The effect of maternal fundal height and abdominal circumference on maternal blood pressure during cesarean delivery

Eslam Albayadi **, Omima T. Taha*, Abdelrahman Soliman**, Mohamed F. Ibrahim*, Shaimaa A. Dahshan**
*Department of Obstetrics and Gynecology, Faculty of Medicine, Suez Canal University, Ismailia, EGYPT.
** Department of anesthesia, Faculty of Medicine, Suez Canal University, Ismailia, EGYPT.
Eslam Albayadi, MD
Lecturer of anesthesia, Department of Anesthesia, Faculty of Medicine, Suez Canal University.
Email: eslamalbayadi@gmail.com
Tel: 01223666764
Omima T. Taha, MD (Corresponding author)
Assistant professor of Obstetrics and Gynecology, Department of Obstetrics and Gynecology
Faculty of Medicine, Suez Canal University.
Email: omimatharwat@yahoo.com
Tel: 002/01223423685
Abdelrahman Soliman, MD
Lecturer of anesthesia, Department of Anesthesia, Faculty of Medicine, Suez Canal University.
Email: abdul_rahman_ahmed@med.suez.edu.eg
Tel: 01001104478
Mohamed F. Ibrahim, MD
Lecturer of Obstetrics and Gynecology, Department of Obstetrics and Gynecology
Faculty of Medicine, Suez Canal University.
Email: egymud@live.com
Tel: 01220770588
Shaimaa A. Dahshan, MD
Lecturer of anesthesia and intensive care, Faculty of Medicine, Suez Canal university
Email: shaimaad2002@med.suez.edu.eg
Tel: 01143410055

Corresponding author:
Omima T. Taha, MD
Assistant professor of Obstetrics and Gynecology, Department of Obstetrics and Gynecology
Faculty of Medicine, Suez Canal University.
Email: omimatharwat@yahoo.com
Tel: 002/01223423685

Abstract

Background: cesarean delivery is the most common surgical procedure practiced in obstetrics. It is associated with hypotension that has maternal and fetal effects.

Objective: This study aimed to determine the correlation between maternal and fetal measures (abdominal circumference, symphyseal fundal height, estimated fetal weight, and amniotic fluid volume) and intraoperative hypotension during cesarean delivery.

Study design: This cross-sectional study was conducted at the Suez Canal University hospital operating theatre from May 2021 to January 2023. We recruited women undergoing elective or emergency cesarean delivery. Maternal and fetal measures were recorded, including abdominal circumference, symphyseal fundal height, fetal weight and amniotic fluid index. Baseline maternal blood pressure and heart rate were determined and repeated measures were done at 1, 5, 10, and 15 minutes of the spinal anesthesia. The dose of ephedrine and the occurrence of nausea/vomiting were recorded.

Results: There was a marked decrease in the systolic, diastolic, and mean arterial BP at 5 minutes (P value < 0.001). Hypotension occurred in 69.4% participants. The abdominal circumference was significantly larger among women who developed hypotension (116.7± 12.5 vs 111.4 ± 10.5, P value 0.007). There was a positive correlation between the abdominal girth and the Ephedrine dose required at 5 minutes only (r= 0.246, P value 0.001).

Conclusion: Maternal abdominal circumference was significantly larger with hypotensive patients and correlated with the ephedrine dose at 5 minutes only.

Keywords: Abdominal circumference; Amniotic fluid index; Cesarean delivery; Fetal weight; Hypotension; Symphyseal fundal height.

Introduction:

Cesarean section (CS) is a commonly practiced obstetrical surgery under spinal anesthesia (1). Spinal

anesthesia is a safe procedure preferred over general anesthesia, which is associated with failed intubation, risk of desaturation and aspiration, and neonatal depression (2). However, spinal anesthesia is associated with nausea, vomiting, and hypotension, even in well-hydrated pregnant women (1). Other complications include total spinal block, post-dural puncture headache, and failed technique (2). Hypotension occurs in 15-33% of cases (3), but increased rates are reported among pregnant women (20- 100%) (4). This would lead to severe consequences such as neonatal hypoxia and acidosis (4). It was explained by the aortocaval compression and cranial spread of the anesthesia exerted by the gravid uterus (5). The latter was noted predominantly in twin pregnancies rather than singleton (6). A large uterus was associated with increased congestion of the epidural veins with a resultant decrease in cerebrospinal fluid (CSF) volume. This plays a crucial role in sensory block level (7), affecting maternal blood pressure (8). The fetal weight and amniotic fluid volume influence the uterine size, which increases the abdominal circumference and symphysial fundal height (9). Other factors contributing to spinal-induced hypotension are maternal age (≥ 35), body mass index (BMI) of more than 25kg/m2, level of spinal injection, the anesthetic dose, and fetal weight (1). Accordingly, we hypothesized that enlarged uterus may cause hypotension during cesarean delivery. This study aimed to evaluate the association between maternal abdominal girth and symphysial fundal height (influenced by fetal weight and amniotic fluid volume) and blood pressure among women undergoing cesarean section.

Methods

This cross-sectional study was conducted at the Suez Canal university hospital operating theatre from May 2021 to January 2023. The study included pregnant women undergoing CS who fulfilled the following inclusion and exclusion criteria: **Inclusion criteria:** a) women aged 18-45 years, b) singleton pregnancy, c) gestational age from 37-41 weeks, d) elective or emergency CS, and e) either booked or unbooked women for antenatal care. **Exclusion criteria:** a) prelabor rupture of membranes, b) gestational hypertensive disorder in the current pregnancy, c) chronic hypertension, d) history of cardiac or renal disease, e) fetal death, f) excessive intraoperative bleeding, g) need for additional oxytocin doses, h) failed spinal block and need for general anesthesia, and i) antepartum hemorrhage.

Eligible patients signed informed written consent before recruitment. They had preoperative evaluation including personal data (age, weight, height, BMI, occupation, level of education), obstetric history (parity, mode of delivery), and any chronic illness. The indication for cesarean delivery was reported. Routine preoperative laboratory investigations were withdrawn (complete blood count, coagulation profile, and group and save).

Abdominal ultrasound was done for all participants to determine fetal biometry, estimated fetal weight (EFW), and amniotic fluid index (AFI). The scan was performed at 38 weeks gestation for booked patients while unbooked patients had their scans on the day of delivery. All participants undergoing elective CS have kept nothing per oral for 8 hours before delivery. The fundal height was measured from the symphysis pubis's upper border to the uterus's upper border while the patient was lying supine in bed. The abdominal circumference (AC) was measured at the lower border of the umbilicus. These measurements were reported in the labor and delivery ward before shifting the patient to the operating theatre. The same obstetrician and anesthesia team that obtained these measurements was blinded to the results.

In the operating theatre, patient monitoring included pulse oximetry, non-invasive blood pressure, and electrocardiogram.

An 18-gauge cannula was inserted, and a preoperative infusion of ringer lactate 10ml/kg was started 15 minutes before spinal anesthesia. Primary heart rate, systolic, and diastolic blood pressure (BP), and mean arterial pressure (MAP) were recorded.

The patients were asked to sit, and sterilization of the back was done. Dural puncture was done using a 25-gauge spinal needle by a paramedian approach at the level of L4-5. Hyperbaric bupivacaine (2 ml) and 20 µg fentanyl were injected after ensuring cerebrospinal fluid flow. The patient was turned supine with a slight left lateral tilt (15◦) immediately after completing spinal anesthesia.

The sensory level was evaluated in the midline at 1, 5, 10, and 15 minutes after completing spinal anesthesia. Regular intravenous fluids were administered at a rate of 100 ml/10 minutes. The patients were monitored for heart rate, systolic and diastolic blood pressure, and mean arterial pressure at the same intervals mentioned above. Oxytocin (5 units) was administered following fetal delivery.

The occurrence of hypotension, nausea, and vomiting was recorded. Hypotension was defined as > 20% decrease in systolic BP from the primary record and was managed by injection of ephedrine 6 mg IV (10). This would be repeated with persistent hypotension after 2 minutes. The total dose of ephedrine was recorded.

The primary outcome measure was the association between abdominal girth, symphyseal fundal height, and maternal hypotension after spinal anesthesia. Secondary outcome measures included the incidence of hypotension, the maximum level of sensory block, the ephedrine dose, and the incidence of nausea and vomiting.

The sample size was calculated at a significance level of 95%and an error level of 20% with a correlation coefficient between abdominal girth and systolic blood pressure of 0.47 (11). A drop-out proportion of 10% was added to the raw result giving a final count of 180 women.

Ethical approval: This study was conducted after approval of the research ethics committee of the faculty of medicine, Suez Canal University, on 26/4/2021, with a reference number of 4538#.

Statistical analysis:

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). Categorical data were represented as numbers and percentages. For continuous data, they were tested for normality by the **Kolmogorov-Smirnov test**. Quantitative data were expressed as a range (minimum and maximum), mean, standard deviation, and median. **Student t-test** was used to compare two groups for normally distributed quantitative variables while **One way ANOVA** test was used for comparing the different studied categories and followed by **Post Hoc test (Tukey)** for pairwise comparison. **Pearson coefficient was used** to correlate between two normally distributed quantitative variables. The significance of the obtained results was judged at the 5% level. P value was considered significant when < 0.05.

Results

One-hundred eighty- five women were eligible for the study. Two women refused to participate in the study, while the other three were excluded because of failed spinal anesthesia and received general anesthesia.

The mean age of the studied population was 28.8 ± 5.5. The mean parity and number of previous CS were 1.8 ± 1.5 and 1.4 ± 1.3, respectively. Almost half of the recruited women had middle education (48.3%), and many were housewives (90%). The mean BMI was 31.7 ± 5.3 (Table 1).

The preoperative measures included SFH,

abdominal circumference, AFI, and EFW, with reported means of 37.6 ± 5.1, 115.1 ± 12.1, 10.2 ± 3.3, and 3328.9 ± 447, respectively. Eighty-five (47.2%) and 95 (52.8%) patients had emergency and elective CS, respectively (Table 2).

There was a marked decrease in the systolic, diastolic, and mean arterial BP at 5 minutes (P value < 0.001). The greatest ephedrine dose was given at 5 minutes also (4.8 ± 6.1) (Table 3).

The median level of sensory block was at T6 (range 4-12) at 1 minute and T4 thereafter.

One hundred twenty-five (69.4%) developed hypotension. The abdominal circumference was significantly larger among women who developed hypotension (116.7± 12.5 vs 111.4 ± 10.5, P value 0.007) (Table 4).

There was a positive correlation between the abdominal girth and the Ephedrine dose required at 5 minutes only (r= 0.246, P value 0.001). There was no significant correlation between abdominal girth and the level of sensory block. The symphyseal fundal height, fetal weight, and AFI showed non-significant correlations with either the ephedrine dose or the level of spinal sensory block (Table 5).

Nausea occurred in 26 (14.4%) patients, while vomiting occurred in 9 (5%). There was a significant difference in the abdominal circumference among women who had vomited than those who did not (112.9 ± 15.1 and 114.7 ± 11.9, respectively, with a p-value of 0.049) (Table 6).

Discussion

There was a marked decrease in the systolic, diastolic, and mean arterial BP, with a greater ephedrine dose at 5 minutes. Hypotension occurred in 69.4% ff the studied population. the abdominal circumference was significantly larger among those who had hypotension. Variable incidences of hypotension at CS were reported as 25% (12) and 52% (13). An earlier study failed to demonstrate a correlation between AC and hypotension after spinal anesthesia (7). This would be explained by different AC measurements between studies (115.1 ± 12.1 vs. 98.4 ± 6.8 cm). Another study reported no correlation between the AC in women with singleton and twin pregnancies and hypotension during CS, despite increased AC in twin gestations (6). Contradicting results were reported where there was no difference in hypotension between maternal AC (7, 14). However, the decline in MAP was prominent in those with large AC (14).

Other factors that affected the maternal hemodynamic state included dehydration, capacity and tone of the peripheral vasculature, blood volume, cardiac output, level of sensory block, the addition of fentanyl to bupivacaine, and the extent of aortocaval compression (15, 16). Additionally, different definitions of hypotension between studies and rapid treatment of hypotension by the anesthesiologist to avoid fetal harm explain these different results (17).

The abdominal circumference correlated significantly with the ephedrine dose given at 5 minutes. However, there was no significant correlation between it and the level of sensory block. A previous study reported a significant correlation between the maternal abdominal circumference and the level of sensory block, especially at 5 minutes while no correlation was reported with the ephedrine dose or the maximum sensory block (7). Another one reported an increased level of spinal block in women with large AC (15). Measuring the AC in the supine position revealed a significant correlation with the level of sensory block at 5, 10, and 15 minutes after spinal anesthesia (13); however, we measured the AC in the standing position.

The AC reflects the intraabdominal pressure exerted by the gravid uterus. Greater AC increased pressure on the inferior vena cava (IVC) and decreased CSF volume in the lumbosacral region (7). Failure to demonstrate a correlation between the

AC and the sensory block level would be rendered to the dose of bupivacaine used. The bupivacaine commonly pools in the lower part of the thoracic curvature. Higher levels of spinal block could be achieved when using increased doses of bupivacaine to reach the upper thoracic region (19). The reported level of sensory block was at T6 at 1 minute and was recorded at T4 for further measurements. Additional factors that might play a role include the dose of the anesthetic, volume, level of its injection, needle type, patients' age and weight, anatomy of the spine, and intra-abdominal pressure (20). However, these factors contribute a little to the level of sensory block. Also, they have unpredictable and out-of-control effects (21). It has been mentioned that the level of sensory block is significantly affected by the baricity of the injected bupivacaine and the patients' position after injection (19). We adopted the same technique for spinal anesthesia and the same dose of bupivacaine to avoid bias.

The symphyseal fundal height as a reflection of the uterine size, fetal weight, and AFI showed non-significant correlations with hypotension, the ephedrine dose, or the level of spinal sensory block. This agreed with previous results where the symphyseal fundal height (SFH) did not correlate with the level of sensory block (22, 23). However, a significant correlation was noted between the SFH and fetal weight and the ephedrine dose (22). Another study reported increased fetal weight associated with hypotension during CS (24). This was explained by increased aortocaval compression and hypotension needing ephedrine with higher SFH (22). The lack of correlation between EFW and intraoperative hypotension was rendered to the fact that the uterine size would be affected by other factors such as uterine anomaly, AFI, or uterine fibroids other than the fetus alone. This makes the effect imparted by the fetus tiny (22).

Nausea/vomiting occurred in 35/180 (19.4%) patients. An earlier study reported a higher rate (20/40, 50%) (7). The abdominal circumference was significantly lower among women who had vomited than those who had not. Nausea and vomiting would be explained by the consequences of hypotension as cerebral ischemia, vagal stimulation, and intraoperative visceral traction (22).

Strength and limitations: The anesthetic team was blinded to the preoperative measures. We used a fixed dose of bupivacaine, which might cause hypotension. The study was carried out as a prospective study. We recruited a relatively large sample.

Conclusion

Maternal AC influenced the level of sensory block at 5 minutes. There was no correlation between the other measurements and the level of sensory block or ephedrine dose.

Conflict of interest: None

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Table (1): Distribution of the studied cases according to demographic data (n = 180)

Age (Mean ± SD)		28.8 ± 5.5
Parity (Mean ± SD)		1.8 ± 1.5
Education	**None**	37 (20.6%)
	Middle	87 (48.3%)
	High	56 (31.1%)
Occupation	**Housewife**	162 (90%)
	Worker	3 (1.7%)
	Employee	15 (8.3%)
Weight (Mean ± SD)		84.3 ± 14.4
Height (Mean ± SD)		162.6 ± 5.6
BMI (Mean ± SD)		31.7 ± 5.3
Number of previous CS (Mean ± SD)		1.4 ± 1.3

BMI: body mass index; CS: cesarean delivery

Table (2): Preoperative evaluation of the studied population: (n = 180)

AC (Mean ± SD)		115.1 ± 12.1
SFH (Mean ± SD)		37.6 ± 5.1
AFI (Mean ± SD)		10.2 ± 3.3
EFW (Mean ± SD)		3328.9 ± 447
Indications for CS	**Emergency**	85 (47.2%)
	Elective	95 (52.8%)

SFH: symphyseal fundal height; AFI: amniotic fluid index; EFW: estimated fetal weight; CS: cesarean section

Table (3): Descriptive analysis of the studied cases according to different parameters (n = 180)

	Preoperative	**1min**	**5min**	**10min**	**15min**	**p**
Systolic Mean ± SD.	124 ± 15.8	112.8 ± 20	101.4 ± 21.5	107.7 ± 16.9	107.5 ± 14.6	<0.001 *F
Diastolic Mean ± SD.	76.6 ± 11.6	65.3 ± 15.1	58 ± 14.6	61.2 ± 11.9	59.2 ± 11.8	<0.001 *F
HR Mean ± SD.	98.6 ± 13.6	104.6 ± 20.8	94.8 ± 20.3	95.8 ± 16.6	96.4 ± 14.7	<0.001 *F
Mean blood pressure Mean ± SD.	92.2 ± 12.1	78.4 ± 14.4	70.8 ± 15.5	75.5 ± 12.3	73.8 ± 10.5	<0.001 *F
Ephidren dose Mean ± SD.	–	3 ± 5.6	4.8 ± 6.1	1.6 ± 3.8	1.5 ± 3.4	

HR: heart rate, MAP: mean arterial blood pressure, SD: **Standard deviation, F: F test (ANOVA) with repeated measures**, Sig. bet. periods was done using **Post Hoc Test (Bonferroni)**

Table (4): Relation between hypotension and maternal and fetal parameters

	Hypotension		P value
	Yes (125)	No (55)	
AC	116.7 ± 12.5	111.4 ± 10.5	0.007*t
SFH	37.5 ± 5.5	37.8 ± 4.1	0.779t
EFW	3333.5 ± 401.1	3318.3 ± 541.1	0.852t
AFI	10.2 ± 3.2	10.4 ± 3.7	0.680t

AC: abdominal circumference, SFH: symphyseal-fundal height, EFW: estimated fetal weight, AFI: amniotic fluid index, t: Student T test.

Table (5): Correlation between AC, SFH, EFW, and AFI with Ephedrine dose and spinal sensory block (n = 180)

	AC		SFH		EFW		AFI	
	r	P	R	P	r	P	r	P
Ephedrine dose								
1 min	0.065	0.383	0.012	0.872	0.005	0.944	-0.021	0.775
5 min	0.246*	0.001*	0.044	0.557	0.115	0.124	0.105	0.162
10 min	0.028	0.709	-0.057	0.450	-0.059	0.432	0.029	0.695
15 min	0.081	0.281	-0.003	0.965	0.047	0.529	-0.003	0.969
Spinal sensory block								
1 min	0.024	0.753	-0.007	0.924	0.049	0.514	0.018	0.812
5 min	-0.086	0.250	0.001	0.989	-0.002	0.975	-0.053	0.476
10 min	-0.077	0.308	-0.046	0.544	-0.014	0.854	-0.056	0.453
15 min	-0.144	0.054	-0.118	0.114	-0.099	0.188	-0.142	0.056

r: Pearson coefficient

*: Statistically significant at $p \leq 0.05$

Table 6: Distribution of nausea and vomiting according to study parameters:

	Nausea (26, 14.4%)		P value	Vomiting (9, 5%)		P value
	Yes	No		Yes	No	
AC	116.1 ± 12.1	115 ± 12.2	0.653t	112.9 ± 15.1	114.7 ± 11.9	0.049*t
SFH	37.2 ± 4.8	37.7 ± 5.2	0.675t	39 ± 5.3	37.5 ± 5.1	0.396t
EFW	3379.6 ± 517.8	3320.3 ± 435.3	0.533t	3582.2 ± 280.7	3315.5 ± 450.7	0.081t
AFI	10.8 ± 3.7	10.1 ± 3.2	0.385t	11.4 ± 3.5	10.2 ± 3.3	0.258t

t: student T-test

The effect of advanced maternal age on pregnancy outcomes: A prospective study

Rana Magdy Ibrahim[1], Mohamed Alaa eldin Mosbah[1]. Abdelhady Abdelhady Zayed[1], Maher Elesawy Kamel[1]
Department of [1]Obstetrics and Gynecology
Faculty of Medicine, Mansoura University, Egypt

Abstract

Background: Women who are 35 years of age or older at the anticipated date of delivery are considered to have advanced maternal age (AMA). This cutoff age was chosen in light of decreasing fertility data and growing concerns about the increased likelihood of genetic defects in the progeny of pregnant women over 35. An increased risk of perinatal deaths, spontaneous abortions, pregnancy complications like diabetes mellitus (DM) and hypertension (HTN), interventions like cesarean deliveries (CS), and foetal adverse events like preterm birth (PTB), low birth weights (LBW), congenital anomalies, and NICU admission is linked to older mothers.

Objective: Evaluation of the impact of advanced maternal age on maternal, obstetric, fetal, and perinatal outcomes was the main objective of the study.

Patients and methods: This study was a prospective cohort study at the Obstetrics and Gynecology Department at Mansoura University Hospitals. This study was conducted on a total of 82 primigravida women who were divided into 2 groups. The study group included 41 women aged 35 years or more. The control group included 41 women aged 20 years to 34 years.

Results: there was a significant difference between both groups about cesarean (CS) deliveries, preterm birth, high mean arterial pressure, and high Rate Pressure Product.

Conclusion: advanced maternal age is accompanied by a higher rate of preterm birth, cesarean delivery, high mean arterial pressure, and rate pressure product more than younger age women.

Keywords: advanced maternal age, obstetric, maternal, fetal, perinatal outcomes, cesarean delivery, preterm birth.

Introduction

A woman is deemed to have an advanced maternal age (AMA) if she is 35 years of age or older at the beginning of her pregnancy or at the time of delivery. There's a tendency in rich countries where older primigravida women decide not to have children out of choice or due to underlying

Corresponding author:
Rana Magdy Ibrahim
Mobile: (+20) 1005382447
E-mail: Ranamg67@gmail.com

infertility, but multiparous women are also choosing to continue having children [1].

Very AMA (VAMA) could be described as women over 40, while extremely AMA (EAMA) is utilized to characterize females over 45. These subcategories of advanced maternal age have also been established [2]. The selection of this age threshold was motivated by dwindling fertility data and growing apprehension over the likelihood of genetic defects in children born to pregnant mothers over 35 [3].

In wealthy countries, ladies in their advanced maternal age are probably primiparous. Unlike underdeveloped nations, where poverty, the cultural predilection for large kids, and inefficient family planning measures make childbirth at AMA the most likely among multiparous women [4].

Preeclampsia (PE), stillbirth, and foetal growth restriction (FGR) are among the pregnancy complications linked to advanced maternal age. These complications can be caused by endothelial damage, which ages with the mother, decreased maternal hemodynamic adaptation during pregnancy, and decreased uterine blood vessel compliance [5].

The older the mother, the higher the chance of premature delivery. Placental pathology explains this and might also explain why preeclampsia is more common in AMA. This adds to the list of iatrogenic factors contributing to premature labor induction [6]. Age significantly raises the risk for CD, whether it is an emergency or elective procedure. Fetal malposition, anomalies during delivery, underlying medical co-morbidities, and even mother requests are some of the factors that explain this [7].

As a mother's age rises, there is a greater chance of spontaneous abortion during the first 14 weeks of pregnancy [8]. Pregnancy at an advanced mother age is strongly linked to unfavorable newborn outcomes, which include preterm delivery, early infant mortality, LBW, and admission to the neonatal intensive care unit (NICU) [9]. The unfavorable consequences stem from insufficient cardiovascular adaptation during gestation, impeding the hemodynamic adjustments necessary to sustain the fetus [10].

Aim of the work

Analyzing the effects of advanced mother age on perinatal, obstetric, fetal, and maternal outcomes throughout pregnancy was the aim of this study.

Study design

This study was a prospective cohort study conducted at Obstetrics and Gynecology Department at Mansoura University Hospitals, from June 2021 to June 2022.

This study included primigravida women aged 20 years or more after the exclusion of the patients who refused to be included in this study, patients aged less than 20 years, and patients with medical disorders such as (pre-existing DM, chronic HTN, or autoimmune diseases).

Study population

The studies cases consisted of 82 primigravida women who were divided into 2 groups. The study group consisted of 41 pregnant women aged 35 years or more. Forty-one pregnant women, ages 20 to 34, made up the control group.

Additionally, the research group was partitioned into two subgroups: the very advanced age group, which included those older than 40, and the advanced age group, which included those between 35 and 40.

Methods

- After getting written consent from all participants. We documented personal, menstrual, obstetric, and history of surgical operation.

- Every prenatal appointment included a general examination to rule out chronic hypertension, monitor blood pressure to diagnose hypertensive diseases of pregnancy after 20 weeks of gestation and assess the mother's body mass index to identify obesity. When necessary, local and abdominal exams were performed.
- Between 24 and 28 weeks of gestation, all pregnant females were evaluated for gestational DM (GDM) using an oral glucose challenge test weighing 50 grams. A three-hour oral glucose tolerance test with a 100g oral glucose load was administered to females who had abnormal glucose challenge test results (140 mg/dL). When blood glucose levels are above 95 mg/dL during fasting, 130–140mg/dL one hour after eating, and 120mg/dL two hours after eating, GDM is diagnosed.
- Pregnancy-induced hypertension, gestational diabetes mellitus (GDM), preeclampsia, early pregnancy bleeding, antepartum hemorrhage, oligohydramnios or polyhydramnios, ICU hospitalization, sepsis, and postpartum hemorrhage were among the obstetric outcomes that were documented.
- Premature rupture of membranes, miscarriage, PTB, and CS or vaginal delivery were among the maternal outcomes that were documented.
- Congenital defects, intrauterine growth limitation, intrauterine fetal mortality, and stillbirth were among the fetal outcomes that were documented.
- The NICU hospitalization, early neonatal mortality, LBW (less than 2500g), very LBW (less than 1500g), and macrosomia (more than 4000g) are the categories into which perinatal outcomes were categorized.

Outcomes

The primary outcome was to detect the difference between the advanced age group and the younger age group about maternal, obstetric, fetal, and perinatal outcomes. The secondary outcome was to detect the difference between the advanced age group and the very advanced age group concerning maternal, obstetric, fetal, and perinatal outcomes.

Ethical consideration

The study protocol was approved by the Institutional Review Board (IRB), code no MS.21.06.1542, Date: 07/07/2021, Faculty of Medicine, Mansoura University.

Every patient received an explanation of the procedure's specifics. At every stage of the study, participants gave their informed written agreement regarding confidentiality and personal privacy. The current study was the only use of the data that was gathered.

Statistical Analysis

IBM Corp., 2020 provided the IBM-SPSS software, which was used for data entry and analysis. Armonk, NY: for Windows, Version 27.0.

The notation for qualitative data was N (%). Shapiro-Wilk's test was first used to determine if quantitative data was regularly distributed. If $p>0.050$, the data was considered normally distributed. Boxplots were examined to see whether any significant outliers (extreme values) were present. The interquartile range (Q1, or 25th percentile, to Q3, or 75th percentile) and median for quantitative data were reported as non-normally distributed.

To compare qualitative data between groups, the chi-square, Fisher's exact, or Fisher-Freeman-Halton exact tests were utilized. The quantitative data between the two groups was compared by utilizing the non-parametric Mann-Whitney U-test. The impact of predictor factors on the probability of an event, such as a mother or newborn being admitted to the ICU or NICU, was

determined using binary logistic regression.

If the p-value is less than 0.050, the results of any test that is employed will be deemed statistically significant.

Results

This study had 82 primigravida and was divided into two groups; study group (A) included 41 pregnant women aged 35 years or more. Control group (B) included 41 pregnant women aged 20 years to 34 years.

No statistically significant difference was detected between both groups concerning residence, educational level, type of conception, abnormal OGTT, DBP, Heart Rate (HR), Hemoglobin level, and platelet count. There was a statistically significant difference in previous relevant surgery such (p =.043), systolic blood pressure (SBP) (p=.019), mean arterial pressure (p=.033), Rate Pressure Product (RPP) = (SBP × heart rate) (p=.018), and body mass index (<.001) (Table 1).

Table (1): Comparisons of baseline characteristics of older age (A) vs. younger age groups (B).

Characteristic	Group A		Group B		Total		p-value
Categorical	N	%	N	%	N	%	
Residence Rural Urban	 28 13	 68.3 31.7	 28 13	 68.3 31.7	 56 26	 68.3 31.7	1.00
Education level Low Middle High	 4 25 12	 9.8 61 29.3	 2 17 22	 4.9 41.5 53.7	 6 42 34	 7.3 51.2 41.5	.076
Type of conception ART Natural	 5 36	 12.2 87.8	 4 37	 9.8 90.2	 9 73	 11 89	1.00
Previous relevant surgery	8	19.5	2	4.9	10	12.2	**.043**
Abnormal OGTT	4/37	10.8	1/38	2.6	5/75	6.7	.200
Numerical	**Median**	**Q1-Q3**	**Median**	**Q1-Q3**	**Median**	**Q1-Q3**	**p-value**
SBP (mmHg)	120	115-150	110	110-140	120	110-140	**.019**
DBP (mmHg)	80	75-90	80	70-90	80	70-90	.072
MAP (mmHg)	93.3	88.3-113.3	90	83.3-106.7	93.3	83.3-107.5	**.033**
Heart rate (beats/ minute)	88	80-90	84	80-90	87	80-90	.824
RPP	10920	9350-13350	9680	8800-11760	10480	9000-12390	**.018**
BMI (kg/m^2)	30	28-32.5	25	22-30	29.5	24-31.3	**<.001**
Hemoglobin level (g/dl)	10.9	10.4-11.6	10.6	9.6-11.1	10.9	10-11.3	.099
Platelet count $\times 10^9/L$	280	187-300	240	192-294.5	273	189.8-300	.192

There was a significant difference between the studied groups regarding delivery by cesarean section either elective or urgent (p=.028) being significantly higher in the advanced age group as compared to the younger age group (89.2% vs. 68.4%, respectively) and preterm birth (p=.001) being significantly higher at advanced age group as compared to younger age group (29.3% vs. 2.4%, respectively) and there was not a statistically significant difference as regards to the risk of miscarriage and PROM (Table 2).

Table (2): Comparisons of maternal outcomes in older age group (A) vs. younger age group (B).

	Group A		Group B		Total		p-value
	N	%	N	%	N	%	
Maternal outcomes							
Mode of delivery Vaginal delivery CS [elective, urgent]	4 33 [12, 21]	10.8 89.2	12 26 [7,19]	31.6 68.4	16 59 [19, 40]	21.3 78.7	**.028**
Miscarriage	4	9.8	3	7.3	7	8.5	1.00
PROM	3	7.3	6	14.6	9	11	.482
Preterm birth	12	29.3	1	2.4	13	15.9	**.001**

There was no statistically significant difference between both groups concerning obstetric outcomes including (all types of bleeding, sepsis, oligohydramnios, polyhydramnios, GDM, PET, HELLP syndrome, PIH, and ICU admission) (Table 3).

Table (3): Comparisons of obstetric outcomes in older age group (A) vs. younger age group (B).

Obstetric outcomes	Group A		Group B		Total		p-value
	N	%	N	%	N	%	
Bleeding APH PPH Bleeding of early pregnancy	8 2 2 4	19.5 4.9 4.9 9.8	8 1 4 3	19.5 2.4 9.8 7.3	16 3 6 7	19.5 3.7 7.3 8.5	1.00 1.00 .678 1.00
Sepsis	1	2.4	0	0	1	1.2	1.00
Oligohydramnios	4	9.8	7	17.1	11	13.4	.331
Polyhydramnios	3	7.3	1	2.4	4	4.9	.616
GDM	4	9.8	1	2.4	5	6.1	.359
PET	10	24.4	8	19.5	18	22	.594
HELLP syndrome	2	4.9	1	2.4	3	3.7	1.00
PIH	5	12.2	3	7.3	8	9.8	.712
ICU admission	6	14.6	2	4.9	8	9.8	.264

There was no statistically significant difference between the studied groups about fetal and perinatal outcomes (low/ very low birth weight, IUGR, NICU admission, early neonatal death, and congenital anomaly) (Table 4).

Table (4): Comparisons of fetal and perinatal outcomes in older age group (A) vs. younger age group (B).

Fetal and perinatal outcomes	Group A		Group B		Total		p-value
	N	%	N	%	N	%	
$$$Birth weight	38		37		75		.666
Very low	3	7.9	4	10.8	7	9.3	
Low	7	18.4	3	8.1	10	13.3	
Normal	28	73.7	30	81.1	58	77.3	
NICU admission	15	38.5	10	24.4	25	31.3	.175
IUGR	3	7.3	4	9.8	7	8.5	1.00
Early neonatal death	4	9.8	1	2.4	5	6.1	.359
Congenital anomaly	3	7.3	1	2.4	4	4.9	.616
Numerical	**Median**	**Q1-Q3**	**Median**	**Q1-Q3**	**Median**	**Q1-Q3**	**p-value**
*Birth weight (g)	3200	2300-3500	3500	2800-3500	3500	2500-3500	.388

There was no statistically significant difference between the advanced age group and very advanced age group concerning type of conception, or mode of delivery "although 100% of cases in the very advanced age group were delivered by cesarean section but with no statistical difference due to decreased number of cases at this group", miscarriage, PROM, and preterm birth (Table 5).

Table (5): Comparisons of maternal outcomes in advanced vs. very advanced age groups.

Maternal outcomes	Advanced		Very advanced		Total		p-value
	N	%	N	%	N	%	
Type of conception							.563
ART	5	15.2	0	0	5	12.2	
Natural	28	84.8	8	100	36	87.8	
Mode of delivery							.556
vaginal delivery	4	13.8	0	0	4	10.8	
cesarean delivery	25	86.2	8	100	33	89.2	
[elective, urgent]	[9,16]		[3,5]		[12,21]		
Miscarriage	4	12.1	0	0	4	9.8	.569
PROM	3	9.1	0	0	3	7.3	1.00
Preterm birth	9	27.3	3	37.5	12	29.3	.672

There was no statistically significant difference between the advanced age group and the very advanced age group about obstetric outcomes including (all types of bleeding, sepsis, oligohydramnios, polyhydramnios, GDM, PET, HELLP syndrome, PIH, and ICU admission) (Table 6).

Table (6): Comparisons of obstetric outcomes in advanced vs. very advanced age groups.

Obstetric outcomes	Advanced		Very advanced		Total		p-value
	N	%	N	%	N	%	
Bleeding	8	24.2	0	0	8	19.5	.318
Placenta previa	2	6.1	0	0	2	4.9	1.00
PPH	2	6.1	0	0	2	4.9	1.00
Bleeding of early pregnancy	4	12.1	0	0	4	9.8	.569
Sepsis	1	3	0	0	1	2.4	1.00
Oligohydramnios	4	12.1	0	0	4	9.8	.569
Polyhydramnios	3	9.1	0	0	3	7.3	1.00
GDM	4	12.1	0	0	4	9.8	.569
PET	7	21.2	3	37.5	10	24.4	.672
HELLP syndrome	2	6.1	0	0	2	4.9	1.00
PIH	5	15.2	0	0	5	12.2	.563
ICU admission	5	15.2	1	12.5	6	14.6	1.00

There was no statistically significant difference between the advanced age group and the very advanced age group regarding fetal and perinatal outcomes including (low/ very low birth weight, IUGR, NICU admission, early neonatal death, and congenital anomaly) (Table 7).

Table (7): Comparisons of fetal and perinatal outcomes in advanced vs. very advanced age groups.

Fetal and perinatal outcomes	Advanced		Very advanced		Total		p-value
	N	%	N	%	N	%	
Birth weight	30		8		38		.088
Very low	1	3.3	2	25	3	7.9	
Low	5	16.7	2	25	70	18.4	
Normal	24	80	4	50	28	73.7	
NICU admission	12	38.7	3	37.5	15	38.5	1.00
IUGR	2	6.1	1	12.5	3	7.3	.488
Early neonatal death	2	6.1	2	25	4	9.8	.165
Congenital anomaly	3	9.1	0	0	3	7.3	1.00
Numerical	**Median**	**Q1-Q3**	**Median**	**Q1-Q3**	**Median**	**Q1-Q3**	**p-value**
Birth weight (g)	3400	2500-3500	2650	1125-3500	3200	2300-3500	.170

Discussion

Pregnancies in females who are 35 years of age or older at the time of conception or birth are classified as AMA. It is becoming very common in affluent nations, mostly observed in older primigravida women who choose to put off having children out of a desire to live a longer life or because of underlying infertility, however, multiparous women are also doing so (1).

It is crucial to assess if and how AMA influences pregnancy outcomes and the maternal and foetal health, given the notable increase in the proportion of older moms. While the majority of research revealed a significant correlation between age and the outcome of pregnancy, other studies yielded inconsistent findings (11).

According to our study, there was no statistically significant difference between

the studied groups' baseline characteristics—such as place of residence, level of education, and mode of conception.

Our investigation revealed a statistically significant difference in the mean arterial pressure (P=.033), systolic blood pressure (P=.019), and rate pressure product (RPP) (p=.018) between the groups under consideration.

More and more people are using the double (rate-pressure) product (DP) as a proxy for cardiac activity and myocardial oxygen demand. It is calculated by multiplying HR by SBP. The robust correlation between left ventricular mass and DP has revealed its role in predicting the risk of acute myocardial infarction (AMI) and cardiovascular disease in hypertensive individuals (12).

In our study, the AMA group's mean RPP was 10920, whereas the younger age group's mean was 9680. This finding was consistent with research that indicated older women were predicted to have a higher incidence of AMI (13). RPP can be used to predict cardiovascular risk in women with AMA.

In terms of delivery mode, our study revealed that there was a statistically significant difference (p=0.028) between the groups under investigation; among the older group, 89.2% had an urgent or elective cesarean section, compared to 68.4% who were younger.

Although, 100% of the cases of the VAMA group were delivered by CD in comparison with 86.1% of the AMA group but with no statistically significant differences.

In accordance with the findings of Rydahi and associates, who revealed that older females had a greater possibility of CD at AMA (aOR=2.18) and VAMA (aOR=3.64). (15). The high risk of CD at AMA is explained by atherosclerosis of the uterine arteries, a decline in oxytocin receptors with age, and inadequate myometrium contractility, which results from the aged uterus's decreased ability to produce uterine contractions (14).

In our study, Preterm delivery showed statistically significantly higher incidence among older age than younger age group (29.3% versus 2.4%) (p=0.001).

Also, preterm delivery was 37.5 in the VAMA group versus 27.1% in the AMA group but of no statistically significant differences.

A significant retrospective analysis supported Waldenstrom et al.'s findings, showing that AMA and VAMA raised the odds of preterm delivery regardless of parity, both spontaneously occurring and when medically recommended. From 35 to 39 years old, age-related relationships were statistically significant but less strong across all parity groups (15).

However, even after accounting for confounding variables, a major retrospective study from Canada by Fuchs et al. and his colleagues indicated that in comparison with pregnancy at 30-34 years of age, pregnancy at a VAMA increased the risk of PTB by 1.2. Moreover, the age-group distribution of premature labor was found to be "U" shaped, indicating that young mother age is a predisposing factor for preterm labor in addition to AMA (16).

The risk of GDM in the AMA group was 9.8% group versus 2.4% in the younger age group and 12.1% in the AMA group versus 0% in the VAMA group with no statistically significant difference.

However, in comparison to women under 35, the GDM incidence at AMA and VAMA is 1.62 (P<0.001) and 2.1 (P<0.001) higher, respectively, according to the retrospective study conducted by Khalil et al. and colleagues (17). Increasing obesity rates in older adults, which are associated with lower insulin sensitivity, might help to explain this (18).

In our study, the risk of PET in the AMA group was 24.4% group versus 19.5% in the younger age group and 21.2% in the AMA

group versus 37.5% in the VAMA group with no statistically significant difference.

The univariate analysis of the retrospective study by Nieto and his colleagues which compared women under 30 in the AMA, VAMA, and EAMA groups to a control group, only revealed a higher risk for PET at EAMA (OR=3.32). When confounding factors (obesity, utilization of ART, tobacco smoking, chronic HTN, and parity) were adjusted for using a multivariable logistic regression, age and PET did not, however, substantially correlate (19).

Regarding the comparison of fetal and perinatal outcomes, our study revealed that; there was no significant difference between studied groups as regards birth weight, congenital anomalies, NICU admission, and early neonatal death.

The risk of miscarriage was 9.8% in the AMA group versus 7.3% in the younger age group and 12.1% in the AMA group versus 0% in the VAMA group with no statistically significant difference.

Magnus et al., in contrast, discovered that there was a considerable variation in the probability of miscarriage with mother age. Women between the ages of 25 and 29 had the lowest miscarriage risk (9.8%), while women over the age of 45 had the greatest risk (53.6%). The absolute lowest risk was at age 27 (9.5%). The risk was 15.8% for moms under the age of twenty (8).

The risk of congenital anomalies in our study was 7.3 in the AMA group versus 2.4% in the younger group and 9.1% in the AMA group versus 0% in the VAMA group with no statistically significant difference.

In line with Goetzinger et al.'s retrospective analysis of congenital anomaly prevalence in AMA pregnancies with euploid babies, they discovered that AMA was protective against congenital malformations (aOR 0.59, 95% CI 0.52–0.66). The "all or none" theory, which postulates that anatomically normal foetuses have a better survival rate at advanced oocyte age, can explain this phenomenon (20).

Nevertheless, it was shown that the rate of foetal chromosomal aberrations in spontaneous miscarriages at VAMA was substantially more than in women of a younger age (60.6% versus 33.5% in women 30-34). This Chinese study examined the connection between 497 pregnancies' spontaneous miscarriages, AMA, and chromosomal abnormalities (21).

The results of our study regarding the risk of NICU admission were 38.5% in the AMA group VS. at 24.4% in the younger group and 38.7% in the AMA group VS. 37.5% in the VAMA group with no statistically significant difference.

The AMA and VAMA groups, on the other hand, had higher rates of NICU admission; their respective AORs were 1.68 (95% CI 1.42–2.15, $P < 0.01$) and 1.52 (95% CI 1.21–1.92, $P < 0.01$) were higher. Kahveci and his colleagues assessed the effects of advanced maternal age on the perinatal and neonatal results of nulliparous singleton pregnancies in Turkey (3).

The risk of FGR in our study was 7.3% in the AMA group vs. 9.8% in the younger age group and 6.1% in the AMA group vs. 12.5% in the VAMA group with no statistically significant difference.

However, FGR was described as birth weight below the 5th percentile. Lean et al. found in a major study that women with AMA had a 1.23 (95% CI 1.01–1.52) higher risk of FGR; among women over 40, the risk increases by 1.53 (95% CI 1.07−2.20) This might be explained by incorrect placentation, which causes FGR but is unrelated to a decline in oocyte fitness (22).

The limitation of our study included the small sample size in the studied group and larger future studies are needed.

Conclusion

Advanced maternal age is accompanied by a higher rate of preterm birth, Cesarean delivery, high mean arterial pressure, and high Rate Pressure Product than younger age women.

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Combined Insulin Sensitizers as Double-Weapon to detonate PCOS-induced Vicious Circle

Mohammad Samir Mohammad Badr MD*†, Walid Mohamed Elnagar MD*, Amr Ahmed Abdelrhman MD*
Department of Obstetrics & Gynecology, Faculty of Medicine, Zagazig University, Egypt* & Sulaiman AlRajhi University, KSA†

Abstract

Objectives : assessment of the outcomes of women had polycystic ovary syndrome (PCOS) received 6-month therapy of metformin (Met) or combination of myoinositol (MI)/D-chiro-inositol (DCI) or both.

Patients & Methods : 210 PCOS women underwent clinical, US and laboratory work-up to determine baseline T0-data and were divided into 3-equal groups: Met group received met 500 mg tab three times daily, MI-group received MI/DCI combination in 40:1 ratio twice daily and MM-group received both Met and MI therapy and at the end of 6-m (T6) therapy, all patients were re-evaluated to assess gynecological outcomes including resumption of regular menstrual pattern (RMP) and getting pregnant for PCOS-infertile women wishing for pregnancy and metabolic and endocrinal outcomes including impact on body mass index (BMI), glucose tolerance (GT), homeostasis model assessment of insulin resistance (HOMA-IR) index, and hyperandrogenemia.

Results: At T6, 126 women resumed RMP and 15.8% of women got pregnant. T6-BMI was significantly decreased in all women with improved GT and only 15 of 67 insulin resistant women were still resistant. The frequency of women had serum total testosterone (TT) >0.8 ng/ml was decreased from 35.2% to 13.3% with significantly lower levels of TT at T6-samples than T0-samples. The percentages of change in the studied parameters were higher with MM-therapy than either Met or MI-therapy. The rate of resumption of RMP and percentages of change of BMI, HOMA-IR and serum TT were positively correlated but showed negative relation to the use of insulin sensitizer monotherapy. The Receiver Operating Characteristic (ROC) curve analysis defined high percentage of decrease of HOMA-IR index as positive and the use of monotherapy as negative predictor for getting RMP.

Conclusion: Insulin sensitizers' therapy is effective and safe for control PCOS-associated endocrinal, metabolic and gynecological deregulations. Inositol is a synergistic additive to metformin and this combination results in favorable outcomes than monotherapy.

Corresponding author:
Walid Mohamed Elnagar,
Whitewhale1977@gmail.com,
01224252626

Introduction

Polycystic ovary syndrome (PCOS) is a common and complex disease affecting women of reproductive age [1] and is characterized by its complex pathological symptoms and mechanisms resulting in endocrine and metabolic dysfunction [2]. Ovulatory dysfunction, increased ovarian volume and/or polycystic ovary morphology with concomitant menstrual abnormalities, chronic anovulation, and decreased fertility or infertility are the characteristic gynecological manifestations of PCOS [3].

PCOS is highly associated with various metabolic and endocrinal disorders, because of the shared common risk factors; PCOS and metabolic-associated fatty liver disease (MAFLD) are concomitant and at the time of PCOS diagnosis, screening for MAFLD is mandatory because it is mostly asymptomatic [4]. The relation between PCOS and epithelial ovarian tumors is biologically plausible because obesity, hyperandrogenemia and fertility disorders, which are inherent to PCOS, are also risk factors for hormone-sensitive tumors [5].

Despite the high prevalence of PCOS, medical treatment is a dilemma because no available pharmacological option can tackle the entire spectrum of PCOS manifestations [6]. Metformin (Met) has pleiotropic actions, but is mainly, used for its glucose-lowering effects for treatment and prevention of type-2 diabetes mellitus (DM), gestational DM and PCOS [7]. Met through decreasing food intake and body weight, and improving lipid profile can influence multiple cardiovascular risk markers, improve MAFLD, modulate inflammatory markers, and possibly reduce cancer risks [8]. Met is widely used because of its positive glycemic control, safety profile, and low costs, but is not well accepted by all patients due to its common gastrointestinal adverse effect [9].

Myo-inositol (MI) is biosynthesized from all MI-containing compounds, by cyclic synthesis and through hydrolysis of phosphatidylinositol [10]. MI protects against MAFLD through reduction of hepatic accumulation of triglycerides [11] and decreases left ventricular stiffness through removal of cholesterol from the myocardium and increasing cardiac function [12]. Hyperglycemia, hypertriglyceridemia and insulin resistance (IR) induces inositol imbalance with deficiency of D-chiro-inositol (DCI) and higher MI levels and DCI administration might improve this imbalance and IR [13].

Objectives

This prospective study compared the effects of MI/DCI combination alone or in conjunction with Met on PCOS-associated endocrinal and metabolic disturbances.

Patients & Methods

All women presented to Gynecology outpatient clinic or Infertility clinic, Zagazig University Hospital with manifestations suggestive of PCOS were clinically evaluated for the presence of at least two of the Rotterdam criteria for diagnosis of PCOS (14, 15) and women had these criteria were evaluated.

Baseline clinical data collection

Collection of clinical data included age, residence, level of education, type of work, marital and fertility statuses, and if infertility was the main complaint. History taking included inquires about the presence of risk factors as sedentary lifestyle, emotional stress and family history of PCOS, obesity-related medical disorders especially DM or MAFLD, history of previous treatment for PCOS and its outcomes. Menstrual pattern such as infrequent menstrual periods with interval between menstrual periods of ≥35 days or amenorrhea which is defined as absence of vaginal bleeding for at least 90 days was discussed

Exclusion criteria

Women had other manifestations of metabolic

syndrome, cardiac manifestations of PCOS, maintained on other therapies or prepared for /received laparoscopic intervention for PCOS, receiving scheduled exercise, lipid-lowering therapies, or maintained on diabetogenic drugs for any other indications were excluded from the study. Also, women had morbid obesity with body mass index (BMI) >35 kg/m2, causes other than PCOS for infertility, manifest DM, hepatic or pancreatic diseases, refused to participate in the study or missed during follow-up were excluded from the study.

Inclusion criteria

Women with diagnostic criteria of PCOS and free of exclusion criteria, accepted to participate in the study and signed the written fully informed consents were included in the study

Study Protocol

The enrolled women were randomly allocated into three groups according to the scheduled therapy for each group. Women were evaluated at time of enrolment (T0) and at the end of 6-m duration of therapy (T6) for:

1. Metabolic disturbances including

- Obesity as judged by BMI which is determined using the equation of weight divided by square height in meter (16).
- Deregulated glucose tolerance as determined using the 75-oral glucose tolerance test (OGTT) that entails estimation of fasting blood glucose (FBG) and postprandial blood glucose (PPBG) at 1-h and 2-h in response to taking 75-g oral glucose and interpreting the results according to the recommendations of the International association of diabetes and pregnancy study groups (IADPSG) (17) as follows: FBG ≥92 mg/dl, 1-h PPBG ≥180 mg/dl and 2-h PPBG ≥153 mg/dl indicates glucose intolerance.
- Insulin resistance was evaluated using homeostasis model assessment of insulin resistance (HOMA-IR) (18) with index ≥2 was indicated IR (19).

2. Clinical hyperandrogenemia was evaluated as

- The presence and severity of hirsutism according to the modified Ferriman-Gallwey (FG) map (20) that divided the body into 9 areas, each area was evaluated using 5-point scale with higher score indicating more extensive hair growth and a score of ≥8 indicates hyperandrogenemia.
- Acne scoring was determined as previously by Adityan et al. (21) as comedones, occasional papules (Grade 1), papules, comedones, few pustules (Grade 2), predominant pustules, nodules, abscesses (Grade 3) and mainly cysts, abscesses, widespread scarring (Grade 4).

3. Ovarian morphology was assessed using either transabdomial or transvaginal ultrasonography (TAU, TVU) for ovarian volume and number of ovarian follicles; ovarian volume >10ml per ovary and/or detection of >12 follicles of 2-9 mm are diagnostic of PCOS.
4. Laboratory evaluations: blood samples were obtained for estimation of FBG & PPBG, fasting serum insulin (FSI), total testosterone (TT) and dehydro-epiandrosterone (DHEA); serum level of TT >0.8 ng/ml indicates biochemical hyperandrogenemia.

Treatment protocol

Patients were divided into three treatment groups; Met-group received metformin hydrochloride (Cidophage tab, Chemical Industrial Development, Cairo Egypt) 500 mg three times daily, MI-group received tablets containing MI/DCI combination in dose of myoinositol 550 mg and DCI 13.8 mg in a 40:1 ratio with 0.2 mg folic acid (Viocyst

tab, Viomix Pharmaceutical Industries, Egypt) twice daily and MM-group received combination of the treatment received by patients of groups Met and MI. Treatment for all groups was continued for six months with no lifestyle changes, dieting regimens or exercise protocols.

Ethical considerations

The study protocol was approved by the departmental committee and discussed freely with women who had PCOS, and those accepted to participate in the study, receive the assigned therapy and attend for follow-up after 6-m had signed a written fully informed consent to undergo the preliminary clinical examination and US and lab evaluations. At the end of 6-m drug therapy and defining the study outcomes, the final approval by the Local Ethical Committee was obtained (ZU-IRB #11195-5/11-23 and the study was registered at Clinical trial.com: NCT06170463. As a reference for lab findings, 16 women who are free of gynecological problems, accepted to give blood samples and meet exclusion criteria were chosen from those attending the family planning clinic.

Randomization & Blindness

Randomization of the enrolled women was conveyed by an assistant who was blinded about the study protocol by computer sequencing system with 1:1:1 sequence and even-numbers dropping to provide the sequence of cases for each group. Patients' sequence was transformed to group title; Met, MI and MM and women were asked to choose an envelope that contained the drug regimen to be followed and scheduled follow-up visit for each woman. The author was blinded about the sequencing process and patients' distribution and drug regimen used. At the 6-m visit and after patients' evaluation, patients' sequence was declared and outcomes were interpreted.

Statistical analysis

One-way ANOVA test and Chi-square test (X2 test) were used to assess the significance of the results. Evaluation of predictability was conducted using the Receiver characteristic curve. The significance of the area under ROC curve (AUC) was assessed in relation to area under the reference curve using IBM® SPSS® Statistics (Version 22, 2015; Armonk, USA). Significance of the results was determined using a P-value at cutoff point of 0.05.

Results

Evaluation process excluded 27 women; 8 women were maintained on PCOS treatment regimens, 4 women had manifest DM, 5 women had bariatric surgery for obesity and eight women had concomitant causes for infertility, while two women refused to participate in the study. Another 15 women did not attend the follow-up visit and 18 women at follow-up assured receiving therapy intermittently and these 34 women were also excluded from the study. At 6-m visit, 70 women per group were evaluated and revision of their enrolment data showed insignificant differences between the three groups (Table 1, Fig. 1).

Table 1: Patients' enrolment data

		Met	MI	MM	P
Age (years)		27.8±4	28.2±4.7	27.5±4.3	0.636
Residence	Urban	38 (54.3%)	31 (44.3%)	43 (61.4%)	0.124
	Rural	32 (45.7%)	39 (55.7%)	27 (38.5%)	
Education	Illiterate	19 (27.1%)	22 (31.4%)	14 (20%)	0.299
	Literate	51 (72.9%)	48 (68.6%)	56 (80%)	

Work	Housewives	26 (37.1%)	18 (25.7%)	24 (34.3%)	0.714
	Officers	17 (24.3%)	22 (31.4%)	19 (27.1%)	
	Workers	15 (21.5%)	19 (27.2%)	14 (20%)	
	Farmers	12 (17.1%)	11(15.7%)	13 (18.6%)	
Menstrual pattern	Infrequent cycles	57 (81.4%)	53 (75.7%)	55 (78.6%)	0.712
	Amenorrhea	13 (18.6%)	17 (24.3%)	15 (21.4%)	
Marital status	Single	16 (22.9%)	10 (14.3%)	12 (17.1%)	0.407
	Married	54 (77.1%)	60 (85.7%)	58 (82.9%)	
Infertility as the main complaint among married women	Yes	32 (45.7%)	28 (40%)	35 (50%)	0.161
	No	22 (31.4%)	32 (45.7%)	20 (28.6%)	

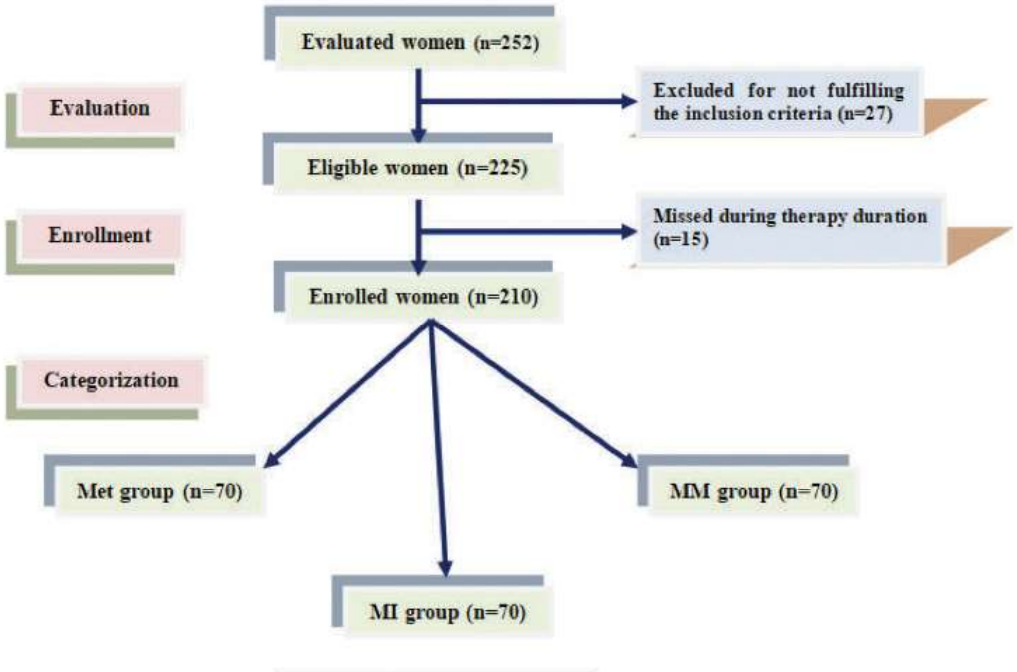


Figure 1: Study Flow Chart

At the end of 6-m therapy (T6), 126 women (60%) resumed regular menstrual cycles and 67 women (31.9%) had infrequent cycles, while 17 women (8.1%) were still had amenorrhea with significantly (P<0.001) reduced deregulated pattern among women of all groups. The frequency of women resumed regular cycles was significantly higher with MM therapy compared to that reported with Met (P=0.041) and MI (P=0.0007) therapies with non-significantly higher frequency with Met therapy (Table 2, Fig. 2).

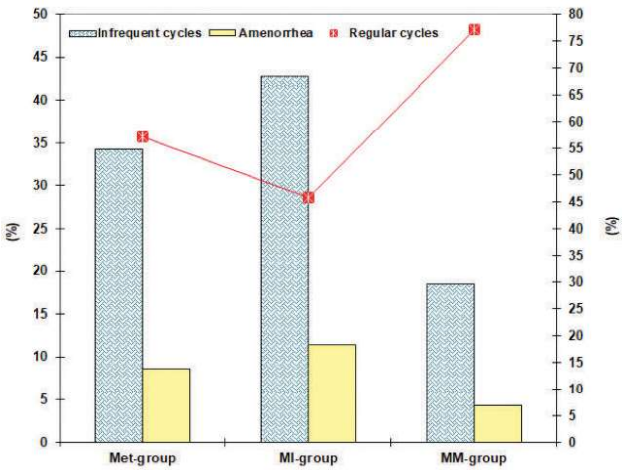


Fig. (2): Patients' distribution according to menstrual outcomes at the end of 6-m therapy

Among women presented with infertility as the main complaint (n=95), 15 women got pregnant for a pregnancy rate of 15.8% that showed insignificant differences between the three groups despite being highest among MM-group (Table 2).

Table 2: Gynecological outcomes

			Met	MI	MM	Total
Menstrual pattern	T0	Regular	0	0	0	0
		Infrequent	55 (78.6%)	53 (75.7%)	57 (81.4%)	165 (78.6%)
		Amenorrhea	15 (21.4%)	17 (24.3%)	13 (18.6%)	45 (21.4%)
	P1			0.687	0.673	
	P2				0.410	
	T6	Regular	40 (57.1%)	32 (45.7%)	54 (77.1%)	126 (60%)
		Infrequent	24 (34.3%)	30 (42.9%)	13 (18.6%)	67 (31.9%)
		Amenorrhea	6 (8.6%)	8 (11.4%)	3 (4.3%)	17 (8.1%)
	P1			0.398	**0.041**	
	P2				**0.0007**	
Pregnancy outcome at T0 for women seeking for pregnancy		Pregnant	5 (15.6%)	3 (10.7%)	7 (20%)	15 (15.8%)
		Not pregnant	27 (84.4%)	25 (89.3%)	28 (80%)	80 (84.2%)
		Total	32 (100%)	28 (100%)	35 (100%)	95 (100%)
		P1		0.577	0.641	
		P2			0.316	

The used therapies significantly (P<0.001) reduced women's BMI at T6 in relation to T0-BMI with non-significant difference between the studied groups both at T0 (P=0.264) and T6 (P=0.209). The percentage of decrease in T6-BMI in relation to T0-BMI was significantly (P<0.001) higher in women of Met and MM groups compared to that of women of MI-group with significantly (P=0.0001) higher in women of MM-group than in women of Met-women (Fig. 3).

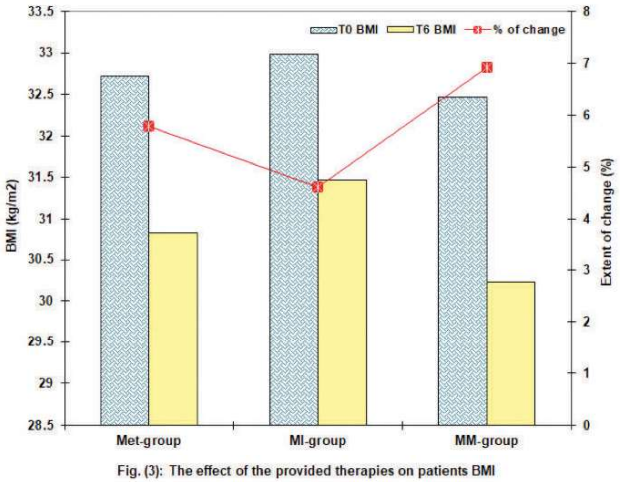


Fig. (3): The effect of the provided therapies on patients BMI

The BG levels estimated at T0 and T6 showed non-significant intergroup differences, apart from FBG that showed significant (P=0.0035) intergroup difference. The estimated BG levels at T6 decreased significantly (P<0.001) in all patients in relation to levels estimated at T0. The percentage of decrease in FBG levels estimated in T6 samples in relation to its T0 levels showed significant (P<0.001, respectively) variance between women of the three groups and was significantly higher with Met- and MM-therapies than MI-therapy (P=0.0009 & <0.001, respectively) with insignificantly (P=0.231) higher percentage of decrease with MM than Met therapies. Despite the significantly lower 1-h and 2-h PPBG levels estimated in T6 than T0 samples of all patients, the intergroup differences were insignificant regarding both the levels and the percentage of decrease.

The results of 75-OGTT conveyed at T0 detected glucose intolerance (GI) of all

women as evidenced by BG levels higher than the diagnostic limits of the IADPSG in all T0 samples; fasting and 1-h and 2-h PP. However, at T6 estimations, 167 patients (79.5%) still had fasting GI, 189 patients (90%) had 1-h GI and 111 patients (52.9%) had 2-h GI with insignificant distribution between the three groups regarding the frequency of women showed FBG level of ≥92 mg/dl or 1-h PPBG level of ≥180 mg/dl. On contrary, the frequency of GI women on 2-h PPBG estimations was significantly lower in MM-group than in MI-group with insignificant difference in distribution of GI women of Met-group and other groups.

Estimated serum insulin levels decreased in all women in T6 samples, but the differences between levels estimated in T0 and T6 samples were insignificant with insignificant intergroup differences both in T0 and T6 samples. However, the percentage of decrease in T6 serum insulin showed significant variance between the three groups and was significantly (P<0.001) higher with MM therapy than Met and MI therapies and significant (P=0.0016) difference in favor of MI therapy. At T0 time, 67 women and at T6 time only 15 women were insulin resistant with HOMA-IR ≥2 with insignificant differences between the distributions of IR women among the three groups. The T6-IR frequency was significantly lower than T0 frequency in the three groups but was lowest with MM therapy. Despite of the insignificant intergroup differences regarding the HOMA-IR index, it was decreased in all patients and the extent of decrease showed significant (P<0.001) intergroup difference and was significantly higher in group MM compared to groups Met (P=0.0004) and MI (P<0.001) with significantly (P=0.027) higher extent of decrease with Met than MI (Table 3, Fig. 4).

Table 3: Metabolic outcomes

Variates Groups			Met	MI	MM	P
BMI (kg/m²)		T0	32.7±1.8	33±2.5	32.5±1.5	0.264
		T6	30.8±1.6	31.5±2.5	30.2±1.5	0.209
		P1	<0.001	<0.001	<0.001	<0.001
		% of change	5.8±1.6	4.62±1.07	6.93±1.65	
		P2		<0.001	0.0001	
		P3			<0.001	
75-OGTT	FBG (mg/dl)	T0	123.7±7.5	125±9.4	124.4±10.6	0.707
		T6	110±12.8	116.2±14.3	109.1±13.2	0.0035
		P1	<0.001	<0.001	<0.001	
		% of change	11.25±7.12	7.27±6.79	12.5±5	<0.001
		P2		0.0009	0.231	
		P3			<0.001	
	1-h PPBG (mg/dl)	T0	187.5±4.6	187.2±5	188.7±5.4	0.177
		T6	166.5±8.8	167.6±8.7	168.58.3	0.389
		P1	<0.001	<0.001	<0.001	
		% of change	11.2±3.9	10.4±4.7	10.7±4.7	0.576
		P2		0.294	0.452	
		P3			0.788	
	2-h PPBG (mg/dl)	T0	165±7	162.6±6.3	164.5±5.1	0.056
		T6	154.9±9.3	151.7±8.9	152.6±7.8	0.083
		P1	<0.001	<0.001	<0.001	
		% of change	6.1±4.1	6.7±3.3	7.2±4.1	0.242
		P2		0.326	0.115	
		P3			0.451	

	Parameter	FBG			1-h PPBG			2-h PPBG		
Glucose intolerance	Group	Met	Met	MM	Met	Met	MM	Met	Met	MM
	Intolerant	56 (80%)	59 (84.3%)	52 (74.3%)	63 (90%)	61 (87.1%)	65 (92.9%)	43 (61.4%)	38 (54.3%)	30 (42.9%)
	Tolerant	14 (20%)	11 (15.7%)	18 (25.7%)	7 (10%)	9 (12.9%)	5 (7.1%)	27 (38.6%)	32 (45.7%)	40 (57.1%)
	P1		0.508	0.421		0.591	0.543		0.392	**0.028**
	P2			0.144			0.255			0.176
HOMA-IR index	Serum fasting insulin levels	T0		5±1.65		4.83±1.7		5.05±1.68		0.737
		T6		4.83±1.63		4.64±1.6		4.74±1.6		0.858
		P1		0.499		0.472		0.265		
		% of change		3.66±1		4.25±1.18		6.26±2		<0.001
		P2				0.0016		<0.001		
		P3						<0.001		
	IR incidence	T0		22 (31.4%)		22 (31.4%)		23 (32.9%)		0.978
		T6		10 (14.3%)		8 (11.4%)		7 (10%)		0.727
		P1		0.016		0.004		0.001		
	Mean index	T0		1.52±0.52		1.5±0.56		1.57±0.59		0.713
		T6		1.31±0.47		1.34±0.51		1.29±0.5		0.886
		P1		0.013		0.075		0.003		
		% of change		14.06±7.64		11.1±6.88		18±4.84		<0.001
		P2				0.017		0.0004		
		P3						<0.001		

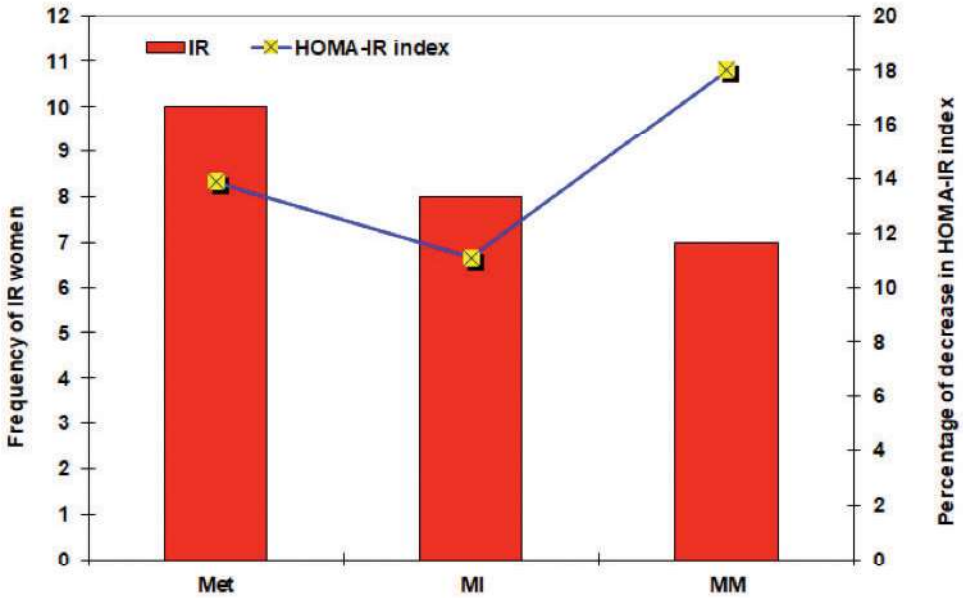


Fig. (4): The frequency of insulin resistant women at T6 evaluation and the percentage of change in HOMA-IR index at T6 in relation to T0

The frequency of women had biochemical hyperandrogenemia, defined as serum TT of ≥0.8 ng/ml, was 35.2% at T0 and was decreased at T6 to 13.3% with significantly lower frequency at T6 than at T0 in all groups. However, the extent of decrease in the frequency of women had hyperandrogenemia showed insignificant differences between the studied groups both at T0 and T6. Moreover, estimated serum TT and DHEA levels were significantly decreased in women of the three groups at T6 in comparison to levels estimated at T0. The inter-group difference was insignificant at T0 for both TT and DHEA, while at T6 the difference was insignificant (P=0.209) in case of TT and was significant (P=0.030) for DHEA levels. The percentage of decrease of serum TT was significantly (P=0.00002) higher in women of MM-group compared to women of other groups, while the percentage of decrease of serum DHEA was significantly higher (P=0.0096) in women of MM-group than in women of Met-group and was insignificantly higher (P=0.151) than in women of MI-group (Table 4).

Clinical hyperandrogenemia manifested as hirsutism was detected in 45 women who showed FG score ≥8 with non-significant distribution among the women of the three groups. Treatment did not improve hirsutism significantly as shown by the insignificant difference in the frequency of women had FG score ≥8 before (21.4%) and after (16.7%) treatment and the non-significant difference between the studied groups. Despite the insignificant differences of mean FG score determined at T0 and T6 between the studied groups, the mean intergroup difference between T0 and T6 FG scores were significant in the three groups (Table 4).

Acne as another manifestation for clinical hyperandrogenemia was frequent among the studied women (68.1%), but unfortunately improved insignificantly with the used therapies and at the end of treatment, the frequency was 61.4%. Regarding the mean acne score, it was decreased insignificantly in patients of groups Met (P=0.205) and MI (0.214) in comparison to mean value of their T0 score, while the difference was significant (P=0.0029) with MM therapy. Further patients' distribution according to the differential items of acne score at T6 showed insignificant difference than that determined at T0 in groups Met and MI (P=0.655 & 0.562, respectively), but the difference was significant (P=0.029) in case of group-MM (Table 4).

Table 4: Endocrinal outcomes

Variates Groups			Met	MI	MM	P
BMI (kg/m²)		T0	25 (35.7%)	22 (31.4%)	27 (38.6%)	0.673
		T6	13 (18.6%)	7 (10%)	8 (11.4%)	0.279
		P1	0.023	0.0018	0.0002	
Hormonal assay	Serum testosterone (ng/ml)	T0	0.77±0.1	0.75±0.09	0.76±0.09	0.264
		T6	0.71±0.09	0.68±0.08	0.69±0.09	0.209
		P1	0.0001	0.0003	<0.001	
		% of change	8.28±2.83	8.42±2.13	10.24±2.46	
		P2		0.739	0.00002	
		P3			0.00002	
	Serum DHEA	T0	296.2±38.8	282.5±29.5	286±38.9	0.066
		T6	273.9±34.5	260.4±28.3	261.5±36.3	0.030
		P1	0.0005	0.00001	0.00018	
		% of change	7.44±2.3	7.82±3.3	8.57±2.75	0.058
		P2		0.425	0.0096	
		P3			0.151	

Hirsutism (FG score)	**Incidence (FG score ≥8)**	T0	19 (27.1%)	13 (18.6%)	13 (18.6%)	0.361
		T6	15 (21.4%)	11 (15.7%)	9 (12.9%)	0.383
		P2	0.403	0.654	0.353	
	Mean FG score	T0	7±1.62	6.9±2.09	6.8±1.16	0.777
		T6	5.7±1.8	6±2	6±1.34	0.494
		P2	0.0001	0.001	0.0002	
Acne score	**Incidence**	T0	43 (61.4%)	47 (67.1%)	53 (75.7%)	0.189
		T6	39 (55.7%)	45 (64.3%)	45 (64.3%)	0.485
		P2	0.674	0.722	0.140	
	Mean score	T0	1.71±0.8	1.79±1	1.85±0.93	0.761
		T6	1.49±0.68	1.56±0.78	1.4±0.54	0.552
		P2	0.205	0.214	0.0052	

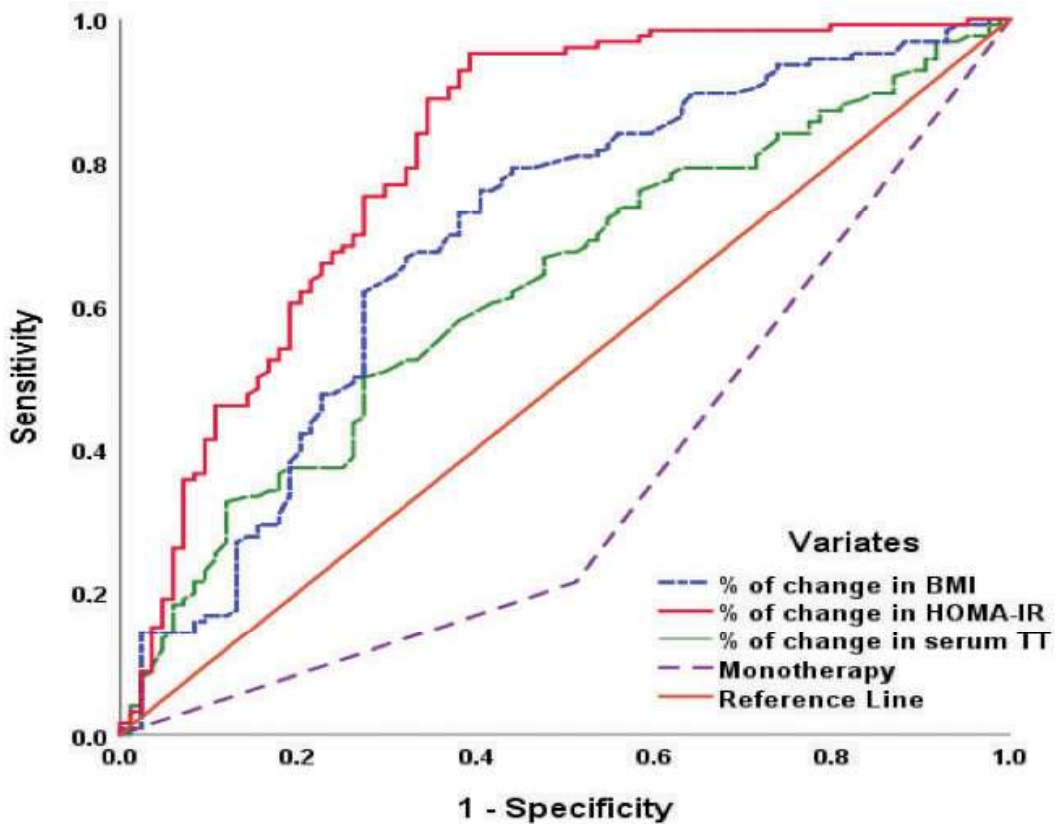
Score items	Time		T0			T6	
	Group	Met	MI	MM	Met	MI	MM
	0	29 (41.4%)	23 (32.9%)	17 (24.3%)	31 (44.3%)	25 (35.7%)	25 (35.7%)
	1	20 (28.6%)	24 (34.3%)	23 (32.9%)	23 (32.9%)	26 (37%)	28 (40%)
	2	15 (21.4%)	13 (18.6%)	19 (27.1%)	14 (20%)	15 (21.4%)	16 (22.9%)
	3	4 (5.7%)	6 (8.6%)	7 (10%)	1 (1.4%)	2 (2.9%)	1 (1.4%)
	4	2 (2.8%)	4 (5.7%)	4 (5.7%)	1 (1.4%)	2 (2.9%)	0

P1	0.609	0.856		
P2		0.655	0.562	0.029

The reported resumption of regular menstrual pattern and percentages of change of BMI, HOMA-IR and serum TT showed negative relation to the use of insulin sensitizer monotherapy. The resumption of regular menstrual pattern was positively related to the percentage of change of HOMA-IR index, BMI and serum TT levels. Also, the percentage of decrease of serum testosterone was positively related to that of HOMAI-IR index and BMI. ROC curve analysis for the predictors for getting regular menstrual pattern showed that the more the control of IR with high percentage of decrease of HOMA-IR index the higher the possibility for getting regular menstrual pattern and defined the use of monotherapy as a negative predictor for such outcome (Table 5, Fig. 5).

Table 5: Statistical analysis for the relation between the study outcomes

	Mono-therapy		Regular menstrual pattern		% of change in serum TT	
	"r"	P	"r"	P	"r"	P
Regular menstrual pattern	-0.309	<0.001	-	-	0.178	0.010
% of change of BMI	-0.474	<0.001	0.295	<0.001	0.145	0.036
% of change of HOMA-IR index	-0.327	<0.001	0.443	<0.001	0.216	0.002
% of change of TT	-0.151	0.029	0.178	0.010		
The Receiver Operating Characteristic (ROC) Curve						
	AUC	**SE**	**P**	**95% CI**		
Monotherapy	0.351	0.040	<0.001	0.274-0.429		
% of change of BMI	0.693	0.038	<0.001	0.618-0.768		
% of change of HOMA-IR index	0.811	0.032	<0.001	0.747-0.874		
% of change of TT	0.626	0.039	0.002	0.550-0.702		



Discussion

Gynecological outcomes of this trial showed that 60% of women resumed regular menstrual pattern and among infertile women wishing to get pregnant a pregnancy rate of 13.7% was reported. Further, resumption of menstrual regularity showed positive relation to the percentage of change in IR-index, BMI and serum androgens. These findings spotlight on the vicious circle of obesity, IR and hyperandrogenemia that deleteriously affects the ovarian function with subsequent menstrual disturbances and subfertility or infertility.

Moreover, the adjustment of menstrual pattern and its underlying pathogenesis factors; obesity, IR and hyperandrogenemia, was significantly higher with combined metformin/inositol combination therapy than with either Met or MI as monotherapy that showed insignificant differences. Also, the ROC curve defined the use of insulin sensitizer monotherapy as a negative predictor for the possibility of resumption of regular menstrual pattern; a finding that illustrated the ability of the applied regimens to detonate this cycle and that better outcomes were obtained with the use of combination therapy as double-weapon to get such improvement.

The reported effects of the used drug regimens on BMI and IR and the relation between resumption of regular menstrual pattern with the extent of decrease in BMI and HOMA-IR assured the assumption that obesity is a hyperinsulinemic state and the relation between IR and ovarian functions. Such relation between IR and hyperandrogenemia was attributed to decreased levels of sex-hormone binding globulin (SHBG) secondary to obesity and IR with subsequently higher levels of free testosterone and free androgen index as evidenced by resumption of serum SHBG levels with reduction of serum free testosterone and decreased free androgen index using various modalities for weight reduction in PCOS obese women including dietary regimens (22), pharmacological interventions (23) or bariatric surgery (24).

Further the comparable effects of both inositol and metformin indicated their efficiency as insulin sensitizers and metabolic adjusting drugs. Similarly, Soldat-Stanković et al. (25) showed comparable effects of MET and MI on BMI, body composition, hormonal profile, metabolism of glucose and insulin, and adiponectin level and concluded that MET and MI, were useful in reducing BMI and improving body composition in PCOS women without significant differences.

Furthermore, the significant differences between women who received combination therapy in comparison to those received monotherapy illustrated the synergism between the effects of each drug to improve outcomes. Similarly, a recent study compared the efficacy of Met as monotherapy versus Met with MI as combination therapy and detected significantly greater improvement of menstrual regularity with combination, but pregnancy rates were comparable and concluded that addition of MI to Met improved menstrual cycle regularity, and QOL in PCOS-women (26).

The reported comparable outcomes of women used Met or MI as monotherapy, go in hand with Rajasekaran et al. (27) who reported comparable effect of MI and Met on ovarian hyperstimulation syndrome in PCOS women prepared to IVF but MI therapy was associated with significantly higher fertilization and cleavage rates and number of good grade embryos and with a systemic review for randomized controlled trials that assured the non-inferiority of inositol compared to metformin regarding effects on BMI, androgen hormonal profile, and insulin action with a risk ratio for getting regular menstrual cycle of 1.79 higher with inositol than placebo (28). Also, Bodepudi et al. (29) detected the comparable effects of Met and MI on clinical, hormonal, and biochemical profiles of PCOS women and documented that the better safety profile and tolerance of MI, due to its minimal side effects, prevents

discontinuation of therapy till getting the desirable effects.

In support of the efficacy of MI as additive to other drugs used for PCOS treatment, Kachhawa et al. (30) compared the effect of using myoinositol and D-chiro-inositol in 3.6:1 ratio versus combined hormonal contraceptive in a series of PCOS women and reported resumed spontaneous menses in about 85% of women, reduction of mean cycle length and these outcomes were continued for three months after stoppage of treatment and concluded that the used inositol combination is effective in regularizing menstrual cycles. Thereafter, Guarano et al. (31) found the addition of MI to alpha-lipoic acid creates synergistic effect that was manifested as improved IR, menstrual regularity and ovulation rhythm of PCOS women especially in obese/overweight patients with T2DM familiarity. Also, Hassan et al. (32) compared resveratrol and MI versus Met and pioglitazone combinations for treatment of PCOS women and reported significant reduction in serum TT, LH and FSH levels with a marked reduction in the ovarian volume with MI combination and significantly higher frequency of menstrual regularity and concluded that combined resveratrol and MI is more effectively ameliorated the altered endocrine, metabolic indices and stress burden especially in high risk group of obese, oligo-anovulatory married PCOS affected women.

The reported beneficial effects of inositol could be attributed to its variant mechanisms of action; experimentally, Bizzarri et al. (33) shown that MI and its epimer D-chiro-inositol (DCI) permits transduction of insulin and improves the complete breakdown of glucose through the citric acid cycle, especially in glucose-greedy tissues, such as the ovary. Also, DCI inhibits generation of reactive oxygen species secondary to the action of NAPH oxidase and improves mitochondrial disruption, (34), MI through inositol triphosphate (IP3) signaling pathway induces calcium ion (Ca2+) release from the endoplasmic reticulum leading to rising of cytosolic Ca2+ levels which in turn activates many enzymes and proteins (35).

Conclusion

Insulin sensitizers' therapy is effective, safe, cheap and in-hand of all PCOS women to control PCOS-associated endocrinal, metabolic and gynecological deregulations. Inositol is a synergistic additive to metformin and this combination results in favorable outcomes than monotherapy. Lack of inositol side effects allowed patients to continue the therapy duration despite of the unpleasant side effects of metformin.

Limitations

The use of minimal acceptable dose of metformin with higher dose of MI/DCO to minimize side effects need to be evaluated. Follow-up after cessation of therapy to detect recurrence of manifestations was mandatory to adjust duration of therapy

Recommendations

Comparative study of the used drug combination versus other treatment regimens for PCOS was required to define the best of which.

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