI centers with high clinical pregnancy and live birth rates, some couples suffer repeated implantation failure [(2)]. Implantation of the transferred embryo is the most important step determining the achievement of clinical pregnancy in IVF/ICSI cycles. Currently, the implantation rate is still not in the desired ranges mainly lower than 20-25% per embryo transfer [(3)].

One of the reasons of implantation failure was suggested to be related to local abnormal immunological reactions in the endometrium. Ledee-Bataille et al. found that there was local abnormal expression of various cytokines, dysregulation of interleukins 12, 15 and 18 and elevation in the level of natural killer cells [(4)]. Also, Inagaki et al. found that there was high IL-1β and low interferon-γ and IL-10 in patient with implantation

Mohamed Sayed Abdelhafez, MD
Department of Obstetrics and Gynecology, Mansoura University Hospitals, Elgomhouria St., Mansoura City 35111, Dakahlia, Egypt
Tel +201124442800
Email: msabdelhafez@gmail.com
2015

failure [5]. Moreover, for implantation to occur, a complex interaction complex between the embryo and the endometrium occurred and it involves leucocytes, interleukins, growth factors stromal cells and extracellular matrix [6]. Glucocorticoids were suggested to have modulatory effect on the implantation process by affecting these factors [7-10].

In this study, we aim to find out whether cortisone administration following embryo transfer could improve pregnancy outcome in couples with previous unexplained implantation failure.

Materials & Methods

This is a prospective, randomized, controlled, parallel-group study conducted during the period from February 2012 through November 2014 in Fertility Care Unit in Mansoura University Hospital and private fertility care centers, Mansoura, Egypt. The study protocol was reviewed and approved by our Institutional Review Board. The participants of this study were recruited from couples planned for management of infertility by ICSI. Eligible participants in our study were woman aged 20-38 years with history of unexplained previous failure of one or two implantations. A written informed consent was taken from each women selected to participate before inclusion in the study. Women with any of the following criteria were excluded from the study: 1) body mass index (BMI) < 19 kg/m^2 or > 35 kg/m^2; 2) moderate or severe endometriosis; 3) hydrosalpinx; 4) uterine abnormalities; 5) uterine myoma; 6) previous uterine surgery; 7) positive results for antiphospholipid antibodies; 8) metabolic or hormonal abnormalities; or 9) hormonal therapy in the preceding 3 months.

A full, precise history was taken from each participant, and the cause of infertility was reported. Thorough clinical examination (including general, abdominal, and pelvic examination) was performed as well. The semen analysis of the husband was checked according to the WHO (2010) guidelines. The results of the previously done hysterosalpingography, laparoscopy and hysteroscopy were evaluated. Basal (day 3) serum follicle stimulating hormone (FSH) and luteinizing hormone (LH) were assayed for each woman within 3 cycles of the scheduled ICSI cycle. A transvaginal sonography (TVS) scan was performed and any deviation from normal pelvic anatomy was looked for and reported.

The long luteal GnRHa protocol was used for COH. The GnRHa used was Triptorelin (Decapeptyl®, Ferring, Germany). Triptorelin was administered subcutaneously in a dose of 0.1 mg/day starting in the mid-luteal phase (day 21) of the preceding cycle then the dose was reduced to half the dose (0.05 mg/day) from the day of ovarian stimulation till the day of HCG administration. Ovarian stimulation using gonadotropin preparation was commenced on day 2 of the next cycle (stimulation cycle) after ensuring adequate pituitary and ovarian suppression (serum E2 < 50 pg/ml), and performing TVS scan to confirm absence of ovarian cysts and presence of endometrial thickness < 3 mm. The gonadotropin was given daily by deep intramuscular injection and the starting dose and type depended on the age of the woman, baseline FSH levels, BMI and previous trials. TVS scan was performed regularly for monitoring of follicular development (folliculometry); starting from day 8 of the cycle and repeated every 2-3 days. The dose and type of gonadotropin were ten modulated according to ovarian response.

The cycle was cancelled when poor ovarian response (< 3 follicles not reaching 18 mm correlated with serum E2 level < 400 pg/ml) was detected during follow up visits after counseling the couple regarding the success rates. The cycle was also cancelled when there was a high risk for ovarian hyperstimulation syndrome (i.e. more than 30 follicles, steep rise in serum E2, or ovarian size > 8 cm).

When there were at least 3 leading follicles > 18 mm in diameter, final oocyte maturation was induced by intramuscular administration of 10000 IU of HCG. Endometrial thickness and pattern were assessed by TVS on the day HCG administration. After HCG injection by 34-36 hours, oocyte retrieval was performed through transvaginal aspiration of follicles under TVS guidance followed by endometrial preparation for embryo transfer (ET) by giving 800 mg/day natural progesterone vaginal supplement (Cyclogest®, Actavis) + 4 mg/day estradiol oral supplement (Cyclo-Progynova® white tablets, Bayer Pharma).

On the day of oocyte retrieval, all women participating in the study were randomly divided into two groups; prednisolone group (study group) and no treatment group (control group) using a computer-generated list and was carried out by a nurse through sealed, unlabeled, opaque envelopes. The participants, caregivers, investigators and outcomes assessors were not blinded to group assignment. All women in the study group received prednisolone (Solupred®, Sanofi-Aventis) in a dose of 20 mg/day starting from the day of oocyte retrieval and continued until documentation of pregnancy while women in the control group received no treatment.

After fertilization through ICSI, 2-3 good quality embryos were transferred transcervically 3-5 days after oocyte retrieval. If there is ≤ 5 good quality cleavage-stage embryos, ET were performed on day 3 after oocyte retrieval while if there is > 5 good quality cleavage-stage embryos, embryos were left to reach

the morula or blastocyst stage and ET was performed on day 4 or 5 after oocyte retrieval. Good quality cleavage-stage embryos display stage-specific cell division, have blastomeres of fairly equal size with few to no cytoplasmic fragments. Women with no transfer of at least one good quality embryo were excluded from final analysis.

Biochemical pregnancy was documented by performing quantitative serum β-HCG assay 2 weeks after the ET and a level of ≥ 50 mIU/ml was considered positive indicator of pregnancy. Cases with positive pregnancy test were examined by TVS 24 weeks later (4-6 weeks after ET) to document clinical intrauterine pregnancy which is defined as presence of at least one intrauterine gestational sac with fetal pole and cardiac activity on TVS scan at 46 weeks after the ET. The primary outcome of this study was the clinical pregnancy rate (number of clinical pregnancies divided by the number of ET procedures) and the secondary outcomes were the implantation rate (number of gestational sacs on TVS scan at 4-6 weeks after ET divided by the number of transferred embryos) and miscarriage rate (number of miscarriages before 12 weeks divided by the number of clinical pregnancies.

Statistical analysis

The statistical analysis was performed using the IBM® SPSS® Statistics, version 20.0 for Windows. Continuous variables were expressed as mean ± standard deviation (SD) and categorical variables were expressed as frequencies and percentages. Differences among continuous variables with normal distribution were analyzed by the t-test while for continuous variables without normal distribution, non-parametric tests were used and differences were analyzed by the Mann-Whitney U-test. Differences between percentages were analyzed by the Fisher's exact test. P value ≤ 0.05 was considered statistically significant.

Results

During the period of the study, 146 women were assessed for eligibility to participate in the study and 124 of them were randomized. Of the 124 women who were randomized, outcome measures were available for 113 women as 9 women were excluded from the study due cancellation of ET. Data were analyzed from 53 women in the study group (prednisoline group) and 55 women in the control group (no treatment group) while 5 women were excluded from final analysis due to no transfer of any good quality embryo (Figure 1).

There was no significant difference between the study and control groups as regards the age, BMI, duration, type and cause of infertility, number of previous implantation failures and hormonal profile (Table 1). Also, no significant difference was between both groups as regards the total gonadotropin dose, stimulation days, number of follicles ≥ 12 mm in diameter by TVS on day of HCG administration, peak serum E2 level, number of oocytes retrieved, oocyte maturation rate, fertilization rate, percentage of good quality embryos, number of transferred embryos and number of transferred good quality embryos (Table 2).

The clinical pregnancy rate was higher in the study group than in the control group (45.3% vs 32.7%) but without significant difference (P = 0.237). Also, there was no significant difference in implantation rate between both groups though it was higher in the study group (22.1% vs 15.2%; P = 0.145). The first trimester miscarriage rate was equal in both groups (33.3% vs 33.3%; P = 1.000) (Table 2).

Figure (1): Study flow diagram:

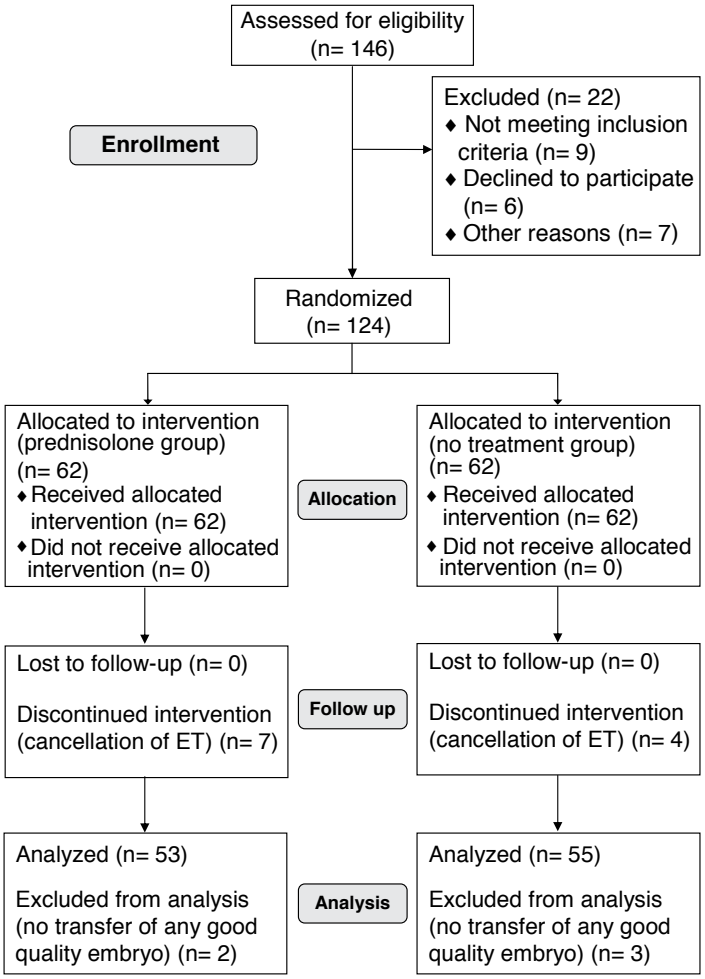

Table (1)
Demographic and clinical characteristics of the study and control groups:

		Study group (n = 53)	Control group (n = 55)	P value
Age (years) *		30.25 ± 5.51	28.96 ± 5.33	0.281
BMI (kg/m^2) *		29.77 ± 3.63	30.48 ± 3.86	0.277
Duration of infertility (years) *		7.40 ± 4.07	6.35 ± 3.70	0.169
Type of infertility †	Primary	39/53 (73.6%)	39/55 (71.0%)	0.831
	Secondary	5/53 (9.4%)	8/55 (14.5%)	0.557
	Relative	9/53 (17.0%)	8/55 (14.5%)	0.795
Cause of infertility †	Male factor	27/53 (50.9%)	29/55 (52.7%)	1.000
	PCOS	22/53 (41.5%)	19/55 (34.5%)	0.553
	Tubal factor	11/53 (20.8%)	8/55 (14.5%)	0.455
	Endometriosis	5/53 (9.4%)	7/55 (12.7%)	0.761
	Unexplained	4/53 (7.5%)	6/55 (10.9%)	0.742
Previous implantation failure †	One	23/53 (43.4%)	26/55 (47.3%)	0.704
	≥ 2	30/53 (56.6%)	29/55 (52.7%)	
Serum TSH (uIU/ml) *		1.94 ± 1.14	1.81 ± 0.77	0.851
Serum prolactin (ng/ml) *		13.12 ± 5.81	13.53 ± 6.90	0.768
Basal serum FSH (mIU/ml) *		6.48 ± 2.05	6.11 ± 1.92	0.400
Basal serum LH (mIU/ml) *		6.98 ± 5.68	6.07 ± 3.57	0.298

* Expressed as mean ± SD and P value was calculated by the Mann-Whitney U-test.
† Expressed as frequency and percentage and P value was calculated by the Fisher's exact test.

Table (2)
COH and ICSI outcomes of the study and control groups:

	Study group (n = 53)	Control group (n = 55)	P value
Total gonadotropin dose (IU) *	2829 ± 777	2690 ± 709	0.337
Stimulation days (days) *	11.62 ± 1.54	11.40 ± 1.84	0.424
Number of follicles ≥ 12 mm in diameter by TVS on day of HCG administration †	15.36 ± 5.91	17.05 ± 7.83	0.208
Peak serum E2 (pg/ml) *	3152 ± 1804	3359 ± 1686	0.312
Number of oocytes retrieved *	10.15 ± 4.05	11.56 ± 5.66	0.249
Oocyte maturation rate (%) *	84.03 ± 16.55	81.23 ± 13.34	0.157
Fertilization rate (%) *	75.35 ± 20.39	75.28 ± 18.95	0.800
Percentage of good quality embryos (%) *	67.72 ± 34.13	66.40 ± 32.45	0.678
Number of transferred embryos *	2.91 ± 0.53	2.87 ± 0.47	0.760
Number of transferred good quality embryos *	2.49 ± 0.64	2.53 ± 0.63	0.738
Clinical pregnancy rate ‡	24/53 (45.3%)	18/55 (32.7%)	0.237
Implantation rate ‡	34/154 (22.1%)	24/158 (15.2%)	0.145
Miscarriage rate ‡	8/24 (33.3%)	6/18 (33.3%)	1.000

* Expressed as mean ± SD and P value was calculated by the Mann-Whitney U-test.
† Expressed as mean ± SD and P value was calculated by the t-test.
‡ Expressed as frequency and percentage and P value was calculated by the Fisher's exact test.

Discussion

Implantation failure in IVF/ICSI cycles is a challenging and distressing subject as it represents a financial and psychological burden on infertile couples subjected to ICSI treatment. Immunosuppressive treatment has been recently used during the standard ICSI protocols to improve the implantation rate, especially in women with previous implantation failure [11]. Glucocorticoids are a class of the famous immunosuppressive drugs to be used [12, 13]. Several studies have proved the benefits of use of glucocorticoids on implantation rate in patients who had zona dissected ET (14) as cortisone decrease the uterine lymphocytes and prevent segmented neutrophils to invade and destroy the zona dissected embryos. Also, other studies revealed the beneficial effect of glucocorticoids in non micro-manipulated embryos by decreasing the release of androgen from the suprarenal gland caused by the stress of ET procedures [15-17].

In this study, which is a prospective randomized trial, infertile couples with previous ICSI treatment failure without known local pathological condition that can prevent implantation or poor ovarian response to ovarian hyperstimulation or previous in utero transfer of bad quality embryos, we tried to study the effect of administration of low dose prednisolone after oocyte retrieval on the clinical pregnancy rate. We assumed that women with previous implantation failure in spite of transfer of at least one good quality embryo can be considered to be caused by local endometrial immunological reaction.

We found increase in clinical pregnancy rate (from 35.7% to 45.3%) and implantation rate (from 15.2% to 22.1%) in patients received 20 mg of prednisolone following oocyte retrieval, a result that can be explained probably by increase in the level or the activity of uterine natural killer (NK) cells by the use of immunosuppressant as proved by previous study [13]. It was proved that NK cells and components of innate immune system are important in development of the placenta by promoting angiogenesis, trophoblastic invasion and spiral arteries remodeling [18-20]. However, that increase in the implantation rate and clinical pregnancy rate in our study group was not statistically significant. Our results agree with a previous study that concluded that use of low dose prednisolone did not improve the clinical pregnancy rate and implantation rate when used regularly in IVF/ICSI cycles for infertile couple [21]; however, this study was conducted on patients without prior implantation failure so, both groups in this study may involve patients with endometrial immunological abnormality that may lead to insignificant results.

The strength of our study comes from that it was a randomized controlled one and the allocation concealment was performed by a sealed, opaque envelopes handled by a nurse though masking was not possible because no intervention was used in the control group. Another strength point in our study lies in exclusion of patients with other possible causes of implantation failure, such as those with uterine fibroid, hydrosalpinx, uterine surgery and positive antiphospholipid antibodies. The limitations of our study are that it was conducted on a relatively small cohort and the intention to treat strategy has not been performed.

Further studies are needed on larger cohorts of women with unexplained implantation failure to confirm or refute the benefit of glucocorticoids therapy on the clinical pregnancy and implantation rates after ET. Also, the effect of other forms and different doses of glucocorticoids therapy and the ideal time for starting therapy in remain to be investigated.

Conclusion

Administration of prednisolone in the luteal phase to women with previous unexplained implantation failure does not result in significant increase in clinical pregnancy or implantation rates.

References

1. Stern K. Assisted reproductive technology - what's new and what's important? Aust Fam Physician. 2012; 41(10): 762-8.
2. Margalioth EJ, Ben-Chetrit A, Gal M, Eldar-Geva T. Investigation and treatment of repeated implantation failure following IVF-ET. Hum Reprod. 2006; 21(12): 3036-43.
3. Duvan CI, Ozmen B, Satiroglu H, Atabekoglu CS, Berker B. Does addition of low-dose aspirin and/or steroid as a standard treatment in nonselected intracytoplasmic sperminjection cycles improve in vitro fertilization success? A randomized, prospective, placebo-controlled study. J Assist Reprod Genet. 2006; 23(1): 15-21.
4. Lédée-Bataille N, Bonnet-Chea K, Hosny G, Dubanchet S, Frydman R, Chaouat G. Role of the endometrial tripod interleukin-18, -15, and -12 in inadequate uterine receptivity in patients with a history of repeated in vitro fertilization-embryo transfer failure. Fertil Steril. 2005; 83(3): 598-605.
5. Inagaki N, Stern C, McBain J, Lopata A, Kornman L, Wilkinson D. Analysis of intra-uterine cytokine concentration and matrix-metalloproteinase activity in women with recurrent failed embryo transfer. Hum Reprod. 2003; 18(3): 608-15.
6. Armant DR, Diaz D. Embryo–uterine interactions during implantation. In: Seil MM, ed. Infertility. A Comprehensive Text of Reproductive Technology. Norwalk: Appleton and Lange 1990: 457-470.
7. Finlay CA, Cristofalo VJ. Autocrine stimulation of WI38 cell proliferation in the presence of glucocorticoids. Characteristics of the stimulatory factor(s) involved in this response. Exp Cell Res. 1987; 168(1): 191-202.
8. Dean DC, Newby RF, Bourgeois S. Regulation of fibronectin biosynthesis by dexamethasone, transforming growth factor beta, and cAMP in human cell lines. J Cell Biol. 1988; 106(6): 2159-70.
9. Durant S, Duval D, Hassid J, Homo-Delarche F. Mouse embryo fibroblast proliferation and prostaglandin production in medium supplemented with fetal bovine serum or serum substitutes (Ultroser SF and G): role of glucocorticoids. J Steroid Biochem. 1989; 33(6): 1103-10.
10. Simo P, Simon-Assmann P, Arnold C, Kedinger M. Mesenchyme-mediated effect of dexamethasone on laminin in cocultures of embryonic gut epithelial cells and mesenchyme-derived cells. J Cell Sci. 1992; 101 (Pt 1): 161-71.
11. Ford HB, Schust DJ. Recurrent pregnancy loss: etiology, diagnosis, and therapy. Rev Obstet Gynecol. 2009; 2(2): 76-83.
12. Alhalabi M, Samawi S, Taha A, Kafri N, Modi S, Khatib A, Sharif J, Othman A. Prednisolone improve implantation in ICSI patients with high peripheral CD69+ NK Cells. Hum Reprod. 2011; 26 Suppl 1: 294
13. Quenby S, Kalumbi C, Bates M, Farquharson R, Vince G. Prednisolone reduces preconceptual endometrial natural killer cells in women with recurrent miscarriage. Fertil Steril. 2005; 84(4): 980-4.
14. Cohen J, Elsner C, Kort H, Malter H, Massey J, Mayer MP, Wiemer K. Impairment of the hatching process following IVF in the human and improvement of implantation by assisting hatching using micromanipulation. Hum Reprod. 1990; 5(1): 7-13.
15. Howles CM, Macnamee MC, Edwards RG, Goswamy R, Steptoe PC. Effect of high tonic levels of luteinising hormone on outcome of in-vitro fertilisation. Lancet. 1986; 2(8505): 521-2.
16. Kemeter P, Feichtinger W. Prednisolone improves the pregnancy rate of IVF. A prospective randomized study. Fertilitat. 1986; 2: 71-6.
17. Rein MS, Jackson KV, Sable DB, Thomas PP, Hornstein MD. Dexamethasone during ovulation induction for in-vitro fertilization: a pilot study. Hum Reprod. 1996; 11(2): 253-5.
18. Loke YW, King A, Burrows TD. Decidua in human implantation. Hum Reprod. 1995; 10 Suppl 2: 14-21.
19. Hanna J, Goldman-Wohl D, Hamani Y, Avraham I, Greenfield C, Natanson-Yaron S, Prus D, Cohen-Daniel L, Arnon TI, Manaster I, Gazit R, Yutkin V, Benharroch D, Porgador A, Keshet E, Yagel S, Mandelboim O. Decidual NK cells regulate key developmental processes at the human fetal-maternal interface. Nat Med. 2006; 12(9): 1065-74.
20. Lash GE, Robson SC, Bulmer JN. Review: Functional role of uterine natural killer (uNK) cells in human early pregnancy decidua. Placenta. 2010; 31 Suppl: S87-92.
21. Ubaldi F, Rienzi L, Ferrero S, Anniballo R, Iacobelli M, Cobellis L, Greco E. Low dose prednisolone administration in routine ICSI patients does not improve pregnancy and implantation rates. Hum Reprod. 2002; 17(6): 1544-7.

Acceptability and Satisfaction towards Copper T 380A versus Single Dose Levonorgestrel as Emergency Contraception among Egyptian women

Mariam Lotfy Mohamed, MD
Department of Obstetrics and Gynecology,
Faculty of Medicine,
Suez Canal University

Abstract

Objective: To assess acceptability & satisfaction towards Cu-T 380A (IUD) versus levonorgestrel (contra plan II) as EC among Egyptian women as primary outcome, and the efficacy, side effects as secondary outcomes.
Method: 336 women fulfill the inclusion & exclusion criteria completed the study distributed as 162 women chose to use levonorgestrel and 174 women chose to use IUD. Patients were followed up for index cycle. Patients were assessed for acceptance of LNG and IUD, side effects, failure rate and resumption of menses.
Results: Acceptability and satisfaction of IUD as EC method were 51.8 % and 98.3%vs. 48.2% and 96.3% of LNG group. 59.3% and 62.1% of LNG and IUD group respectively have resumed their menses within expected time. LNG showed tolerated side effects. The most common side effect among LNG group was heavy bleeding (9.3%) and nausea (7.4%). IUD was left in place as long-term contraception in most of cases (67.2%). Only one woman of IUD group and 2 women of LNG group had pregnancy. Most of participants have been satisfied with their method.
Conclusion: both methods are highly effective methods of contraception after unprotected intercourse and IUDs are cost-effective when left in place as ongoing contraception.

Key Words: emergency contraception, levonorgestrel.

Introduction

Emergency contraception (EC) is a term that refers to all methods of contraception that are administered for usage after intercourse and before implantation It is well established that many unintended pregnancies occur as a result of unprotected intercourse, inadequate contraceptive measures, or failure of a method [1]. In developing countries, about 75 million pregnancies annually are unintended, a number close to the 80 million growth of world population each year [2]. In conservative societies, as in Egypt, many of women with unintended pregnancies will seek unsafe abortion [3]. EC can help reducing mortality and morbidity associated with unsafe abortions [1].

The most commonly used methods of EC can reduce the risk of pregnancy by 75% to 89% [4]. One of the most fictions about EC that they is abortifacient –the idea that can be important obstacle for its usage in Islamic societies as in Egypt. The World Health Organization's "Medical Eligibility Criteria for Contraceptive Use" include no conditions in which the risks of emergency contraception outweigh the benefits [5].

There are two known methods of emergency contraception: hormonal methods (Estrogen only pills, Combined pills [6], antiprogestin pills and progestin only pills), also known as emergency contraceptive pills, and insertion of a copper intrauterine device (IUD) post-coitally [7].

Only the progestin levonorgetrel has been studied for use as an emergency contraceptive method. The original treatment schedule was one 0.75 mg dose within 72 hours after unprotected intercourse and a second 0.75 mg dose 12 hours after the first dose. However, recent studies have shown that

Mariam Lotfy Mohamed
Tel: 01066149478
E-mail: mariam4466@yahoo.com

a single dose of 1.5 mg is as effective as two 0.75 doses 12 hours apart [8].

The insertion of a copper IUD within 5 days of unprotected intercourse has been shown to prevent pregnancy and is an important option for women presented after the 72-hour time frame of when hormonal EC is most effective. Since it is well accepted that implantation occurs 6 to 7 days after ovulation, extending insertion of an IUD up to 7 days after unprotected intercourse may be acceptable if it falls within 5 days of the ovulation day. The post-coital IUD may remain in place to provide ongoing contraception [9].

The aim of the present study was to assess acceptability & satisfaction towards Cu-T 380A (IUD) versus levonorgestrel (contra plan II) as EC among Egyptian women as primary outcome, and the efficacy, side effects as secondary outcomes.

Patients and Methods

After approval of research and ethics committee of faculty of medicine, Suez Canal University, this prospective comparative study was conducted among women presented to outpatient clinic of Obstetrics and Gynecology department, Suez Canal University Hospital. During the period of the study from 0ctober 2013 to April 2014, women of reproductive age (18 – 45 years old) who visited the hospital within 72 hours of single unprotected intercourse wishing to avoid unwanted pregnancy were selected. For women presented within 72 hours, the advantages and disadvantages of both methods (Levonorgestrel and Copper T 380A) were explained and they were asked to choose one of these methods.. The least required sample size for each group were estimated depending on the previously reported efficacy of EC with each method [10] using α error of 0.05 and power of study 80% [11] with (n) not less than 50 participants for each group.

Women were included in the study after fulfilling previously determined inclusion and exclusion criteria. Women 18 – 45 years old with regular menstrual cycle for last 3 months, in need of emergency contraception (had unprotected intercourse within 72 hours), willing to comply with study requirements, and available for follow up (accessible by telephone) and willing not to have further acts of intercourse during the same cycle. Women with pelvic inflammatory disease or septic abortion within the past 3 months or had gonorrhea, abnormalities of the uterus that distort the uterine cavity, mucopurulent cervicitis, vaginal bleeding of an unknown etiology, ovarian, cervical, or endometrial cancer, previous ectopic pregnancy, thromboembolism, and migraine were also excluded from the study. Patients have reported allergy to copper or Wilson's disease (for participants selecting the copper IUD) or allergy to Levonorgestrel (for participants selecting oral Levonorgestrel) were excluded from the study.

Women who fulfilled the criteria for inclusion and were willing to participate were enrolled for the study. Participants were divided into two groups A and B. Group A included women opted for LNG treatment. Single dose (two tablets of 0.75 mg tablets) was given orally within 72 hours of single unprotected intercourse (known as contra plan II manufactured and marketed by DKT Egypt Co. Group B included women who opted for Cu T 380 came within 72 hours and chose this method Cu T380 was inserted under aseptic conditions.

At the beginning of the study, 420 women were presented requesting EC. 336/420 (80%) fulfill the inclusion criteria. 162 chose LNG (48.2%) and 174/336 (51.8%) chose IUD.

At first visit, history was taken about age, parity, coitus-EC interval in hours. The reason for seeking EC was recorded. As women presented within 72 hours were asked to choose one of the studied methods, and acceptance of LNG and Cu T 380 was estimated based on the percentages of women chose each method after explanation of each method for all participants. Participants were followed up within 7 days of vaginal bleeding or spotting. Participants were assessed for resumption of menses, whether early (< 7 days), delayed > 7 days beyond expected date of next menses or within expected time (± 7 days of expected date of next menses). Any side effects were reported as nausea, vomiting, abdominal pain, heavy bleeding, or irregular bleeding. Displacement or expulsion of IUD was reported. Efficacy of EC method was evaluated based on failure rate estimated by occurrence of pregnancy within index cycle as documented by positive urine pregnancy test or ultrasonography examination. Participants were asked if they were satisfied or not by used method. Number of participants willing to continue use IUD after the index cycle as long term contraception method was recorded.

Statistical analysis

Data were processed using SPSS version 15 (SPSS Inc., Chicago, IL, USA). Quantities data were expressed as means ±SD and qualitative data were expressed as numbers and percentages. Student's T-test was used to test significance of difference for quantitative variables while Chi-square and fisher's exact tests were used to test significance for qualitative variables. A probability value (p-value) < 0.05 was considered statistically significant.

Results

Table 1 presents the baseline characteristics of participants in both groups. There was no statistically significant difference between women in IUD and LNG groups regarding all characteristics. As regard to acceptability of each method, 174/336 women have chosen IUD (51.8%) and 162/336 (48.2%) have chosen LNG with no statistically significant difference. Mean age was 28.6 and 29.5 years old in LNG and IUD group respectively. Most of women were para 1 – 2 (70.4% and 82.8% in LNG and IUD group respectively. Most of participants in both groups have previously used contraceptive method (77.8% of LNG group women and 86.2% of IUD group women). Thirty women of LNG group and thirty-six of IUD group have previously used EC. Most of women in IUD group who have previously used EC have used IUD while most of women in LNG group who have previously used EC have used pills either POP or combined pills. 27.8% and 15.5% of women in LNG and IUD groups respectively have presented for EC within 24 hours post-coital while 53.7% of LNG group and 48.3% of IUD group have been presented from 24 – 48 hours post-coital and 18.5% and 36.2% of LNG and IUD groups respectively have been presented 48 -72 hours. Most common indication for EC among studied women was none use of contraceptive method (59.3% and 48.3% in LNG and IUD groups respectively). One patient has presented after rape and was presented after 65 hours and has chosen to be allocated to levonorgestrel group. More than half of the participants in both groups have resumed their menses with ± 7 days of expected time (59.3% and 62.1% of LNG and IUD group respectively). 24.1% of IUD group women had resumed their menses as early as more than 7 days before expected time of next menstruation while 13.8% of the same group and 22.2% of LNG groups had delayed menstruation more than 7 days of expected time of next menstruation. Most of patients have no side effects. The most common side effect among LNG group was heavy bleeding (9.3%) and nausea (7.4%) while 27.6% of IUD group participants have heavy bleeding and 12.1% have irregular menses. Most of women of IUD group have continued to use IUD as long term contraceptive method (67.2%). Failure rate was very low among both groups; only one woman of IUD group and 2 women of LNG group had pregnancy diagnosed by positive pregnancy test and ultrasonography after the index cycle (Table 2).

Most of participants have been satisfied with their method (96.3% of LNG group and 98.3% of IUD group). Only 2 patients of LNG group and 1 patient of IUD group are not satisfied (Table 3).

Table (1)
Characteristics of participants in both groups of the study:

Characteristics		LNG group (n=162)	IUD group (n=174)	P-value
Age	Mean ± SD	28.6 ± 7.3	29.5 ± 6.7	0.5 (NS)
	Range	20 – 38	19 – 39	
Parity	NP	15 (9.2%)	3 (1.7%)	0.1 (NS)
	P1-2	114 (70.4%)	144 (82.8%)	
	≥P3	33 (20.4%)	27 (15.5%)	
History of abortion		6 (3.7%)	9 (5.2%)	0.9 (NS)
History of previous contraception		126 (77.8%)	150 (86.2%)	0.4 (NS)
Previous used method of contraception#	IUD	39 (30.9%)	93 (62%)	0.01*
	OCP	75 (59.6%)	42 (28%)	
	Condoms	12 (9.5%)	15 (10%)	
	Others	18 (14.3%)	15 (10%)	
History of previous EC		30 (18.5%)	36 (20.7%)	0.9 (NS)
Previous method for EC	IUD	6 (20%)	21 (58.3%)	0.2 (NS)
	POP	15 (50%)	9 (25%)	
	Combined pills	9 (30%)	6 (16.7%)	
Coitus-EC interval (hours	< 24 hours	45 (27.8%)	27 (15.5%)	0.07 (NS)
	24 – 48 hours	87 (53.7%)	84 (48.3%)	
	48 – 72 hours	30 (18.5%)	63 (36.2%)	
Indications for EC	Non use of contraception	96 (59.3%)	84 (48.3%)	0.3 (NS)
	Slippage of condom	9 (5.6%)	21 (12.1%)	0.4 (NS)
	Breakage of condom	21 (12.9%)	18 (10.4%)	0.9 (NS)
	Incorrect use of contraception	21 (12.9%)	27 (15.5%)	0.9 (NS)
	Displaced/expelled IUD	14 (8.6%)	24 (13.7%)	0.4 (NS)
	Rape	1 (0.6%)	0 (0%)	0.9 (NS)

*Statistically significant difference, NS: no statistically significant difference,
LNG: Levonorgestrel, POP: progestin only pills, EC: emergency contraception,
IUD: Intrauterine device, OCP: oral contraceptive pills, NP: nulliparous
#More than method could have been previously used.

Table (2)
Resumption of menses and side effects:

Characteristics		LNG group (n=162)	IUD group (n=174)	P-value
Resumption of menses	Early	30 (18.5%)	42 (24.1%)	0.5 (NS)
	On time	96 (59.3%)	108 (62.1%)	
	Delayed	36 (22.2%)	24 (13.8%)	
Side effects	Nausea	12 (7.4%)	0 (0%)	0.1 (NS)
	Vomiting	9 (5.6%)	0 (0%)	0.2 (NS)
	Abdominal pain	6 (3.7%)	18 (10.3%)	0.3 (NS)
	Heavy bleeding	15 (9.3%)	48 (27.6%)	0.02*
	Irregular menses	12 (7.4%)	21 (12.1%)	0.6 (NS)
	Displaced/expelled IUD	-	3 (1.7%)	-
Continue to use method for long term contraception		-	117 (67.2%)	-
Pregnancy within index cycle (failure rate)		2 (1.2%)	1 (0.6%)	0.5 (NS)

*Statistically significant difference, NS: no statistically significant difference,
LNG: Levonorgestrel, IUD: Intrauterine device
#Percentages are of women who didn't continue to use long term contraceptive method after current cycle.

Table (3)
Satisfaction of participants among both groups:

	LNG group (n=162)	IUD group (n=174)	p-value
Satisfied	156 (96.3%)	171 (98.3%)	0.6 (NS)
Not satisfied	6 (3.7%)	3 (1.7%)	

NS: no statistically significant difference, LNG: Levonorgestrel, IUD: Intrauterine device

Discussion

Basically, there are two accepted methods for emergency contraception: the first one is hormonal methods and the second one is insertion of a postcoital intrauterine contraceptive device (IUCD). Hormonal method should be initiated within 72 hours of intercourse [3].

In the present study only 72/336 (21.4%) women have been present within 24 hours postcoital. In the study of Chen and colleagues [12], 82.7% of participants took the drug during the first 24 h after unprotected intercourse. This difference can be ascribed mainly to cultural difference and knowledge concerning emergency contraception. Time-effect relationship that was shown in few of previous reports [4, 13], was not seen in others studies [14 – 16] as same as the present study.

Results of most of previous results regarding efficacy and failure of levonorgestrel are consistent with the present study and prove the high efficacy of this regimen [4] while others show higher failure rates [17]. Gainer and colleagues have reported failure rate with the use of levonorgestrel about 1.3% [18] that is similar to the present study however rates low as 0.2 have been also reported [12].

Unlike levonorgestrel, we didn't find any differences in findings of previous reports regarding its efficacy. Reported failure rates were as low as reported in our study [19, 20]. Another recent meta-analysis in 2012 by Cleland et al., [21] has reported that IUD is highly effective method of EC with failure rate of 0.09%.

As regarding side effects, present findings were consistent with previous findings as no major side effects were reported with either method with only reported cases of tolerable gastrointestinal side effects with levonorgestrel [3, 4, 12]. The post-coital IUCD is associated with potential complications such as cramps, bleeding, infection, perforation, and expulsion [3]. This supports the findings of the present study. We have reported expulsion of IUD in three cases (1.7%) besides patients experienced heavy bleeding (27.6%) and irregular menses (12.1%).

The majority of the participants in the present study have resumed their menses within the expected time (59.3% and 62.1% in levonorgestrel group and IUD group respectively). Similarly in the 1998 WHO study [4], the onset of next menses for women taking the 2-dose levonorgestrel regimen shows that 15% of women having an early onset of menses, 57% having menses return within 3 days of the expected day, and 28% experiencing a delay of more than 3 days. In other trials, a higher frequency of women tended to have an early onset of menses. The time to resumption of menses may be affected by the timing of EC use related to the expected date of ovulation [15].

Menstrual patterns following use of levonorgestrel has been well studied in 2006 by Gainer and coworkers [18]. They have showed that Levonorgestrel emergency contraception is associated with significant but transient changes in menstrual patterns in a significant proportion of users [18].

As regarding acceptability of IUD as a method for EC, a total of 174/336 (51.8%) preferred to use IUD. An interest in IUD as EC has been previously evaluated by Schwarz et al., [22]. They have surveyed a total of 412 women who requested EC, 12% of them expressed interest in same-day insertion of an IUD. They have reported that interest in IUD as EC method among EC seekers increased with higher educational level.

Conclusion

Both levonorgestrel and IUDs are highly acceptable methods of contraception after unprotected intercourse. Because they are safe, highly effective with tolerable side effects. IUDs can be left in place as ongoing long contraception. Women of reproductive age should be provided with a prescription for hormonal EC in advance of need. We should recommend option of IUDs in the range of emergency contraception offered to patients presenting after unprotected intercourse, increasing both public and professional awareness of emergency contraception and on improving access to this important therapeutic intervention.

References

1. Shaikh S. Family Planning, Contraception and Abortion in Islam: Undertaking Khilafah: Moral Agency, Justice and Compassion. In: Maguire DC, editor. Sacred Choices: the Case for Contraception and Abortion in World Religions. Oxford: Oxford University Press; 2003.
2. Singh S, Darroch JE, Ashford L, et al, editors. Adding it up: the costs and benefits of investing in family planning and maternal and newborn health. New York (NY): Guttmacher Institute and United Nations Population Fund; 2009. p. 1-40.
3. Davis V and Dunn S. Emergency Postcoital Contraception. J Soc Obstet Gynaecol Can 2000;22(7):544-48
4. Task Force on Postovulatory Methods of Fertility Regulation. Randomized controlled trial of levonorgestrel versus the Yuzpe regimen of combined oral contraceptives for emergency contraception. Lancet 1998; 352:428–33.
5. World Health Organization. Medical Eligibility Criteria for Contraceptive Use. 3rd ed. Geneva; WHO; 2004, (Level III).
6. US Department of Health and Human Services. Food and Drug Administration. Prescription drug products; certain combined oral contraceptives for use as post-coital emergency contraception. Federal Register 1997; 62:8610–2.
7. Glasier A,Thong KJ,Dewar M, Mackie M, Baird D. Mifepristone (RU486) compared with high-dose estrogen and progestogen for emergency post-coital contraception. N Engl J Med 1992; 327:1041–4.
8. Cheng L, Gülmezoglu AM, Piaggio G, Ezcurra E, Van Look PFA. Interventions for emergency contraception. Cochrane database Sys Rev. 2008, Issue 2
9. Lippes J, Malik T,Tatum HJ.The postcoital copper-T. Adv Plan Parent 1976;11:24–9.
10. Dunn S and Guilbert E. Emergency Contraception. J Obstet Gynaecol Can 2012;34(9):870–878
11. Fleiss JL. Statistical Methods for Rates and Proportions. John Wiley & Sons, Inc., New York, 1981.
12. Chen Q, Xiang W, Zhang D, Wang R, Luo Y, Kang J, Cheng L. Efficacy and safety of a levonorgestrel enteric-coated tablet as an over-the counter drug for emergency contraception: a Phase IV clinical trial. Human Reproduction. 2011;.26(9): pp. 2316–2321.
13. Piaggio G, von Hertzen H, Grimes DA,Van Look PFA.Timing of emergency contraception with levonorgestrel or the Yuzpe regimen. Lancet 1999; 353:721.
14. von Hertzen H, Piaggio G, Ding J, Chen J, Song S, Bartfai G, et al. Low dose Mifepristone and two regimens of levonorgestrel for emergency contraception: a WHO multicentre randomized trial. Lancet 2002; 360:1803–10.
15. Ellertson C, Evans M, Ferden S, Lead better C, Spears A, Johnstone K, et al. Extending the time limit for starting the Yuzpe regimen of emergency contraception to 120 hours. Obstet Gynecol 2003; 101:1168-71.
16. Task Force on Postovulatory Methods of Fertility Regulation. Comparison of three single doses of Mifepristone as emergency contraception: a randomized trial. Lancet 1999;353:697–702
17. Trussell J, Ellertson C, Dorflinger L. Effectiveness of the Yuzpe regimen of emergency contraception by cycle day of intercourse: implications for mechanism of action. Contraception 2003;67:167–71.
18. Gainer E, Kenfack B, Mboudou E, Doh A, Bouyer J. Menstrual Bleeding Patterns Following Levonorgestrel Emergency Contraception. Contraception. 2006; 74(2): 118-24
19. Trussell J and Raymond E. Emergency Contraception: A Last Chance to Prevent Unintended Pregnancy. 2009 (Accessed September 2012, at http://ec.princeton.edu/questions/ec-review.pdf)
20. Wu S, Godfrey EM, Wojdyla D, Dong J, Cong J, Wang C, von Hertzen H. Copper T380A intrauterine device for emergency contraception: a prospective, multicentre, cohort clinical trial. BJOG. 2010; 117(10): 1205-10.
21. Cleland K, Zhu H, Goldstuck N, Cheng L, Trussell J. The efficacy of intrauterine devices for emergency contraception: a systematic review of 35 years of experience. Hum. Reprod. 2012
22. Schwarz EB, Kavanaugh M, Douglas E, Dubowitz T, Creinin MD. Interest in Intrauterine Contraception Among Seekers of Emergency Contraception and Pregnancy Testing. Obstet Gynecol. 2009; 113(4): 833 – 839.

Cervical cerclage versus weekly progesterone injection in prevention of preterm labor

Abdel-Samie Abdel- Moneim*, Mahmoud El-Seheimy**, Wael Samir*, Hazem G.Abdel-Hamid*, Ahmed Taha Abdel Fatth****
*Faculty of Medicine, Fayoum University, OB/GYN Department.
***Faculty of Medicine, AL-Azhar University, Assiut, OB/GYN Department
**** Faculty of Medicine, AL-Azhar University, Cairo, OB/GYN Department

Abstract

Objective: Prematurity is the leading cause of neonatal death and handicap. Although all births before 37 weeks of gestation are defined as preterm, most damage and death occurs in infants delivered before 34 weeks. Improvements in neonatal care have led to higher rates of survival among very premature infants, but a major effect on the associated mortality and morbidity will be achieved by better Identification of women at high risk for preterm delivery and by development of an effective intervention to prevent this complication. The aim of this study is to compare the effect of weekly progesterone injection and cervical cerclage on the outcomes of pregnancy in patients with history of preterm labor.

Materials & Methods: The study comprised of 80 patients involved in the study then, 20 patients were excluded from the study due to different causes. Patients were randomly allocated to two groups. Randomization was done by sealed envelopes. **Group A:** (30 patients); in this group we had given them 17 OH progesterone (cidulot depot 250 mg) IM weekly starting from 16-20 Weeks till 36 weeks gestation. **Group B:** (30 patients); in this group we had done cervical cerclage operation at 14 weeks. First we assessed the effect of cidulot depot on the gestational age in comparison to the gestational age at previous preterm deliveries in group A. Secondly we assessed the effect of cervical cerclage on the gestational age in comparison to the gestational age at previous preterm deliveries in group B. The primary outcome was the gestational age at time of delivery documented by the LMP and abdominal US. The secondary outcomes were the need to the tocolytic therapy, estimated fetal weight at the time of delivery, the neonatal outcome regarding admission to the incubator or the need to ICU admission and neonatal mortality.

Results: of the study were analyzed, matched and compared.

Conclusion: We concluded that the prophylactic administration of progesterone beginning in mid-gestation to women who previously had a preterm birth has been shown to reduce the rate of recurrence. Also use of prophylactic cervical cerclage reduces preterm labor but the preference of which method remains an area of discussion.

Key Words: Preterm labor, 17-OH progesterone, cervical cerclage.

Introduction

Preterm birth, defined as childbirth occurring at less than 37 weeks. Preterm labor is a major determinant of neonatal mortality and morbidity and has long term adverse consequences on health (1). Preterm birth rates have been reported to range from 5% to 7% of live births in some developed countries, but are estimated to be substantially higher in developing countries (2).

These figures appear to be on the rise. Events leading to preterm birth are still not completely understood, although the etiology is thought to be multifactorial. It is, however, unclear whether preterm birth results from the interaction of several pathways or the independent effect of each pathway. Causal factors linked to preterm birth include medical conditions of the mother or fetus, genetic influences, environmental exposure, infertility

treatments, behavioral and socioeconomic factors and iatrogenic prematurity (3).

Children who are born prematurely have higher rates of cerebral palsy, sensory deficits, learning disabilities and respiratory illnesses compared with children born at term. The morbidity associated with preterm birth often extend to later life, resulting in enormous physical, psychological and economic cost (4). Although progesterone is known to have many actions beneficial to the maintenance of pregnancy, the exact mode of action of 17 alpha hydroxyprogesteronecaproate therapy in preventing preterm labor is not known (5). Intervention with weekly progesterone injections (250 mg 17 alpha hydroxyprogesteronecaproate (17OHPC) from 16–20 weeks up to 36 weeks of gestation had been chosen as it has been proven that this prophylactic administration of 17OHPC injections is effective in reducing the preterm birth rate in singleton pregnancies at high risk for spontaneous preterm delivery but, there are no data on the effectiveness of progesterone in the prevention of preterm birth in multiple pregnancy.(6).

In four trials that compared elective cerclage versus no cerclage or bed rest, no overall reduction in total pregnancy loss and early pregnancy loss (less than 24 weeks' gestation) was observed in the women who underwent cerclage [relative risk (RR) 0.86; 95% confidence interval (CI) 0.59–1.25]. There were also no overall significant differences between preterm delivery rates (RR 0.88; 95% CI 0.76–1.03). The largest among the four trials was coordinated by MRC/RCOG and this trial yielded a small reduction in births under 33 weeks of gestation (RR 0.75; 95% CI 0.58–0.98) (7).

The aim of this study is to compare the effect of cervical cerclage and weekly progesterone injection on outcome of pregnancy in patients with past history of preterm labor.

Subjects and methods

The patients were selected from the outpatient clinics in Fayoum, kaser Al- Alini and AL-Azhar university hospitals. 60 patients were involved in this study and the study started in Jun 2011 for a period of two years.

Inclusion criteria:

- Age of patients between 20-40years.
- Single living fetus at least
- The patient has history of preterm labour (preterm labour between 28 weeks and 34 weeks) once or more.
- Intact membrane.
- Time of inclusion at 12 weeks gestational age .
- Non smokers or Alcoholic women .
- Average BMI 20-25.
- Women are getting pregnant spontaneously or by induction of ovulation but not by ART.
- Women not known to have uterine anomalies documented by previously done HSG.
- No history of Scarred uterus (previous CS or myomectomy).
- Not known diabetic patient or hypertensive.
- No history of ablative or excision procedures of the cervix.

Exclusion criteria:

- Cervical length less than 2.5cm during antenatal period.
- Congenital anomalies in the fetus discovered during the follow up.
- Myoma with pregnancy.
- Polyhydramnios.
- Rupture of membranes during follow up
- Placenta previa diagnosed during the follow up.
- Accidental hemorrhage happens during the follow up.
- IUFD.
- Medical disorders predisposing to preterm delivery.

All the patients will be submitted to the following steps:

- Informed consent was taken from each patient.
- Full history.
- General, abdominal examination and obstetric ultrasound for checking the number of the fetuses, viability, gestational age and placental location.
- Routine antenatal investigations.
- Single course dexamethasone 12 mg IM every 12 hours for 48hs for improvement of fetal lung maturity given at gestational age 32 weeks.
- Documentation of receiving tocolytic drugs or not and time of delivery.

First, we selected 80 patients involved in the study then, 20 patients were excluded from the study due to different causes. Patients were randomly allocated to two groups. Randomization was done by sealed envelopes.

Group A: (30 patients); in this group we had given them 17 OH progesterone (cidulot depot 250 mg) IM weekly starting from 16-20 Weeks till 36 weeks gestation. **Group B:** (30 patients); in this group we had done cervical cerclage operation at 14 weeks.
First we assessed the effect of cidulot depot on the gestational age in comparison to the gestational age at previous preterm deliveries in group A. Secondly we assessed the effect of cervical cerclage on the gestational age in comparison to the gestational age at previous preterm deliveries in group B.
then, we compared between the 2 groups regarding:
The primary outcome was the gestational age at time of delivery documented by the LMP and abdominal US. The secondary outcomes were the need to the tocolytic therapy, estimated fetal weight at the time of delivery, the neonatal outcome regarding admission to the incubator or the need to ICU admission and neonatal mortality.

Statistical analysis:

Results were expressed as means ±standard deviation of the means (SD) or number (%).Comparison between different parameters in the two studied groups was performed using unpaired T test. Comparison between categorical data was performed using Chi square test. The data were considered significant if P value was equal to or less than 0.05and highly significant if P value<0.01. Statistical analysis was performed with the aid of the SPSS computer program.

Results

Table (1)
Mean age in the two studied groups.

	Cidulotdepot group(n=30)	Cerclage group (n=30)	P value
Age (yrs.)	27.43±4.00	27.77±3.48	0.732(NS)

Table (2)
Gravidity and parity in the two studied groups.

	Cidulot depot group (n=30)	Cerclage group (n=30)	P value
G2P1	14 (46.67%)	11 (36.67%)	0.272 (NS)
G3P1	0 (0%)	2 (6.66%)	
G3P1A1	2 (6.67%)	5 (16.67%)	
G3P2	9 (30%)	7 (23.33%)	
G4P1A2	1 (3.33%)	0 (0%)	
G4P2A1	2 (6.67%)	2 (6.67%)	
G4P3	2 (6.67%)	0 (0%)	
G5P2A2	0 (0%)	1 (3.33%)	
G5P3A1	0 (0%)	2 (6.67%)	

Table (3)
GA in previous delivery in comparison to GA at current delivery (weeks) in group A (Cidulot depot group).

	Previous delivery	Current delivery	P value
< 34	30 (100%)	6 (20%)	0.001**
≥ 34	0 (0%)	24 (80%)	

Table (4)
GA in previous delivery in comparison to GA at current delivery (weeks) after cerclage in group B (Cerclage group).

	Previous delivery	Current delivery	P value
< 34	30 (100%)	10 (33.3%)	0.001**
≥ 34	0 (0%)	20 (66.7%)	

Table (5)
Mean gestational age in the two studied groups.

	Cidulot depot group (n=30)	Cerclage group (n=30)	P value
Gestational age (wks.)	36.33 ± 2.51	34.60 ± 2.55	0.010**
< 37 wks.	11 (36.67%)	20 (66.67%)	P= 0.020* RR= 0.5500 95% CI= 0.3224 -0.9382
≥ 37wks	19 (63.33%)	10 (33.33%)	

RR= Relative risk CI= confidence interval*p< 0.05= significant.**p< 0.01= highly significant

Table (6)
Need for Tocolysis between the two studied groups.

	Cidulot depot group (n=30)	Cerclage group (n=30)	P value
Positive	7 (23.33%)	25 (83.33%)	P= 0.001** RR= 0.2800 CI= 0.1436 - 0.5461
Negative	23 (76.67%)	5 (16.67%)	

Table (7)
Fetal birth weight in the two studied groups.

	Cidulot depot group (n=30)	Cerclage group (n=30)	P value
FBW (kg.)	2.58 ± 0.66	2.26 ± 0.64	0.065 (NS)
< 2.5 kg	8 (26.67%)	14 (46.67%)	0.108 (NS) RR = 0.5714 95 % CI= 0.2821 - 1.1577
≥ 2.5 kg	22 (73.33%)	16 (53.33%)	

Table (8)
Need for NICU admission in the two studied groups

	Cidulot depot group (n=30)	Cerclage group (n=30)	P value
Positive	8 (26.67%)	13 (43.33%)	0.176 (NS) RR= 0.6154 95% CI= 0.2993 - 1.2653
Negative	22 (73.33%)	17 (56.67%)	

Table (9)
Neonatal deaths in the two studied groups.

	Cidulot depot group (n=30)	Cerclage group (n=30)	P value
Positive	5 (16.7%)	11 (36.7%)	0.080 (NS) RR= 0.4545 95% CI= 0.1797 - 1.1499
Negative	25 (83.3%)	19 (63.3%)	

Discussion

Preterm labor defined as childbirth occurring at less than 37 weeks is estimated to annually affect approximately 12.9 million births or 9.7% of all births worldwide. Although the prognosis of preterm infants has significantly improved through recent developments in neonatal medicine, complications and aftereffects influencing preterm infants are still a major concern not only for medical management but also for the medical cost of neonatal care(8) Prematurity is the leading cause of neonatal death and handicap. Although all births before 37 weeks of gestation are defined as preterm, most damage and deaths occurs in infants delivered before 34 weeks. Progesterone has an important role in maintaining quiescence acting to reduce calcium influx to smooth muscles through suppression of calcium-calmodulin-myosin light chain kinase system. In four trials that compared elective cerclage versus no cerclage or bed rest, no overall reduction in total pregnancy loss was observed in women who underwent cerclage (7).

In study done by Groom et al 2004 comparison between elective cerclage in the first trimester and the control group but in this control group cerclage done only if short cervix proved by serial vaginal ultrasound done in the second trimester. this is done to be matched with the ethics of research (9). So the results showed no difference between both groups regarding the gestational age at time of delivery and cerclage is indicated to the ultrasound finding of short cervix .In present study cerclage is done based on history indication and not on ultrasound indication and done at 13- 14 weeks and is found to improve the gestational age at time of delivery.

Alfirevic et al., 2004 (10) selected the high-risk group for early preterm delivery depending on the transvaginal sonographic measurement of cervical length. They undertook a multicenter randomized controlled trial to investigate whether, in women with a short cervix identified by routine transvaginal scanning at 22-24 weeks' gestation, the insertion of a Shirodkar suture reduces early preterm delivery. Cervical length was measured in 547pregnant women. One hundred and twenty three women were excluded. The cervix was 15 mm or less in 470, and 253 (54%) of these women participated in the study and were randomized to cervical cerclage (127) or to expectant management (126) no cerclage. Primary outcome was the frequency of delivery before 33 completed weeks of pregnancy. The results were the proportion of preterm delivery before 33 weeks was similar in both groups, 22% (28 of 127) in the cerclage group versus 26% (33 of 126) in the control group (relative risk=0.84, 95% CI 0.54-1.31, p=0.44), with no significant differences in perinatal or maternal morbidity or mortality. They concluded that the insertion of a Shirodkar suture in women with a short cervix does not substantially reduce the risk of early preterm delivery. In this study we see that the cerclage has no significant benefit even in cases with short cervix.(Alfirevic et al.,2004) .This is in contrast to present study, cerclage improved the gestational age depending on history of preterm labour.

Berghella et al 2005 (11) carried out A meta-analysis of trials of women with singleton gestations and second-trimester transvaginal sonographic CL < 25 mm randomized to cerclage or no cerclage. The degree of CL shortening was correlated to the efficacy of cerclage in preventing preterm birth. There was a significant reduction in preterm birth < 35 weeks in the cerclage compared with no cerclage groups in 208 singleton gestations with both a previous preterm birth and CL < 25 mm (relative risk, 0.61; 95% CI, 0.40-0.92). In these women, preterm birth < 37 weeks was significantly reduced with cerclage for CL more than15 mm and < 25 mm. None of the analyses for 344 women without a previous preterm birth was significant. They concluded that cerclage, when performed in women with a singleton gestation, previous preterm birth and cervical length < 25 mm, seems to have a similar effect regardless of the degree of cervical shortening, including CL 16-24 mm. In this study the comparison between 2 groups, both having short cervix, one group undergo cerclage and the other group no cerclage and the study shows that the cerclage improves the pregnancy outcome regardless the degree of cervical shortening.This study goes in favor with our study, where cerclage improves the gestational outcome of patients with history of preterm labour.

Meis et al 2003 (6) conducted a double-blind, placebo-controlled trial involving pregnant women with a documented history of spontaneous preterm delivery. Women were enrolled at 19 clinical centers at 16 to 20

weeks of gestation and randomly assigned by a central data center, in a 2:1 ratio, to receive either weekly injections of 250 mg of 17P or weekly injections of an inert oil placebo; injections were continued until delivery or to 36 weeks of gestation. The primary outcome was preterm delivery before 37 weeks of gestation. Analysis was performed according to the intention-to-treat principle. Base-line characteristics of the 310 women in the progesterone group and the 153 women in the placebo group were similar. Treatment with 17P significantly reduced the risk of delivery at less than 37 weeks of gestation (incidence, 36.3 percent in the progesterone group vs. 54.9 percent in the placebo group; relative risk, 0.66 [95 percent confidence interval, 0.54 to 0.81]), delivery at less than 35 weeks of gestation (incidence, 20.6 percent vs. 30.7 percent; relative risk, 0.67 [95 percent confidence interval, 0.48 to 0.93]), and delivery at less than 32 weeks of gestation (11.4 percent vs. 19.6 percent; relative risk, 0.58 [95 percent confidence interval, 0.37 to 0.91]). Infants of women treated with17 P had significantly lower rates of necrotizing enterocolitis, intraventricular hemorrhage, and need for supplemental oxygen.

Meis et al 2003 (6) concluded that weekly injections of 17P resulted in a substantial reduction in the rate of recurrent preterm delivery among women who were at particularly high risk for preterm delivery and reduced the likelihood of several complications in their infants. So there is difference between our study and Meis et al 2003, as the second group in our study did not take placebo but undergo cervical cerclage. Our study Support the results of Meis t al 2003 regarding that 17 OH progesterone reduce the rate of preterm labor and decrease the infant morbidity and mortality and when 17OH progesterone compared to cerclage ,progesterone was better regarding the gestational age with (RR=0.5500 ,95% CI= 0.3224 -0.9382) and less need for tocolysis with RR= 0.2800, CI= 0.1436 - 0.5461). Moustafa Ibrahim 2009 has compared between 2 groups. Both have history of spontaneous preterm labor .One group received cidulot depot 250 mg (17 hydroxy progesterone) once weekly and the other group received placebo (12).

According to Moustafa Ibrahim 2009 (11), the mean age in progesterone group was 25.32±4.15 vs. 25.60±3.85years in placebo group with no significant difference (P>0.05) between both groups. Gravidity in progesterone group was 3.96±1.06 vs. 4.08±0.997 in placebo group with no significant difference (P>0.05). The mean gestational age was 37.47±1.559 in progesterone group vs. 34.71±2.49 in placebo group (P<0.05). In the progesterone group 8 of 25 women delivered before completion of 37 weeks of gestation (32%) and 17 women delivered full term (68%). In placebo group 13 of 25 women delivered before completion of 37weeks of gestation (52%) and 12 women delivered full term (48%).

Fetal birth weight (FBwt) in progesterone group was 2988.00±477.031 vs. 2702.00±501.140 in placebo group with significant difference (P>0.05) while an increase in the rate of fetal birth weight over 2500g that occurred in progesterone group was 20 (80%) vs. 15 (60%) in placebo group. Three of neonates in progesterone group needed NICU for different causes and represented 12% vs. 9 and represented 36% in placebo group. Also 1 neonatal death occurred in progesterone group and represented 4% vs. 4 and represented 16% in placebo group with significant difference (P<0.05) between two groups. The results of Moustafa study demonstrated the positive effect of injectable progesterone on the incidence of preterm labor. Delivery at <37 gestational weeks was reduced by 20% compared with the placebo group. Similar reductions were seen in delivery less than 34weeks. Additionally, he had demonstrated that patient compliance with the use of the inexpensive injectable progesterone is not of concern (12).

The results of our study support Moustafa Ibrahim study 2009 as the progesterone improve the gestational age in group A with the mean gestational age in our study is 36.33 ± 2.51and higher in Mostafa Ibrahim study in the same group 37.47±1.559. Regarding the fetal weight the mean Fetal birth weight (FBwt) in progesterone group was 2988.00±477.031 and the mean FBW in our study in group A(injectable progesterone) 2.58 ± 0.66 and the rate of fetal birth weight over 2500g that occurred in progesterone group according to Mostafa Ibrahim study 2009 was 20 (80%) and according to our study 22 (73.33%)(12).

Condo et al 2013 (13) had done a retrospective indirect comparison between progesterone and cervical cerclage in prevention of preterm labor as no randomized controlled trial has compared vaginal progesterone and cervical cerclage directly for the prevention of preterm birth in women with a sonographic short cervix in the mid trimester, singleton gestation, and previous spontaneous preterm birth. Condo et al 2013 performed an indirect comparison of vaginal progesterone versus cerclage using placebo/no cerclage as the common comparator .They taken four studies that evaluated vaginal progesterone versus placebo (158 patients) and 5 studies that evaluated cerclage versus no cerclage (504 patients) were included in women with a sonographic short cervix in the mid trimester, singleton gestation, and previous spontaneous preterm birth. Both interventions were associated with a statistically significant reduction in the risk of preterm birth at <32 weeks of gestation and composite perinatal morbidity and mortality compared with placebo/no cerclage. Adjusted indirect meta analyses did not show statistically significant differences between vaginal progesterone and cerclage in the reduction of preterm birth or adverse perinatal outcomes. Based on state-of-the-art

methods for indirect comparisons, either vaginal progesterone or cerclage are equally efficacious in the prevention of preterm birth in women with a sonographic short cervix in the mid trimester, singleton gestation, and previous preterm birth. Selection of the optimal treatment needs to consider adverse events, cost and patient/clinician preferences (13).This study goes in contrast to our study as our study is direct comparison between cerclage and progesterone and our study shows that progesterone is better than cerclage regarding the gestational age and less need for tocolysis
17 OH progesterone 250 mg weekly IM injection starting at 16- 20 weeks gestational age and prophylactic cervical cerclage operation reduce the recurrence of preterm labor. 17 OH progesterone 250 mg weekly IM injection more superior as this method was associated with longer gestational age at time of delivery, less need to tocolysis and patient's compliance is good. Moreover more complications associated with cerclage regarding need to tocolysis.

References

1. Huddy CL, Johnson A, Hope PL 2001: Educational and behavioral problems in babies of 32–35 weeks gestation. Arch Dis Child Fetal Neonatal Ed; 85: 23F-8.
2. Cousens SN, Darmstadt GL, Bhutta ZA, et al 2006: Neonatal Survival Series Lancet367:1541-7.
3. Goldenberg RL, Culhane JF, Iams JD, et al 2008: Epidemiology and causes of preterm birth. Lancet. Vol. 371, No. 9606, pp 75-84.
4. Petrou S, Mehta Z, Hockley C, Cook-Mozaffari P, et al 2003: The impact of preterm birth on hospital inpatient admissions and costs during the first 5 years of life. Pediatrics; 112:1290.
5. Meis PJ, 2005:17- hydroxyprogesterone for the prevention of preterm delivery. Obstet Gynecol.105 (5 pt 1): 1125-28.
6. Meis PJ, Klebanoff M, Thom E, et al 2003: Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesteronecaproate. N Engl J Med, 348.
7. MRC/RCOG 1993: Working Party on Cervical Cerclage. Final report of the Medical Research Council/ Royal College of Obstetricians and Gynaecologists multicenter randomized trial of cervical cerclage. Br J ObstetGynaecol; 100:516-23.
8. Beck S,Wojdyla D,Say L,Betran AP,Merialdi M.,et al,2010 : The worldwide incidence of preterm birth:a systematic review of maternal mortality and morbidity. Bull World Health Organ.2010 jan;88(1):31-8.
9. Groom KM, Bennett PR, Golara M, et al 2004: Elective cervical cerclage versus serial ultrasound surveillance of cervical length in a population at high risk for preterm delivery. Eur J ObstetGynecolReprod Biol. Feb 10;112(2):158-61.
10. Alfirevic Z, To MS, Heath VC, et al 2004: Cervical cerclage for the prevention of preterm delivery in women with short cervix:randomised controlled trial. Lancet 363; 1849-53.
11. Berghella V, Odibo AO, To MS, et al 2005: Cerclage for short cervix on ultrasonography: Meta-analysis of trials using individual patient-level data. Obstet Gynecol106 (1):181.
12. Moustafa Ibrahim 2009: Progesterone supplementation for prevention of preterm labor: A randomized controlled trial. Department of Obstetrics and Gynecology Faculty of Medicine, Ain Shams University,
13. Conde-Agudelo A, Romero R, Nicolaides K, et al 2013: Vaginal progesterone vs. cervical cerclage for the prevention of preterm birth in women with a sonographic short cervix, previous preterm birth, and singleton gestation: a systematic review and indirect comparison metaanalysis. Am J Obstet Gynecol. Jan;208(1):42.e1-42.e18

NEWS AND VIEWS

Compiled and abstracted by prof. Ahmed Badawy, MD FRCOG PhD

- **Do clothes make the doctor? U-M researchers report on patient perceptions of physicians based on attire**

University of Michigan Health System, 02/11/2015

Age, culture & type of care matter – and new survey will look at impact further. What should doctors wear? And how does something as simple as their choice of a suit, scrubs or slacks influence how patients view them? A new analysis takes a comprehensive look – and finds that the answer isn't as simple as you might think. It also finds that doctors don't seem to be getting a lot of guidance on how to dress – despite the influence their attire can have on patients' perceptions. In general, the study finds, people prefer their physicians dress on the formal side – and definitely not in casual wear. Doctors of either gender in suits, or a white coat, are more likely to inspire trust and confidence. But fashion takes a back seat when it comes to emergency, surgical or critical care, where data show clothes don't matter as much – and patients may even prefer to see doctors in scrubs. In general, Europeans and Asians of any age, and Americans over age 50, trusted a formally dressed doctor more, while Americans in Generation X and Y tended to accept less–dressy physicians more willingly. The findings were compiled by a University of Michigan Health System team, from a comprehensive international review of studies on physician attire, and other sources. In all, the data they reviewed came from 30 studies involving 11,533 adult patients in 14 countries. Their review has been published in British Medical Journal Open.

- **1.Metformin use in patients undergoing in vitro fertilization treatment: Results of a worldwide web-based survey**

Journal of Assisted Reproduction and Genetics, 02/24/2015 by Christianson MS, et al.

In this study, authors wanted to identify trends regarding therapeutic approaches to metformin administration in patients undergoing in vitro fertilization (IVF) treatment worldwide. While metformin is used worldwide as an adjunct to standard IVF protocols, there is much variation in its use and the majority of centers report lack of evidence supporting its use.

- A retrospective evaluation utilizing the results of a web–based survey, IVFWorldwide (www.IVF–worldwide.com/), was performed.
- Responses from 101 centers performing a total of 50,800 annual IVF cycles were performed.
- Of these cycles, 10.4 % (n = 5,260) reported metformin use during IVF cycles.
- Indications for metformin use in IVF cycles included polycystic ovary syndrome (PCOS) patients who were habitual abortions (67 %), had prior poor egg quality (61 %), had high serum insulin levels (56 %).
- Less reported was PCOS with obesity/anvoulation (29 %), PCOS with multiple manifestations (23 %) and glucose intolerance and insulin resistance (23 %).
- Over half of cycles (54 %) treated patients with metformin up to 3 months prior to starting IVF.
- A majority (82 %) of IVF cycles utilized 1500–2000 mg/day of metformin.
- A nearly equal percentage of centers continued metformin up to a positive β–HCG test (35 %) or to 12 weeks gestation (33 %).
- 70 % of IVF cycles reported increased pregnancy rates and decreased miscarriage rates due to the use of metformin.
- 75 % reported the data in the literature is not sufficient for reaching a definitive conclusion concerning metformin treatment in patients undergoing IVF.

- **Assisted reproductive technology and somatic morbidity in childhood: A systematic review**

Fertility and Sterility, 02/06/2015 by Kettner LO, et al.

The authors want to assess whether children conceived by assisted reproductive technology are at increased risk of somatic morbidity in childhood compared with spontaneously conceived children. Children conceived by assisted reproductive technology may be at increased risk of somatic morbidity in childhood compared with spontaneously conceived children, although some inconsistency exists between study results.

- **1.Impact of metformin on Anti-Mullerian Hormone in women with PCOS: A secondary analysis of a randomized controlled trial.**

Acta Obstetricia et Gynecologica Scandinavica, 02/26/2015 by Madsen HN, et al.

- Comparing individual metformin/placebo AMH values, a small absolute decrease of 9.3 pmol/l (p=0.03) was observed in obese women after six months relative to baseline, suggesting a trend toeards decreasing values after metformin treatment, mainly in obese women.
- Conclusions on the effect of metformin on circulating anti–Mullerian hormone (AMH) levels in women with polycystic ovary syndrome (PCOS) are ambiguous.

- Authors performed a secondary analysis of a randomized, double–blind, placebo–controlled cross–over trial.
- Fifty–six women with hyperandrogenemic PCOS were included.
- Each woman served as her own control receiving a daily dose of either 1700 mg metformin or placebo for six months. After a three months wash–out period they received the opposite treatment. The decrease in AMH from a median of 49.5 to 46.9 pmol/l after six months on metformin was overall not significant (p=0.81), nor were changes in obese women (49.5 to 38.2 pmol/l; p=0.53).

- **1.Luteal phase supplementation after gonadotropin-releasing hormone agonist trigger in fresh embryo transfer: the American versus European approaches**

Fertility Sterility, February 11, 2015 by Peter Humaidan

The challenges in attaining an adequate luteal phase after GnRH agonist (GnRHa) trigger to induce final oocyte maturation have resulted in different approaches focused on rescuing the luteal phase insufficiency so that a fresh transfer can be carried out without jeopardizing IVF outcomes. Over the years, two different concepts have emerged: intensive luteal support with aggressive exogenous administration of E2 and P; and low-dose hCG rescue in the form of a small dose of hCG either on the day of oocyte retrieva or on the day of GnRHa trigger (the so called "dual trigger"). Both approaches have been shown to be effective in achieving pregnancy rates similar to those obtained after conventional hCG trigger and resulting in a very low risk of ovarian hyperstimulation syndrome (OHSS). Although the idea of freezing all embryos after GnRHa trigger and transferring them in a subsequent frozen-thawed cycle has been gaining momentum, a fresh transfer leading to the live birth of a healthy child is currently considered to be the goal of IVF treatment.

- **1.Risk of uterine perforation with levonorgestrel-releasing and copper intrauterine devices in the European active surveillance study on intrauterine devices**

Contraception, 01/30/2015 by Heinemann K, et al.

In this study, authors want to identify and compare the incidence of uterine perforation and other medically adverse events associated with levonorgestrel–releasing IUDs (LNG–IUSs, releasing 20 mcg LNG daily) and copper IUDs under routine conditions of use in a study population representative of typical users. Uterine perforation incidence in this study was low, with a benign clinical course thereafter. The LNG–IUS and copper IUDs did not have clinically important differences in perforation rates.

- **1.Age at menopause in women with type 1 diabetes mellitus: The OVADIA study**

Human Reproduction, 01/26/2015 by Yarde F, et al.

In this study, authors want to explore the type 1 diabetes a determinant of advanced ovarian ageing, resulting in an early age at natural menopause. No clear evidence was provided that type 1 diabetes is a determinant of accelerated ovarian ageing resulting in an early menopause.

A cross–sectional study was performed in 140 post–menopausal women with, and 5426 post–menopausal women without, diabetes. Both women with and without diabetes had experienced natural menopause. Study participants filled out a standardized questionnaire including report of their age at last menstrual period. Differences in menopausal age were analysed using linear regression analyses, with adjustment for possible confounders.

Mean age at natural menopause was 49.8 ± 4.7 years in women with type 1 diabetes and 49.8 ± 4.1 in women without diabetes. Linear regression analyses showed that type 1 diabetes was not associated with an earlier menopause compared with the reference group without diabetes, after adjustment for age, smoking history and parity (difference in age at menopause between women with type 1 diabetes and reference group 0.34 years, 95% confidence interval –0.34, 1.01).

- **1.Impact of newly diagnosed endometrial polyps during controlled ovarian hyperstimulation on IVF outcomes**

Journal of Minimally Invasive Gynecology, 01/23/2015 by Elias RT, et al.

In this study, authors want to investigate the impact of newly diagnosed endometrial polyps during controlled ovarian hyperstimulation (COH) on the outcomes of fresh in vitro fertilization (IVF)–embryo transfer (ET) cycles. Newly diagnosed endometrial polyps during COH is associated with an increased biochemical pregnancy rate, but ultimately does not adversely impact clinical pregnancy or live birth rates after fresh IVF–ET.