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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.

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2- Books:

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Letter from the Editor:

Dear colleagues,

Very interesting subjects are included in this edition. Routine office hysteroscopy was not an added cost before ICSI even in cases with normal trans vaginal ultrasonography. It can diagnose and treat uterine cavity lesions on the same setting. An appreciable level of awareness about the HPV infection and the vaccination. Females had better awareness regarding the infection as well as the vaccine. Medical education has a positive impact on raising awareness regarding the causes of cervical cancer, the availability of the vaccine, and its protective efficacy.

The GnRH agonist could be an effective and safe alternative to the traditional HCG in ovulation triggering after sequential minimal ovarian stimulation in PCOS patients without affecting ovulation and clinical pregnancy rates. Progesterone primed ovarian stimulation is safe and effective for infertile PCOS women. It achieved appropriate LH suppression with nearly no profound suppression or moderate-to-severe OHSS. The outcomes of this protocol were comparable to the GnRH-antagonist protocol; however, it is more cost-effective.

Histopathological examination seemed to be a promising tool in the context of assessment of products of conception in which the prevalence of molar pregnancy was 7%. In addition, incidence of molar pregnancy has no significant correlations with all clinical features as well as with blood groups. Random PCR may be employed in urgent situations as a quick, simple, and accurate diagnostic for the detection of substantial proteinuria in hypertensive diseases during pregnancy. A short anovaginal distance predicted the occurrence of perineal tears significantly.

There is no clinical difference between using a multiple-dose regimen and using long-acting insulin analogues to control gestational diabetes regarding maternal and foetal outcomes. However, a multiple-dose regimen needs a shorter time for blood glucose control than long-acting insulin. It is to be noted that long-acting insulin is more expensive.

Best regards.

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Evaluation of the analgesic effect of Intraperitoneal instillation of lidocaine with and without meperidine versus non-steroidal anti-inflammatory drugs during and after gynecological laparoscopic procedures

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Abstract

Background: Drugs are used in a wide range to control pain as they are easy to apply by any route, fast, and effective. Also, they do not need special skills or techniques. But it may be dangerous if overdoses are given, leading to addiction or withdrawal symptoms, especially if used alone without sedation or muscle relaxant.

Methods: In this study, two hundred cases were classified into four groups of patients undergoing minor laparoscopic procedures as diagnostic, ovarian drilling, adhesiolysis, ovarian cystectomy, ectopic pregnancy, endometriosis ablation, etc. Every group included 50 patients. Group I received intraperitoneal lidocaine. Group II received intraperitoneal lidocaine with meperidine. Group III received intramuscular NSAID drugs (diclofenac sodium) 75 mg. Group IV received intraperitoneal saline. Postoperative pain was assessed using a numeric pain rating scale. A highly significant difference between Group II and Group I or III was seen when the pain score across the four groups was examined at 0, 2, and 6 hours postoperatively. Comparing Group IV to the other groups, it is highly significant (high score). When the pain scores from the four groups were assessed at 12 hours postoperatively, groups I and II revealed a significant difference compared to group III. Comparing Group IV to the other groups reveals it is highly significant. So, We concluded that the "intraperitoneal lidocaine with or without meperidine" procedure was simple, risk-free, and without side effects. In contrast to non-steroidal anti-inflammatory drugs, intraperitoneally administered lidocaine, both with and without meperidine, significantly reduces postoperative discomfort after minor gynecologic laparoscopic surgery.

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INTRODUCTION

Minor gynecological laparoscopic surgeries need the appropriate basic and special equipment to make challenging procedures technically viable and safe. A

suction and irrigator probe, two or three forceps, and a bipolar electrocoagulator are sufficient for most surgeries. Semi-reusable and reusable instruments are now readily available because of the operative laparoscopy industry's rapid growth. Cost and efficacy are taken into account while choosing the right instruments because having too many instruments might complicate operations and increase field clutter (1)

Hence, laparoscopy describes the surgical strategy and is linked to pain in addition to that brought on by intra-abdominal damage. Nonetheless, compared to the same surgical operation made possible via a laparotomy, discomfort experienced after laparoscopy is substantially less and lasts less time. The procedure's overall costs are lower, and the long-term morbidity is lower (2).

Early hospital discharge has been made possible by decreased pain, provided that the medication used to treat the pain is not simultaneously used to prohibit discharge due to nausea, ileus, or decreased consciousness and autonomous function. The early discharge also compromises the effectiveness of strong analgesics and makes it challenging to adequately assess and treat post-laparoscopy pain (3).

As they are simple to administer via any method, quick, and practical, drugs are used widely to manage pain. They don't also require any specialized knowledge or expertise. However, if an overdose is administered, especially if it is used without sedation or a muscle relaxant, it could be harmful and cause addiction or withdrawal symptoms. They are also pricey. These substances can be categorized as opioids, cyclo-oxygenase inhibitors, non-steroidal anti-inflammatory drugs, anti-depressants, anti-convulsants, neuroleptic agents, corticosteroids, and systemic administration of local anesthesia (4).

The study aimed to examine the effects of intraperitoneal lidocaine (local anesthesia) following minor gynecological laparoscopic procedures with and without meperidine and non-steroidal anti-inflammatory medicines (NSAIDs).

Patients and methods

Study design:

This study is a comparative interventional study in a randomized manner conducted at United Doctors Hospital, Jeddah, and Sajir General Hospital, KSA, in the period from July 2021 to January 2023. It included 200 patients.

Inclusion criteria:

200 cases were classified into four patients undergoing minor laparoscopic procedures: diagnostic, ovarian drills, adhesiolysis, ovarian cystectomy, ectopic pregnancy, endometriosis ablation, etc. Every group included 50 patients.

Group I received intraperitoneal lidocaine. **Group II** received intraperitoneal lidocaine with meperidine. **Group III** received intramuscular NSAID drugs (diclofenac sodium) 75mg. **Group IV** received intraperitoneal saline.

Exclusion criteria:

Laparoscopic hysterectomy and myomectomy patients were omitted. Cardiovascular, metabolic, hepatic, and vascular disorders were prohibited in the patients. Regular analgesic users and those with allergies to meperidine or lidocaine were excluded from the study.

Each patient underwent a standard gynecological examination and a general, abdominal, and local one. Patients were instructed verbally and in writing on how to complete the pain evaluation questionnaires during the pre-assessment session.

Preoperative tests: CBC, liver and kidney functions, coagulation profile (PT and PTT), and fasting blood sugar.

Methods:

All operations were performed in the same manner, under general anesthesia.

Analgesia for the four groups was as follows:

(1)Group I (n = 50 patients):

They received 20 cm lidocaine 2% (400 mg) injected into the intraperitoneal cavity at the end of surgery.

(2)Group II (n = 50 patients):

They received 20 cm lidocaine 2% (400 mg) intraperitoneally and 50 mg of meperidine diluted to 10 ml by normal saline injected into the intraperitoneal cavity at the end of surgery in the same manner.

(3)Group III (n = 50 patients):

They received non-steroidal anti-inflammatory drug (declofenac sodium 75 mg intramuscularly) after recovery.

(4)Group IV (n = 50 patients):

They received 20 ml normal saline intraperitoneally at the end of the surgery in the same manner.

Assessment of pain:

With the help of the facial rating scale, postoperative pain was evaluated. six faces in a pictogram, each with a different expression—from pleased or smiling to teary—are displayed. This scale is appropriate for patients with communication issues, such as young children, elderly patients, confused patients, or patients who do not speak the local language. In each group, the pain level was measured at recovery at two, six, and twelve hours. analysis of data Using Epi-Info version 6 and SPP for Windows version 8 for data entry, verification, and analysis.

Results

Age, weight, and height were equivalent amongst the study groups ($p > 0.05$). Laparoscopic diagnostic procedures, ovarian cystectomy, drilling, IUd extraction, and adhesiolysis are among the mentioned indications for laparoscopy in table 1 and 2, respectively. Table (3) contrasts the duration of the operation. The length of the operation varied between the analyzed groups, with group II having the least time and group I having the longest. When the pain scores from the four groups were compared at the halfway point after surgery, group II had a significantly lower score than either group I or group III (p 0.001). Comparing Group IV to the other groups, Group IV has a very significant (high score) result (8.5 0). ($p < 0.001$). Comparing the pain scores of the four groups at 2 hours postoperatively revealed a significantly significant difference in group II (3 0.2) as opposed to the group I (4.36 0.6) or group III (5.3 0.5) (p 0.001). Comparing Group IV to the other groups, it is extremely significant (7 0; p 0.001). When the pain scores for the four groups were examined at 6 hours postoperatively, group II (2 0) demonstrated a significantly significant difference when compared to group I (2.4 0.4) or group III (3.3 0.4) (p 0.001). Comparing Group IV (6 0) to the other groups, the difference is highly significant (p 0.001). Comparison of the pain score between the four groups after 12 hours postoperatively revealed a highly significant difference in groups I and II compared with group III (1 ± 0 and 1 ± 1 versus 2 ± 0.1) ($p < 0.001$). Group IV is highly significant compared to the other groups ($p < 0.001$). (Table 4).

Table (1): Demographic characteristics

	I	II	III	IV
Age (years)	31.8 ± 3	32.1 ± 4	32 ± 4	31.6 ± 3
Weight (kg)	67.1 ± 6.1	66.5 ±4.2	64.5 ± 9	65.9 ± 7
Height (cm)	160 ± 11	159 ± 12	158 ± 15	159 ± 11.9

ANOVA test

Table (2): Indications for laparoscopy

Indications	**I (n = 50)**		**II (n = 50)**		**III (n = 50)**		**IV (n = 50)**	
	No	%	No	%	No	%	No	%
Diagnostic	12	24	15	30	17	34	20	40
Ovarian cystectomy	10	20	7	14	8	16	5	10
Drilling	18	36	20	40	15	30	16	32
Extraction of IUd	7	14	5	10	8	16	6	12
Adhesiolysis	3	6	3	6	2	4	3	6
Ectopic pregnancy	1	2	2	4	1	2	1	2

ANOVA test

Table (3): Operative time among study groups

Operative time (minutes)	**I**	**II**	**III**	**IV**
Mean ± SD	48.1 ± 9	45.5 ± 10	46.1 ± 11	47.1 ± 10
Range	40-60	40-60	40-60	40-60

ANOVA test

Table (4): postoperative Pain score

Pain score after ½ hour	**Mean ± SD (range)**
I	6.2 ± 0.5 (5-7)
II	4.5 ± 0.5 (4-5)
III	7.5 ± 0.5 (7-8)
IV	8.5 ± 0
Pain score after 2 hours	**Mean ± SD (range)**
I	4.Mean ± SD (range)
II	3 ± 0.2 (3-4)
III	5.3 ± 0.5 (5-6)
IV	7 ± 0

Pain score after 6 hours	**Mean ± SD (range)**
I	2.4 ± 0.4 (2-3)
II	2 ± 0
III	3.3 ± 0.4 (3-4)
IV	6 ± 0
Pain score after 12 hours	**Mean ± SD (range)**
I	1 ± 1
II	1 ± 0
III	2 ± 0.1 (3-4)
IV	5 ± 0

$p < 0.001$

Discussion

Following laparoscopic operations, acute postoperative pain is typical. After laparoscopy, using local anesthetics for postoperative pain reduction may enhance initial pain management and reduce the requirement for postoperative analgesia (5).

Improved early postoperative pain management is crucial because some laparoscopic surgeries are done on a day-case or fast-track basis. Laparoscopic day-case surgery may be made more common by using local anesthetic infiltration for postoperative analgesia (6).

Many analgesics have been researched in the quest for the ideal postoperative regimen. Local anesthetic drugs have potential theoretical and practical benefits for day-case surgery. The use of local anesthetics to relieve peripheral discomfort during laparoscopic procedures has been studied in more than 60 published trials. Nonetheless, despite the abundance of published data, the results of these trials are challenging to evaluate due to the range of clinical situations, medications, doses, application sites, comparators, and reported pain effects (7).

The main goal of the current study was to assess non-steroidal anti-inflammatory drugs (NSAIDs) and intraperitoneal local anesthesia with and without meperidine for analgesics following minor gynecological laparoscopic procedures.

The current study was conducted on patients receiving quick diagnostic or minimally invasive surgical gynecologic laparoscopic procedures. We predicted that these operations would take about the same time to complete.

Comparison of the pain scores across the four groups in our study at 30 minutes, 2 hours, and 6 hours postoperatively revealed a significant difference in group II compared with group I or III. Group IV is highly significant (high score) compared to the other groups.

When the pain scores from the four groups were assessed at 12 hours postoperatively, groups I and II revealed a significant difference compared to group III. In comparison to the other groups, Group IV is very important.

Due to the handling during surgery and the irritation of the diaphragm by dissolved carbon dioxide, this form of surgery resulted in significant postoperative discomfort.

The abdominal wall holes made for the trocars also contributed less to the somatic component of the pain. Other than nausea and vomiting in the patients, which may have been caused by lidocaine or other factors, no side effects were noted. Drugs can be easily, safely, and without side effects administered intraperitoneally for analgesia. (8)

The primary benefit of utilizing local anesthetics is that they do not have the side effects of opioids, which can cause recovery and hospital discharge to be delayed. Common side effects include pruritis, drowsiness, impaired gastrointestinal motility recovery, and postoperative nausea. Also, if the use of opioids is avoided by using local anesthetics during the postoperative period, the time it takes for bowel function to return may be shortened (9).

For minimally invasive procedures like gynecological laparoscopy, local anesthetics have been injected into the peritoneal cavity (10).

Meperidine's local anesthetic effects after subarachnoid delivery seem comparable to lidocaine's. Along with having a local anesthetic effect when administered alone, meperidine has also been proven to increase the block level generated by another established local anesthetic (11).

In our study, lidocaine and meperidine administered intraperitoneally showed efficacy and decreased pain scores at each period tested compared to IM NSAIDs.

After local anesthetic and an opioid have been administered, the intraperitoneal cavity is a useful postoperative analgesia route. In our clinical study of 200 patients undergoing minor laparoscopic procedures, patients who received a combination of intraperitoneal meperidine 50 mg and intraperitoneal lidocaine 400 mg showed significantly lower pain scores at rest when compared to patients who received an intramuscular non-steroidal administration.

Rapid peritoneal distension may be accompanied by blood vessel tearing, traumatized nerve traction, and the release of inflammatory mediators. The pain is present often after laparotomy, and both laparotomy and laparoscopy are associated with persistent pneumoperitoneum, sometimes for three days (12).

Hohlrieder et al. (2017) discovered that whereas 70% of patients experienced the most pain 24 hours following gynecological laparoscopic surgery, only 1% of patients experienced it two hours after the procedure. (13).

Conclusion

t is easy, secure, and free from side effects to administer intraperitoneal lidocaine with or without meperidine. Compared to non-steroidal anti-inflammatory medicines, intraperitoneally administered lidocaine, both with and without meperidine, effectively lessens postoperative discomfort following minor gynecologic laparoscopic surgery.

References

1. Nezhat C, Nezhat F, Seidman DS, Nezhat C. Incisional hernias after operative laparoscopy. J Laparoendosc Adv Surg Tech A. 1997;7(2):111-5.
2. Barkun JS, Barkun AN, Sampalis JS, Fried G, Taylor B, Wexler MJ, et al. Randomised controlled trial of laparoscopic versus mini cholecystectomy. The McGill Gallstone Treatment Group. Lancet. 1992 7;340(8828):1116-9.
3. Wagner LE 2nd, Eaton M, Sabnis SS, Gingrich KJ. Meperidine and lidocaine block of recombinant voltage-dependent Na+ channels: evidence that meperidine is a local anesthetic. Anesthesiology. 1999;91(5):1481-90.
4. Warden SJ. Prophylactic Use of NSAIDs by Athletes: A Risk/Benefit Assessment. The Physician and Sports Medicine.

2019; 38 (1): 132–138.

5. Argoff CE. Pain management secrets. American College of Chest Physicians. 2019 ;12(34): 15-18.
6. Carbonell AM, Joels CS, Kercher KW, Matthews BD, Sing RF, Heniford BT. A comparison of laparoscopic bipolar vessel sealing devices in the hemostasis of small-, medium-, and large-sized arteries. J Laparoendosc Adv Surg Tech A. 2003;13(6):377-80.
7. Piper SN, Fent MT, Rohm KD. Meperidine does not prevent postanesthetic shivering: A dose-ranging study. Can J Anaesth. 2020; 48(8): 742-7.
8. Pickard J. Guidelines and the adoption of 'lipid rescue' therapy for local anaesthetic toxicity. Anaesthesia. 2009; 64:122-5.
9. Ng A, Parker J, Toogood L, Cotton BR, Smith G. Does the opioid-sparing effect of rectal diclofenac following total abdominal hysterectomy benefit the patient? Br J Anaesth. 2002;88(5):714-6.
10. Møiniche S, Jørgensen H, Wetterslev J, Dahl JB. Local anesthetic infiltration for postoperative pain relief after laparoscopy: a qualitative and quantitative systematic review of intraperitoneal, port-site infiltration and mesosalpinx block. Anesth Analg. 2000;90(4):899-912.
11. Carter JE , McCarus SD. Laparoscopic myomectomy: time and cost analysis of power vs. manual morcellation. J Reprod Med 2017; 42: 383.
12. Schoeffler P, Diemunsch P, Fourgeaud L. Coelioscopie ambulatoire. Cahiers d'Anesthesiologie. 2013; 41: 385–391.
13. Hohlrieder M, Brimacombe J, Eschertzhuber S. A study of airway management using the ProSeal LMA compared with the tracheal tube on postoperative analgesia requirements following gynecological laparoscopic surgery. Anesthesia. 2017; 62:913–8.

Use of Hysteroscopy and Pregnancy Outcomes during Assisted Reproduction by ICSI, Add on cost or certified indication!

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Abstract

Aim: To evaluate the clinical efficacy of office hysteroscopy (OH) in infertile women with looking normal uterine cavity as detected in by TV/US, before starting primary ICSI cycles. Also to evaluate the value of hysteroscopy (HSC) and new ICSI outcomes in women with RIF, (history at least two previous failed ICSI attempts).

Study Design: A prospective clinical comparative cohort study.

Setting: Obstetrics and Gynecology Department, Menofia University and a private assisted reproduction unit in Cairo, Egypt.

Methodology: ICSI after hysteroscopy was performed in two groups of infertile women. Patients with normal uterine cavity (group I, No. 125) and patients with RIF (group II, No. 125). Then, ICSI was performed for all enrolled women in study groups with no statistically significant difference ($p > 0.05$) regarding demographic data (except age) and the number of oocytes retrieved and the number of embryo transfer. Then, all subjects were followed up for 3 weeks after embryo transfer for detection of pregnancy by ultrasound.

Result: There was no statistically significant difference in IR both groups (15.8% Vs. 10.2%). Also, the PR showed no statistically significant difference (32% vs. 22.4%). There was a statistically significant association between PR and hysteroscopy before ICSI in group II. Also, hysteroscopy had detected uterine cavity lesions in more than half of cases with normal TV/US.

Conclusions: In this study routine office hysteroscopy (OH) was not an added cost before ICSI even in cases with normal TV/US. OH can diagnose and treat uterine cavity lesions on the same setting. Robust and high-quality multicentric RCTs are advised before hysteroscopy can be included during the basic clinical infertility investigation.

Keywords: Hysteroscopy; ICSI; pregnancy rate; uterine cavity lesions.

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Introduction

Implantation is vital and complex process to start pregnancy, its failure could be due to a variety of reasons, including embryonic and/or endometrial factors, but remains unexplained in many cases. RIF is diagnosed in women having history of at least two previous failed ICSI attempts[1].

The presence of intrauterine pathologies can negatively affect the chance of implantation and pregnancy rates in women undergoing assisted reproduction, as implantation failure were present , has been reported to be as high as 50% in women with uterine pathology [2,3].

Hysteroscopy is considered as the gold standard for diagnosis of intrauterine pathologies. HSG, TV/US and saline infusion sonography are other tools to assess the inner architecture of the uterus [4,5] . World Health Organization (WHO) recommends HSG alone as one of the basic investigations for infertile couples. Office hysteroscopy is only recommended by the WHO when clinical or complementary exams (ultrasound, HSG) suggest or diagnose uterine cavity abnormality or there is IVF/ICSI failure [4].

Currently, there a debate for examination of uterine cavity by OH before starting IVF/ICSI[5]. Basically ,the best methods for assessing uterine abnormalities typically include some combination of TV/US, HSG, and hysteroscopy (HSC) can only be used if uterine cavity pathology is suspected [6]. But, HSG has low specificity, high false-negative and false-positive rates[7]. TV/US is a non-invasive and reproducible technique, but it is not very sensitive [11]. . OH can be typically performed after RIF , if there is evidence of an abnormal uterine cavity from investigations[8,9]. HSC allows reliable visual assessment of the uterine cavity to diagnose intrauterine adhesions, endometrial polyps, submucous fibroids, endometritis, or uterine malformations that could interfere with implantation, and on the same time provides the opportunity to perform therapy in the same setting such as removing endometrial polyps, submucosal fibroids[10,11]. Therefore, hysteroscopy is considered as one of the common investigations proposed for women undergoing IVF treatment is to evaluate the uterine cavity[13].

HSC can identify minor intra uterine abnormalities in 30% to 45% in cases with normal TV/US. The abnormalities found by HSC were significantly higher in women with previous assisted reproductive techniques failure[13-16]. The value of HSC in women with RIF were confirmed by two prospective RCTs demonstrating significantly increased clinical pregnancy rates [17,18]. Pregnancy outcomes can be improved in patients with/without RIF or with/without identifiable uterine pathology undergoing routine OH before IVF [14,19]. Also, a meta-analysis performed in 2008 suggested that HSC could improve the outcomes in women with RIF[12]. On the other hand, other studies have suggested there is no value for routine OH in patients undergoing ICSI assessment or in patients with RIF. In a RCT, study was designed to assess whether routine OH before the first IVF treatment cycle could increase the PR. But these results revealed that routine OH does not improve live birth rates in infertile women with a normal TV/US of the uterine cavity [20]. A retrospective study suggested that HSC should be used as a routine infertility examination because its diagnostic rate is high in patients with repeated IVF failure. However, the clinical outcomes in patients with repeated IVF failure who had HSC with no pathology and with pathology when compared, no statistical differences were found . So, doing OH before ICSI was of no significant value in improving pregnancy outcomes [21]. On the other hand in a review the conclusion was that small number of prospective RCTs cannot clearly demonstrate that removal of uterine cavity lesions by HSC can improve IVF outcomes[22].

Nowadays hysteroscopes are available with smaller diameter and this has made the use of outpatient or office hysteroscopy feasible as a routine examination[1,6].

OH can provide accurate visual assessment, and on the same time provides a therapeutic chance to treat any detected cavitary pathology. The concept nowadays, in women with one or more failed ICSI cycles there is evidence that hysteroscopy before starting ICSI treatment could increase the chance of pregnancy rate in the subsequent ICSI cycle. On the other hand, the value of routine hysteroscopy prior to starting the first ICSI treatment cycle are lacking and not recommended [1,6,9].

Aim of study

The aim of the present study was designed to evaluate the clinical efficacy of office hysteroscopy (OH) before starting primary ICSI cycle in women with normal uterine cavity by TV/US, also to evaluate the effect of hysteroscopy (HSC) on new ICSI cycle outcomes in women RIF.

Patients and Methods

Study design: Clinical prospective observational comparative study.

Setting: at Obstetrics and Gynecology Department, Menofia University and a private Reproduction & IVF Unit, Cairo ,Egypt.

Duration: Started May 2019 and completed April 2021

Patients: 250 participants selected for ICSI divided in two groups

- ***Group 1:*** included 125 participants, for office hysteroscopy (OH) that was done before starting primary ICSI cycle.
- ***Group 2:*** included 125 participants with history of RIF after ICSI. Hysteroscopy (HSC) was done before starting new ICSI cycles.

Ethical consideration: Ethical approval No. 19519OSGN-2019 of the institutional board committee before the start was given and a written informed consent from each included patient was a must during the study.

Inclusion Criteria:

- Women indicated for IVF/ICSI using the standard long GnRH-a protocol.
- Ages eligible for the study: 20 years to 38 years.
- No evidence of uterine pathology by TV/US and HSG .
- BMI between 20 and 35.
- Normal male factor (WHO semen critrria,2010)

Exclusion Criteria:

- Unexplained poor responders during the pending ICSI cycle,(AFC 4 or less and AMH 0.8 ng /m)
- Past or current medical disorders.

All patients that included in the study the following were done:

- Proper history, examination and investigations including TV/US, HSG and fertility hormonal profile ,FSH,LH,AMH,E2.
- Office hysteroscopy performed during the he proceeding menstrual cycle, using a rigid hysteroscope.
- Controlled ovarian hyper stimulation-embryo transfer (COH-ET) using the standard long protocol of the private ART Unite.
- **Study Outcomes documented :** by
- **Biochemical pregnancy:** a positive pregnancy test performed 2 weeks after ET. HCG >5 IU/l was considered as chemical pregnancy.
- **Clinical pregnancy:** using B-mode TV/US performed 5 weeks after E T. shows a gestational sac.

- **Implantation rate:** calculated as the viable embryo numbers divided by the transferred embryo numbers, multiplied by 100.
- **Live birth rate:** based on the number of live births out of the total number of transfer cycles.
- **Miscarriage rate:** the miscarriages before 20 weeks of pregnancy out of the total pregnancies.

Results

This study was conducted at Obstetrics and Gynecology Department, Menofia University and ART private center, Cairo, Egypt . The included women were 250 who were selected and prepared for hysteroscopy and ICSI.

The enrolled women were divided into 2 main groups:

- **Group 1:** 125 women without any uterine cavity abnormalities detected by TV/US.
- **Group 2:** 125 women with RIF (at least 2 previous failed ICSI attempts)

The analyzed data were collected and tabulated.

The following results were obtained.

Table (1): Personal and demographic data of women in the study groups

	Group 1 (n= 125)		Group 2 (n= 125)		P-value[3]
Age: (years)					
Mean ± SD	29.57 ± 5.31		31.45 ± 5.13		0.005*
Duration of marriage: (years)					
Mean ± SD	7.57 ± 4.83		8.63 ± 5.02		0.092
Median (Range)	7 (3-15)		8 (2-20)		
Weight (kg):					
Mean ± SD	72.59 ± 12.81		71.85 ± 10.45		0.621
Height (cm):					
Mean ± SD	156.25 ± 6.35		157.39 ± 6.19		0.157
BMI:					
Mean ± SD	29.75 ± 5.01		29.02 ± 3.99		0.209
Duration of infertility: (years)					
Mean ± SD	7.15 ± 4.69		7.72 ± 4.82		0.311
Median (Range)	5.5 (1.0-20.0)		7.0 (1.0-22.0)		
Type of infertility:					
Primary	90	72%	92	73.6%	0.882
Secondary	35	28%	33	26.4%	

*p <0.05 is significant

No statistically significant differences between the demographic data of women in the two groups. Age only was statistically significant higher group 2 .

Mean infertility duration in the two groups was more than 7 years with no statistical differences. Most of the women had primary infertility (more than 72% in the study groups) with no statistically significant differences.

	Group 1 (No 125)		Group 2 (No 125)		p-value
	No.	%	No.	%	
C P R	40	32%	28	22.4%	0.089
Chemical pregnancy	3.3	7.6%	0	0.0	0.251
Pregnancy:					
Single	30	75%	22	78.6%	
Twins	10	25%	6	21.4%	0.406
Miscarriage	10	25%	8	28.6	0.245
Implantation rate:	15.80% (49/310)		10.2% (37/363)		0.03*
Mean ± SD no. of embryo transferred	2.22 ± 0.84		2.46 ± 0.95		0.419
Maturity:					
Pre-term	10*	33.3%	10#	50%	0.485
Full-term	20	66.7%	10	50%	
Take home baby rate	30	24%	20	16%	0.334

* <0.05 is significant

The results of ICSI cycles in both groups were presented in table (2) CPR was 32% in group 1 Vs. 22.4% in group 2 with no statistically significant difference.

Also were no statistically significant differences in miscarriage rate and take-home-baby in both groups . There was no statistically significant difference between the mode of delivery between the two groups as 26 women of group 1 patients delivered by CS, only 4 underwent normal vaginal delivery, and 18 women of group 2 patients delivered by CS, only 2 underwent normal vaginal delivery.

This highlighted the high rate of CS nearly in 88% of patients.

In each group one preterm newborn died in the incubator within hours.

Table (3): Cases with positive pregnancy test for each specific detected subtle lesions

	No.(82)	% of cases with +ve pregnancy test in each lesion	+ve pregnancy test	CP	CPR
Mucosal elevation	6	33.3%	2	2	33.3%
Uni cornuate uterus	2	50.0%	1	1	50.0%
Pale endometrium	14	50%	7	6	85.71%
Endometrial defect	2	0.0%	0	0	0.0%
Arcuate uterus	30	40%	12	12	40%
Hypervascularization	8	37.5%	3	3	37.5%
Single adhesion band	6	16.7%	1	1	16,7%
Micro polypi	14	7.1%	1	1	7.1%
Total	**82**	**36.6%**	**30**	**29**	**35.4%**

This table shows the numbers and type of subtle lesions and the clinical pregnancy rate for each specific lesion.

Table (4) Clinical pregnancy rate in each specific corrected lesion by hysteroscopy in group 2.

	No. (125)	%	CP	CPR
Polyp	44	33.6%	14	31,8%
Septum	16	128%	6	37.5%
Adhesions	10	8%	3	30%
Hysteroscopic myomectomy, grade 0	6	4.8%	2	33.3%
Myoma and polyp	2	1.6%	0	0%
(CS Niche)	2	1.6%	0	0%

Table 4 shows the type of detected and corrected lesions in group 2 with RIF and the clinical pregnancy rate for each specific lesion. All lesions were treated by hysteroscopy. The CPR after correction and ICSI occurred in 64% ,(80/125).. The CPR was 22.4% in group 2 in comparison with 32% in group 1.

Discussion

In clinical practice, evaluation of the uterine cavity is usually done TV/US prior to IVF/ICSI. Due to the perceived advantages of hysteroscopy ,it is considered the gold standard for the diagnosis of uterine cavity pathology [23, 24]. Also it has the potential for simultaneous detection and treatment of diagnosed intrauterine lesions, so pre-IVF/ICSI screening OH has gained widespread acceptance[25].

Hysteroscopy prior to IVF/ICSI is an issue with debate. Pre-IVF hysteroscopy in women with unexplained infertility for detecting effect of unsuspected intrauterine lesions on pregnancy outcome was evaluated. High prevalence rate of unsuspected intrauterine lesions was found in women with unexplained infertility and clinical pregnancy rates were not significantly higher in patients who underwent pre-IVF hysteroscopy[26].

All women included in our study were selected and prepared for ICSI and hysteroscopy, in group 1 women had normal uterine cavity as revealed by TV/US. In group 2 ,all included women had history of RIF after previous ICSI. Unification of study parameters and exclusions of fertility barriers were done in both groups to avoid their effect on the results. Women in groups 1 and 2 were comparable with their demographic data , duration, and type of infertility. Age and AMH were statistically significant higher in group 2. This difference can be zexplained by time needed for diagnosis and correction of lesions.

In this work the mean duration of infertility at the time of ICSI was relatively long, more than 7 years in study groups. Which to some extent may be reflected in the decrease in the take home baby rate.

There was no statistically significant difference in the basal endometrial thickness in the group of women with corrected uterine lesions and those with normal uterine cavity.

The AMH level as a test for ovarian reserve was lower in group 2 women with uterine lesions than those with normal uterine cavity in group 1. This can be explained by the statistically significant increased age of women in both groups (31.45 years in group 2 versus 29.57 years in group 1; respectively). Throughout the induction period there were no statistically significant response differences in both groups. Also IR, CPR and take-home baby rate were insignificant in both groups.

In 12% of women undergoing first IVF [20] and in 27% of women with RIF [27], screening hysteroscopy prior to IVF revealed intrauterine pathology that may not be detected by routine TV/US. Hysteroscopy allows detection and treatment of many of uterine cavity lesions which may improve IVF outcomes[13]. In our study uterine cavity lesions were detected during HSC before new ICSI in 64%,(80/125) of women with RIF . Endometrial polypi were found and treated in 33.6% (44/125).

Implantation and subsequent ICSI outcomes can be affected by different intracavitary lesions. Endometrial polyps are the most frequently observed pathological finding, reported 82% of the women implicated in about 50% of cases of abnormal uterine bleeding and in 35% of infertility cases [29], and are usually benign lesions.[28]. Polyp removal by hysteroscopy prior to IUI can increase the chance of CPR compared with simple diagnostic hysteroscopy [24]. This clearly explains the comparable CPR and take-home baby rate in both groups in our present study . CPR after polyp removal in our study was 31.8% in women underwent ICSI after polypectomy .

Cochrane review about hysteroscopic resection of endometrial polyps prior to infertility treatments, did not identify any analyzable randomized trials which allow them to reach any sound scientific evidence on the safety and efficacy of endometrial polypectomy in sub fertile women, and concluded that well designed, methodologically sound, randomized controlled trials are urgently needed. On the other hand, removal of endometrial polyps in sub fertile women is commonly practiced in many clinics to improve the reproductive outcome because the procedure is minimally invasive and hysteroscopic polypectomy provides an opportunity for a histological diagnosis to exclude malignancy[24].

Based on that if an endometrial polyp is detected during an ART cycle and less than 20 mm in size, it can be managed expectantly without compromising clinical pregnancy or live birth rates. Also, when polyp 10 mm in size are found in symptom-free patients prior to ART, expectant management may be considered, given that spontaneous regression following the menstrual cycle has been observed in 27% of cases [30].

Hysteroscopic polypectomy prior to infertility treatment was cost-effective for both IUI and IVF/ICSI treated women when comparing sensitivity analysis between pregnancy rates and polypectomy costs. The procedure doubles the pregnancy rate, shortens time to pregnancy, and is cost-effective across a range of polyp sizes.

It was found in Cochrane review that there is a large benefit with the hysteroscopic removal of submucous fibroids for improving the chance of clinical pregnancy in women, but unexplained subfertility cannot be excluded. Removal of endometrial polyps suspected on ultrasound in women by HSC prior to IUI may increase the clinical pregnancy rate. The review advised randomized studies to substantiate the effectiveness of the hysteroscopic removal of suspected endometrial lesions in women with unexplained subfertility or prior to IUI, IVF or ICSI[24].

Results in our study were in favor of hysteroscopic adhesolysis in 8%, (10/125) of cases with mild to moderate intrauterine synechia with improved CPR of 30% ,(3/10) comparable to the 32% in group 1.

The most common subtle abnormality observed in the current study were arcuate uterus, pale endometrium and micro polypi with 35.9% and 16.7% and 11.5% of cases and their pregnancy rate were 39.3%, 53.8% and 11.1% respectively. These results matched with the finding of the In-SIGHT study performed in 2016 that found women who were known to have small submucous myoma or polyp in the endometrium or other subtle uterine cavity lesion had not decrease pregnancy outcomes[32].

Reproductive performance in women with subtle lesions in comparison to women with normal uterine cavity, there was no statistically significant difference. CPR and take-home baby rate were comparable in both groups. So the presence of these subtle uterine lesions did not affect the take-home baby rate and hence it does not need any specific treatment.

This confirms the data of TROPHY study published in the Lancet in 2016 concluded that OH before IVF in women with a normal TV/US of the uterine cavity and a history of failed IVF treatment cycles does not improve the live birth rate. Further research was recommended to evaluate the value of surgical correction or therapy of specific uterine cavity abnormalities before IVF.

The results of this didn't match also with meta-analysis that was done in 2014 and found women who had OH before doing IVF, got high live birth rate[33]. Also, didn't match with several studies that found performing hysteroscopy preceding IVF improve rate of pregnancy [20, 34, 35].

Finally, although "statistically significant" generally means that the result obtained is real and cannot be chancified, yet not everything that can be counted counts , and not everything that counts can be counted. This is because, the statistical significance is based on three factors; the magnitude of difference observed, the range of variations in the values obtained, and the sample size taken.

Therefore, p value is not an absolute indication of the importance of the result as it depends on the result itself and its implications.

Having said that, statistically significant or even highly significant differences may be of little or no importance in itself. In another words, difference is a difference if it makes difference. And attaching a fancy p value to trivial observations does little to enhance their importance.

In contrast, difference may not be statistically significant - but still important - may be because the number of subjects is not large enough to show the difference, i.e. the study may not have the power to show an effect of that size.

Conclusions

In this study routine office hysteroscopy (OH) was not an add cost before ICSI even in cases with normal TV/US. OH can diagnose and treat uterine cavity lesions on the same setting.

Recommendations

- The study supports the importance of the correction of any significant uterine cavity lesion to have a successful IVF/ICSI cycle with outcomes comparative to patients with normal uterine cavity.
- Intervention to correct any subtle uterine abnormalities is not needed as this does not add to the success rate of IVF/ICSI cycle.
- Robust and high-quality multicentric RCTs are advised before hysteroscopy can be included during the basic clinical infertility investigation.

Conflict

There were no conflicts of interest.

References

1. Xiaoyan Mao, Ling Wu, Qiuju Chen, Yanping Kuang, and Shaozhen Zhang. Effect of hysteroscopy before starting in-vitro fertilization for women with recurrent implantation failure, A meta-analysis and systematic review.,2019; 98 (7): 14075 .
2. Zohni KM, Gat I, Librach C. Recurrent implantation failure: a comprehensive review. Minerva Ginecol 2019;68: 653–67.

3. Genovese F, D'Urso G, Di Guardo F, Insalaco G, Tuscano A, Ciotta L, et al. Failed diagnostic hysteroscopy: analysis of 62 cases. Eur J Obstet Gynecol Reprod Biol. 2020;245:193–197.
4. Gaviño-Gaviño F, Guzmán-González E, Reyes-Muñoz E, et al. Impact of office hysteroscopy in patients with a history of two or more failed cycles of IVF-ET and pre-ICSI in assisted an reproduction center. Ginecol Obstet Mex 2010 ;78:9–14.
5. Fatemi HM, Popovic-Todorovic B. Implantation in assisted reproduction: a look at endometrial receptivity. Reprod Biomed Online 2013;27:530–8.
6. Shawki HE, Elmorsy M, Eissa MK. Routine office hysteroscopy prior to ICSI and its impact on assisted reproduction program outcome: a randomized controlled trial. Middle East Fertil Soc J2012;17:14–21
7. Dalal RJ, Pai HD, Palshetkar NP. Role of hysteroscopy prior to assisted reproductive techniques in patients with previous IVF failure. Int J Infertil Fetal Med 2011;2:19–22.
8. Shohayeb A, El-Khayat W. Does a single endometrial biopsy regimen (S-EBR) improve ICSI outcome in patients with repeated implantation failure? A randomized controlled trial. Eur J Obstet Gynecol Reprod Biol2012;164:176–9.
9. Phillips CH, Benson CB, Ginsburg ES, et al. Comparison of uterine and tubal pathology identified by transvaginal sonography, hysterosalpingography, and hysteroscopy in female patients with infertility. Fertil. Res Pract 2015 ;1:20.
10. Taskin EA, Berker B, Ozmen B, et al. Comparison of hysterosalpingography and hysteroscopy in the evaluation of the uterine cavity in patients undergoing assisted reproductive techniques. Fertil Steril 2011;96:349–52.
11. Palshetkar N, Pai H ,Pisat S. Role of Hysteroscopy Prior to Assisted Reproductive Techniques Journal of Gynecological Endoscopy and Surgery,2009 ;1: 27-30.
12. El-Toukhy T, Sunkara SK, Coomara Samy A, et al. Outpatient hysteroscopy and subsequent IVF cycle outcome: a systematic review and meta-analysis. Reprod Biomed Online 2008 ;16:712–9.
13. Oliveira FG, Abdelmassih VG, Diamond MP, et al. Uterine cavity findings and hysteroscopic interventions in patients undergoing in vitro fertilization-embryo transfer who repeatedly cannot conceive.Fertil Steril2003;80:1371–5.
14. Gao M, Sun Y, Xie H, et al. Hysteroscopy prior to repeat embryo transfer may improve pregnancy outcomes for asymptomatic women with repeated implantation failure. J Obstet Gynaecol Res 2015;41:1569–76.
15. Moini A, Kiani K, Ghaffari F, et al. Hysteroscopic findings in patients with a history of two implantation failures following in vitro fertilization. Int J Fertil Steril 2012;6:27–30.
16. Cenksoy, P., C. Ficicioglu, G. Yıldırım, and M. Yesiladali. Hysteroscopic Findings in Women with Recurrent IVF Failures and the Effect of Correction of Hysteroscopic Findings on Subsequent Pregnancy Rates." Arch Gynecol Obstet 2013;287 (2): 357–60.
17. Demirol A, Gurgan T. Effect of treatment of intrauterine pathologies with office hysteroscopy in patients with recurrent IVF failure. Reprod Biomed Online 2004;8:590–4.
18. Rama Raju GA, Shashi Kumari G, Krishna KM, et al. Assessment of uterine cavity by hysteroscopy in assisted reproduction programme and its influence on pregnancy outcome. Arch Gynecol Obstet 2006;274:160–4.

19. Mooney SB, Milki AA. Effect of hysteroscopy performed in the cycle preceding controlled ovarian hyperstimulation on the outcome of in vitro fertilization Fertil Steril 2003;79:637–8.

20. Smit, Janine G., Jenneke C. Kasius, Marinus J. C. Eijkemans, Carolien A. M. Koks, Ronald van Golde, Annemiek W. Nap, Gabrielle J. Scheffer, et al. Hysteroscopy before In-Vitro Fertilisation (InSIGHT): A Multicentre, Randomised Controlled Trial. The Lancet 2016; 387 (10038): 2622–29.

21. Lorusso F, Ceci O, Bettocchi S, et al. Office hysteroscopy in an in vitro fertilization program. Gynecol Endocrinol 2008;24:465–9.

22. Surrey ES. Should diagnostic hysteroscopy be performed before in vitro fertilization-embryo transfer Minim Invasive Gynecol 2012;19:643–6.

23. Taylor, Elizabeth, and Victor Gomel. The Uterus and Fertility. Fertil Steril 2008; 89,1: 1–16.

24. Bosteels Jan, Steffi van Wessel, Steven Weyers, Frank J Broekmans, Thomas M D'Hooghe, M Y Bongers, and Ben Willem J Mol. Hysteroscopy for Treating Subfertility Associated with Suspected Major Uterine Cavity Abnormalities. The Cochrane Database of Systematic Reviews 2018; 12 (12): CD009461–CD009461.

25. Campo, R., R. Meier, N. Dhont, G. Mestdagh, and W. Ombelet. Implementation of Hysteroscopy in an Infertility Clinic: The One-Stop Uterine Diagnosis and Treatment. Facts, Views & Vision in ObGyn 2014; 6 (4): 235–39.

26. Singla, Shipra, Sweta Gupta, Rachita Munjal, Sonia Chawla, and BiswaBhusan Dash. Role of Pre IVF Hysteroscopy in Women with Unexplained Infertility for Detecting Unsuspected Intrauterine Lesions and Effect on Pregnancy Outcome. Fertility Science and Research 2020;7,1: 105.

27. Dreisler, E., Stampe Sorensen, S., Ibsen, P. H. & Lose, G. Prevalence of endometrial polyps and abnormal uterine bleeding in a Danish population aged 20-74 years. Ultrasound Obstet Gynecol 2009; 33, 102-8.

28. El-Toukhy, Tarek, Rudi Campo, Yacoub Khalaf, Carla Tabanelli, Luca Gianaroli, Sylvie S. Gordts, Stephan Gordts, et al. Hysteroscopy in Recurrent In-Vitro Fertilisation Failure (TROPHY): A Multicentre, Randomised Controlled Trial. The Lancet 2016; 387 (10038): 2614–21.

29. Check, J. H., C. A. Bostick-Smith, J. K. Choe, J. Amui, and D. Brasile. Matched Controlled Study to Evaluate the Effect of Endometrial Polyps on Pregnancy and Implantation Rates Following in Vitro Fertilization-Embryo Transfer (IVF-ET). Clinical and Experimental Obstetrics & Gynecology 2011; 38 (3): 206–8.

30. Galliano, Daniela, José Bellver, César Díaz-García, Carlos Simón, and Antonio Pellicer. ART and Uterine Pathology: How Relevant Is the Maternal Side for Implantation? Human Reproduction Update 2015; 21 (1): 13–38.

31. Stamatellos, Ioannis, Aristotelis Apostolides, Panagiotis Stamatopoulos, and John Bontis. Pregnancy Rates after Hysteroscopic Polypectomy Depending on the Size or Number of the Polyps. Archives of Gynecology and Obstetrics 2008; 277 (5): 395–99.

32. Pundir, Jyotsna, Vishal Pundir, Kireki Omanwa, Yacoub Khalaf, and Tarek El-Toukhy. Hysteroscopy Prior to the First IVF Cycle: A Systematic Review and Meta-Analysis. Reproductive Biomedicine Online 2014; 28 (2): 151–61.

33. Elsetohy, Khaled Ahmed Abdel Aziz, Ahmed H. Askalany, Mohamed Hassan, and Zamam Dawood. Routine Office Hysteroscopy Prior to ICSI vs. ICSI Alone in Patients with Normal Transvaginal Ultrasound: A Randomized Controlled Trial. Archives of Gynecology and Obstetrics 2015; 291 (1): 193–99.

34. Mouhayar, Youssef, Ophelia Yin, Sunni L. Mumford, and James H. Segars. Hysteroscopic Polypectomy Prior to Infertility Treatment: A Cost Analysis and Systematic Review. European Journal of Obstetrics, Gynecology, and Reproductive Biology 2017;213 (6): 107–15.

35. Doldi, Nicola, Paola Persico, Francesca Di Sebastiano, Elena Marsiglio, Lucia De Santis, Elisa Rabellotti, Francesco Fusi, Claudio Brigante, and Augusto Ferrari. Pathologic Findings in Hysteroscopy before in Vitro Fertilization-Embryo Transfer (IVF-ET). Gynecological Endocrinology 2005; 21 (4): 235–37.

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Assessment of Awareness, Knowledge, and Attitude of Suez University medical students towards Human Papilloma Virus vaccine (HPV): A Cross-sectional Study

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Abstract

Background: Cervical neoplasm is the second most common type of malignancy in female genital organs worldwide, and it affects quality of life in most cases. The most important risk factor for cervical cancer is exposure to Human Papilloma Virus types 16 and 18. Although vaccines are available and eliminate HPV infection, there is a lack of awareness regarding them. Therefore, the present study has been proposed.

Objective: was to study the awareness of human papilloma virus (HPV) vaccination among the medical students at Suez University.

Methods: An observational cross-sectional study through a structured online questionnaire about HPV Awareness.

Results : The study included 157 Suez University medical students. They were classified according to their gender (male vs. female), Marital status (single, married, divorced, and widowed), and residence (rural vs. urban areas). The medical colleges included faculty of Medicine students who were also classified according to their age (≤ 21 years vs. > 21 years). Of the total medical students, female students showed higher knowledge about the HPV but no statistical difference (68.1%, p = 0.08), and the diseases caused by it (84.1%, p = 0.18), and also showed significantly higher awareness about the mode of HPV transmission (79.1%, p = 0.04). Female students also showed higher knowledge about the presence of a vaccine against the HPV (75.8%, p = 0.75), as well as the safety of the vaccine (74.7%, p = 0.48) compared to male students, but with no statistical difference.), and also showed significantly higher awareness about the mode of HPV transmission (79.1%, p=0.04), female students also showed higher knowledge about the presence of a vaccine against the HPV (75.8%, p =0.75.8) as well as the safety of the vaccine (74.7%, p =0.48) compared to male students but with no statistical difference.

Conclusion: Our study revealed an appreciable level of awareness about the HPV infection and the vaccination. Females had better awareness regarding the infection as

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well as the vaccine. We found that medical education has a positive impact on raising awareness regarding the causes of cervical cancer, the availability of the vaccine, and its protective efficacy.

Introduction

Human papillomavirus (HPV) can affect different parts of the body in males and females [1].

There are over 100 sub-types of HPV, including types that cause skin warts, especially on the hands, feet, and face. About 30 HPV strains can affect the anogenital region, including the cervix, vagina, vulva, penis, and scrotum, in addition to the rectum and anus. [2].

The different sub-types of the virus can be subclassified into low-risk and high-risk according to their ability to induce dysplasia [3].

The low-risk HPV types (6 and 11) are non-oncogenic and are associated with anogenital warts, cutaneous warts, and recurrent respiratory papillomatosis [4,5].

However, high-risk types (16 and 18) are oncogenic and are associated with cervical, vaginal, vulvar, anal, penile, and oropharyngeal cancers [6].

Regular screening and treatment of precancerous lesions can prevent the progression of cervical cancer. Identification of precancerous lesions has been primarily achieved by cytologic screening of cervical cells (Pap testing), HPV primary screening, and HPV co-testing and cytology [7].

The HPV vaccine could dramatically reduce the number of new cases of cervical cancer and other malignancies caused by HPV exposure. Globally, there are three types of vaccines available on the market: bivalent, quadrivalent, and nonavalent [8].

The Quadrivalent vaccine protects against four HPV types (6, 11, 16, and 18), and the bivalent vaccine guards against 16 and 18. Finally, the nonavalent (nine-valent) vaccine offers protection against five HPV types: 31, 33, 45, 52, and 58, in addition to the types covered by the quadrivalent vaccine [8].

WHO has recommended that the HPV vaccine be given to girls and boys at the age of 9. It's ideal to receive at least one dose of the vaccine before sexual contact [9].

It has been reported that HPV types 6, 11, 16, and 18 have decreased by approximately 90%, with a reduction in condyloma acuminata of approximately 90% and high-grade cervical lesions of approximately 85%. The estimated vaccine compatibility with one dose or more of the HPV vaccine was 83–96.1% [10].

Studies have reported that all three vaccines are tolerated excellently with no to minimal side effects [13]. The most commonly encountered adverse effects were injection-site reactions such as pain and swelling, headaches, and fatigue. Fever, dizziness, nausea, vomiting, and diarrhea have also been reported [11].

Despite the protective and preventive value of the HPV vaccine, not all people are aware of it, so we aim to assess the awareness, knowledge, and attitude of Suez University medical students towards the Human Papilloma Virus vaccine (HPV).

Materials and Methods

Study area and subjects

The study was conducted during May and June 2023 at Suez University. The targeted population was Suez University medical students. A structured online questionnaire designed by the lecturers of the OBS & GYN department of Suez University is used in this observational cross-sectional study to assess the awareness, knowledge, and attitude of Suez University medical students toward the Human Papilloma Virus vaccine. (HPV). The questionnaire consisted of 15 questions:

4 questions assessing the demographic information (age, marital status, residence, gender), 2 questions assessing the knowledge about HPV (Do you know HPV? Do you know about diseases caused by the virus?), four questions assessing awareness about HPV (Do you know about the mode of transmission of HPV? To your knowledge, Is there a vaccine for protection from HPV? What do you know about the safety of the vaccine? Do you know from where you can buy it?), and two questions assessing the attitude towards HPV (If there is a vaccine, Will you accept to receive it?). If you know that the price is around $937 per dose, will you think about receiving it? The questionnaire was in English. You can access the online form of the questionnaire through this link.

https://docs.google.com/forms/d/12ESF48-WCJdKxmRae32cMEo__HDOExeuo1i-tORKBIc/edit?usp=drivesdk

Consent

It was written at the top of the online form of the questionnaire. "Filling out this **Questionnaire** means you agree to be part of this study."

Sample size and questionnaire

For a confidence level of 95%, the margin of error equals 0.05, and assuming the population proportion (P) equals 50%, these conditions require at least 384 students. 157 questionnaires were collected. Students were categorized into groups based on three factors: age, gender, and residence, in order to examine which of these factors is strongly associated with their knowledge, awareness, and attitude towards HPV.

Statistical Analysis

Statistical analysis was done using SPSS application version 26.0. Demographic and other qualitative variables were expressed in frequencies and percentages. Data was described as mean +/- SD, and categorical data was analyzed using the Chi-square test. A P-value <= 0.05 is considered statistically significant.

Results

The study included 157 Suez University medical students. They were classified according to their gender (male vs. female), Marital status (single, married, divorced, and widowed), and residence (rural vs. urban areas). The medical colleges included a faculty of medicine. Students were also classified according to their age (≤ 21 years vs. > 21 years), as shown in **Table I**.

Of the total medical students, female students showed higher knowledge about the HPV but no statistical difference (68.1%, p =0.08.) and the diseases caused by it(84.1% ,p =0.18.), and also showed significantly higher awareness about the mode of HPV transmission (79.1%, p=0.04), female students also showed higher knowledge about the presence of vaccine against it (75.8%, p =0.75.8), the safety of the vaccine (74.7%, p =0.48) as well as from where to get the vaccine (11.0%, p 0.06) compared to male students but with no statistical difference as illustrated in **Tables II & III**.

Discussion

Carcinoma of the cervix is the second most common female malignant tumor worldwide and has a high incidence of morbidity and mortality. The lady is usually diagnosed in a locally advanced stage, so most cases will not be candidates for surgery at the time of the diagnosis [12].

It has been proven that high-risk HPV types are the main cause of cervical cancer [13].

According to the WHO and the International Agency for Research on Cancer (IARC), there were 529,000 new cases of cervical cancer globally in 2008. In developing countries, the prevalence of cervical cancer was 452,000 and ranked second among malignancies in female patients [14].

Conversely, the number of new cases of cervical cancer was 77,000 among developed countries and ranked tenth among female malignancies. Recently, the incidence of cervical malignancy has increased without a corresponding increase in awareness regarding screening programs, vaccinations, reporting

any abnormal symptoms, and early detection.

A screening program of the cervix plays an essential role in prevention and detection of early cellular changes and can diagnose pre-invasive lesions along with HPV infection [15].

The present study was carried out at Suez University to get information regarding the level of Awareness, Knowledge, and Attitude of Suez University medical students towards the Human Papilloma Virus vaccine (HPV). The study participants included undergraduate medical students at our medical school. In the present study, there were 58% female and 42% male medical students; only one participant was married at the time of the study, and more than half (60.55%) were aged more than 21 years. [Table 1] Among the study participants, 84.1% were aware of HPV-related diseases and cancers caused by HPV infections. This result was higher compared to the results reported by Netra G et al. (72.4%) and Mehta et al. (50%) and low compared to the studies held by Panday et al. (81.5%) and Joshi et al. (96%) [16, 17, 18, 19].

This difference might be because the majority of the participants in our study were from the 3rd year of medical students who were aware of the infection, compared to other studies in which the majority of the participants were from the first academic year and might not be aware of the infection yet [17].

The awareness regarding modes of transmission of HPV was lower in the present study (77.7%) when compared to the study done by Nagasireesha Challa et al. (81.1%) [20]. The awareness regarding the availability of vaccines is low in this study (75.2%) compared to the results reported in the study by Nagasireesha Challa et al. (90.5%) [20].

The awareness is higher than in the study performed by Snigdha Kamini et al. (50.4%) [21].

Awareness regarding the mode of transmission of HPV infection and availability of vaccines for female students is higher than for male students (77.7% and 75.8%), and the same results were reported by Priya et al.'s study (999.7% and 789.8%) [22]. This may be attributed to the higher number of female students participating in our study.

With the increase in the study year, the knowledge has been increasing, indicating that the study curriculum also plays a vital role in creating awareness, which will help to increase the knowledge provided to the general population. Moreover, the present study showed a greater percentage of students (77%) lack knowledge regarding how they can get the vaccine, and about 1.3% are worried about the safety of the vaccine. These findings were like those of Mehta et al. and Kamini et al. [17, 21].

The power of our study was that we had continuous data collection, and we held an awareness session about the HPV vaccination. The limitation of our study was that we could not approach all the students as they were occupied in exam preparation and due to their absence during data collection. The level of knowledge, information, and awareness regarding HPV hazards should be raised through awareness campaigns, audio-visual programs, and flyers. It is suggested that HPV vaccination should be a part of the national immunization program in order to eliminate cervical cancer.

Conclusion

Our study revealed an appreciable level of awareness regarding the HPV infection and vaccination. Females had better awareness regarding the infection as well as the vaccine. We found that medical teaching had a positive impact on awareness regarding the etiology of cervical cancer, the availability of the vaccine, and its protective efficacy. This will have a positive impact on increased awareness and knowledge among the general population in the near future.

References

1. Ljubojevic S, Skerlev M. HPV-associated diseases. Clinics in Dermatology 2014;32:227–34. https://doi.org/10.1016/j.clindermatol.2013.08.007.
2. Bodaghi S, Wood LV, Roby G, Ryder C,

Steinberg SM, Zheng Z-M. Could Human Papillomaviruses Be Spread through Blood? Journal of Clinical Microbiology 2005;43:5428–34. https://doi.org/10.1128/jcm.43.11.5428-5434.2005.

3. Cubie HA. Diseases associated with human papillomavirus infection. Virology 2013;445:21–34. https://doi.org/10.1016/j.virol.2013.06.007.
4. Vinzón SE, Rösl F. HPV vaccination for prevention of skin cancer. Human Vaccines & Immunotherapeutics 2015;11:353–7. https://doi.org/10.4161/21645515.2014.983858.
5. Sankaranarayanan R, Prabhu PR, Pawlita M, Gheit T, Bhatla N, Muwonge R, et al. Immunogenicity and HPV infection after one, two, and three doses of quadrivalent HPV vaccine in girls in India: a multicentre prospective cohort study. The Lancet Oncology 2016;17:67–77. https://doi.org/10.1016/s1470-2045(15)00414-3.
6. Alhamlan FS, Khayat HH, Obeid DA, Tulba AM, Baduwais TS, Alfageeh MB, et al. Clinical comparison of two human papillomavirus detection assays: GenoFlow and reverse line blot. The Journal of Infection in Developing Countries 2020;14:97–103. https://doi.org/10.3855/jidc.11769.
7. Eun TJ, Perkins RB. Screening for Cervical Cancer. Medical Clinics of North America 2020;104:1063–78. https://doi.org/10.1016/j.mcna.2020.08.006.
8. Kamolratanakul S, Pitisuttithum P. Human Papillomavirus Vaccine Efficacy and Effectiveness against Cancer. Vaccines 2021;9:1413. https://doi.org/10.3390/vaccines9121413.
9. Pinto LA, Dillner J, Beddows S, Unger ER. Immunogenicity of HPV prophylactic vaccines: Serology assays and their use in HPV vaccine evaluation and development. Vaccine 2018;36:4792–9. https://doi.org/10.1016/j.vaccine.2017.11.089.
10. Meites E, Szilagyi PG, Chesson HW, Unger ER, Romero JR, Markowitz LE. Human Papillomavirus Vaccination for Adults: Updated Recommendations of the Advisory Committee on Immunization Practices. MMWR Morbidity and Mortality Weekly Report 2019;68:698–702. https://doi.org/10.15585/mmwr.mm6832a3.
11. Drolet M, Bénard É, Pérez N, Brisson M. Population Level-Impact and Herd Effects Following the Introduction of Human Papillomavirus Vaccination Programmes: Updated Systematic Review and Meta-analysis. Obstetrical & Gynecological Survey 2019;74:590–2. https://doi.org/10.1097/ogx.0000000000000724.
12. zur Hausen H. Human papillomaviruses in the pathogenesis of anogenital cancer. Virology 1991;184:9–13. https://doi.org/10.1016/0042-6822(91)90816-t.
13. Yarchoan M, Johnson BA, Lutz ER, Laheru DA, Jaffee EM. Targeting neoantigens to augment antitumour immunity. Nature Reviews Cancer 2017;17:209–22. https://doi.org/10.1038/nrc.2016.154.
14. Ferlay J, Shin H-R, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. International Journal of Cancer 2010;127:2893–917. https://doi.org/10.1002/ijc.25516.
15. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA: A Cancer Journal for Clinicians 2016;66:7–30. https://doi.org/10.3322/caac.21332.
16. G. N, G. GR. Awareness of human papilloma virus infection and vaccination among the medical students of Davangere. International Journal Of Community Medicine And Public Health 2021;8:3316. https://doi.org/10.18203/2394-6040.ijcmph20212579.
17. Goel G, Goel N, Mehta S, Rajaram S. Awareness about Human Papilloma Virus and its vaccine among medical students.

Indian Journal of Community Medicine 2013;38:92. https://doi.org/10.4103/0970-0218.112438.

18. Pandey D, Vanya V, Bhagat S, VS B, Shetty J. Awareness and Attitude towards Human Papillomavirus (HPV) Vaccine among Medical Students in a Premier Medical School in India. PLoS ONE 2012;7:e40619. https://doi.org/10.1371/journal.pone.0040619.
19. Joshi A, Bhagat S, Patil K, Gambre R, Patel S. To evaluate the awareness about human papilloma virus (HPV) vaccine in the prevention of cervical cancer amongst the medical students: A KAP study. Int J of Allied Med Sci and Clin Res. 2014;2(4):358-66. https://doi.org/10.18203/2320-1770.ijrcog20141964.
20. [1]Challa N, Madras V, Challa S. Awareness and attitude regarding human papilloma virus and its vaccine among medical students in a medical school in India. International Journal of Research in Medical Sciences 2014;2:1607. https://doi.org/10.5455/2320-6012.ijrms20141168.
21. Kamini S, Bhimarasetty DM. Awareness about human papilloma virus vaccine among medical students. Asian Journal of Medical Sciences 2016;7:64–7. https://doi.org/10.3126/ajms.v7i4.14613.
22. Mathi A, Priya M, Inuganti R. Awareness and knowledge regarding human papilloma virus vaccine among medical students. Journal of Dr NTR University of Health Sciences 2022;11:220. https://doi.org/10.4103/jdrntruhs.jdrntruhs_135_22.

Table I: Baseline demographic characteristics of the participants (N = 157)

Characteristics	Categories	Number (N)	Percentage %
College	**Medical**		
Gender	Male	66	42.0
	Female	91	58.0
Marital status	Single	156	99.4
	Married	1	0.6
	Divorced	0	0
	Widow	0	0
Residence	Urban	94	59.9
	Rural	63	40.1
Age	≤ 21	95	60.5
	> 21	62	39.5

Mean ± SD (Min – Max)

Table II: Knowledge of Suez University medical students about the Human Papilloma Virus (HPV) based on their medical background

Parameter		(N = 157)			P-value
		Male N (%)	Female N (%)	Total N (%)	
1. Do you find HPV infection related to evident health problems in EGYPT?	Yes	47 (71.2%)	62 (68.1%)	109 (69.4%)	0.08
	No	10 (15.2%)	19 (20.9%)	29 (18.5%)	
	Abstinence	9 (13.6%)	10 (11.0%)	19 (12.1%)	
2. Are cervical, anal, vulvar and oropharyngeal cancers can be directly caused by HPV infection	Yes	52 (78.8%)	80 (87.9%)	132 (84.1%)	0.18
	No	11 (16.7%)	5 (5.5%)	16 (10.8%)	
	Abstinence	3 (4.5%)	6 (6.6%)	9 (5.7%)	

X^2; Chi-Square test

Table III: Awareness of Suez University students about the Human Papilloma Virus (HPV) based on their medical background

Parameter		Male N (%)	Female N (%)	Total N (%)	P-value
1. Do you know about mode of transmission of HPV?	**Yes**	50 (75.8%)	72 (79.1%)	122 (77.7%)	**0.04***
	No	12 (18.2%)	14 (15.4%)	26 (16.6%)	
	Abstinence	4 (6.1%)	5 (5.5%)	9 (5.7%)	
2. Many countries have adopted HPV vaccine in their routine programs	**Yes**	49 (74.2%)	69 (75.8%)	118 (75.2%)	0.78
	No	8 (12.1%)	8 (8.8%)	16 (10.2%)	
	I don't know	9 (13.6%)	14 (15.4%)	23 (14.6%)	
3. To your knowledge, HPV infection can be prevented by 2 or 3 doses of HPV vaccine	**Yes**	44 (66.7%)	50 (54.9%)	94 (59.9%)	0.19
	No	5 (7.6%)	15 (16.5%)	20 (12.7%)	
	I don't know	17 (25.8%)	26 (28.6%)	43 (27.4%)	
4-To your knowledge, Cost of HPV vaccine (1 dose = 937EGP) is too much for average Egyptian families	**Yes**	50 (75.8%)	77 (84.6%)	127 (80.9%)	0.37
	No	7 (10.6%)	6 (6.6%)	13 (8.3%)	
	I don't know	9 (13.6%)	8 (8.8%)	17 (10.8%)	
5. Do you know from where you can buy it?	**Yes**	12 (18.2%)	10 (11.0%)	22 (14.0%)	0.06
	No	47 (71.2%)	78 (85.7%)	125 (79.6%)	
	I don't know	7 (10.6%)	3 (3.3%)	10 (6.4%)	
6. HPV vaccine can be given in national projects supplied by governments	**Yes**	51 (77.3%)	71 (78.0%)	122 (77.7%)	0.34
	No	9 (13.6%)	7 (7.7%)	16 (10.2%)	
	I don't know	6 (9.1%)	13 (14.3%)	19 (12.1%)	
7. What do you know about the safety of the vaccine?	**Safe**	50 (75.8%)	68 (74.7%)	118 (75.2%)	0.48
	Unsafe	0 (0%)	2 (2.2%)	2 (1.3%)	
	I don't know	16 (24.2%)	21 (23.1%	37 (23.6%)	

Gonadotropin releasing hormone agonist (GnRHa) versus human chorionic gonadotropin (HCG) for triggering of ovulation in ovarian stimulation cycles in polycystic ovarian syndrome (PCOS) women

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Abstract

Objective: To assess the efficacy and safety of gonadotropin releasing hormone agonist (GnRHa) as an alternative to conventional human chorionic gonadotropin (HCG) for triggering of ovulation in patients with polycystic ovarian syndrome (PCOS) undergoing sequential minimal ovarian stimulation followed timed intercourse.

Methods: A randomized controlled study that was conducted on PCOS patients subjected to sequential minimal ovarian stimulation followed by timed intercourse. All participants were randomly allocated at time of triggering of ovulation into 2 groups; GnRHa group in which ovulation was triggered by single SC injection of 0.2 mg of triptorelin, and HCG group in which ovulation was triggered by single IM injection of 5000 IU of urinary HCG. The main study's outcome measures included ovulation rate, clinical pregnancy rate and incidence of early ovarian hyperstimulation syndrome (OHSS).

Results: Final analysis was performed for data of 47 participants in the GnRHa group and 46 participants in the HCG group. There was no significant difference between the GnRHa and the HCG groups in the ovulation rate (95.7% vs 93.5%; P = 0.628) and clinical pregnancy rate (23.4% vs 21.7%; P = 0.848). There was no cases of OHSS in the GnRHa group and just one case in the HCG group, with no significant difference in the incidence of OHSS between the 2 groups (P = 0.495).

Conclusion: The GnRHa could be an effective and safe alternative to the traditional HCG in ovulation triggering after sequential minimal ovarian stimulation in PCOS patients without affecting ovulation and clinical pregnancy rates.

Keywords: PCOS, GnRHa, HCG, OHSS.

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Introduction

The polycystic ovarian syndrome (PCOS) is a condition affecting 5-20% of women in the child bearing period worldwide, and it is the commonest cause of

oligomenorrhea. Many of PCOS women are subfertile, however, only a small percentage require fertility treatment and most of them require long time to become pregnant naturally. There are different phenotypes of PCOS women, based on the definition of PCOS. Many possible treatment options are suggested for management of subfertility in PCOS women. The success and morbidity of these treatment options could be affected by the PCOS phenotype (1).

A class of medications known as aromatase inhibitors was first introduced in 2001 to induce ovulation in subfertile women, both in ovulatory and anovulatory cycles (2). Letrozole is the most popular aromatase inhibitor used for induction of ovulation, and is administered in a typical dose of 5 mg every day for 5 days (3). When used for induction of ovulation with timed intercourse, letrozole was found to have higher pregnancy rates and similar ovarian hyperstimulation syndrome (OHSS) rate, compared to clomiphene citrate (CC) (4). Sequential minimal ovarian stimulation protocol consists of administration of CC or letrozole, followed by low dose of gonadotropins. This protocol was used in both assisted reductive technology (ART) and non-ART treatment of subfertility with comparable safety and efficacy in comparison to other ovarian stimulation regimens (5-8).

Gonadotropin releasing hormone (GnRH) is a hormone secreted from the hypothalamus in pulses. It binds to surface receptors on the gonadotrophs of the anterior pituitary, and this results in secretion of follicle stimulating hormone (FSH) and luteinizing hormone (LH) into peripheral circulation. Within the ovary, FSH binds to receptors on granulosa cell, while LH binds to receptors on theca cell, and this simulates folliculogenesis and ovarian steroidogenesis. At the midcycle, estrogen level rises rapidly resulting in LH surge which is responsible for final oocyte maturation (completion of the first meiotic division then progression to the metaphase stage of the second meiotic division). Ovulation occurs approximately 36-40 hours after LH surge (9).

Human chorionic gonadotropin (HCG) is usually used as a substitute for endogenous LH surge to trigger final oocyte maturation and ovulation at the end of the ovarian stimulation. The main disadvantage of HCG is its longer half-life than LH, which results in a prolonged luteotropic effect and as a result increases the risk of OHSS especially in high risk cases that have large number of preovulatory follicles (10).

In in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) cycles that use the GnRH antagonist protocol, triggering of final oocyte maturation could be achieve by a single injection of a GnRH agonist (GnRHa) preparation (11). Because GnRHa acts by inducing the endogenous LH (mimics the normal physiological mechanism), it was found that single injection of a GnRHa preparation may be useful in reducing the risk of occurrence of OHSS when compared to HCG (12). In IVF/ICSI cycles, HCG is used in doses of 5000-10000 IU, while GnRHa is used in variable doses with the most commonly used drug is triptorelin in a dose of 0.2 mg subcutaneously (13).

To the best of our knowledge, very few studies had evaluated the efficacy and safety of using GnRHa in comparison to HCG for triggering of ovulation in timed intercourse cycles stimulated by CC or letrozole (14, 15), or stimulated by sequential minimal ovarian stimulation protocol (16, 17). Therefore, we aimed in the current study to assess the efficacy (in terms of ovulation rate and clinical pregnancy rate) and safety (in terms of prevention of OHSS) of GnRHa as an alternative to conventional HCG for triggering of ovulation in patients with PCOS undergoing sequential minimal ovarian stimulation followed timed intercourse.

Patients and methods

Study design and population:

This was a randomized controlled trial that was conducted during the period from June 2021 through September 2022 in the Fertility Care Unit in Mansoura University Hospital, Egypt. The study protocol was reviewed and approved by the Mansoura Faculty of Medicine Institutional Research Board (Code No. MS.21.03.1399). Women selected for participation in the study were those with PCOS, diagnosed according to the Rotterdam Consensus 2004 (18), based on presence of at least two criteria of the following three criteria: 1) anovulation or oligo-ovulation; 2) clinical or biochemical evidence of hyperandrogenism; and 3) polycystic ovarian morphology on transvaginal sonography (TVS) assessment. All the possible participating women were interviewed, received sufficient information on the protocol of the study, and then counseled to be enrolled in the study.

The potential participants were then assessed for meeting the inclusion and exclusion criteria. The main inclusion criterion were PCOS women who were planned to be subjected to sequential minimal ovarian stimulation followed by timed intercourse. The exclusion criteria were: 1) age is > 35 or < 18 years; 2) body mass index (BMI) is ≥ 35 < 18.5 kg/m2; 3) abnormal hysterosalpingography (HSG); 4) pelvic adhesions with disturbance of the tubo-ovarian relationship diagnosed by laparoscopy; and 5) abnormal husband semen analysis according to WHO 2010 criteria (19).

Initial evaluation:

Complete history was taken from each participant, including personal history, menstrual history, obstetric history (gravidity and parity to clarify the type and duration of infertility), medical history, and surgical history. General examination was performed with recording of the patient's height in centimeter (cm) and weight in kilograms (kg) and calculation of the BMI. Basal serum FSH, LH, prolactin, thyroid stimulating hormone (TSH), and antimullerian hormone (AMH) levels were assessed for all participants.

Ovarian stimulation protocol:

The sequential minimal ovarian stimulation was started by giving letrozole (Femara®, Letrozole 2.5 mg, oral tablets, NOVARTIS, New Jersey, United States) in a dose of 5 mg every day for 5 days (from the 2nd day to the 6th day of the menstrual cycle) followed by a gonadotropin preparation (Gonapure®, Follitropin alpha 75 IU, IM/SC injection, MINA PHARM, Egypt) in a low dose (75 IU every day) from the 7th day to the 9th day of the menstrual cycle. Monitoring of growth of the follicles by TVS scanning (folliculometry) was started on the 10th day of the stimulation cycle. In women with at least one follicle ≥ 12 mm, the gonadotropin was continued without further increase in the dose and folliculometry was performed every 2-3 days, then ovulation was triggered when there was at least one follicle with a diameter ≥ 18 mm. Women who did not achieve mature follicle ≥ 18 mm were excluded from randomization.

At the time of ovulation triggering, the study's participants were randomly allocated into 2 groups; the GnRHa group and the HCG group. The randomization process was performed by a nurse using opaque, unlabeled, sealed envelopes containing computer-generated random numbers. The randomization was balanced (allocation ratio to each group was 1:1) and simple, and the study was an open label study (i.e. the participants, investigators and caregivers were aware of group allocation).

For participants in the GnRHa group, ovulation was triggered by single SC injection of 0.2 mg of a GnRHa preparation (Decapeptyl®, Triptorelin 0.1 mg, SC injection, Ferring, Germany) while for participants in the HCG group, ovulation was triggered by single IM injection of 5000 IU of urinary HCG (Choriomon®, HCG 5000 IU, IM injection, IBSA, Switzerland). All women were then

advised for a timed intercourse at the day of triggering of ovulation and the next day.

Documentation of ovulation:

All participants were subjected for follow up 3 days after ovulation triggering by TVS scanning for detection of signs of ovulation including: 1) vanishing of the follicle or sudden reduction in its size; 2) presence of free fluid in the pelvis or Douglas pouch; 3) increased echogenicity of the follicle, indicating formation of corpus luteum; and 4) replacement of the triple line endometrial shape by the hyperechoic, homogenous luteinized endometrium.

Luteal phase support:

All participants were supplemented one day following triggering of ovulation with progesterone vaginal suppositories (Prontogest®, Progesterone 200 mg, vaginal or rectal pessaries, MARCYRL, Egypt) in a dose of 200 mg every 12 hours.

Documentation of pregnancy:

In women who missed a menstrual period for one week, quantitative serum beta-HCG (β-HCG) level was assessed using immunoassay and a serum β-HCG level > 10 mIU/ml was considered an indicator of biochemical pregnancy. Women with biochemical pregnancy were examined by TVS scanning at 6-8 weeks from the first day of the last menstrual period to diagnose clinical intrauterine pregnancy which was defined as the presence of at least one intrauterine gestational sac with fetal pole and cardiac pulsation on TVS scanning at 6-8 weeks of gestation.

Outcome measures:

The main study's outcome measures were:

- Ovulation rate: calculated by dividing the number of women with documented ovulation by the number of women received triggering of ovulation.
- Clinical pregnancy rate: calculated by dividing the number of women with clinical pregnancy by the number of women received triggering of ovulation.
- Incidence of early OHSS.

Statistical analysis:

The IBM® SPSS® Statistics, version 20.0 for Windows was used for tabulation and analysis of data. Quantitative variables were displayed as mean ± standard deviation (SD) and median (minimum and maximum) while qualitative variables were displayed as number and percentage. The Student t test and the Mann Whitney U test were used to compare between the 2 groups for normally and non-normally distributed quantitative variables, respectively after testing normality distribution using Kolmogorov-Smirnov and Shapiro-Wilk tests. The Chi-Square and Fischer's exact tests were used for comparison of the qualitative variables between the 2 groups as appropriate (Fischer's exact was used when > 25% of cells have count less than 5). The P values were considered statistically significant at level ≤ 0.05.

Results

As shown in the flow diagram of the study (Figure 1), 264 women were evaluated for eligibility to participate in the study; and 164 of these women were excluded (82 women did not meet the inclusion criteria of the study, 17 women refused to participate in the study, and 65 women did not achieve mature follicle ≥ 18 mm). The remaining 100 women were included in the study and were randomized into the 2 study groups. Out of the 100 participants who were randomized, 3 women in the GnRHa group and 4 women in the HCG group were lost to follow-up. Therefore, data of 47 participants in the GnRHa group and 46 participants in the HCG group were subjected to final analysis.

No significant difference between the 2 groups in the demographic, clinical and hormonal characteristics (tables 1 and 2). Regarding the cycle characteristics and outcomes (table 3), the number of follicles ≥ 18 mm and the

endometrial thickness were comparable among both groups. Also, there was no significant difference between the GnRHa group and the HCG group in ovulation rate (95.7% vs 93.5%; P = 0.628) and clinical pregnancy rate (23.4% vs 21.7%; P = 0.848). There was no cases of OHSS in the GnRHa group and only one case in the HCG group with no significant difference between both groups in the incidence of OHSS (P = 0.495).

Figure 1. Study flow diagram

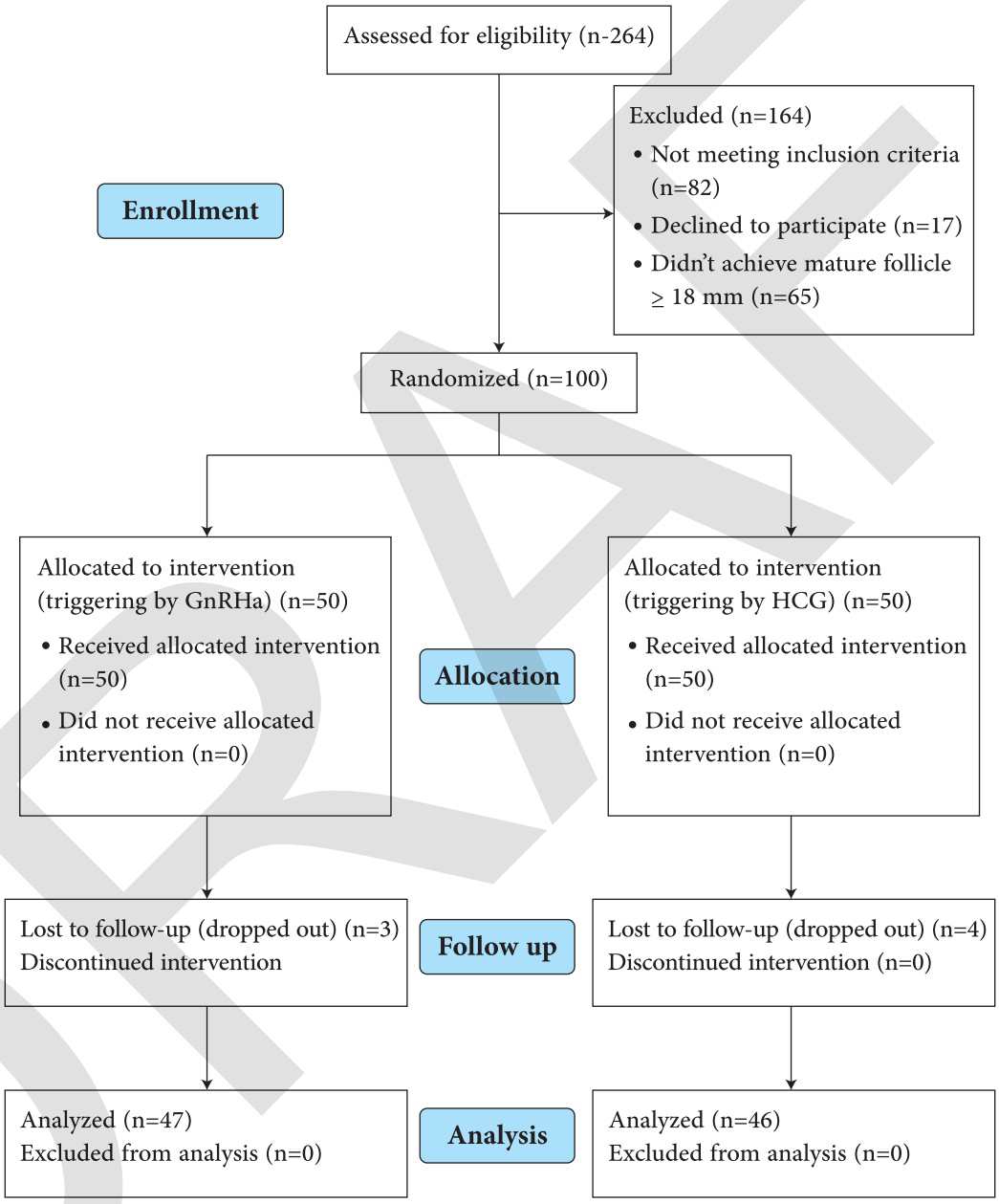

Table 1. Demographic and clinical characteristics among both groups

	GnRHa group (n = 47)	HCG group (n = 46)	P value
Age (years)			
Mean ± SD	24.02 ± 3.25	24.11 ± 3.44	0.877
Median (min-max)	24 (19-35)	24 (19-35)	
BMI (kg/m^2)			
Mean ± SD	28.28 ±1.72	27.80 ± 1.61	0.170
Median (min-max)	28.20 (24.84-32.37)	28.08 (24.84-31.21)	
Infertility type			
Primary	34 (72.3%)	36 (78.3%)	0.508
Secondary	13 (27.7%)	10 (21.7%)	
Duration of infertility (years)			
Mean ± SD	1.74 ± 0.98	1.75 ± 1.17	0.555
Median (min-max)	1.5 (1-5)	1.25 (1-5)	

Table 2. Hormonal characteristics among both groups

	GnRHa group (n = 47)	HCG group (n = 46)	P value
Serum AMH (ng/ml)			
Mean ± SD	4.88 ± 1.70	4.69 ± 1.38	0.570
Median (min-max)	4.25 (3.17-11.50)	4.19 (3.21-10.60)	
Basal serum FSH (mIU/ml)			
Mean ± SD	6.52 ± 1.76	6.56 ± 1.65	0.899
Median (min-max)	6.36 (2.03-9.80)	6.27(2.80-9.90)	
Basal serum LH (mIU/ml)			
Mean ± SD	5.98 ± 1.97	5.67 ± 2.07	0.356
Median (min-max)	5.72 (2.60-9.83)	5.15 (2.03-9.70)	
Serum prolactin (ng/ml)			
Mean ± SD	13.64 ± 4.73	13.63 ± 5.33	0.996
Median (min-max)	12.77 (5.60-21.61)	13.20 (0.66-21.70)	
Serum TSH (mIU/ml)			
Mean ± SD	1.82 ± 0.82	1.77 ± 0.78	0.730
Median (min-max)	1.77 (0.38-3.40)	1.62 (0.38-3.15)	

Table 3. Cycle characteristics and outcomes among both groups

	GnRHa group (n = 47)	HCG group (n = 46)	P value
No. of follicles ≥ 18 mm	2 (1-6)	1 (1-5)	0.148
Endometrial thickness (mm)			0.706
Mean ± SD	11.06 ±1.94	10.91 ± 1.99	
Median (min-max)	11 (8-14)	11 8-14)	
Ovulation	45 (95.7%)	43 (93.5%)	0.628
Clinical pregnancy	11 (23.4%)	10 (21.7%)	0.848
OHSS	0 (0.0%)	1 (2.2%)	0.495

Discussion

Many treatment options are available for subfertile women with PCOS, including: 1) weight reduction and lifestyle modification in obese women; 2) metformin and/or inositol administration for several months; 3) induction of ovulation with CC or letrozole; 3) low-dose gonadotropin stimulation or laparoscopic ovarian drilling in case of resistance to CC and/or letrozole; and 4) IVF/ICSI in case of failure of the other management option (20). Sequential minimal ovarian stimulation, consisting of administration of CC or letrozole followed by low dose of gonadotropins, has been used for induction of ovulation in PCOS women with comparable safety and efficacy to other ovarian stimulation regimens (7). Ovulation triggering is a crucial step in infertility treatments, both in natural and stimulated cycles (21, 22).

Both LH and HCG have biological and structural similarities and therefore, they can bind to and stimulate the same receptor but HCG has much longer half-life (24 hours) than LH (1 hour). For several decades, HCG has been the traditional method used, as a substitute for LH surge, for triggering of ovulation but due to its longer half-life than LH, HCG exerts a continuous stimulation of ovarian steroid hormones production for up to 5 days, and thus predisposes to OHSS. Moreover, there were reported negative effects of HCG on oocyte quality and endometrial receptivity (23).

Administration of a GnRHa preparation can activate the GnRH receptor in the pituitary, resulting in LH surge that mimic the natural LH surge. This GnRHa-induced LH surge can efficiently trigger oocyte maturation and ovulation. The natural LH surge consists of 3 phases, with a duration of 48 hours while the GnRHa-induced LH surge is composed of 2 phases, with a total duration of 24-36 hours. Therefore, the amount of gonadotropins secreted from the pituitary are lower with using GnRHa for ovulation triggering (24, 25).

Triggering of ovulation with GnRHa instead of HCG has the advantage of being more physiological as it acts by inducing the endogenous LH surge and it is well known that LH has a shorter half-life than HCG. Not only that but also, GnRHa stimulates the midcycle FSH surge which was shown to up regulate the LH receptors on granulosa cells. However, the main drawback of using GnRHa for triggering of ovulation is early corpus luteum degeneration that results in reduction of the serum progesterone level which is known as a luteal phase deficiency, which lowers the chance of pregnancy and increase the pregnancy loss rate. Thus, adequate luteal phase support is required

when using GnRHa as an ovulation trigger (26).

Many studies have evaluated the efficacy and safety of GnRHa as an ovulation triggering agent in comparison to HCG in IVF/ICSI treatment (27-30), however, to the best of our knowledge, very limited number of studies had evaluated both types of trigger in stimulated intrauterine insemination cycles (31, 32), and in timed intercourse cycles stimulated by CC or letrozole (14, 15), or by sequential minimal ovarian stimulation protocol (16, 17). Therefore, the current study was conducted to assess the efficacy and safety of GnRHa as an alternative to HCG for triggering of ovulation in PCOS women undergoing sequential minimal ovarian stimulation followed by timed intercourse.

Concerning demographic, clinical and hormonal characteristics in the current study, no significant difference was found between the GnRHa group and the HCG group in these parameters. Also, the number of mature dominant follicles and the endometrial thickness on the triggering day were comparable between both groups. These findings agree with what was reported in other studies (14-17, 31, 32), and indicate that adequate randomization was conducted in the current study, and also, refute any bias that might have slanted the results in favor of one group rather than the other.

In the current study, the used GnRHa preparation was triptorelin in a dose of 0.2 mg SC and the used HCG preparation was urinary HCG (uHCG) in a dose of 5000 IU IM. Similar to the current study, Li et al used the same triptorelin and uHCG doses (32). On the other hand, some authors used the same triptorelin dose (0.2 mg) and a higher uHCG dose (10000 IU) in their studied (15-17). Bathwal et al used a lower triptorelin dose (0.1 mg) and the same uHCG dose (5000 IU) (31), and Shalev et al used a lower triptorelin dose (0.1 mg) and a higher uHCG dose (10000 IU) (14).

Ovulation was assessed in our study by TVS scanning for detection of signs of ovulation. The ovulation rate was high in both groups but without significant difference (95.7% in the GnRHa group vs 93.5% in the HCG group, P = 0.628). Similar to our study, Le and his colleagues (32) and Bathwal and his colleagues (31) have assessed ovulation by TVS scanning for detection of ovulation signs and they did not find significant difference in the ovulation rate between both groups. In other studies, ovulation was assessed by midluteal measurement of serum progesterone level, however, in agreement with our results, the ovulation rate was comparable between the GnRHa and the HCG groups (14, 15).

In our study, we provided luteal phase support to all patients in the form of progesterone vaginal suppositories in a dose of 200 mg every 12 hours. Likewise, luteal phase support was provided in some studies (17, 31, 32), however, in contrast, Ammar and his colleagues (15) and Shalev and his colleagues (14) did not provide luteal phase support.

Our results revealed clinical pregnancy rate of 23.4% (11 cases) in the GnRHa group and 21.7% (10 cases) in the HCG group without significant difference between both groups (P = 0.848). These results were keeping with Ammar and his colleagues who did not find significant difference in the clinical pregnancy rate between the GnRH group and the HCG group (21.6% vs 22.6%, P = 0.87) (15). In the same line, Shalev et al. reported similar pregnancy rates in their GnRH and HCG groups, however, their reported clinical pregnancy rates were lower than what was reported in the current study (12% in the GnRHa group and 12.6% in the HCG group) (14). In contrast to our findings, Elmahdy and Elsharkawy have found a significantly higher pregnancy rate in the HCG group than in the GnRHa group (30.5% vs 21.1%, P = 0.049) (17). On the other hand, Bathwal and his colleagues disagreed with Elmahdy

and Elsharkawy by finding a significantly higher clinical pregnancy rate in favor of the GnRHa group (10.33% in the GnRHa group vs 4.96% in the HCG group, P = 0.026) (31).

In the current study, no recorded cases of OHSS in the GnRHa group while only one case of mild OHSS was detected in the HCG group. This OHSS developed 3 days following trigger and the patient was candidate for conservative management. In the same line, Elmahdy and Elsharkawy found one case of moderate OHSS in the HCG group, and there were no such cases in the GnRHa group (17). Also, Ammar et al reported 3 case of mild OHSS in the HCG group, and they did not report any case of OHSS in the GnRHa group (15). Moreover, no reported cases of OHSS in either groups in the study by Shalev and his colleagues (14). In contrast, BuTalag and his colleagues reported a significantly higher OHSS rate in the HCG group than in the GnRHa group after one cycle of ovarian stimulation (17.39% vs 4.33%, P < 0.05) (16). This could be attributed to the use of high HCG dose (10000 IU) in a high risk group of patient (PCOS patients) having different phenotypes that could affect the morbidity of treatment (1).

The main strength point in the current study came from the fact that it was a randomized study with adequate randomization that appeared in absence of significant difference between the two groups regarding any demographic, clinical or hormonal parameter. Another strength point in our study is that, to the best of our knowledge, this is one of the very limited number of studies that assessed the efficacy and safety of GnRHa as an alternative to HCG for triggering of ovulation in PCOS women undergoing sequential minimal ovarian stimulation followed by timed intercourse. A limitation of the current study lies in the lack of blinding of participants and assessors. Another limitation is the small sample size which may have limited the study's power to detect significant differences in the outcomes measures.

In conclusion, the GnRHa could be an effective and safe alternative to the traditional HCG in ovulation triggering after sequential minimal ovarian stimulation in PCOS patients without affecting ovulation and clinical pregnancy rates. Using GnRHa for triggering of ovulation could avoid the occurrence of OHSS, which is one of the nightmares in patients with PCOS undergoing fertility treatment.

Conflicts of Interest: The authors declare that they have no conflicts of interest.

Ethical considerations: This paper has been adapted from the MSc. thesis written by Mr. Ammar Hesham Dorra.

References

1. Lizneva D, Suturina L, Walker W, Brakta S, Gavrilova-Jordan L, Azziz R. Criteria, prevalence, and phenotypes of polycystic ovary syndrome. Fertility and sterility. 2016;106(1):6-15.
2. Mitwally MF, Casper RF. Use of an aromatase inhibitor for induction of ovulation in patients with an inadequate response to clomiphene citrate. Fertility and sterility. 2001;75(2):305-9.
3. Lee VC, Ledger W. Aromatase inhibitors for ovulation induction and ovarian stimulation. Clinical endocrinology. 2011;74(5):537-46.
4. Franik S, Le QK, Kremer JA, Kiesel L, Farquhar C. Aromatase inhibitors (letrozole) for ovulation induction in infertile women with polycystic ovary syndrome. The Cochrane database of systematic reviews. 2022;9(9):Cd010287.
5. Corfman RS, Milad MP, Bellavance TL, Ory SJ, Erickson LD, Ball GD. A novel ovarian stimulation protocol for use with the assisted reproductive technologies. Fertility and sterility. 1993;60(5):864-70.
6. Lu PY, Chen AL, Atkinson EJ, Lee SH, Erickson LD, Ory SJ. Minimal stimulation

achieves pregnancy rates comparable to human menopausal gonadotropins in the treatment of infertility. Fertility and sterility. 1996;65(3):583-7.

7. Abu Hashim H, Bazeed M, Abd Elaal I. Minimal stimulation or clomiphene citrate as first-line therapy in women with polycystic ovary syndrome: a randomized controlled trial. Gynecological endocrinology : the official journal of the International Society of Gynecological Endocrinology. 2012;28(2):87-90.
8. Pilehvari S, ShahrokhTehraninejad E, Hosseinrashidi B, Keikhah F, Haghollahi F, Aziminekoo E. Comparison Pregnancy Outcomes Between Minimal Stimulation Protocol and Conventional GnRH Antagonist Protocols in Poor Ovarian Responders. Journal of family & reproductive health. 2016;10(1):35-42.
9. Apter D. Development of the hypothalamic-pituitary-ovarian axis. Annals of the New York Academy of Sciences. 1997;816:9-21.
10. Taheripanah R, Zamaniyan M, Moridi A, Taheripanah A, Malih N. Comparing the effect of gonadotropin-releasing hormone agonist and human chorionic gonadotropin on final oocytes for ovulation triggering among infertile women undergoing intrauterine insemination: An RCT. International journal of reproductive biomedicine. 2017;15(6):351-6.
11. Gonen Y, Balakier H, Powell W, Casper RF. Use of gonadotropin-releasing hormone agonist to trigger follicular maturation for in vitro fertilization. The Journal of clinical endocrinology and metabolism. 1990;71(4):918-22.
12. Casper RF. Basic understanding of gonadotropin-releasing hormone-agonist triggering. Fertility and sterility. 2015;103(4):867-9.
13. Youssef MA, Abdelmoty HI, Ahmed MA, Elmohamady M. GnRH agonist for final oocyte maturation in GnRH antagonist co-treated IVF/ICSI treatment cycles: Systematic review and meta-analysis. Journal of advanced research. 2015;6(3):341-9.
14. Shalev E, Geslevich Y, Matilsky M, Ben-Ami M. Gonadotrophin-releasing hormone agonist compared with human chorionic gonadotrophin for ovulation induction after clomiphene citrate treatment. Human reproduction (Oxford, England). 1995;10(10):2541-4.
15. Ammar IMM, Alnemr AAA, Abdou AM, Shazly SA. Gonadotropin-releasing hormone agonist versus human chorionic gonadotropin for ovulation triggering in letrozole stimulated cycles. Middle East Fertility Society Journal. 2018;23(4):303-9.
16. BuTalag I, Sarhan A, Harira M. Gonadotropin Releasing Hormone Agonist versus Human Chorionic Gonadotropin in Patients with PCOS as Trigger of Ovulation. Zagazig University Medical Journal. 2020;26(4):574-81.
17. Elmahdy M, Elsharkawy S. GnRH-Agonist Trigger versus Human Chorionic Gonadotrophin (HCG) Trigger in Cases of Controlled Ovarian Stimulation; Randomized Controlled Trial. Open Journal of Obstetrics and Gynecology. 2021;11:1452-60.
18. ESHRE TR, Group A-SPCW. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. Fertility and sterility. 2004;81(1):19-25.
19. Cui W. Mother or nothing: the agony of infertility. World Health Organization Bulletin of the World Health Organization. 2010;88(12):881.
20. Tanbo T, Mellembakken J, Bjercke S, Ring E, Åbyholm T, Fedorcsak P. Ovulation induction in polycystic ovary syndrome. Acta obstetricia et gynecologica Scandinavica. 2018;97(10):1162-7.

21. Helmer A, Magaton I, Stalder O, Stute P, Surbek D, von Wolff M. Optimal Timing of Ovulation Triggering to Achieve Highest Success Rates in Natural Cycles-An Analysis Based on Follicle Size and Oestradiol Concentration in Natural Cycle IVF. Frontiers in endocrinology. 2022;13:855131.

22. George K, Kamath MS, Nair R, Tharyan P. Ovulation triggers in anovulatory women undergoing ovulation induction. The Cochrane database of systematic reviews. 2014(1):Cd006900.

23. Smitz J, Platteau P. Influence of human chorionic gonadotrophin during ovarian stimulation: an overview. 2020;18(1):80.

24. Humaidan P, Kol S, Papanikolaou EG. GnRH agonist for triggering of final oocyte maturation: time for a change of practice? Human reproduction update. 2011;17(4):510-24.

25. Iliodromiti S, Blockeel C, Tremellen KP, Fleming R, Tournaye H, Humaidan P, et al. Consistent high clinical pregnancy rates and low ovarian hyperstimulation syndrome rates in high-risk patients after GnRH agonist triggering and modified luteal support: a retrospective multicentre study. Human reproduction (Oxford, England). 2013;28(9):2529-36.

26. Yding Andersen C, Vilbour Andersen K. Improving the luteal phase after ovarian stimulation: reviewing new options. Reproductive biomedicine online. 2014;28(5):552-9.

27. Tan J, Jing C, Zhang L, Lo J, Kan A, Nakhuda G. GnRH triggering may improve euploidy and live birth rate in hyper-responders: a retrospective cohort study. Journal of assisted reproduction and genetics. 2020;37(8):1939-48.

28. Christopoulos G, Vlismas A, Carby A, Lavery S, Trew G. GnRH agonist trigger with intensive luteal phase support vs. human chorionic gonadotropin trigger in high responders: an observational study reporting pregnancy outcomes and incidence of ovarian hyperstimulation syndrome. Human fertility (Cambridge, England). 2016;19(3):199-206.

29. Krishna D, Dhoble S, Praneesh G, Rathore S, Upadhaya A, Rao K. Gonadotropin-releasing hormone agonist trigger is a better alternative than human chorionic gonadotropin in PCOS undergoing IVF cycles for an OHSS Free Clinic: A Randomized control trial. Journal of human reproductive sciences. 2016;9(3):164.

30. Thorne J, Loza A, Kaye L, Nulsen J, Benadiva C, Grow D, et al. Euploidy rates between cycles triggered with gonadotropin-releasing hormone agonist and human chorionic gonadotropin. Fertility and sterility. 2019;112(2):258-65.

31. Bathwal S, Chakravarty A, Sharma S. Efficacy of GnRH agonist trigger in women having history of follicular-endometrial asynchrony with clomiphene/IUI cycles in unexplained infertility. 2018;298(2):427-32.

32. Le MT, Nguyen DN, Zolton J, Nguyen VQH. GnRH Agonist versus hCG Trigger in Ovulation Induction with Intrauterine Insemination: A Randomized Controlled Trial. International journal of endocrinology. 2019;2019:2487067.

Prevalence of Molar Pregnancy in Histopathological Examination of Products of Conception Following First Trimester Miscarriages

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Abstract

Background: Molar pregnancy is a rare complication of pregnancy characterized by the abnormal growth of trophoblasts, the cells that normally develop into the placenta. Routine histopathologic examination of uterine products is beneficial in protecting obstetrician and gynecologist from medico legal recrimination, but it is unclear whether this practice is medically justified.

Objective: The aim of this study is to evaluate Prevalence of molar pregnancy in histopathological examination of products of conception following first trimester miscarriages.

Patients and Methods: This was a cross sectional study conducted on cases with products of conception in the first trimester miscarriages up to 12 weeks gestation. Entire cases were subjected to full history taking, clinical examination after that the samples were collected via manual vacuum aspiration for histopathological analysis.

Results: The prevalence of molar pregnancy among the studied cases was 7%. About 93% of the studied cases were normal. Most of the studied histological specimens were products of conception which accounts for 85% of cases. The incidence of complete vesicular mole, degenerated Products of conception, Hyper secretory Endometrium, Infected Products of conception, Necrotic Products of conception and Partial Hydatidiform moles were 4.2, 1.4, 2.8, 1.4, 1.4 and 2.8 respectively.

Conclusion: Histopathological examination seemed to be a promising tool in the context of assessment of products of conception in which the prevalence of molar pregnancy was 7%. In addition, incidence of molar pregnancy has no significant correlations with all clinical features as well as with blood groups.

Keywords: Molar pregnancy, Histopathological examination, Products of conception.

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Introduction

Molar pregnancy is a subcategory of diseases under gestational trophoblastic disease (GTD), which originates from the placenta and can metastasize. It is unique because the tumor originates from gestational tissue rather than from maternal tissue (1). Vaginal bleeding and early pregnancy loss are the most common problems encountered in the first trimester. The miscarriages can be classified as incomplete or complete miscarriage, missed and anembryonic miscarriage (2, 3).

There is a medico-legal aspect related to clinical practice suggesting that in all uterine evacuations, a sample of tissues should be submitted for histopathological examination to confirm the presence of intra-uterine fetal tissue (4). Examples of such areas are subsequent trophoblastic disease, and missed ectopic pregnancies or heterotopic gestations that might lead to claims of negligence. In some cases, this examination may be of some value in determining the possible causes of recurrent pregnancy loss, or it may show an unexpected pathology (5). Traditionally, most women who had spontaneous miscarriage have undergone surgical uterine evacuation of retained products of conception (RPOC). In recent years, more women are being treated on an outpatient basis and more diagnostic techniques and therapeutic interventions are being applied (6).

The majority of these women have evacuation of retained product of conception; but there is no agreement about the value of histopathological evaluation of products of conception in these cases. Routine histopathologic examination of uterine products passed spontaneously or evacuated surgically or medically is beneficial in protecting obstetrician and gynecologist from medico legal recrimination, but it is unclear whether this practice is medically justified. An alternative approach is to examine the products only when there is a definite indication, such as when there is uncertainty about the diagnosis, either preoperatively or at the time of surgery (7).

Aim of the Work

The aim of this study is to evaluate Prevalence of molar pregnancy in histopathological examination of products of conception following first trimester miscarriages.

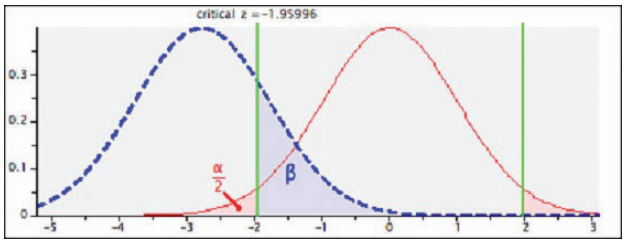
Patients and methods

Study Design:

This was a cross sectional study conducted on a total of 71 cases with products of conception of patients with first trimester miscarriages up to 12 weeks gestation were histopathologically analyzed at Mansoura University Hospital, Obstetrics and Gynecology Department from February 2020 to February 2021. Inclusion criteria include all ages with missed, incomplete abortion and anemberyonic miscarriage, gestational age between 5 weeks up to 12 weeks. Cases with illegal abortion and criminal miscarriage were excluded from the study.

Sample Size Calculation:

Sample size calculation was based on results of histo-pathological examination of products of misconception depending on proportion of complete hyditiform mole (0.2) retrieved from previous study (Zanco ,2017) . Using G*power version 3.0.10 to calculate difference between 2 proportions (the other expected from other study with the difference of 0.23 in proportion) using Z test =1.95 ,2-tailed , With α error =0.05 and power = 80.0%. The total calculated sample size is 63 and by adding 10% to compensate for drop out then the total calculated sample size is 70 patients at least.



Methods:

All patients were subjected to full history taking which include age, sex, occupation, residency and special habits. Complete general examination was performed which include blood pressure, heart rate, respiratory rate and temperature. After that; the samples were collected via manual vacuum aspiration kit under general anesthesia and complete aseptic precautions. The samples were examined macroscopically by a histopathologist before being embedded in paraffin blocks for further processing. The paraffin blocks were stained with haematoxylin and eosin. The sections were examined microscopically by a histopathologist. Averages of five blocks were examined for each patient, and additional blocks were sometimes being required to detect chorionic villi.

An intrauterine pregnancy was confirmed if fetal tissues, trophoblasts, or chorionic villi were identified in addition to other tissues, such as deciduae or secretory endometrium. For each patient, the report included a note about the absence or presence of trophoblastic disease, including molar pregnancy.

Ethical considerations:

The study was submitted to IRB committee in faculty of medicine, Mansoura University for approval. Informed verbal consent was obtained from every patient share in the study after confirmation of confidentiality and personal privacy. The data collected from patients were used in other purposes rather than the present research.

Statistical analysis:

Data were fed to the computer and analyzed using IBM SPSS Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp. Qualitative data were described using number and percent. Quantitative data were described using mean, standard deviation for parametric data after testing normality using Kolmogrov-Smirnov test. Significance of the obtained results was judged at the (0.05) level. Concerning qualitative data; Chi-Square , Fischer exact and Monte Carlo test for comparison of 2 or more groups of qualitative variables as appropriate. Regarding quantitative data between groups (Parametric tests) Student t-test was used to compare 2 independent groups.

Results

Table (1) demonstrates socio-demographic characteristics and obstetric history of the studied cases. The mean age of the studied cases was 30. Most of the studied cases were living in rural areas (64.8%), while 35.2% of which were living in urban areas. The median gravidity value was 3 in which 50% were ≤3 and 49.3% were >4. The median parity value was 2 in which 66.2 % were ≤2 and 33.8% were >3. The mean gestational age was 9. All patients had normal vital signs.

Table (1): Socio-demographic characteristics and obstetric history of the studied cases:

	N=71	%
Age/years mean±SD (min-max)	30.44±7.39 (17-45)	
Residence		
Rural	46	64.8
Urban	25	35.2
Gravidity Median (min-max)	3(1-9)	
≤3	36	50.7
>4	35	49.3

Parity **Median (min-max)**	2(0-7)	
≤2 **>3**	47 24	66.2 33.8
Gestational age /weeks **mean±SD** **(min-max)**	9.02±2.17 (5-15)	
Vitals **normal**	71	100.0

Table (2) demonstrates associated medical conditions of the studied cases. Most of the studied cases were associated with no medical conditions (80.3%), while only 19.7% of which had positive history of medical troubles. Diabetes (9.9%) and hypertension (8.5%) were the most frequently recorded medical problems followed by IHD or cardiomyopathy (4.2%) and lastly APS, Bronchial asthma, Hepatic lobe and Hypothyroidism representing 1.4% of each.

Table (2): Associated medical conditions of the studied cases:

	N=71	**%**
Associated medical conditions **- ve** **+ve**	 57 14	 80.3 19.7
APS	1	1.4
Bronchial asthma	1	1.4
Hypertension	6	8.5
Diabetes	7	9.9
IHD or cardiomyopathy	3	4.2
Hepatic lobe	1	1.4
Hypothyroidism	1	1.4

Table (3) and figure (1) illustrate histological report of the studied cases. Most of the studied histological specimens were products of conception which accounts for 85% of cases. The incidence of complete vesicular mole, degenerated Products of conception, Hyper secretory Endometrium, Infected Products of conception, Necrotic Products of conception and Partial Hydatidiform moles were 4.2, 1.4, 2.8, 1.4, 1.4 and 2.8 respectively.

Table (3): Histological report of the studied cases:

Histological report	n	%
Complete vesicular mole	3	4.2
Degenerated Products of conception	1	1.4
Hyper secretory Endometrium	2	2.8
Infected Products of conception	1	1.4
Necrotic Products of conception	1	1.4
Partial Hydatidiform mole	2	2.8
Products of conception	61	85.9
Total	71	100.0

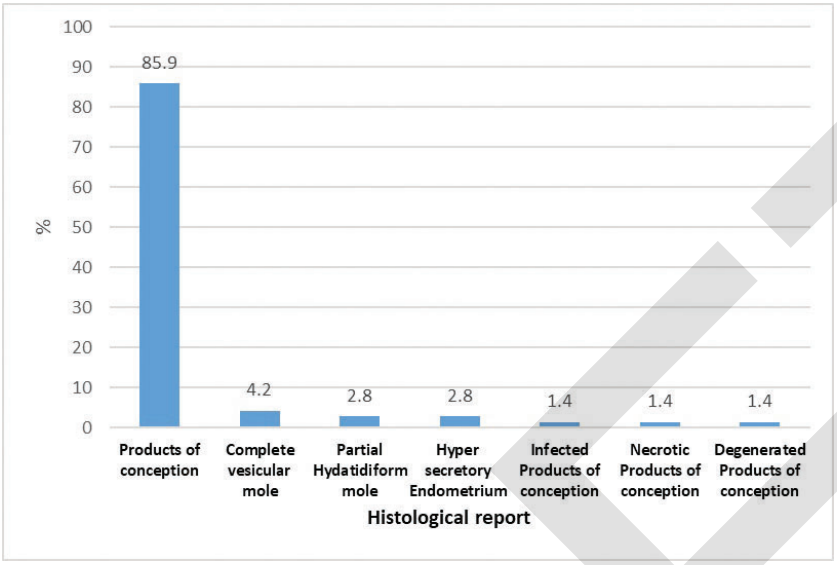


Figure (1): Histological report of the studied cases.

Table (4) and figure (2) display total incidence (molar vs normal), partial to total, partial to complete. About 93% of the studied cases were normal. The incidence of Partial mole, complete vesicular mole, Molar vs normal, Partial to total and Partial to complete were 2.8, 4.2, 7.6, 2.8 and 66.7 respectively.

Table (4): Total incidence (molar vs normal), partial to total, partial to complete:

	N=71	%
Normal	66	93.0
Partial mole	2	2.8
Complete vesicular mole	3	4.2
Molar vs. normal **Partial to total** **Partial to complete**	5/66 2/71 2/3	7.6 2.8 66.7

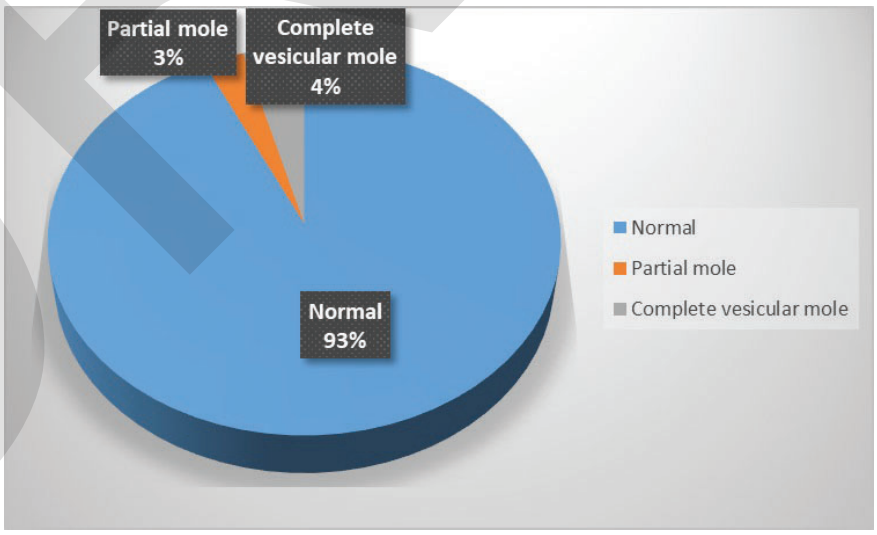


Figure (2): Total incidence (molar vs. normal), partial to total, partial to complete.

able (5) illustrates relation between clinical characteristics and incidence of molar pregnancy. There were no statistically significant correlations between all clinical characteristics (Maternal age, Gestational age, Gravidity, Parity, Residence, Associated medical conditions, APS, Bronchial asthma, Hypertension, Diabetes, IHD or cardiomyopathy, Hepatic lobe, Hypothyroidism, N/A and Hb) and incidence of molar pregnancy (P>0.05).

Table (5): Relation between clinical characteristics and incidence of molar pregnancy:

	Normal	Molar	Test of significance
Maternal age/years mean±SD	30.63±7.31	27.80±8.98	t=0.825 p=0.412
Gestational age/weeks mean±SD	9.0±2.24	9.40±1.14	t=0.394 p=0.695
Gravidity **≤3** **>4**	 33(50) 33(50)	 3(60) 2(40)	$\square^{2FET}$=0.186 P=0.666
Parity **≤2** **>3**	 43(65.2) 23(34.8)	 4(80) 1(20)	$\square^{2}$=0.458 P=0.499
Residence **Rural** **urban**	 42(63.6) 24(36.4)	 4(80) 1(20)	$\square^{2FET}$=0.546 P=0.460
Associated medical conditions **-ve** **+ve**	 52(78.8) 14(21.2)	 5(100) 0	$\square^{2}$=1.32 P=0.250
APS **-ve** **+ve**	 65(98.5) 1(1.5)	 5(100) 0	$\square^{2FET}$=0.08 P=0.782
Bronchial asthma	1(1.5)	0	$\square^{2FET}$=0.08 P=0.782
Hypertension	6(9.1)	0	$\square^{2}$=0.497 P=0.481
Diabetes	7(10.6)	0	$\square^{2}$=0.588 P=0.443
IHD or cardiomyopathy	3(4.5)	0	$\square^{2FET}$=0.237 P=0.626
Hepatic lobe	1(1.5)	0	$\square^{2FET}$=0.08 P=0.782
Hypothyroidism	1(1.5)	0	$\square^{2FET}$=0.08 P=0.782

N/A **A +ve** **A -ve** **AB +v** **AB- v** **B +ve** **B -ve** **O +ve** **O -ve**	28(42.4) 15(22.7) 3(4.5) 4(6.1) 1(1.5) 7(10.6) 2(3.0) 5(7.6) 1(1.5)	1(20) 2(40) 0 0 0 0 0 2(40) 0	$\square^{2MC}$=7.47 P=0.487
Hb (gm/dl) **mean±SD**	11.58±0.95	11.20±0.0	t=0.387 p=0.702

t:Student t test MC: Monte Carlo test , FET: Fischer exact test
□2:Chi-Square test *statistically significant

Table (6) reveals relation between clinical characteristics and incidence of partial molar pregnancy. There were no statistically significant differences among all clinical characteristics (Maternal age, Gestational age, Gravidity, Parity Residence, Associated medical conditions and Blood groups) and incidence of partial molar pregnancy (P>0.05).

Table (6): Relation between clinical characteristics and incidence of partial molar pregnancy:

	Partial	**Complete**	**Test of significance**
Maternal age/years **mean±SD**	22.50±0.707	31.33±10.69	t=1.11 p=0.349
Gestational age/weeks **mean±SD**	9.0±1.41	9.67±1.15	t=0.586 p=0.599
Gravidity **≤3** **>4**	 1(50) 1(50)	 2(66.7) 1(33.3)	$\square^{2FET}$=0.139 P=1.0
Parity **≤2** **>3**	 2(100) 0	 2(66.7) 1(33.3)	$\square^{2FET}$=0.833 P=0.361
Residence **Rural** **urban**	 2(100) 0	 2(66.7) 1(33.3)	$\square^{2FET}$=0.833 P=1.0
Associated medical conditions **-ve** **+ve**	 2(100) 0	 3(100) 0	
Blood groups **N/A** **A +ve** **O +ve**	 0 1(50) 1(50)	 1(33.3) 1(33.3) 1(33.3)	$\square^{2MC}$=0.833 P=0.659

t:Student t test MC: Monte Carlo test , FET: Fischer exact test,
*statistically significant

Discussion

Hydatiform mole is a subcategory of diseases under gestational trophoblastic disease (GTD), which originates from the placenta and can metastasize. It is unique because the tumor originates from gestational tissue rather than from maternal tissue. The management of gestational trophoblastic disease (GTD) depicts one of the success stories of modern medicine. As the majority, if not all, GTDs are potentially curable with the retention of reproductive function, once the correct diagnosis is made and treatment is commenced early enough (8). The incidence of GTD varies greatly in different parts of the world, with 0.4 per 1000 birth in United States of America to 12.5 per 1000 births in Taiwan (9). In Nepal, hospitals in Kathmandu valley have recorded its incidence as 5.1, 2.9, 2.8, and 4.1 per 1000 live births (10).

This was a cross sectional study conducted on a total of 71 specimens of the products of conception of patients with first trimester miscarriages up to 12 weeks gestation who were histopathologically analyzed to evaluate Prevalence of molar pregnancy in histopathological examination of products of conception following first trimester miscarriages.

Concerning socio-demographic characteristics and obstetric history of the studied cases, the current study demonstrated that the mean age of the studied cases was 30. Most of the studied cases were living in rural areas (64.8%), while 35.2% of which were living in urban areas. The median gravidity value was 3 in which 50% were ≤3 and 49.3% were >4. The median parity value was 2 in which 66.2 % were ≤2 and 33.8% were >3. The mean gestational age was 9. All patients had normal vital signs.

Alsibianiand his colleagues have found that; during the study period, a total of 558 women were admitted with the diagnosis of first-trimester miscarriage. Their mean age was 33.7 ± 7.5 years and mean parity was 3.1 ± 2.2. A history of miscarriage was present in 0.45 ± 1.0 patients (11). **Agrawal and his colleagues** have illustrated that more than one third of the patients were in the age group of 20–35 years and majority of them were of Hindu religion. For more than one third (41.7 %) of the patients, it was their first pregnancy while about 10 % gave a positive past history of molar pregnancy. Abnormal uterine bleeding (86.3 %) was the most frequent complaint, suction evacuation was the most common method of treatment and more than half of the patients required prolonged care after initial management (12).

The current study demonstrated that; the prevalence of molar pregnancy was7% of which 4.2% were complete vesicular mole and 2.8% were Partial Hydatidiform mole. Such prevalence came in the average values of the previously foamed researches. **Mulisya and his colleagues** have illustrated that; the prevalence of hydatidiform mole was 6.1% (11/181). All detected moles were complete hydatidiform moles, and there were no diagnosed partial hydatidiform moles. Clinical diagnosis of molar pregnancy was suspected in 13 patients, but only 69.2% (9/13) were confirmed as molar pregnancies histologically. Two cases were clinically unsuspected (13). Likewise, in Germany, Horn and his colleagues found a similar prevalence, to ours, of 5.1% of HM, specifically complete hydatidiform mole confirmed with a molecular genotyping (14).

Higher incidence was recorded by **Thirukumar** who have reported that; the Molar pregnancy was confirmed in 32.8% samples and the majority (78.3%) was dominated by complete mole. There were 66 patients ultrasonically suspected to have H Mole; among them 46 patients had either complete or partial mole. Further, this study showed no molar pregnancies were identified from specimens obtained following evacuation of ultrasonically diagnosed missed or incomplete miscarriage where no H Mole was suspected (15).

In addition, our prevalence is lower than the rates of 12.8% in Tanzania reported in a cross-sectional study in a similar setting (16). But in this study in Tanzania, there was no quality control by expert review or special studies. They reported 20/180 (11.1%) as partial mole and 3/180 (1.7%) as complete mole. The diagnosis of partial hydatidiform mole based solely on histopathology is difficult even for experienced pathologists (17). Their report of 1.7% of complete moles is lower than our findings of 4.2%. We suggest that, in the study in Tanzania, many of the cases diagnosed as partial hydatidiform moles were in fact complete moles and many others likely nonmolar, but this would require reexamination of their histology to confirm.

In the context of histopathologic examination, the current study demonstrated that; most of the studied histological specimens were products of conception which accounts for 85% of cases. The incidence of complete vesicular mole, degenerated Products of conception, Hyper secretory Endometrium, Infected Products of conception, Necrotic Products of conception and Partial Hydatidiform moles were 4.2, 1.4, 2.8, 1.4, 1.4 and 2.8 respectively. In addition, about 93% of the studied cases were normal. The incidence of Partial mole, complete vesicular mole, Molar vs normal, Partial to total and Partial to complete were 2.8, 4.2, 7.6, 2.8 and 66.7 respectively.

Histologic examination is a reliable method of diagnosing pathologic pregnancies. Excluding hydatidiform mole histologically has obvious medical value, as it rules out the possibility of persistent trophoblastic disease or choriocarcinoma. To rule out gestational trophoblastic disease after miscarriage, the pathologist should examine all recovered material. The material should be examined macroscopically and microscopically with at least five cassettes if the appearance suggests gestational trophoblastic disease (18).

This came in the same line with **Alsibianiand his colleagues**, who have demonstrated that histopathologic examination confirmed products of conception in 537 (96.2%) patients, no products of conception in 17 (3%) patients, molar pregnancy in 2 (0.4%) patients, and decidual tissues without chorionic villi (Arias-Stella reaction) in 2 (0.4%) patients (11).

Likewise, **Tasci and his colleagues** have displayed that histopathologic examination revealed the product of conception in 1119 patients (69.7%), while partial hydatidiform mole was diagnosed in 33 patients (2.1%). Complete hydatidiform mole was detected in only seven cases (0.43%). Exaggerated placental site and placental site trophoblastic nodule was detected in two cases (0.12%). Decidual tissue without chorionic villi was reported in 272 patients (16.9%), raising the suspicion of presence of other pathology (19). Also, Paradinas showed that 120 patients (18%) with unsuspected molar pregnancy in a series of 670 non-selected cases were diagnosed as having molar pregnancies on account of their abundant trophoblastic features in early pregnancy or in the presence of hydrops (20).

In addition, **Sebire and his colleagues** reported that in a series of 155 cases with histologically confirmed complete or partial hydatidiform moles, only 34% were suspected to have molar pregnancy following ultrasonography (21). Fram has displayed that; the histopathology reports confirmed the pregnancy in all patients and revealed partial mole in 51 patients (17%), undiagnosed abnormality in 8 patients (2.7%), suggesting the possible cause for recurrent pregnancy loss in 4 patients (1.4%) (18).

The incidence of gestational trophoblastic disease in the region is a factor that may influence the value of routine histopathologic examination of obtained tissues. In Asia, the incidence of hydatidiform mole is as high as 1 in 80 pregnancies, whereas in the western world, it is 1 in 500–1500 pregnancies (22, 23). The incidence in Saudi Arabia is similar to the latter: 1 in 452–1098 pregnancies,

and it has decreased over time, paralleling sociomedical improvements (24, 25).

The current study demonstrated that there was no significant correlation between blood groups and incidence of molar pregnancy (P>0.5). In accordance, **Sasaki and his colleagues** have displayed that; the distribution of ABO blood groups in patients with hydatidiform mole did not deviate significantly from the distribution in the controls (26).

With regard to relation between clinical characteristics, the current study demonstrated that there were no statistically significant correlations between all clinical characteristics (Maternal age, Gestational age, associated medical conditions, Parity, Residence and Gravidity) and incidence of molar pregnancy. **Mulisya and his colleagues** were in agreement regarding the fact that, the parity, socioeconomic status, blood group, and history of contraception use were not associated with hydatidiform mole. However they were in disagreement as regards that factors that had a significant relationship with complete hydatidiform mole included maternal age of 35 years and above (p=0.00), gestational age beyond the first trimester at the time of uterine evacuation (p=0.04), and history of previous abortion (p=0.05) (13). Also, **Al-Talib and his colleagues** have displayed that advanced maternal age and nullipara could be risk factors of molar pregnancy development. They have reported that the majority of patients with molar pregnancy (63.7%) were older than 35 years, and were nulliparous (45.5%) (27).

It is likely that the oocytes of the older women are more apt to unnatural fertilization (28). Studies show a significant increase in risk in women with pregnancy above the age of 35 years and even further increase of 10-fold beyond the age of 40 years (29).

Previous history of abortion was reported in 44 (24.3%) participants of our study, and 7 (15.9%) of them were found to have complete mole. We found this history to be strongly associated with a diagnosis of hydatidiform mole, which is in accordance with others (30, 31). Hydatidiform mole was found to be more common in women with history of two or more abortions as well in the study in Ethiopia (30). This could be due to the fact that many women do not know the nature of the previous abortion because histopathological examination is rarely done, yet hydatidiform mole may be one of the previous causes because history of hydatidiform mole has been established as a strong risk factor for subsequent hydatidiform mole (32).

Conclusion

Histopathological analysis seemed to be a promising tool in the context of assessment of products of conception in which the prevalence of molar pregnancy was 7%. In addition, incidence of molar pregnancy has no significant correlations with all clinical features as well as with blood groups.

References

1. 1. Sarmadi S, Izadi-Mood N, Sanii S, Motevalli D. Inter-observer variability in the histologic criteria of diagnosis of hydatidiform moles. The Malaysian journal of pathology. 2019;41(1):15-24.
2. Johnstone C. Vaginal examination does not improve diagnostic accuracy in early pregnancy bleeding. Emergency Medicine Australasia. 2013;25(3):219-21.
3. Verma M, Thakur V, Awasiya P. A comparative study of misoprostol versus surgical management of incomplete and missed miscarriage. International Journal of Reproduction, Contraception, Obstetrics and Gynecology. 2016;5(11):3654-9.
4. Nisa N, Singh S, Shafi F, Rani G. Clinical Study of Intra Uterine Fetal Death. Congenital anomalies. 2018;10:10.

5. Lattouf I, Lu C, Pixton S, Reid S, Condous G. Is there a difference in the behaviour and subsequent management of ectopic pregnancies seen at first scan compared to those ectopic pregnancies which commence as pregnancies of unknown location? Australian and New Zealand Journal of Obstetrics and Gynaecology. 2016;56(1):107-12.
6. WHO. Safe abortion: technical and policy guidance for health systems: World Health Organization; 2012.; 0- 22.
7. Heath V, Chadwick V, Cooke I, Manek S, MacKenzie I. Should tissue from pregnancy termination and uterine evacuation routinely be examined histologically? BJOG: An International Journal of Obstetrics & Gynaecology. 2000;107(6):727-30.
8. Chakrabarti BK, Mondal NR, Chatterjee T. Gestational trophoblastic tumor at a tertiary level cancer center: a retrospective study. The Journal of Reproductive Medicine. 2006;51(11):875-8.
9. Chhabra A, Sinha P. Gestational Trophoblastic Disease–some observation. J Obs Gynecol India. 1988;38:590-3.
10. Thapa K, Shrestha M, Sharma S, Pandey S. Trend of complete hydatidiform mole. JNMA; Journal of the Nepal Medical Association. 2010;49(177):10-3.
11. Alsibiani SA. Value of histopathologic examination of uterine products after first-trimester miscarriage. BioMed research international. 2014; (2014); 5.
12. Agrawal N, Sagtani RA, Budhathoki SS, Pokharel HP. Clinico-epidemiological profile of molar pregnancies in a tertiary care centre of Eastern Nepal: a retrospective review of medical records. Gynecologic Oncology Research and Practice. 2015;2(1):1-7.
13. Mulisya O, Roberts DJ, Sengupta ES, Agaba E, Laffita D, Tobias T, et al. Prevalence and factors associated with hydatidiform mole among patients undergoing uterine evacuation at mbarara regional referral hospital. Obstetrics and gynecology international. 2018; (2018): 7-13.
14. Horn L, Rosenkranz M, Bilek K. The value of placental histology for the detection of genetically-induced abortions. Zeitschrift fur Geburtshilfe und Perinatologie. 1991;195(2):47-53.
15. Thirukumar M. Histopathological examination of products of conception after first-trimester miscarriage. 2019; CJMS 2019; 56(I): 12-15
16. City M. Prevalence and associated risk factors of hydatidiform moles among patients with incomplete abortion evacuated at Bugando Medical Centre and Sekou Toure Hospital in, Catholic University of Health and Allied Sciences. African Health Sciences. 2013;15(4):1081-6.
17. Banet N, DeScipio C, Murphy KM, Beierl K, Adams E, Vang R, et al. Characteristics of hydatidiform moles: analysis of a prospective series with p57 immunohistochemistry and molecular genotyping. Modern Pathology. 2014;27(2):238-54.
18. Fram KM. Histological analysis of the products of conception following first trimester abortion at Jordan University Hospital. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2002;105(2):147-9.
19. Tasci Y, Dilbaz S, Secilmis O, Dilbaz B, Ozfuttu A, Haberal A. Routine histopathologic analysis of product of conception following first-trimester spontaneous miscarriages. Journal of Obstetrics and Gynaecology Research. 2005;31(6):579-82.
20. Paradinas F. The histological diagnosis of hydatidiform moles. Current Diagnostic Pathology. 1994;1(1):24-31.

21. Sebire N, Rees H, Paradinas F, Seckl M, Newlands E. The diagnostic implications of routine ultrasound examination in histologically confirmed early molar pregnancies. Ultrasound in Obstetrics and Gynecology: The Official Journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2001;18(6):662-5.
22. Steigrad SJ. Epidemiology of gestational trophoblastic diseases. Best practice & research Clinical obstetrics & gynaecology. 2003;17(6):837-47.
23. Sebire N, Seckl M. Gestational trophoblastic disease: current management of hydatidiform mole. Bmj. 2008;337: 1193
24. Al-Ghamdi AA. Recurrent hydatidiform mole: a case report of six consecutive molar pregnancies complicated by choriocarcinoma, and review of the literature. Journal of Family and Community Medicine. 2011;18(3):159.
25. Khashoggi TY. Prevalence of gestational trophoblastic disease. A single institution experience. Saudi medical journal. 2003;24(12):1329-33.
26. Sasaki K, Hata H, Nakano R. ABO blood group in patients with malignant trophoblastic disease. Gynecologic and obstetric investigation. 1985;20(1):23-6.
27. Al-Talib AA. Clinical presentation and treatment outcome of molar pregnancy: Ten years experience at a Tertiary Care Hospital in Dammam, Saudi Arabia. Journal of family & community medicine. 2016;23(3):161.
28. MOHAMMAD JR, Abedi P, TADAYON NM. The gestational trophoblastic diseases: a ten year retrospective study. 2010.
29. Bugti QA, Baloch N, Baloch MA. Gestational trophoblastic disease in Quetta. Pakistan J Med Res. 2005;44(2):200.
30. Negussie D, Belachew T. Profile of gestational trophoblastic diseases in two teaching hospitals, Addis Ababa, Ethiopia. Ethiopian Journal of Health Sciences. 2008;18(1): 195- 201.
31. Schorge JO. Williams gynecology: McGraw-Hill Medical New York; 2008; (2008): 313; 315
32. Taboo ZA-A. A prospective study of gestational trophoblastic disease in Al-Mosul City. Iraqi Postgraduate Medical Journal. 2013;12(2): 268- 276

Urine albumin/creatinine ratio for the assessment of albuminuria in hypertensive disorders of pregnancy

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Abstract

Background: The Protein-Creatinine ratio (P/C Ratio) measurement is an alternative diagnostic method for quantitatively evaluating proteinuria in pre-eclampsia. This study aimed to assess the precision of the protein/creatinine ratio as a diagnostic tool for proteinuria in preeclamptic pregnant patients.

Methods: A prospective study was conducted at the Obstetrics and Gynecology Department of a private hospital in KSA from July 2021 to January 2023, 100 pregnant women with preeclampsia were included in the study. All patients in the study underwent a history taking, physical examination, routine laboratory investigations, and urine protein/creatinine ratio assessment.

Results: The findings found substantial positive connections between 24-hour protein, proteinuria, and serum creatinine, as well as strong positive P/C ratio and 24-hour protein correlations. Urine creatinine and P/C ratio were shown to have strong negative correlations. The P/C ratio needs to be less than 0.29 to detect more than 300 mg of protein excretion per 24 hours, detecting 300 mg/24 hours of protein excretion with sensitivity of 95.3% and specificity of 71%.

Conclusion: Random PCR may be employed in urgent situations as a quick, simple, and accurate diagnostic for the detection of substantial proteinuria in hypertensive diseases during pregnancy.

Introduction

Many illnesses can raise blood pressure and even cause proteinuria; hence, as the diagnosis becomes more precise, so does the need for meticulous evaluation and delivery planning. (1,2).

Quantifying proteinuria in preeclampsia is essential for diagnosing the disease's severity and prognosis. (3). Although the gold standard for quantifying proteinuria, 24-hour urine collection has some drawbacks. The patient finds it difficult; it is frequently inaccurate due to under-collection, and results are delayed for at least 24 hours while the collection is finished. (4). In non-

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pregnant people, the threshold for urine protein excretion is typically 150 mg/day, while lower and higher amounts have been proposed. These threshold values often double during pregnancy, with 300 mg/d being the most typical value (5).

The spot P/C ratio has been tested for usage during pregnancy with inconsistent results. While some researchers have emphasized caution in its implementation because the renal function can become unstable in preeclampsia within hours, others have endorsed its use by establishing significant correlations between spot P/C and 24-hour collections. (6)

The ratios of spot albumin to creatinine and spot protein to creatinine have both been extensively studied and are used outside of pregnancy. The National Kidney Foundation currently recommends these tests (instead of 24-hour urine collection) to detect proteinuria, without addressing pregnancy specifically (7).

The Society of Obstetric Medicine of Australia and New Zealand, the International Society for the Study of Hypertension in Pregnancy, and the Society of Obstetricians and Gynecologists of Canada have all approved the spot urine ACR, but not all international consensus bodies, including the American Congress (2).

This study's objective is to evaluate the accuracy of the protein/creatinine ratio as a diagnostic tool for pregnant people with preeclampsia who have proteinuria.

Patients and methods

A prospective investigation was conducted at the Obstetrics and Gynecology Department of a private hospital in KSA in the period from July 2021 to January 2023, hundred of pregnant women with a possible preeclampsia diagnosis were included in the study after being fully told of its purpose, the necessary procedure, and the follow-up schedule. After agreeing to participate, they signed the consent form.

Exclusion standards:

- A recognised kidney disorder.
- Vigorous workout (more than one hour of vigorous exercise on the day of urine collection).
- Bacteriuria is present.
- More than 24 hours in bed.
- Gestational diabetes.
- Ladies gave birth on the day that urine was collected.

Methods: Each pregnant participant in the study underwent:

Complete history taking and physical assessment come first:

- Vital indicators, including respiration rate, temperature, blood pressure, and heart rate.
- A thorough examination of the heart, lungs, legs, eyes, and nervous system.
- Fundal examination of the abdomen ,Leopard's manouver, FHS.

3- Investigations:

Full blood count, blood and Rh grouping, kidney function tests, urine analysis and culture, determination of urine protein/ creatinine ratio, Urine from the previous 24 hours was also taken in order to measure total protein , liver function tests

The amount of protein in urine was detected using the Bradford method using BSA (also from Bio-Rad) as a calibrator (Bio-Rad Protein Assay Kit, Bio-Rad Laboratories). Spinreact kits were used to measure the creatinine levels in urine using the modified kinetic Jaffe reaction in a 96-well plate with a filter at 490 nm. The CVs for each assay were under 1.2%. By dividing the urinary protein concentration by the urine creatinine concentration, both stated in (mg/dl), one can determine the urine protein to creatinine ratio.

The shift in the complex's absorption spectra from 460 to 600 nm that happens at an acidic pH between Pyrogallol Red and Molibdate is the primary way to evaluate the presence of protein in urine (PRM) and the basic amino groups of urine. The intensity of the colored complex formed if proportional to the concentration of protein in the sample.

Statistical analysis

Data were entered checked and analyzed using Epi-Info version 6 and SPP for Windows version 8.

RESULTS

The included women's median age was 29.1 ± 6.7 years (range:19-42) At recruiting, the average gestational age was 32.2 weeks (range: 20-38). The mean blood pressure readings were 100± 12.2 mmHg for the mean diastolic reading and 154.3± 12.9 mmHg for the mean systolic reading. (table 1). Significantly favourable relationships between 24 hour protein, proteinuria, and serum creatinine were found. (table 3). Very positive relationships between the P/C ratio and the 24 hour protein were found. P/C ratio and urine creatinine were shown to have substantial negative associations. (table 4) To detect protein excretion greater than 300 mg per 24 hours, the P/C ratio must be less than 0.29..(table 5).

able (1): Demographic data

	Median (range)
Age	(19-42)
Gestational age (week)	32.2 ± 3.6 (20-38)
Systolic blood pressure	154.3 ± 12.9 (110-180)
Disatolic blood pressure	100 ± 12.2 (70-110)

Table (2): Laboratory findings, liver function tests and urine examination among studied cases

Laboratory findings	**Mean ± SD**
Hb	11.2 ± 1.6
Platelet x 10^3	185.5 ± 70.7
creatinine level(mg / dl)	0.80 ± 0.12
Liver function tests	
Albumin	2.6 ± 0.7
SGOT	26± 2
SGPT	28± 6
Urine examination	
Volume (ml)	1315 ± 690.7
Protein (mg/dl)	189.6± 56
Creatinine (mg/dl)	81.5± 26
24 hour protein(mg/24h)	1965± 43
P/C ratio	2.1± 0.3

Table (3): Correlation between protein and other parameters

24 hour protein	**R**	**P**
Volume	-0.04	0.76 (NS)
Proteinuria	0.37	0.01 (S)
Creatinine	0.12	0.47 (NS)
Serum creatinine	0.47	0.00 (S)
Albumin	-0.27	0.05 (NS)
SGOT	0.04	0.76 (NS)
SGPT	0.01	0.97 (NS)
GA	-0.06	0.66 (NS)
SBP	0.17	0.25 (NS)
DBP	0.19	0.62 (NS)
Hb	0.39	0.29 (NS)
Platelets	-0.08	0.56 (NS)

Table (4): The correlation between P/C ratio and other variables

P/C ratio	R	P
Proteinuria	0.65	0.00 (S)
Volume	-0.2	0.16 (NS)
Creatinine	-0.32	0.02 (S)
24 hour proteinuria	0.122	0.039 (S)
Serum creatinine	0.12	0.41 (NS)
Albumin	0.19	0.19 (NS)
SGOT	0.03	0.86 (NS)
SGPT	0.03	0.84 (NS)
GA	-0.007	0.96 (NS)
SBP	0.12	0.41 (NS)
DBP	0.36	0.34 (NS)
Hb	0.04	0.8 (NS)

Table (5): Accuracy of P/C ratio at cut off < 0.29

cutoff value of P/C ratio	0.29
Sensitivity	95.3%
Specificity	71%
PPV	98.4%
NPV	94.8%

Discussion

Hypertensive disorders of pregnancy complicate 12-22% of pregnancies. It includes a spectrum ranging from non-proteinuric gestational hypertension to severe pre-eclampsia with heavy proteinuria (8,9).

The main goal of this study was to assess the precision of the protein/creatinine ratio as a diagnostic tool for proteinuria in a sample of 100 preeclamptic pregnant patients. Pregnancy-related hypertension, such as gestational hypertension, mild pre-eclampsia, or severe pre-eclampsia, is present in all of the women who were included in the study. This condition is identified by a systolic arterial blood pressure of at least 140 mm Hg and a diastolic arterial blood pressure of at least 90 mm Hg, with or without proteinuria. (detected by dipsticks).

The included women's median age was 29.1± 6.7 years (range: 19-42 years). At recruiting, the average gestational age was 32.2 weeks (range: 20-38weeks).

A random urine sample from each included woman was collected to examine her levels of protein and creatinine, and the urinary protein-to-creatinine ratio was computed. Urine from the previous 24 hours was also taken in order to measure total protein.

Very positive relationships between the P/C ratio and the 24 hour protein were found. P/C ratio and urine creatinine were shown to have substantial negative associations. The cutoff value for the P/C ratio is 0.29 to identify protein excretion > 300 mg / 24 hours with sensitivity 95.3% and specificity 71%. The correlation coefficient between random urine p/c ratio and 24-hour urine protein and the cutoff point for the P/C ratio is 0.29

Numerous studies have been conducted over the past 20 years on the reliability of measuring the protein to creatinine ratio in random urine samples as an alternative to the gold standard 24-hour urinary total protein. Some of these studies found a strong correlation between the two, while others found a weak correlation.

The findings of this study concur with those of Wheeler et al(2017) .'s investigation into the predictability of a random urine protein to creatinine ratio in determining the presence of severe proteinuria. The study comprised 126 women with comparable demographics who were admitted for pre-eclampsia evaluation. In this investigation, the connection between

the 24-hour urine protein and the random urine protein to creatinine ratio was highly significant (r=0.88, p0.001). Random urine protein's ideal cutoff value is used to 0.21 for 24-hour urine protein ≥ 300 mg per 24h .(10)

A P/C ratio of less than 0.21 (300 mg every 24 hours) exhibited an 83.3% NPV, or negative predictive value.

According to the International Society for the Study of Hypertension in Pregnancy's (ISSHP) guidelines for classification and diagnosis of hypertensive disorders of pregnancy, the random protein to creatinine ratio is said to be equivalent to total protein excretion in a 24-hour sample when it comes to identifying significant proteinuria (11)

The value of the random urine protein to creatinine ratio in the diagnosis of severe proteinuria was thoroughly reviewed by Price et al. (2015), who looked at 16 studies. The 24-hour urine protein concentration and the random urine protein to creatinine ratio have consistently been reported to have strong, positive associations, with correlation values ranging from 0.8 to 0.97..(12)

The first urine protein to creatinine ratio after 4 hours was investigated by Saikul et al. (2016) as a potential indicator of severe proteinuria. With similar demographics, 164 pregnant women who also experienced hypertension during pregnancy were included. The included women had a pre-eclampsia severity of 48, 74 mild cases, and 52 gestational hypertension. The optimal cutoff value according to the ROC curve was 0.3 (area under the curve = 0.845; 95% confidence interval: 0.79-0.9, p0.001). The sensitivity and specificity of this value were 81% and 88% respectively. (13)

(2018) Shahbazian and Hosseini-Asl investigated the relationship between spot urine P/C ratio and 24-hour urine protein excretion in patients undergoing preeclampsia evaluation. They came to the conclusion that a random urine P/C ratio can forecast the amount of protein excretion in urine during a 24-hour period collection in pregnant women. (14)

The usefulness of this ratio to identify substantial albuminuria in patients with a suspicion of preeclampsia was also assessed by Nisell et al. in a 2016 study. They recommended that the more practical protein/creatinine ratio on spot pee can typically take the place of the more time-consuming 24-hour urine collection (15)

In order to find the optimum spot PC ratio cutoff values for moderate and severe preeclampsia, Haung et al. (2019) analysed the correlation between albuminuria as measured by PCR and the amount of albumin in a 24-hour urine collection in women with preeclampsia. It was discovered that a spot PC ratio in a midstream urine samples is less complicated, more practical, and more precise than measuring total protein in a 24-hour urine collection. (2)

The findings of a study carried out by Ragip et al. (2014) were not particularly encouraging. In the later study, records of 185 pregnant women with late-pregnancy moderate hypertension were examined. (9)\s. The correlation coefficient between the 24-hour urine protein and the random urine protein to creatinine ratio was less than what was predicted in the current investigation. The random urine protein to creatinine ratio's best cutoff value was 0.19 (sensitivity: 85%, specificity: 73%).

Ragip et al(2014) .'s study came to the conclusion that the random urine protein to creatinine ratio was not a reliable indicator of severe proteinuria in this group of women. (9)

Wikstrom et al. (2016) investigated the relationship between the amount of albumin in 24-hour urine samples from women with pre-eclampsia and severe albuminuria, as defined by the protein to creatinine ratio. (11) They did not advise using a random PC ratio to detect proteinuria in manifest pre-eclampsia because this ratio varies during the

day and has a limited correlation to the 24-hour urine protein test. In order to quantify proteinuria in preeclamptic women with substantial proteinuria, they advised 24-hour urine collection with protein to creatinine ratio or total albumin measurement(11)

Conclusion

In hypertensive diseases during pregnancy, severe proteinuria might be diagnosed quickly, easily, and accurately using random PCR, making it useful in urgent cases. With sensitivity of 95.3% and specificity of 71%, PCR in random urine correlates well with 24-hour urine protein at a threshold value of 0.29.

References

1. Munir S. Role of growth factors in preeclampsia: Early detection and treatment, Avicenna 2013;1:1-9
2. Huang Q, Gao Y, Yu Y, Wang W, Wang S , Zhong M. Urinary Spot Albumin:Creatinine Ratio for Documenting Proteinuria in Women With Preeclampsia. Rev Obstet Gynecol. 2019; 5(1):9-15
3. Cunningham FG , Gant NE, Leveno KJ, Steven LB, John CH, Larry CG et al. Hypertensive disorders in pregnancy. In Williams Obstetrics, 22nd ed., New York, Mcgraw- Hill 2018; P.761-808.
4. Maynard SE , Thadhani R. Pregnancy and the Kidney. J Am Soc Nephrol 2019;20: 14–22.
5. Lindheimer MD, Kanter D. Interpreting abnormal proteinuria in pregnancy: the need for a more pathophysiological approach. Obstet Gynecol. 2020; 115: 365–375.
6. Waite LL, Atwood AK, Taylor RN. Preeclampsia, an implantation disorder. Reviews in Endocrine & Metabolic Disorders 2020; 3 (2): 151–8.
7. Côté AM, Firoz T, Mattman A, Lam EM, von Dadelszen P, Magee LA. The 24-hour urine collection: gold standard or historical practice? Am J Obstet Gynecol. 2008;199(6):625.e1-6.
8. James DK, Steer PJ, Weiner CP. Pregnancy antecedent of high risk pregnancy. In: High risk pregnancy 3rd edition. Elsevier. 2018; Chapter 1; 7-25.
9. Raqib A, Baykal C, Karacay O, Geyik PO, Altun S, Dolen I. Random urine protein-creatinine ratio to predict proteinuria in new-onset mild hypertension in late pregnancy. Obstet Gynecol. 2004;104(2):367-71.
10. Wheeler TL 2nd, Blackhurst DW, Dellinger EH, Ramsey PS. Usage of spot urine protein to creatinine ratios in the evaluation of preeclampsia. Am J Obstet Gynecol. 2007;196(5):465.e1-4.
11. Wikström AK, Wikström J, Larsson A, Olovsson M. Random albumin/creatinine ratio for quantification of proteinuria in manifest pre-eclampsia. BJOG. 2006;113(8):930-4.
12. Price CP, Newall RG, Boyd JC. Use of protein:creatinine ratio measurements on random urine samples for prediction of significant proteinuria: a systematic review. Clin Chem. 2005;51(9):1577-86.
13. Saikul FA, Mamsouri. Using 2 hour/6hour urine protein measurement as substitute. Diagnostic Methods for evaluation of preeclampsia. The Internet Journal of Gynecology and Obstetrics.2016 ;10:1-5
14. Shahbazian N , Hosseini-Asl F. Comparison of spot urine protein-creatinine ratio with 24-hour urine protein excretion in women with preeclampsia. IJKD 2018; 2:127-31.
15. Nisell H, Trygg M , Back R. Urine albumin/creatinine ratio for the assessment of albuminuria in pregnancy hypertension. Acta Obstetricia et Gynecologica. 2016; 85: 1327-1330.

Comparison between Clomiphene Citrate / Metformin Stair Step Protocol and Traditional Protocol in Treatment of Polycystic Ovary Syndrome

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Abstract

Background: As Clomiphene citrate (CC) is widely used in treatment of infertility in polycystic ovarian syndrome (PCOS).

Aim: To evaluate rate of ovulation using CC "stair step protocol" compared to "traditional protocol".

Methods: A randomized clinical trial conducted on 60 infertile PCO were randomly divided to 2 groups, group (A) "Stair Step protocol" in which CC was administrated on day 2 to day 6 of menses then transvaginal ultrasound (TVUS) was done, if follicular diameter less than 18 mm on day 14 increasing dose to 100 mg days for further 5 days, then TVUS on day 21, if no response, an increasing the dose to 150 mg daily. In group (B), "Traditional protocol" started with CC 50 mg on day 2 to day 6 of menses, if no response, in subsequent cycles the dose increased by 50 mg till dose 150 mg daily.

Metformin dose was 500mg daily then increased weekly by 500 mg till 1500 mg daily.

Results: the rate of ovulation and pregnancy were higher in the stair-step than the traditional group (76.7 vs. 63.3 %, respectively) (40 vs. 26.7 %, respectively). With significantly shorter duration of treatment was in stair-step than traditional protocol (21 ± 7.0 vs. 49 ± 24 days, respectively).

Conclusion: the stair step protocol has a higher efficacy than traditional protocol.

Keywords: Clomiphene citrate, metformin, ovulation, stair-step.

Synopsis: stair step protocol has higher ovulation and pregnancy rate and significant shorter duration of treatment making it superior on traditional protocol.

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Introduction

PCOS is common endocrinal metabolic disorder affecting females at childbearing period [(1)], with reported global prevalence varies between 3-10%[(2)]. Diagnosis of

PCOS is based on the Rotterdam criteria[3] that requires 2 of the 3 diagnostic criteria, namely: - Oligo\anovulatory menstrual cycle, - Hyperandrogenic state that presented clinically or biochemically, and - Polycystic ovaries by high resolution transvaginal Ultrasound, in this setting follicle count per ovary should be ≥ 20 or ovarian volume ≥ 10 mL[4]. Treatment of infertility in women with PCOS includes non-pharmacological counseling about importance of life style modification and weight loss that would improve ovulation rates resulting in higher birth rates [5]. Pharmacological treatment for ovulation induction in PCOS includes CC and aromatase inhibitors are considered the first line, while gonadotropins are considered as second line, when the previous lines fail the next steps are laparoscopic ovarian drilling or assisted reproductive technologies[6]. CC acts as selective estrogen receptor modulator (SERM) that competes with estrogen ,consequently increasing levels of endogenous gonadotropins and the dominant follicle with highest number of FSH receptors is recruited, the antiestrogenic effect affects endometrium as well as cervical mucus thus potentially inhibits implantation[7].According to the "traditional dosage protocol" an initial dose 50 mg daily is given for five days starting in days 2 to day 5 of menstrual cycle then TVUS is done to measure follicular diameter, if it is found less than 18 mm on cycle day 14, the dose increased by 50 mg in the subsequent cycles till reaching maximum dose 150 mg daily [7]. On the other hand, in "stair step protocol" CC is administrated after onset of menses for 5 days then TVUS is done to measure follicular diameter, if it is found less than 18 mm on cycle day 14, the dosage is increased to 100 mg daily for 5 days and re-evaluate by TVUS after one week of increasing dose, an increasing of in the same manner till reaching a maximum dose [8]. Previous studies showed that the ovulation rate was increased in the stair step group in comparison with traditional group[9]. This study aims to compare the efficacy of clomiphene citrate by stair step protocol with traditional protocol in combination with metformin in induction of ovulation of PCOS patients.

Aim of the work: To evaluate the rate of ovulation using Clomiphene Citrate (CC) and Metformin "stair step protocol" versus "traditional protocol" in PCO and determine the uterine side effect & systemic side effects of cumulative doses in one cycle.

Patients and Methods

Study design: Randomized clinical trial (RCT)

Study setting: The study was carried out at obstetrics and Gynecology department outpatient clinic in Suez Canal University Hospital from the start of August 2021 to July 2022.

Study population and sample: A 60 participants diagnosed as PCO based on "Rotterdam 2003 criteria" after approval by local ethics committee and filling an informed written consent to participate in the study after receiving full information about the study.

Inclusion criteria:

1. Patients ages between 20 -35 years.
2. Patients diagnosed as PCOS based on "Rotterdam 2003 criteria".
3. Tubal patency confirmed by either hysterosalpingogram or during diagnostic laparoscope.
4. Normal husband semen analysis according to WHO criteria (2010).

Exclusion criteria:

- Patient ages < 20 years or > 35 years.
- Patients who do not meet criteria for PCOS.
- Other causes of infertility as tubal factor or male abnormalities.
- Presence of endocrinological disease as

hypo, hyperthyroidism, hyperprolactinemia or other pelvic causes of infertility.

- Pregnancy or receiving other ovulation induction medications.

Randomization and Allocation: A probability simple random sampling was done by computer generated program. -

Allocation: two groups with 1:1 ratio.
- **Group (A):** stair step protocol (n=30).
- **Group (B):** traditional protocol (n=30).

Procedure

All selected patients are subjected to:

1. complete history.
2. full general and local examination.
3. laboratory tests: liver, renal function tests, TSH, prolactin, FSH, LH and husband semen analysis
4. TVUS: 7.5 MHz vaginal probe of ultrasound (Models DC 60, MINDRAY, CHINA) to identify ovarian cysts before starting treatment.

Ovulation induction groups:

Group (A): 50 mg of CC was administrated daily on cycle day 2 for consecutive 5 days then TVUS is done on day 9 to measure follicular mean diameter. If less than 18 mm on day 14, the dose i ncreased immediately to 100 mg daily for consecutive 5 days and re-evaluated by TVUS on day 21, if follicular mean diameter less than 18 mm, the dose increased immediately to 150 mg for consecutive 5 days and U/S is performed 1 week after the second U/S, as shown in figure (1).

Group (B): 50 mg of clomiphene citrate was administrated daily on cycle day 2 for consecutive 5 days then transvaginal ultrasound is done on day 9 and day after day to measure follicular mean diameter. If less than 18 mm on cycle day 14, the dose increased to 100 mg in the next cycle in the same manner till reaching 150 mg of CC. When the follicular mean diameter was18 mm or more, HCG was administered.
Metformin: For both protocols, the starting dose was 500 mg once daily then increased weekly by 500 mg till reaching maximum dose of 1500 mg daily.

The measures of primary outcome through:

- Rate of ovulation: TVUS folliculometry assessing number and mean diameter of growing follicles during the given cycle.
- Detection of the ovulation by transvaginal ultrasound through:
- Sudden decrease in follicular size with irregularity of margins.
- appearance of intra follicular echoes.
- Follicle suddenly becomes more echogenic.
- Free fluid in pouch of Douglas.

The measures of secondary outcome through:

Uterine side effect of CC through:

- Uterine artery doppler US pulsatility and resistivity index between 8:00 am-12:00 pm
- Endometrial thickness by TVUS as an indirect marker for endometrial receptivity

Systemic side effect of CC: was evaluated by questionnaire that investigates hot flushes, mood changes, nausea, vomiting, breast tenderness and headache.

Statistical Analysis:

- The collected data was computerized and statistically analyzed using SPSS program (Statistical Package for Social Science) version 26.
- Data was tested for normal distribution using the Shapiro Walk test.
- Qualitative data was represented as frequencies and relative percentages.
- Chi square test ($\chi 2$) and Fisher exact was used to calculate difference between qualitative variables as indicated.
- Quantitative data was expressed as mean and standard deviation.

- Student t test and Mann Whitney test were used to calculate difference between quantitative variables in two groups for parametric and non-parametric variables.
- Level of P-value < 0.05 indicates significant while, P≥ 0.05 indicates non-significant difference.

Results

from the beginnings of August 2021 to the end of July 2022, RCT study conducted on 60 infertile PCO patients after exclusion of 18 patients who dropped out during study, then were randomly allocated into Group (A)" stairstep protocol" & Group(B) " traditional protocol". there were no statistically significant differences between the study group means regarding: the age, BMI, parity, residency & occupation, as shown in table (1).

There was a higher ovulation rate in the group (A) than group B (76.7% V.S 63.3%), although not statistically significant. When comparing ovulation rates by dose, there was higher ovulation rate (43.3%) on dose 100 mg at group (A) compared to higher ovulation rate (33.3%) on 150 mg in group B. regarding clinical pregnancy rate, group (A) was significant higher clinical pregnancy rate compared to group B. When comparing pregnancy rate by dose, there was higher pregnancy rate on dose 100 mg at group (A) while the rate was higher on dose 150 mg in group B. That was statistically significant. Overall, the treatment duration was statistically significantly shorter in group (A) (21±7 days) compared to group B (49±24 days), as shown in table (2).

There was no statistically significant difference for systemic side effects of CC between the two studied groups, as shown in figure (2). While local side effects, the endometrial thickness was less in group (A) than group (B) that was statistically significant. Regarding mean uterine artery PI and RI, the mean for each was significantly higher in group (A), as shown in table (3).

Discussion

In the current study, CC was administrated with metformin using stair step protocol compared with traditional protocol to assess the ovulation rate in both protocol and to compare the systemic and local side effect of both protocols.

A meta-analysis had suggested that about 52% ovulate in response to treatment with clomiphene citrate 50 mg, the dose dependent ovulation rate was higher " 64%" at 100 mg in stairstep protocol compared to "22%" for traditional protocol, with shorter duration of treatment by 32-53 days in comparison to traditional protocol[10]. on these grounds, the use of stairstep protocol in ovulation induction shows higher ovulation rate with shorter duration of treatment and this effect enchanced with combination with metformin in order to improve ovulation and pregnancy rate. This is why the study was selected to compare the efficacy of use of clomiphene citrate combined with metformin by stairstep protocol with traditional protocol regarding ovulation, pregnancy rate and duration of treatment for both protocols.

In the current study results have revealed that There was a higher ovulation rate of (76.7%) in the stair-step protocol group when compared to (63.3%) in the traditional protocol group, however it did not reach statistical significance. When comparing ovulation rates by dose, there was higher ovulation rate 43.3% on dose 100 mg and 23.3% at dose 150 mg observed at stair step protocol compared with 20% ovulation on 100 mg and 33.3% ovulation on 150 mg in traditional protocol. These results were in coincidence with Ali et al., 2018 study that found that the ovulation rate was higher in stair step group (80%) in comparison to traditional group (63.3%) but not statistically significance[9]. In addition Deveci et al., 2014 study found the higher ovulation rate in stair step group 43.3% versus 33.3% in traditional group was not statistically significance [8]. However, Kader et al., 2021 study stated that the ovulation

rate was statistically significant higher in stairstep group (71.43%) compared with traditional group (55.68%) with higher dose dependent ovulation rate at dose 150 mg in stairstep group 34.52% compared to 20.45% in traditional group[11]. High ovulation rate is thought to be the result of a cumulative effect of multiple doses. As Clomiphene citrate formed of two geometric isomers mixed in 3:2 ratio , Enclomiphene and Zuclomiphene, respectively. Enclomiphene is more potent with short half-life about 5–7 days and is primarily responsible for ovulation induction. When patients take their next dose, active isomers are still circulating in the system, making the total circulating concentration higher than in traditional protocols. In current study, there was statistically significant difference between the two groups regarding clinical pregnancy rate that was about 40% in stair step group compared to 26% in traditional group. That was high at dose 100 mg in stair step group (23.33%) but was high at dose 150 mg in traditional group (13.33%) Which is consistent with previous studies. In line with our results, Kader et al., 2021 study showed higher pregnancy rate difference that reach significance statistically between both groups, that was 45.24% in stairstep, while 30.68% for traditional group[11]. These results disagreed with result obtained by Jones et al., 2018 study that revealed there was no difference in pregnancy rates per ovulatory cycle in the stair-step (16.3%) and traditional groups (18.1%) [12].This difference in pregnancy rate between our study and his study could be explained that in Jones retrospective study depended on historical results not comparison of study and control groups ,also administration of metformin play important role in improving ovulation and pregnancy rate as demonstrated in previous studies [13]. although the ovulation rate increased significantly, the pregnancy rates remain low. the low pregnancy rates explained by many reports through antiestrogenic effect of clomiphene and its metabolites on cervical mucus, endometrial, and oocytes. Further, decrease in uterine vascularity in periovulatory period and endometrial thinning may disturb implantation and cause increase in pregnancy loss [13] . The results of our work revealed that there was no statistically significant difference between the two studied groups regarding the distribution of systematic side effects of the used drugs including hot flushes, mood changes, nausea, vomiting, breast tenderness and headache. These results are similar to that of studies conducted by Ali et al., 2018 and Deveci et al., 2014 studies [8, 9].

Since CC causes a central misperception of low estrogen levels, natural vasomotor symptoms may be observed. Nausea and vomiting are the most side effects related to CC (60%). Mood changes and transient hot flushes occur in 56.7 % of women. Headache was reported in 50 % and breast tenderness in 43.3% of cases. Visual disturbances were the least side effects (36.7%). In the current study, the rate of systemic side effects was higher in the stair-step protocol but did not reach statistical significance. The major anti-estrogenic effect of CC interferes with the estrogen proliferation of endometrium. Endometrial receptivity is evaluated indirectly by measuring the endometrial. That was reported that the endometrial thickness should be at least 6 mm for implantation.

In the current study, there was statistically significant difference between both groups regarding endometrial thickness, RI and PI. These results showed disagreement with those of Eran Horowitz and Ariel Weissman 2020 and Deveci et al., 2014 studies which showed no statistically significant difference between the two groups regarding endometrial thickness and uterine artery Doppler ultrasound [7, 10]. On the other hand, there was partial agreement between our results and those of Ali et al., 2018 study which showed the difference between both groups was statistically significant regarding endometrial thickness and RI but not the PI.

that may explain decreased pregnancy rate in comparison to ovulation rate in each group [9].

The strengths and limitations of the current study:

The main strengths of this study include prospective study between study group and control group with strict selection of our samples and evaluation of different clinical outcomes and assessment of the ultrasound images in ovulation induction by clomiphene citrate in both groups. While the main limitation of this study was the small sample size of the study. Therefore, the presented study is accepted as a pilot study. A multicenter study is needed to provide required sample size for power. Also, this protocol requires multiple visits in a shorter period of time and more ultrasound monitoring.

Recommendations for future studies:

Further studies are needed to assess the efficacy of stair step protocol using letrozole and gonadotropins in ovulation induction.

Conclusion

The current study outcomes suggest that stair step regimen combined with metformin improves the ovulation rate and pregnancy rate with shorter course of treatment of infertility in PCOS.

Ethical approval

This study was approved by the research Ethical committee, faculty of medicine, Suez Canal university.

Competing of interest

There is no competing of interest to declare.

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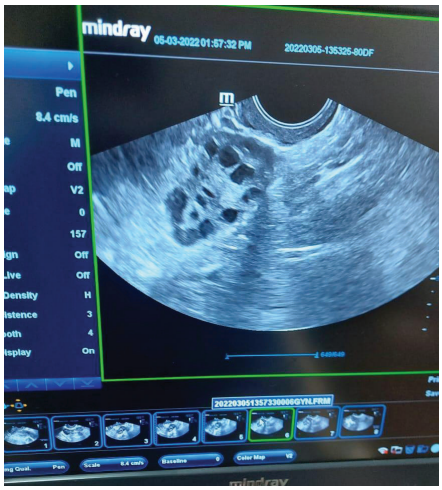
References

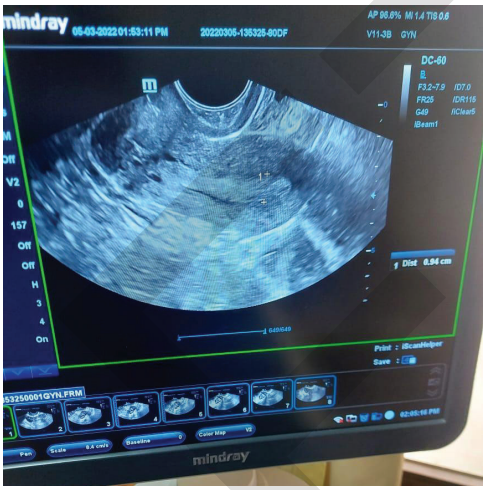
1. Ajmal N, Khan SZ, Shaikh R. Polycystic ovary syndrome (PCOS) and genetic predisposition: A review article. Eur J Obstet Gynecol Reprod Biol X 2019; 3: 100060.
2. Wolf WM, Wattick RA, Kinkade ON, Olfert MD. Geographical prevalence of polycystic ovary syndrome as determined by region and race/ethnicity. Int J Environ Res Public Health. 2018;15(11) : 2589.
3. Fauser BCJM, Tarlatzis, Fauser, et al. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Hum Reprod. 2004;19(1):41-47.
4. Hoeger KM, Dokras A, Piltonen T. Update on PCOS: Consequences, Challenges, and Guiding Treatment. J Clin Endocrinol Metab. 2021;106(3):e1071-e1083.
5. Li M, Ruan X, Mueck AO. Management strategy of infertility in polycystic ovary syndrome. Glob Heal J. 2022;6(2):70-74.
6. Cunha A, Póvoa AM. Infertility management in women with polycystic ovary syndrome: a review. Porto Biomed J. 2021;6(1):e116.
7. Feh MKM, Wadhwa R. Clomiphene. StatPearls 2022.
8. Deveci CD, Demir B, Sengul O, Dilbaz B, Goktolga U. Clomiphene citrate 'stair-step' protocol vs. traditional protocol in patients with polycystic ovary syndrome: a randomized controlled trial. Arch Gynecol Obstet. 2015;291(1):179-184.
9. Abdel Hay Ali A, Fouad Khalaf S, Mohamed Farahat M. Clomiphene Citrate and Metformin" Stair Step" Protocol Vs. Traditional Protocol in Patients with Polycystic Ovary Syndrome "PCOS." Vol 72. Ain Shams University, Faculty of Medicine, Pan Arab League of Continuous Medical Education; 2018 ;72 (5): 4463-4468.
10. Horowitz E, Weissman A. The stair-step approach in treatment of anovulatory PCOS patients. Therapeutic Advances in Reproductive Health. 2020;14:1–6.
11. Kader ASA El, Dawood AS, Morsy AT, Salem HA. Clomiphene Stair-Step Protocol versus Traditional Protocol for Ovulation Induction in Polycystic Ovarian Syndrome Patients. J Adv Med Med Res 2021; 33(18): 1-12.
12. Jones T, Ho JR, Gualtieri M, et al. Clomiphene Stair-Step Protocol for Women With Polycystic Ovary Syndrome. Obstet Gynecol. 2018;131(1):91-95.
13. Johnson NP. Metformin use in women with polycystic ovary syndrome. Ann Transl Med. 2014;2(6):56.

Figure (1): these images demonstrating the ovarian morphology" left image" and endometrial thickness "RT image"

Before starting ovulation induction using stair step protocol

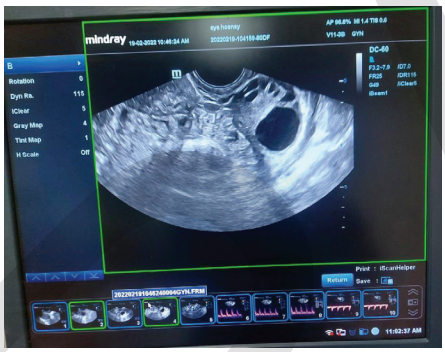


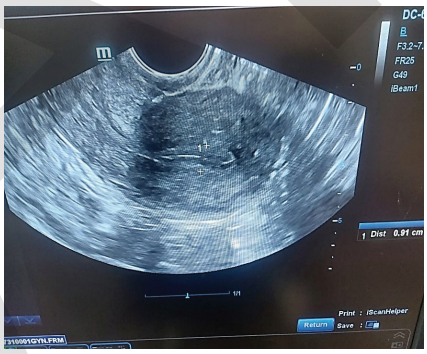
(a) PCOM



(b) Endometrial thickness was 9 mm

After ovulation induction using stair step protocol on dose 100 mg of CC





(c) Dominant follicle measuring 19*21 mm (d) Endometrial thickness was 7 mm

Table (1): Basic characteristtics of the two studied groups.

Variable		Group A n= 30	Group B n= 30	P value
Age (years)	Mean ± SD	26.9± 4.5	27.8± 4.9	0.495
	Median (Range)	26.5 (21, 35)	29 (20, 35)	
BMI	Mean ± SD	25.8± 2.5	27.0± 2.6	0.066
	Median (Range)	25 (22, 31)	27 (20,30)	
Parity	Mean ± SD	1.0± 0.9	1.0± 0.9	0.910
	Median (Range)	1 (0, 3)	1 (0, 3)	
Residency	Rural, n (%)	13 (43.3)	16 (53.3)	0.606
	Urban, n (%)	17 (56.7)	14 (46.7)	
Occupation	Employed, n (%)	11 (36.7)	10 (33.3)	>0.999
	Unemployed, n (%)	19 (63.3)	20 (66.7)	

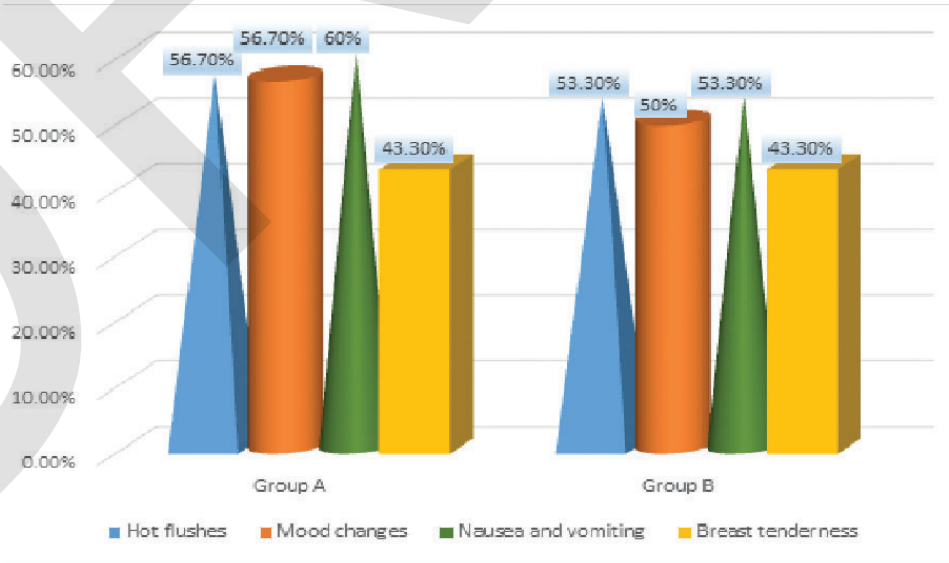
Table (2): Ovulation rate and pregnancy rate among the two studied groups.

Variable		Group A n= 30	Group B n= 30	P value
Ovulation rate	**Yes, n (%)**	**23 (76.7)**	**19 (63.3)**	0.260
	No, n (%)	**7 (23.3)**	**11 (36.6)**	
Dose dependent ovulation rate	50 mg	3 (10)	3 (10)	
	100 mg	13 (43.3)	6 (20)	
	150 mg	7 (23.3)	10 (33.3)	
Clinical Pregnancy rate \ cycle	**Yes, n (%)**	**12 (40.0)**	**8 (26.7)**	**0.017***
	50 mg	2 (6.67)	1 (3.33)	
	100 mg	7 (23.33)	3 (10)	
	150 mg	3 (10)	4 (13.33)	
	No, n (%)	**18 (60.0)**	22 (73.3)	
Duration of treatment (days)	Mean ± SD	21± 7	49± 24	**<0.001***
	Median (Range)	21 (14, 28)	49 (21, 73)	

Table (3): Endometrial thickness and uterine artery doppler US among the two studied groups.

Variable		Group A n= 30	Group B n= 30	P value
Endometrial thickness	Mean ± SD	7.4± 1.1	8.8± 1.8	**0.001***
	Median (Range)	7.7 (6.2, 9.2)	8.5 (6.3, 11.9)	
PI	Mean ± SD	1.1± 0.19	0.9± 0.31	**<0.001***
	Median (Range)	1.2 (0.98, 1.58)	1.41 (0.85, 1.84)	
RI	Mean ± SD	0.66± 0.19	0.57± 0.11	**0.020***
	Median (Range)	0.71 (0.21, 0.9)	0.58 (0.40, 0.78)	

Figure (2): Side effects of used drugs among the two studied groups.



Ultrasound assessment of the anovaginal distance as a predictor of obstetric perineal tears

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Abstract

Background: Vaginal delivery is an important event in women's life. It has a great impact on maternal health and efforts are directed towards safe vaginal delivery. Perineal tears cause great distress to laboring women.

Objective: to determine the role of the anovaginal distance in the prediction of perineal tears in primiparous women.

Study design: This prospective observational study was conducted at the labor and delivery ward at Suez Canal University hospital from June 2021 to December 2022. We recruited primiparous women attending for delivery at the labor ward following predetermined inclusion and exclusion criteria. At 36 weeks of gestation, the recruited women had transvaginal ultrasound for evaluation of the anovaginal distance. Intrapartum evaluation included nature of labor (spontaneous or induced), gestational age, duration of the first stage of labor, duration of the second stage of labor, state of the membranes, the number of vaginal examinations, and fetal biometry.

Results: The mean age of the studied population was 25.52 ± 3.84 years. The mean BMI was 22.95 ± 1.12. The anovaginal distance was 15.33 ± 2.45 mm. Perineal tears occurred in 39/102 (38.2%) patients. There was no significant difference in the anovaginal distance between both groups (p value 0.834). A decrease in the anovaginal distance and smaller gestational age at birth predicted the occurrence of perineal tears significantly (p value 0.037 and 0.006, respectively). ROC curve determined a cut off value of 13.1mm for the AVD, below which perineal tears would occur with a sensitivity of 25.64% and a specificity of 88.89%.

Conclusions: A short anovaginal distance predicted the occurrence of perineal tears significantly.

Keywords: vaginal delivery; perineal tears; anovaginal distance; prediction.

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Introduction

Childbirth is a great event in women's life with a series of processes that result in expulsion of the baby and its

appendices from the female genital tract. This would result in tears or lacerations of the genital tract with variable extensions from the vaginal mucosa to the anal sphincter and rectum. Such tears would result in postpartum hemorrhage (PPH) which constitute about 20% of cases in addition to episiotomies (1). Transperineal ultrasound has been used in the diagnosis of pelvic floor injuries after vaginal delivery and in postpartum follow up to diagnose hidden tears that were associated with increased risk of future pelvic floor disorders (2). Intrapartum ultrasound was associated with possible artifact because of hiatal distension, suturing, and tissue edema (3). The direction should be towards early prediction to accomplish preventative measure as antenatal prediction of perineal tears was not possible (4). A previous study evaluated the perineal length among Caucasian and Asian women using a measuring tape and reported a strong associated between short perinium and 3rd degree perineal tears (5). Accordingly, this study was conducted to evaluate the role of the anovaginal distance measured by endo-vaginal ultrasound among Egyptian women in the prediction of perineal tears.

Methods

This prospective observational study was conducted at the labor and delivery ward at Suez Canal University hospital from June 2021 to December 2022. We recruited women attending for delivery at the labor ward following predetermined inclusion and exclusion criteria. Inclusion criteria: a) women aged 18 - 45 years, b) primiparous women, c) gestational age from 37-41 weeks, d) women undergoing trial of vaginal delivery after previous cesarean section (VBAC), e) singleton pregnancy, and f) cephalic presentation. Exclusion criteria: a) women refusing to participate in the study, b) planned cesarean delivery, c) emergency cesarean delivery due to intrapartum causes, and d) instrumental delivery.

Eligible women were subjected to: a) history taking for age, occupation, and level of education, b) measuring weight and height ant BMI calculation, and c) abdominal ultrasound for determination of fetal biometry -biparietal diameter (BPD), fetal weight, and presentation.

At 36 weeks of gestation, the recruited women had transvaginal ultrasound using transvaginal probe (Mindray DC- 60 machine with a transvaginal probe V 11-3B, 7 MHz) for evaluation of the anovaginal distance (AVD). The participants were asked to lie in the lithotomy position with an empty bladder. The probe was placed at the posterior fourchette and was introduced cranially gently until the internal anal sphincter and anal mucosa could be seen. The distance between the anal edge of the internal sphincter and the probe represented the AVD and was measured in mm (6).

Intrapartum evaluation included nature of labor either spontaneous or induced labor, the gestational age upon admission, the duration of the first stage of labor, duration of the second stage of labor, the state of the membranes, and the number of vaginal examinations.

Perineal tears and the need for episiotomy were recorded. Perineal tears were classified as follows: a) first degree tears where the laceration was limited to the vaginal mucosa or the superficial perineal skin, b) second degree tears where the tears extended to the superficial perineal muscles, and c) third degree tears where the laceration extended to the anal sphincter either less than 50% of the sphincter, more than the 50% of the external sphincter, or reached the internal anal sphincter (7). Lateral vaginal wall tears and paraurethral tears were recorded also.

The sample size was calculated at a significance level of 96.5 % and an error level of 4.5% with an incidence of perineal tears of 79.33 (6). A drop-out proportion of 10% was added to the raw result giving a final count of 102 women.

Ethical approval: This study was conducted after approval of the research ethics committee of faculty of medicine, Suez Canal University, in 24/5/2021 with an approval number of 4505#.

Results

The mean age of the studied population was 25.52 ± 3.84 years. The great majority was from rural areas (71.6%) and highly educated (52%). The mean BMI was 22.95 ± 1.12. The patients were recruited at 38.5 ± 1.09 weeks (Table 1).

Ultrasound measurements included the BPD (96.52 ± 0.57 mm), the EFW (3015.84 ± 229.8 gm), fetal sex (52.9% were female fetuses), and the AVD (15.33 ± 2.45 mm) (Table 2).

A great proportion of the participants labored spontaneously 88/102 (86.3%) and oxytocin augmentation was required in 9/102 (8.8%). The membranes were ruptured in 62/102 (60.8%) patients. Episiotomy was performed in 81/102 (79.4%) participants. The majority of them had no perineal tears 63/102 (61.8%). First and 2nd degree tears occurred in 30/102 (29.4%) and 9/102 (8.8%) patients respectively (Table 3).

Perineal tears occurred in 39/102 (38.2%) patients. There were significant differences between parturient who had perineal tears and those who did not in fetal sex, state of the membranes, performing episiotomy, and the presence of other perineal tears. Women who had perineal tears gave birth to male fetuses (61.5%), had ruptured membranes (46.2%), had episiotomy (64.1%), and had associated tears (15.4%). There was no significant difference in the AVG between both groups (p value 0.834) (Table 4).

Using regression analysis, a decrease in the AVD and smaller gestational age at birth predicted the occurrence of perineal tears significantly (p value 0.037 and 0.006, respectively).

ROC curve determined a cut off value of 13.1mm for the AVD, below which perineal tears would occur with a sensitivity of 25.64% and a specificity of 88.89% (Table 5).

Discussion

The AVD was 15.33 ± 2.45 mm. It was reported that the mean AVD was 11.6 mm among parturient with anal sphincter injury while it was 17.8 mm among those without injuries (6). An earlier study reported different perineal lengths for different races. It was 3.7 ± 0.09 cm in Caucasian women and 3.6 ± 0.09 cm in Asian women (5). This discrepancy would be related to different races of recruited populations and different measuring methods as the mentioned study measured the perineal length using measuring tape and the length was considered from the fourchette to the center of the anal opening (5).

Perineal tears occurred in 39/102 (38.2%) patients. Tears were mainly of 1st and 2nd degree tears with no patient reporting 3rd degree one. This agreed with previous results with different total incidence of perineal tears (7.84%) (8). An earlier study reported an incidence of 92.6% for genital tract lacerations, with only 1 (0.8%) patient having 3rd degree perineal tear (1). Different results would be rendered to different race of the recruited patients, different parity among studies as a previous scar was found to be fragile to resist distension (9).

There was no significant difference in the AVG between both groups. This was confirmed by another study as there was a week insignificant correlation between the perineal length and third-degree tears in primiparous women (5). Additional results failed to report an association between perineal length and perineal tears and this was rendered to their increased rates of episiotomy, occiput posterior position, and instrumental delivery (10, 11).

A decrease in the AVD predicted the occurrence of perineal tears significantly.

Similar results were mentioned before as there was a decrease in the incidence of perineal tears by 32% for each 1 cm increase in the perineal length, however this failed to be statistically significant. Although this study recruited women with different ethnicity (Caucasian and Asian women), they reached a conclusion that ethnicity has no impact on the degree of perineal tears (5). This contradicted others as different ethnic groups contributed to variability in the perineal length measurements leading to different perineal tear incidence (12). Another study reported that a short perineum < 4 cm was more prone to perineal tears (33 times) (1).

Surprisingly, the current study reported that smaller gestational age at delivery predicted the occurrence of perineal tears significantly. This contradicted previous results as a gestational age > 39 weeks was linked to perineal tears. This was rendered to the strong association between gestational age and fetal weight (13). However, this study reported 3rd and 4th degree perineal tears among women with multiple gestation, breech presentation, having diabetes, shoulder dystocia and with instrumental delivery which different greatly from the current one.

ROC curve determined a cut off value of 13.1 mm for the AVD, below which perineal tears would occur with a sensitivity of 25.64% and a specificity of 88.89%. Another one reported an AVD >20mm was sensitive and specific for sphincter injuries by 96% and 25% respectively, however this study evaluated the AVD after being diagnosed to have a perineal tear (6). Other studies reported a perineal body length of <2.5cm to be significantly predictive for perineal tears (11, 14).

Strength and limitations: We recruited primiparous women to avoid possible bias due to changes in the AVD in multiparous women. Single investigator evaluated the AVD by ultrasound to avoid inter-observer variability. Measurements were done at 36 weeks gestation to avoid changes in the perinium associated with different stages of labor. Obstetricians commencing delivery were blinded to the results of the AVD. We did not recruit women with multiple gestation. The studied population was of the same ethnic group.

Conclusion

short AVD predicted the occurrence of perineal tears significantly.

Conflict of interest

None.

References

1. Fouelifack F, Essiben F, Kemadjou L, Fouedjio J, Fouogue J, Mbu R. Risk Factors of Genital Tract Lacerations at Yaoundé Central Hospital-Cameroon: A Case Control Study. British Journal of Medicine and Medical Research. 2017;20(2):1-8.
2. Atan IK, Lin S, Dietz HP, Herbison P, Wilson PD. It is the first birth that does the damage: a cross-sectional study 20 years after delivery. International urogynecology journal. 2018;29(11):1637-43.
3. Blasi I, Fuchs I, D'amico R, Vinci V, La Sala GB, Mazza V, Henrich W. Intrapartum translabial three-dimensional ultrasound visualization of levator trauma. Ultrasound in obstetrics & gynecology. 2011;37(1):88-92.
4. Dietz HP. Ultrasound imaging of maternal birth trauma. International Urogynecology Journal. 2021; 32:1953-62.
5. Dua A, Whitworth M, Dugdale A, Hill S. Perineal length: norms in gravid women in the first stage of labour. International Urogynecology Journal. 2009; 20:1361-4.
6. Pihl S, Uustal E, Blomberg M. Anovaginal distance and obstetric anal sphincter injury: a prospective observational study.

International Urogynecology Journal. 2019; 30:939-44.

7. No GT. The management of third-and fourth-degree perineal tears. MIDIRS. 2015; 2:9.
8. Eko F, Vivian V, Fouelifack YF, Mbu RE. Sitz bath vs iodine antiseptic (Betadine) imbibed gauze for the management of perineal and vaginal tears. Int J Translation Community Dis. 2015;3(2):59-63.
9. Martin S, Labrecque M, Marcoux S, Bérubé S, Pinault J. The association between perineal trauma and spontaneous perineal lacerations. J Fan Pract. 2001; 50(4):333-7.
10. Nager CW, Helliwell JP. Episiotomy increases perineal laceration length in primiparous women. American journal of obstetrics and gynecology. 2001;185(2):444-50.
11. Mboua Batoum V, Ngo Um Meka E, Essiben F, Robinson ME. Perineal body length and prevention of perineal lacerations during delivery in cameroonian primigravid patients. International Journal of Gynecology & Obstetrics. 2021;154(3):481-4.
12. Hopkins LM, Caughey AB, Glidden DV, Laros Jr RK. Racial/ethnic differences in perineal, vaginal and cervical lacerations. American journal of obstetrics and gynecology. 2005;193(2):455-9.
13. Deering SH, Carlson N, Stitely M, Allaire AD, Satin AJ. Perineal body length and lacerations at delivery. The Journal of reproductive medicine. 2004;49(4):306-10.
14. Von Theobald P, Bohrer M, Lorrain S, Iacobelli S. Risk factors associated with severe perineal tears: A five-year study. Journal of Gynecology Obstetrics and Human Reproduction. 2020;49(7):101820.

Table (1): Basic characteristics of the studied females (n = 102).

Age (years) Mean ± SD		25.52 ± 3.84
Residence	**Urban**	29 (28.4%)
	Rural	73 (71.6%)
Level of education	**Illiterate**	9 (8.8%)
	Middle	40 (39.2%)
	High	53 (52%)
Weight (Kg) (Mean ± SD)		68.05 ± 3.92
Height (cm) (Mean ± SD)		164.3 ± 4.21
BMI (Mean ± SD)		22.95 ± 1.12
Gestational age (Mean ± SD)		38.5 ± 1.09

Table (2): Prenatal ultrasound findings of the studied females (n = 102):

Biparietal diameter (mm) (Mean ± SD)		96.52 ± 0.576
Estimated fetal weight (gm) (Mean ± SD)		3015.84 ± 229.8
Fetal sex	**Male**	48 (47.1%)
	Female	54 (52.9%)
Anovaginal distance (mm) (Mean ± SD)		15.33 ± 2.45

Table (3): Assessment of the studied females in labor room (n = 102):

Type of labor	**Spontaneous**	88 (86.3%)
	Induced	14 (13.7%)
Use of oxytocin	**Yes**	9 (8.8.5)
	No	93 (91.2%)
Membrane state	**Ruptured**	62 (60.8%)
	Intact	40 (39.2%)
Duration of the first stage of labor (hours) (Mean ± SD)		1.84 ± 0.84
Duration of the second stage of labor (minutes) (Mean ± SD)		24.38 ± 7.47
Number of pelvic examinations		5.44 ± 2.5
Need for episiotomy	**Yes**	81 (79.4%)
	No	21 (20.6%)
Degree of perineal tears	**No tears**	63 (61.8%)
	Garde I	30 (29.4%)
	Grade II	9 (8.8%)
Other vaginal tears	**No tears**	92 (90.2%)
	Lateral vaginal wall tears	8 (7.8%)
	Paraurethral tears	2 (2%)

Table (2): Prenatal ultrasound findings of the studied females (n = 102):

	Perineal tears		P value
	Yes (N=39)	No (N=63)	
Age (Mean ± SD)	25.85 ± 4.14563	25.32 ± 3.67	0.503
Weight	67.62 ± 4.04	68.32 ± 3.87	0.383
Height (Mean ± SD)	164.76 ± 2.54	164.09 ± 2.42	0.187
BMI Mean ± SD	22.85 ± 1.13	23.03 ± 1.13	0.445
Gestational age at delivery (weeks) Mean ± SD	38.19 ± 0.78	38.74 ± 1.21	0.084

Biparietal diameter Mean ± SD		96.56 ± 0.60	96.49 ± 0.56	0.542
Estimated fetal weight (gm) Mean ± SD		2994.97 ± 185.62	3028.76 ± 253.92	0.473
Sex	Female	15 (38.5%)	39 (61.9%)	0.021
	Male	24 (61.5%)	24 (38.1%)	
Anovaginal distance (mm) Mean ± SD		15.27 ± 2.56	15.37 ± 2.41	0.834
Type of Labor	Induced	6 (15.4%)	8 (12.7%)	0.702
	Spont	33 (84.6%)	55 (87.3%)	
Use of oxytocin	No	34 (87.2%)	59 (93.7%)	0.263
	Yes	5 (12.8%)	4 (6.3%)	
Ruptured membrane	No	21 (53.8%)	19 (30.2%)	0.017
	Yes	18 (46.2%)	44 (69.8%)	
1st Stage Mean ± SD		1.92 ± 0.65	1.84 ± 0.93	0.656
2nd Stage Mean ± SD		25.77 ± 7.91	23.52 ± 7.12	0.141
Number of pelvic examinations		5.41 ± 2.06	5.46 ± 2.87	0.925
Episiotomy	No	14 (35.9%)	7 (11.1%)	0.003
	Yes	25 (64.1%)	56 (88.9%)	
Other vaginal tears	No	33 (84.6%)	59 (93.7%)	0.004
	Lateral vaginal tears	6 (15.4%)	2 (3.2%)	
	Paraurethral tears	0 (0.0%)	2 (3.2%)	

Table (5): ROC curve for the Anovaginal distance (mm)

	Cut of point	AUC	Sensitivity	Specificity	+PV	-PV
Anovaginal distance (mm)	<=13.1 *	0.51	25.64	88.89	58.8	65.9

Platelet Indices Signaling in Early and Late Onset Preeclampsia

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Abstract

Pre-eclampsia (PE) is a heterogeneous disease affecting different body systems and often associated by morbimortality. Early PE prediction could reduce this accompanied morbimortality as it will give the chance for proper surveillance and utilization of prophylactic measures. This study was a cross-sectional study done to evaluate platelet indices (PI) as potential predictors for the onset and severity of preeclampsia, and it was conducted at Department of Obstetrics and Gynecology at Mansoura University Hospital from July 2021 to June 2022, on 87 pregnant women divided into 3 groups: (Group I): Healthy normotensive (NT) pregnant females with a gestation period>20 weeks are included as control group, (Group II &III): early and late onset preeclampsia (before and after 34 weeks respectively). The results showed significant difference among the three studied groups in the context of Platelet crit (PCT). We concluded that PI have been demonstrated as potential markers for PE prediction and could act as diagnostic criteria for PE.

Keyword: Platelet Indices, Platelet Count, Mean Platelet Volume, Platelet Distribution Width, Preeclampsia.

INTRODUCTION

Hypertensive disorders of pregnancy (HDP) have been demonstrated to be accompanied by a high maternal mortality rates (1). PE is one of these disorders featured by hypertension (HTN) with a blood pressure (BP) of ≥140/90mmHg and proteinuria with ≥300mg/24h urine or ≥2+ dipstick following 20th week of gestation in women who had no previous HTN or proteinuria (2). It is classified as early-onset PE (EOPE) and late-onset PE (LOPE) when present prior to or after 34 weeks of gestation, correspondingly (3).

As a result, worse maternal-fetal outcomes could be developed among cases with earlier onset (4) due to presence of neurological adverse events more in EOPE than in LOPE. Many proposed theories about preeclampsia. First, defective trophoblast invasion dysfunction (5).

It has also been suggested that platelets (PLT) have an essential role in the PE pathogenesis when they are in an active state coming in contact with damaged ,activated endothelial wall (6).

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Based on the enzymatic and metabolic backgrounds, larger PLT are very active and have greater possibility for thrombotic complications compared to matched smaller ones. As a result, coagulative and fibrinolytic conditions have been considered as good predictors for the onset and degree of PE. Different indices are utilized to measure PLT functions, among them, platelet count (PC), platelet-crit (PCT), mean PLT volume (MPV), and PLT distribution width (PDW) (7).

They are a group of PLT parameters detected together in automated complete blood count (CBC); they are associated with PLTs' morphology and proliferation kinetics. Of note, PCT is the PLT equivalent of HCT. It is the volume of PLT expressed as a percentage of total blood volume and measured based on the formula PCT = PC × MPV/10,000 (normal value of PCT is ranging from 0.22% to 0.24%). PCT parallels the PC (8).

MPV, PLT volume is a marker of PLT functions and stimulation. It is a calculation of PLT volume expressed in femtoliter (Fl). Once there is a reduction in the production, immature PLT are triggered with pseudopod formation which ultimately ends in an increase in MPV. As a result, increased MPV could be utilized as a marker of production rate and platelet activation (9). Normal range of MPV is ranging from 7.2fL to 11.7fL. High MPV with thrombocytopenia indicates peripheral destruction.

PDW in a direct manner measures variability in PLT size, alterations with PLT stimulation, and reveals the heterogeneity in PLT shape (10). It is an indicator of PLT anisocytosis. The PDW differs significantly, with ranging from 8.3% to 56.6%. Higher PDW is associated with a higher MPV (11). So, the current study aimed to assess PLT indices as potential predictors for the onset and severity of PE.

Patients And Methods

This was a cross sectional study, included 87 pregnant women with a gestational age from 20 to 40 week. attending the antenatal clinic and /or admitted in maternity ward, in obstetrics and gynecology department at Mansoura University Hospital, from July 2021 to June 2022. The study was approved by the Institutional review Board (IRB), Code no MS.21.05.1499, Faculty of Medicine, Mansoura University.

The study included patients with age ranged from 18 to 40 years with hemoglobin ratio > 10gm/dl and with gestational age > 20 weeks. patients in group I had a blood pressure <140/90, without proteinuria and without any medical disorders, while patients in group II and III had a blood pressure >140/90, with proteinuria ≥300 mg/24 h urine or ≥2+ dipstick and without any medical disorders other than HTN. Patients younger than 18 years, platelet disorders as ITP, hemoglobin ratio < 10 g/dl, with Multifetal pregnancy, with diabetes mellitus, with chronic HTN, with infectious diseases, with premature rupture of membrane (PROM), with active labor, with polyhydramnios, with inflammatory diseases, with renal diseases, or with any manifestations of other associated medical adverse events were ruled out.

Methods

After getting a written consent form all participants, we documented their personal, obstetric, past, and surgical history. The patients were examined generally and by ultrasonography to exclude any pathology.

Procedure (sampling collection)

Blood Sample

Under aseptic conditions, blood sample collection (2ml) was done for all participants

via antecubital vein puncture by a qualified nurse in tubes with potassium EDTA as an anticoagulant; then analysis for PLT indices by the Sysmex Xe-2100 automated quantitative hematology analyzer (Sysmex Corp, Japan).

Urine sample

10 ml of midstream urine was collected in sterile tube for detection of proteinuria by urinary dipsticks.

Outcome Measure

Platelet indices (PI) (PC, MPV, PDW and platelet crit (PCT) had been measured; then comparing the results of the 3 groups (control group, early onset PE, late onset PE) together.

RESULTS

There was a significant difference among the three studied groups in the context of gestational age (p<0.001) and there was no significant difference regarding gravidity, parity, history of miscarriage and previous CS (p- value was >0.05) (Table I).

Table (I): Sociodemographic data among the studied groups.

		Normal control group (n.= 31)		Early onset preeclampsia (n.= 29)		Late onset preeclampsia (n.= 27)		Test value	P-value
		No.	%	No.	%	No.	%		
Age (years)	**Mean± SD**	28.52± 6.09		28.86± 6.74		29.37± 6.57		KW= 0.322	0.851
Gravidity	**Mean± SD**	3.06± 1.63		2.82± 1.91		2.70± 1.41		KW= 0.946	0.623
Parity	**Mean± SD**	1.61± 1.23		1.17± 1.26		1.37± 1.18		KW= 2.204	0.332
Gestational age (weeks)	**Mean± SD**	36.42± 3.15		31.90± 2.02		36.41± 1.05		KW= 41.65	**<0.001**
Abortion	**Nil miscarriage**	20	64.5%	22	75.9%	19	70.4%	X^2= 5.07	0.535
	Once	9	29.0%	3	10.3%	5	18.5%		
	Twice	2	6.5%	2	6.9%	2	7.4%		
	> 2	0	0.0%	2	6.9%	1	3.7%		
Previous CS	**Nil c.s**	7	22.6%	15	51.7%	10	37.0%	X^2= 6.80	0.339
	Once	10	32.3%	8	27.6%	6	22.2%		
	Twice	9	29.0%	4	13.8%	7	25.9%		
	> 2	5	16.1%	2	6.9%	4	14.8%		

There was a significant difference among the three studied groups in the context of platelet crit (PCT) (p<0.001) and was no significant difference among the three studied groups as regards Hb and PC, MPV and PDW (p- value was >0.05) (Table II).

Table (II): Comparison among the studied groups as regards CBC.

	Normal control group (n.= 31)		Early onset preeclampsia (n.= 29)		Late onset preeclampsia (n.= 27)		Test value	P-value
	Mean	± SD	Mean	± SD	Mean	± SD		
Hb (g/dl)	11.02	0.82	11.58	1.11	11.13	1.17	KW= 4.53	0.104
PC (×103/mm3)	239.16	59.27	212.17	98.83	214.56	80.44	KW= 4.482	0.106
MPV (µm3)	13.64	15.94	11.20	2.50	10.39	1.69	KW= 2.800	0.247
PDW (%)	12.74	2.44	13.91	2.70	13.22	2.42	KW= 3.144	0.208
PCT	0.23	0.07	0.13	0.07	0.18	0.09	F= 12.37	<0.001

There was a significant difference among the three studied groups as regards proteinuria, SBD, DBP and edema (p<0.001) (Table III).

Table (III): Comparison between the studied groups clinically.

		Normal control group (n.= 31)		**Early onset preeclampsia (n.= 29)**		**Late onset preeclampsia (n.= 27)**		**est value**	**P-valu**
		No.	%	No.	%	No.	%		
Blood pressure									
SBP (mm/ Hg)	**Mean± SD**	105.81± 9.92		152.41± 11.23		153.33± 18.40		W=56.52	**<0.001**
	Range	90.0- 130.0		140.0- 180.0		90.0- 180.0			
	Median	110.0		150.0		150.0			
DBP (mm/ Hg)	**Mean± SD**	67.74± 7.62		97.59± 5.77		98.52± 10.27		W=63.41	**<0.001**
	Range	60.0- 80.0		90.0- 110.0		90.0- 140.0			
	Median	70.0		100.0		100.0			
Protein-uria	**Nil**	31	100.0%	0	0.0%	0	0.0%	^{2}=88.15	**<0.001**
	1+	0	0.0%	2	6.9%	1	3.7%		
	2+	0	0.0%	17	58.6%	14	51.9%		
	3+	0	0.0%	4	13.8%	5	18.5%		
	4+	0	0.0%	6	20.7%	7	25.9%		
Edema	**Nil**	31	100.0%	3	10.3%	8	29.6%	^{2}=54.91	**<0.001**
	1+	0	0.0%	6	20.7%	4	14.8%		
	2+	0	0.0%	15	51.7%	12	44.4%		
	3+	0	0.0%	4	13.8%	3	11.1%		
	4+	0	0.0%	1	3.4%	0	0.0%		

Table (IV): Comparison among the studied groups as regards basic investigation.

	Normal control group (n.= 31)				Early onset preeclampsia (n.= 29)				Late onset preeclampsia (n.= 27)				Test value	P-value
	Mean ± SD	Median	Min.	Max.	Mean ± SD	Median	Min.	Max.	Mean ± SD	Median	Min.	Max.		
S. Creatinine (mg/dl)	.55± .15	0.60	0.20	0.80	0.68 ±0.17	0.70	0.30	1.00	0.67 ±.12	0.70	0.40	1.00	KW= 11.04	**0.004**
AST (U/L)	21.45 ± 4.11	21.00	15.00	31.00	29.9±11.47	25.00	16.00	56.00	26.45 ±12.54	25.00	15.00	82.00	KW= 10.35	**0.006**
ALT(U/L)	20.84± 4.20	20.00	15.00	30.00	26.44 ±12.96	21.80	11.00	65.00	24.60 ±8.82	23.00	15.20	58.00	KW = 3.77	0.152

PC can significantly determine early preeclampsia from healthy group at cut off 213 with the sensitivity (Sn), specificity (Sp), PPV and NPV was 69%, 67.7%, 68% and 68.5% respectively (p=0.016). PCT can significantly determine early preeclampsia from healthy group at cut off 0.19 with the sensitivity, Sp, PPV and NPV was 86.2%, 71%, 75% and 83.7% respectively (p< 0.001). PDW can insignificantly determine early preeclampsia from healthy group at cut off 13.1 with the sensitivity, Sp, PPV and NPV was 62.1%, 64.5%, 63.8% and 63% respectively (p=0.077). MPV can insignificantly determine early preeclampsia from healthy group at cut off 9 with the Sn, Sp, PPV and NPV was 79.3%, 35.5%, 55% and 63% respectively (p=0.090) (Table V).

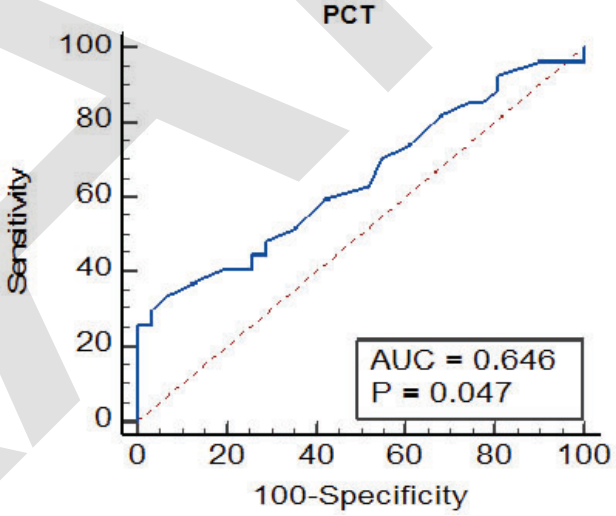

Table (V): Validity of Platelet Indices in determination of early preeclampsia from healthy group.

parameters	Cutoff value	AUC	Sensitivity	Specificity	PPV	NPV	P value
PC	≤ 213	0.674	69%	67.7%	68%	68.5%	**0.016**
PCT	≤ 0.19	0.830	86.2%	71%	75%	83.7%	**<0.001**
PDW	>13.1	0.628	62.1%	64.5%	63.8%	63%	0.077
MPV	>9.6	0.530	79.3%	35.5%	55%	63%	0.690

PC can insignificantly determine late preeclampsia from healthy group at cut off 150 with the Sn, Sp, PPV and NPV was 29.6%, 100%, 100% and 58.7% respectively (p=0.321). PCT can significantly determine late preeclampsia from healthy group at cut off 0.14 with the Sn, Sp, PPV and NPV was 33.3%, 93.5%, 83.7% and 58.5% respectively (p=0.047). PDW can insignificantly determine early preeclampsia from healthy group at cut off 11 with the Sn, Sp, PPV and NPV was 88.9%, 29%, 55.6% and 72.3% respectively (p=0.567). MPV can insignificantly determine early preeclampsia from healthy group at cut off 10 with the Sn, Sp, PPV and NPV was 66.7%, 58.1%, 61.4% and 63.6% respectively (p=0.090) (Table VI).

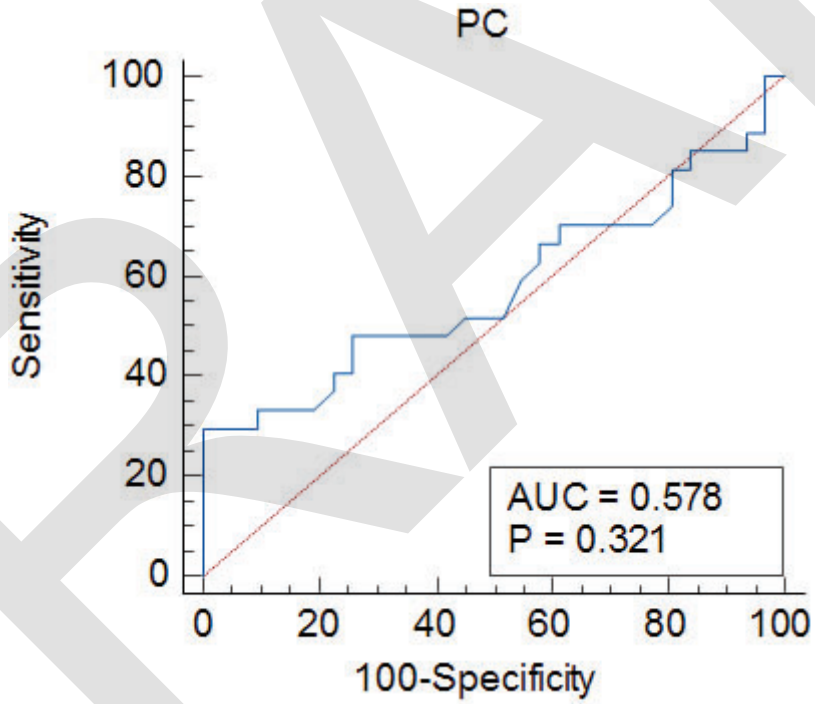

Table (VI) Validity of Platelet Indices in determination of late preeclampsia from healthy group.

parameters	Cutoff value	AUC	Sensitivity (Sn)	Specificity (Sp)	PPV	NPV	P value
PC	≤ 150	0.578	29.6%	100%	100%	58.7%	0.321
PCT	≤ 0.14	0.646	33.3%	93.5%	83.7%	58.5%	**0.047**
PDW	>11	0.544	88.9%	29%	55.6%	72.3%	0.567
MPV	≤ 10	0.590	66.7%	58.1%	61.4%	63.6%	0.233

Preeclampsia (PE) is a HDP featured by either proteinuria or end-organ dysfunction following 20th gestational week. It is due to abnormal placental vascular response, accompanied by an increase in the vascular resistance, improved PLT aggregations and stimulation of the coagulation system (12).

Platelet count (PC), PCT, MPV, and PDW are among the PI acquired from an automated CBC test. Alterations in PLT parameters have been considered as common hematologic changes in PE. In addition, such parameters are recognized as promising candidates in the context of PE pathogenesis and diagnosis (13).

In the current study, we found that there was a significant difference among the three studied groups as regards PCT ($p<0.001$) as early preeclampsia group reported significant lower platelet crit compared to healthy controls ($p<0.001$) and late preeclampsia group ($p=0.036$). There was no significant difference among the three studied groups with regard to Hb, PC, MVP and PDW (p- value was >0.05). Also, Karateke et al., reported that preeclampsia group had a significant lower platelet crit levels compared to control group ($p<0.001$)(14). Freitas et al., displayed that PCT levels were lower in severely preeclamptic cases compared to non-pregnant controls. Their study included only women with severe preeclampsia. However, we evaluated early and late onset preeclampsia (6).

On the other hand, in a study by Walle et al., PCT didn't demonstrate a significant difference among their studied groups. By using ROC-curve analysis in our study, PC can significantly determine early preeclampsia from healthy group at cut off 213 with the Sn, Sp, PPV and NPV was 69%, 67.7%, 68% and 68.5% respectively ($p=0.016$). Our results were in accordance with Walle et al., (15) as the ROC curve in the study displayed that PC had the 2nd-largest AUC (0.79), allowing it to differentiate PE cases from normotensive (NT) pregnant females at a cutoff value 176.5 × 109 /L with a Sn of 65.1%, Sp of 87.3%, and test accuracy of 76.19%.

Bawore et al., also demonstrated that there were significant differences among the NT and non-severe PE group, and severe PE groups in terms of PC and PCT that displayed significantly decreasing value with the disease severity (16).

Also, our study showed that PCT can significantly determine early preeclampsia from healthy group at cut off 0.19 with the Sn, Sp, PPV and NPV were 86.2%, 71%, 75% and 83.7% correspondingly ($p<0.001$). However, While PDW and MPV can insignificantly determine early preeclampsia from healthy group. Moreover, PCT was the only parameter that can significantly determine late preeclampsia from healthy group at cut off 0.14 with the Sn, Sp, PPV and NPV was 33.3%, 93.5%, 83.7% and 58.5% respectively ($p=0.047$). This recommends that PCT could be used as a marker for PE prediction.

Such value came in the same line with the findings of researches conducted at several studies (11, 17, 18). However, the authors of these studies didn't compare between Platelets indices as regard to early and late preeclampsia

In contrast, the ROC analysis in recent study displayed that PDW had the smallest AUC (0.68). In spite of having the shortest AUC, PDW could differentiate PE cases from NT pre. gnant females with 42.9% Sn, 93.7% Sp, and 68.2% test accuracy at a cutoff value of ≥16.75 fl (15).

According to Bawore et al., outcomes, PCT could differentiate NT pregnant females from preeclamptic pregnant ones, at a cutoff value of 0.1915% with a Sn of 68.3% and Sp of 69.2% has an AUC of 0.776 ($p=0.001$). Hence, it is considered as a good predictor of PE (16).

CONCLUSION

The current study demonstrated that; PI are potential candidate markers for PE prediction. PCT could act as diagnostic criteria for PE. Our results showed that PCT is the best parameter for predicting both Early and Late PE. In addition, PI could be used more extensively as they are a simple, effortless and cost-effective tool.

REFERENCES

1. Vijaya C, Lekha M, Shetty A, Geethamani V. Evaluation of platelet counts and platelet indices and their significant role in pre-eclampsia and eclampsia. Journal of Evolution of Medical and Dental Sciences. 2014;3(12):3216-3219.
2. Nooh AM, Abdeldayem HM. Changes in platelet indices during pregnancy as potential markers for prediction of preeclampsia development. Open Journal of Obstetrics and Gynecology. 2015;5(12):703.
3. Reis ZSN, Lage EM, Teixeira PG, Porto LB, Guedes LR, Oliveira ÉCLd, et al. Early-onset preeclampsia: is it a better classification for maternal and perinatal outcomes? Revista Brasileira de Ginecologia e Obstetrícia. 2010;32(12):584-90.
4. Schreurs MP, Hubel CA, Bernstein IM, Jeyabalan A, Cipolla MJ. Increased oxidized low-density lipoprotein causes blood-brain barrier disruption in early-onset preeclampsia through LOX-1. The FASEB Journal. 2013;27(3):1254-63.
5. Burton G, Woods A, Jauniaux E, Kingdom J. Rheological and physiological consequences of conversion of the maternal spiral arteries for uteroplacental blood flow during human pregnancy. Placenta. 2009;30(6):473-82.
6. Freitas LG, Alpoim PN, Komatsuzaki F, Carvalho MdG, Dusse LMS. Preeclampsia: are platelet count and indices useful for its prognostic? Hematology. 2013;18(6):360-4.
7. AlSheeha M, Alaboudi R, Alghasham M, Iqbal J, Adam I. Platelet count and platelet indices in women with preeclampsia. Vascular health and risk management. 2016;12(10):477-80.
8. Yuri Gasparyan A, Ayvazyan L, P Mikhailidis D, D Kitas G. Mean platelet volume: a link between thrombosis and inflammation? Current pharmaceutical design. 2011;17(1):47-58.
9. A. Jagroop IC, J. Lewin, DP Mikhailidis, I. Shape change in human platelets: measurement with a channelyzer and visualisation by electron microscopy. Platelets. 2000;11(1):28-32.
10. Izzi B, Gialluisi A, Gianfagna F, Orlandi S, De Curtis A, Magnacca S,Costanzo S, Di Castelnuovo A, Donati M, De Gaetano G, Hoylaerts M, Cerletti C, Iacoviello L. Platelet distribution width is associated with P-selectin dependent platelet function: results from the moli-family cohort study. Cells. 2021;10(10):2737.
11. Doğan K, Guraslan H, Senturk MB, Helvacioglu C, İdil S, Ekin M. Can platelet count and platelet indices predict the risk and the prognosis of preeclampsia? Hypertension in pregnancy. 2015;34(4):434-42.
12. Nirupama R, Divyashree S, Janhavi P, Muthukumar SP, Ravindra PV. Preeclampsia: Pathophysiology and management. Journal of Gynecology Obstetrics and Human Reproduction. 2021;50(2): 101975.
13. Budak YU, Polat M, Huysal K. The use of platelet indices, plateletcrit, mean platelet volume and platelet distribution width in emergency non-traumatic abdominal surgery: a systematic review. Biochemia medica. 2016;26(2):178-93.
14. Karateke A, Kurt RK, Baloğlu A. Relation

of platelet distribution width (PDW) and platelet crit (PCT) to preeclampsia. Ginekologia polska. 2015;86(5):372-5.

15. Walle M, Asrie F, Gelaw Y, Getaneh Z. The role of platelet parameters for the diagnosis of preeclampsia among pregnant women attending at the University of Gondar Comprehensive Specialized Hospital antenatal care unit, Gondar, Ethiopia. Journal of Clinical Laboratory Analysis. 2022;36(4):e24305.
16. Bawore SG, Adissu W, Niguse B, Larebo YM, Ermolo NA, Gedefaw L. A pattern of platelet indices as a potential marker for prediction of pre-eclampsia among pregnant women attending a Tertiary Hospital, Ethiopia. Journal pone. 2021;16(11):e0259543.
17. Chen Y, Lin L. Potential value of coagulation parameters for suggesting pre eclampsia during the third trimester of pregnancy. The American journal of the medical sciences. 2017;354(1):39-43.
18. Alkholy E, Farag E, Behery M, Ibrahim M. The significance of platelet count, mean platelet volume and platelet width distribution in preeclampsia. Al-Azhar Assiut Medical Journal. 2013;11(1):200.

Comparative study between the use of long-acting insulin versus multiple dose regimen in control of Gestational Diabetes Mellitus: a randomized controlled trial

Maii Nawara, Mohammad Abd El Hameed, Sara Ahmad, Tamer Borg, Noha Abdel Satar Sakna

Abstract

Objective : The aim of our work is the comparison between long-acting insulin and multiple dose regimens in control of gestational diabetes.

Patients and Methods : This prospective randomized controlled trial included 128 Pregnant women with gestational DM who required insulin treatment after failure of diet control in Ain Shams maternity hospital from September 2019 to December 2020. Patients were randomized into two groups; Group A: received long-acting insulin analogs as a single dose once daily at bedtime, while Group B received intermediate-acting insulin (NPH) besides short-acting insulin (lispro) in divided doses.

Results: Group B showed a shorter statistically significant time to control blood sugar than Group A (10+1 vs 14+2 days, respectively). ▪ There was no statistically significant difference between groups regarding Maternal hypoglycemia ($P<0.05$). Group A had a non-significant higher rate of obstetric complications as PIH, Preterm delivery, Shoulder dystocia, and CS delivery rate and lower Polyhydramnios rate than group B. Group (A) had a non-significant higher rate of fetal/Neonatal complications such as fetal macrosomia, congenital anomalies, IUFD, NICU admission, and Neonatal death than group (B) by Per protocol (PP) analysis ($P<0.05$).

Conclusion: We can conclude that there is no clinical difference between using a multiple-dose regimen and using long-acting insulin analogs to control gestational diabetes regarding maternal and fetal outcomes. However, a multiple-dose regimen needs a shorter time for blood glucose control than long-acting insulin. It is to be noted that long-acting insulin is more expensive.

Key Words: long-acting insulin, multiple-dose regimen, Gestational Diabetes Mellitus.

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INTRODUCTION

Gestational Diabetes Mellitus (GDM) is defined as any degree of glucose intolerance to be first diagnosed during pregnancy. (1) Risk factors for GDM are previous GDM, increase maternal BMI, family history of DM, advanced maternal age, previous history of macrosomia, recurrent abortions, and congenital fetal malformations. (2)

GDM can lead to severe complications in pregnancy, including gestational hypertension, preeclampsia, and eclampsia. It can also cause preterm labor, macrosomia, shoulder dystocia, and an increased rate of Caesarean deliveries. (3) Adopting the criteria of the International Association of Diabetes and Pregnancy Study Groups (IADPSG) has increased the prevalence of GDM by 2-3 folds. (4-5) The IADPSG recommends universal screening for GDM and requires one single glucose value above the cut-off value during the oral glucose tolerance test (OGTT) for diagnosis (4).

There have been several changes in the management of diabetes during pregnancy, including the use of insulin analogs. Antibody-free human insulin is to be considered by most practitioners to be the gold standard for use in pregnancy because it does not cross the placenta and is highly effective (6).

Insulin analogs offer some advantages that may reduce "resistance" to using insulin during pregnancy. Currently, available insulin analogs include rapid-acting mealtime insulins: lispro and aspart, intermediate-acting insulin: Neutral Protamine Hagedorn (NPH), and long-acting basal insulin: glargine(longer-lasting insulin analog; the basal level of insulin will be maintained up to 24 hours) all are considered safe in pregnancy as are included in Food and Drug Administration(FDA) (7).

Commonly prescribed regimens consisting of combined short-acting (Regular) and intermediate-acting insulins have been used to mimic endogenous insulin response. However, these regimens are sometimes incapable of adequately simulating the basal or meal-stimulated components of normal insulin secretion. (8).

AIM:

The aim of our work is the comparison between long-acting insulin and multiple dose regimens in control of gestational diabetes.

Patients and Methods:

This study is a Prospective randomized controlled trial Study conducted in Ain Shams University - Maternity Hospital from September 2019 to December 2020. The study had been approved by the ethical and research committee of the Obstetrics and Gynecology Department, Ain Shams University, and the Faculty of Medicine Research Ethics Committee with number M S 323/ 2019. The study was registered in the clinicaltrial.gov (NCT04674332)

We included pregnant women with gestational diabetes from the Ain Shams Maternity Hospital antenatal clinic who required insulin therapy after diet and medical therapy failed.

Women with pregestational DM or patients with complicated diabetes such as neuropathy, nephropathy, or retinopathy were excluded from the study. Other exclusion criteria included patients with endocrine abnormalities or medical diseases (hypertension, cardiac problems, hepatic diseases, renal disorders, and systemic lupus). Patients with bad obstetric history (intrauterine growth retardation, previous intrauterine fetal death, threatened preterm labor) were also excluded from the study.

◊ **Method of randomization:** A computer-developed randomization sheet contains 148 patients randomly assigned into two groups (group A & group B), each group of 74 patients. The randomization had been concealed using the sequentially

numbered opaque sealed envelope (SNOSE). 148 opaque easy-opening envelopes had been numbered serially; in each envelope, the corresponding letter in the randomization sheet had been put. Participant women had been allocated to each group according to the letter inside the envelope.

- ***Group A:*** patients receiving long-acting insulin analogs as a single dose (insulin glargine), one daily injection of long-acting insulin at an initial dose of (0.44 IU/kg) once daily at bedtime (11, 12).
- ***Group B:*** patients receiving intermediate-acting insulin (NPH) and short-acting insulin (lispro) in divided doses. (13).

The study purpose and methods had been explained to all enrolled women, and written informed consent had been obtained from all participants before enrolment.

Our hospital protocol for initial insulin requirements is based on a woman's body weight and gestational age; the total daily insulin requirement in the second trimester is 0.8 units/kg/day (9-10, 14).

Our patients were admitted to the hospital for insulin treatment until they reached normal glycemic values and were discharged. Follow-up after discharge was done by regular visits twice monthly in high-risk clinics and weekly from the 36th gestational week for patients who had the facility for that or by regular phone calls or internet messaging for patients who didn't have the facility to attend the regular visits.

> **Primary outcome:** The time needed to reach target levels of plasma glucose; fasting ≤ (90-95 mg/dl) and two h post-prandial ≤ (120 mg/dl). The duration was determined after being controlled for three consecutive days. (9):

◊ **Secondary outcomes:** Maternal hypoglycemia, PIH, polyhydramnios, Shoulder dystocia PTL, CS, GA, Birth Weight, macrosomia, Congenital anomalies, IUFD, neonatal death, NICU admission

◊ **Sample size justification**

The required sample size has been calculated using the G*power software (Universitat Dusseldorf, Germany). Currently, there is no adequate information regarding the difference between both methods for glycemic control on the outcome measures; therefore, the present exploratory study would target clinically relevant effect size. So, it is estimated that a sample size of 148 patients, after calculating a 15% anticipated drop-out ratio, equally randomized into either study group (74 per group) would achieve a power of 80% (type II error, 0.2) to detect a statistically significant difference between the two groups as regards the quantitative outcome measures (e.g.; FBS, PPBS, HbA1C or birth weight) for a medium effect size corresponding to a Cohen d coefficient of 0.5 using a two-sided unpaired t-test and the targeted test confidence set at a level of 95% (type I error, 0.05). The effect size ***(d)*** is calculated as follows): d = (m1 – m2) sd, where m1 and m2 are the means of group I and group II, respectively, and sd is the common standard deviation (17).

◊ **Statistical Methods**

Data were analyzed using IBM© SPSS© Statistics version 26 (IBM© Corp., Armonk, NY). Categorical variables are presented as numbers and percentages, and intergroup differences are compared using Fisher's exact test. Ordinal data are compared using linear by-linear association. Numerical data are presented as mean, standard deviation, and between-group differences are compared using the independent-samples t-test. The time-to-event analysis uses the Kaplan-Meier (KM) method by comparing KM curves with the log-rank test. Two-sided P- values <0.05 are considered statistically significant.

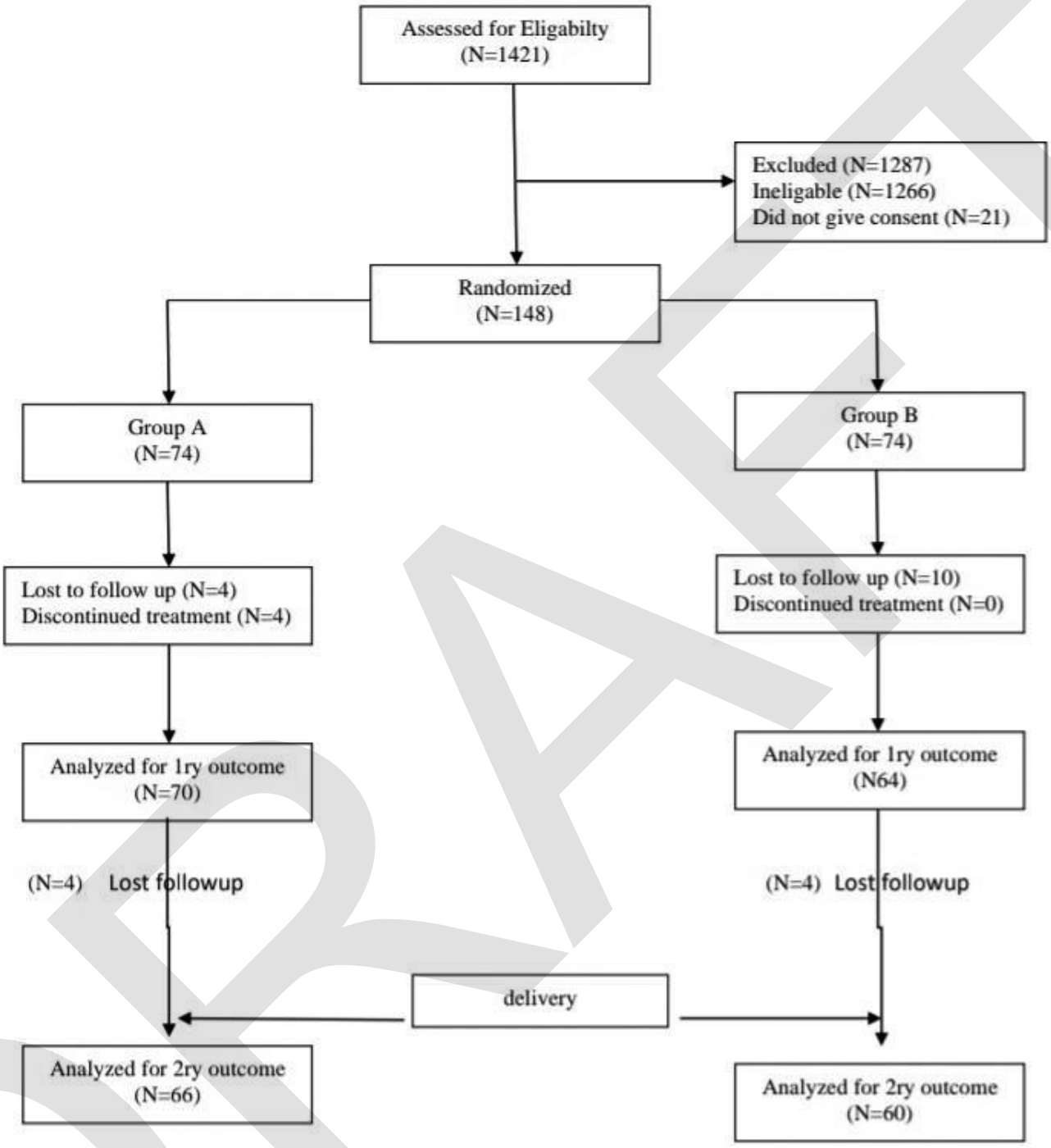

Figure 1. CONSORT flow chart showing patient recruitment and follow up.

Results

As regards demographic characteristics of patients in both study groups, mean age was (26.3±5.2 SD), BMI (29.1±2.1 SD), and GA at recruitment (25.3±1.5 SD). No statistically significant difference exists between the two groups regarding age (P=0.172), BMI (P=0.172), or GA at recruitment (P=0.321). There is no statistically significant difference between the two groups regarding parity and Previous abortions, **with P values of** 0.603 0.941, **respectively** (Data not tabulated).

The Means of Pre-treatment FBS, 2h-PPBS, and HbA1c are near in both groups with no statistically significant difference. (Table 2)

As shown in Table 3, the means of Pre-treatment FBS, 2h-PPBS, and HbA1c in both groups show no statistically significant differences. In contrast, group B shows a lower statistically significant time to control blood sugar than group A (10+1 vs 15+2 days, respectively). Fig 1. Show **Kaplan-Meier curves that show a statistically significant difference between both KM curves (log-rank test chi-squared = 104.251, df = 1, P-value < 0.001).**

Regarding secondary outcomes, there is no statistically significant difference between the studied groups regarding the **Incidence and frequency of maternal hypoglycemia in both study groups, with P values of 0.518 and 0.206, respectively** (Data not tabulated). Table 4 and Figure 2 show the obstetric outcomes by Per protocol (PP) analysis. Group A has a non-significant higher rate of obstetric complications such as PIH, Preterm delivery, Shoulder dystocia, and CS delivery rate and a lower Polyhydramnios rate than group B.

Group (A) has a higher non-significant mean of Birth weight than group (B) 3517+351 gm vs. 3427+305 gm with a P value of 0.128, and both groups have the same mean of GA at delivery 37.2+1.1 vs. 37.2+1.0 with a P value 0.782 (Data not tabulated). Table 6 shows that group (A) has higher nonsignificant Fetal/Neonatal outcomes, Fetal macrosomia, Congenital anomalies, IUFD, NICU admission, and Neonatal death than group (B) by Per protocol (PP) analysis.

Table 1. Measures of glycemic control before treatment in both study groups

	Group A		Group B						
Variable	Mean	SD	Mean	SD	Mean	SE	Lower 95% CI	Upper 95% CI	P-value†
Pre-treatment FBS (mg/dl)	156.5	7.8	158.8	12.0	-2.3	1.8	-5.8	1.2	0.192
Pre-treatment 2h-PPBS (mg/dl)	175.0	13.7	178.6	14.9	-3.5	2.5	-8.4	1.3	0.154
Pre-treatment HbA1c (%)	6.1	0.5	6.2	0.5	-0.1	0.1	-0.3	0.0	0.13

SD = standard deviation, SE = standard error, 95% CI = 95% confidence interval.
†. Independent-samples t-test.

Table 2. Measures of glycemic control after treatment in both study groups

	Group A		Group B						
Variable	Mean	SD	Mean	SD	Mean	SE	Lower 95% CI	Upper 95% CI	P-value†
Post-treatment FBS (mg/dl)	84.1	10.3	81.1	8.5	3.1	1.6	-0.2	6.3	0.064
Post-treatment 2h-PPBS (mg/dl)	110.3	12.4	114.3	11.1	-4.0	2.0	-8.0	0.1	0.053
Post-treatment HbA1c (%)	5.3	0.4	5.4	0.5	-0.1	0.1	-0.2	0.1	0.319
Time to control blood sugar (days)	15	2	10	1	4.7	0.3	4.1	5.4	<0.001

SD = standard deviation, SE = standard error, 95% CI = 95% confidence interval.
†. Independent-samples t-test.

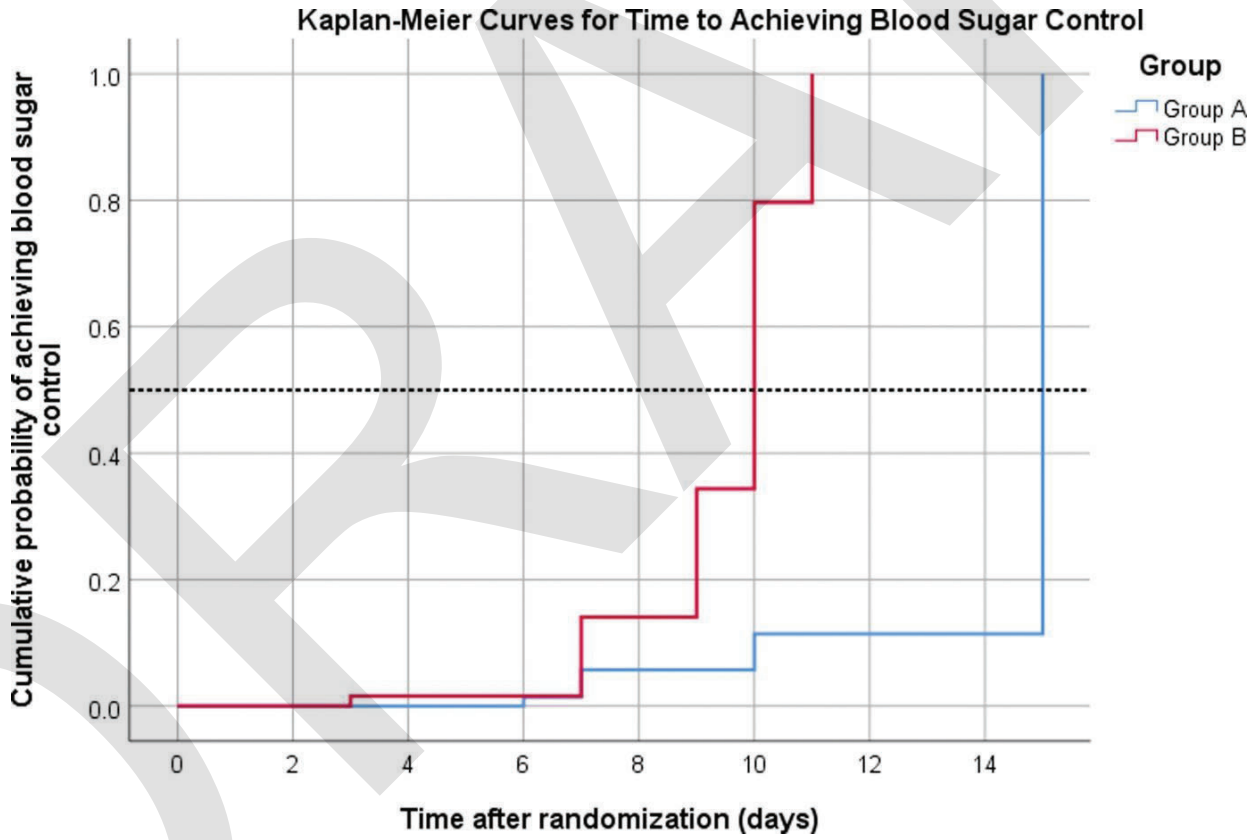

Figure 1. shows Kaplan-Meier curves for time to achieve blood sugar control. Median time to achieve control of blood sugar = 15 days in Group A versus ten days in Group B. Difference between both KM curves is statistically significant (log-rank test chi-squared = 104.251, df = 1, P-value < 0.001).

Table 3. Obstetric outcomes in both study groups: Per protocol (PP) analysis

	Group A		Group B		
Variable	n	%	n	%	P-value†
PIH	3	4.5%	2	3.3%	1.000
Polyhydramnios	5	7.6%	7	11.7%	0.548
Preterm delivery	15	22.7%	10	16.7%	0.503
Shoulder dystocia	5	7.6%	2	3.3%	0.503
CS delivery	32	48.5%	27	45%	0.724

n = number. †. Fisher's exact test

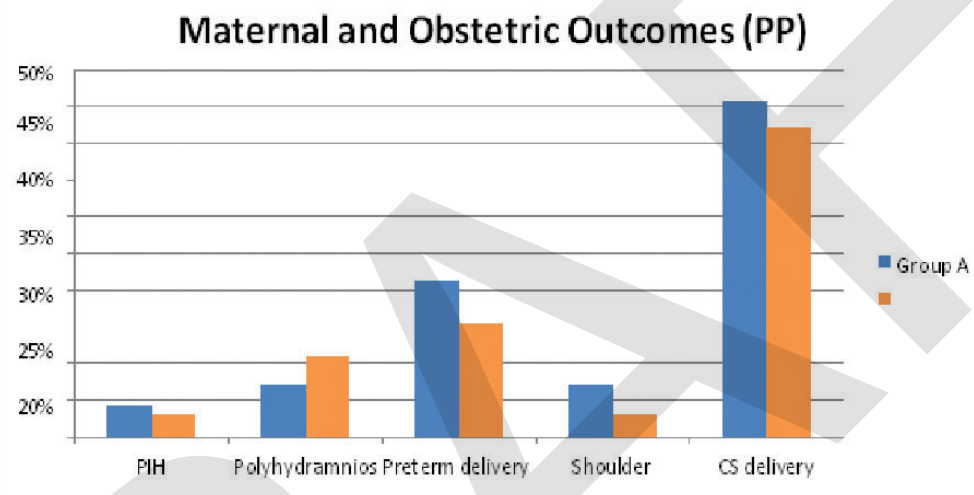

Figure 2 Maternal and obstetric outcomes in both study groups by per protocol (PP) analysis.

Table 4. Risk analysis for main maternal/obstetric outcomes (PP)

	Group A		Group B			
Maternal hypoglycemia	0.61		0.807	0.420	25.4	8.2 (Harm) to 7.5 (Benefit)
PIH	1.36	0.18 to 2.04	0.346	0.729	82.5	12.4 (Harm) to 17.8 (Benefit)
Polyhydramnios	0.65	0.24 to 1.94	0.774	0.439	24.4	6.3 (Harm) to 7.0 (Benefit)
Preterm delivery	1.36	0.66 to 2.80	0.845	0.398	16.5	5.0 (Harm) to 12.8 (Benefit
Shoulder dystocia	2.27	0.46 to 11.28	1.004	0.315	23.6	8.2 (Harm) to 26.8 (Benefit)
CS delivery	1.08	0.741 to 1.5666	0.391	0.696	28.7	4.8 (Harm) to 7.2 (Benefit)

95% CI = 95% confidence interval

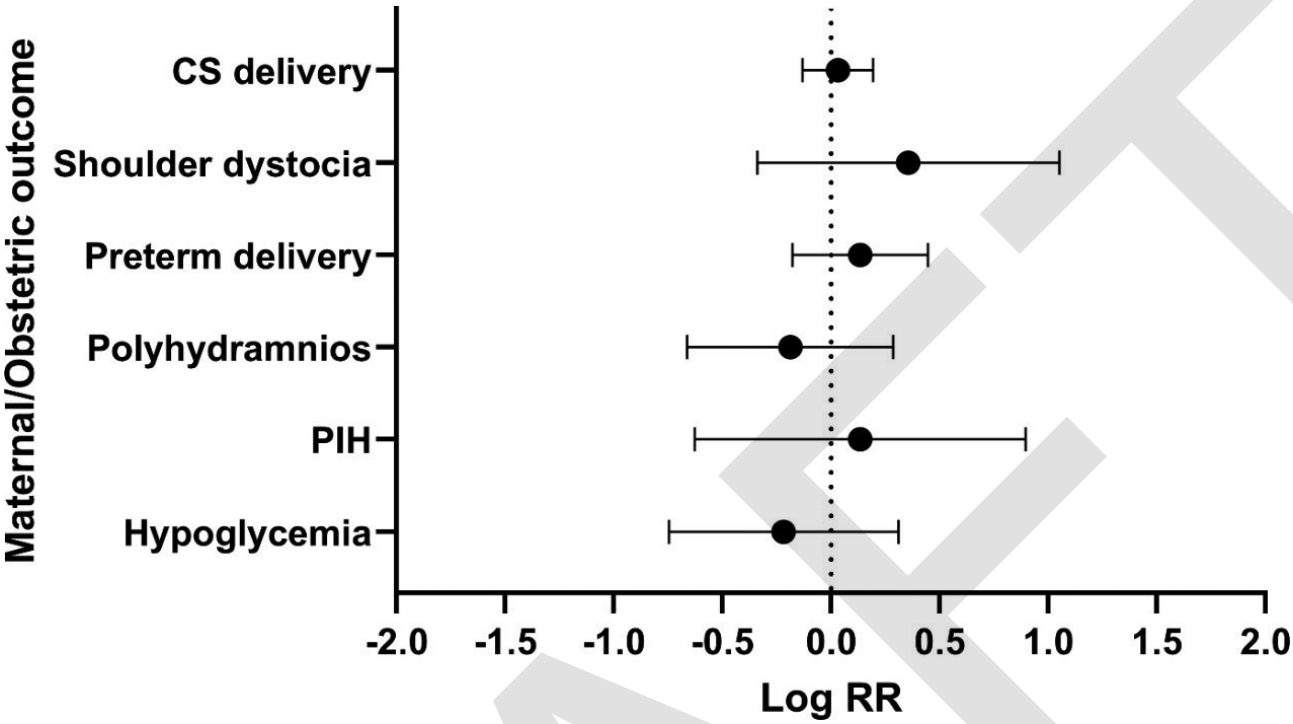

Figure 3. Relative risk (RR, rounded marker) with 95% confidence limits (95% CI, error bars) for maternal and obstetric outcomes in both study groups by per protocol (PP) analysis. There is no statistically significant difference between long-acting or intermediate-acting insulin regarding maternal or obstetric outcomes.

Table 5. Fetal/Neonatal outcomes in both study groups: Per protocol (PP) analysis

	Group A		Group B		
Variable	n	%	n	%	P- value†
Fetal macrosomia	8	12.1%	2	3.3%	0.099
Congenital anomalies	2	3.0%	1	1.7%	1.000
IUFD	2	3.0%	2	3.3%	1.000
NICU admission	7	10.6%	5	8.3%	0.766
Neonatal death	3	4.5%	2	3.3%	1.000

n = number. †. Fisher's exact test.

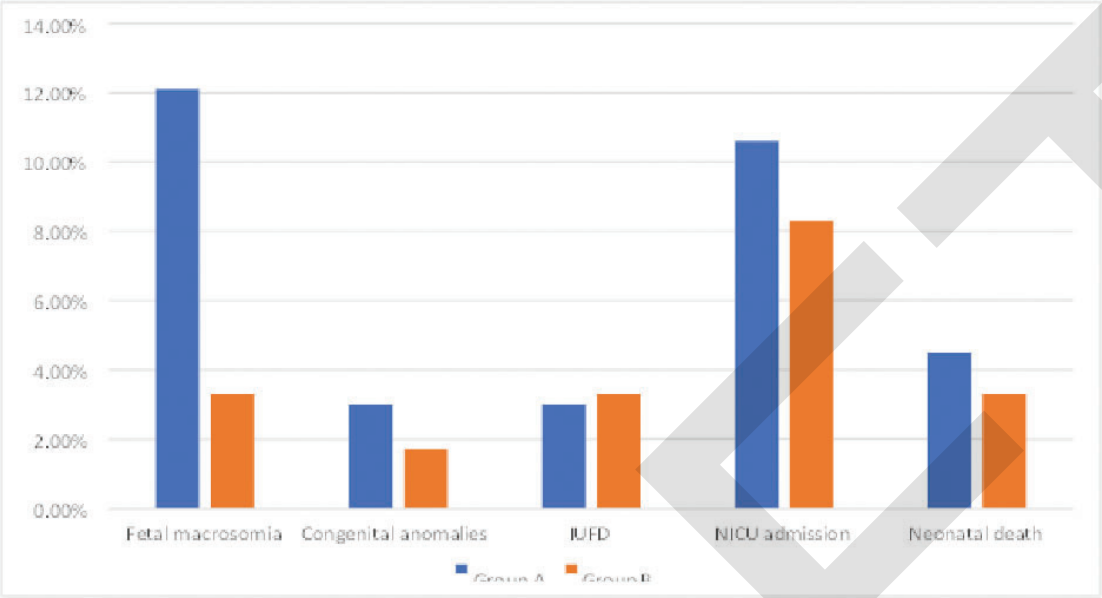

Figure 4. Fetal/Neonatal outcomes in both study groups: Per protocol (PP) analysis.

Table 6. Risk analysis for main fetal/neonatal outcomes: Per protocol (PP) analysis

	Group A					
Feta macrosomia	3.64	0.80 to 16.45	1.676	0.094	11.4	5.5 (Harm) to 186.2 (Benefit)
Congenital anomalies	3.64	0.80 to 16.45	1.676	0.094	11.4	5.5 (Harm) to 186.2 (Benefit)
IUFD	3.64	0.80 to 16.45	1.676	0.094	11.4	5.5 (Harm) to 186.2 (Benefit)
Low Apgar 5	3.64	0.80 to 16.45	1.676	0.094	11.4	5.5 (Harm) to 186.2 (Benefit)
Low Apgar 10	1.27	0.80 to 16.45	0.432	0.665	44.0	8.0 (Harm) to 12.5 (Benefit)
NICU admission	1.36	0.43 to 3.80	0.346	0.729	82.5	12.4 (Harm) to 17.8 (Benefit)
Neonatal death	3.64	0.80 to 16.45	1.676	0.094	11.4	5.5 (Harm) to 186.2 (Benefit)

95% CI = 95% confidence interval, NNT = number needed to treat.

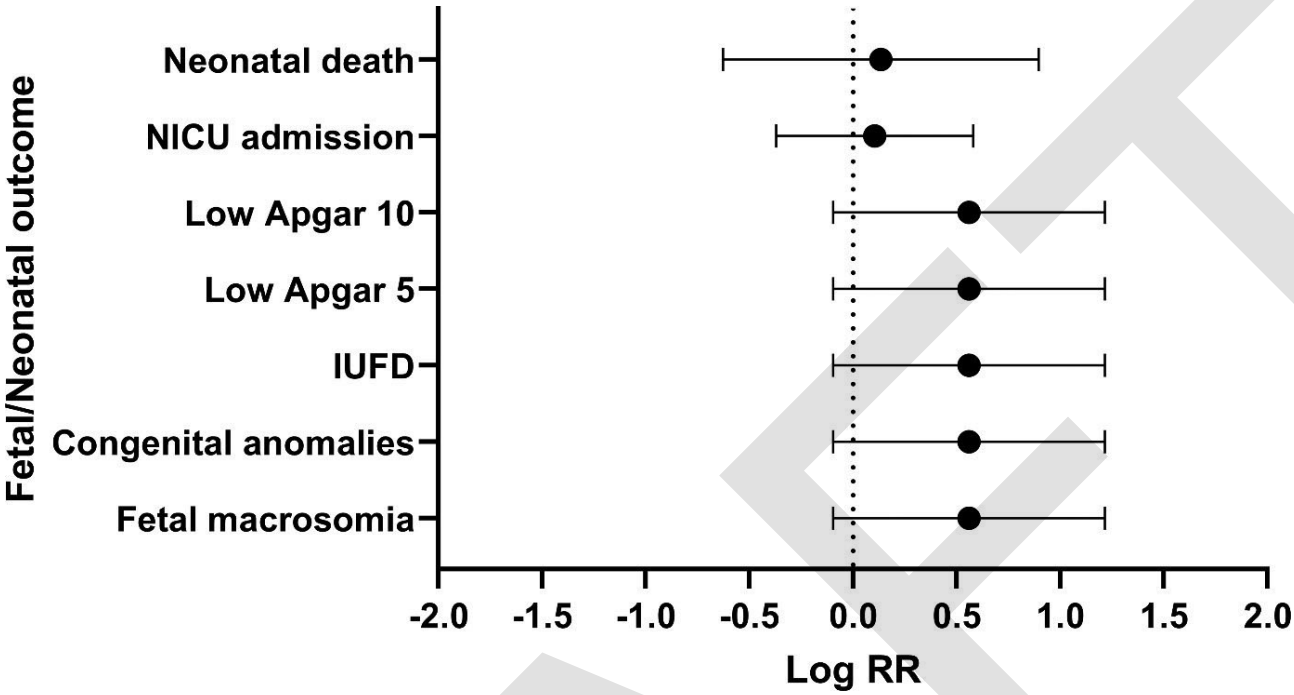

Figure 5. Relative risk (RR, rounded marker) with 95% confidence limits (95% CI, error bars) for fetal and neonatal outcomes in both study groups by per protocol (PP) analysis. There is no statistically significant difference between long-acting or intermediate-acting insulin regarding maternal or obstetric outcomes.

Discussion

Pregnancy is a potentially glucose-intolerant condition. Insulin sensitivity decreases as the pregnancy advances. Some women develop GDM due to inadequate insulin secretion, particularly in obese women with pre-existing insulin resistance (18-20).

The standard therapy for gestational diabetes is insulin. On the other hand, Insulin has several disadvantages, including daily injections, the risk of hypoglycemia, and maternal weight gain (21-22). Different types of insulin have different time for control of blood glucose levels due to different pharmacological composition, and that cause difference in the total time needed for reaching normal glycemic levels and difference in the number of hypoglycemic attacks occurring to the patients during the time to reach normal glucose levels. (23-25) GDM causes higher risks for polyhydramnios and excessive fetal growth, increasing the risk of shoulder dystocia. All these factors cause higher rates of caesarian section in patients with gestational diabetes (9).

Our Results and their interpretation

Our work aimed to compare the long-acting insulin injected once daily at bedtime and multiple-dose regimens of NPH and short-acting insulin to control gestational diabetes.

There was no statistically significant regarding patients' demographic characteristics in both study groups (age, BMI, and GA at recruitment). There was no statistically significant difference between studied groups regarding Parity or previous abortions.

Regarding glycemic control, there was no statistically significant difference between groups regarding pre-medication glucose and HbA1C level. Regarding post-treatment measures:

In Group A, long-acting insulin had a better effect on mean 2h-PPBS than Group B but

didn't reach statistical significance. While in Group B: patients showed better control in mean FBS than in Group A (not yet statistically significant). Group B showed a shorter time to achieve blood sugar control in the studied patients.

Our patients had a mean HbA1c of 6.53 +/− 1.05%; we observed an improvement in metabolic control throughout the gestation, regardless of the type of insulin treatment. Our data confirm other reports (26). Also, no significant difference between both groups regarding HbA1c post-treatment. These results declared that a multiple-dose regimen better controls GDM than long regimens.

Comparison of our results to similar studies

The study of Pöyhönen-Alho et al., 2002, compared the effect of short-acting insulin and long-acting insulin on perinatal outcomes in insulin-requiring gestational diabetes mellitus. Similar to our results, they concluded that GDM is better to be treated with short-acting insulin and using long-acting insulin doesn't differ in controlling GDM (12).

In another study that agreed with our results, Lv et al., 2013, examined the potential differences between multiple daily injections (MDI) regimens based on new long-acting insulin analogs (glargine or detemir) and continuous subcutaneous insulin infusion (CSII) by insulin aspart. They included 119 patients; 48 males, 71 females) with poorly controlled type 2 diabetes of a duration exceeding five years were randomly assigned into three groups: Group A treated with CSII using insulin aspart, Group B treated with glargine-based MDI, and Group C treated with detemir-based MDI. Good glycemic control was achieved by patients in Group A in a relatively shorter duration (4 days) than patients in Groups B and C (7 days). (27) This study correlates with our results as it declares the good control of diabetes with long-acting insulin analogs yet over a longer duration to achieve control.

Similar to our results, A study by López-Tinoco et al., 2019, compared the effect of different insulin therapies on obstetric-fetal Outcomes. They evaluated the effectiveness of the different insulin therapies on obstetrics-fetal outcomes in women with pregestational diabetes mellitus. They enrolled 147 pregnant women with pre-existing type 1 or 2 diabetes mellitus. Clinical and biochemical parameters were analyzed for obstetric and fetal outcomes. A percent of 14.2% of the patients received treatment with Neutral Protamine Hagedorn insulin and short-acting insulin analogs; 19% with premixed human insulin; 40.1% with insulin glargine and lispro, 6.2% with detemir and aspart and 20% with continuous subcutaneous insulin infusion. All five types of treatment achieved a reduction of the mean HbA1c during pregnancy (p=0.01). They reported that no significant difference was observed between all regimens regarding episodes of hypoglycemia or obstetric outcomes. (28)

Strength and weakness points in our study:

Our study is a prospective one. Our patients were strictly followed up during hospitalization. Most of the patients were followed up till delivery through regular follow-up visits or other contacting methods as taking more than a phone number for the patient and internet contacting this helped us to collect more data about the obstetric and fetal outcomes of our patients.

We believe that the weak point in our study is that it didn't prescribe other lines of treatment for gestational diabetes as oral hypoglycemic drugs for the patients. This is to avoid undesirable side effects of oral hypoglycemic drugs. also to avoid a lack of patient compliance to oral treatment that will surely affect the accuracy of the results. So,

we preferred to use insulin as the patient will have precise and accurate follow-up and good compliance during hospitalization. Also, We didn't include patients with pregestational diabetes because that would increase the heterogenicity of the sample of patients causing inaccurate results.

Implication for the clinical practice

We can introduce long-acting insulin as a protocol for treating gestational diabetes mellitus as long as the patient has no obstetric complication or emergency or fetal risk, is aware of the number of injections, and can afford the price of long-acting insulin.

Recommendations for future research

After recognizing the safety and efficacy of insulin analogs, we recommend treating them with long-acting analogs, especially if there is a risk of nocturnal hypoglycemia. Also, further studies are required to demonstrate the benefits over the rest of insulin therapies,

Conclusion

e can conclude that there is no clinical difference between using a multiple-dose regimen and using long-acting insulin analogs to control gestational diabetes regarding maternal and fetal outcomes. However, a multiple-dose regimen needs a shorter time for blood glucose control than long-acting insulin. It is to be noted that long-acting insulin is more expensive.

Ethics approval

Study approved by Ethical Committee

Consent for publication

Nonapplicable

Availability and data material

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Competing interests

The author reports there are no competing interests to declare

Funding

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References

1. Pandit MK, Burke J, Gustafson AB, et al. Drug-induced disorders of glucose tolerance. Ann Intern Med 2011;118:529–39.
2. Coustan DR. Screening and diagnosis of gestational diabetes mellitus. UpToDate 2016. Available from.http://www.uptodate.com accessed on 29 Aug, 2016.
3. Blumer I, Hadar E, Hadden DR, Jovanovič L, Mestman JH, Murad MH et al. Diabetes and pregnancy: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 2013; 98: 4227-4249.
4. Panel, Metzger BE, Gabbe SG, Persson B, Buchanan TA, Catalano PA et al. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. Diabetes Care 2010; 33: 676-682.
5. Agarwal MM, Dhatt GS, Shah SM. Gestational Diabetes Mellitus Simplifying the International Association o f Diabetes and Pregnancy diagnostic algorithm using fasting plasma glucose. Diabetes Care 2010; 33: 2018-2020.

6. Riddle MC. The underuse of insulin therapy in North America. DiabetesMetab Res Rev. 2002 ; 18(3):S42-9.

7. Zinman B. Newer insulin analogs: advances in basal insulin replacement. Diabetes ObesMetab. 2013;15 Suppl 1:6-10.

8. Mecacci F, Carignani L, Cioni R, Bartoli E, Parretti E, La Torre P et al. Maternal metabolic control and perinatal outcome in women with gestational diabetes treated with regular or lispro insulin: comparison with non-diabetic pregnant women. Eur J ObstetGynecolReprod Biol. 2003 10;111(1):19-24.

9. Metzger BE, Buchanan TA, Coustan DR, de Leiva A, Dunger DB, Hadden DR, et al. : Summary and recommendations of the fifth international workshop-conference on gestational diabetes. Diabetes Care 2016 .; 30(2):S251-S260

10. Feig D, Berger H, Donovan L, Godbout A, Kader T, Keely E et al. Diabetes Canada 2018 Clinical Practice Guidelines. Diabetes and Pregnancy@guidelines@ diabetes.ca. last accessed at april 4 2019.

11. Rosenstock J , Davies M, Home PD, Larsen J, Koenen C, Schernthaner G. A randomised, 52-week, treat-to-target trial comparing insulin detemir with insulin glargine when administered as add-on to glucose-lowering drugs in insulin-naive people with type 2 diabetesDiabetologia (2008) 51:408–416

12. Poyhonen-Alho M, Teramo K, Kaaja R. Treatment of gestational diabetes with short-or long-acting insulin and neonatal outcome:a pilot study. Acta ObstetGynecolScand 2002: 81: 258–259.

13. IDF Diabetes Atlas 2015 available from http://www.diabetesatlas.org/acessed on5th September 2016

14. Jovanovic L. Role of diet and insulin treatment of diabetes in pregnancy. Clin Obstet Gynecol 2000; 43: 46-55.

15. Meltzer SJ and Alsayari R. Insulin Use in Gestational Diabetes – Pragmatic Protocols for Self-Management and for Labour and Delivery McGill University Health Centre, Montreal, QC Canada available from http://cdn.intechopen.com/ pdfs wm/23188.pdf accessed on 25 August 2016.

16. Kitzmiller JL, Block JM, Brown FM. Managing preexisting diabetes for pregnancy: summary of evidence and consensus recommendations for care. Diabetes Care 2008;31:1060–1079

17. Chow S.C, Shao J,Wang H : sample size calculation in clinical research, pharmaceutical statistics (2004),3:40-63.

18. Colberg, S. R., Sigal, R. J., Yardley, J. E., Riddell, M. C., Dunstan, D. W., Dempsey, et al., : Physical activity/exercise and diabetes: A Position Statement of the American Diabetes Association. Diabetes Care. 2016;39(11):2065-2079.

19. Griffith, R. J., Alsweiler, J., Moore, A. E., Brown, S., Middleton, P., Shepherd, E. et al. Interventions to prevent women developing gestational diabetes mellitus: an overview of Cochrane Reviews. The Cochrane Database of Systematic Reviews, 2019(5): CD012394.

20. Mackin, S. T., Nelson, S. M., Kerssens, J. J., Wood, R., Wild, S., Colhoun, H. M. et al.: Diabetes and pregnancy: national trends over a 15 year period. Diabetologia,2018: 61(5): 1081-1088.

21. American Diabetes Association : Classification and diagnosis of diabetes. Diabetes care, 2017; 40(Supplement 1): S11-S24.

22. Simeonova-Krstevska, S., Bogoev, M., Bogoeva, K., Zisovska, E., Samardziski, I., Velkoska-Nakova, V. et al. Maternal and neonatal outcomes in pregnant women with gestational diabetes mellitustreated with diet, metformin or insulin. Open access Macedonian Journal of Medical Sciences, 2018: 6(5): 803-807.

23. Pampanelli S, Torlone E, Ialli C, Del Sindaco P, Ciofetta M, Lepore M, et al. Improved postprandial metabolic control after subcutaneous injection of a short-acting insulin analog in IDDM of short duration with residual pancreatic beta-cell function. Diabetes Care. 1995;18:1452–9.

24. Tupola S, Komulainen J, Jaaskelainen J, Sipila I. Post-prandial insulin lispro vs. human regular insulin in prepubertal children with Type 1 diabetes mellitus. Diabet Med. 2001;18:654–8

25. Mudaliar S, Mohideen P, Deutsch R, Ciaraldi TP, Armstrong D, Kim B, et al. Intravenous glargine and regular insulin have similar effects on endogenous glucose output and peripheral activation/ deactivation kinetic profiles. Diabetes Care. 2002;25:1597–602

26. Acosta D, Balsells M, Ballesteros M, Bandres MO, Bartha JL, Bellart J, et al. Asistencia a la gestantecon diabetes. Guía de práctica clínica actualizadaen. Avancesen Diabetología. 2015; 1;31(2):45-59.

27. Lv WS, Li L, Wen JP, Pan RF, Sun RX, Wang J et al. Comparison of a multiple daily insulin injection regimen (glargine or detemir once daily plus prandial insulin aspart) and continuous subcutaneous insulin infusion (aspart) in short-term intensive insulin therapy for poorly controlled type 2 diabetes patients. Int J Endocrinol. 2013:614242.

28. López-Tinoco C, Jiménez-Blázquez JL, Larrán-Escandón L, del Mar Roca-Rodríguez M, Bugatto F, Aguilar-Diosdado M. Effect of Different Insulin Therapies on Obstetric-Fetal Outcomes. Scientific reports. 2019 27;9(1):1-6.

Progesterone-Primed Ovarian Stimulation might be a Safe and Effective Alternative to GnRH-antagonist Protocol for Controlled-Ovarian Stimulation of Infertile PCOS Women

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Abstract

Objectives : This study evaluated the safety and efficacy of the progesterone-primed ovarian stimulation (PPOS) coupled with gonadotropin (FSH) for infertile women with polycystic ovary syndrome (PCOS) who were assigned for ICSI and frozen blastocyst transfer.

Patients : 200 infertile women were divided randomly into Group C, which received Cetrorelix injection (0.25 mg daily) on day-6, and Group S, which received oral dydrogesterone (20 mg/day) on day-2 of the menstrual cycle till the trigger day. All patients received an FSH injection of 225 IU daily from day-2 till triggering day. ICSI was performed and day-5 blastocysts underwent vitrification ultra-rapid cryopreservation till being transferred. Outcomes included the ability of PPOS to suppress the premature luteinizing hormone (LH) surge and prevent the development of ovarian hyperstimulation syndrome (OHSS), the incidence of profound LH suppression, the number of retrieved M2 oocyte and fertilization, chemical and clinical pregnancy rates, and the miscarriage rate.

Results: No moderate-to-severe OHSS or premature LH surge was reported in all patients. Serum levels of estradiol and LH increased significantly in all patients with insignificant differences between both groups. The numbers of mature follicles on triggering day, retrieved M2 oocytes and D-5 good-quality blastocysts, pregnancy rates and the miscarriage rate showed non-significant differences between the studied groups.

Conclusion: PPOS protocol for OS is safe and effective for infertile PCOS women. PPOS protocol achieved appropriate LH suppression with nearly no profound suppression or moderate-to-severe OHSS. The outcomes of PPOS protocol were comparable to the GnRH-antagonist protocol, however, PPOS is more cost-effective.

Keywords: Progesterone-primed ovarian stimulation, Premature LH surge, ovarian hyperstimulation syndrome, ICSI outcomes

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INTRODUCTION

Polycystic ovary syndrome (PCOS) is an endocrine disorder that affects women of reproductive age and is one of the most common causes of infertility [1]. PCOS is a composite endocrinal disorder characterized by hyperandrogenism; ovulatory dysfunction and polycystic ovarian morphology [2]. PCOS women are more frequently confronted with multiple reproductive problems, especially poor oocyte quality and fertilization failure, thus assisted reproductive techniques (ART) might be the sanctuary for infertile PCOS women [3]. The key factor for successful ART is the controlled ovarian stimulation (COS), using either gonadotropin-releasing hormone (GnRH) agonist or an antagonist protocol [4].

However, no protocol is immune; the agonist protocol through pituitary desensitization facilitates antral follicle synchronization, but triggering using the human chorionic gonadotropin (hCG) increases the risk of ovarian hyperstimulation syndrome (OHSS) [5]. On the contrary, the antagonist protocol induces rapid and reversible suppression of luteinizing hormone (LH) secretion, but a varied percentage of patients would experience premature LH surge that was defined as a serum LH level of >10 IU/L before the trigger day [6] and leads to luteinisation of the immature follicles [7].

Infertile PCOS women are mostly at high risk of using any of the COS protocols because of their vulnerability to developing OHSS [2] and have high basal LH levels that were reported in about 30-50% of PCOS women [8].

The rise in the circulating estradiol (E2) level that occurs synchronously with pre-ovulatory ovarian follicle development results in the pre-ovulatory GnRH/LH surge that was prevented by high progesterone levels during the luteal phase [9]. Earlier animal studies assured the ability of progesterone to block LH surge, even if applied after activation of the surge-generating system by high estradiol levels, through inhibition of the transmission of the estradiol signal and/or prevention of the release of the GnRH/LH surge [10]. These findings were the basis for priming with progesterone through the progesterone-primed OS (PPOS) protocol [11].

Objectives

This study tried to evaluate the applicability of PPOS protocol coupled with gonadotropin (FSH) for infertile PCOS women and assigned for ICSI using frozen blastocyst transfer (FBT).

Design

Prospective two-phase randomized comparative study.

Setting

Gynecology & Obstetrics Department, Faculty of Medicine, Zagazig University and multiple private centers.

Patients

All women attending the Infertility clinic were evaluated for selection of infertile PCOS women, who are the study target. PCOS was diagnosed according to the Rotterdam criteria for PCOS diagnosis, which include the presence of oligomenorrhea, anovulation, hyperandrogenism, ovaries containing ≥ 12 follicles that measure 2-9 mm in diameter per ovary, ovarian volume of more than 10 ml (12). PCOS was diagnosed in the presence of at least two of the Rotterdam criteria (13). PCOS women underwent full history taking including age, and menstrual, obstetric and medical history. Clinical examinations for determination of body mass index (BMI) calculated as weight divided by the square of the height in meters and gynecological examination including transvaginal ultrasonography (TVU) for assurance of the presence of PCO and/or large ovary, presence of genital tract congenital anomalies and

other causes for infertility. Then, blood samples were withdrawn for estimation of serum levels of the anti-Müllerian hormone (AMH), follicle-stimulating hormone (FSH), E2, LH, prolactin and thyroid-stimulating hormone in hospital lab.

Exclusion criteria

Women who were younger than 20 or older than 35 years, obese of grade II or III, had poor OR, other causes of infertility, had previous attempts of IVF, had a history of repeated pregnancy loss, endocrinopathies other than PCOS, congenital anomalies of the genital system, concomitant other cause for infertility, maintenance on hormonal therapy for any indication were excluded from the study.

Inclusion criteria

Infertile PCOS women, aged 20-35 years, had BMI <35 kg/m2 and free of exclusion criteria

Ethical Consideration

After the departmental approval of the study protocol, it was discussed with enrolled women and their husbands for acceptance to participate in the study. At the end of the study duration from June 2021 till Jan 2023, the final approval of the study protocol and outcomes was obtained by the University Ethical Committee on 25-6-2023 by approval number: ZU-IRB#10874-25/6-2023 and was registered by Clinical Trial.com by number NCT05939284. The enrolled couples signed a written fully informed consent to participate in the study and accept the result of randomization.

Randomization and grouping

The enrolled women were randomly allocated into Group-C and Group-S groups according to the OS protocol. Randomization was performed using computer software (Excel 2010, Microsoft, Redmond, WA, USA) using a 1:1 sequence with the irregular dropping of numbers to allow proper randomization. The generated sequences were transformed into letters; C and S that were printed on cards given to patients by an assistant who was blind about the significance of the letters. The cards were provided to the gynecologist in charge to carry on the OS protocol assigned for each group.

Study Protocol

The study was divided into two phases: the enrolled women during phase-I received OS according to the protocol assigned for each group and on oocyte retrieval, ICSI was performed. On day-5, the resultant blastocysts were frozen using the vitrification ultra-rapid cryopreservation as previously described by Balaban et al. (14). During phase II, the frozen blastocysts were graded according to the ASEBIR classification system, which entails grading the internal cell mass as A-to-C grades and the degree of expansion of the blastocele expansion on a 2-6 scale; good quality blastocysts must be graded as AA6 on day-5 (15). All women received the same preparation protocol, and good quality blastocysts of grade AA6 were selected for transfer and all women received single FBT.

Phase-I

All patients received FSH (Fostimon, IBSA, Switzerland) intramuscular injections of a daily dose of 225 IU, starting from day-2 of the menstrual cycle till the trigger day. Group-C patients received Cetrorelix subcutaneous injection (Cetrotide, MerckSerono, Germany) on the day-6 in a dose of 0.25 daily till the trigger day. Group-S patients received dydrogesterone (DYG; Duphaston, Abbott Biologicals B.V., Netherlands) in an oral dose of 20 mg/day in parallel with gonadotropin injection from day-2 of the menstrual cycle till the trigger day using 2 amp triptorelin (Decapeptyl, Ferring Pharmaceuticals Ltd., Wittland, Germany; 0.1 mg amp) when the most follicles were 17-18 mm.

Phase-II

Gonadotropin-releasing hormone agonist (GnRH-a) therapy was started at 7-day before the expected day of the menstrual cycle in the form of triptorelin (Decapeptyl, Ferring Pharmaceuticals Ltd., Wittland, Germany) subcutaneous injection in a dose of 0.1 mg. Estradiol valerate (Progynova, 2 mg, Bayer Schering Pharma, UK) was started on day-2 of the menstrual cycle as a daily dose of 6 mg for four days and then the dose was adjusted according to the endometrial thickness (ET). Using TVU (Sonoline Prima 7.5 MHz, Siemens) ET was determined in the midsagittal plane as the distance between the outer edges of the endometrial/myometrial interface on days 10 to 12. At ET of 8 mm, progesterone vaginal supp. (Cyclogest; Actavis Co., USA) were received for the 5-day duration, and on the 6th day, the frozen blastocyst was rapidly thawed and transferred. Thereafter, progesterone therapy continued for 14 days whenever chemical testing for pregnancy was performed, and in case of a positive chemical pregnancy test, clinical pregnancy was assured by detecting viable embryos with pulsating heart using US examination.

Evaluated variate

1. Hormonal assay: serum levels of FSH, LH, E2 and prolactin were estimated at the time of enrolment as baseline levels. On day-7 of OS and at the time of triggering, serum E2 and LH were re-estimated.
2. The incidence of premature LH surge, profound LH suppression and moderate-to-severe OHSS. Profound LH suppression was defined as a serum LH level <1 IU/L during OS (6).
3. The numbers of mature follicles, oocytes retrieved M2 oocytes and number of AA6 blastocytes on day-5.
4. Positive chemical pregnancy was determined on detection of serum β-hCG level ≥5 IU/L at 2-wk after FBT. Positive clinical pregnancy was determined on detection of at least one gestational sac with fetal heart activity. The miscarriage rate calculated as the percent of spontaneous or therapeutic abortion during follow-up.

Study outcomes

1. The primary outcome is the success rate of PPOS as regards the suppression of premature LH surge and prevention of the development of OHSS.
2. The secondary outcomes include

- The incidence of profound LH suppression
- The number of retrieved M2 oocytes and fertilization rate
- The pregnancy rates and the incidence of miscarriage.

Results

Through 2-year study since June 2021, 238 PCOS infertile women were evaluated, 16 women were out of age range, 7 women had BMI>35 kg/m2, 4 women had previous failed ART trials, 3 women were maintained on hormonal therapy, and a woman had endocrinopathy. These 31 women and another 7 women, who were missed during follow-up, were excluded, and 200 women were enrolled in the study (Fig. 1). The enrolment data of women of both groups showed insignificant differences as shown in Table 1.

Table (1): Enrolment data

Variate		Group C	Group S	P-value
Age (years)		28.2±3.4	28±4.2	0.711
BMI (Kg/m2)		29.9±2.2	30.3±2.6	0.158
Duration of infertility (years)		2.98±1.1	2.66±1.2	0.056
Hormonal assay	AMH (ng/ml)	5.08±0.5	4.97±0.5	0.141
	FSH (IU/L)	5.96±1	6.19±0.7	0.057
	Prolactin (ng/ml)	18.6±4.1	18.3±3.2	0.568
TVU data	Ovarian volume (cc)	11.33±1.2	11.38±1.7	0.808
	Antral follicular count (follicles)	12.1±1.7	12.3±1.9	0.433

LH: Luteinizing hormone; *: indicates significant difference versus baseline level

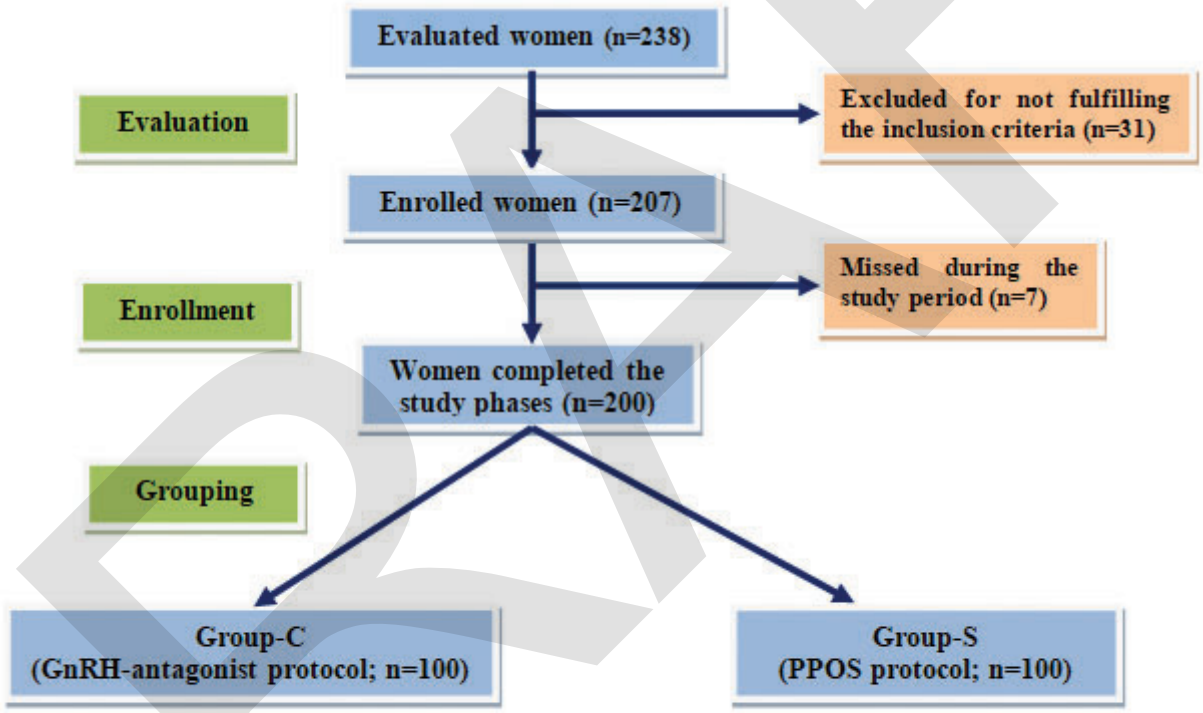

Figure 1: Study Flow Chart

All women had passed Phase-I concerning OS uneventfully and no patient developed moderate-to-severe OHSS. Estimated serum LH levels decreased significantly (P<0.001) at D-7 and time of triggering in patients of both groups in comparison to their respective baseline levels. However, both applied protocols provided perfect LH suppression during OS as manifested by the non-significant differences between mean LH levels estimated in samples of both groups at baseline, D-7 of OS and at triggering time (Fig. 2). Fortunately, no patient developed premature LH surge and on D-7, 53 women developed profound suppression and at triggering time 7 women had profound LH suppression with non-significantly lower incidence of profound LH suppression in Group-S patients (Table 2).

Table (2): LH dynamics during OS

Variate		Group C	Group S	P-value
Serum LH (IU/L)	Baseline	5.86±1.58	5.95±1.75	0.703
	D-7 of OS	4.85±2.91*	4.48±2.44*	0.332
	Triggering time	5.1±1.96*	4.79±1.65*	0.228
Incidence of premature surge (>10 IU/L)		0	0	
Incidence of profound suppression	D-7 of OS	30 (30%)	23 (23%)	0.262
	Triggering time	5 (5%)	2 (2%)	0.248

*: indicates significant difference versus baseline level; P-value indicates the significance of difference between both groups; P>0.05 indicates insignificant difference

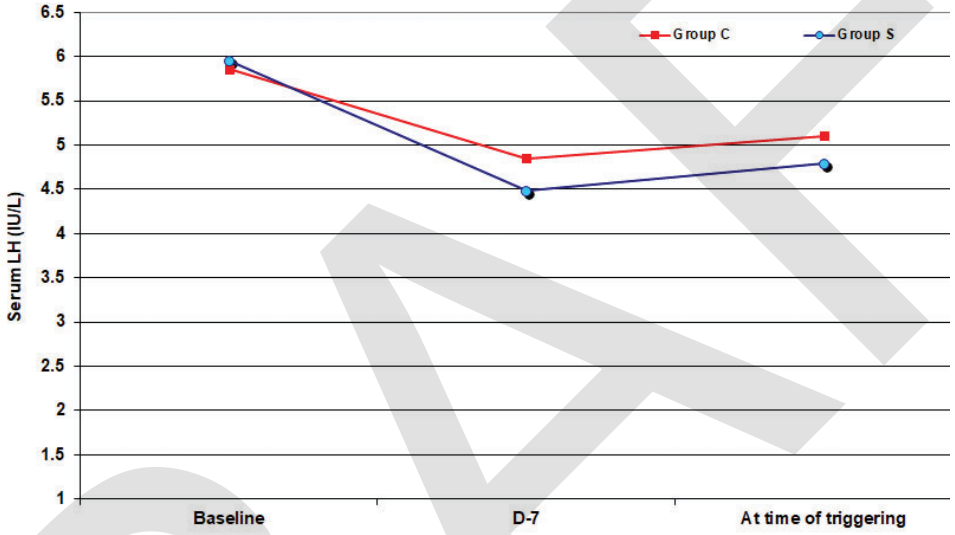

Fig. 2: Mean serum LH levels estimated in samples of women of the studied groups

The estimated serum E2 levels increased progressively and significantly in samples obtained at D-7 of OS and the triggering day in comparison to baseline levels in patients of both groups. However, the differences in estimated serum E2 levels in samples of both groups were insignificantly higher in favor of Group-S (Fig. 3). Correlation analysis showed a positive insignificant relation between the percentage of increase in serum levels of E2 and LH at the triggering day in relation to levels estimated in D-7 samples of Group-C (r=0.126, p=0.213) and Group-S (r=0.064, p=0.527); however, the relation in case of Group-C was nearer to be significant (Fig. 4). The numbers of mature follicles on triggering day, retrieved M2 oocytes and D-5 good quality blastocysts were non-significantly higher in Group-C than Group-S (Table 3).

Table (3): Phase-I outcomes

Variate		Group C	Group S	P-value
Serum E2	Baseline	39.92±16.6	44.2±20.3	0.104
	D-7 of OS	1298.5±466.6*	1347±604*	0.525
	Triggering time	2199.7±507.8*	2281.7±586.2*	0.292
Number of	Mature follicle on triggering day	21.9±4.4	20.5±5.7	0.054
	Retrieved M2 oocytes	18.9±4.2	17.8±5.4	0.109
	D-5 good quality embryos	14.7±3.5	13.6±4.7	0.061

*: indicates significant difference versus baseline level; P-value indicates the significance of difference between both groups; P>0.05 indicates insignificant difference

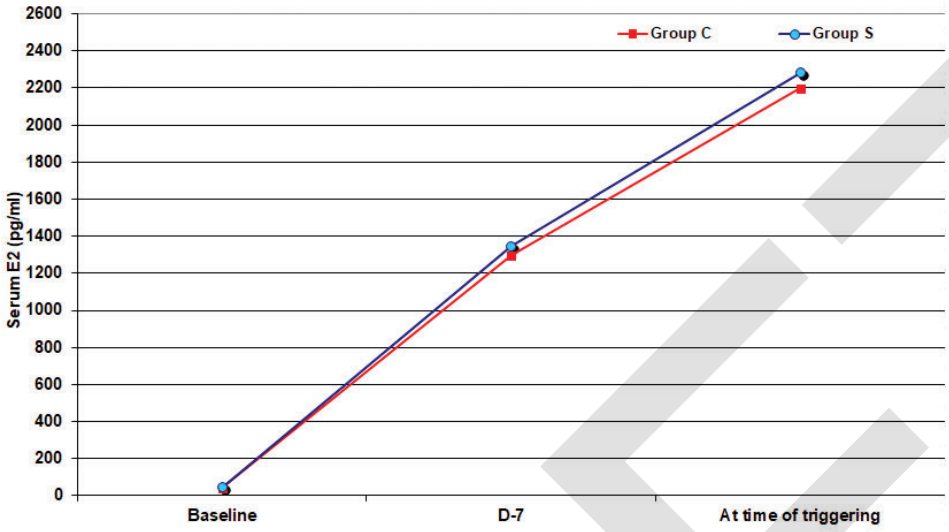

Fig. 3: Mean serum E2 levels estimated in samples of women of the studied groups

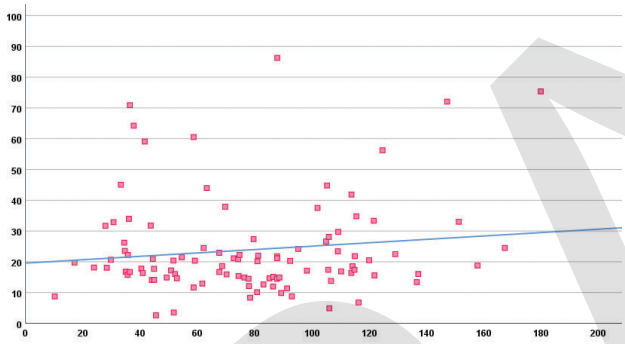

Fig. 4a

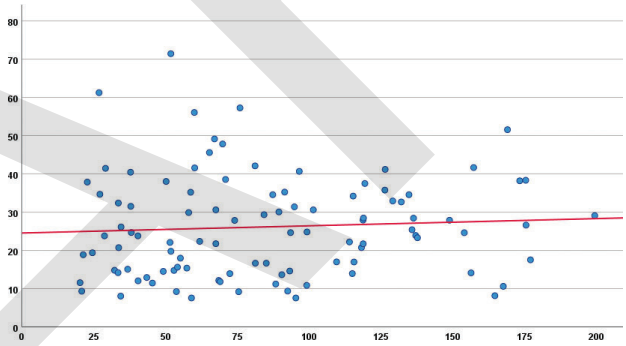

Fig. 4b

Correlation between the percentage of change in serum levels of LH & E2 estimated in D-7 and triggering day samples of patients of groups C (Fig. 4a) & S (Fig. 4b)

Regarding the Phase-II outcomes, the total chemical pregnancy rate was 71.5% with a non-significant (P=0.434) difference between both groups. Totally, 90 women showed viable gestational sac on US examination for clinical pregnancy rate of 45%; 49% and 41% in groups C and S, respectively. Unfortunately, 12 women had miscarriages that account for 13.3% of women who had viable gestational sacs, and Group-S women had a higher miscarriage rate (17.1%) than Group-C women (10.2%), but the difference is insignificant (P=0.339) as shown in Table 4

Table (3): Phase-I outcomes

Variate		Group C	Group S	P-value
Pregnancy rates	Chemical	74 (74%)	69 (69%)	0.434
	Clinical	49 (49%)	41 (41%)	0.256
Miscarriage rate		5 (10.2%)	7 (17.1%)	0.339

The P-value indicates the significance of the difference between both groups; P>0.05 indicates the insignificant difference

Discussion

The main target for the OS protocols is to be safe and successful in the provision of the required M2 oocyte without complications that mainly for PCOS women include premature LH surge [8] and/or development of OHSS [2]. Fortunately, the studied PPOS protocol using dydrogesterone (DYG) could achieve this target with results comparable to that of the settled GnRH-antagonist protocol. These findings supported the document by Zhu et al. [16] that oral utrogestan achieved LH suppression during controlled OS (COS) with no premature LH surge. Thereafter, Guan et al. [17] reported a lower rate of OHSS with PPOS versus GnRH-antagonist protocol and Khurana et al. [18] reported no cases of severe OHSS and insignificantly lower incidence of mild-to-moderate OHSS with PPOS than antagonist protocol. Recently, Xu et al. [19] retrospectively documented the clinical efficacy of PPOS and GnRH-a long protocol applied for patients with normal OR and found PPOS could reduce the incidence of OHSS, especially in risky women. Further, Tandulwadkar et al. [20] prospectively documented the ability of PPOS using medroxyprogesterone acetate (MPA) and Gn-RH-antagonist protocols to prevent the premature LH surge in hyper-responders undergoing COS.

Regarding the progesterone formula, the used oral DYG resulted in outcomes comparable to that of the GnRH-antagonist protocol as regards abolishment of OHSS and LH suppression. In line with the efficacy of DYG, Huang et al. [21] reported consistent LH suppression with no premature surge with DYG and MPA, but DYG induced lower LH levels with lower consumption of hMG than MPA.

Further, the outcomes of the fixed PPOS protocol using a fixed daily dose of DYG started on day-2 of the menstrual cycle were efficient, in line with these findings, Durdağ et al. [22] compared the outcomes of the fixed versus the flexible PPOS protocol that entails giving DYG 20 mg daily starting when the leading follicle was 12 mm or serum E2 level >200 pg/ml and reported insignificant differences between both protocols but in favor of the fixed one especially for preventing LH surge.

Evaluated dynamics of LH secretion showed progressively decreased incidence of profound suppression (<1 ng/ml) with insignificant difference between both protocols, despite being higher with Gn-RH-antagonist. Further, the reported non-significant difference between the numbers of retrieved oocytes indicated the absence of a relation between the extent of suppression and OS yield. This finding is coincident with Goh et al. [23] who found Gn-RH antagonist is associated with a risk of profound LH suppression, but without significant differences in IVF and pregnancy outcomes in comparison to women without significant LH suppression.

Interestingly, the dynamics of both LH and E2 showed a positive insignificant relation with both protocols, but the significance was more with Gn-RH-antagonist. This finding indicated the multiplicity of the mechanisms of LH suppression by progesterone other than desensitization of the pituitary to the raising levels of E2 and supports the results of earlier animal studies that progesterone inhibits the transmission of the estradiol signal and prevents the release of the GnRH/LH surge [10]. Recent animal studies found progesterone also suppresses LH surge at the hypothalamic levels through increased dynorphin and GABAA receptor signaling that act through kisspeptin neurons in the anteroventral periventricular hypothalamic nucleus [24, 25].

Regarding the outcomes of frozen blastocyte transfer (Phase II), there was an insignificant difference between the effect of applied OS protocols on pregnancy rates or the miscarriage rate, despite being in favor of the GnHR-antagonist protocol. These data

are in line with multiple studies documenting the non-significant differences between PPOS and antagonist protocols regarding pregnancy outcomes after frozen embryo transfer [17, 26-28].

Patients' selection based on normal OR was targeted to equalize the results for comparative purposes and such selection was in line with the findings of Zhou et al. [28] who retrospectively found the cumulative living birth rate (LBR) after PPOS was significantly lower with normal, while was higher with poor OR than with Gn-RH-antagonist protocol, but for PCOS women the fertilization and pregnancy rates and the LBR was comparable with insignificant differences between PPOS and antagonist protocols.

Further, the PPOS protocol is a cost-effective protocol, where the cost of DYG is meaningless compared to that of Cetrorelix (4 vs. 500 EP/day), considering the reported non-significant differences in outcomes, PPOS is a resource-sparing and safe protocol. In support of these suggestions, Guo et al. [29] found PPOS protocol applied for women with advanced ovarian endometriosis resulted in significantly lower hMG doses and shorter duration of therapy with no differences in outcomes, but with lower costs. Also, Filippi et al. [30] found PPOS protocol for OS in cancer women who wish to preserve their fertility is an easy and affordable protocol with similar efficacy, but is friendlier and more economical than the recombinant FSH and GnRH-antagonist protocol. Furthermore, Zhao & Wang [31] found combining the PPOS protocol with clomiphene citrate and gonadotropin for IVF-ET in older women with poor OR effectively blocked the premature LH surge with an increased number of mature oocytes and recommended this protocol for such a population of women. Also, Kao et al. [32] found flexible GnRH-antagonist protocol had a higher risk of premature LH surges without improved pregnancy rates in poor ovarian responders compared to PPOS.

Conclusion

PPOS protocol for COS is the apropos choice for infertile PCOS women as preparatory for ICSI. PPOS protocol achieved appropriate LH suppression with nearly no profound suppression and no moderate-to-severe OHSS. The outcomes of PPOS were comparable to the GnRH-antagonist protocol; however, PPOS is more cost-effective.

References

1. 1.Liu C, Wang M, Yao H, Cui M, Gong X, Wang L, et al.: Inhibition of Oocyte Maturation by Follicular Extracellular Vesicles of Nonhyperandrogenic PCOS Patients Requiring IVF. J Clin Endocrinol Metab. 2023; 108(6):1394-1404.
2. Rodrigues P, Marques M, Manero J, Marujo M, Carvalho M, Plancha C: In vitro maturation of oocytes as a laboratory approach to polycystic ovarian syndrome (PCOS): From oocyte to embryo. WIREs Mech Dis. 2023; 15(3):e1600.
3. Xie Q, Hong W, Li Y, Ling S, Zhou Z, Dai Y, et al.: Chitosan oligosaccharide improves ovarian granulosa cells inflammation and oxidative stress in patients with polycystic ovary syndrome. Front Immunol. 2023; 14:1086232.
4. Gallos ID, Eapen A, Price M, Sunkara S, Macklon N, Bhattacharya S, et al.: Controlled ovarian stimulation protocols for assisted reproduction: a network meta-analysis. Cochrane Database Syst Rev. 2017; 2017(3): CD012586.
5. Al-Inany HG, Youssef MAFM, Aboulghar M, Broekmans FJ, Sterrenburg MD, Smit JG: Gonadotrophin-releasing hormone antagonists for assisted reproductive technology. Cochrane Database of Systematic Reviews 2016, Issue 4.
6. Liu Y, Chen Q, Yu S, Wang Y, He W, Chang H, et al.: Progestin-primed ovarian stimulation with or without

clomiphene citrate supplementation in normal ovulatory women undergoing in vitro fertilization/intracytoplasmic sperm injection: A prospective randomized controlled trial. Clin Endocrinol (Oxf). 2018; 88(3):442-52.

7. Han E, Lyu S, Kwak I, Kwon H, Choi D, Kim J, et al.: Efficacy and safety of newly developed ganirelix acetate in infertile women for assisted reproductive technology: a prospective, randomised, controlled study. J Obstet Gynaecol. 2022; 42(6):2197-202.
8. Yang X, Jiang M, Deng M, Zhang H, Lin Z, Fei X, et al.: Clomiphene citrate mild stimulation improved follicular development outcomes in PCOS women with high luteinizing hormone and poor ovarian response: A case report. Medicine (Baltimore). 2022; 101(42):e31323.
9. Kauffman AS: Neuroendocrine mechanisms underlying estrogen positive feedback and the LH surge. Front Neurosci. 2022; 16:953252.
10. Harris T, Dye S, Robinson J, Skinner D, Evans N: Progesterone can block transmission of the estradiol-induced signal for luteinizing hormone surge generation during a specific period of time immediately after activation of the gonadotropin-releasing hormone surge-generating system. Endocrinology. 1999; 140(2):827-34.
11. Messinis IE, Messini C, Anifandis G, Daponte A: Exogenous progesterone for LH surge prevention is redundant in ovarian stimulation protocols. Reprod Biomed Online. 2021; 42(4):694-7.
12. Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group: Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS).Hum Reprod2004;19(1): 41–7.
13. Smet M, McLennan A: Rotterdam criteria, the end. Australas J Ultrasound Med. 2018; 21(2): 59–60.
14. Balaban B, Urman B, Ata B, Isiklar A, Larman M, Hamilton R, et al.: A randomized controlled study of human day 3 embryo cryopreservation by slow freezing or vitrification: vitrification is associated with higher survival, metabolism and blastocyst formation. Hum Reprod, 2008; 23: 1976-82
15. Peña F, Dávalos R, Rechkemmer A, Ascenzo A, Gonzales M: Embryo development until blastocyst stage with and without renewal of single medium on day 3. JBRA Assist Reprod. 2018; 22(1): 49–51.
16. Zhu X, Zhang X, Fu Y: Utrogestan as an effective oral alternative for preventing premature luteinizing hormone surges in women undergoing controlled ovarian hyperstimulation for in vitro fertilization. Medicine (Baltimore). 2015; 94(21):e909.
17. Guan S, Feng Y, Huang Y, Huan J: Progestin-Primed Ovarian Stimulation Protocol for Patients in Assisted Reproductive Technology: A Meta-Analysis of Randomized Controlled Trials. Front Endocrinol (Lausanne). 2021; 12:702558.
18. Khurana R, Rao V, Nayak C, Pranesh G, Rao K: Comparing Progesterone Primed Ovarian Stimulation (PPOS) to GnRH Antagonist Protocol in Oocyte Donation Cycles. J Hum Reprod Sci. 2022; 15(3):278-83.
19. Xu S, Wang X, Zhang Y, Han Y, Zhang C: Comparison the effects of progestin-primed ovarian stimulation (PPOS) protocol and GnRH-a long protocol in patients with normal ovarian reserve function. Gynecol Endocrinol. 2023; 39(1):2217263.
20. Tandulwadkar S, Gupta S, Singh A, Mishra S, Singhania S: Medroxyprogesterone

Acetate versus Gonadotropin-Releasing Hormone Antagonist for the Prevention of Premature Luteinizing Hormone Surge in hyper-responder women undergoing controlled ovarian stimulation for IVF/ ICSI Cycles. JBRA Assist Reprod. 2023; 27(1):15-9.

21. Huang J, Xie Q, Lin J, Lu X, Zhu J, Gao H, et al.: Progestin-Primed Ovarian Stimulation with Dydrogesterone versus Medroxyprogesterone Acetate in Women with Polycystic Ovarian Syndrome for in vitro Fertilization: A Retrospective Cohort Study. Drug Des Devel Ther. 2019; 13:4461-70.
22. Durdağ G, Aytaç P, Yağınç D, Yetkinel S, Çok T, Şimşek E: Comparison of fixed and flexible progestin-primed ovarian stimulation protocols to prevent premature luteinization in patients with diminished ovarian reserve. Arch Gynecol Obstet. 2023; 308(2): 579-86.
23. Goh J, Lee J, Chan J, Allen J, Ng X, Nadarajah S, et al.: The Effect of Luteinising Hormone Suppression in In Vitro Fertilisation Antagonist Cycles. Reprod Sci. 2021; 28(11):3164-70.
24. Liu Y, Li X, Ivanova D, Lass G, He W, Chen Q, et al.: Dynorphin and GABAA Receptor Signaling Contribute to Progesterone's Inhibition of the LH Surge in Female Mice. Endocrinology. 2020 May 1; 161(5):bqaa036.
25. Mohr M, Esparza L, Steffen P, Micevych P, Kauffman A: Progesterone Receptors in AVPV Kisspeptin Neurons Are Sufficient for Positive Feedback Induction of the LH Surge. Endocrinology. 2021; 162(11):bqab161.
26. Eftekhar M, Hoseini M, Saeed L: Progesterone-primed ovarian stimulation in polycystic ovarian syndrome: An RCT. Int J Reprod Biomed. 2019; 17(9):671-6.
27. Devesa M, Racca A, Clúa E, Casato C, García S, Polyzos N, et al.: Progesterone-primed ovarian stimulation in oocyte donation: a model for elective fertility preservation? Reprod Biomed Online. 2022; 44(6):1015-22.
28. Zhou R, Dong M, Huang L, Wang S, Fan L, Liang X, et al.: Comparison of cumulative live birth rates between progestin-primed ovarian stimulation protocol and gonadotropin-releasing hormone antagonist protocol in different populations. Front Endocrinol (Lausanne). 2023; 14:1117513.
29. Guo H, Du T, Gao H, Xi Q, Wu L, Lyu Q, et al.: The comparison of two different protocols ultra-long versus medroxyprogesterone acetate in women with ovarian endometriosis: a prospective randomized controlled trial. Reprod Health. 2022; 19(1):198.
30. Filippi F, Reschini M, Polledri E, Cecchele A, Guarneri C, Vigano P, et al.: Progestin-primed ovarian stimulation for fertility preservation in women with cancer: A comparative study. PLoS One. 2023; 18(3):e0280238.
31. Zhao S, Wang C: Efficacy of progestin-primed ovarian stimulation (PPOS) versus minimal stimulation in women of advanced maternal age with poor ovarian response under the Patient-Oriented Strategies Encompassing Individualized Oocyte Number (POSEIDON) criteria. Ann Palliat Med. 2023; 12(1):133-40.
32. Kao T, Hsieh Y, Yang I, Wu M, Chen M, Yang J, Chen S: Progestin-primed ovarian stimulation versus GnRH antagonist protocol in poor responders: Risk of premature LH surge and outcome of oocyte retrieval. J Formos Med Assoc. 2023; 122(1):29-35.

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Cons and Pros of Interventions for Management of Ovarian Endometrioma in Infertile Women with Good Ovarian Reserve

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Abstract

Objectives : Assessment of the outcomes of surgical management of ovarian endometrioma (OMA) regarding ovarian reserve (OR), endometriosis-induced manifestations, and recurrence rate (RR).

Patients : 90 women with uniloculus OMA of >3 cm diameter in infertile women with good OR were randomly divided into three (A-C) groups according to the procedure: laparoscopic cystectomy, laparoscopic cyst evacuation and cauterization of the endocytic wall, and transvaginal aspiration and ethanol sclerotherapy. Serum anti-Müllerian hormone (AMH) and antral follicular count (AFC) were determined as baseline and 3-m and 6-m postoperative (PO). The study outcome is the impact of the applied procedures on OR, pain scores and consumption of analgesia, and the RR of OMA.

Results: The applied procedures significantly reduced pain scores and frequencies of patients according to the type of pain and analgesia consumed. At 3-m PO, serum AMH levels were decreased with non-significant differences in the percentage of decrease between the three groups. At 6-m PO, serum AMH levels were increased in Group-C patients, while progressively decreased in Group-B and did not change in Group-A patients. The decrease of AFC was maximal in group B with significantly lower counts than other groups that showed non-significant differences. Nineteen cases (21.1%) developed recurrent cysts with significantly lower RR in Group-A than in other groups.

Conclusion: No procedure was immune to disadvantages, thus proper evaluation of patients' concerns is mandatory. Transvaginal aspiration with sclerotherapy is appropriate if the pain is the main concern, while cystectomy was advocated to reduce recurrence, but for infertility management, no procedure was advantageous.

Keywords: Ovarian endometrioma, Laparoscopic cystectomy, Ethanol sclerotherapy, Ovarian reserve, recurrence

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INTRODUCTION

Endometriosis is lesions containing the endometrial glands and stroma outside the uterine cavity usually in the pelvis [1], but endometrial tissues transfer to more distant abdominal organs or spread as extra-peritoneal lesions involving the pleura or abdominal wall where recorded [2]. Endometriosis was broadly classified as either superficial peritoneal or deep infiltrating endometriosis or ovarian endometrioma (OMA) [3]. A mini-review suggested an incidence of OMAs of 17–44% among young women with endometriosis [4]. According to the recent ESHRE guideline for the management of endometriosis, the plan for OMA management depends on the main presenting manifestations and the size of the OMA [5] and may be either or a combination of multiple lines including expectant management, medical treatment, surgical treatment, in vitro fertilization in case of infertility-associated endometriosis [6]. Endometriosis has detrimental effects on fertility and this effect is multifactorial, ovarian tissue compression by the OMA may result in corrupted circulation with subsequent loss of follicles, and the increased inflammation resulting from endometriosis might alter the functions of the ovary, tubes or endometrium most probable through inflammation-induced overproduction of local ovarian and peritoneal inflammatory cytokines [7] and reactive oxygen species [8] leading to the production of poor quality oocytes [9]. Different techniques were supposed for the surgical treatment of OMAs as cystectomy, electrocoagulation, laser ablation, plasma-energy ablation, and combined techniques [10]. Laparoscopy for the management of endometriosis provided better visualization of endometriosis lesions, shorter hospitalization, and return to daily activities, so it is favored over laparotomy \ [11].

Objectives

This study tried to assess the outcomes of the management of ovarian endometrioma (OMAs) regarding ovarian reserve (OR), endometriosis-induced manifestations and recurrence rate (RR).

Design

A Prospective randomized interventional study

Setting

Department of Obstetrics and Gynecology, Faculty of Medicine, Benha University, in conjunction with multiple private gynecology centers

Ethical approvals

The study protocol was approved by the Departmental committee before the case collection in Jan 2020. The supposed therapeutic lines were discussed with patients before enrolment, and those accepted to receive any of these lines signed a written fully informed consent before inclusion in the study. After the case collection and at the end of follow-up, the study protocol with its outcomes was approved by the Ethical Committee at Benha Faculty of Medicine with RC :15-6-2023

Patients

Preliminary evaluations were performed for all patients attending the infertility clinic to select those with manifestations suggestive of endometriosis as the cause of infertility and were free of exclusion criteria. Patients' age and body mass index (BMI) were determined, and family history of endometriosis, history of medical diseases, special habits, menstrual history regarding its regularity, flow characteristics and associated manifestations were taken. Fertility status, number of living offspring, duration of infertility, the received therapeutic lines for infertility, if any, and other associated clinical manifestations were recorded. Pain history taking included the

evaluation of the presence of pain, its type, location and severity, duration, and type of analgesia received to allow pain relief. For comparative purposes, pain severity was evaluated numerically using a visual pain analogue scale of 10 points. History taking also included previous lines of medical treatment and previous aspiration or surgical interference.

Clinical examination

All women underwent complete gynecological examination and transvaginal (TVU) and transabdominal ultrasonography to detect the lesions. Using TUV (7.5MHz vaginal probe of the General Electric Voluson E8 ultrasound unit; GE Healthcare Austria GmbH, Seoul, Korea) the OMA was described as regards laterality, its greatest diameter, locularity, and the presence of associated lesions or deposits in the tube, ligaments, vaginal wall, Douglas pouch, urinary bladder or rectum. The intra-cystic fluid was described to assure its character as the homogeneous fluid of low-level ground glass echogenicity. The baseline antral follicular count (AFC) was determined.

Exclusion criteria

Exclusion criteria included the presence of irregular menses, manifestations or evidence of premature ovarian failure as judged by AFC and serum anti-Müllerian hormone (AMH) level, bilateral, multilocular, or recurrent cysts, cysts of <3 cm in its greatest diameter, deep endometriosis, cyst suspicious to be malignant, rapidly growing or with abnormal fluid characters, diabetes mellitus, endocrinopathy with special regard to hyperprolactinemia and disturbed thyroid functions, polycystic ovary syndrome, maintenance on hormonal therapy during three months ago. Also, women who had a BMI of >30 kg/m2, associated uterine fibroid, adenomyosis, previous ovarian or pelvic surgeries or pelvic radiotherapy that resulted in pelvic adhesions were excluded as well.

Inclusion criteria

Inclusion criteria are the presence of OMA of diameter wider than 3 cm in infertile women with good OR as manifested by AFC of >4 and serum AMH of >1 ng/ml, regular menstrual cycle, free of exclusion criteria and accepted to participate in the study according to its protocol lines.

Randomization & Grouping

Women who accepted to participate in the study and signed the written informed consent were randomly allocated into three groups according to the procedure, to be provided using a software program with a sequence of 1:1:1 and irregular dropping of sequences to assure randomization. The provided sequences were translated into letters A, B, and C that were printed on cards blindly and were provided to the gynecologist in charge carrying the patient's name and the procedure to be undertaken.

The study protocol

The applied procedures were laparoscopic cystectomy (Lap C) for patients of group A, laparoscopic cyst evacuation and cauterization of (Lap E&C) the endo-cystic wall for group B and transvaginal aspiration and ethanol sclerotherapy (TV AEST) for patients of group C. All patients gave blood samples for the estimation of serum AMH using an Abcam ELISA kit (Cat No. ab267629, Abcam Co., USA), TVS for the determination of AFC before undertaking the procedure, and 3-m and 6-m after the procedure, to be used as a judge for the impact of the procedure on the OR, and this was evaluated as the percentage of change at follow-up estimated levels concerning baseline levels.

Operative procedures

Laparoscopic surgery was performed using the 4-port approach with Storz endoscopic instruments (Karl Storz) under general anesthesia with endotracheal intubation. All patients received prophylactic broad-spectrum antibiotics with induction of anesthesia. The patient was placed supine and a 1-1.5 cm just subumbilical incision is made along the skin crease, Verres needle was inserted to create pneumoperitoneum with a gradual elevation of abdominal pressure till 14 mmHg. A 10-mm trocar and telescope were inserted through the subumbilical incision, and then the other trocars were inserted and the patient was positioned in Trendelenburg position and exploratory laparoscopy and examination of the targeted cyst were performed to confirm the characteristics of the cyst.

A.Laparoscopic cystectomy (Lap C)

The cyst was dissected from any adhesions and its posterior surface is exposed and an incision is made in the outer ovarian cortical layer to expose the cyst. If the cyst was tense, a 0/4 Vicryl purse-string suture was performed and a small incision is made in the wall of the cyst to allow insertion of the suction cannula, to evaluate the cyst to allow cyst grasping, then the cannula was removed and the purse-string suture was tightened to prevent soiling with the cyst contents. Then, two atraumatic grasping forceps were used to pull the cyst, which was dissected carefully by stripping technique and hemostasis was performed using a bipolar coagulation set that was adjusted to provide 30-40W with a shot every 3-5 sec till complete cyst dissection (12). To minimize the use of electrocautery for control of oozing, a layer of Surgicel (ETHICON Surgicel Absorbable Hemostat; 2in x 4in, 10 pieces; Ethicon, Raritan, USA) that was made of oxidized regenerated cellulose and documented to be safe and effective in different surgical settings (13) was applied to the oozing surface. Then, a few simple interrupted sutures using 0/4 Vicryl absorbable suture material were applied to the edge of the cortical incision to control bleeding and reduce the resultant raw surface to minimize adhesions. The cyst was extracted and sent for pathological confirmation of the diagnosis.

B. **Laparoscopic cyst evacuation and cauterization (Lap E&C)**

Through a purse-string 0/4 vicryl stitch applied in the cystic wall, a small snip was made to allow a double-way catheter to be inserted to evacuate the cystic contents and to rinse the cyst with saline till the suction fluid returned clear. Then, the orifice is widened and the inner layer of the cystic wall is cauterized with bipolar energy provided at 40 W to deliver 640 J. Simple oozing was not cauterized and pieces of surgical were applied for control of oozing.

C.Transvaginal ultrasound-guided aspiration and ethanol sclerotherapy:

With the patient in a lithotomy position, the size and site of the cysts were identified, and under US guidance, the needle was passed through the lateral fornix to puncture the cyst and its contents were aspirated through a 16-Fr double lumen oocyte retrieval needle. Normal saline was injected to irrigate the cyst simultaneously while aspirating until a clear aspirate was obtained. Thereafter, 95% ethanol was injected according to cyst volume (García-Tejedor et al., 2015) (14).

Immediate postoperative (PO) care

- Patients of groups A and B were transferred to the post-anesthetic care unit till being able for walking independently and were home-discharged. Time to 1st ambulation and oral intake was recorded.
- PO analgesia was provided as ketorolac intravenous injection as 1:10 dilution. Patients of group C were managed as

outpatient cases and were discharged on completion of the procedure.

- PO treatment included oral antibiotics, anti-inflammatory and analgesic therapy and no hormonal therapy. Patients were asked to attend the outpatient clinic after 1 week and underwent TVU for evaluation of the presence of any pelvic collection; if any.

Follow-up

Patients were re-evaluated at 1-m PO for their preoperative symptoms and signs to evaluate the clinical outcomes. Further, Then, follow-up visits were arranged at the 3rd and 6th PO months, for estimation of serum AMH, determination of AFC and check for OMA recurrence. Pain scores were re-determined during each visit and the frequency of consumption and type of analgesia were reported.

Study outcomes

1. The primary outcome is the impact of the applied procedures on OR as judged by the changes in serum AMH and AFC.
2. The secondary outcomes included:

- The effect of the applied procedures on pain scores and consumption of analgesia.
- The recurrence rate of EO

Statistical analysis

The obtained results were analyzed using analysis of variance between each two groups to explore the differences and Chi-square test for variates' frequencies between each two groups. The cutoff point for significant was considered at P=0.05 with smaller values indicated significance. Statistical analyses were conducted using SPSS software program (IBM, USA, 2017).

Results

The evaluation process encompassed 137 infertile women suspicious to have endometriosis, 47 women were excluded and 90 women fulfilled the inclusion criteria and were randomly divided into the three interventional groups (Fig. 1). The reported inclusion criteria as shown in Table 1 showed insignificant differences between the studied groups.

Table 1: Patients' enrolment data

		Group A	Group B	Group C	P
Age (Years)		32.4±4.1	31.2±3.2	30.4v3.6	0.109
BMI (kg/m²)		29.3±2.3	30.6±2.5	30.2±2.8	0.128
Family history of endometriosis		9 (30%)	6 (20%)	7 (23.3%)	0.656
Smoking		3 (10%)	2 (6.7%)	3 (10%)	0.872
Type of infertility	Primary	11 (36.7%)	7 (23.3%)	9 (30%)	0.53
	Secondary	19 (63.3%)	23 (76.7%)	21 (70%)	
Gravidity	Nulligravida	14 (46.7%)	9 (30%)	11 (36.7%)	0.424
	Once	12 (40%)	14 (46.7%)	16 (53.3%)	
	Twice	4 (13.3%)	4 (13.3%)	2 (6.7%)	
	≥3	0	3 (10%)	1 (3.3%)	
Parity	Nulliparous	21 (70%)	14 (46.7%)	17 (56.7%)	0.161
	Once	5 (16.7%)	12 (40%)	13 (43.3%)	
	Twice	3 (10%)	3 (10%)	0	
	≥3	1 (3.3%)	1 (3.3%)	0	

Living offspring	No	21 (70%)	18 (60%)	22 (73.3%)	0.077
	One	5 (16.7%)	12 (40%)	8 (26.7%)	
	Two	4 (13.3%)	0	0	
Other complaints	No	10 (33.3%)	7 (23.3%)	11 (36.7%)	0.406
	Pelvic tenderness	16 (53.4%)	14 (46.7%)	15 (50%)	
	Abdominal tenderness	4 (13.3%)	9 (30%)	4 (13.3%)	
Duration of pain (years)		6.7±2	5.7±1.7	5.6±2.4	0.073
Cyst diameter (mm)		52.4±8.3	50. 7±9.5	52.6±8.8	0.662

Operative time for patients of group C was significantly (P<0.001) shorter than that for patients of groups A and B with non-significantly (P=0.254) longer operative time for patients of group A. PO durations till 1st ambulation and oral intake and hospital stay were insignificantly longer for group A (Table 2)

Table 2: Operative and immediate PO data of patients of the studied groups

		Group A	Group B	Group C	P1	P2	P3
Operative time (min)		52±7.5	49±6.6	39.5±8	0.106	<0.001	<0.001
Duration till 1st (min)	Ambulation	30.5±8.8	28±6.6	-	0.254	-	-
	Oral intake	62.5±13.8	56.5±12.3	-	0.079	-	-
Duration of hospital stay (h)		5±0.9	5.3±1.4	-	0.327	-	-

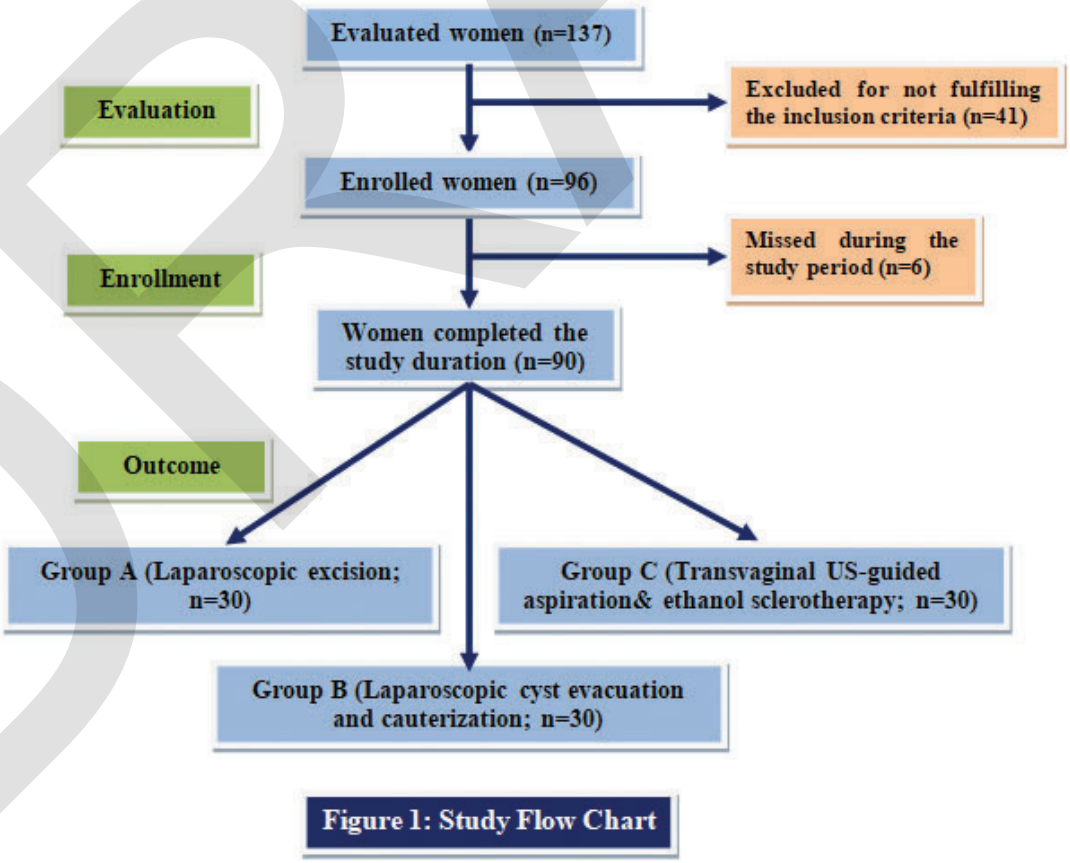

Figure 1: Study Flow Chart

Mean values of total pain scores of the studied patients decreased progressively during follow-up with significant differences in comparison to preoperative scores but with non-significant differences between the three groups. Patients' frequency according to the type of pain showed a progressive decrease at 3-m and 6-m PO and showed non-significant differences between the three groups. The frequency of patients who had dysmenorrhea was decreased at 3-m PO significantly in group A (P=0.038), but insignificantly in other groups, but at 6-m PO the decrease was significant in all groups in comparison to the preoperative frequencies. However, the differences between the reported frequencies of patients who had dysmenorrhea at 3-m and 6-m PO showed non-significant differences in groups B and C, but were significant in group A (P=0.044). The applied procedures significantly decreased the reported frequencies of patients who had dyspareunia at 3-m and 6-m PO in comparison to preoperative frequencies with insignificant differences between the frequencies reported at 3-m and 6-m PO. On the contrary, NMPP at 3-m and 6-m decreased non-significantly in all patients compared to the preoperative frequencies. The frequencies of patients receiving analgesia significantly decreased in all patients at 3-m and 6-m PO in comparison to the preoperative frequencies but with non-significantly lower frequency at 3-m PO compared to 6-m PO (Table 3).

Table 3: The PO pain data of patients of the studied groups

		Group A	Group B	Group C	P
Pain score	Preoperative	6±1.5	6±1.8	6.2±1.9	0.814
	1-m PO	4.6±1.6	4.4±1.8	4.6±1.7	0.716
	P1	0.002	0.001	0.0003	
	3-m PO	3.4±2.1	3.1±2	3.2±1.5	0.768
	P1	<0.001	<0.001	<0.001	
	6-m PO	1.4±1.4	1.7±1.3	1.8±1.5	0.457
	P1	<0.001	<0.001	<0.001	
Dysmenorrhea	Preoperative	20 (66.7%)	17 (56.7%)	22 (73.3%)	0.393
	3-m PO	12 (40%)	10 (33.3%)	17 (56.7%)	0.171
	P1 value	0.038	0.069	0.175	
	6-m PO	5 (16.7%)	7 (23.3%)	11 (36.7%)	0.195
	P1 value	0.0001	0.0084	0.0043	
	P2 value	0.045	0.391	0.121	
Dyspareunia	Preoperative	22 (73.3%)	20 (66.7%)	23 (76.7%)	0.679
	3-m PO	13 (43.3%)	12 (40%)	15 (50%)	0.729
	P1 value	0.018	0.038	0.032	
	6-m PO	6 (20%)	9 (30%)	10 (33.3%)	0.487
	P1 value	<0.001	0.0045	0.0007	
	P2 value	0.052	0.417	0.190	
NMPP	Preoperative	5 (16.7%)	8 (26.7%)	4 (13.3%)	0.389
	3-m PO	3 (10%)	5 (16.7%)	2 (6.7%)	0.455
	P1 value	0.448	0.347	0.389	
	6-m PO	1 (3.3%)	2 (6.7%)	1 (3.3%)	0.227
	P1 value	0.085	0.095	0.161	
	P2 value	0.301	0.447	0.554	

Analgesia	Preoperative	Oral NSAID	15 (50%)	14 (46.7%)	13 (43.3%)	0.442
		Injectable NSAID	13 (43.3%)	16 (53.3%)	12 (40%)	
		Others	2 (6.7%)	0	5 (16.7%)	
	3-m PO	No	6 (20%)	5 (16.7%)	7 (23.3%)	0.429
		Oral NSAID	19 (63.3%)	15 (50%)	12 (40%)	
		Injectable NSAID	5 (16.7%)	10 (33.3%)	10 (33.3%)	
		Others	0	0	1 (3.4%)	
		P1	0.0073	0.04	0.02	
	6-m PO	No	13 (43.3%)	7 (23.3%)	9 (30%)	0.088
		Oral NSAID	15 (50%)	16 (53.4%)	11 (36.7%)	
		Injectable NSAID	2 (6.7%)	7 (23.3%)	10 (33.3%)	
		P1	<0.001	0.005	0.0025	
		P2	0.114	0.639	0.731	

The preoperative serum AMH levels and US-detected AFC showed non-significant differences between patients of the three groups. Unfortunately, all of the applied procedures induced a decrease of serum AMH levels estimated at 3-m PO with non-significant differences in the percentage concerning preoperative levels between the three groups. The extent of decrease in serum AMH was the least in group C and the estimated levels were higher than the levels estimated in samples of patients of group A (P=0.064) and B (P=0.006). Interestingly, serum AMH levels estimated at 6-m PO were increased in samples of patients of group C, while showed a progressive decrease in samples of patients group B and did not change in group A. Estimated serum levels of AMH were significantly lower in samples of group B in comparison to that of patients of groups A (P=0.0008) and C (P<0.001), while were significantly higher in samples of group C (P=0.0003) than in group A. Further, the percentages of decrease of serum AMH estimated at 6-m PO concerning preoperative levels were significantly lower in samples of group C than in samples of group A (P=0.028) and B (P=0.0042) as shown in Table 4 and Figure 2.

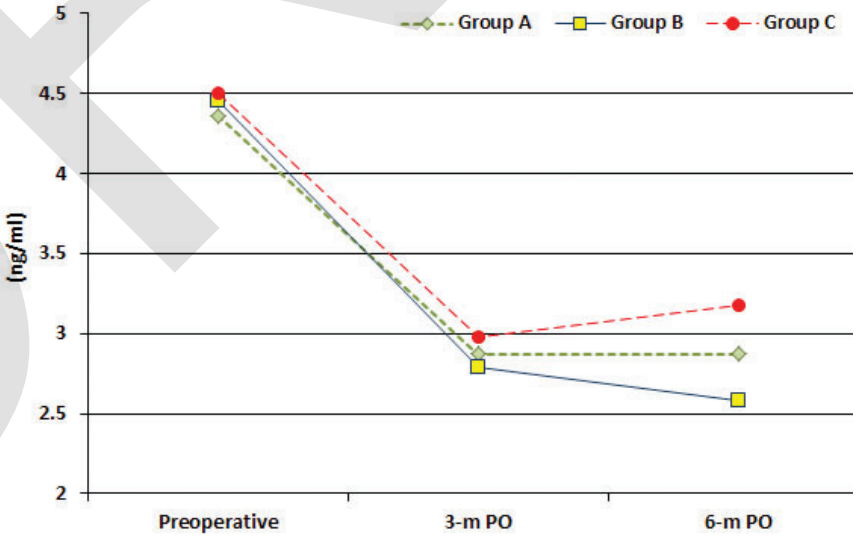

Fig. (2): Mean serum AMH levels estimated at 3-m & 6-m PO in comparison to preoperative levels estimated in studied women

Regarding the AFC, it was decreased in all patients concerning the preoperative count, however, at 3-m PO, the decrease was maximal in group B and the detected count was significantly (P<0.001) lower and the percentage of decrease was significantly (P<0.001) higher than that of other groups with significantly (P=0.0006) lower percentage of decrease in group C than group A. At 6-m PO, the detected AFC increased in all patients, despite being still lower than the preoperative count. The detected AFC in patients of group B was significantly lower compared to patients of groups A (P=0.0094) and C (P=0.0024) with a non-significant difference between groups A and B. Concerning preoperative AFC, the percentage of decrease was significantly (P<0.001) higher in patients of group B than in other groups with significantly (P=0.0256) lower percentage of decrease in patients of group C than patients of group A (Table 4, Fig. 3).

Table 4: The PO serum AMH levels and AFC data of patients of the studied groups

Variants	Time		Group A	Group B	Group C	P1	P2	P3
Serum AMH	Preoperative		4.36±0.8	4.45±1.33	4.5±1.4	0.757	0.642	0.887
	3-m	Level	2.87±0.2	2.79±±0.27	2.98±0.24	0.205	0.064	0.006
		% of change	32.4±10.2	33.3±15.6	28.7±18.2	0.788	0.335	0.295
	6-m	Level	2.87±0.32	2.58±0.29	3.18±0.3	0.0008	0.0003	<0.001
		% of change	32.9±10.4	37.7±16.9	24.7±16.9	0.190	0.028	0.0042
AFC	Preoperative		9.9±1.5	10.1±1.3	9.5±1.5	0.582	0.302	0.100
	3-m	Count	8.5±1.4	6±0.9	8.7±1.5	<0.001	0.589	<0.001
		% of change	14.1±6.6	40.2±8.5	8.5±5.4	<0.001	<0.001	0.0006
	6-m	Count	8.8±1.5	7.9±1	9±1.6	0.0094	0.616	0.0024
		% of change	10.8±10.1	21.4±8	5.2±8.9	<0.001	<0.001	0.0256

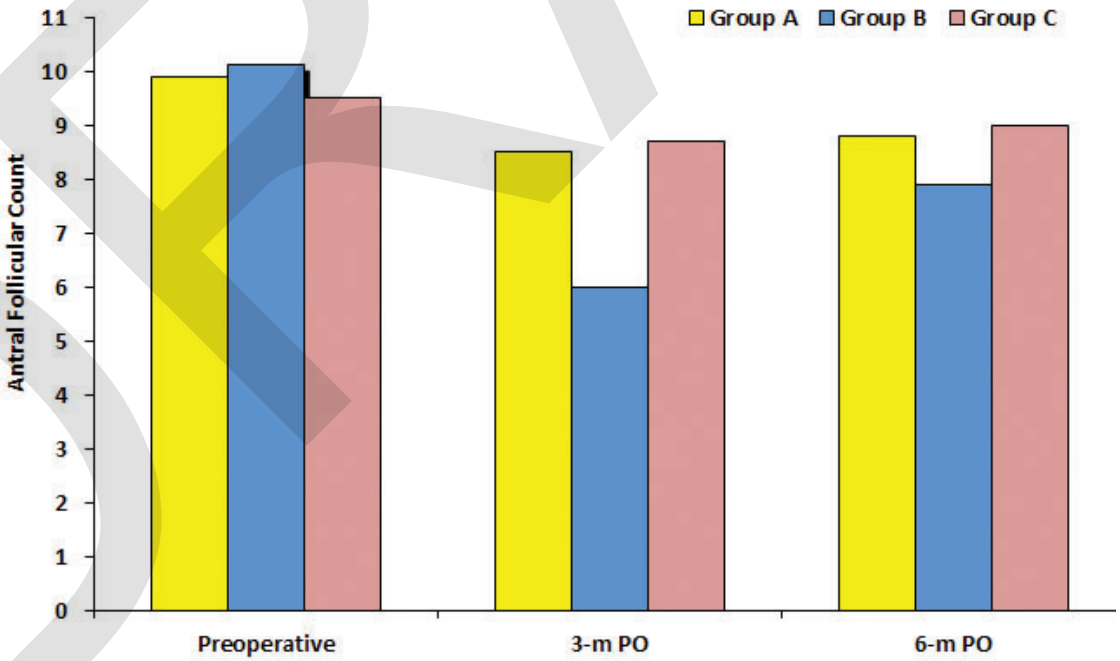

Fig. (3): Mean AFC detected on TVU of the studied women at 3-m & 6-m PO in comparison to preoperative count

During the follow-up period, 19 cases (21.1%) developed recurrent cysts; 9 in group C and 8 in group B with a non-significant (P=0.775) difference between both groups. Only two women in group A had recurrent cysts with a significantly lower incidence of recurrence in comparison to that reported in group B (P=0.037) and C (P=0.019) as shown in Figure 4.

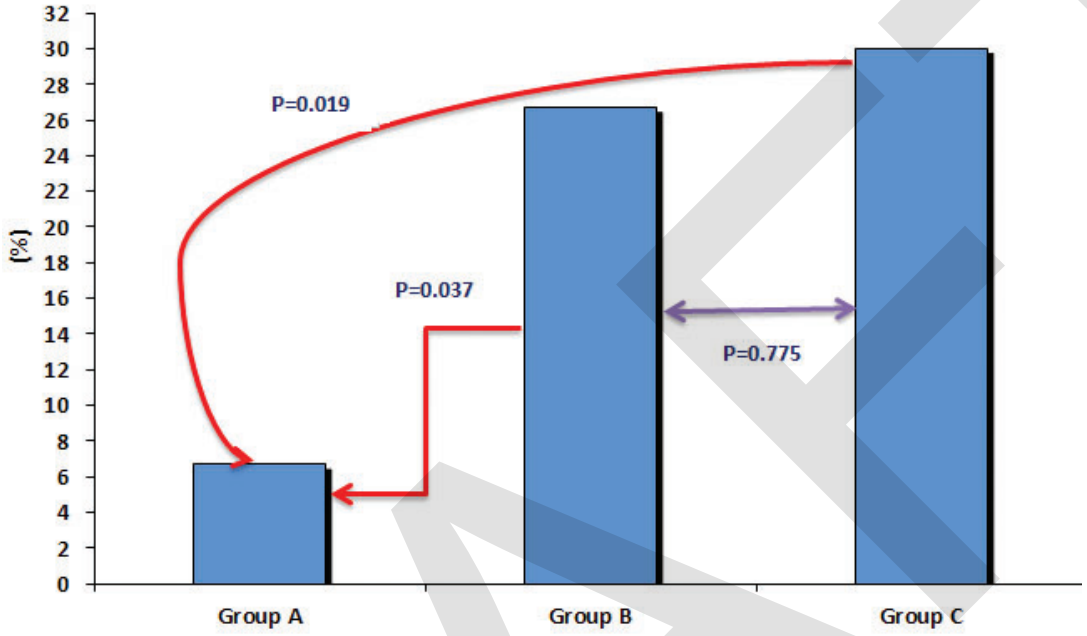

Fig. (4): Cyst recurrence rate at 6-m PO as detected by TVU for women of the studied groups

Discussion

Management of OMAs showed discrepant outcomes, despite the improved constitutional manifestations, management using any of the applied procedures negatively impacted the ovarian reserve as appraised by serum AMH and AFC. This outcome coincided with Mansouri et al. [15] who prospectively reported reduced AMH levels after laparoscopic cystectomy of OMA and found its levels negatively related to the number of cauterizations and type and location of the cyst. Further, Zhang et al. [16] in a meta-analysis of the effect of cystectomy versus ablation on OR of women undergoing treatment of OMAs found both procedures have significant detrimental impacts on OR as judged by PO serum AMH but are dependent on AFC, the ablation causes relatively less damage. Also, Crestani et al., [17] reported a significant decrease in serum AMH after laparoscopic sclerotherapy for OMA during surgery for deep infiltrative endometriosis. Considering pregnancy rate after surgical treatment of OMAs as a judge for OR, Puscasiu et al. [18] reported pregnancy rate after cystectomy, ablation, and drainage of 27%, 32%, and 16% at 12 months, but the probability of conception after simple drainage was increased with the use of assisted reproductive technology. The obtained results and literature spotlight the deleterious effects of ovarian manipulations for the management of any lesion on the OR of the affected women. In support of this assumption, Liang et al. [19] detected significantly lower serum AMH levels at 3-m and 12-m after excision of ovarian mature cystic teratoma and dead-space closure using either conventional or barbed sutures.

The reported impact on OR was procedure-dependent where TV-AEST resulted in the least effects on AMH levels and AFC, and laparoscopic cystectomy non-significantly decreased the

AFC in comparison to TV-AEST at 3-m and 6-m PO, while the outcomes of Lap E&C were worse than the other two procedure for having the highest deleterious effects on the levels of serum AMH and AFC. In support of the procedure-dependency of deteriorated OR after OMA management, Fakehi et al. (20) detected an AMH decline rate of 30% after laparoscopic cystectomy and found the decline was insignificantly related to the demographic characteristics, preoperative AMH, and the amount of CA125

Regarding PO recurrence of OMA as a target for intervention, the total 6-m RR was 21.1% and differentially was 6.7%, 26.7% and 30% after cystectomy, evacuation and sclerotherapy, respectively. The reported low recurrence rate after cystectomy could be attributed to the meticulous dissection while applying the stripping technique. Such attribution goes in hand with Becker et al. [5] who documented that the stripping technique for OMA surgical excision provided lower pain and cyst recurrence rates. In a trial to reduce the RR after OMA cystectomy, Shaltout et al. [21] compared cystectomy versus drainage with and without surgical application to the ovarian or cystic remnants and found surgical effectively reduced the RR after either drainage or cystectomy with a non-significant difference. However, during the current procedures, surgical was applied after Lap E&C and did not reduce the RR in comparison to TV-AEST. Further, the constituents of surgical, which act as hemostatic bio-absorbable material [22] could not explain its effect on recurrence, and the authors who reported such effect did not explain the mechanism through which surgical reduced the RR, especially with drainage.

The obtained results point to the fact that OMA recurrence seemed to be an unavoidable complication for the reported high recurrence rate, irrespective of the procedure, within 6-m and might allow us to consider OMA recurrence as both disease-related and procedure-related. In support of this assumption, Del Forno et al. [23] used estroprogestins or progestins continuous therapy starting immediately after cystectomy in a trial to prevent a recurrence, but reported an RR of 36% during a median follow-up duration of 3.7 years with dysmenorrhea was the first symptom to reappear and affected 43.2% of the studied population.

In a trial to investigate the pathogenesis of OMA recurrence, Xu et al. [24] experimentally and using an animal model, attributed the recurrence of OMA especially after drainage, irrespective of cauterization or sclerotherapy to the presence of living endometrial cells with high adhesion ability in OMA fluid that could leak after drainage or aspiration or rupture of the cyst.

Regarding the effects on the constitutional manifestations, the three techniques significantly reduced PO pain scores concerning preoperative scores with a significant reduction of the frequencies of patients according to the type of pain and type of analgesia consumed. The improved pain scores could be attributed to the removal of cystic fluid with its constituents of inflammatory and nociceptive cytokines and free radicals that proved to be concomitant to endometriosis disease [8, 7, 25, 26, 27].

The current study found complete cystic excision significantly improved the constitutional symptoms than other procedures that depended on the evacuation of the cyst. However, TV-AEST was advantageous for being an outpatient procedure, needing no general anesthesia or hospital admission and thus minimizes the cost, while both laparoscopic procedures share in being more invasive and consuming longer theater time and PO hospital stay and costs. These data supported previous work, wherein Huang et al. [28] documented the effectiveness of TV-AEST of OMA in preserving RR and Miquel et al. [29] found OMAs ethanol sclerotherapy is a rapid outpatient procedure that requires little equipment and low cost.

Conclusion

Each procedure had its cons and pros and this indicated the necessity for proper evaluation of patients' concerns. Thus, if pain is the main concern, transvaginal aspiration and sclerotherapy is the appropriate, if the risk of recurrence is the concern, laparoscopic cystectomy was advocated, while for infertility management, no procedure was advantageous.

Limitations

The small sample size, short duration of follow-up, and the missing evaluation of post-procedural pregnancy rates are the study limitation

Recommendations

Wider-scale studies with long-duration of follow-ups are required to provide more precise guidelines for surgical decision-making. Also, evaluation of the pregnancy rate after each procedure using assisted reproductive technology or not is mandatory.

References

1. DavisD, RasheidS, BoucherZ, Burgueno-Vega D, Molina M: Endometrioma Within the Anterior Abdominal Wall Causing Cyclic Abdominal Pain . Am Surg . 2023;62 (3) 232-240 .
2. Fernandez H, Faivre E, Gervaise A, Deffieux X: Laparoscopic ovarian drilling using a 5-French bipolar energy probe. Fertil Steril. 2010;94:740–1
3. Nirgianakis K, Ma L, McKinnon B, Mueller M: Recurrence Patterns after Surgery in Patients with Different Endometriosis Subtypes: A Long-Term Hospital-Based Cohort Study. J. Clin. Med. 2020; 9:496.
4. Gałczyński K, Jóźwik M, Lewkowicz D, Semczuk-Sikora A, Semczuk A: Ovarian endometrioma—A possible finding in adolescent girls and young women: A mini-review. J. Ovarian Res. 2019; 12(4)104-112.
5. Becker CM, Bokor A, Heikinheimo O, Horne A, Jansen F, Kiesel L, et al.: Endometriosis. Hum. Reprod. Open. 2022:hoac009.
6. Muzii L, Di Tucci C, Di Feliciantonio M, Galati G, Verrelli L, Di Donato V, et al.: Management of endometriomas. Semin. Reprod. Med. 2017; 35:25–30.
7. Kolanska K, Alijotas-Reig J, Cohen J, Cheloufi M, Selleret L, d'Argent E, et al.: Endometriosis with infertility: A comprehensive review on the role of immune deregulation and immunomodulation therapy. Am J Reprod Immunol. 2021; 85(3):e13384.
8. Lin X, Dai Y, Tong X, Xu W, Huang Q, Jin X, et al. : Excessive oxidative stress in cumulus granulosa cells induced cell senescence contributes to endometriosis-associated infertility. Redox Biol. 2020; 30:101431.
9. Simopoulou M, Rapani A, Grigoriadis S, Pantou A, Tsioulou P, Maziotis E, et al.: Getting to Know Endometriosis-Related Infertility Better: A Review on How Endometriosis Affects Oocyte Quality and Embryo Development. Biomedicines. 2021; 9(3):273.
10. Bhagavath B: The current and future state of surgery in reproductive endocrinology. Curr Opin Obstet Gynecol. 2022; 34(4):164-171.
11. Bahrami F, Maheux-Lacroix S, Bougie O, Boutin A: Complications following surgeries for endometriosis: A systematic review protocol. PLoS One. 2023; 18(5):e0285929..
12. Mahmoud MS: Laparoscopic ovarian cystectomy with stripping technique. J Minimally Invasive Gynecology, 2013; 20(6): S181
13. Keshavarzi S, MacDougall M, Lulic D, Kasasbeh A, Levy M: Clinical experience with the surgicel family of absorbable hemostats (oxidized regenerated cellulose) in neurosurgical applications: a review. Wounds, 2013;

25(6):160-7.

14. García-Tejedor A, Castellarnau M, Ponce J, Fernández ME, Burdio F: Ethanol sclerotherapy of ovarian endometrioma: a safe and effective minimal invasive procedure. Preliminary results. Eur J Obstet Gynecol Reprod Biol. 2015; 187:25-9.
15. Mansouri G, Safinataj M, Shahesmaeili A, Allahqoli L, Salehiniya H, Alkatout I: Effect of laparoscopic cystectomy on ovarian reserve in patients with ovarian cyst. Front Endocrinol (Lausanne). 2022; 13:964-975
16. Zhang Y, Zhang S, Zhao Z, Wang C, Xu S, Wang F: Impact of cystectomy versus ablation for endometrioma on ovarian reserve: a systematic review and meta-analysis. Fertil Steril. 2022; 118(6):1172-1182.
17. Crestani A, Merlot B, Dennis T, Chanavaz-Lacheray I, Roman H: Impact of Laparoscopic Sclerotherapy for Ovarian Endometriomas on Ovarian Reserve. J Minim Invasive Gynecol. 2023; 30(1):32-38.
18. Puscasiu L, Mircea O, Hennetier C, Rubod C, Schmied R, Resch B, et al.: Pregnancy rate following endometriomas management by ablation using plasma energy, cystectomy and drainage: A three-arm comparative study. Int J Gynaecol Obstet. 2023; 160(3):947-954.
19. Liang Y, Liu J, Yu Y, Sun J, Yang S, Zhang J: Effect of barbed suture versus conventional suture in laparo-endoscopic single-site cystectomy for ovarian mature cystic teratoma: An ambispective cohort study. Int J Gynaecol Obstet. 2023; 161(1):93-99.
20. Fakehi M, Tanha F, Asgari Z, Mohazzab A, Ghaemi M: Risk Factors for Anti Mullerian Hormone Decline after Laparoscopic Excision of Endometrioma: A Prospective Study. Int J Fertil Steril. 2022; 16(3):167-171.
21. Shaltout MF, Elsheikhah A, Maged A, Elsherbini M, Zaki S, Dahab S, et al.: A randomized controlled trial of a new technique for laparoscopic management of ovarian endometriosis preventing recurrence and keeping ovarian reserve. J Ovarian Res. 2019; 12(1):66-74.
22. Wang A, Rafalko J, MacDonald M, Ming X, Kocharian R: Absorbable Hemostatic Aggregates. ACS Biomater Sci Eng. 2017; 3(12):3675-3686. .
23. Del Forno S, Cofano M, Esposti E, Manzara F, Lenzi J, Raimondo D, et al.: Long-Term Medical Therapy after Laparoscopic Excision of Ovarian Endometriomas: Can We Reduce and Predict the Risk of Recurrence? Gynecol Obstet Invest. 2021; 86(1-2):170-176.
24. Xu X, Chen Y, Yu Q, Wang J, Xu P, Zhu L, et al.: The presence of living endometrial cells in ovarian endometriotic cyst fluid may contribute to the recurrence of endometriosis after surgical excision of endometriomas. J Ovarian Res. 2022; 15(1):89-104.
25. Aksak T, Gümürdülü D, Çetin M, Polat S: Expression of monocyte chemotactic protein 2 and tumor necrosis factor alpha in human normal endometrium and endometriotic tissues. J Gynecol Obstet Hum Reprod. 2021; 50(5): 643-657.
26. Agostinis C, Zorzet S, Balduit A, Zito G, Mangogna A, Macor P, et al.: The Inflammatory Feed-Forward Loop Triggered by the Complement Component C3 as a Potential Target in Endometriosis. Front Immunol. 2021; 12: 693118.
27. Shi J, Zheng Z, Chen M, Shen H, Li M, Shao J: IL-17: an important pathogenic factor in endometriosis. Int J Med Sci., 2022; 19(4): 769-778.
28. Huang L, Chang M, Shiau C, Hsieh T: Changes in anti-müllerian hormone after ultrasound guided aspiration and ethanol sclerotic therapy of ovarian cyst. Taiwan J Obstet Gynecol. 2021; 60(3):509-512.
29. Miquel L, Preaubert L, Gnisci A, Netter A, Courbiere B, Agostini A, et al.: Transvaginal ethanol sclerotherapy for an endometrioma in 10 steps. Fertil Steril. 2021; 115(1):259-260.