2. REVIEW OF LITERATURE

2.1 PSYCHOLOGICAL STRESS

- Leader A et al (1984) reported that duration of infertility increases of stress\textsuperscript{108} and according to Donkor ES et al (2007), the greater the number of years women spent in infertility treatment, the more their stress levels increased\textsuperscript{109}. The survey conducted in Southern Ghana revealed that the majority (64\%) of women felt stigmatized, and that higher levels of perceived stigma were associated with increased infertility-related stress as well as lower levels of education.

- In view with Harrison et al (1986)\textsuperscript{110}, Edelmann and Golombok (1989)\textsuperscript{111}, high levels of anxiety have been suggested possibly to have a direct effect in reducing conception rates. The mechanism whereby increased depression and anxiety may lead to infertility may be explained by a link between hormonal changes and the psychological states.

- Freeman et al (1987) conducted a pilot investigation on emotional and psychosocial factors in follow-up of women after in vitro fertilization (IVF) treatment. One hundred and fifty-six women who enrolled for treatment in an IVF program were interviewed, 15 months (mean interval) after the last program contact. Perceptions of treatment stress, decisions about further treatment and the extent of resolution of the infertility crisis were investigated. Standard self-report instruments were used to assess emotional status, self-esteem and marital adjustment. The results showed that about half of the couples described infertility as the most upsetting experience of their lives\textsuperscript{112}. About 77\% of the couples (n=94) describe
their experience of infertility to be either stressful or very stressful according to Mahlstedtet PP et al (1987)\textsuperscript{113}.

- **Cook et al (1989)** stated that the major difficulty facing patients during infertility is anxiety\textsuperscript{114}.

- **Berg B et al (1991)\textsuperscript{115}, Hsu and Kuo (2002)\textsuperscript{116}** found that couples who spent more years in infertility treatment showed a higher level of psychological distress. They found an increase of emotional stress after the third year of infertility treatment. But **Guz H et al (2003)** reported that depression and anxiety were improved in infertile women as their age and duration of infertility increased. Women were more distressed by infertility whether they or their spouse caused the reproductive impairment\textsuperscript{117}.

- Research among infertile women done by **Domar AD et al (1992)** has shown that infertile women are likely to experience higher levels of depression when compared to fertile women\textsuperscript{118}.

- **Sanders KA et al (1997)** conducted a prospective study of psychosocial stress and fertility in women and concluded that psychosocial stress influences fertility in females but as yet mechanisms remain unclear\textsuperscript{119}.

- **Greil (1997)** stated that anxiety and depression were frequently observed in infertile women compared to controls. Infertility causes a higher psychological distress level at women than men. Qualitative studies on the psychological consequences of infertility present infertility as a devastating experience, especially for women\textsuperscript{120}.

- **Oddens BJ et al (1999)** conducted a comparative survey in Belgian women and proved that infertile Belgian women had more depressed mood, memory/concentration problems and anxiety than a control
population. Infertility can indeed be very stressful for the affected couples. The survey involves 281 patients awaiting assisted reproduction treatment at five centers in three countries, and 289 population controls. It was investigated whether the patients had experienced more negative emotional feelings and negative emotional impact during periods when they were attempting to conceive as compared with the controls, and whether there was any difference in their well-being at the time of consultation. The study was performed in the context of burden of fertility problems. The survey was carried out using questionnaires of the self-administration type. Women with fertility problems reported higher prevalence of negative emotions than the controls. They reported more changes in inter partner relationships (either negative or positive). Sexuality was negatively affected among them. One in four (24.9%) of women had scores indicating depressive disorders as compared with only 6.8% of the controls. Current well-being was even more markedly affected in women with previous unsuccessful in-vitro fertilization (IVF) experience. The 'infertility' life event was perceived as severe by both patients and controls. Both prior to consultation and during diagnosis and treatment, women with fertility problems had a higher prevalence of reported negative psycho-emotional experiences than women without fertility problems.

- Kee BS et al (2000) compared the level of stress in infertile women with fertile women in different stages of medical investigation for infertility. One hundred thirty-eight (138) women receiving medical treatment for infertility were administered the State Trait Anxiety Inventory (STAI) and
the Beck Depression Inventory (BDI). Infertile women showed significant increase in anxiety and depressive symptoms than the fertile women. Anxiety and depression in the In Vitro fertilization (IVF)-failed women were significantly higher than the IVF-success women. According to the duration of infertility, STAI and BDI were moderately elevated in the first stage (< 3 year). There was a decreased psychological stress with advanced infertility duration. On depression scales, the intermediate and final duration of infertility patients showed less symptomatology than the first-stage patients.

- **Matsubayashi H (2001)** studied the emotional distress in a Japanese population. This study was carried out in order to clarify whether Japanese infertile women experience emotional distress. A cross-sectional questionnaire study was performed to assess the psychological states of 101 infertile women compared to 81 healthy pregnant women. The hospital anxiety and depression scale (HADS) and the profile of mood states (POMS) were administered. These questionnaires produced scores for depression/dejection, anxiety, aggression/hostility, lack of vigour, fatigue, tension anxiety, and confusion. The HADS and the POMS scores of infertile women were significantly higher than those of pregnant women, except for fatigue score. Infertile women with positive HADS indicating emotional disorders (39/101, 38.6%) were significantly more than those of pregnant women. The HADS scores were not affected by the women’s age, duration of infertility, experience of conception, routine tests, and work states. In this Japanese population, infertile women
reported higher levels of emotional distress than pregnant women, suggesting psychological support is needed for infertile women.  

- **Lee TY et al (2001)** conducted a study in Taiwan to determine the effect of an infertility diagnosis on treatment-related stresses. Only wives with diagnosed female infertility expressed higher distress to infertility than their husbands. Although no differences in psychosocial responses were found among husbands, regardless of the diagnosis, wives with diagnosed female infertility experienced higher distress in self-esteem and less satisfaction in acceptance by in-laws than wives experiencing a diagnosed male infertility. Women appear to experience significantly more stress from infertility tests and treatment than men, regardless of whether female infertility was present. Husbands, regardless of the diagnosis, showed no difference in psychological responses. Similar findings were reported in an investigation of 138 couples where men’s levels of distress and perceived marital and sexual satisfaction were unrelated to cause of infertility.  

- **Campagne DM (2006)** performed a study in Spain and stated that acute and chronic stress may cause infertility, or lower the success rate of fertility treatments.  

- **Fatoye GK et al (2008)** studied the emotional burden of infertility in Nigerian women. The subscales of the Hospital Anxiety and Depression Scale and a schedule detailing socio-demographic and infertility-related variables were administered on women with infertility and a matched control group. The rates of significant anxiety symptoms (39.4) and depressive symptoms (40.4) among the women with infertility were higher than the corresponding rates of 11.1 and 10.1 in the control group. Their
mean anxiety and depression scores were also higher (P<0.001). Low religiosity, friction with husband's family, polygamous relationship and family pressure on husband predicted symptoms among the women with infertility. Public campaign to improve attitude towards women with infertility is advocated. Therapeutic mental health services are important for these women\textsuperscript{125}.

- A Greek study done by Lykeridou K et al, (2009) in 404 women attending infertility clinic using State-Trait Anxiety Inventory questionnaire (STAI), underlines that women undergoing infertility have high levels of anxiety\textsuperscript{126}. 
2.2 OXIDATIVE ENZYMES

- **Sabatini et al. (1999)** determined the activity of superoxide dismutase (SOD) in women undergoing in vitro fertilization in Royal London Hospital, and reported that the SOD activity was inversely related to the fertilization of oocytes. Superoxide dismutase activity was present in all the Follicular Fluid (FF) studied and mean levels were statistically significantly higher than in serum. Total protein concentrations in serum were statistically significantly correlated with corresponding concentrations in FF. Follicular fluid from patients whose oocytes did not become fertilized had a statistically significantly higher level of SOD activity than that from patients whose oocytes did become fertilized. Superoxide dismutase activity is present in FF and is higher than in serum$^{127}$.  

- **Polak et al (2001)** reported that the levels of antioxidants in patients with infertility were significantly lower than those in fertile patients and the levels of malondialdehyde (MDA), a lipid peroxidation end-product were higher in patients with infertility than in fertile women. Total antioxidant status was measured in peritoneal fluid obtained from 18 infertile women suffering from minimal or mild endometriosis, 23 patients with unexplained infertility, 12 women with tubal infertility and 13 fertile women. Low antioxidant status in peritoneal fluid may play a role in the pathogenesis of infertility$^{83}$.  

- **Agarwal A et al (2005)** found that oxidative stress (OS) affects multiple physiological processes from oocyte maturation to fertilization, embryo development and pregnancy$^{90}$.  


• **Pyari JS et al. (2006)** assessed the free radicals in infertile women in North Indian population and found that infertile women had high MDA levels and low SOD levels. A prospective study was conducted on 75 women with primary infertility, 20 with secondary infertility and 30 fertile controls. Markers of oxidative stress viz., level of malonyldialdehyde (MDA) for free radicals and antioxidants catalase (CAT) and superoxide dismutase (SOD) as scavenging enzymes were measured in blood and endometrial tissue. Infertile women had significantly (P<0.001) high MDA levels and significantly (P<0.001) low CAT and SOD levels in both blood and endometrium as compared to those in controls. Unexplained infertility group of patients had significantly (P<0.001) high levels of oxidant (MDA) while antioxidant (CAT and SOD) levels were significantly low (P<0.001)

• **Mehendale et al. (2009)** examined the oxidative stress-mediated polyunsaturated fatty acid alterations in female infertility in North Indian population and reported that the levels of MDA were increased in infertile women. Forty-five infertile and 30 control women were enrolled via the Department of Obstetrics and Gynecology of Bharati Medical College Hospital, Pune, India. Essential polyunsaturated fatty acids, malondialdehyde (MDA; oxidative stress-marker) levels and antioxidants (vitamins E and C) were measured in both groups. Results show that plasma eicosapentaenoic acid and erythrocyte docosahexaenoic acid levels were reduced (p < 0.05) in infertile women as compared to controls. Likewise, levels of MDA, a peroxidative product of essential fatty acids, were increased (p < 0.05) and vitamin E concentrations were decreased
(p < 0.05) in infertile women, suggesting that increased oxidative stress and consequent altered essential polyunsaturated fatty acids are associated with infertility\textsuperscript{129}. 
2.3 COUNSELING

- Psychological interventions, such as behavioural treatment, aimed at reducing stress have shown to be effective in a number of studies by Sarrel and DeCherney (1985)\textsuperscript{130}, Domar AD et al (1990,2000)\textsuperscript{131,132}, Facchinetti F et al (2004)\textsuperscript{133}.

- In view with Dunkel-Schetter C et al (1991), the goal of psychological interventions should be the minimization of identified risk factors for infertility-related distress and the strengthening of protective factors\textsuperscript{134}.

- Domar AD et al (1992) have shown that psychological interventions were successful at decreasing anxiety and at improving conception\textsuperscript{118}.

- A number of studies stated that reduction in stress would not only be beneficial for the couples’ well-being – it could also possibly enhance their chances of achieving a pregnancy (Facchinetti et al, 1997\textsuperscript{135}; Eugster and Vingerrhoets, 1999\textsuperscript{136}; Gallinelli et al 2001\textsuperscript{137}; Boivin J and Schmidt 2005\textsuperscript{138}).

- Domar AD et al (2000) revealed that infertile women express higher levels of distress than fertile women, with distress peaking between the 2\textsuperscript{nd} and 3\textsuperscript{rd} year. The study was performed to determine whether group psychological interventions could prevent this surge. One hundred and eighty-four women who had been trying to conceive between 1 and 2 years were randomized into a cognitive-behavioral group, a support group, or a control group. All experimental participants attended a 10-session group program. Participants completed psychological questionnaires before treatment and again at 6 and 12 months. The cognitive-behavioral and support participants experienced significant psychological improvement at
6 and 12 months compared with the control participants, with the cognitive--behavioral participants experiencing the greatest positive change\textsuperscript{132}.

- **Kee BS et al (2000)** reported that psychological support and counseling should be provided for women who experience severe stress\textsuperscript{122}.

- **Matsubayashi H et al (2001)** stated that psychological support is needed for infertile women\textsuperscript{44}.

- **Boivin J et al (2001)** stated that professional psychological interventions might have significant therapeutic benefits for women attending infertility clinics\textsuperscript{139}.

- According to **De Liz TM et al (2005)**, psychotherapy (Group and individual/couple therapies) showed positive effects on infertile patients. Group and individual/couple psychotherapy led to a decrease in feelings of anxiety. Upon termination of psychotherapy, a reduction of depressive symptoms in patients was greater after 6 months. Psychotherapy accompanying IVF treatment yielded similar conception success rates to psychological interventions administered to patients not in specific medical care. Results are suggestive of positive effects of psychotherapy for infertile patients\textsuperscript{140}.

- In line with a study in Nigeria by **Upkong D and Orji E (2006)**, psychological interventions and improvements in the organization of care is essential to positively impact on outcome during treatment in infertile women. The General Health Questionnaire (GHQ-30), Beck Depression Inventory (BDI) and the Anxiety Subscale of the Hospital Anxiety and Depression Scale (HADSA) were administered to 112 women with
infertility at the time of their first presentation to a fertility clinic in a tertiary referral centre. The comparison group comprised of 96 women presenting at the family planning clinic of the same institution. In addition to demographic data, a structured questionnaire was used to collect obstetric information and clinical details from the participants. The prevalence of psychiatric morbidity was 46.4% (GHQ cases) in the infertile women, 37.5% and 42.9% were cases of anxiety and depression respectively. Women suffering from infertility scored significantly higher on all outcome measures of psychopathology. The results of the multiple regression analysis showed that the sociodemographic variables of the women with infertility contributed to the prediction of psychiatric morbidity (GHQ-30 score), because of the effects of age, not having at least one child and poor support from spouse (R2 =0.26 Adjusted R2=0.19 F (10,101) =3.57 p=.001). Lack of support from husband also predicted depression and anxiety. Low level of education, polygamous marriage, unemployment, lack of support from in-laws and duration of illness were not predictors of mental ill health. Infertility is associated with high levels of psychiatric morbidity\textsuperscript{141}.

- **Campagne DM (2006)** performed a study in Spain and stated that first reducing stress may diminish the number of treatment cycles needed before pregnancy is obtained, may prepare the couple for an initial failure of treatment or even make the more invasive techniques unnecessary\textsuperscript{124}.

- According to **Lykeridou K et al (2009)**, women who participate in fertility treatment should receive a professional individualized
psychological support, in order to diminish or relieve the perceived infertility-related stress of these women$^{126}$. 