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Investigating the relationship between infertility and depression in women

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Abstract: Depression plays a clear and undeniable role in infertility. In this study, we investigated the status of depression and the levels of fertility hormones in infertile women. One hundred infertile women and 50 fertile controls participated in this study. The serum levels of cortisol, anti-mullerian hormone (AMH), luteinizing hormone (LH), follicle-stimulating hormone (FSH) and inhibin B markers were measured using electro-quantitative luminescence and ELISA techniques. The results showed a significant difference between the case and control groups in terms of the serum levels of LH, FSH, and AMH (*P*-value< 0.05). Depression was significantly associated with AMH in infertile women (*P*-value = 0.049). AMH and FSH showed a significant difference between the two groups of depressed fertile and depressed infertile women (*P*-value = 0.005, *P*-value = 0.042, respectively). In addition, there was a significant difference between the two groups regarding depression status (*P*-value = 0.003). We concluded that depression might affect AMH, FSH levels, and infertility. As a result, examining all the important and relevant markers of infertility and paying attention to the psychological conditions of women are highly important. Thus, it is possible to prioritize these cases to improve couples' fertility.

Keywords: Infertility; Depression; Women; AMH; FSH

1.0 INTRODUCTION

Infertility is defined as unsuccessful fertility after a one-year effort at getting pregnant by a couple under 35 years of age or a six-month effort at getting pregnant in couples over 35 years old without using any preventive fertility methods (Gurunath et al., 2011). About 50 to 80 million people worldwide have infertility, i.e., one couple suffers from infertility in every six couples (Kalkhoran et al., 2011). Depression plays a clear and undisputed role in infertility (Ngai & Loke, 2021). Stress was associated with an increased risk of infertility (Martins et al., 2014). Studies have shown that infertility has many psychological consequences, including depression, stress, and anxiety (Cox et al., 2006; Kiani et al., 2021; Schneid-Kofman & Sheiner, 2005). Many studies have shown a high level of depression among infertile women (Boivin et al., 2011; Matthiesen et al., 2011). Depression has been observed in 40% of infertile women (Chen et al., 2004; Domar et al., 1992). Depression significantly correlates with the decline in

ovarian function; specifically, the serum levels of LH and FSH were increased in depressed women (Harlow et al., 2003; Welt et al., 2001). Thus, depression can interfere with the functional levels of the brain, the anterior pituitary gland, and the ovaries. The same stress from infertility can further inhibit ovulation and sexual behaviours and thus worsen infertility (Ngai & Loke, 2021). Similarly, stress increases cortisol synthesis, like in Cushing's syndrome, depression, and metabolic syndrome. High cortisol levels are associated with dysfunctions of the reproductive system (Breen et al., 2004; Polyzos et al., 2015). The specific mechanism involved may revolve around the fact that high-stress level promotes the synthesis of cortisol which increases metabolism, blood pressure and weight gain with its associated abundance of fat cells and disturbance of hormonal balance. Cortisol also lower the level of LH and thus delays the follicular phase of the menstrual cycle, increases estradiol, and blocks FSH secretion. Cortisol also interferes with the positive feedback effects of estradiol in response to severe immune-inflammatory stress (Roozitalab et al., 2021). In addition, stress enlists the pituitary gland to produce large amounts of prolactin hormone, which promotes irregular ovulation. It also promotes spasms in the fallopian tubes and the uterus, which can interfere with the movement and implantation of a fertilized egg (Iordăchescu et al., 2021; Simionescu et al., 2021). Stress and cortisol contribute to infertility (Massey et al., 2014). The fertility potential of women depends on the proper functioning of the ovaries and the follicles.

The anti-Müllerian Hormone (AMH) is a secreted glycoprotein synthesized and distributed by the granulosa cells of the grown follicles and is not regulated by gonadotrophins (Grynnerup et al., 2014; Kwee et al., 2008). AMH is not controlled by gonadotrophins (Visser et al., 2006). The secretion of AMH decreases after the production of the Follicle Stimulating Hormone (FSH) from a young age, reaching its maximum secretion at the age of 24 (unit-years/Months/ days), after which the secretion of this hormone decreases with age (Coccia & Rizzello, 2008). AMH plays an important role in developing the reproductive organs in both sexes during the embryonic period. Measurements of this hormone are used to screen for the ovarian reserve and to assess infertility and ovarian defects in immature and hypogonadotropic, hypogonadism, and polycystic ovaries (Coccia & Rizzello, 2008; Hagen et al., 2012). Low levels of AMH have been reported in smokers (Dolleman et al., 2013). AMH levels decrease faster in smokers (Florek et al., 2022; KaboodMehri et al., 2021). FSH levels are measured on the third day of the menstrual cycle. AMH is more useful than FSH and Inhibin B for predicting ovarian conditions and its response to treatments such as Controlled Ovarian Stimulation (COS) and in vitro fertilization (IVF) (Klein et al., 2004). The level of Inhibin B in women is derived from granulosa cells, and it directly reflects the ovarian reserve during the follicular phase of the menstrual cycle. Inhibin B levels are lower in older women compared to young ones (Wen et al., 2021). Reductions in serum levels of Inhibin B constitute one of the early signs of a reduction in (or the loss of) the ovarian reserve, and it occurs with increasing age and Body Mass Index (BMI) (Wang et al., 2022). In obese people, inflammatory markers, fatty acids, insulin, insulin resistance, and free androgen increase while Globulin Sex Hormone Binding (SHBG) concentration decreases. However, these are related to the accumulation of adipokines, such as adiponectin, resistin, and leptin (Ghaderpour et al., 2021). Because depression and stress constitute a big problem and play an important role in pregnancy, this study tried to investigate the hormonal changes in infertility as well as the roles played by stress, anxiety, and depression in infertile women.

2.0 MATERIALS AND METHODS

In this study, Inclusion criteria included infertility in couples carrying out adequate attempts to conceive without contraception for at least one year for a couple under 35 years old and at least six months for a couple over 35 years old without using any preventive fertility measures. Therefore, women who had fertility tests following a clinical diagnosis of infertility by a trained gynaecologist were included in an infertile group. Inclusion criteria for fertile women were individuals between 20-35 years who fathered a child during the last year. Exclusion criteria for both groups (fertile /infertile) included having a history of abortion, ovarian surgery, or bladder surgery; taking hormonal drugs; high blood pressure in the last three months; and mental illness (Gourounti et al., 2011; Nakamura et al., 2008). All respondents were informed about the objectives of the study, data confidentiality, and they signed the informed consent willingly to partake in the study. Clinical and Socio-demographic information of age, weight, height, occupation, smoking habits, use of hormonal drugs, blood pressure measurement, and history of abortion or ovarian and bladder surgery were obtained using an appropriate questionnaire. After completing the Beck (Depression) questionnaire, fertile women were divided into two groups: depressed fertile and non-depressed fertile women (Jackson-Koku,

2016). Infertile women were divided into depressed infertile and non-depressed infertile women. By scoring individual grades of the BECK depression ratings for each participant, the individual's score for depression was obtained directly (a score from zero to 63). The following scores indicated the overall level of depression: 0 to 13, indicating none to least depression, 14 to 19 indicating mild depression, 20 to 28 indicating moderate depression, and 29 to 63 indicating severe depression. After completing the Beck (Depression) questionnaire, fertile women were divided into depressed fertile and non-depressed fertile - infertile women were divided into depressed infertile and non-depressed infertile groups.

Blood samples were taken to measure LH, FSH, Inhibin B, AMH and cortisol. To measure AMH levels, individuals were on days 2-4 of their period, and 10 mL of blood samples were taken from the patients. After centrifuging blood at 1000 g for 15 minutes, serum was extracted for analysis. AMH level was measured by electro-quantitative luminescence technique with VIDAS device and BIOMERIEUX kit. ELISA technique, Monobind kit and Inhibin B GEN2 kit were used to measure LH, FSH and InhibinB. To measure cortisol, a serum sample was used at 8-11 am. The data obtained were analyzed using chi-square (for which of the analysis-mention please), independent t-test (for which of the analysis-mention please), Pearson's correlation coefficient (for which of the analysis-mention please), one-way ANOVA (for which of the analysis-mention please), and linear regression (for which of the analysis-mention please) using IBM-SPSS Statistics tool version 24 with P<0.05 considered to be statistically significant.

3.0 RESULTS

Hundred infertile women (average age of 34.4± 7.1 years?) and 50 fertile women (average age of 34.2± 6.2 years?) participated in this study. Socio-demographic information is presented in **Table 1**. The results showed no significant difference in age, BMI, smoking, and employment status between the two groups, i.e., fertile and infertile groups.

In the current study, infertility markers and stress hormones (cortisol) were evaluated in the two groups. There was a significant difference in serum levels of AMH between the two groups (*P*-value <0.0001). The ovarian reserve in the infertile women was significantly lower than in the control group. The levels of gonadotropin hormones, i.e., LH and FSH, were significantly different between the two groups (*P*-value <0.0001). However, no significant differences were seen in the serum levels of cortisol and Inhibin B (*P*-value = 0.777, *P*-value = 0.789, respectively). These aforementioned results are demonstrated in **Figure 1.**

Table 1. Socio-demographic variables among infertile and fertile women (mean ± deviation).

	Fertile women (N=50)	Infertile women (N=100)	*P*-value
Mean age (year)	34.2±6	34.4±7	0.248
Mean BMI (Kg/m2)	24.7±5.4	25.4±4.7	0.365
Smoking	3 (6%)	12 (12%)	0.248
Employment status (Employed)	16 (32%)	40 (40%)	0.220

To evaluate the relationship between the biomarkers, Spearman's correlation coefficient was calculated, and the results were presented in **Table 2**. According to the results, a strong significant relationship was observed between AMH and other studied biomarkers (i.e., LH, FSH, and Inhibin B) (*P*-value <0.0001). There was also a significant relationship between gonadotropin and Inhibin B hormones (*P*-value <0.0001). A strong significant relationship was observed between AMH and other studied biomarkers (i.e., LH, FSH, and Inhibin B) (*P*-value <0.0001), and there was also a significant relationship between gonadotropins LH, FSH, and Inhibin B hormones (*P*-value<0.0001) **(Table 2)**. Cortisol showed a significant association with the FSH hormone (*P*-value= 0.022). There was also a significant relationship between depression and FSH, AMH, LH, and Inhibin B (*P*-value< 0.05) **(Table 2)**.

Based on the Beck's Depression Inventory results, the two groups were evaluated for the severity of depression, and the results are given in **Table 3**. According to the results and statistical studies, there was a significant difference between the two groups regarding depression (*P*-value = 0.003). These results suggest that depression is significantly more common in infertile women.

A comparison in terms of the concentration of studied biomarkers was performed between depressed fertile and non-depressed fertile women **(Table 4)**. Based on the results, no significant difference was observed between the two groups in the concentration of

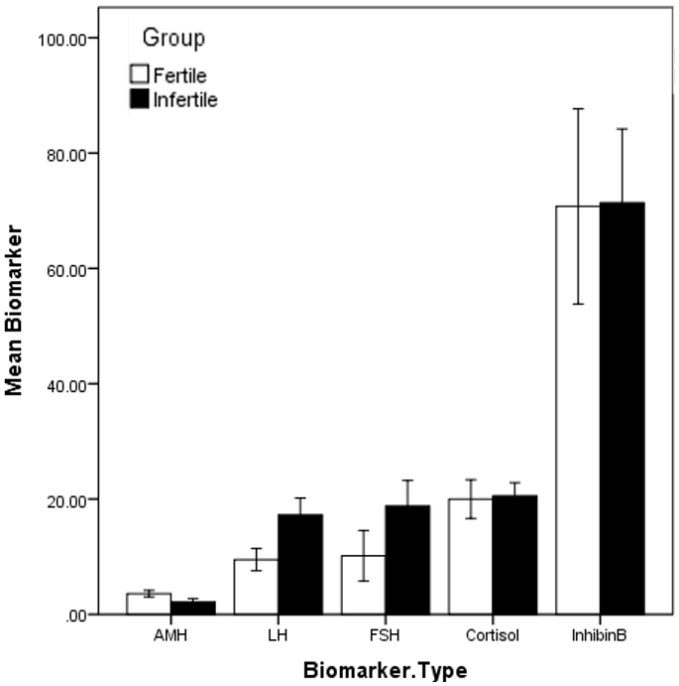

Figure 1. Serum levels of the Anti-Müllerian Hormone (AMH), Luteinizing hormone (LH), Follicle-stimulating hormone (FSH), cortisol, and Inhibin B based on fertility status. There was a significant difference in the serum levels of AMH, LH, and FSH between the two groups (*P*-value <0.0001). However, no significant differences were seen in the serum levels of cortisol and Inhibin B (*P*-value = 0.777, *P*-value = 0.789, respectively) between the two groups.

markers of AMH, LH, FSH, Cortisol & Inhibin B (P value > 0.05). A comparison of AMH, LH, FSH, Cortisol and Inhibin B biomarkers was also performed between depressed and non-depressed infertile women **(Table 5)**. According to the results, depression is significantly associated with AMH in infertile women (*P*-value = 0.049). In other words, it can be concluded that among infertile women, depression has affected the concentration of AMH hormone and has caused a greater decrease than in the non-depressed infertile group. Other hormones were not significantly different between the two groups. Finally, the concentrations of AMH, LH, FSH, Cortisol and Inhibin B biomarkers were compared between depressed infertile and depressed fertile women **(Table 6)**. Based on the results, AMH and FSH showed a significant difference between the two groups of depressed fertile and depressed infertile women (*P*-value = 0.005, *P*-value = 0.042).

4.0 DISCUSSION

Many studies show increased stress, anxiety and depression in today's society, followed by infertility in women. The prevalence of depression and stress is high in infertile women (Hashimoto et al., 2021; Lambert-Messerlian & Harlow, 2006). These increases have prolonged infertility and also caused damage to marital relationships, reducing mental health and quality of life (Berg & Wilson, 1991; Sargolzaee et al., 2001). The present study was conducted to investigate the relationship between infertility and its markers with stress and depression in women. In our study, the prevalence of depression was significantly higher in infertile women (54%) than in fertile women (30%). Our results are confirmed by the studies that will be mentioned below. Haririan et al. estimated the prevalence of depression to be 21%, in infertile women (Haririan et al., 2010). The study by Ramazanzadeh et al. showed that 151 women (40.8%) had depression and 321 women (86.8%) had anxiety. Depression had a significant relation with the cause of infertility, duration of infertility, educational level, and women's jobs. Findings showed that anxiety and depression were most common after 4–6 years of infertility, and especially severe depression could be found in those who had infertility for 7–9 years (Ramezanzadeh et al., 2004). Holley et al. estimated the prevalence of depression in 448 people (>8 locations) in the San Francisco Bay Area at 39.1 %. A total of 174 women and 144 of their male partners did not have a successful child-related outcome (Holley et al., 2015).

The pathological mechanism of depression is not very clear. It has been reported that patients with depression have shown neurotransmitter changes in monoamines and neurological dysfunction in the cerebral cortex and hippocampus (Pasch et al., 2012; Wang et al., 2017). However, many hormones, including sex hormones, are involved in depression. Depression is estimated to be twice as common in women as in men (Gu et al., 2016). This may be due to the possible effect of estradiol on depression. Despite the reduced estradiol emissions in depressed individuals, LH and FSH levels have been greatly increased. This is probably due to the removal of the inhibitory effect of estradiol on gonadotropin hormones (Chhibber et al., 2017; Goel et al., 2014).

Our study showed a significant relationship between LH and FSH concentrations in fertile and infertile women. FSH also showed a significant association with cortisol concentration. Our study is consistent with Gu et al. In this study (Gu et al., 2018), rats with removed ovaries showed depression-like behaviours, with increased LH and FSH and decreased monoamine. The levels of these monoamines in the stress-treated groups changed only after the

Table 2. The correlation coefficient in LH, FSH, AMH, Cortisol, Inhibin B, and depression.

	AMH	LH	FSH	Cortisol	Inhibin B	Depression
AMH Correlation Coefficient	-	.488**	.508**	.115	.413**	.414**
***P*-Value**	-	.000	.000	.161	.000	.000
LH Correlation Coefficient	.488**	-	.731**	.129	.182*	.210**
***P*-Value**	.000	-	.000	.116	.026	.010
FSH Correlation Coefficient	.508**	.731**	-	.187*	-.201*	.194*
***P*-Value**	.000	.000	-	.022	.014	.017
Cortisol Correlation Coefficient	.115	.129	.187*	-	.105	.054
***P*-Value**	.161	.116	.022	-	.203	.509
Inhibin B Correlation Coefficient	.413**	.182*	-.201*	.105	-	.212**
***P*-Value**	.000	.026	.014	.203	-	.009
Depression Correlation Coefficient	.414**	.210**	.194*	.054	.212**	-
***P*-Value**	.000	.010	.017	.509	.009	-

** Correlation is significant at the 0.05 level (2-tailed).*

*** Correlation is significant at the 0.01 level (2-tailed).*

There were significant differences between correlation of AMH/depression P-Value < 0.001, LH/ depression P-Value < 0.05, FSH/ depression P-Value < 0.05, inhibin B/depression P-Value < 0.001, inhibin B/AMH P-value <0.001, inhibin B/LH P-value <0.05, inhibin B/FSH P-value <0.05, inhibin B/Depression P-value <0.001, Cortisol/ FSH P-Value <0.05, Cortisol/ depression P-Value <0.05, FSH/AMH P-Value <0.001, FSH/LH P-Value <0.001, FSH/Cortisol P-Value <0.05, FSH/Inhibin B P-Value <0.05, FSH/Depression P-Value <0.05, LH/AMH P-Value <0.001, LH/FSH P-Value <0.001, LH/Inhibin B P-Value <0.05, LH/Depression P-Value <0.05, AMH/LH P-Value < 0.001, AMH/FSH P-Value < 0.001, AMH/ Inhibin B P-Value < 0.001 and AMH/ Depression P-Value < 0.001. Spearman's correlation test.

Table 3. Depression scores in the two groups of fertile and infertile women. Chi-square test, *P*-Value<0.05.

			Depression scores				*P*-Value
			0-13 (None depression)	**14-19 (Mild depression)**	**20-28 (Moderate depression)**	**29-63 (Severe depression)**	
Groups	**Fertile**	Count	35	8	7	0	
		N(%)	50 (70)	50 (16)	50 (14.0)	50 (0)	<0.05
	Infertile	Count	46	23	23	8	
		N(%)	100 (46.0%)	100 (23.0%)	100 (23.0%)	100 (8)	0.003
Total		Count	81	31	30	8	
		N(%)	150 (54)	150 (20.7)	150 (20)	150 (5.3)	--

stressful treatment. The cortisol and ACTH in the serum of the surgery/stress group were much higher than those in the sham surgery group (Gu et al., 2018).

In our study, cortisol did not show significant differences between the fertile and infertile groups of women. Some studies have shown that higher levels of cortisol were associated with decreased pregnancy rates. The cortisol levels of 485 individuals were measured at 7 to 8 am, and a significant difference was observed between fertile and infertile women (Cesta et al., 2018). Also, a study conducted to determine the role of a coping-ineffectiveness, and psychoendocrine stress responses upon the outcome of in vitro fertilization treatment among 40 women revealed that the women with a high Zung depression score, high anticipatory state anxiety levels and high anticipatory cortisol concentrations have lower pregnancy rates (Demyttenaere et al., 1992). One reason for the discrepancy between the finding in the current study and the literature may be due to the time of the sample collection. In our study, the serum sample was collected from 8 am to 11 am.

Ovarian reserve is the basis of women's fertility, and reproductive potential in women is based on the quantity and quality of primary follicles. Our study showed a significant difference in the mean AMH concentration in both fertile and infertile women. Our study was consistent with Broer et al. suggestion that AMH could be used to predict response during ovulation and the reproductive process, whereas some studies reported on AMH and antral follicle count (AFC) (Han et al., 2022; Iuliano et al., 2022; Lan et al., 2013; Muharam et al., 2022; Mutlu et al., 2013; Scheffer et al., 2014).

Table 4. Serum hormones levels in depressed and not depressed groups of fertile women

	Hormones	Depression*	No depression**	*P*-value
Fertile (control group)	AMH	2.87±2.14	3.90±1.83	0.097
	LH	11.93±9.00	8.41±5.43	0.067
	FSH	15.52±28.03	7.85±2.29	0.907
	Cortisol	21.90±9.45	19.16±12.80	0.315
	Inhibin B	55.59±38.82	77.25±66.26	0.300

**N (%)=15 (30%); **N (%)=35 (70%)*

Data are presented as mean ± std deviation—a comparison between studied biomarkers in depressed fertile and non-depressed fertile women. No significant differences were observed between the two groups. Chi-square test, *P*-value< 0.05.

Table5. Serum hormones levels in depressed and not depressed groups of infertile women

	Hormones	Depression*	No depression**	*P*-value
Infertile (Case group)	AMH	1.51±2.47	2.89±3.46	0.049
	LH	18.52±16.93	15.74±11.41	0.594
	FSH	22.10±27.77	14.90±11.66	0.496
	Cortisol	20.16±11.34	21.01±11.50	0.666
	Inhibin B	69.09±68.80	74.08±59.60	0.439

** N=54 (54%)** N=46 (46%)*

Data are presented as mean ± std deviation—a comparison between studied biomarkers in depressed infertile and non-depressed infertile women. There was a significant difference in AMH serum levels between the two groups. Chi-square test, *P*-value< 0.05.

Table 6. Serum hormones levels in depressed infertile and depressed fertile women groups

Hormones	Depressed fertile *	Depressed infertile **	*P*-value
AMH	2.87±2.14	1.51±2.47	0.005
LH	11.93±9.00	18.52±16.93	0.152
FSH	15.52±28.03	22.10±27.77	0.042
Cortisol	21.90±9.45	20.16±11.34	0.521
Inhibin B	55.59±38.82	69.09±67.80	0.700

**N=15(22%); ** N=54(78%)*

Data are presented as mean ± std deviation. There were significant differences in AMH and FSH serum levels between the two groups. Chi-square test, *P*-value< 0.05.

Summary estimates of sensitivity and specificity for AMH were 82 and 76%, respectively, and 82 and 80%, respectively, for AFC (Broer et al., 2011). Also, in another study, it was reported that low levels of AMH were associated with infertility, which was consistent with our study (van Rooij et al., 2002). But another study showed that pregnancy could occur even at low levels of serum AMH, which is inconsistent with our finding (Lamazou et al., 2021). In this study, Patients were divided into three groups according to their serum AMH level: group 1 was defined by patients with AMH level <0.97 ng/mL, group 2 were patients with AMH level between 0.97 ng/mL and 2.60 ng/mL, and group 3 were patients with AMH level between 2.61 ng/mL and 6.99 ng/mL. The primary outcomes were cancellation, embryo transfer and clinical pregnancy, ongoing pregnancy and implantation rates and their statistical evaluation was insignificant. The serum AMH level seems to represent a quantitative marker of the ovary but not a qualitative marker (Lamazou et al., 2011).

Finally, in our study, the analysis of the studied hormones showed that only AMH was significantly different between the two groups of depressed and non-depressed infertile women. It can be interpreted that among infertile women, depression affected the concentration of AMH and caused a greater decrease than in the non-depressed infertile group. Our study also concluded that infertility-induced depression might affect AMH and FSH levels. Due to the increase in infertility, investigating its causes and factors can play an important role in eliminating and treating infertility.

In this study, we examined hormonal factors and the mental state of infertile women. Our study shows the relationship between depression and infertility. This article suggested that to achieve successful fertility, the mother's mental state and depression must be considered.

5.0 CONCLUSIONS

The results of the present study showed that depression and psychological conditions of women have a meaningful and significant relationship with their fertility markers of AMH, LH, FSH, cortisol and Inhibin B.

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Conflicts of Interest: The authors declare no conflict of interest.

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