Effects of N-Acetylcysteine Supplementation on Semen Analysis, Hormonal Profile and Spontaneous Pregnancy Rate in Idiopathic Infertile Men: Before and After Clinical Trial

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ABSTRACT

Objective: To compare sperm quality and quantity, hormonal profiles and spontaneous pregnancy rates before and after administering a 3 months course of N-Acetylcysteine (NAC).

Material and Methods: This prospective clinical trial was conducted at the Infertility Unit of the Obstetrics and Gynecology Department at Bhumibol Adulyadej Hospital, Thailand. The study period was from June 1, 2023 to September 30, 2023. Subjects were idiopathic infertile males aged between 20 and 50 years old. All subjects received 600 mg of NAC orally per day. Semen analysis (SA) and male hormonal profiles (MHP; testosterone, LH, FSH and prolactin) were performed before and three months after NAC administration. Demographic, clinical characters and laboratory change were recorded.

Results: The 92 participants were recruited. The mean age of couples was 34.5 years old. The average duration of infertility was 3.6 years. Increase of semen volume (2.1 vs 2.4 ml, $p < 0.001$), semen concentration (30.5 vs 43.1 x 10^6/mL, $p < 0.001$), total motility (59.57 vs 72.38 %, $p < 0.001$), progressive motility (59 vs 69.8 %, $p < 0.001$), normozoospermia (60 vs 83 %, $p < 0.001$), testosterone (452.8 vs 479.0 ng/dL, $p = 0.038$), LH (4.6 vs 5.3 mIU/mL, $p = 0.004$) and FSH (4.4 vs 4.6 mIU/mL, $p = 0.009$) were observed after three months of NAC administration. No changes in sperm morphology and prolactin level. One-third (27/92) of each participant's spouse conceived spontaneously.

Conclusion: NAC potentially enhances male hormonal profiles, sperm quality and quantity with an impressive spontaneous pregnancy rate.

Keywords: Infertile; male; semen analysis; N-Acetylcysteine; pregnancy (Siriraj Med J 2024; 76: 125-134)

INTRODUCTION

Infertility is defined as one year of regular unprotected intercourse without conception.[1] Eighty percent of normal couples conceive within the first 6 months of unprotected sexual intercourse among couples living in the same residence.[2] It is estimated that 30 million men are infertile worldwide, with highest rates in Africa and Eastern Europe.[3] Male factors ranged from 20 to 73 percent in different regions worldwide. Among Asian regions, 37 percent was reported.[3] The male factor made up half of infertility issues.[4,5]

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Semen analysis (SA) is a basic laboratory test used for male factor evaluation. SA consists of semen volume, sperm concentration, motility, and morphology.[6] Acceptable values for SA are a semen volume of 1.4 mL, sperm concentration of 16 million per mL, total sperm motility of 42 percent, normal sperm morphology of at least 4 percent and WBC concentration less than one million per mL.[6] The past 16 years of data reported motile sperm count trends declining at approximately ten percent.[7] Sperm quality identified a declining tendency from 2015-2021 with increased male age.[8]

Based on well-established data, sperm concentration of less than one million sperm per mL (severe oligozoospermia) typically resulted in failed impregnation.[9] Male infertility was a result of abnormal function of testes, hypothalamic pituitary axis and other unexplained causes. Half of male infertility is still unexplained.[10]

Depletion of GSH pool is a consequence of oxidative stress and inflammatory processes.[11] Unexplained male infertility has been associated with oxidative stress.[12] Highly reactive oxygen species (ROS) are described to be responsible for the oxidative damage to nucleic acids, namely DNA and RNA. Oxidative stress is maintained in homeostasis by antioxidants.[13] This results from various factors, such as exercise, altered immune system, and antioxidant deficiencies.[14] This condition can cause pathological disorders, namely aging, neurodegenerative diseases, and cancers.[13,15,16]

Appropriate ROS levels affect sperm acrosome reaction, capacitation, and motility according to multiple studies via improving the efficacy of sperm binding to zona pellucida of the oocyte.[4,17-19] Excess antioxidants could alter sperm function and maturation, especially the function of superoxide dismutase.[4] Infertile men were reported to have oxidation imbalances when compared to healthy individuals, with findings suggesting sperm dysfunction in concentration, volume, and motility.[18,20]

There are multiple modalities to treat infertile males.[5] Medical treatment using antioxidant food supplements had been studied. Works demonstrated an association of zinc and folic acid with improved sperm morphology and concentration. There has yet to be conclusive evidence in the use of N-acetylcysteine (NAC) for such a cause.[5]

NAC is a derivative of amino acid L-cysteine agent. It is widely available over the counter and administered for upper viral infection of respiratory tract enterally.[21] Clinical usage of NAC is for mucolytic, antioxidant and anti-inflammatory properties.[22] NAC has an anti-oxidation effect by restoring the depleted pool of glutathione (GSH) synthesis.[23]

Previous literatures reported the effect of NAC in improving sperm concentration and acrosome reaction by reducing oxidative stress of sperm DNA.[11,24] There were some suggestions of NAC increasing SA quality.[25-28] Still, there remains controversy regarding effects on hormonal analysis.

This study aimed to investigate the improving effect of NAC on sperm quality, hormonal profile and spontaneous pregnancy rate.

MATERIALS AND METHODS

This study was conducted as a prospective clinical trial. Idiopathic infertile males between 20 and 50 years who came to the Infertility Unit of Obstetrics and Gynecology Department at Bhumibol Adulyadej Hospital (BAH), Bangkok, Thailand from June 1, 2023 to September 30, 2023 were enrolled. This study was approved by the Ethics Committee of BAH Institutional Review Board (IRB 47/65). Registration number obtained on the Thai Clinical Trial website (www.thaiclinicaltrials.org) was TCTR20230510002. All individuals gave written informed consent prior to their participation in the study. Inclusion criteria included primary infertile men with regular sexual intercourse (at least every two days of sexual intercourse) with partners. Stopping all medical treatments for at least three months before participating in the study was also a requirement for all participants.

Exclusion criteria were subjects who had well-known pathologic features, such as varicocele, leukocytospermia, hormonal abnormalities, and/or blockage that prevented sperm delivery, azoospermia, aspermia of semen analysis, the presence of cryptorchidism, vasectomy, history of testosterone and other exogenous hormone use, abnormal liver function, regular cigarette smoking, regular alcohol consumption, anatomical disorders, Klinefelter syndrome, cancer, and fever within 90 days prior to semen analysis. We defined the non, infrequent and regular smokers as non, one to six cigarettes and seven or more cigarettes per week, respectively.[29] Male who consumed more than 2 drinks per day were excluded from the study. One drink defined as 15 mL of pure ethanol.[30] All subjects' spouses were investigated by hysterosalpingography or laparoscopy and hormonal profiles namely luteinizing hormone (LH), follicle stimulating hormone (FSH), estradiol (E2), progesterone and prolactin (PRL). Healthy female in the current study was defined as subject with normal genital tract finding, normal ovulatory cycles, normal hormonal profiles and the absence of endometriosis.

Couple age and duration of infertility were recorded at the time of study. In addition, male height (m), weight (kg), body mass index (BMI, kg/m^2), underlying diseases, history of orchitis, sexually transmitted diseases (STDs), history of regular smoking or alcohol intake, occupation, income and partners' age were recorded. Subjects were requested to consume 600 mg of NAC (Fluimucil A, Zambon, Switzerland) dissolving tablets in 120 mL in room temperature water orally once daily before sleep for three months. Safety of prolong NAC administration was reassured to subjects.[31]

Variables including SA, hormonal parameters namely LH, FSH, testosterone and PRL and successful pregnancy outcomes were measured before and after three months of orally administered NAC.

For effective communication between participants and the investigation team, an official group LINE chat (communication application on smartphone) account was created. All subjects and the investigation team were invited to participate in this application. Any problem and concern mentioned in the group forum were promptly responded to by members of the investigation team. Appointment reminders, regular NAC administration, and side effects were monitored via enquiry input in the LINE application, which is a code-encrypted program controlled by the investigator. Confirmation of NAC administration was checked daily via application by participants.

Semen samples were obtained through masturbation directly into the container without a condom, after 3-5 days of sexual abstinence. The collected sample was allowed to liquify at room temperature for one hour. Semen parameters (volume, sperm count, progressive and non-progressive motility and normal morphology) were evaluated according to 2021 WHO SA guidelines.[6] Standardized SA was assessed by one single trained laboratory technician at the at the Infertility Unit at BAH. Sperm count was evaluated by a sperm counting chamber under microscopy (10x, model CHS, Olympus, Japan) and expressed as million per milliliter. The spermatozoa's motility was classified as progressive, non-progressive, and immotile.[6] Spermatozoa's morphologies were investigated by Papanicolaou staining technique. Normal WHO 2021 criteria included a sperm concentration of 16 x 10^6 per ml or greater, 42 percent or greater motility with forward progression under light microscopy inspection. According to the Tygerberg Strict criteria, greater than four percent of normal form of spermatozoa was classified as normal morphology of spermatozoa.

A three milliliters peripheral blood sample was obtained from each participant in the morning and immediately centrifuged for 7 minutes at 3,500 rpm. Serum samples were collected then stored at (2-8 degree Celsius) for no more than one day for further evaluation and analysis. The serum levels of FSH (mIU/mL), LH (mIU/mL), PRL (ng/ml) and testosterone (ng/dL) in all samples were measured by using electrochemiluminescence immunoassay (ECLIA, Cobas 801, Roche, Thailand) for hormonal profile.

Sample size calculation was based on Jannatifar's study.[28] Mean difference, alpha error, and beta error were set at 0.44, 0.05 and 0.1, respectively. The minimal sample size needed was 92 cases. Categorized variables were expressed as percent (%). Continuous variables were expressed as mean ± standard deviation (SD). Normal distribution of data was assessed by Kolmogorov-Smirnov test. Data before and after NAC treatment were compared by the paired t-test, chi-square tests or Fischer exact tests when appropriate. Two-sided significance level of less than 0.05 was considered statistically significant. Analyses were performed using SPSS (Statistical Package for the Social Science for Window), version 18 (SPSS Inc., Chicago, IL, USA).

RESULTS

During the study period, 92 participants were recruited as presented in Fig 1. Mean age of male and female participants was 35.1 ± 5.6 and 33.8 ± 4.2 years old, respectively (p-value < 0.001). Duration of infertility was 3.6 ± 3.2 years (p-value = 0.001). Average BMI of male participants was 26.4 ± 4.3 kg/m^2. Most participants (87/92: 94.6%) were government officers and employees as depicted in Table 1. Thirteen percent (12/92) of subjects had underlying diseases including hypertension, dyslipidemia, and diabetes mellitus. Among the participants, 17 individuals (18.5%) were smokers, and 42 individuals (45.7%) socially consumed alcohol. All subjects' education level was of bachelor's degree or higher. Two-thirds (65/72: 90.3%) of women had normal genital structure and function. The timing of pregnancy after NAC intervention was 2.63 ± 1.12 months (Table 1).

Quality of SA improvement after NAC administration is demonstrated in Fig 2 and Table 2. Regarding the semen analysis, an increase in normozoospermia was observed. There was a statistically significant increase of the semen volume, sperm concentration, and all attributes of motility, namely total, progressive and non-progressive motility. No change was observed with semen pH and sperm morphology. Hormonal profile revealed increases in testosterone, LH and FSH levels with statistical difference at p-value = .038, .004 and .009, respectively. PRL levels were not changed (Fig 2 and Table 2).

Spontaneous conception was observed among male participants aged younger than 31 years old regardless of their partner's age of whom featured no female anatomical

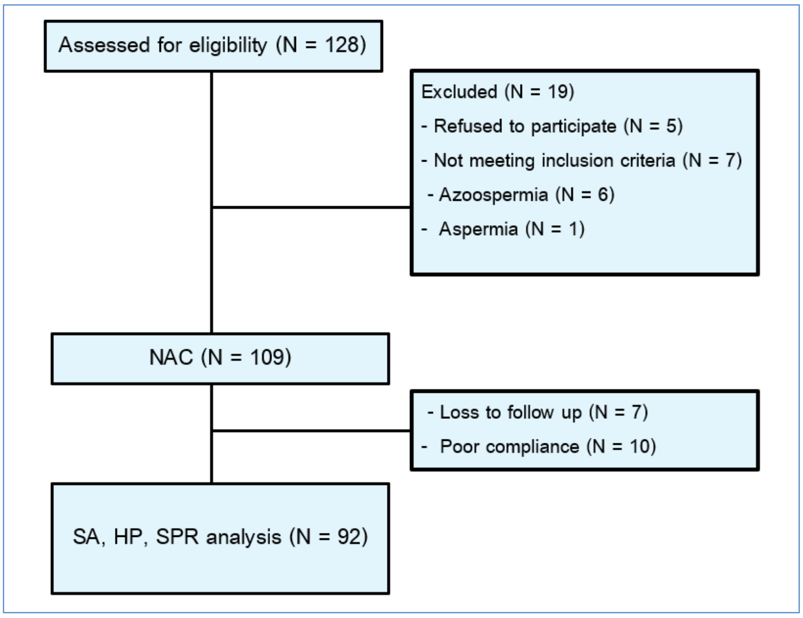

Fig 1. Flow chart of study. NAC = N-acetylcysteine supplement; SA = Semen Analysis; HP = Hormonal profile which includes: Testosterone (ng/dL); Luteinizing hormone (mIU/mL); Follicle stimulating hormone (mIU/mL); Prolactin (ng/ml); SPR = Spontaneous Pregnancy Rate.

TABLE 1. Demographic character of infertile couples who receive NAC before and after.

		Pregnancy		*p*-value
	Total (92)	Yes (27)	No (65)	
Age				
Female	33.8 ± 4.2	31.1 ± 2.8	35.0 ± 4.1	<.001*
Male	35.1 ± 5.6	31.7 ± 5.4	36.6 ± 5.1	<.001*
Duration (years)	3.4 ± 3.0	2.0 ± 1.9	3.9 ± 3.2	.001*
NAC (months)		2.6 ± 1.1	3.0	
NF	65 (70.7)	27 (100)	38 (58.5)	<.001*
PF	27 (29.3)	0 (0)	27 (41.5)	
Smoker	42 (45.7)	8 (29.6)	34 (52.3)	.047*
Non-smoker	50 (54.3)	19 (70.4)	31 (47.7)	
BMI	26.4 ± 4.3	26.3 ± 4.33	26.41 ± 4.37	.914
Underweight	1 (1.1)	0 (0)	1 (1.5)	.015*
Normal weight	19 (20.7)	9 (33.3)	10 (15.4)	
Overweight	22 (23.9)	1 (3.7)	21 (32.3)	
Obesity	50 (54.3)	17 (63)	33 (50.8)	
Occupation				
Government Officer	59 (64.1)	16 (59.3)	43 (66.2)	.638
Own Business	5 (5.4)	1 (3.7)	4 (6.2)	
Employee	28 (30.4)	10 (37)	18 (27.6)	
Income (Baht)				
< 20,000	4 (4.3)	0 (0)	4 (6.2)	.361
20,000 - 50,000	59 (64.1)	17 (63)	42 (64.6)	
>50,000	29 (31.5)	10 (37)	19 (29.2)	
UD	12 (13)	3 (11.1)	9 (13.8)	.723
Hypertension	8 (8.7)	0 (0)	8 (12.3)	
Dyslipidemia	3 (3.2)	3 (11.1)	0 (0)	
Diabetes mellitus	1 (1.1)	0 (0)	1 (1.5)	
Bachelor or more	92 (100)	27 (100)	65 (100)	

Note: Data are presented as mean (SD) for continuous variables, and as frequency (percentage) for categorical variables. NF = Normal female's factors; PF = Pathologic female's factors (diminished ovarian reserve (DOR); polycystic ovarian syndrome (PCOS); abnormal fallopian tube; abnormalities of the uterus; endometriosis; luteal phase defect); BMI = body mass index (kg/m^2); NAC = duration of N-Acetylcholine administration (months); Duration = duration of infertility before infertile clinic appointment (years); UD = underlying disease of participants namely hypertension, dyslipidemia, and diabetes mellitus.
*$p < .05$

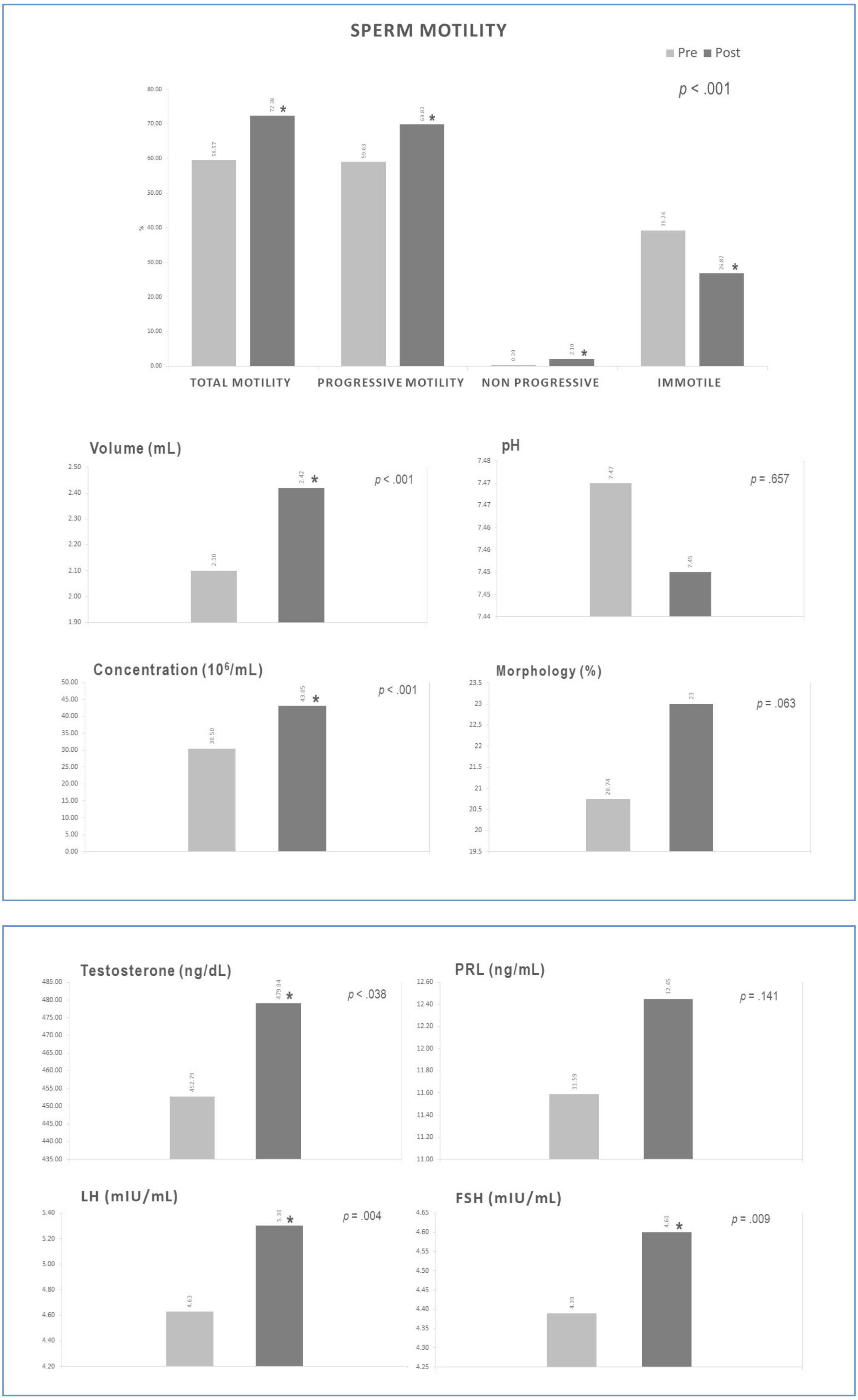

Fig 2. Comparison of semen analysis and male's hormonal profiles between pre and post-NAC administration. Volume = volume of semen (mL); pH = pH of semen; Concentration = concentration of sperm (10^6/mL); Total motility = total motility of sperm (%); Progressive motility = progressive motility of sperm (%); Non-progressive = non-progressive motility of sperm (%); Immotile: immotile sperm (%); Morphology = morphology of sperm; Testosterone (ng/dL); LH = Luteinizing hormone (mIU/mL); FSH = Follicle stimulating hormone (mIU/mL); PRL = Prolactin (ng/ml).

*$p < .05$

TABLE 2. Comparison of semen analysis and male's hormonal profile between pre and post-NAC administration

Outcome	Comparative risk Pre	Post	MD, 95%CI	*p*-value
Volume (mL)	2.1 ± 0.6	2.42 ± 0.5	0.32 (0.15, 0.49)	<.001*
pH	7.47 ± 0.3	7.45 ± 0.5	-0.03 (-0.15, 0.09)	.657
Concentration	30.5 ± 23.2	43.1 ± 27.2	12.55 (7.84, 17.27)	<.001*
Motility (%)				
Total	59.6 ± 17.9	72.4 ± 14.9	12.82 (9.29, 16.34)	<.001*
Progressive	59.0 ± 18.4	69.8 ± 16.3	10.78 (6.94, 14.62)	<.001*
Non- progressive	0.4 ± 1.4	2.1 ± 4.4	1.71 (0.72, 2.69)	.001*
Immotile	39.2 ± 18.9	26.8 ± 14.6	-12.42 (-16.17, -8.68)	<.001*
Morphology (%)	20.74 ± 11.5	23 ± 11.6	2.26 (-0.13, 4.65)	.063
Testosterone (ng/dL)	452.8 ± 155.1	479.0 ± 163.6	26.25 (1.43, 51.07)	.038*
LH (mIU/mL)	4.6 ± 1.7	5.3 ± 2.3	0.68 (0.22, 1.13)	.004*
FSH (mIU/mL)	4.4 ± 1.9	4.6 ± 1.9	0.21 (0.05, 0.37)	.009*
PRL (ng/mL)	11.6 ± 6.3	12.5 ± 6.1	0.86 (-0.29, 2.02)	.141

Mean (SD) for continuous variables, and as frequency (percentage) for categorical variables Volume = volume of semen (mL); pH = pH of semen; Concentration = concentration of sperm (10^6/mL); Total motility = total motility of sperm (%); Progressive motility = progressive motility of sperm (%); Non-progressive = non-progressive motility of sperm (%); Immotile: immotile sperm (%); Morphology = morphology of sperm; Testosterone (ng/dL); LH = Luteinizing hormone (mIU/mL); FSH = Follicle stimulating hormone (mIU/mL); PRL = Prolactin (ng/ml).
$^*p < .05$

abnormalities or dysfunction. Overall pregnancy rate was 29.3 (27/92) percent. Non-smoking participants were associated with positive pregnancy outcomes (19/27: 70 percent) as stated in Table 1.

DISCUSSION

The demographic characteristics of participants were as follows: age was around 35 years old. Mean ages of our participants were similar to Jannatifar's study whereas other studies included participants in their early 30s.[25-28] The duration of infertility in the current study was three years. Safarinejad, Barekats and Jannatifar's works reported shorter duration of around two years while participants in Ciftci's study had infertile durations exceeding 4 years.[26-28]

Report from Iran by Barekat in 2016 identified average female spouses at around 26 years old.[27] Ciftci, Safarinejad and Jannatifar's studies reported from Turkiya and Iran did not state the average age of female spouses.[25,26,28] Most muslim women married at a young age. It implied that women's age was not a contributing factor for infertility problems in these studies.

For studies conducted during 2009.[25,26] It was a period of time with a culture respecting traditional values, where starting a family early was a milestone in life. When compared to 2019 having an increased trend in career driven lifestyle moreover the social media namely facebook, twitter, and instagram were not as widely used as they are in the present day, causing a later start in family growth. Barekat's study in 2016 consisted of participants with infertile male post-varicocelectomy, explaining the early concern regarding infertility treatment.[27]

Subjects in Safarinejad's (BMI 26.2 kg/m^2) and Jannatifar's (BMI 29.2 kg/m^2) studies had overweight participants (BMI 25-29.9 kg/m^2).[26,28] Subjects in the current study (26.4 kg/m^2) were obese according to the WHO 2021 for Asian people.[32] The current study presented an obese demographic (54.3%).

Male infertility remains an important issue for couples. Its remedies remain controversial and so further exploration of optimal treatment was needed.[34] The effects of NAC from the current study were increased semen volume, sperm concentration and sperm motility. Sperm morphology did not change as the result of receiving oral NAC. The percentage of normospermia presented a marked increase from 65 to 90 after NAC treatment. All studies with NAC reported increased semen volume except for Barekat's study.[25-28] Reports identified concentration of spermatozoa increased in Safarinejad's and Jannatifar's studies while others' works informed no change.[25-28] Many works reported that ROS generation was associated with DNA fragmentation.[17-19] Poor chromatin packaging, apoptosis promoting were also relevant consequences on spermatozoa count.[35,36] High ROS generation and DNA damage were demonstrated in immature spermatozoa that could be the explanation of male infertility by inducing oxidation among mature spermatozoa.[37] These processes occurred during sperm migration from the seminiferous tubules to the epididymis.[38]

Motility of spermatozoa was increased as a result of NAC intake in the current study. The findings of the current study are in line with the works of Ciftci's, Barekat's and Jannatifar's while no motility change was reported by Safarinejad.[25-28] Asthenozoospermia (poor motility) was a consequence of increased oxidative stress, excess of tyrosine nitration, and sperm mitochondrial dysfunction.[19,39]

The quality of SA in this study was improved, in line with the previous studies.[25-28] This might come from the antioxidant effects of NAC. Oxidative stress impaired sperm motility and morphology of spermatozoa via lipid peroxidation at cell membrane spermatozoa.[17-19,40] Elevated concentrations of reactive oxygen species (ROS), when concomitant with an insufficiency in antioxidant defenses, precipitate a state of oxidative stress (OS). This caused nuclear and mitochondrial DNA impairments, reduced telomeric length, integrity, and alterations in chromatin structure.[17-19,41]

NAC has a mucolytic effect. Presently, minimal side effects of oral NAC had been reported such as nausea and vomiting. The toxicity of NAC overdose remains incompletely defined within previous literature so it is considered a safe supplement.[42] It was reported to reduce ROS and improve all aspects of sperm parameters. NAC could reduce sperm viscosity, thus making it easier for seminal plasma to pass through the cervix.[43] Sperm morphologies in the current and Ciftci's study[25] were not changed because the base value of morphology was already within normal range, resulting in an insignificant improvement. The morphology of spermatozoa from the previous study reported significantly better results due to their starting morphology parameters being under normal range.[25-28]

PRL levels in the current study declared no change. This finding was similar to previous reports.[25-28] As NAC leads to increased testosterone level, improving sperm quality but it has no effect on PRL level. From the current study, there was a significant increase in FSH and LH (both values staying within normal range) as well as testosterone levels. Trends of increasing testosterone level after NAC administration were also reported in Safarinejad's work in 2009 and Jannatifar's study in 2019 despite representing significant decrease in FSH and LH.[26,28] Testosterone levels within normal range had been reported to improve spermatogenesis.[44] The increase in testosterone level explained the decreased effect in FSH and LH as per negative feedback in the hypothalamic-pituitary axis.[45] It is unexplainable to why this study had an increase in FSH and LH unlike other studies. The rise of FSH and LH is statistically significant with a lack of clinical significance. Average age of male participants in the current study was around 35 years old which made our participants older than those in previous studies. Average male age in the studies by Ciftci, Safarinejad, Barekat and Jannatifar ranged from 30.1 to 34.7 years old.[25-28] The rising in FSH and LH among male participants in the current study might stem from increasing age. Even though our participants exhibited elevated normal level of FSH and LH, the testosterone level was increased in comparison to previous literature.[26,28] Steiner et al reported the large RCT in year 2020 that combination of antioxidant agents namely ascorbic acid, vitamin E, selenium, L-carnitine, zinc, folic acid, lycopene and vitamin D did not improve semen parameters among male infertility couples.[46] Another large RCT by Schisterman in year 2020 also stated that supplement of folic acid and zinc to male infertility couples did not improve semen quality and clinical live birth.[47] Comparisons of the current study to the previous studies were reported in Table 3. Antioxidant in the current study was NAC. It was a new data for one member of antioxidants that needed further investigation. The findings of the current study could not argue the landmark RCT papers of Schisterman and Steiner.[46,47]

Limitation of the study was single data measurement of SA and hormonal levels. Fluctuation of SA and hormonal levels should be corrected by multiple measurement and average calculation. One-third of female couples (27/92) were initially included and later diagnosed of pathologic female during process of infertile investigation. Incidental findings of pregnancy were reported among normal female during process of investigation. Randomized controlled trial with placebo and study group should be performed in the next study.

Among spontaneous pregnancy groups, infertility duration was shorter (2.0 vs 3.9 years), male participants were younger in age (31.7 vs 36.6 years old), apparently normal females (27 vs 0 cases), and non-smoking males (19/27) compared to non-pregnancy group (31/65). Suggestion among normal females in younger age group,

TABLE 3. Comparison Outcome of semen analysis, hormonal profiles and pregnancy outcome in NAC supplement in infertile men from various study.

Authors	Cifci		Safarinejad		Barekat		Jannatifar		Present	
Years	2009		2009		2016		2019		2023	
Country	Turkiya		Iran		Iran		Iran		Thailand	
Designs	RCT		RCT		RCT		RCT		SCT	
Population	IN		IOST		IVV		IAT		IMN	
Age (years)	33.1		32.0		30.1		34.7		35.1	
BMI			26.2				29.2		26.4	
UD	No		No		No		No		Yes*	
Duration	4.1		≥ 2		2.1		2.1		3.4	
WHO	1999		1992		2010		2010		2021	
S/C (n)	60/60		105/106		15/20		50/50		92/92	
Cases (n)	120		211		35		100		92	
NAC	600		600		200		600		600	
Control group	Placebo		Placebo		Untreated		Placebo		After	
INT	12		26		12		12		12	
SA	C	S	B	A	C	S	B	A	B	A
Vol	4.0	2.5	2.8	3.4	3.5	3.9	3.6	4.0	2.1	2.4
Conc	22.3	21.9	22.6	26.8	42.4	45.4	46.5	51.1	30.5	43.1
Mot	22.4	31.3	20.3	24.8	43.6	58.2	31.4	35.2	59.6	72.4
Morph	25.4	26.4	7.4	9.2	1.9	2.7	1.9	4.0	20.7	23.0
HP	C	S	B	A	C	S	B	A	B	A
T			522.2	579.9			387	437	452.8	479.0
LH			4.6	4.2			4.2	4.1	4.6	5.3
FSH			2.6	2.1			4.1	3.7	4.4	4.6
PRL			159.6	97.8			10.6	10.6	11.6	12.5
SPO					10	33.1			0	29.34

Note: Data are presented as mean (SD) for continuous variables, and as frequency (percentage) for categorical variables. RCT = Randomized Controlled Trial's literature; SCT = Self-controlled study design's literature; IN = Idiopathic with normozoospermia; IOST = Idiopathic oligoasthenoteratozoospermia; IVV = Infertile male with varicocele with varicocelectomy; IAT = Infertile male with asthenoteratozoospermia; IMN = Idiopathic Infertile male with most normozoospermia; BMI = Body Mass Index (kg/m^2); UD = underlying Disease of participants namely hypertension, dyslipidemia, and diabetes mellitus; Duration = Duration of Infertility (years); WHO = World Health Organization Manual for Human Semen Analysis; S = Study's group; C = Control's group; n = Number of participants; NAC = N-Acetylcysteine (mg/day); INT = duration of NAC oral supplement (weeks); SA = Semen Analysis; B = Before study's group, A = After study's group; Vol = Volume of semen (mL); Conc = Concentration of sperm (x10^6/ml); Mot = Motility of sperm (%); Morph = Normal Morphology of sperm (%); HP = Hormonal Profile; T = Testosterone (ng/dL); LH = Luteinizing hormone (mIU/mL); FSH = Follicle stimulating hormone (mIU/mL); PRL = Prolactin (ng/ml); SPO = Spontaneous Pregnancy Outcome (%)

three months NAC consuming by their male partners could result in spontaneous pregnancy at the rate of approximately 30 percent (27/92). NAC's mucolytic activity could explain the increased pregnancy rate by improving cervical mucus quality without estrogen supplementation.[27]

CONCLUSION

Oral NAC improves male hormonal profiles, sperm quality and quantity with a 30 percent spontaneous pregnancy rate. Young couples, short infertile duration (two years), apparently normal female and non-smoking males were good candidates for oral NAC during the waiting period for appointment of infertile clinic.

What is already known on this topic?

Male infertility was a result of abnormal function of testis, hypothalamic pituitary axis and unexplained causes. NAC exhibited mucolytic, antioxidant and anti-inflammatory properties. Unexplained male infertility had been associated with oxidative stress. Effects of NAC for improving sperm concentration and acrosome reaction were consequences of reducing oxidative stress of sperm DNA. There had yet to be conclusive evidence in the use of NAC to treat male infertility issues.

What does this study add?

Oral NAC demonstrates potential as a treatment with a 30 percent spontaneous pregnancy among young couples with short infertility duration within three months.

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