1. INTRODUCTION

Parenthood is the most dreamt of and the happiest stage in the life of every married couple. It is undeniable that children not only bring in happiness to the family, but leads to a change in the whole perspective of the couple and family concerned: and a continuum in purpose of life is ushered in. "Nonetheless, 10% of the couples face emotional trauma due to non conception and miscarriages during the early married period or planned parenthood. Though the maternal and child health have improved significantly in the past decade, mainly through focusing on reproductive health (Cousen et al, 2011), Infertility is often a neglected area in these efforts. Infertility often leads to distress and depression in modern societies, and a more severe discrimination and ostracism in many parts of the world (Cui et al, 2010), precipitated by small family norms and gender equations.

In recent times, the definitions of infertility and its treatment modalities have changed. According to National Institute for Health and Clinical Excellence (NICE) 2004, Infertility is defined as failure to conceive after regular unprotected sexual intercourse for two years in the absence of known reproductive pathology. Then the American Society for Reproductive Medicine (ASRM) 2008, defined infertility is a disease defined by failure to achieve a successful pregnancy after 12 months or more of regular unprotected intercourse. According to the International Committee for Monitoring Assisted Reproductive Technology (ICMART) and the World Health Organization (WHO), infertility is ‘a disease of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse (Zegers-Hochschild et al, 2009). Demographic studies define infertility as the absence of a live birth in sexually active non-contracepting women (Larsen et al, 2005).

As on date, infertility remains as a highly prevalent global emotional burden, affecting 8 to 12% of reproductive-age couples (Ombelet et al, 2008a & 2008b, Biovin et al, 2007). In some parts of the world, the rates of infertility are much higher, reaching as high as 30% of the population (Nachtigall et al, 2006; Ombelet et al, 2008a & 2008b). This is especially true in a number of regions of high
infertility prevalent countries such as South Asia, sub-Saharan Africa, the Middle East and North Africa, Central and Eastern Europe and Central Asia (Mascarenhas et al., 2012). Further, there is a terrible gender bias in attributing the cause of infertility. More often, women are blamed as the sole reason for the childlessness, many times leading to domestic violence and divorce. Now we know that men are equally responsible for infertility (Stellar et al., 2016).

There are two types of infertility i.e., Primary and Secondary. The absence of a live birth for a couple who desire to have a child and not using any contraceptives is known as primary infertility (PI). The absence of a second live birth for a couple who desire to have a child and not using any contraceptives is defined as secondary infertility. In both the cases, couples should have been in a union for at least five years (Mascarenhas et al., 2012). The prevalence of primary infertility in India lies between 3.9-16.8% (WHO, 2004). The estimates vary in between different states; 3.7% in Uttar Pradesh, Himachal Pradesh, Maharashtra (Talwar et al, 1986), 5% in Andhra Pradesh (Unisa et al, 1999) and 12% in Kashmir. Moreover the prevalence also varies across the castes and tribes of the same region in India (Zargar et al., 1997; Kumar et al, 2007). Infertility is further categorized into four types based on the partner responsible for infertility 1) Female factor - Female partner of the couple is responsible, 2) Male factor - Male partner of the couple is responsible, 3) Combined - Both male and female partners are responsible and 4) Unexplained - Both male and female are normal and the underlying cause unknown. Numerous studies have attempted to find the distribution of infertility based on these particular criteria and reported that female factor infertility accounts for 30-35%, male factor infertility accounts 30-35%, combined 15-20% and unexplained infertility around 10-15% (Malekshah et al, 2011; Osman et al, 2010).

The etiology of infertility is an important criterion for recognition and characterization of infertile women and men. (Romero et al, 2008). The major causes of female infertility include ovulatory dysfunctions, tubal obstructions, unexplained, endometriosis and pelvic inflammatory disease. Ovulatory dysfunctions have been noticed in a large proportion of female infertility patients. Anovulation affects 17-37% of infertile women, primarily due to Poly Cystic
Ovarian Syndrome (PCOS), Hormonal imbalance. Premature ovarian failure (POF) and Decreased ovarian reserve (DOR) may also lead to infertility though the frequency is low (Farhi et al., 2011). Patency of fallopian tubes is necessary for the transport of gametes and fertilization. Obstructions in the fallopian tubes may cause tubal factor infertility ranging from 11-33%. The blocks may be unilateral or bilateral. A few infertile women may have normal ovaries and fallopian tubes but still suffer from infertility in 5-20% i.e., unexplained infertility (Farhi et al., 2011).

Among the males, the impaired spermatogenesis or abnormal semen parameters are the major cause of infertility. The WHO categorized men into different categories based on the spermiogram/ semen analysis Normozoospermia - Normal semen parameters: 1) Azoospermia - Lack of spermatozoa in semen, 2) Oligozoospermia - Sperm count <15 million/ml, 3) Asthenozoospermia - Sperm motility <40%, 4) Teratozoospermia - Normal Sperm morphology <4%, 5) Oligo Asthenozoospermia (OA) - Sperm concentration and motility are impaired, 6) OligoAsthenoTeratozoospermia (OAT) - Sperm concentration, motility and morphology are impaired. Apart from the above mentioned traditional factors, Stress and depression, reduced testosterone level, varicocele, pesticides, wifi and smoking alter the semen parameters (Gollenberg et al., 2010; Li et al., 2011; Petrelli et al., 2002; Naughton et al., 2001; Aavendano et al., 2012). The factors implicated in facilitating conception are: Lifestyle, nutrition, (Mendiola et al., 2010; Wong et al., 2003) antioxidants rich diet (Cocuzza et al., 2007) moderate exercise (Vaamonde et al., 2009).

With the advent of modern DNA technology, every disease is studied for their genetic basis. Many genes have been identified to be associated with both male and female infertility. It is evident that abnormal semen parameters of men and PCOS or tubal obstructions of women are reasons for causing infertility (Ohman et al., 2009; Liaqat et al., 2014; Omrani et al., 2005). These conditions are mainly influenced or caused by specific genes and infections in the human (Keck et al., 1998; Svenstrup et al., 2008). The expression of sex hormone genes and receptors must be properly regulated for achieving the spontaneous pregnancy, implantation in women (Almawi et al., 2015; Khafagi et al., 2014). The invasion of pathogens into
the reproductive system can be resolved many times by the first line defense/ innate immunity. Cytokines play many roles in reproductive physiology like mediation of inflammatory responses, regulation of gonadal steroid production and release (Simon et al, 1994). The study selected two gene SNPs; one from the sex hormones (ESR β) and the other from cytokines (IL 1β) based on the following features.

- The two genes play a role in ovulation either directly or indirectly (Takehara et al, 1994; Krege et al, 1998).
- The presence of their expression in both male and female reproductive systems and in successful pregnancy (Fertilization, Implantation, completing gestational period, etc) (Huang et al, 2007; Aquila et al, 2004)
- The presence of both the gene products in seminal plasma (Egger kruse et al, 2007; Solakidi et al, 2005).

Many infectious agents are implicated in infertility thus far. Some of them may cause STDs and some infections remain asymptomatic in many cases (Keck et al, 1998). The presence of asymptomatic infections may reduce the fertility (Egger kruse et al, 2007). Since the discovery of HLA in 1970s, they have been implicated as candidates for genetic susceptibility for genetic disease (Blackwell et al, 2009). To our knowledge there is no genetic association study on HLA DRB1* alleles association with infertility thus far creating a lacuna in this field. The most polymorphic HLA class II molecules i.e., HLA DRB1* alleles were evaluated for the association with infertility in the present study. Thus, the main objective of the study was to evaluate the genetic association of selected candidate genes/ SNPs and HLA DRB1* using the state of the art PCR technologies and also to look for other epidemiological variables and confounders that might influence the disease outcome. Similarly the two polymorphisms (rs1143634 and rs4986938) were studied either in male infertile patients or female infertile patients, whereas in our study we attempted to evaluate the polymorphisms association in both male and female infertile patients of same population.