Original Research Article

Patterns of lipids and estrogen in women visiting the fertility clinic of Komfo Anokye Teaching Hospital, Kumasi, Ghana

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ABSTRACT

Background: Infertility, which affects one in six couples, is a major clinical and social problem. Pelvic inflammatory diseases (PID) and sexually transmitted infections are but two of the several causes of infertility. The influence of lipid patterns and estrogen on infertility in the setting is however not fully explained. Therefore, the study sought to establish the Patterns of lipids and estrogen among infertile women visiting Komfo Anokye Teaching Hospital, Kumasi.

Methods: The design was both retrospective and introspective study. Sampling technique was convenience and random probability sampling using a list of women with fertility challenges who attended KATH for infertility treatment. Univariable associations were tested using chi-square and a logistic regression was performed to assess the influence of lipids and estrogen on infertility. Associations were considered significant at p values of <0.05.

Results: BMI was significantly associated with fertility in this study. The percentage of respondents who were overweight and obese was significantly higher among the women who were non-fertile as compared to those who were in the control group ((81.4% vrs 18.6% and 84% vrs 16% respectively). An increase in LDL cholesterol and total cholesterol were associated with increased likelihood of infertility among the subjects (OR, 95% CI=4.34, 2.18-8.65) and (OR, 95% CI=1.86, 1.03-3.35) respectively. A unit increase in BMI of the women is associated with 13% increase in the odds of being infertile, (OR, 95% CI=1.13, 1.01-1.65). A unit increase in estrogen level was also associated with 11% decrease in the odds of becoming infertile among the women studied (OR, 95% CI=0.89, 0.85-0.92).

Conclusions: This study shows the influence of body mass index and high cholesterol levels on infertility. This finding will be useful in directing educational interventions aimed at promoting healthy lifestyles to reduce lipid levels and improve fertility among women.

Keywords: BMI, Cholesterol, Estrogen, Fecundity, Infertility

INTRODUCTION

The time taken to conceive is a useful epidemiological measure of fecundity.[1,2] Approximately 90% of fertile couples conceive within 12 months of trying.[3-5] and a delay of more than 12 months is therefore usually taken to define infertility or subfertility for clinical purposes.[6]

Infertility can be defined as inability of a couple to conceive naturally after one year of regular unprotected sexual intercourse or the failure to achieve conception after a minimum of 12 months of exposure.[7,8] Infertility remains a major clinical and social problem, affecting perhaps one couple in six.[7]

Several studies have reported different causes of infertility.[9-11] Some causes are more common in some countries than others. These include pelvic inflammatory diseases (PID) and sexually transmitted infections (STI) in Africa.[12] Some personal habits are considered risk factors for infertility. These include excess alcohol intake and cigarette smoking.[13,14] According to the literature survey, there are so many factors that contribute to infertility. The factors can be grouped into male factors, female factors, combined male and female factors and ideopathic infertility. The most common causes of infertility in relation to the male factors include sperm abnormalities.[15-18] The female factors on the other hand include ovulation dysfunction and tubal pathology.[9,19] There is also combined male and female factors and unexplained infertility; where no obvious cause could be detected.[17] Obesity in women can also increase the risk of miscarriages and impair the outcomes of assisted reproductive technologies and pregnancy, when the body mass index exceeds 30 kg/m^2.[20] Increasing age has also been found to reduce a woman's fertility and the likelihood of successful treatment.[21] Other infertility factors were associated with an increased frequency of antibodies to *Clamydia trachomatis*.

The appropriate method for investigating female infertility continues to be debated.[22] Recent findings on fecundity and the conception window in humans have important implications for the timing of the investigation of female infertility.[22] Within a year of regular intercourse, 90% of fertile couples should become pregnant. After two years, this rises to 95%. Thus, 5-10% of normal fertile couples take more than a year or two to conceive. Some couples therefore present with a delay in conceiving purely by chance, having low normal fertility rather than sub fertility.[21] The exact prevalence of infertility in developing countries however, is unknown due to a lack of registration and well-performed studies.[23]

Additionally, a limited knowledge of the causes of infertility among Ghanaians has been reported, with only 46.5% of the population indicating any cause. Most respondents failed to identify reproductive tract infections as causes of infertility.[8] While the appropriate method for the investigation of female infertility continues to be debated, the timing of the investigation has received less attention. Additionally, recent findings on fecundity and the conception window in humans have important implications for the timing of the investigation of female infertility. Under appropriate circumstances, female infertility should be investigated after 6 months of fertility-oriented intercourse.[22] This cross-sectional study was conducted at Komfo Anokye Teaching Hospital to add knowledge to the existing factors that have been identified as contributing to the challenges associated with infertility and its probable treatment. Understanding the aetiology of fertility or sub-fertility and female reproductive tract disorders at a molecular level may improve success rates of fertility treatment.[24]

METHODS

The study design was retrospective cross-sectional, and involved women visiting KATH for the treatment of infertility. The study sought to find out how infertility among women in the study area were affected by factors such as estrogen levels, obesity, sexually transmitted infections, age, changes in lipid profile, and other factors affecting female fertility.

The research study was done at the Obstetrics and Gynaecological Department of Komfo Anokye Teaching Hospital (KATH), located in the Ashanti region of Ghana. KATH is located in the middle zone of the country and functions as a referral point for all health facilities within both the middle and northern zones of the country.

The study population comprised of infertile women visiting the Komfo Anokye Teaching Hospital for treatment of infertility.

The exclusion criteria were as follows:

- Patients who refused to consent
- Patients who were known or found to have had hysterectomy done
- Patients who were known or found not to be ovulating for the past and over five years.

The sampling technique was convenience and random probability sampling using a list of women with fertility challenges who attended KATH for infertility treatment. The sample size was calculated based on a simple random sampling.[25] A total of 100 infertile women and 50 fertile (controls) were involved in this study.

Information from the study population was collected at several stages of the study. A structured interview questionnaire was used to obtain information on basic demographic, medical, surgical, and reproductive history. Other information on recent illnesses and treatment, infertility, sexuality, occupational and familial history of the study population were also taken.

Respondents' socio-demographic data, information of medication and drug usage, lifestyle and other quantitative data was taken with the use of semi-structured questionnaires which were open ended and closed. Information on respondents' exposures to environmental and other chemical hazards was also obtained with the questionnaires.

The body weight was measured without shoes using an electronic measuring scale, and height to the nearest cm was taken. Waist circumference (WC) in cm was measured midway between the lower costal margin and iliac crest during the end-expiratory phase (World Health Organisation, 1995). Hip circumference (HC) in cm was measured at the level of the greater trochanters.[25] The

waist-to-hip (W/H) ratio was defined as the waist circumference divided by the hip circumference, while the waist/height (W/Ht) ratio was defined as the waist circumference divided by the height in cm.

The body mass index (BMI) was calculated as weight in kg divided by the height (in m^2)

BMI= Weight in kilograms/(Height in meters) ^{2}

The following (BMI) definitions were adopted for this study:

- Underweight: BMI = Below 18.5
- Normal: BMI = 18.5 to 24.9
- Overweight: BMI = 25 to 29.9
- Obese: BMI = Over 30 (WHO, 2006).

The participants were instructed to fast for 12 to 14 hours after eating a low fat diet before the test and not to take alcohol 24 hours before the test to ensure accuracy of the result.[26] The blood was mixed thoroughly and analyzed within five hours of collection. The blood was allowed to stand for at least 30 minutes after which serum was separated by centrifugation at 3000 rpm for 10 minutes. The separated serum and the sample from the fluoride tubes were analysed using a BT3000 auto analyser, manufactured by Biotechnical Instruments S.p.A. Rome, Italy. Total cholesterol (TC), high density lipoprotein cholesterol (HDL), triglycerides (TG) and low-density lipoprotein cholesterol (LDL) were measured.

The following normal serum lipids levels in millimoles (mmol) were adopted for the study:

- Total cholesterol = 3.90-5.20
- Triglyceride = 0.30-2.26
- HDL cholesterol = 0.00-2.59
- LDL cholesterol = 0.0-3.99

The subjects were given clear, written and oral instructions concerning the collection of the blood sample at the Microbiology Laboratory of Komfo Anokye Teaching Hospital. A blood sample of about 3-4mls was taken intravenously from participants and stored in a fridge at the temperature of -35°C at the laboratory.

Estrogen was analyzed using Microparticle Enzyme Immunoassay (MEIA) technology. This technology used a solution of suspended, submicron sized latex particles to measure estrogen. The particles were coated with a capture molecule specific for the estrogen being measured. The effective surface area of microparticles increased assay kinetics and decreased assay incubation time. This permitted MEIA assays to be completed in less time than other immunoassays.

In the Sampling Centre, reactants and sample for one assay were transferred to a Reaction Vessel. The Reaction Vessel was transferred to the Processing Center where reagents and sample were incubated to allow them to come to reaction temperature (18° - 40°C). The reagents and sample were combined, and the reaction mixture was transferred to an inert glass fiber matrix.

An Alkaline Phosphatase-labelled conjugate was added to the glass fiber matrix prior to the addition of 4-Methylumbelliferyl phosphate (MUP). The conjugate catalyzed the hydrolysis of MUP to Methylumbelliferone (MU). Measurement of the fluorescent MU as it was generated on the matrix was proportional to the concentration of the estrogen in the test sample.

The reactants necessary for MEIA assays were:

- Microparticles coated with a capture molecule (antigen, antibody, or viral particles)
- Bulk Solution 1-Fluorescent substrate, 4-Methylumbelliferyl Phosphate (MUP)
- Alkaline Phosphatase-labeled conjugate.

Statistical analysis

Comparisons among different factors were done using the Chi-square (χ^2) test for categorical variables, and the T-test and analysis of variance/co-variance for continuous variables. All analyses were carried out using SPSS. A logistic regression was performed to assess the influence of lipids and estrogen on infertility. Associations were considered significant at p values of <0.05.

RESULTS

The mean age of the respondents was 34 years (SD=5.9) and the minimum and maximum ages were 28 and 43 years respectively. Majority (76%) were within the age range of 31 to 40 years whereas 19% were 20 to 30 years. Majority (85%) of the respondents were employed and among these, 36% were self-employed whereas 21% and 12% were traders and government employees respectively. With respect to respondents' educational background, majority had basic education (elementary and Junior secondary school). Only 16% had post-secondary or tertiary education whereas 18% had no basic education. The mean height and weight of the respondents were 1.6 meters (SD=0.67) and 72.2 (SD=7.29) respectively. In the control group, 48% were within the age range of 31 to 40 years whereas 30% were above 40 years.

The mean age of the respondents was 33.5 (SD=8.71). Majority (62%) of the respondents employed and trading was the most cited occupation among the respondents in control group. Government employees and private employees constituted 18% and 24% respectively. About 10% of the respondents had no formal education whereas 36% and 22% had Junior and Senior Secondary education respectively. The mean height and weight among the control group were 160.35 (SD=5.08) and 76.82 (SD=15.59) respectively (Table 1).

Table 1: Background characteristics of respondents.

Variables	Study group Frequency (N=100)	%	Controls Frequency (N=50)	%
Age				
20-30	19	19.0	11	22.0
31-40	76	76.0	24	48.0
>40	5	5.0	15	30
Mean (SD)	34 (5.9)		33.5 (8.71)	
Employment status				
Employed	85	85.0	31	62.0
Unemployed	15	15.0	19	38.0
Occupation (n=85)				
Trading	21	21.0	16	32.0
Self employed	36	36.0	13	26.0
Government employee	12	12.0	9	18.0
Private employee	16	16.0	12	24.0
Education				
Non-formal	18	18.0	5	10.0
Elementary	32	32.0	12	24.0
Junior Secondary School	20	20.0	18	36.0
Senior Secondary School	14	14.0	11	22.0
Post-Secondary	16	16.0	4	8.0
Height, m				
Mean (SD)	1.6 (0.67)		1.60 (5.08)	
Min /max	1.51/1.81		1.45/1.72	
Weight, Kg				
Mean (SD)	72.2 (7.29)		76.82 (15.59)	
Min/max	58/88		54.2/144	

Majority (57%) had BMI of between 25 and 29.99kg/m^2 indicating that majority were overweight (Figure 1).
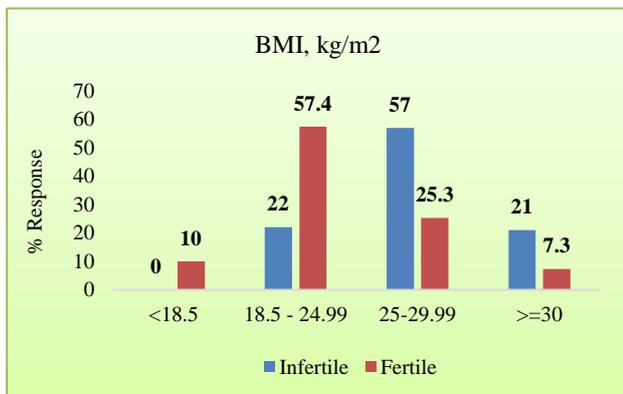

Figure 1: Respondents lipid profile.

The mean estrogen level was 221.63 pg/mL and the minimum and maximum levels were 28 and 973pg/mL

respectively. The mean BMI of the control group was 24.88 and the maximum and minim values were 17.2 and 45Kg/m^2. Majority of the respondents were within the normal BMI range (had BMI of 18.5-24.99 Kg/m^2).

As shown in Table 2 the mean LDL of the respondents was 3.48 mmol/L (SD=1.21). Majority of the respondents were above optimal level of LDL. The mean HDL was 1.55 (SD=0.34) and majority of the respondents had HDL levels of more than 1.54 mmmol/Liter. The mean total cholesterol level among the respondents was 5.2 (1.82) and most respondents had total cholesterol level of less than 5.2 mmol/L whiles 24% had total cholesterol levels of greater than 6.2mmol/L.

Table 2: Respondents lipid profile.

Variables	Study group Frequency (N=100)	%	Controls Frequency (N=50)	%
Low density lipoprotein mmol/L				
<2.59 (optimal)	27	27.0	34	68.0
2.59-3.34 (near or above optimal)	23	23.0	15	30.0
3.35-4.12 (borderline high)	14	14.0	1	2.0
>4.12 (high)	36	36.0	0	0.0
Mean (SD)	3.48 (1.21)		2.05 (0.73)	
High density lipoprotein mmol/L				
<1.04	5	5.0	2	4.0
1.04-1.54	33	33.0	18	36.0
>1.54	62	62.0	30	60.0
Mean (SD)	1.55 (0.34)		1.49 (0.38)	
Total cholesterol mmol/L (n=100)				
<5.2	62	62.0	44	88.0
5.2-6.2	14	14.0	3	6.0
>6.2	24	24.0	3	6.0
Mean (SD)	5.21 (1.38)		4.39 (0.53)	
Triglyceride mmol/L				
<1.7	81	81.0	42	84.0
1.7-9.9	19	19.0	8	16.0
>9.9	0	0.0	0	0.0
Mean (SD)	1.36 (0.78)		1.35 (0.79)	
Systolic BP mmHg				
<120	37	37.0		
120-139	60	60.0		
≥140	3	3.0		
mean (SD)	126.29 (12.4)			
min/max	100/140			
Diastolic BP mmHg				
<80	30	30.0		
80-89	37	37.0		
≥90	33	33.0		
mean (SD)	77.72 (9.10)			
min/max	60/100			

Triglyceride levels were low (less than 1.7mmol/L) among more than 75% of the respondents and none of the respondents had triglyceride level of more than 9.9mmol/L. The mean triglyceride level was 1.36 (SD=0.78). The mean systolic and diastolic pressures were 126.29 (SD=12.84) and 77.72 (SD=9.1) respectively. Majority (60%) had systolic pressure of 120-139 mmHg with only 3% having systolic pressure of ≥140 mmHg. However, about 33% had diastolic pressure of ≥90mmHg whereas 30% had pressure of less than 80mmHg.

The mean LDL of the subjects in the control group was 2.05 mmol/L (SD=0.73) and most (68%) of them had lower levels of LDL whereas 2% were at the borderline. Their mean HDL was 1.49 (SD=0.38). Sixty percent of them had HDL levels of more than 1.54 mmmol/L. More than 85% of the control subjects had low levels of total cholesterol, with mean value of 4.35 (SD=0.53).

Only 6% had total cholesterol levels higher than 6.2mmol/L. Similar to the study subjects, triglyceride levels were low (less than 1.7mmol/L) among most (84%) of the control subjects and none of them had triglyceride level higher than 9.9mmol/L. The mean estrogen level of the fertile women was 387.06 pg/mL (SD=11.68) with a range of 101.9 pg/mL to 611.1 pg/mL. Majority (68%) of the women had estrogen levels of 350 pg/mL or more whereas 32% had estrogen levels lower than 350 pg/mL.

Table 3 presents results of the bivariate association between BMI and the fertility status of women in this study. As shown, BMI was significantly associated with fertility in this study. The percentage of respondents who were overweight and obese were significantly higher among the women who were non-fertile compared to those who were in the control group (81.4% vrs 18.6% and 84% vrs 16% respectively).

The level of estrogen also differed significantly with respect to the fertility status of the women. In a chi-square analysis, the percentage of women with estrogen levels lower than 350 pg/mL was significantly higher among the infertile women as compared to the fertile women (72.5% versus 27.5% respectively; p<0.001). All those who had estrogen levels of 350pg/mL or higher were fertile women.

The results also showed a significant difference in the level of LDL cholesterol between the non-fertile subjects and the control group.

The proportion of subjects who had lower levels of LDL cholesterol was significantly higher among the fertile subjects (53.7%) as compared to the non-fertile subjects, whereas higher levels of LDL cholesterol was significantly higher in the non-fertile than the fertile subjects (p<0.001).

A similar trend of association was observed for total cholesterol as shown in Table 3 (p<0.001). There was however no significant difference in the levels of HDL cholesterol and triglycerides between the fertile and non-fertile subjects.

Table 3: Differences in BMI and estrogen of fertile and non-fertile women.

Variables	Statuses		Test statistic	p-value
	Non-fertile N (%)	Fertile (control group) N (%)		
BMI				
<18.5	0 (0)	5 (100)	31.804*	<0.001
18.5-24.99	22 (44.0)	28 (56.0)		
25-29.99	57 (81.4)	13 (18.6)		
≥30	21 (84.0)	4 (16.0)		
Estrogen				
<350	100 (72.5)	38 (27.5)	26.087**	<0.001
≥350	0 (0.0)	12 (100.0)		
Low density lipoprotein mmol/L				
<2.59	27 (44.3)	34 (55.7)	37.160*	<0.001
2.59-3.34	23 (60.5)	15 (39.5)		
3.35-4.12)	18 (94.7)	1 (5.3)		
>4.12	32 (100.0)	0 (0.0)		
High density lipoprotein mmol/L				
<1.04	5 (71.4)	2 (28.6)	0.400**	0.819
1.04-1.54	33 (63.5)	19 (36.5)		
>1.54	62 (68.1)	29 (31.9)		
Total cholesterol mmol/L				
<5.2	57 (56.4)	44 (43.6)	19.819**	<0.001
5.2-6.2	14 (82.4)	3 (17.6)		
>6.2	26 (89.7)	3 (10.3)		
Triglyceride mmol/L				
<1.7	82 (66.7)	41 (33.3)	0.000**	1.000
1.7-9.9	18 (66.7)	9 (33.3)		

Field data, 2013 *Fisher's exact **Chi-square

Table 4: Logistic regression analysis of influence of BMI and estrogen level on infertility.

Covariates	Odds ratio	95% CI	p-value
BMI	1.13	1.01-1.65	0.037
Estrogen level	0.89	0.85-0.92	<0.001
LDL cholesterol	4.34	2.18-8.65	<0.001
HDL cholesterol	1.84	0.53-6.37	0.337
Total cholesterol	1.86	1.03-3.35	0.040
Triglycerides	1.01	0.54-1.91	0.967
Constant	4.42		
R Square	0.801		
Chi square	79.421***		
-2 log likelihood	239.964		

***p<0.001

Table 4 presents a logistic regression analysis of the influence of estrogen, BMI and lipid profile on the odds of being fertile. The R-square from the model showed that the fitted model could explain about 80.1% of the

relationship between the variables and infertility and the overall chi-square test was significant for the model (chi-square =79.421).

The output shows that, a unit increase in BMI of the women is associated with 13% increase in the odds of being infertile, holding estrogen level constant (OR, 95% CI=1.13, 1.01-1.65). Estrogen level on the other hand had an inverse relationship with infertility. A unit increase in estrogen level was associated with 11% decrease in the odds of becoming infertile among the women studied (OR, 95% CI=0.89, 0.85-0.92). An increase in LDL cholesterol and total cholesterol were also associated with increased likelihood of infertility among the subjects (OR, 95% CI=4.34, 2.18-8.65) and (OR, 95% CI=1.86, 1.03-3.35) respectively. These associations could however be confounded by other factors which were not considered under this study.

DISCUSSION

Infertility in most cultural settings including Ghana is associated with stigmatization and social ridicule and this has devastating psychosocial consequences on infertile couples. The feelings experienced by the infertile couples include depression, grief, guilt, shame, and inadequacy with social isolation.[27] Pelvic inflammatory diseases (PID) and sexually transmitted infections (STI) have been reported to be causes of infertility in Africa.[12] Other personal habits such as excess alcohol intake and cigarette smoking are considered risk factors for infertility.[14] This study was conducted to measure estrogen concentration among the study population and to assess the correlation among BMI, lipid profile and infertility. Estrogen levels and lipid profile were assessed among 100 infertile women presenting at the Komfo Anokye Teaching Hospital, Kumasi.

Estrogen has been described as one of the most important female reproductive hormones. It is produced by the developing follicles in a woman's ovaries, as well as the corpus luteum and the placenta. High levels of estrogen are known to be present in females of reproductive age. However, very high levels of estrogen as well as low levels have been associated with female reproductive problems and infertility.

As revealed by the study, the level of estrogen differed significantly with respect to the fertility status of the women. The percentage of women with estrogen levels lower than 350 pg/mL was significantly higher among the infertile women as compared to the fertile women. The multivariable analysis also showed that women with decreased estrogen levels were more likely to be infertile as compared to those with high levels of estrogen. A unit increase in estrogen level was associated with 11% decrease in the odds of becoming infertile among the women studied. The importance of estrogen in the endometrial development compatible with successful pregnancy has been well known.[28] Ovarian function and

female reproduction is dependent on the action of estrogen on its target tissues in the body. During their reproductive years, adult women have tightly regulated cyclic levels of estrogen with negative and positive feedback on the hypothalamus and anterior pituitary. Alterations in either the cyclic nature of these hormones or the levels produced can affect ovarian function and therefore fertility.[29]

This study further assessed the influence of lipids on infertility among the female respondents. The mean total cholesterol level among the respondents 5.2 (1.82) and most respondents had total cholesterol level of less than 5.2 mmol/L whiles 24% had total cholesterol levels of greater than 6.2mmol/L. Cholesterol levels were significantly higher among the non-fertile subjects than the control subjects and the odds ratio shows increased propensity of being infertile with increasing levels of cholesterol. A study found a strong link between higher levels of free cholesterol in couples and their time to become pregnant.[30]

This study further assessed other lipids including the LDL, HDL and triglycerides. The mean LDL of the non-fertile subjects was 3.48mmol/L (SD=1.21) and this was higher than the borderline. The mean LDL levels were also higher among the non-fertile than the fertile subjects (2.05, SD=0.73). The proportion of subjects with high levels of LDL was higher among the non-fertile subjects as compared to the control subjects. In the multivariable regression analysis, an increase in levels of LDL was linked with increased likelihood of infertility. These were explained on the basis of a negative correlation between serum total LDL and triglycerides and serum estradiol.[31] This indicates that increased levels of LDL and triglycerides is associated with decreased levels of estradiol. As discussed earlier in this chapter, estradiol is important in women fertility. It is essential in the regulation of the menstrual female reproductive cycles and the development and maintenance of female reproductive tissues.

Studies surrounding Body mass index and fertility have also gained interest in recent fertility research. Studies have found a link between BMI and infertility.[31] The negative effect of obesity upon fertility dates back to Hippocrates, who wrote in his Essay on the Scythians 'People of such constitution cannot be prolific …fatness and flabbiness are to blame. The womb is unable to receive the semen and they menstruate infrequently and little'.[32] Putative causes for conception delay in obese women can conceptually be categorized as pathophysiological, psychosocial and sociobiological.

According to the study outcome, majority of the women in the study group were overweight (BMI of between 25 and 29.99kg/m2) whereas majority of women in the control group had normal weights. A statistically significant association between BMI and fertility (p<0.001) was observed. The percentage of respondents

who were overweight and obese were significantly higher among the women who were non-fertile as compared to those who were in the control group (81.4% vrs 18.6% and 84% vrs 16% respectively).

Similar to this study outcome, many previous studies have also reported a correlation between BMI and infertility.[33-35] Some researches show that obesity is a known risk factor for ovulation problems and it also contributes to infertility in women who ovulate normally. Studies have found a significant influence of obesity on fertility. Women who were severely obese were 43% less likely to achieve pregnancy than normal-weight women or women who were considered overweight but not obese during the yearlong study.[36] Again, obese women are three times more likely to suffer infertility than women with a normal body mass index.[34]

Based on the analysis and discussions of the study, it could be concluded that, estrogen level was significantly lower among infertile women as compared to the fertile women and it significantly influenced the odds of becoming fertile. BMI, total cholesterol, LDL cholesterol and triglycerides were equally higher among the non-fertile women and were significantly associated with infertility. These findings suggest the urgent need to encourage women in reproductive age stay healthy and maintain normal weights. Female partners must also be educated on their diets to help stay healthy and maintain normal lipid levels.

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