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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

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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.

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Contents :

Letter from the Editor:

Dear colleagues,

Happy New Year 2020. Very interesting subjects are included in this issue. The importance of treatment of iron deficiency anaemia after bariatric surgery and before pregnancy. There is a remarkable reduction in the level of AMH after laparoscopic cystectomy of endometrioma. The beneficial effect of sildenafil citrate in pregnancies at high risk for fetal growth restriction. It increases blood flow in the umbilical arteries and normalizes blood flow in fetal middle cerebral arteries restoring a normal fetal circulation and corrects the "brain sparing" adaptive mechanism. It is recommended using electrical bipolar vessel sealing clamp during vaginal hysterectomy. It showed less pain on the first few hours after surgery but not in the following days, shorter operative time, less operative blood loss. Mini laparotomy is a suitable option for the management of benign gynecologic conditions in patients with high BMI. Treatment of adolescent PCOS patient with L-carnitine help in regaining regular cycles and proved to be efficient in decreasing BMI. We welcome your comments.

Best regards.

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Timing of endometrial scratching for women undergoing ICSI: A randomized clinical trial

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Abstract

Aim: To determine the optimum time for endometrial scratching in patients with unexplained primary infertility undergoing ICSI-ET cycles after one or more implantation failure.

Methods: A randomized clinical trial wasconducted at fertility care unit, Mansoura University Hospital and 2 private fertility centers, Egypt, fromNovember 2016 tillJune 2018. Eligible participants [142] had unexplained primary infertility, were prepared and scheduled to obligate for ICSIcycles. Patients were randomly allocated into two equal groups using computer-generated tables and sealed opaque envelopes. Endometrial scratching was done either just after oocyte retrieval in (group 1) or mid-luteal in the cycle before induction (group 2). Patients, investigators, and data analysts were not masked to group assignment. The primary outcome measure was implantation rate while the clinical pregnancy rate was settled as the secondary outcome measure.

Results: one hundred forty two clients were included (71 in each group). Baseline characteristics did not differ between both groups as regard the age, BMI, duration of infertility and basic laboratory investigations ($p>0.05$). The mean estimated day of triggering (14.2 ± 2.1 in G1 vs 13.6 ± 2.2 in G2) together with the mean follicular size (19.3 ± 0.8 in G1 vs 18.5 ± 1.8 in G2) showed also no statistical significance (p values 0.690 and 0.751 respectively). Again, the mean estimated number of ova retrieved (7.4+ 2.1 in G1 vs 7.1+ 1.3 in G2) and zygote transferred (2 in each group) presented no significant differences together with the chemical pregnancy rates (54 in G1 vs 52 in G2, $p>0.05$). On the other hand, IR and CPR are found significantly higher in group 1 compared to group 2, (IR 53.5% vs, 40.8%; whilst CPR 49.3% vs 35.2%, $p<0.05$).

Conclusion: retrieval day endometrial scratching seemed to improve clinical pregnancy and implantation rates than does mid-luteal endometrial scratching in patients with unexplained infertility.

Keywords: Endometrial Scratch, retrieval day, IVF/ICSI cycles.

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INTRODUCTION

Embryos' implantation within the endometrial cavity is actually a critical step in assisted reproductive techniques (ART). Previous researches have suggested that intentional endometrial damage, scratching, might increase the probability of pregnancy in women undergoing ART especially in those who had repeated failed im-

plantation inspite of good quality embryos transfer [1]. For a genetically normal blastocyst to implant successfully, it should hatch, appose, adhere, penetrate, and then finally invade a well-synchronized endometrium prepared by estrogens and progesterone [2, 3]. For this synchronization to occur, a number of locally acting molecules, namely, growth factors, cytokines, matrix metalloproteinase, adhesion molecules, extracellular matrix components, should be present in sufficient amounts and endometrial scratching (ES) is supposed to enhance the presence of these molecules [2-5].The usual timing to perform ES was commonly thought to be one week before starting IVF, ICSI treatment in cases of repeated implantation failure with no available evidence supporting its use for those going through first IVF/ICSI cycles as it perhaps do more harm than a good effect [3]. Some authors demonstrated a significant doubling of the implantation rate (IR), clinical pregnancy rate (CPR) and live birth rates in patients who underwent ES in the cycle immediately preceding the IVF cycle [1, 3, 6, and 7]. Consequently, multiple studies have been performed to investigate the effect of ES in those undergoing ART cycles, but the method of scratching, the population being scratched and the study quality varies widely from locality to another [8-10].Moreover, some stated that there is no consensus on the optimal timing and the number of procedure(s) required for the endometrial injury to exert its maximal benefits [11]. Due to this heterogeneity in design and variability in quality, it remains unclear for whom this treatment could be beneficial and for whom it will be jobless [9]. Therefore, the aim of the present study was to compare the usefulness and the safety of retrieval day versus mid-luteal ES on reproductive outcomes for women undergoing ICSI cycles with unexplained infertility hoping to clear out some disparity put around this maneuver.

Patients and methods

A prospective randomized clinical trial involving patients undergoing intra-cytoplasmic sperm injection/embryo transfer [ICSI-ET] treatment for unexplained primary infertility at fertility care unite Mansoura University Hospitals, Mansoura, Egypt and 2 private fertility centers, between November 1, 2016 and June, 30, 2018.Our research was registered as a randomized clinical trial with a clinical trial identifier [NCT03470298] and also approved by local ethical committee, institutional research board [IRB number R/16.11.11 therefore been performed in accordance with the ethical standards laid down in the Helsinki Declaration of 1975 as revised in 1983 and its later amendments. During the study period, the whole cohort interviewed and enrolled was 270 cycles of women coming for treatment of unexplained infertility, 128of which were excluded. The sample size was calculated using Graph Pad Inset software version 3.01.Seventy-onepatient in each group were required to give the study a power of 80% and α of 0.05. All patients were verbally consented and then each participant gave a written consent before inclusion after receiving detailed written and verbal information about the research. Participation was voluntary and can be withdrawn by the patient at any time with no disadvantages. Included patients were those prepared for fresh ICSI-ET cycle with previous failed ICSI cycle(s), known to be good responders to previous ovulation induction protocol(s), aged less than or equal to 30 years. Our included patients were diagnosed also to have unexplained infertility as evidenced by both partners complete basic investigations, namely semen analysis, mid-luteal progesterone, patent tubes as verified by HSG or previous laparoscopy. We excluded patients having intramural or sub-mucous myoma distorting the endometrial cavity, A sherman's syndrome, those with evident tubal pathology as hydrosalpinix or peritubal adhesions and patients beyond 30 years or those having disturbed hormonal profile. Those with their husbands having abnormal seminogram not fulfilling WHO criteria 2010 [12] were also excluded. From these recruited females, 142 were eligible and divided into two equal groups. Endometrial scratching was done either just after oval retrieval in (group 1) or mid-luteal in the cycle before induction (group 2).The authors selected ICSI cycle protocol that has been previously published by Ghanem et al 2009[13]where they used antagonist protocol in all cases of both groups. Ovarian stimulation was started on the second or third day of menstruation by daily use of two ampoules Fostimon 75 mg and one ampoule Merional 75 mg [IBSA institute Biochimique SA Laugano 3, Suise, manufactured in Switzerland] given subcutaneously. Then the antagonist, Cetrotide 0.25 mg, [Cetrorelix, IBSA institute Biochimique SA Lau-

gano 3, Suise, manufactured in Switzerland] was started when the leading follicle reached 14 mm and stopped when it reached 18 mm or more where hCG 10000 IU injection was given to trigger ovulation [IBSA institute Biochimique SA Laugano 3, Suise, manufactured in Switzerland]. Folliculometry was carried out at the beginning from the sixth day of starting Fostimon then daily or every other day until three or more mature follicles reached 18 mm or more.Egg retrieval was scheduled 35-36 hours later. All patients were followed up by the same sonographer to measure the size of the growing follicles before using Citrotide or hCG and during egg retrieval. The oocyte retrieval was performed by the transvaginal route under ultrasound guidancewhile the patient under mindful sedation. Endometrial scratching using IUD sheath wasdone for group 1 patients just after egg retrieval without use of any septic solution part from normal saline; meanwhile it was done for group 2 patients on the day 21 in the cycle before induction under asepsis using povidone-iodine. The same gynecologist carried out the procedure in a systematic manner for patients in both groupsby moving from below upwards with scratching the anterior then the posterior wall followed by the left lateral and the right lateral uterine walls and lastly the fundus. The morphology of each aspirated oocyte was then noted after denudation with hyaluronidase. Semen samples were obtained by masturbation on the day of oval retrieval and then processed within one hour of ejaculation to prevent damage from leukocytes and other cells present. To separate the motile sperms from the semen samples, the swim up method was used [14].On the day of ovum retrieval, intracytoplasmic sperm injection and fertilization was performed for all cases. All metaphases II (MII) were injected by ICSI 3–4 hours post retrieval. All zygotes were cultured individually in 50 µl droplets of P-1 medium, supplemented with 10% Synthetic Serum Substitute (Irvine Scientific, Santa Ana, CA). After 44-46 hours, embryos were moved to complete blastocyst medium (Irvine Scientific, Santa Ana, CA). The newly formed embryos were evaluated by the embryologist and classified according to Veeck's grading [15]: Grade 1 were pre-embryos with blastomeres of equal size and no cytoplasmic fragmentations, Grade 2; pre-embryos with blastomeres of equal size with cytoplasmic fragmentations equal to 15% of the total embryonic volume; Grade 3; pre-embryoswith unevenblastomeres with no fragmentation while Grade 4 are those of uneven blastomeres with gross fragmentation equal to or more than 20%. All selected embryos were transferred on day 3involving two good quality grade 1 embryosusing the tactile technique. The embryos were deposited high up in the cavity 1-2 cm below the uterine fundus by the same catheter (Labottect Gmbh, Labor-Technic-Göttingen, Germany) under ultrasound guidance via a senior consultant in all transfers using the maneuver described by Ghanem et al; 2016 [16]. Luteal phase support wasinitiated in both groups on the day of egg retrieval and involved a daily dose of Prontogest 100 mg IM (Progesterone, Marcyl Pharmaceutical industries, Obour city, Egypt) until the day of β- hCG test 14 days after embryo transfer. We compared the number of eggs retrieved, fertilization rate, cycle outcome regarding IR and clinical CPR in both groups. The primary outcome measure was(IR) while (CPR) was considered as the secondary outcome measure. Implantation rate was defined as the number of gestational sacs seen on trans-vaginal sonography divided by the number of embryos transferred meanwhile CPRwas defined as ultrasound evidence of fetal heart beating and calculated as the number of patients with clinical pregnancy divided by the number of patients who had embryo transfer.

Statistical analysis

The data were collected, tabulated and statistically analyzed by IBM computer using SPSS for windows version 17.0 (SPSS, Chicago, IL). Continuous data were expressed as mean ±SD and compared between the two groups using independent Student's t test. Categorical data were expressed in number and percent and compared using the $\chi 2$ test. Statistical significance was set at $p<0.05$.

Results

A total of 270 patients with unexplained infertility were interviewed, screened and enrolled in the study, of them 128 patients were excluded due to failure for fulfilling the inclusion criteria and the rest were divided into two equal groups (figure 1).

Baseline characteristics are shown in Table (1); there were no recorded significant differences be-

tween both groups as regard the age, BMI, duration of infertility, base line investigations namely FSH, LH, prolactin levels as well as mid-luteal progesterone level, p>0.05.

The mean estimated day of triggering (14.2 ± 2.1 in G1 vs 13.6 ± 2.2 in G2) together with the mean follicular size (19.3 ± 0.8 in G1 vs 18.5 ± 1.8 in G2) showed also no statistic al significance (p values 0.690 and 0.751 respectively), [table 2]. Again, the mean estimated number of ova retrieved (7.4+ 2.1 in G1 vs 7.1+ 1.3 in G2) and zygote transferred (2 in each group), presented no significant differences together with chemical pregnancy rates (54 in G1 versus 52 in G2), p>0.05 [table 2].On the other hand, IR and CPR are found significantly higher in group 1 compared to group 2,(IR 38 (53%) vs, 29 (40%); CPR 35 (49.2%) vs 25 (35.2%), p<0.05 as shown in table [2].

Discussion

The main findings of the study confirmed endometrial scratching on the oval retrieval day is more effective thanif did mid-luteal in managing couples with unexplained infertility.This is indicated by the determination of higher implantation and clinical pregnancy rates in the study group (1).

Indeed implantation failure is considered as a major barrier in human's fertility and is mainly attributed to failure of the uterus to acquire normal receptivity. The term 'implantation failure' is used commonly for women with failure of at least three attempts of high-quality embryo's transfer [17-19]. The treatment of this failure remains a challenge in spite of transfer of good-quality embryos at sometimes [19, 20]. Thisstudy focused to examine the effectiveness of ES with IVF/ICSI cycles selecting a clear population; namely those who have had at least one failed implantation keeping in mind both patient burden and healthcare costs.

The notion of using induced endometrial injury to increase clinical pregnancy rates and live birth rates[19, 20]arises from the fact that the genes responsible for implantation are sometimes 'switched off' during the time when the embryos are supposed to implant. Endometrialinjury might 'switch on' these genes with a subsequent tissues'repair associated with release of many growth factors, hormones, chemicals and cytokines that make the new lining is more receptive to an implanting embryo with a positive crosstalk [22-24].Endometrial injury was earlier investigated by Barash et al. 2003 [1] in a prospective studyand concluded that women assigned to endometrial biopsy in the preceding cyclesdemonstrated twice more likely to get pregnant as compared to controls with no scratching. Since then a dynamic talk and many researches moved to study this issuebut with heterogeneity of methods used and the proper timing. The best time to perform ES is principally thought to be approximately 7- 14 days before starting controlled ovarian hyper-stimulation to increases the chance of clinical pregnancy and live birth. Raziel et al., 2007 [25]; reported in a case control study for ICSI patients with higher order implantation failure performed twice on days 21 and 26 an increased implantation and clinical pregnancy and even ongoing pregnancy rates in the intervention group.Moreover; demonstrated endometrial injury on days 11 - 13 and 21 – 24of the non-transfer cycle or at least 7- 14 days before the transfer cycle, during the luteal phase, resulted in improving pregnancy outcomes in women with unexplained repeatedimplantation failure [2, 26-30]. Ourresults come permitting the effect of endometrial injury andinvestigating the impact of timing too. Here, the authors found endometrial scratching done on the oval retrieval day is better and more effective than if done in the previous mid-luteal cycle as proved by higher IR and CPR in group 1 compared to group 2 being 53% vs, 40% and 49.2% vs 35.2% respectively [p<0.05 in table 2].These results come supporting the advantageous effect of ES, but the new incident is the higher effectivity in those with recent intentional endometrial injury (group 1). This might be explained by the fact that, inflammation process in the first group is still fresh with abundant switched on genes and inflammatory mediators making the endometrium in a good quiescent and cross talk state. An additional advantage of performing ES in the same cycle, according to the authors' opinion, is the patient's convenience, less visit, and no long time until transfer and this gave no chance for drop out cases.

Two recent studies published from our locality [31, 32] and supporting our results where they

did ES in the mid proliferative phase of the same transfer cycles and both found increase in IR and CPR.The latter studyusedendometrial scratch-suction maneuver and reporting that using suction is more advantageous as it can remove any small polyp or blood clots that may be hazardous for the implanting embryos. In this study, we did not use suction maneuver during ES, a point that in needto be more investigated to clear out whether it adds to scratching or not. In addition, our findings come in agreement with those results proved by some other authors [33-37] who studied the effectiveness and impact of timing of ES on the outcome of unexplained infertility management. Though, they studied the maneuver effectiveness with intrauterine insemination after repeated implantation failure, but their results showed significantly higher CPR in groups that underwent ES in the same stimulation-transfer cycles than those who had the maneuver at the mid-luteal time of the preceding cycle or those without scratch. Again they explained the prior failure to implant was due to poor endometrial receptivity as the sole cause of infertility which probably improved by ES. Moreover; Parsanezhad et al. 2013 [38] studied the role of intentional endometrial injury, induced by pipelle endometrial sampling after controlled ovarian hyper-stimulationperformed during the pre-ovulatory days then followed by regularly timed intercourse. They concluded that local endometrial injury could increase pregnancy rate compared to the control group. This also supports the role and effectiveness of ES when become more close to ovulation, like our findings, even when there is no extra maneuver and leaving the pregnancy for natural chances. In addition, the study published by Huang et al 2011 [39], verified results that came supporting our findings despite they used asite-specific hysteroscopic endometrial injury. They concluded that endometrial injury performed during the ongoing IVF cycle, between days 4–7, instead of those received during prior cycles, significantly improves the outcomein patients with repeated implantation failure.

On the other hand there are some studies which have shown minimal [40] or no benefit of injuring the endometrium in the previous cycle in improving implantation or pregnancy rates[6, 41-43]. The possible explanation may be thelonger time passed after scratching with limited benefit due to fading out the effectivemediators and cytokines responsible for good endometrial receptivity. Despite this supports our believe for ES to be as close as much to ovulation and transfer days, as indicated by results obtained from group 2 (less IR and CPR) compared to group 1, but further data is required to explain this disparity. Moreover, contrary to our detections; there are few results reporting a negative and at sometimes detrimental effect of endometrial injury on IR and CPRespecially when performed in the transfer cycle near to or on the day of oocyte retrieval [44,45].Was this attributed to persisted blood clots and endometrial fragments that need time to be cleared from the uterus?

Our study may add to facts regarding benefits of endometrial scratching in IVF/ICSI cycles management of infertile couples being a cost-effective, cheap and well-tolerated procedure. In addition, some strength of this study appears from being aprospective randomized controlled trial of good power (80%).However, the main limitations of the study are the small size in each arm and absence of the miscarriage and live birth rates estimation.This stresses the need for further large randomized trials, better to be multi-centric, to verify the findings and improve the statistical power.Another point of discussion is whether the use of povidone-iodine in group 2 during the endometrial scratch could decrease IR and CPR. To our information, no studies have investigated the effect of scrubbing the cervix with povidone-iodineat the preceding mid-luteal day on the embryo transfer and or implantation rate.

Conclusion

Endometrialscratch in the transfer cycle especially on the oval retrieval day can improve endometrial receptivity with subsequent increase in implantation and clinical pregnancy rates than when achieved at mid-luteal day of the previous cycle.

Conflict of Interest

The authors declare that they have no conflict of interest.

Authors' contribution

Abdelhady Zayed; Protocol development, data collection

Osama Warda; Protocol development and data collection
Ahmed Ragab; Data analysis, manuscript writing.
Yasser Mesbah; Data collection and patient management
Ahmed El-Zayadi; Data collection and analysis
Ahmed Badawy; Data analysis, manuscript writing.

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Tables' legend:

Table [1]:Baseline characteristics of both studied groups together with the results of basic laboratory investigations.

Table [2]: Result of ovulation induction, mean day of triggering, mean follicular size, primary and secondary outcome measures in the two studied groups.

Table 1: Baseline characteristics of both studied groups together with the results of basic laboratory investigations.

	G1	G2	P value
	(n=71)	(n=71)	
Age (years)	25.4±3.1	26.1±.3.1	0.225
Body mass index	25±0.8	25±0.2	1.00
Duration of infertility (years)	3.2±0.3	3.3±0.4	0.094
Baseline lab investigations:			
FSH (mIU/ml)	5.5± 1.3	5.8± 1.02	0. 6
LH (mIU/ml)	6.3± 1.5	6.2 ± 1.3	0.41
Mid-luteal progesterone level	20.5± 3.4	19.2± 4.05	0.184
PRL(mIU/ml)	12.56 ± 2.3	12.5 ± 2.8	0.852

Data are presented by mean ± SD, p value was set statistically significant when <0.05. Abbreviations: FSH; follicle stimulating hormone, LH; luteinizing hormone; PRL, prolactin hormone.

Table 2: Result of ovulation induction, mean day of triggering, mean follicular size, primary and secondary outcome measures in the two studied groups.

Characteristics	G1	G2	P value
	(n=71)	(n=71)	
Mean day of triggering	14.2 ± 2.1	13.6 ± 2.2	0.690
Mean follicular size/mm	19.3 ± 0.8	18.5 ± 1.8	0.751
Number of ova retrieved	7.4+ 2.1	7.1+1.3	0.31
Number of zygote transferred	2	2	000
Chemical pregnancy rate	54 (76.05%)	52 (73.2%)	0.21
Implantation rate	38 (53.5%)	29 (40.8%)	0.01*
Clinical pregnancy rate	35 (49.3%)	25 (35.2%)	0.001*

Values are presented as mean ± SD, number (percentage), p value was set significant when <0.05. (*) significant P value

Adenomyosis a forgotten cause of infertility

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Abstract

Objectives: To review whether adenomyosis causes infertility or not, the current available methods of its diagnosis, the lines of adenomyosis associated infertility treatment, and why future research is needed.

Materials and methods: Electronic databases for studies on adenomyosis and infertility published between 1995-2020 were searched and reviewed using the PUBMED as a search engine. The following keywords were used: adenomyosis, infertility, ultrasonography, MRI, IVF/ICSI, cytoreductive surgery, GnRHa, NSAIDs and HIFU. No language limitations were applied.

Findings: Adenomyosis is a disease of women in reproductive age and contributes to infertility. It can be accurately diagnosed by non invasive imaging. There are different lines of treatment of adenomyosis associated infertility. However all currently available methods have their limitations. There is a need to expand research in this area to be able to answer the enigma of adenomyosis and infertility.

Conclusion: Reproductive medicine physicians should be aware of the possible contribution of adenomyosis to infertility and look for its presence during infertility workup. This will enable them to properly counsel the patients and choose the most appropriate methods for management of their infertility.

Keywords: adenomyosis, Junctional Zone, infertility, IVF, cytoreductive surgery, IVF/ICSI, ultrasonography, MRI.

INTRODUCTION

Early in the last decade a systematic review of prevalence diagnosis, treatment and fertility outcome, was published from a reputable center of research in one of the top journals of human reproduction, concluded that more studies are needed to determine adenomyosis implications on reproductive outcomes, with or without treatment. The authors suggested until then, there is no indication for finding or treating adenomyosis in women who wish to conceive (1). However with the improvement and wider use of diagnostic imaging and application of various treatment modalities, whether medical, surgical or assisted reproductive technology (ART), it is time to change this metto regarding adenomyosis and infertility. This review addresses the recent developments in the various aspects of adenomyosis and infertility and makes the argument why reproductive medicine physicians should change their old approach to adenomyosis in their infertile patients, and counsel patients accordingly.

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Materials and Methods

The author searched 16 electronic databases for studies published between 1995-2020, using the PUBMED as a searching engine, on the incidence of adenomyosis among infertile patients, whether it causes infertility or not, accuracy of modern non invasive methods of its diagnosis, the current available methods for treatment of patients with adenomyosis associated infertility. The review included systematic reviews, meta-analysis and studies, without language limitations, comparing the outcome of infertile women with and without adenomyosis which accounted for confounders. The following Keywords were used: adenomyosis, infertility, Junctional zone (JZ), ultrasonography, MRI, IVF/ICSI, cytoreductive surgery, GnRHa, NSAIDs and HIFU.

Findings

The author included 112 unique references and assessed 72 full-text articles. It would be appropriate to discuss separately the outcome of search on each of the different items looked at.

Is adenomyosis a disease of older women and is not common among infertile patients?

Though endometriosis was first explained in the Egyptian scrolls in 16th century BC, it was only in 1860 that Rokitansky described adenomyosis as a common gynecological disorder in women aged 40-50 years characterized by the presence of heterotopic endometrial glands and stroma in the myometrium with adjacent smooth muscle hyperplasia (2,3). With a quoted prevalence ranging from 8-27% based on histological examination of hysterectomy specimen, it was usually thought that adenomyosis is a condition of elderly parous women and an association between subfertility and adenomyosis has not been fully established (1). However today with the development of modern imaging, several authors believe that the disease is no longer considered typical of women over 40 years of age and it affects 20-30% of women in reproductive age (4-7). Punete et al 2016 (8) using 3D ultrasonography reported adenomyosis incidence of 24.4% in patient with repeated implantation failure and recurrent miscarriage. Khandeparker et al (2018) (9) using MRI reported an incidence of 33.3% of adenomyosis among infertile patients. Kunz et al (2005) and Chapron et al (2017) respectively reported an incidence of adenomyosis of 79% and 59.9% among infertile patients when adenomyosis is associated with endometriosis (10, 11). With the use of ultrasonography and MRI for the diagnosis of adenomyosis a new epidemiological scenario had developed with an increasing number of women of reproductive age with adenomyosis due to the wider use of ultrasound and MRI for its diagnosis. (12). Adenomyosis was found in 22% of infertile women less than 40 years old undergoing ART (8). Furthermore with the global delay of the age of women at first child birth, it is not surprising that adenomyosis is likely to be encountered in a substantial percentage of infertile patients (13). Several reports have indicated that between 11.9-31% of women undergoing ART are at the age of >40 (14-17).

Is accurate diagnosis of adenomyosis still only possible by invasive techniques?

In the near past adenomyosis was under diagnosed and the diagnosis was only established at pathological examination of hysterectomy specimens or via invasive diagnostic procedures such as percutaneous or laparoscopic uterine biopsy. In the 1960s when laparoscopy was introduced the diagnosis and management of endometriosis were revolutionalized but leaving behind adenomyosis which continued to be diagnosed retrospectively only in hysterectomy specimens. In the mid 1980s the situation changed dramatically when non invasive imaging techniques became available enabling a prospective diagnosis of adenomyosis. The higher frequencies (5-7MHZ) vaginal ultrasonography made it invaluable in the diagnosis and follow up of patients with adenomyosis due its high accuracy. The use of routine real-time TVS in patients with suspected adenomyosis became highly recommended (18, 13). The 2D ultrasonographic criteria for diagnosis of adenomyosis were described by several authors in the literature. They included; globular enlarged uterus, asymmetrical enlargement of anterior and posterior walls, diffusely irregular myometrial echotexture with hyperechoic

features, subendometrial myometrial cysts and echogenic islands, hypoechoic linear striations within a heterogeneous myometrium, increased blood flow in affected areas, and irregular, ill defined or interrupted junctional zone (JZ) (19-21). A systematic review and a meta-analysis by Champaneria et al 2010 reported a sensitivity and a specificity of 2D US of 72% (95% C/65-79%) and 81% (95% C/77-85%) respectively (22). 3D ultrasonograpy was also successfully used in the diagnosis of adenomyosis. The 3D focuses predominantly on the junctional zone (JZ) as there is a strong association between thickening and disruption of the junctional zone (JZ) and the occurrence of adenomyosis (23,24). In a study on 45 patients who have had hysterectomy for adenomyosis, Exacoustos et al (2011) found that the features with the highest specificity were a junctional zone (JZ) thickness of > 8mm, myometrial asymmetry and hypoechoic striations. When at least 2 of these features are present, the overall accuracy was reported to be 90% with sensitivity and specificity of 92% and 83% respectively (25). Most researchers suggested that 3D US is more accurate than 2D US in the diagnosis of adenomyosis. However a recent meta-analysis by Andres et al (2018) suggested there was no improvement in the overall accuracy in TV US 3D compared with TV US 2D for the diagnosis of adenomyosis (26). The accuracy of diagnosis of adenomyosis by ultrasonography is highly dependent on the experience of the operator, with significant intra-observer and inter-observer variability in the findings and therefore the use of MRI for the assessment and follow up of patients with adenomyosis was recommended (9). High resolution pelvic MRI is now considered the current reference standard for non invasive imaging of adenomyosis due to its multiplanar capabilities, excellent soft tissue resolution, repeatability and reproducibility and less operator dependent with a sensitivity and specifity of 86-100% in asymptomatic patients (27, 9). Several workers reported on the criteria for adenomyosis diagnosis using MRI. These included focal or diffuse thickening of the JZ thickness > 5mm or >12mm, poor definitions of JZ borders, low signal intensity uterine mass with ill defined border, localized high signal foci within an area of low signal intensity, linear striations of increased signal radiating out from the endometrium into the myometrium and bright foci in endometrium isointense with myometrium (28-30, 13). Review of 57 out of 687 articles by Bazot et al 2018 concluded that MRI is more useful than TVS in the diagnosis of subtle nuances of uterine adenomyosis and whether it is internal adenomyosis, adenomyomas or external adenomyosis (21). Very recently Chapron et al 2020 have indicated that imaging techniques, including 2D and 3D US as well as MRI allow proper identification of the different phenotypes of adenomyosis (diffuse and/or focal). However while the diagnosis of diffuse adenomyosis is straight forward, in more limited disease , the diagnosis has poor inter-observer reproducibility leading to extreme variations in the prevalence of disease (12).

Is it true that adenomyosis does not cause infertility, and it is the usually associated reproductive disorders, what cause infertility?

Adenomyosis is frequently associated with fibroids, endometriosis or muscular hypertrophy. MRI can be useful in differentiating the nature of the condition whether adenomyosis alone or whether it is associated with other pathology (31). In the experimental animal the baboon, endometriosis is statistically significantly associated to adenomyosis and adenomyosis is strongly associated with lifelong primary infertility (32), Kunz et al in 2005 suggested that uterine adenomyosis is significantly associated with pelvic endometriosis, yet it constitutes an important factor of sterility in endometriosis presumably by impairing uterine sperm transport (10). Just one year later Kissler et al published their work on the radionuclides transport in women with diffuse adenomyosis and primary infertility. When radionuclides mimicking sperm size were placed into the posterior vaginal fornix, no utero-tubal transport of the radionuclides was detected and radionuclides remained in the uterine cavity in 70% of cases (33). Kusakabe et al in 2005 made the observation that in Knock-out mice their gestational capacity is impaired if these animals are deprived of perforin. Perforin induces apoptosis in target cells. Thickening of the JZ myometrium, a common finding in adenomyosis, occurs in the absence of perforin (34). Several researchers have proved and suggested many factors in the pathophysiolo-

gy of adenomyosis to account for infertility in adenomyosis. These include abnormal concentration of intra-uterine free radicals (35) , abnormal uterine contractility (36) an increase in cytokines and inflammatory mediators, VEGF and microvessel density (37), gene dysregulation (38), impaired implantation due to decrease in HOXA10 (39), altered endometrial function and receptivity (40), immune dysfunction and alterations of adhesion molecules, (41), impaired decidualization due to decreased expression of NR4A nuclear receptors (42,43), possible disturbance of the role of microbiota for a receptive and fertile endometrium (44). Several workers have demonstrated reduced concentrations of various implantation factors in adenomyosis - associated infertility. These included decrease in leukemia inhibitory factor (45, 46) HOXA10, (39) and RCASI (47). Though adenomyosis is frequently associated with other reproductive disorders which could cause infertility, yet adenomyosis by itself could account for infertility in a number of patients. Adenomyosis may also have a deleterious effect on the outcomes of infertility treatment when associated with other reproductive disorders. This concept is supported by research in basic science and has been emphasized by clinical research particularly in assisted reproductive programs. Chapron et al 2020 suggested an integrated non-invasive diagnostic approach of adenomyosis, considering risk factors profile, clinical symptoms, clinical examination and imaging to adequately identify and characterize adenomyosis and its contribution to patients infertility (12).

Are there robust clinical studies to support the negative effect of adenomyosis on fertility and fertility treatment?

A direct causal relationship between adenomyosis and subfertility has been proposed in the literature. However, no robust data is available due to the lack of prospective randomized controlled trials (48). This is mostly because it is extremely difficult to conduct such trials without violating the ethical principles of research. Furthermore with its poorly understood pathogenesis, the impact of the different phenotypes of adenomyosis on reproduction stays unclear. Furthermore, interpretation is rendered difficult because of the high incidence of concomitant pathology as fibroids and endometriosis (49). Nevertheless a lot of evidence is accumulating from basic and clinical studies in ART to support the deleterious effect of adenomyosis on fertility and fertility treatment. An early study in 1998 by Fanchin et al measured the frequency of JZ contractions and its effect on pregnancy rate in IVF program. They found a stepwise decrease in clinical pregnancy rates with increased frequency of JZ contractions. Pregnancy rates decreased from 50% to below 20% when JZ contractions increased from < 3 contractions to >5 contractions per minute $P < 0.001$ (50). Piver studied the JZ thickness and implantation failure in IVF cycles. The pregnancy rate/transfer was 45%, 16% and 5% when JZ thickness was < 10mm, 10-12mm and >12mm respectively (51). MRI evaluation of JZ thickness was the best negative predictive factor of implantation failure in IVF cycles. In another prospective study on 152 patients undergoing IVF, implantation failure was 37.5% and 95.8% when the JZ thickness was <7mm and 7-10mm respectively $P<0.0001$ (52). Thus the increase in JZ thickness can be significantly correlated with implantation failure in IVF independently of the cause of infertility or patient's age. A meta-analysis and systematic review by Vercillini et al on women with adenomyosis undergoing ART (304 patients) showed a 28% reduction in the likelihood of clinical pregnancy and increased miscarriage rates when compared with women without adenomyosis (1262 patients) (48) . A more recent retrospective study of 973 patients undergoing IVF by Sharma et al found adenomyosis adversely affects the life birth rate and miscarriage rate whether alone or when associated with endometriosis. Live birth rate was 27.4%, 26.4%, 11.3% and 12.5% for patients with tubal, endometriosis only, endometriosis+adenomyosis and adenomyosis only respectively. The miscarriage rate was 13%, 14.6%, 35% and 40% for these patients respectively. The differences were statistically significant. The study concluded that screening for adenomyosis might be considered before IVF. Affected couples should be counseled about the reduced success rates after IVF treatment and about the associated complications of pregnancy (53) . Park et al in 2016 performed a retrospective study of 241 IVF cycles for women with adenomyosis

between the years 2006-2012. They compared IVF results in women without versus with GnRHa pretreatment, fresh embryo transfer versus frozen embryo transfer and in women with focal versus diffuse adenomyosis. The clinical pregnancy rate was 25.2% (37/147) in fresh ET without GnRHa pretreatment versus 30.5% (32/105) in fresh ET with GnRHa pretreatment and 39.5% (17/43) in FET with GnRHa pretreatment. The clinical pregnancy rate was 32.9% (23/70) in fresh ET following GnRHa pretreatment in women with focal adenomyosis compared with a pregnancy rate of 25.7% (9/35) in women with diffuse adenomyosis. In FET with GnRHa pretreatment, pregnancy rate was 43.5% (10/23) versus 35% (7/20) in focal and diffuse adenomyosis respectively (54). A recent meta-analysis by Younes et al 2017 compared the effect of adenomyosis on IVF treatment outcomes in 519 patients with adenomyosis versus 1535 patients without adenomyosis (55). They found adenomyosis has a detrimental effect on IVF clinical outcomes concerning live birth rates and miscarriage rates. The use of long term GnRHa or long protocol could be beneficial for women with adenomyosis undergoing IVF. Cumulative spontaneous clinical pregnancy rates in women who underwent surgery for adenomyosis and who did not favoured surgery. Clinical pregnancy rate after fresh ET in women with diffuse adenomyosis was less than in women with focal adenomyosis. Recently Razavi et al performed a systematic review and meta-analysis to study the possible adverse pregnancy outcomes in women with adenomyosis (56). The number of women with adenomyosis was 322 and those without adenomyosis 9420. They found three fold increase in preterm birth rate ($z = 5.47$ $p < 0.00001$), higher incidence of pre-eclampsia ($z = 2.06$ $p = 0.04$), higher incidence of small gestational age ($z = 3.61$ $p = 0.0003$) in women with adenomyosis compared with women who did not have adenomyosis.

Are there standardized guidelines on treatment of infertility associated with adenomyosis?

It is difficult to standardize guidelines on the management of infertility associated with adenomyosis. This is simply because the pathogenic mechanisms of adenomyosis development are still unclear and because there are different phynotypical expressions of adenomyosis. It is not proven yet that all the evidence available may be applied to different forms of the disease (57). Sex steroid hormones, inflammation, neoangiogenesis, growth factors, ECM enzymes and neurogenic factors are key pathogenic mediators of pain, abnormal uterine bleeding and infertility. More research is needed to better understand the pathophysiology and early pathways implicated in the initiation of adenomyosis to develop adequate therapeutic strategies. The current treatment of adenomyosis associated infertility can be summarized as follows:

Medical Treatment

Few RCTs focused on medical treatment for adenomyosis. However, no drug is currently labeled for adenomyosis and there are no specific guidelines to follow for the best management of these patients (58). Adenomyosis is usually associated with chronic pelvic pain and severe dysmenorrhoea which affects quality of life of patients. If the pain is not alleviated for a long time it can change how the brain perceives it and processes signals leading to an amplification of pain (59). It is important to relief the pain and minimize the abnormal uterine bleeding frequently associated with adenomyosis even if the primary complaint of the patient is infertility. (60).

1. Non steroidal anti-inflammatory drugs (NSAIDs).

NSAIDs and acetaminophen remain the first line in the pharmacological management of pain. They may be used alone or in combination with other medications. NSAIDs like ibrufen and naproxen are effective and well tolerated drugs. It is best to schedule the initiation of the medication 1-2 days prior to the onset of bleeding to improve the pain and reduce menstrual flow (60).

2. Suppressive hormonal therapy:

Hormonal suppression is usually a first line treatment of adenomyosis related pain and menstrual bleeding. For the infertile patient it may be the only treatment required for few patients or it may be an adjuvant pretreatment or post treatment to improve the results of other definitive treatments as surgery or IVF.

2.1- Combined estrogen and progesterone therapy (pills, vaginal ring, or transdermal patch).

2.2- Progesterone- only pills or intramuscular depot-medroxy progesterone.

2.3- Levonorgestrel - containing intrauterine device.

These medications lead to atrophy of the intrauterine endometrial tissues and reduction of the size of the adenoma. These various drugs have been shown to be equally effective in several comparative randomized controlled trials. The reproductive medicine physician should choose the treatment option based on cost, side effects and prior experience in individual patient. (61).
2.4- GnRHa produces a hypogonadotropic state by down regulating luteinizing hormone and follicle stimulating hormone: A high proportion of patients develop troublesome side effects including vasomotor symptoms, vaginal atrophy and sleep disturbance. If used for a period of more than 6 months they should be used with adds-on to avoid osteoporosis. They may be used for infertile patients followed by spontaneous pregnancy. More commonly they are used before IVF to improve its results or following surgical treatment for adenomyosis. Long term suppressive therapy with GnRHa before IVF has been shown to improve outcomes (58). Several authors reported on spontaneous successful pregnancies and live births in small series following treatment with GnRHa for adenomyosis in infertile patients (13).

3. Anti coagulation therapy:

Liu et al 2016 had published corroborating evidence for platelets induced epithelial -mesenchymal transition and fibroblast-to-myofibrolast transdifferentiation in the development of adenomyosis. These findings underscore the possibility for the use of anti-coagulation therapy in adenomyosis and holds promise for the development of novel biomarkers for adenomyosis (62).

4. High intensity focused ultrasound (HIFU):

There has been a number of publications on the use of HIFU for the treatment of infertility in patients with adenomyosis (63-67). A review of the literature between 2000- March 2017 by Zhang et al (2017) concluded that HIFU is a non invasive, ablation technique for both focal and diffuse adenomyosis (68). It is associated with a high conception and live birth rates. Zhou et al (2016) reported on 68 patients in whom 54 patient conceived and 21 patients (30.1%) delivered (67). HIFU is associated with a low rate of minor and or major complications. Several factors contribute to its efficacy including distance from the skin to the adenomyoma, volume of the adenomyoma, number of hyperintense foci, location of the uterus and the adenomyoma, and whether it is associated with endometriosis or not. Strict selection criteria have been used to achieve higher success rate. Patients with associated pelvic endometriosis, adhesions between the bowel and uterus and abdominal surgical scar wider than 10mm are relative contra-indication for the procedure.

5. Cytoreductive Surgery:

Cytoreductive Surgery has been used for the treatment of adenomyosis in infertile patients. However, the operation is associated with complications particularly hemorrhage and rupture scar in subsequent pregnancy. Cytoreductive Surgery is feasible for patients with localised or focal adenoma. However, for diffuse adenomyosis the operation is difficult and associated with massive hemorrhage and high incidence of scar rupture in subsequent pregnancy and labour. To reduce the amount of hemorrhage Pitressin is first injected in the uterine wall. This is followed by excision of the adenoma either via laparotomy or possibly laparoscopy in experienced hands. For diffuse adenomyosis the classic V shaped wedge resection is performed followed by suturing the uterine wall. If the lesion is large the uterine muscle flap method is used with asymmetric dissection of the lesion (69). Diffuse adenomyosis may also be excised using the triple flap method which involves extensive dissection of the adenomyosis (69,70). When surgical excision is performed contraception should be administered for periods of 6-24 months depending upon the extent of the dissection and the operative restoration of the uterine wall (69,71). Most publications of cytoreductive surgery for adenomyosis come from Japan. Between the year 1990-2018, 2365 cases were reported globally. 2123 (89.8%) cases were reported from Japan. Pregnancy was reported in 397 (16%) cases which ended in a live birth in 337 (84.89%) cases . Rupture uterus was reported in 23 (5.79%) cas-

es. There was a higher incidence of miscarriage, placenta accrete and percreta compared to CS and myomectomy scars (70).

6. ART:

Based on accumulating evidence from previously published studies, discussed earlier in this review, ART is an important line of treatment to achieve pregnancy in infertile patients with adenomyosis. If medical or surgical treatment failed then IVF becomes an option. In some other cases it may be the first option such as when associated with male factor or tubal factor infertility, advanced maternal age or long duration of infertility. Long term GnRHa pretreatment seems beneficial to improve results of ART. The use of long down regulations GnRHa protocol is preferred to the antagonist or short protocols. Frozen ET with GnRHa pretreatment seems to be superior to fresh ET. The results of ART in patients with focal adenomyosis are likely to be superior to those in patient with diffuse adenomyosis. Adenomyosis seems to have a deleterious effect on the outcome of pregnancy including preterm birth, pre-eclampsia and small gestation for age. Should surgery be performed before ART contraception should be applied for a period of 6-24 months depending on the extent of weakening of the uterine wall. There is no agreement in the literature on guidelines for the treatment of adenomyosis associated infertility. A recent national survey was conducted in Japan as an official project of the Japanese Society of Obstetrics and Gynecology (JSOG) using questionnaires to assess modalities of treatment of adenomyosis associated infertility. Questionnaires were sent to 1149 Japanese medical facilities including 725 institutes that were authorized as training facilities by JSOG and 582 institutes that were registered to JSOG for ART (72). No management policies were found in 106 facilities. The pregnancy rate was 41.7% and abortion rate was 29.8%. Eighty five patients received medications, 89 patients underwent surgery as a pretreatment before infertility treatment and 361 patients had no pretreatment.

Conclusion

Uterine adenomyosis is another enigmatic disease of our time which may cause infertility, repeated implantation failure and recurrent miscarriage. There are different phenotypes of adenomyosis and treatment should be patient centered according to patient's needs and symptoms. Medical pretreatment may improve chances of occurrence of pregnancy and live birth whether spontaneous or following IVF. Long term GnRHa therapy prior to IVF increases pregnancy rate and live birth rate. Though surgical treatment may be beneficial, it is associated with intra operative, post operative, and long term complications. There is an urgent need to establish some systematic classification and research into new molecules in the pathogenic mechanism of adenomyosis to result in guidelines for management of adenomyosis in infertile patients

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Does Antenatal Dexamethasone before FullTerm Planned Cesarean Section Affect the Incidence or Severity of neonatal Jaundice? A Randomized Controlled Trial

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Abstract

Objectives: Toevaluate the effectiveness of antenatal dexamethasone before elective caesarean section at 37-39 weeks of gestation in reducing incidence and/or severity of neonatal jaundice.Patients and.

Methods: A randomized controlled study was done in the Department of Obstetrics and Gynecology, Mansoura University Hospital. The study group received three doses of intramuscular dexamethasone 8 mg ampoules at 8-hourly interval over 24 hours ended 48 hours before time of elective CS. Control group received the usual management without dexamethasone. Neonates were followed up and those who presented with neonatal jaundice within the first 72 hour of delivery (physiologic jaundice) the level of total bilirubin was measured.

Results: The study included 200 cases. Hundred cases (50 %), received single course of antenatal dexamethasone and 100 control cases (50%). the incidence of neonatal jaundice (group 1 was 34% and group 2 was 38%) and the mean level of bilirubin in neonates who develop jaundice (group1 was 11.52±0.56 mg/dl) and (group 2 was 13.08±0.72 mg/dl). No significant difference were found between the intervention and the control groups regarding the incidence of jaundice ($p=0.56$) while there was a significant difference in bilirubin level in neonates who developed jaundice ($P<0.001$).

Conclusion: Administration of antenatal dexamethasone before elective CS at 37-39 gestational weeks was associated with reduced incidence of neonatal jaundice and lower level of bilirubin in cases that developed jaundice.

Keywords: Words: Elective CS; Antenatal corticosteroids; Neonates. Neonatal jaundice .

INTRODUCTION

Neonatal jaundice that classically appear on the first few days after delivery resulted from higher production of bilirubin since the relatively larger circulating red cell mass with short life span. Moreover, there is slight decrease in the concentration of hepatocyte binding protein and limited activity of some liver enzymes that normally occurs in the newborn babies[(1)].

Corticosteroids have been studied in many clinical trials for their benefit regarding lung maturation and consequently reducing neonatal morbidity and mortality[(2)].

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Steroids act as promoters of maturation in different organs of the fetus is widelyevidenced.The principle mechanism supporting the use of antenatal corticosteroids is attributed to alteration of a large number of genes associated with surfactant protein synthesis and different antioxidant enzyme production affecting as well as the expression of vascular endothelial growth factors[3].

Several other differentiating organs like liver, pancreas, kidney, and heart have been shown to be affected by the promoting effect of Corticosteroids-This was proved through many animal studies [4,5].

Two doses betamethasone given antenatally for full term pregnant women before elective cesarean section was studied by Stutchfield et al in 2005 on 998 pregnant women. They described their results as " antenatal betamethasone reduced the incidence of transient tachypnea of the newborn from 4% of elective caesarean sections to 2.1% and that of respiratory distress syndrome from 1.1% to 0.2%"[6].

Many studies lasting between 3 and 20 years, have studied the potential unfavorable side effects of a single course of antenatal corticosteroids. However differences in results , data points to that there is no increase in frequency of infection of fetus or mother or long-term neurological or intellectual effects [7,8]as well as other reveled the potential increase in the placental and fetal blood flow after administration[9].

Eighty four percent of full term babied is diagnosedwith mold neonatal jaundice where total bilirubin is less than 15 mg per dL(10)and is the most common cause of admission to neonatal care unit in the early neonatal period. Severe hyperbilirubinemia (total serum bilirubin more than 20 mg per dL) affects less than 2% of full-term babies and may cause kernicterus and permanent neurological and developmental delay[11].

The aim of our study was to evaluate the proposed enhancing effect of corticosteroids on fetal liver maturation and the effect of antenatal corticosteroids before elective CS at term on the incidence and severity of neonatal hyperbilirubinemia.

Patients and method

This randomized controlled trial was done in, Mansoura University Hospitals, Department of Obstetrics and Gynecology during the period from 1/1/2016 to 31/12/2017 (24 months). It included the admitted pregnant women planned for elective caesarean section at 37 to 39 completed weeks of gestation.

History taking and full examination initiallywas done for evaluation of the patients. Ultrasound was performedto assessfetal well-being. Routine laboratory investigations were done. A written informed consent was obtained from all participating women. The local ethical committee of Mansoura University Hospitals approved the study.

Inclusion criteria were, pregnant women at 37-39 weeks of gestation who were planned for elective C. S and accepted to be enrolled in the study.

- Exclusion criteria were:
- Multiple pregnancies.
- Premature rupture of membranes.
- Presence of fetal congenital malformations or intrauterine growth restriction.
- Women with medical disease with pregnancy (DM, hypertensive disorders or cardiac disease, viral or non viral hepatitis).
- History of neonatal jaundice in previous deliveries

Eligible patients were randomized by asking her to choose one of 2 closed envelopes, one of them for the study and the other for the control group. The study group received 3 doses of intramuscular dexamethasone 8 mg ampoules (Elamrya co., Egypt) at 8-hourly interval over 24 hours to be ended 48 hours before time of elective CS. Neonatal resuscitation and management was performed by a specialized neonatology team.

Neonates were followed up and those who presented with neonatal jaundice within the first 72 hour of delivery (physiologic jaundice) the level of total bilirubin was measured.

Results

The study included 200 cases. Group 1 (n= 100 cases) received single course of antenatal dexamethasone and Group 2 (n= 100 controls) control cases who did not receive antenatal Dexamethasone.

The mean maternal age, gravidity, parity, gestational age (GA), and neonatal gender of the studied cases were shown in table (1).

These criteria showed that both groups were comparable regarding maternal age, gravidity, parity, gestational age (GA), and neonatal gender (p = 0.26, 0.76,0.14,0. 0.19 and 0.78 respectively).

Table (1) Demographic criteria of the intervention and control group.

	Group 1 N=100	Group 2 N=100	Test of significance
Maternal Age /year mean±SD	28.0±4.83	27.22±4.94	t=1.13 P=0.26
Gravidity mean ± SD	2.48±0.93	2.44±0.95	t=0.30 P=0.76
Parity mean ± SD	1.36±0.96	1.16±0.95	t=1.48 p=0.14
Gestational age mean ± SD	38.26±0.72	38.12±0.74	t=1.35 ,P=0.19
Newborn gender Male Female	N(%) 54(54.0) 46(46.0)	N(%) 56(56.0) 44(44.0)	χ^2=0.08 p=0.78

Table (2) summarizes the impact of antenatal dexamethasone on the incidence of neonatal jaundice (group 1 was 34% and group 2 was 38%) and the mean level of bilirubin in neonates who develop jaundice (group1 was 11.52±0.56 mg/dl) and (group 2 was 13.08±0.72 mg/dl).

As can be noted,no significant difference were found between the intervention and the control groups regarding the incidence of jaundice (p=0.56) while there was a significant difference in bilirubin level in neonates who developed jaundice (P<0.001). Administration of antenatal dexamethasone before elective CS at 37-39 gestational weeks was associated with reduced incidence of neonatal jaundice and lower level of bilirubin in cases that developed jaundice.

Table (2) neonatal jaundice and bilirubin level

Jaundice -VE +VE	Group 1 N=100(%) 66(66.0) 34(34.0)	Group 2 N= 100(%) 62(62.0) 38(38.0)	χ^2=0.35 p=0.56
Jaundice level mg/dl Mean ± SD	11.52±0.56	N13.08±0.72	t=10.22 , P<0.001*

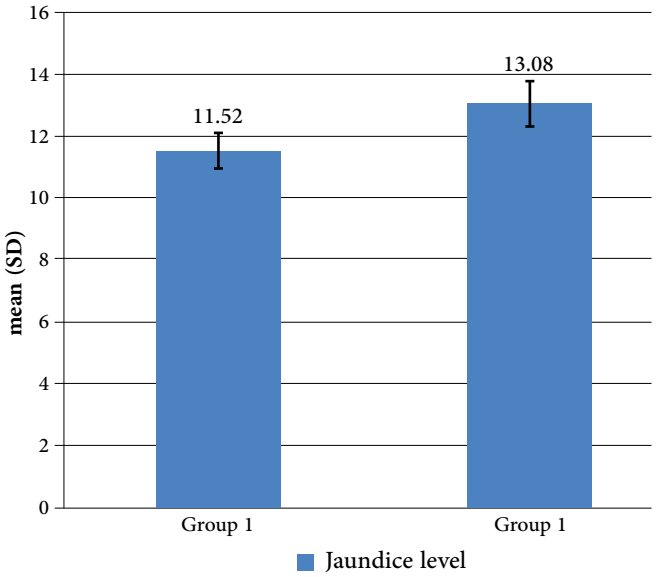

Figure (1): Mean level of bilirubin in neonates who developed jaundice (group1 where mothers received dexamethasone) (group 2 where mothers did not receive dexamethasone).

Discussion

Neonatal jaundice affects more than 2/3 of term newbornsand is the commonest cause of hospital readmission in the neonatal period. Therefore, it is important to systemically appraise the possibility to reduce the incidence of hyperbilirubinemia prenatally and early postnatal evaluation of all infants.

The potential effect of corticosteroids on maturation of fetal organs made them widely used in women with threatened preterm labor, who usually gain a significant beneficial effect on morbidity and mortality in premature neonates(3).

The mechanism that is played by antenatal corticosteroid in enhancement lung maturity was studied many years ago. Expression of certain genes was found to be involved in surfactant protein synthesis. However stimulation of other organs in the fetus like liver, pancreas, kidney was also evaluated (4,5).

In the current study, the comparison was done between100 full term pregnant women received dexamethasone 48 hours before performing elective Cs and those who did notreceive steroids as regard the development of neonatal jaundice. Although the number of delivered neonates who developed jaundice are higher than those who their mother did not receive corticosteroid but the difference in incidence was found to be notsignificant.These results could be explained by a study done by Khulan al 2016 that was concerned with an animal rat model study. They suggested that glucocorticoids associate with alterations in DNA methylation thatmay facilitate gene transcription(5).In addition, another study showed thatglucocorticoids induce demethylation of the hepatic tyrosineaminotransferase gene promoter in late gestation, which is permissive fortranscription bindingfactor , isin agreement also with our results(12).

Data showed that prenatal glucocorticoids induce transient changes in gene expression and DNA methylation as key genes in the heme biosynthesis pathway made authors suggested a mechanism through which glucocorticoids associate with accelerated maturation that may prevent neonatal hyperbilirubinemia. Since the high safety of providing antenatal corticosteroids even in term pregnancy for different issues, our study was based on the rational of that it may favor prevention of high postnatal bilirubin

Although , non-significant difference in the incidence of neonatal jaundice between both groups was found (group 1 was 34% and group 2 was 38%, p0.56),authors in the current study found that the mean level of bilirubin is significantly higher in those who their mothers did notreceivecorticosteroids prior to delivery, (the mean level of bilirubin in neonates who develop jaundice (group1 was 11.52±0.56 mg/dl) and (group 2 was 13.08±0.72 mg/dl).

Alternatively, Pettit et al 2016(13), found thatsignificantly higher rates of neonatal hypoglycemia in neonates exposed to antenatal betamethasone(5.7% versus 4.2%, $p<0.05$) and hyperbilirubinemia (45.9% versus 24.1%, $p<0.05$) were also observed. They assess the effect of betamethasone on 6675 preterm deliveries. These findings persisted with betamethasone-exposed neonates, 1.6 times more likely to have hypoglycemia and 3.2 times more likely to have hyperbilirubinemia.Higherincidence of hyperbilirubinemia can be explained by smaller gestational age at deliveries(13). Further studies to determine whether this association is related to maternal hyperglycemia, neonatal immaturity should behandled.

Conclusion

Neonatal jaundice, being one of the commonest neonatal disoreders confronting neonatologists and proved to be linked greatly to organs maturity,provoke the idea of using corticosteroids in term pregnancy before delivery to limit its development.

To our knowledge, this is the first randomized trial concerning the use of such protocol of management to appraise its effect on neonatal jaundice. Further studies including larger numbers and different groups of patients.

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BRIEFREPORT

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Different methods of termination of second trimester pregnancy with scarred uterus at Mansoura University Hospitals

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Abstract

Objective: To describe different methods used in termination of second trimester pregnancy in those with previous uterine scare(s) and compare their efficacy and safety at a tertiary care center.

Patients and Methods: a prospective, randomizedcontrolled comparative trial conducted at Mansoura University Hospitals, Egypt during February 2018 through March 2019 and involved 105 healthy pregnant women at 14-28 weeks of gestation diagnosed to have missed abortion or intrauterine fetal death with a previous one or more caesarean delivery (CD). They divided into 3 equal groups, GI; received misoprostolalone for termination of pregnancy via either vaginal or sublingual routes as 400 μg / 6 hours for pregnancy at 14- 20 weeks; 200 μg / 6 hours for pregnancy at 20 -25 weeks or 100 μg / 6hours at 26 -27 weeks; G (II) for whom a Foley's catheter was inserted under complete aseptic precautions, passed beyond the internal os then its balloon inflated by 20-30 ml normal saline for pregnancy at 14 - 20 weeks; 40-50 ml for pregnancy at 20 - 27 weeks and its position was confirmed by TAS then oxytocin infusion was commenced after the catheter expulsion, GIII; involved women who received a combination of Foley's catheter inserted intracervical and a misoprostol dose 200 μg for pregnancy from 14-20 weeks or 100 μg for those between 20-27 weeks that was dissolved in 30 ml saline and injected intrauterine through the catheter lumen. Any of the previous method continued for 24 hours otherwise the fetus comes out earlier. All patients in the three groups received oxytocin infusion 20 units in 500 ml normal saline after fetal expulsion to avoid placental retention and post-abortive bleeding.The primary outcome was induction-to-abortion interval (IAI) plus the mean time (SD) needed for complete uterine evacuation.

Results: The patients' characteristics and baseline data for the three groups including the age, weight, gravidity, parity, duration of pregnancy, number of previous scar(s) showed no significant difference ($p > 0.05$).Studying the mean (SD) of IAI/hourtogether with data observed after starting treatment and postoperative complications recorded a significant difference among the three groups as regard IAI (being shortest in GIII;11.6 ±2.6, longest in GII; 17.3 ±3.4 and in between for GI;15.9 ±3.4 respectively; $P< 0.001$), the success rate (100% for GIII, 91.4 % for GI and 85.7% for GII, p 0.02) and the occurrence of diarrhea being lowest in GII (no cases), highest in GI (5 cases) in compare to 1 case only recorded in GIII (P0.024). On the other hand, insignificant difference among the study groups was observed as regard the mean (SD) of time/minutes needed for placenta expulsion after the fetal descent being 31.09 ± 5.01, 27.8 ± 7.61 and 26.57 ± 12.17 for the three groupsrespectively, the occurrence of post induction nausea and vomiting, fever or post-evacuation bleeding ($p> 0.05$). Somecases

needed MVA after placental expulsion (6 cases in GI, 7 cases in GII and 4 in GIII) but again with no significant difference.

Conclusion:Combined use of misoprostol and Foley's catheter for termination of mid-trimester pregnancy with previous uterine scar(s) is found more superior than the use of either method alone regarding the success rate and shorter duration with minimal non serious complications and side effects.

Keywords: mid-trimester, pregnancy, termination.

Introduction

Second trimester, mid-trimester pregnancy, is defined as the period of gestation between 13 to 28 weeks and is commonly subdivided into early ranging from 13-20 weeks and late from 20-28 weeks gestation [1,2]. The Termination of pregnancy by induced abortion is practiced worldwide, 22 % of pregnancies, but the majority of this terminations, nearly 90 %, takes place in the first trimester [3]. Now the universal prenatal screening programs have led to an increase in the diagnosis of congenital malformations and consequently gradual increase in the second trimester pregnancy termination [4].

Essentially pregnancy termination in cases with prior cesarean delivery become an increasingly common situation facing obstetricians due to progressive increase in the rate and incidence of cesarean births [5]. Despite various mechanical and pharmacological methods listed in the literature for termination of such pregnancy but the safety and efficacy of every method are the main factors governing its choice [5.].

Medical termination of second trimester pregnancy, mainly by misoprostol (PGE1)use, offers a high possibility for improving access and relative safety owing to its simplicity in compare to surgical techniques butmight be complicated by uterine hyperstimulation and subsequent rupture especially in women with previous scars [6, 7, 8]. The use of intracervical extra-amniotic Foley's catheter placement is another procedure used for mechanical cervical ripeningand stimulating endogenous release of prostaglandins and cytokines that make the cervix inducible and eases the process of termination [9,10, 11]. Some stated the combination of Foley's catheter for mechanical induction and cervical preparation withmisoprostol simultaneously gave shorter induction-to-abortion intervals [12,13] despite some others have failed to state this difference [14]

This study was thoughtto describe different methods used in termination of second trimester pregnancy in those with previous uterine scare comparing their efficacy and safety profile at tertiary care center.

Patients and methods

This study is a prospective randomized clinical comparative study conducted at Department of Obstetrics and Gynecology, Mansoura University Hospitals, Egypt, from February 2018 to march 2019. Local institutional research board approval for the study was obtained with IRB number [MS/17.12.124] together with a written and verbal informed consent from all the participant after clearly explaining the nature of the study, health benefits, possible side effects and expected complications. Therefore, the study was performed in accordance with the ethical standards laid down with the Helsinki Declaration at 1975, as revised in 1983and its later amendments. The total number of patients recruited and met to participate were 200 but only 105 patients had the study inclusion and allocated to participate.Inclusion criteria comprised patient's age ranged between 20-43 years, gestational age from 14- 28 weeks as calculated according to either sure due date of last normal menstrual period or reliable first trimester sonography or TAS at the time of admission, had a scarred uterus, one or more lower segment caesarean delivery (CD) scars, and were entitled for second trimester pregnancy termination due to either intrauterine fetal death (IUFD) or fetal congenital anomalies incompatible with life. Exclusion criteria involved gestational age less than 13 weeks or more than 28 weeks, patient with low lying placenta, history of previous rupture uterus as well as those who diagnosed to have bleeding tendency or preterm premature rupture of membranes. One hundred and five women were allocated and randomized using closed envelope method into 3 equal groups. Group (I) who received misoprostol alone (prostaglandin E1 analog, Cytotec® 200 micrograms imported and distributed by Pfizer Inc, Egypt))for termination of pregnancy via either vaginal or sublingual routes with the dosage based on gestational age as following: from 14 weeks up to 20 weeks; 400 µg / 6 hours, from 21 weeks up to 25 weeks; 200 µg / 6 hours, then at 26 -27

weeks; 100 µg / 6hours. Group (II) for whom a Foley's catheter (16F silicon coated foley's catheter manufactured by Ultra for medical products Co) was inserted under complete aseptic precautions in minor operative room with no sedation where Cusco's speculum was inserted after sterilization of the vulva and vagina by iodine betadine then a 16F foley's catheter tip is passed beyond internal osand the balloon was inflated by normal saline depending on gestational age as following; from 14 weeks up to 20 weeks; the balloon was filled by 20-30 ml, from 20 weeks up to 27 weeks; the balloon was filled by 40-50 ml, then traction was applied on Foley's catheter as much as the patient can withstand then tapped to patient's upper inner thigh to facilitate their mobility and the position of the catheter balloon was confirmed by transabdominalultrasound (Chison model ECO 5, PIN 95-0016-01, Chison medical technologies co. Ltd. Shanghai International Holding Corp. GmbH(Europe), Eiffestrasse 80, 20537 Hamburg, Germany). Oxytocin infusion (Oxytocin ® 10 I.U. Ampoules, Minapharm, Egypt)as 10 units in 500 ml normal saline started after the catheter expulsion occurred in this group. Group (III) involved women who received a combination of misoprostol with Foley's catheter as follows: the catheter is inserted as described before and then after applying traction upon it, misoprostol dose (200 µg for pregnancy from 14-20 weeks or 100 µg for those between 20-27 weeks) was dissolved by putting it in a 50 ml syringe containing 30 ml normal saline then injected intrauterine through the catheter lumen and tapped into the inside of the patients' upper thigh and the tip of catheter was then closed. All patients in the three groups received oxytocin infusion 20 units in 500 ml normal saline after expulsion of the fetus to avoid placental retention and post-evacuation hemorrhage. Failure of induction by any of the three methods was determined as no uterine activity or change in cervical parameters after 24 hours from start of the procedure. In such situations, the procedure may be extended for extra 24 hours or terminated by hysterotomy or dilatation and evacuation (D&E). Incomplete evacuation that need for manual vacuum aspiration (MVA) for retained parts of the placenta or membranes in any case was considered when intrauterine remnants exceeds 2 cm by vaginal ultrasonography (by the same machine described before) after finishing oxytocin infusion. The primary outcomes: success to achieve complete uterine evacuation with the placenta and membranes with proposed method, induction-to-abortion interval whilst secondary outcomes included drug induced side effects mainly fever, nausea, vomiting, diarrhea, lower abdominal pain and/or bleeding or method dependent complications as rupture uterus, infection, retained parts of the placenta and post-abortive hemorrhage. Basic demographic data was collected from all patients in the three groups including detailed history involving the age, height, weight, gravidity, parity, gestational age, methods of previous parities, types and numbers of uterine scars, history of previous termination of pregnancy, indication for termination of this pregnancy and gestational age at the time of termination, previous uterine surgeries. Thorough clinical examination including general examination for exclusion of contraindications for prostaglandins and vaginal examination for cervical dilatation, effacement and position. Transabdominal ultrasound was done to confirm gestational age, IUFD, congenital malformation, amniotic fluid and to approve placental localization.

Statistical analysis

The collected data were coded, processed and analyzed using the SPSS (Statistical Package for Social Sciences) version 17 for Windows® (SPSS Inc, Chicago, IL, USA). Qualitative data was presented as number and percent. Comparison between groups was done by Chi-Square test. Quantitative data was presented as mean ± SD. F-test (One Way Anova) was used to compare between more than two groups. $P < 0.05$ was considered to be statistically significant.

Results

The study cohort involved 105 participants in 3 equal groups. The basic demographic data including the age, weight, gravidity, parity, gestational age together with history of uterine section scar(s) are presented in table (1) with non-recorded any significant differences among the three groups of these variables ($p > 0.05$), table (1).

Table (2) shows the mean ± SD of IAI/hour together with data observed after starting treatment

and postoperative complications if any. There was a significant difference among the three groups as regard IAI being shortest in combined treatment group [GIII], longest in foley's catheter group [GII] and in between for misoprostol only dependent group [GI] (11.6 ±2.6, 17.3 ±3.4 and 15.9 ±3.4 respectively) (P< 0.001). As regard the time needed for placental expulsion after the fetal descent, there is no significant difference recorded among the 3 groups as the time needed for GI patients is 31.09 ± 5.01 minutes while it is 27.8 ± 7.61 and 26.57 ± 12.17 for GII and GIII respectively (P = 0.45) despite some cases needed manual vacuum aspiration (MVA) in all groups, 6 cases in G!; 7 cases in GII and 4 in GIII, table (2). The success rate of complete uterine evacuation after 24 hours of initiating the method recorded 100% for patients in GIII compared to 91.4 %for GI and 85.7% for GIIpatients (p 0.02), table 2. In cases where failed evacuation occurred after 24 hours, for GI, 1 case needed hysterotomy to terminate pregnancy and 2 cases succeed to evacuate with prolongation of the procedure for 24 hours more meanwhile for GII cases, 3 cases evacuated after prolongation for 1 day more, 2 cases needed dilatation and evacuation (D&E) and 1 case needed hysterotomy. Again, complications after induction and post evacuation are recorded in table (2); there is a significant difference regarding the occurrence of diarrhea being lowest in GII (no cases), highest in GI (5 cases) in compare to 1 case only recorded in GIII, P (0.024), table (2). Similarly, the occurrence of post induction nausea and vomiting, fever or post-evacuation bleeding shows insignificant difference among the three study groups; (p> 0.05), table (2).

Discussion

The main findingof the study results confirmed that the second trimester termination of pregnancy is bestfound when a combination of misoprostol and intrauterine catheterwas used despite the three methods are apparently safe with no evident morbidities threatening the patients' life recorded. Nowadays termination of the second trimester abortionappeared riskier than the first owing mainly to the increasing rate of CD. Henceforward; the pharmacologic management seems to be an appealing method despite there is no clear information on the safety profile of any termination technique, as no method is risk free, particularlyin settings of prior uterine surgery and moreover, the technique used for second trimester termination is probably influenced by physician's opinion and expertise than objective outcome data [7, 15].The synthetic prostaglandins have largely replaced other techniques for pregnancy termination chiefly in the second trimester because of its efficacy, safety, cost, easy-to-use and easy-to-store properties [8]. On the other hand; some authors reported a higher incidence of life-threateninguterine rupture and major hemorrhage in women with prior caesarean scar(s) as compared to those with unscarred uteri following various techniques of mid-trimester pregnancy terminationand this increases dramatically almost many times, up to 11% in some researches, among those with a history of two or more CD [16-19]. Thispushed some others to state that misoprostol dosage of 100 μg should not be exceeded in patients with a history of CD due to the risk of uterine rupture [20].This discrepancy among different results published make us to prepare for judicious use of prostaglandin for abortion induction in our patients as the dose protocol is changed according the gestational age being higher in early second trimester, 400μgwhen the uterus is small and there is a difficulty in initiating uterine contraction and inducibility of the cervix, and lowest at the end of this gestational period, 100 μg when the uterus is supposed to have more receptors for prostaglandins and oxytocics with favorability for induction. In our study, cases used prostaglandin analogue (misoprostol) only as a method for pregnancy termination, had the success rate for initiation of uterine contraction and expulsion of the fetusof 91.4 % for GI(32/35), 2 cases evacuated after prolongation for 24 hours more and one case evacuated by hysterotomy. Of all patients in this group; 6 cases were subjected for MVA to remove some placental remnants.Our results, as regard this efficacy and safety are found slightly better than those proved by Rezk et al. 2014 [14], 87%success rate, and Naguib et al. [21], 90% success rate as well as Ranjan et al, 2016 [22] who proved 82% success rate in patients using misoprostol only for pregnancy termination at a similar gestational age.

Considering the Foley's catheter induction method, it has been used successfully for induction of second trimester missed abortionespeciallywhen

traction is correctly and properly applied [23, 24]. This actually is proved in our study where the success rate documented was 85.7%(30/35). Two of failed cases to expel the fetus in this group evacuated actually after prolongation for 1 day more, 2 cases needed dilatation and evacuation (D&E) meanwhile 1 case only needed hysterotomy. This method appeared inferior to misoprostol only method (GI) as this time needed to evacuate the uterus was longer and more cases needed MVA, 7 cases vs 6 respectively, the same findings also stated by some authors [14, 21, 26].Contrary to this; Sciscione et al. 2004 [25] stated that the Foley's catheter appears to be superior to prostaglandins for pre-induction cervical ripening being exerting its effect by disrupting the integrity of amnion-chorion, separating chorion from the decidua hence releasing local prostaglandin and cytokines. As regard the combined method treatment; our results proved that it is the most effective and with relative safety compared to other methods. It had the shortest IAI (11.66 ± 2.63 hours, $p < 0.001$)and the highest success rate (100%, p 0.02) and consequently considered the best one used. Thiscomes in accordance with results observed in many studies[13, 14, 15, 25, 27, 28]. However, some other studies disagree with our results regarding this short IAI asthey reported insignificant difference between patients used combined treatment and misoprostol only treatment, moreover, they describeda significant increase in IAI in those usingcombined methods than in misoprostol only and considered Foley's catheter use had shorter duration [29].Also; some authors [22] reported less effectiveness and success rate, being 90%, of the combined method than ours.

Investigating the complications associated with different treatments used for our patients, we found that there are more cases of diarrhea for misoprostol only users, 5 cases compared to no cases for Foley's catheter usersand only 1 case for those used both methods (p 0.024). Also, higher incidence of nausea and vomiting for patients using prostaglandin only, 8.6% vs 5.7% in patients of combined group, only 2.9% for those used Foley's catheter. These findings come similarto results found by other authors (15, 26, 29). Fever, being a side effect of misoprostol and not due to infection, was also found higher in patients used misoprostol only, 8.6% vs 2.9% in those used the combined method while no fever reported in foley's catheter group. To this findings, similar results wereproved in a study by Ercan et al., 2015 [13]. Some of our cases in all groups experienced some post-abortive bleeding but not massive or associated with the need for blood transfusion. Surprisingto us it was reported higher (8.6%) in misoprostol dependent group vs 5.7% in combined treatment group whilst only 2.9% in foley's catheter using group. These results are in accordance to those proved by Ranjan et al 2016 [22].

From the results obtained in our study, we recommend a combination of misoprostol and foley's catheter to be the best method for second trimester pregnancy termination in patients with previous CD but infact, our study has some drawbacks being one center study and the decreased number of the patients involved in each group compared to a large number of caesarean deliveries at a tertiary care center like ours. Form this aspect the authors recommend large scale studies to be investigated and published as multicentric study involving larger number of patients.

Conclusions: there are different methods available for second trimester termination of pregnancy with scarred uterus but a combination of misoprostol and Foley's catheter is considered as the most effective being have the shortest duration needed for induction beside minimal complications with negligible and accepted side effects.

Conflict of interest:the authors affirm any conflict of interest.

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Table [1]: patients 's demographic data in the studied groups.

Variables	G (I) (n = 35)	G (II) (n = 35)	Group (III)	P
Age	28.43 ± 6.08	27.49 ± 5.93	28.6 ± 6.62	0.723
Weight	79.74 ± 10.67	85.77 ± 11.6	78.37 ± 10.38	0.13
Gravidity	3.4 ± 1.74	3.49 ± 1.63	3.29 ± 1.36	0.869
Parity	1.69 ± 0.9	1.83 ± 1.1	1.94 ± 0.97	0.556
Gestationalage	18.86 ± 3.84	18.74 ± 3.86	19.09 ± 3.58	0.927
Number of LSCS **1 LSCS** **2 LSCS** **3 LSCS** **4 LSCS**	 20 (57.1) 10 (28.6) 5 (14.3) 0	 20 (57.1) 9 (25.7) 4 (11.4) 2 (5.7)	 17 (48.6) 12 (34.3) 4 (11.4) 2 (5.7)	0.819

Data presented as number (%), mean +SD, $p < 0.05$ was set significant.
Abbreviations: LSCS, lower segment caesarean section.

Table [2]: operative and postoperative data for the studied groups.

Variables	Group (I)	Group (II)	Group (III)	P
IAI (hours)	15.94 ± 3.4	17.33 ± 3.42	11.66 ± 2.63	<0.001*
Intervalfor PE/minutes	31.09 ± 5.01	27.8 ± 7.61	26.57 ± 12.17	0.450
Evacuation: Complete Incomplete	 26 (81.25) 6 (18.75)	 23 (76.67) 7 (23.33)	 31 (88.57) 4 (11.42)	0.442
The success rate:	32/35 (91.4)	30/35 (85.7)	35/35 (100)	0.02*
Complications: N&V Fever Diarrhea Bleeding	 3 (8.6) 3 (8.6) 5 (14.3) 3 (8.6)	 1 (2.9) 0 (0) 0 (0) 1 (2.9)	 2 (5.8) 1 (2.9) 1 (2.9) 2 (5.8)	 0.588 0.162 0.024* 0.588

Data presented in numbers (%), means ± SD, P <0.05 wasset significant (*).
Abbreviations:IAI; induction abortion interval, PE, placental expulsion, N&V; nausea and vomiting.

Different factors affecting the success of intrauterine insemination

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Abstract

Objective: The purpose of this study was to investigate the influence of various factors on the outcome of intrauterine insemination (IUI) as a trial for improving the quality of health care provided for women with infertility problems as well as infertility center outcomes.

Methods: Cohort study conducted over two years between December 2016 and December 2018 in IVF\ICSI center. Two hundred forty-nine couples diagnosed with different infertility etiologies underwent 487 cycles of IUI were enrolled. Ultrasound follicular measurements were recorded around time of ovulation as well as different factors were collected and compared between pregnant and non-pregnant groups. Main outcome measures were clinical pregnancy rate and risk of OHSS according to the woman's age, BMI, infertility type, different etiology of female infertility, the ovulation drug used and the quantity and size of ovarian follicles before hCG injection.

Setting: Department of Obstetrics and Gynecology, Suez Canal University Hospitals, Ismailia.

Results: Pregnancy was achieved in 21.4% of cycles enrolled in the analysis being significantly higher in women with mean follicular diameter of leading follicle of (19.8 +/- 1.97mm) in women with shorter infertility duration. The highest pregnancy rate was achieved in third IUI cycle.

Conclusion: Leading follicle mean diameter of 19.8 mm was the optimum diameter to trigger the ovulation and to have pregnancy. Early treatment of infertility is recommended as the success rate of IUI seems to get less with longer duration of infertility.

Introduction

Numerous couples, as of late, are looking for clinical guidance for sub-fertility and its management. Intrauterine insemination (IUI) is one of the treatment modalities for helping fruitless couples [1].

IUI utilizing various strategies for semen readiness is viewed as a more affordable and less intrusive treatment choice than other assisted reproduction procedures [2]. Additionally, it tends to be performed with or without controlled ovarian hyperstimulation (COH). [1]

IUI is indicated for couples suffering unexplained infertility, anti sperm antibodies, endometriosis, cervical antagonistic vibe and male sexual dysfunctions like impotency, hypospadias, and retrograde ejaculation. [3]. The viability of IUI is generally acknowledged for couples in whom infertility is brought about by a male factor or whom etiology is unexplained. [4]

IUI joined with COH utilizing gonadotropins has been demonstrated to be increasingly viable treatment of sub-fertility when contrasted with

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planned vaginal intercourse [5,6], intra-cervical insemination [7], or with IUI in natural cycles [8], apparently on the grounds that it expands the quantity of accessible oocytes for fertilization as well as the quantity of spermatozoa that arrive at the oocyte.

Pregnancy rates after IUI could be impacted by numerous components, for example, maternal age, interval of sub-fertility, indication (etiology), number of pre-ovulatory (antral) follicles, endometrial thickness. [9,10] However, various specialists didn't concur the nature and validation of these criteria.

For instance, there are clashing information about the relationship between lady's age and pregnancy rates. [11] Furthermore, the count of pre-ovulatory follicles, [10] endometrial thicknesses [11,12] and absolute motile sperms that are inseminated [9,10] have likewise been accounted for as potential indicators for pregnancy rates.[10] Notwithstanding, the agreement is fading between them.[13,14].
This cohort meant to examine the value of different contributing factors in the prediction of IUI success and to assess their role regarding clinical pregnancy rate that resulted from IUI, for example; woman's demographics, infertility status, ovarian incitement technique and sperm quality parameters. The factors mulled over for our investigation depended on past productions and the individual experience.

Research Design and Methods

Retrospective study among couples with a history of infertility (n=249) who were treated with IUI in IVF center. The data was collected between December 2016 and December 2018. The study protocol was approved by local institutional research ethics board in Benha University Hospital. Women underwent a basic fertility workup which was consisted of comprehensive medical history, hysterosalpingography (HSG), pituitary hormonal assays on the 1st five days of the menstrual cycle (FSH, LH and estradiol), semen analysis (the total motile sperms [TMS] count) and antral follicle count by transvaginal sonography (TVS).
Based on hospital data, there were 487 IUI cycles included. Women were excluded from the study if HCG trigger was postponed due to small follicular size, HSG showed bilateral tubal block, semen analysis of the partner showed sperm count of less than 5 million /ml , athsthenospermia more than 40% and women who lost follow up after the cycles.

For each couple, we registered maternal age, duration of infertility, primary or secondary and cause of female infertility were also investigated and recorded. Other parameters including the number and size of pre-ovulatory follicles, endometrial thickness, type of medication used in controlled ovarian hyper stimulation, cycle number and semen parameters were also recorded.

Ovarian Stimulation:
It was achieved by oral clomiphene citrate (clomid), different type of gonadotrophins available in our hospital or combination of both. The induction was started on the second or third day of the cycle and women were monitored until follicular size of > 18 mm achieved.

We used highly purified urinary FSH, recombinant-FSH (Gonal-F; Ares-Serono, Geneva, Switzerland; or HMG (Menogon , Ferring SAS, St. Prex, Switzerland). The initial dose of gonadotropin prescribed was (75 IU/day) depended on the woman's hormonal status, age and the infertility duration. After calculation, the starting dose was kept for five days, there after left for the function of the ovarian response as monitored by vaginal ultrasound on alternate days evaluating follicles' number and their sizes as well as endometrial thickness.

Ovulation was triggered when at least one follicle reaching(>18mm) diameter. Timed ovulation was triggered intramuscular injection of Urinary hCG 10,000IU of choriomon (IBSA pharmaceutical company, Switzerland). Women underwent insemination after 36 hours of the hCG injection).

Intrauterine insemination procedure:
Semen was obtained in a specifically designed comfortable near the laboratory two hours before the insemination and after at least48–72 hours of abstinence and left for 30 minutes at room temperature for liquefaction. The semen quality parameters (count, morphology, vitality and motility)was assessed using WHO guidelines 2010. [15]

A soft catheter (Wallace IUI catheter ©Cooper Surgical Medical Devices, Knardrupvej Målov Denmark)was used for the insemination process. The prepared semen (0.2–0.4 mL.) was slowly injected throughout the catheter which was placed at mid-uterine cavityover15 seconds.

The woman, within two weeks interval, was asked to perform a serum pregnancy test (quantitative B-hCG assay). If positive, it was repeated after 48 hours to check the doubling. The clinical pregnancy rate (CPR), confirmed with a gestational sac and fetal heartbeat on ultrasonography at 7-8 weeks, was the primary outcome measured.

Statistical method

MedCalc© version 12.5 (MedCalc© Software bvba, Ostend, Belgium) and IBM© SPSS© Statistics version 21 (IBM© Corp., Armonk, NY) were used for statistical analysis. The normality of numerically distributed data was examined with the aid of Shapiro-Wilk test. Normally distributed ones were shown as mean±SD and differences between groups were compared using the independent-samples (t-test). Median and inter-quartile range were used to present skewed numerical data and comparisons between groups were performed by the Mann-Whitney U test non-parametrically. Qualitative data were presented in number and frequency. Comparison of the two groups was performed by chi square test or Fisher's exact test whenever appropriate.

Results

We studied 487 IUI cycle in 249 couple between December 2016 and December 2018. On average each couple underwent 1.8 cycles. The descriptive data of the study participants and IUI cycles' details are shown in table (1). The couples included suffered from primary infertility (56.9%) more than secondary type. Ovarian etiology of infertility (26.9%) was the commonest among cases studied, while oligospermia was the most prevalent finding between male cases. One third of cases (30.6%) was diagnosed as unexplained infertility, on the other hand (7.4%) of cases had mixed etiologies.

Clomid was the most commonly used drug for induction of ovulation either alone or in combination (32.8% and 43% respectively). r-FSH was the commonly used form of injectable hormones followed by HPuFSH. 21.4% of our participants came pregnant within three cycles as per our hospital protocols. Moreover, 6.1% of women developed OHSS during their induction cycles.

Table (2) shows comparison between multiple parameters between women who achieved pregnancy and those who did not. The socio-demographic data as age, parity and BMI were not significantly different between both groups. Also, the infertility criteria such; type and etiology were comparable between pregnant and non-pregnant women. On the other hand, infertility duration was significantly shorter in couples with successful trials.

When we compared drug types used for induction of ovulation as well as natural cycles, there was no statistically significant difference. The mean ± SD diameter of the leading follicle was significantly larger in the pregnant group, while the thickness of endometrial line and the diameter of second follicles did not show the same difference. Pregnancy was successfully achieved in 98 cycles out of the enrolled 487 cycles with a rate of 21.4%. Moreover, the pregnancy rate was statistically significant higher in the third IUI trial. Finally, the incidence of OHSS was comparable between both groups.

Discussion

IUI is commonly performed initially as1stlinemanagement option for subfertile couples complaining of because of ejaculatory dysfunction, cervical hostility; moderate degree impaired semen parameters as well as mainly unexplained infertility. For decades, continuous work on various predictive factors that could influence the successful pregnancy rates and live birth ratio after IUI was published.

Different articles reported the influence of covariates such as female age, BMI, infertility duration, infertility type, hormone levels, different ovarian stimulation protocols, timing/induction of ovulation, pre-ovulatory follicles, endometrial thickness, frequency of IUI(once or double), sperm parameters and sperm washing procedures. [16]

Among those who achieved pregnancy, the woman's age was not significantly influencing the result (P value 0.544) this may be attributed to the relatively young age group of the studied population (29.74+/-5.24 year). Similar to our study, Brzechffa et al. [17] reported that the women's age lower than 40 years did not significantly affect the clinical pregnancy rate after IUI.

On the other hand, Bronte et al. [18] noticed a difference in the pregnancy rate in examined 9963 cycles that was age-related: (18.9%)below 26 years, (13.9%)between 26 and 30 years, (12.4%) between 31 and 35 years, (11.1%) between 36 and 40 years and declined to reach(0.5%)at 45 years or more (P<.001). Moreover, Goverde et al. [19] stated that, whatever the applied management (IUI or IVF), the case's age remained the most determinant factor for pregnancy chances. A meta-analysis showed that both woman's age as well as partner's age showed inverse relationship with clinical pregnancy rate. [16]

BMI did not significantly differ between both groups in our results. Although Dodson and Legros [20] observed that the obese woman needed higher doses of gonadotropin, they did not find any difference regarding BMI. A higher woman's BMI,up to 30 kg/m2, resulted in a significantly higher pregnancy rate (P = 0.0319). [16]

Different causes of infertility whether male, female, combined or even unexplained infertility did not significantly differ between groups. Our data showed that the longer the period of infertility the significantly lower possibility for the pregnancy to result from an IUI cycles.

Different results were found by Vlahos et al. who achieved pregnancy in 19.1% of their study population suffered anovulation Vs11% sub-fertile male factor, 10% in unexplained infertility and 9.1% in endometriosis. [21] The same result appeared by Dickey et al. who presented that the pregnancy was achieved in (46%) anovulation, (38%) male factor, (34%) endometriosis and (26%) tubal factor. [22] However, a univariate analysis revealed no statistical significant difference among couples complained of1ry or 2rysub-fertility. [16]

Other factors related to mode of induction of ovulation before insemination which might have an impact on pregnancy rate. When we compared the natural cycle versus stimulated cycle, there was no significant difference. In other studies evaluating this issue, Gallot-Lavallee et al. showed that when IUI was performed after monitoring natural cycles, the mean pregnancy rate was lower than gonadotropin stimulated cycles. [23]On the other hand, other reports revealed that the cumulative pregnancy rate reached 43% whether IUI was or was not preceded by ovulation induction. [24]Thus, in our center the regular practice is induction of ovulation in IUI cycle, and hence we don't have enough data (only nine women were followed up during natural cycles) to draw a conclusion on the pregnancy rate associated with natural cycle.

Ovarian stimulation seemed to be the only IUI contributing variable that significantly influenced pregnancy rate per cycle. IUI cycles associated with ovarian stimulation using clomid resulted in a significantly lower pregnancy rates(P = 0.0102) than HMG/r FSH stimulated ones. Hormonal measurements of estradiol or progesterone during stimulation as well as interval period between HCG injection and insemination process did not significantly influence on pregnancy rate. [16]

In contrast, our results did not show any significant difference between pregnant and non-pregnant participants regarding the drug used for ovarian stimulation. Also, the incidence of OHSS occurrence was comparable between groups and not related significantly to one drug or other. OHHS seems to be related more to the case demographics, number of pre-ovulatory follicles and the number of growing follicles during ovulation induction.

When we studied further procedure-related factors during ovulation induction follow-up using transvaginal ultrasound, the mean primary follicle diameter was the only factor that showed significant difference between both groups. The diameter of primary follicle was significantly larger among pregnant women. However, the diameter of secondary follicles or endometrial line thickness did seem to show the same significant difference.

Several studies tested the leading follicle size as a predictor of determining the IUI success. [25] Silverberg et al. reported that ovulation was successfully achieved better in cases with follicles (> 20 mm) on the hCG administration day during IUI cycles using human menopausal gonadotropins for ovulation induction and, but that was not related to the cycle outcome. [26]

Ghosh et al. reported that women with smaller follicle size (15 and 19.99 mm) achieved pregnancy in a higher rate when compared with cycles with the leading follicle of 20 mm, but they used clomid and gonadotropins. [27] Iberico et al. stated that the larger leading follicle (>20 mm) was associ-

ated with statistically non-significant higher pregnancy rates. [10]

Regarding number of follicles (>14 mm) in diameter priors to HCG administration, our study didn't show a significant effect on pregnancy rate. In contrast to our findings, Plosker and Amato showed when at least two follicles were recruited during induction of ovulation, the success possibility of IUI increased significantly (P<.006) from 2% for one follicle to reach 15% for at least two follicles. [28] Similarly, the study results of lberico et al. and Erdem et al. who reported that the antral follicle count and number of dominant follicles before hCGare both significant independent factors for live birth ratio prediction. [10, 29]

In this work, endometrial thickness did not impact the pregnancy rate. Endometrial thickness in our studied groups recorded to be (11.18 +3. 03 mm). Although pregnancy was achieved in a higher rate among women with thicker ET (12.17 +-2.86) mm versus ET (11.47+-2.83mm), but this didn't significantly differ (P value = 0.156). In study done by Zenke et al. documented significant pregnancy rates' differences above and below a cut-off endometrial thickness of 8-10mm. [30]

Pregnancy rate rose successively with increasing order of IUI cycle (16%, 18% and 49%) respectively, presumably because of the improvement of ovulation with successive stimulation. Thus, (>80%) of pregnancies were achieved within three cycles. For that some authors like Plosker and Amato advised shifting treatment to IVF\ICSI cycle after three unsuccessful IUI trials. [28]

Although in 2013, the UK National Institute for Health and Care Excellence (NICE) recommended that IUI should not be routinely performed for couples with unexplained infertility, the study of Farquhar et al.,[31]showed that IUI with ovarian stimulation is a safe and effective treatment for women with unexplained infertility and an unfavorable prognosis for natural conception .Nevertheless, recently published higher quality multi-center RCTs fail to devalue IUI in the world of more advanced medically ART. Therefore, IUI, often in combination with OS, remains a first line treatment option for many infertile couples as this strategy is supported by the results of cost-effectiveness trials.

This study was conducted to find out the influence of different contributing factors for IUI, which is widely used for infertility management, success as well as risks as OHSS. IUI with clomid or any other stimulation drug, before using IVF/ICSI, is relatively cheaper and many couples will conceive without requiring extra management. IUI in stimulated cycles might not be effective in patients with long duration of infertility. In conclusion, duration of infertility and size of leading follicle at the time of ovulation triggering were the significant contributors for pregnancy in our study population. There is a rising need for bigger trials to investigate the order of treatment and efficacy of management options based on clinical outcomes as well as cost settings

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Table (1): shows the descriptivestatistics of study participants and IUI cycle details.

Parameter			
Age*(years)			29.74 ± 5.2
Parity#			0 (0- 2)
BMI*(kg/m2)			28.39 ± 5.5
Infertility duration#(years)			4 (3- 7)
Type of infertility	**Primary infertility (n, %)**		260 (56.9%)
	Secondary infertility(n, %)		197 (43.1%)
Etiology of infertility	**Female factors**	**Unilateral tubal(n, %)**	20 (4.4%)
		Ovarian(n, %)	123 (26.9%)
		Uterine(n, %)	7 (1.5%)
		None(n, %)	307 (67.1%)
	Male factors	**Oligospermia(n, %)**	107 (23.4%)
		Asthenospermia(n, %)	59 (12.2%)
		Mixed(n, %)	33 (7.2%)
		None(n, %)	258 (56.5%)
	Combined factors(n, %)		34 (7.4%)
	Unexplained(n, %)		140 (30.6%)
Induction of ovulation medications	**None(n, %)**		9 (2%)
	Clomid alone(n, %)		150 (32.8 %)
	Clomid ± others(n, %)		198 (43%)
	r-FSH alone(n, %)		114 (24.9 %)
	r-FSH ± others(n, %)		141 (30.9 %)
	HPuFSH alone(n, %)		74 (16.2 %)
	HPuFSH ± others(n, %)		95 (20.8 %)
	HMG alone(n, %)		43 (9.4 %)
	HMG ± others(n, %)		76 (16.6 %)
	Combined(n, %)		67 (14.7%)
Ultrasound findings at time of triggering ovulation	**Endometrial line*(mm)**		11.18 ± 3.03
	Leading follicle*(mm)		18.53 ± 2.54
	2nd Leading follicle*(mm)		17,18 ± 1.98
Outcomes	**Pregnancy(n, %)**		98 (21.4 %)
	OHHS(n, %)		28 (6.1 %)
No. of follicles at triggering in cycles of OHSS#			3(3 – 4)

*mean and SD, #median and interquartile range

Table (2): shows Comparison between successful and non-successful IUI trials.

Parameter			Pregnancy n=98	No pregnancy n=389	P value
Age*(years)			29.75 ± 4.36	29.06 ± 4.98	0.544
Parity#			0 (0-2)	0 (0-2)	0.79
BMI*(kg/m2)			27.73 ± 5.81	28.68 ± 5.14	0.301
Infertility duration#			4 (3-5)	4(3-7)	0.013
Type of infertility	**Primary infertility (n, %)**		203 (56.5 %)	57 (58.2) %	0.774
	Secondary infertility(n, %)		156 (43.5) %	41(41.8) %	
Etiology of infertility	**Female factors**	**Unilateral tubal (n, %)**	3 (3.1%)	17 (4.7%)	0.746
		Ovarian(n, %)	18 (18.4%)	105 (29.2%)	
		Uterine(n, %)	2 (2.0%)	5 (1.4%)	
		None	232 (64.6%)	75 (76.5%)	
	Combined factors(n, %)		6 (6.1%)	28 (7.8%)	0.575
	Unexplained(n, %)		37 (37.8%)	103 (28.7%)	0.084
Induction of ovulation medications	**None(n, %)**		2 (2.0%)	7 (1.9%)	0.176
	Clomid alone(n, %)		32 (32.7%)	115 (32.0%)	
	r-FSH alone(n, %)		35 (35.7%)	82 (22.8%)	
	HPuFSH alone(n, %)		10 (10.2%)	64 (17.8%)	
	HMG alone(n, %)		6 (6.1%)	37 (10.3%)	
	Combined(n, %)		13 (13.3%)	54 (15.0%)	
Ultrasound findings at time of triggering ovulation	**Endometrial line***		12.17 ± 2.86	11.47 ± 2.83	0.156
	Leading follicle* (mm)		19.80 ± 1.97	18.8 ± 2.9	0.033
	2nd Leading follicle*(mm)		17.58 ± 1.62	17.03 ± 2.07	0.104
OHHS			8 (8.2%)	20 (5.6%)	0.343
Cycle order	**1st trial(n, %)**		39 (16%)	210 (84%)	0.001
	2nd trial(n, %)		27 (18%)	116 (82%)	
	3rd trial(n, %)		33 (51%)	32(49%)	

*mean and SD, #median and interquartile range

Predicting pregnancy outcome by Doppler study evaluation of fetal middle cerebral artery, umbilical artery and ductus venosus

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Abstract

Objective: To investigate the sensitivity and specify of MCA, UA and DV Doppler pulsatility index as a diagnostic value for antepartum assessment of fetal wellbeing and prediction of adverse perinatal out come in both low and high-risk pregnancies.

Patients and methods: Aprospective observational case control study conducted at Mansoura university hospitals from February 2018 through march 2019 and involved 100 pregnant ladies with a singleton pregnancy divided into two equal groups, G1 cases with high risk pregnancy, and G2 cases with low risk pregnancy as a control group. Both groups were matched for age, parity and gestational age.

Results: The basic socio-demographic characteristics of the studied cases and controls were similar in age, gravidity, parity and body mass index ($p > 0.05$) but in G1 cases had significantly higher frequencies of mean systolic blood pressure, gestational hypertension, gestational DM, mild or severe PET, oligo- hydraminions, IUGR ($p < 0.001$). Despite there was no significant difference among cases and control as regard mean (SD) of gestational age in weeks, BPD (mm), UA PI ($p > 0.05$), but there is a highly significant difference as regard FL (mm), AC (mm), MCA PI, DV PI (p values < 0.05). Also; there is a significant difference regarding the reactivity of NST being more reactive in control than cases (35 vs 2, $p < 0.001$). Again; there is a significant difference between cases and control regarding mean (SD) of gestational age at delivery (34±2 vs 39±1 in G2, $p < 0.001$), Fetal weight (gm) (2255±1047 vs 2944±976, $p < 0.001$), Agar score at 5 minutes (4.9±1.1 vs 8.3±1.4, $p < 0.001$), occurrence of hypoxia (68% vs 2%, $p < 0.001$), need for NICU admission (66% vs 2% $p < 0.001$) and acidotic cord blood with PH < 7.2 (33 cases vs 1 case only, $p < 0.001$). Logistic regression analysis revealed the cut off value MCA PI (1.62) had high sensitivity (82%), specificity (78%), PV(79%), NPV (81%) and a diagnostic accuracy of (80%). Also, UA PI cut off value was found (1.12) with sensitivity (60%), specificity (68%), PPV(65%), NPV (63%) with a diagnostic accuracy of (64%). Regarding the best cut off value of DV study by the same method, DVPI cut off value was(0.77), with sensitivity (84%), specificity (80%), PPV(80%), NPV(83%) with diagnostic accuracy (82%).

Conclusions: Doppler velocimetry studies of placental and fetal circulation can provide important information regarding fetal well-being thus yielding an opportunity to improve fetal and neonatal outcome.

Keywords: Doppler, pre-eclampsia, gestational hypertension.

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Introduction

During the first and second trimester, an ultrasound examination is used to screen the fetal malformations and assess the fetal growth disorders, a problem which is commonly encountered in pregnancy associated medical disorders namely, diabetes, pre-eclampsia, hematological diseases, cardiac problems and many others with a resultant maternal morbidity and premature iatrogenic deliveries[1]. Doppler ultrasound has emerged as a beneficial tool in the assessment of the fetal and placental circulation thus helping for prediction of adverse pregnancy outcome as the obtained data has been identified to decrease the figure of emergency operations, hospital admissions, and hospital stay for both the mother and the newborn especially with cases of suspected intrauterine growth restriction (IUGR)[2, 3]. Also, recent findings aided in timing delivery of severely growth-restricted fetuses by promoting the use of ductus venosus (DV) Doppler study. [4]. Additionally; Doppler investigation of middle cerebral artery (MCA) in combination with umbilical artery (UA) seems to improve prediction of adverse outcome in near-term pregnancies [5]. Therefore; it is postulated that Doppler ultrasound study for fetal circulations would be a useful addition to the obstetrician catalog of tests for antenatal fetal well-being and timely intervention that might be effective in reducing mortality and major morbidity in high-risk pregnancy [4]. The present study was held aiming for evaluation of the fetal MCA, UA and DV Doppler study for prediction of pregnancy outcomes in cases with high risk pregnancy.

Patients and methods

This study is a prospective clinical case control study conducted at Department of Obstetrics and Gynecology, Mansoura University Hospitals, Egypt, from February 2018 to march 2019. Local institutional research board approval for the study was obtained with IRB number [17.02.02] together with a written and verbal informed consent from all the participant after clearly explaining the nature of the study, its health benefits, possible side effects and expected complications. Therefore, the study was performed in accordance with the ethical standards laid down with the Helsinki Declaration at 1975, as revised in 1983and its later amendments. This study is prospective observational study that carried out at Mansoura university hospitals to pregnant ladies with singleton pregnancy which serially selected and divided into two groups (50 control group & 50 high risk pregnancy women) both were matched for age, parity, gestational age. The number of allocated cases selected according the formula; (N =Z2P (1 - P)d2) used by Daniel, 1999 [6].Inclusion criteria included those at gestational age from 28-34 weeks as confirmed by sure due date or TAS, viable singleton pregnancy, diagnosed as high-risk pregnancy (e.g. PET, DM, heart disease, …. etc.), not using medication during pregnancy apart from iron supplements. Those having multiple pregnancies, placenta previa, fibroid, fetal congenital anomalies, auto immune or vascular disorders, history of nicotine use, alcoholism were excluded. Those in the control group exhibited apparently normal pregnancy. Patients' basic characteristics in both groups including full detailed history together with data obtained by examination, whether general or abdominal are collected and tabulated. Subsequently, trans-abdominal ultrasound was performed for all patients in both groups while in a slightly tilted position with the head raised 30 degrees and with a small pillow under the right loin using Samsung H60 ultrasound machine with Doppler unit and a convex linear transducer (3-5 MHz)and all cases were investigated by the same sonographer. Biometric measurement to assess gestational age, fetal growth through the determination of the fetal biparietal diameter, abdominal circumference and femur length were held and recorded. Measurement of the BPD was obtained at the level of the thalamus and cavum septum pellucidum meanwhile, the abdominal circumference was obtained from the junction of the umbilical vein and the lateral left portal vein. Estimated fetal weight was detected using the head, abdominal and femur measurements [7].On measuring umbilical artery Doppler, the uterine contents are scanned to select an area of amniotic cavity with several loops of umbilical cord, then using a pulsed wave Doppler on a free loop of cord, the characteristic sound and shape of the umbilical artery identified [8].When the screen showed at least 3 consecutive wave forms of similar height, the image was frozen and UA Doppler pulsatility index (PI), resistance index (RI), systolic/diastolic ratio (S/D)were estimated and recorded. Middle cerebral artery Doppler (MCA) was measured by standardizing aplan for measuring the biparietal diameter which includ-

ed the thalamus and cavum septum pellucidum, then the color and flow mapping function was then superimposed as the middle cerebral artery seen pulsating at the level of the origin of the circle of Willis. When the screen showed at least three consecutive wave forms of similar height, the image was frozen and MCA PI, RI and S/D were also estimated. Care was taken to apply minimal pressure by the transducer on the maternal abdomen as fetal head compression can alter fetal intracranial pressure and hence the arterial flow velocity wave forms. Ductus venosus (DV) Doppler was estimated by identifying the DV using two-dimensional and color Doppler imaging in a mid-sagittal section or oblique transaction of the fetal abdomen. The sample volume was placed in the distal smallest portion of the vessel in order to record the highest blood velocities and to avoid interference from blood flow in the IVC. The ductus venosus blood velocity waveform was a peak velocity during systole (S), end-systolic blood velocity (ES), peak velocity during diastole (D) and velocity corresponding to atrial contraction (A) The DV S/A-ratio was calculated and related to the normal reference value [9]. It is noted that all ultrasound recordings were obtained during periods of fetal apnea and quietness with absent movements while the mother is normoglycemic. All patients in both groups were followed up till delivery, then the mode of delivery and neonatal outcome were recorded and tabulated. All neonates were subjected to Apgar scoring after 1 and 5 minutes by an expert neonatologist attending delivery. Adverse neonatal outcome is considered when Apgar score is less than 7 at 5 minutes according to Caseyet al., 2001[10],neonatal admissions to intensive care units, fetal death either intrauterine or early after birth or cord blood sample PH showed acidosis i.e. pH less than 7.25[11].

Statistical analysis

The collected data were coded, processed and analyzed using the SPSS (Statistical Package for Social Sciences) version 17 for Windows® (SPSS Inc, Chicago, IL, USA). Qualitative data was presented as number and percent. Comparison between groups was done by Chi-Square test. Quantitative data was presented as mean ± SD. F-test (One Way Anova) was used to compare between more than two groups. $P < 0.05$ was considered to be statistically significant. Independent-samples t-test of significance was used when comparing between two means. Chi-square (X2) test of significance was used in order to compare proportions between two qualitative parameters. Receiver operating characteristic (ROC curve) analysis was used to find out the overall predictivity of parameter in and to find out the best cut-off value with detection of sensitivity and specificity at this cut-off value.

Results

The basic socio-demographic characteristics of the studied cases and controls are shown in Table 1. Both groups were similar in age, gravidity, parity and body mass index ($p> 0.05$). Compared to controls, women in G1 (cases) had significantly higher frequencies of mean systolic blood pressure (145.4±20.2 vs 105.7±17.6, $p <0.001$), newly developed gestational Hypertension, gestational DM, per-eclampsia (mild or severe), oligo- hydraminions, IUGR or combined severe preeclampsia, oligo- hyarminions & IUGR ($p <0.001$), table [1].

Data showing comparison of fetal and neonatal characteristics in both groups were presented in table 2. Despite there was no significant difference among cases and control as regard mean (SD) of gestational age in weeks at examination, BPD (mm), UA PI (31±2.2 vs 31±2.3, 84.86±17.63 vs 85.21±15.42, 1.19±0.43 vs 1.37±0.24, $p >0.05$), but there is a highly significant difference as regard FL (mm), AC (mm), MCA PI, DV PI (51.17±11.46 vs 62.03±9.60, 203.44±87.13 vs 268.53±99.62, 1.22±0.31 vs 1.94±0.33, 0.84±0.48 vs 0.70±0.23 respectively, p values < 0.05). Also; there is a significant difference regarding the reactivity of non-stress test being more reactive in control than cases (35 vs 2, $p <0.001$).Again; there is a significant difference between cases and control regarding mean (SD) of gestational age at delivery (34±2 vs 39±1 in G2, $p <0.001$), Fetal weight (gm) (2255±1047 vs 2944±976, $p <0.001$), Agar score at 5 minutes (4.9±1.1 vs 8.3±1.4, $p <0.001$), occurrence of hypoxia (68% vs 2%, $p <0.001$), need for NICU admission (66% vs 2% $p <0.001$) and acidotic cord blood with PH < 7.2 (33 cases vs 1 case only, $p <0.001$), table [2].Receiver operating characteristics (ROC curve) analysis in table (3) was used to define the best cut off value of MCA

PI and revealed the cut off value 1.62 had high sensitivity(82%), high specificity (78%), positive predictive value 79%, negative predictive value of 81% and this means a valuable diagnostic accuracy of 80%. Also, in table (3) ROC curve study for UA showed that UA PI at the cut off value 1.12 with sensitivity 60%, specificity 68%, positive predictive value 65%, negative predictive value 63% with diagnostic accuracy of 64%. Regarding the best cut off value of DV, the same method used showed that DVPI cut off value 0.77, with sensitivity of 84%, specificity 80%, positive predictive value 80%, negative predictive value 83% with diagnostic accuracy 82%, table [3].

Discussion

To our knowledge, no previous data had been published from our locality on Doppler study involving UA, MCA and DV PI and S/D ratios for predicting the outcome of high-risk pregnancies. There are many researches performed involving each parameter separately but results from our study confirmed the fact that; studying DV PI had highest sensitivity (84%), negative predictive value (83%) and a valuable diagnostic accuracy (82%).

It is well known that Doppler study in obstetrics is largely used to examine the vascular system as the elevated impedance to blood flow in the placenta is reflected by abnormal umbilical artery velocimetry with subsequent placental insufficiency and fetal growth restriction but this may be associated with a change in the fetal cerebral waveforms suggesting increased blood flow to the brain [1, 12]. However, an abnormal umbilical artery signal and the brain-sparing effect do not necessarily predict the outcome in growth-restricted fetuses. Recently, more attention has been paid to the venous system as umbilical vein pulsations and reversed flow in the ductus venosus as threatening signs of perinatal mortality [13] as the ductus venosus is considered as the only direct link between the inferior vena cava and the umbilical vein[14]. Few studies have evaluated the fetal MCA, UA and ductus venosus Doppler study for prediction of pregnancy outcomes as stated by Gardosi, et al., 2018 [15].

Our study results regarding preliminary ultrasonography data showed that patient's group had statistically significant lower FL, AC than those of control group and this comes in agreement with data proved by some authors [16, 17].

The clinical findings of the study cohort demonstrated that patients group displayed lower statistically significant reactive non-stress than control group ($p < 0.001$) and this came in agreement with those proved by Garg, et al., 2016 [18]but contrary to Verma, et al., 2015 [19]who verified the predicting value of NST for fetal compromise is negligible. In our patients, the gestational hypertension represented the highest percentage of risk factors while gestational DM and Mild per- eclampsia had nearly equal prevalence, severe per- eclampsia displayed the 4thrisk factor rank, Oligo-hydraminions, IUGR and Severe PET, oligo- hyarminions & IUGR come as last. These results came in agreement with many authors [20-22] but not in agreement with some others [23-25] who reported that the incidence of GDM to be first and the overall incidence of gestational hypertension to be as low as 5.9% with annual fluctuations.

Also, the results obtained by the current study indicated significant differences between patients and controls group regarding MCA and DV Doppler ultrasound and this came in consistent with Turan, et al, 2008 who identified the sequence of progression of arterial and venous Doppler abnormalities from the onset of placental insufficiency in IUGR. In other words, our Doppler indices gained by studying multiple vessels in the feto placental circulation can help in the monitoring of compromised fetus, predicting neonatal morbidity and useful in determining the optimal time of delivery in complicated pregnancies, a notion which is recently proved by some researchers [1, 26, 27].

Again; our study proved a statistically significant difference between patients and healthy group regarding gestational age at delivery, being shorter in patients than control, lower fetal weight, lower average Apgar core with more need for NICU as well as more acidotic blood and hypoxia, the findings which stated before by li, et al., 2013 and Harper, et al., 2016 [29, 30]. Despite our research verifies the advantage of studying multiple vessels in the placental and fetal circulations simultaneously for governing the pregnancy and neonatal outcome but indeed it has some drawbacks. First, it is a uncenter study involving only 100 patients and actually this is a relatively low number in

comparison to the total number of high risk pregnancy seen, booked, followed up in a tertiary care hospital likeours, so the authors advice for a large multicenter study for the results to be more convenient, appropriate and impressive. Second, the neonatal outcome recorded in our results depend only on the short period follow up for the first day and later follow up records, including early or late deaths or even short term morbidities, were missed as this point was the concern of neonatologist thus adding a point of weakness to our work.

Conclusion

Doppler velocimetry studies of placental and fetal circulation can provide important information regarding fetal well-being, yielding an opportunity to improve fetal outcome.

Conflict of interest: no conflict of interest to be declare.

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