IUG Journal of Natural Studies
Peer-reviewed Journal of Islamic University-Gaza

ISSN 2409-4587

IUGNES
Vol. 25, No 2, 2017, pp 33-41

Accepted on (14-03-2017)

Follicle-Stimulating Hormone Receptor Polymorphism in Infertile Palestinian Men

Nader N. Nahal[1,*]
Abd Allah A. Abed[1]
Maged M. Yassin[1]

[1]Department of Biotechnology, Faculty of Science, Islamic University of Gaza, Gaza Strip, Palestine

*** Corresponding author**
e-mail address:nader_20059@hotmail.com

Abstract

Follicle stimulating hormone (FSH) is necessary for normal reproduction. Follicle stimulating hormone receptor (FSHR) signaling stimulates proliferation of Sertoli cells and maintains spermatogenesis. This work aimed toinvestigate FSHR polymorphism in infertile Palestinian men. 56 males grouped into 24 normozoospermic controls, and 32 infertile males. Infertile males were grouped into 11 azoospermic males, and 21 oligozoospermic males. Semen analysis, FSH, Luteinizing hormone (LH) and Total testosterone were determined. Allelic variant of FSHR gene was determined by PCR-RFLP. Sperm count was significantly decreased in oligospermia and azoospermia compared to control. Sperm motility showed significant differences between the different groups of men.LH and FSH were significantly increased in azoospermia compared to controls and compared to oligospermia. The T testosterone was significantly decreased in oligospermia and azoospermia compared to controls. The SNPs of FSHR allele showed no significant difference in the prevalence of FSHR among the three groups. Sperm count was significantly decreased in mutant (Ser/Ser) FSHR allele compared to wild (Asn/Asn) FSHR allele. On the other hand, sperm motility showed no significant differences among various groups. LH was significantly increased in mutant FSHR allele compared to wildFSHR allele, whereas the T testosterone was significantly decreased in mutant FSHR allele compared to wildFSHR allele. However, there was no significant difference in FSH among various groups. It is conclude that the presence of mutant (Ser/Ser) FSHR allele is observed to be a cause for a decreased in a sperm count and T testosterone and increased of LH level.

Keywords:
Male infertility,
FSH,
LH,
T testosterone,
FSHR.

1. Introduction:

Follicle stimulating hormone (FSH) is a pituitary glycoprotein, which is necessary for normal reproduction in both male and female mammals (Foresta et al., 2008). The biological actions of FSH are exerted by binding to its membrane receptor (FSHR) in Sertoli cells of the testes and initiating signaling events via the G protein and/or other receptor coupling mechanisms (Meduri et al., 2008 and Zhang et al., 2012). The FSHR gene consists of 9 introns and 10 exons and a promoter region and is

located on chromosome 2p21 (Laan et al., 2012). Follicle stimulating hormone receptor signaling stimulates proliferation of Sertoli cells and maintain normal sperm production (spermatogenesis) by promoting intercellular communication with neighboring germ cells as well as other somatic cells (Zhang et al., 2012). In addition, FSH helps to determine testicular size and germ cell number per testis (Wang et al., 2014).Secretion of FSH is regulated by hypothalamic-anterior pituitary-testicular axis (Holt and Hanlley, 2012). Male infertility is a complex disease that involves both environmental and genetic factors. Impaired sperm production and function can be related to different congenital or acquired factors acting at pretesticular, post-testicular, or directly at the testicular level (Poongothai et al., 2009).In about 15% of the cases of male infertility, genetic abnormalities could be present, including chromosomal aberrations and single gene mutations (Ferlin et al., 2007 and O'Flynn O'Brien et al., 2010). A number of polymorphisms have been studied as potential risk factors for spermatogenetic failure, in particular, abnormalities of the FSHR gene, as well as FSH gene, would be expected to affect sperm production in males (Li et al., 2011). Mutation screening showed that the FSHR gene contained several single-nucleotide polymorphisms (SNPs) in the core promoter and coding region (Wunsch et al., 2005). The 2 most common SNPs in the coding region occur at nucleotide positions 919 (919A>G, Thr307Ala, and rs6165) and 2039 (2039G>A, Asn680Ser, and rs6166) in exon 10, in which A>G transitions cause amino acid exchange from threonine to alanine at codon 307 and from asparagine to serine at codon 680, respectively (Safarinejad et al., 2010, Grigorova et al., 2013 and Wu et al., 2015). Several studies have investigated the possible associations between the Thr307Ala and Asn680Ser polymorphisms in the FSHR gene and male infertility. Shimoda et al. (2009) reported that the combination of heterozygous FSHR variants might be responsible for male infertility in Japanese population. Similar results were found by Zalata et al. (2008) in Egyptian population, Balkan et al. (2010) in Turkish population, Safarinejad et al. (2010) and Gharesi-Fard et al. (2015) in Iranian population and Song et al. (2013) and Wu et al. (2015) in Chinese population. To our best knowledge, no previous study investigated FSHR gene and male fertility in Palestine. Therefore, the present study is the first to assess FSHR polymorphism in Infertile Palestinian men.

2. FSHR polymorphism and male infertility:

FSH regulates the function of testicular Sertoli cells, where spermatogenesis takes place. Mutations in the hormone and its receptor can cause impaired spermatogenesis in men, which could lead to infertility or subfertility. The association between FSHR gene polymorphisms, particularly Thr307Ala and Asn680Ser and male infertility risk has attracted widespread attention due to the unique biological functions of FSH. Some investigations in normal and infertile men and women reported no difference, while other studies revealed significant differences in the distribution of allelic variants between infertile subjects and normal controls.

Ahda et al. (2005) analyzed SNP in codon 680 in 438 Germen men with nonobstructiveazoospermia and in 304 controls. That no significant correlation between serum FSH levels and FSHR allele was found.

The possible role of three FSHR SNP was evaluated in Italian male infertility (Pengo et al., 2006). The data showed that in the Italian population, FSHR genotypes have no influence on FSH concentrations both in normal and infertile males and do not associate with spermatogenetic impairment.

Zalata et al. (2008) investigated the occurrence of Asn and Ser FSHR gene variants and its relationship with seminal anti-Müllerian hormone (AMH) among normozoospermic and infertile oligoasthenozoospermic (OAT) Egyptian males. There was significant increase in seminal AMH with Asn/Asn variant of FSHR gene than those with Asn/Ser or Ser/Ser.

The discrete codon combination with homo/heterozygous variation of the exon 10 in the FSHR gene was assessed in infertile Japanese men (Shimoda et al., 2009). The heterozygous genotype Thr/Ala-Ser/Asn was significantly increased in infertile patients compared with the controls. This finding showed that the combination of heterozygous FSHR can be responsible for male infertility. Safarinejad et al. (2010) analyzed FSH-R polymorphisms at codons 680 and 307 by RFLP in 172 Iranian infertile men and in an equal number of age-matched healthy fertile men. The results show no significant correlation between serum FSH levels and semen characteristics, or fertility status and FSH-R gene polymorphisms was found.

Wu et al. (2015) explored the associations between the Thr307Ala and Asn680Ser polymorphisms of the FSHR gene and male infertility. However, the combined genotypes Thr/Thr + Asn/Asn had an increased risk of

male infertility (OR=1.238; 95%CI: 1.001-1.537, P=0.049).

3. Materials and Methods:

The study population comprised 56 Palestinian males grouped into 24 normozoospermic healthy controls (normal sperm count≥20 X 10^6/milliliter), and 32 infertile males. Infertile males were grouped into 11 azoospermic males (zero sperm count), and 21 oligozoospermic males (sperm count <15 X 10^6/milliliter) were selected and recruited from assisted reproduction centers and private infertility clinics, from January to December, 2014. Semen samples were collected for each patient that performed according to the WHO (2010). In addition, hormone profile (FSH, LH and T testosterone) were determined using a solid phase ELISA based on the sandwich principle. DNA was extracted from ethylenediaminetetraacetic acid (EDTA) blood samples using the Wizard Genomic DNA Extraction Kit from Promega, USA according to the manufacturer recommendations. DNA extracted from blood samples was analyzed for the presence of FSHR gene Asn/Ser680 allele. Genomic DNA was analyzed using the PCR-RFLP technique with the primers which were designed based on the published sequence of the human FSHR gene at nucleotide 1624-2143 (codon 680) of exon 10. The PCR products were then digested with the restriction enzymes (BsrI for SNP at 2039 Ser680Asn), according to the manufacturer's protocol. The resulting DNA fragments were separated by length through agarose gel electrophoresis. Data were computer analyzed the Statistical Package for the Social Sciences (SPSS) version 21.

4. Results and Discussion:

4.1. Spermatogenic potential of the study population:

The present data revealed at Tables 1 and 2 that infertility had a negative impact on both sperm count and motility. Similar result was addressed (Zalata et al., 2008;Sableafarinejad et al., 2011; Grigorova et al., 2013). Our study showed that sperm count was significantly decreased in azoospermia and oligospermia compared to control.In sperm motility active andsluggish sperms was significantly decreased in azoospermia and oligospermia compared to control.Sluggish sperm was significantly decreased in azoospermia compared to oligospermia. Dead sperm was significantly decreased in azoospermia compared to control and oligospermia.Conversely, dead sperm was significantly increased in oligospermia compared to control.Decreased sperm count andmotility observed that result from destruction in seminiferous epithelium and hormonal abnormalities in the present study are in agreement with that reported in infertile men by Zalata et al. (2008) in Egyptian population,Safarinejad et al. (2011) in Iranian population, Li et al. (2011) in Chinese population and Grigorova et al. (2013) in Estonianpopulation.

Table 1 *Sperm parameters of fertile and infertile (oligospermia and azoospermia) groups*

Items	Group		t-test	P-value
	Fertile (n=24) Mean±SD	**Infertile** (n=32) Mean±SD		
Sperm count X10^6/milliliter	39.8±11.7	3.8±4.5	15.951	0.000
Active%	49.7±12.6	2.4±4.4	19.684	0.000
Sluggish%	25.8±4.5	15.9±12.6	3.646	0.001
Dead%	24.5±9.5	47.6±35.7	-3.083	0.003

Table 2 *Spermatogenic potential of the study population (n=56)*

Items	Group			F	P-value
	Azoospermia (n=11) Mean±SD	Oligospermia (n=21) Mean±SD	Control (n=24) Mean±SD		
Sperm count X 10^6/milliliter (mini-max)	0.0±0.0* (0.0-0.0)	5.7±4.4* (0.20-15.0)	39.8±11.7 (23.0-66.0)	135.007	0.000
Active% (mini-max)	0.0±0.0* (0.0-0.0)	3.7±5.0* (0.0-13.0)	49.7±12.6 (20.0-70.0)	195.321	0.000
Sluggish% (mini-max)	0.0±0.0* (0.0-0.0)	24.3±5.9# (10.0-40.0)	25.8±4.6 (20.0-35.0)	123.926	0.000
Dead% (mini-max)	0.0±0.0* (0.0-0.0)	72.5±8.9*# (50.0-90.0)	24.5±9.5 (10.0-45.0)	326.021	0.000

(*, # Significant, P<0.05): *Compare control group versus oligospermia and azoospermia, #compare oligospermia and azoospermia. Normozoospermic ≥20million/milliliter, oligozoospermic<15million/milliliter.
Source:*(WHO, 2010).*

4.2. Hormonal levels of the study population:

In our study we found the LH and FSH were significantly increased in azoospermia compared to controls. In addition, LH and FSH were significantly increased in azoospermia compared to oligospermia. Conversely, the T testosterone was significantly decreased inazoospermia and oligospermia compared to control (Tables 3 and 4). In Egyptian population by Zalata et al. (2008) agrees with our finding that the serum FSH levels was significantly increased in infertile men compared with normozoospermic group and serum testosterone levels were significantly decreased whereasno statistically significant association was identified with serum LH.Elevated FSH levels are usually a reliable indicator of germinal epithelial damage and are usually associated with azoospermia or oligospermia and low T testosterone level is indicators of hypogonadism of hypothalamic or pituitary origin. Safarinejad et al. (2010) in Iranian population, found the serum FSH level in the infertile men was higher than in the control and serum LH and T levels in the infertile men were lower compared with the control group but the difference did not reach statistical significance between two groups (P=0.08 and P=0.06, respectively). In addition, Grigorova et al., (2013) found the association with higher circulating FSH (P=0.01) and lower Inhibin B (P=0.046) were significant in the oligozoospermia subgroup. Interestingly, meta-analysis across the Estonian idiopathic infertility group and the Baltic male cohort reached statistically significant association not only with lower serum Inhibin B (P=0.037) but also with reduced T testosterone level (P=0.034) Lubbad (2015) in Infertile Men in Gaza Strip, found that testicular biopsy of infertile men with germ cell aplasia showed Sertoli cell partial atrophy that reflect the destruction in seminiferous epithelium which may lead to hormonal abnormalities of T testosterone, PRL, LH and FSH.

Table 3 *Hormonal levels of fertile and infertile groups*

Items	Group		t-test	P-value
	Fertile (n=24) Mean±SD	Infertile (n=32) Mean±SD		
LH (mIU/ml)	4.2±1.2	6.3±3.3	-2.977	0.004
FSH (mIU/ml)	4.5±1.2	14.0±11.0	-4.190	0.000
Testosterone (ng/ml)	6.0±1.1	3.3±1.3	7.837	0.000

Table 4 *Hormonal levels of the study population (n=56)*

Items	Group Azoospermia (n=11) Mean±SD	Oligospermia (n=21) Mean±SD	Control (n=24) Mean±SD	F	P-value
LH(mIU/ml) (mini-max)	8.4±4.5* (2.6-19.3)	5.3±1.7# (1.8-9.9)	4.2±1.2 (2.4-6.0)	11.798	0.000
FSH(mIU/ml) (mini-max)	22.9±14.6* (4.4-46.7)	9.2±3.7# (4.0-18.5)	4.5±1.2 (2.5-6.6)	28.305	0.000
Testosterone (ng/ml) (mini-max)	2.7±1.4* (0.93-5.0)	3.6±1.2* (1.39-5.5)	5.9±1.1 (3.1-8.2)	34.650	0.000

(*, # Significant, P<0.05): *Compare control group versus oligospermia and azoospermia, #compare oligospermia and azoospermia

4.3. Frequency of FSHR gene Asn/Ser variants among studied groups:

In the present study, variant screening was carried out among azoospermia, oligospermia and control fertile men to determine FSHR variants, Asn680 and Ser680, identified by BsrI restriction endonuclease (Figures 2 and 3). There was a tendency of Asn/Asn variant of FSHR gene to be higher in fertile men, while Ser/Ser variant to be higher in infertile men, however, there was nonsignificant difference of these variants among groups that presented in Tables 5 and 6. This finding is in accordance with that reported byPengo et al. (2006), Foresta et al. (2006), Zalata et al. (2008),Li et al. (2011)and Song et al. (2013). In addition, Gharesi-Fard et al. (2015), in Iranian population, found no significant separate association between the FSHR polymorphisms and male infertility risk as well as between patient and the healthy controls regarding both genotype and allele frequencies (P>0.05). On the other hand our result was not supported by other investigators who found FSHR variants differently distributed among normal and infertile men (Ahda et al., 2005; Shimoda et al., 2009; Safarinejad et al., 2010; Balkan et al., 2010; Wu et al., 2015).

Figure 1 *Representative gel analysis for FSHR genotyping*

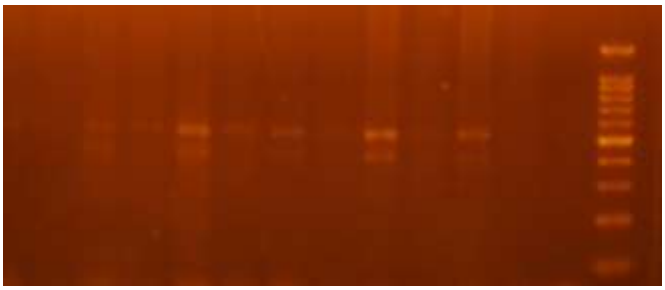

Figure 2 *Representative gel analysis of restriction of FSHR PCR product*

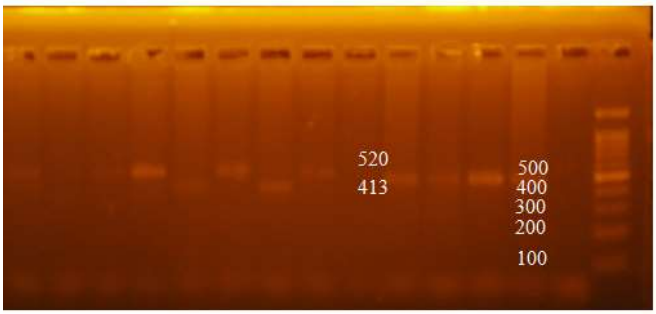

Figure 3 *Representative gel analysis of restriction of FSHR PCR product*

Table 5 *Distribution of male group by allelic frequency of FSHR allele*

Items	azoospermia (n=11)	Oligospermia (n=21)	Control (n=24)	allele frequency	X^2	P value
Wild Asn/Asn (n = 24)	3 (27.3%)	8 (38.1%)	13 (54.2%)	33.93%	8.428	0.077
Heterozygous Asn/Ser (n=26)	7 (63.6%)	8 (38.1%)	11 (45.8%)			
Mutant Ser/Ser (n=6)	1 (9.1%)	5 (23.8%)	0 (0%)			

Table 6 *Frequency of FSHR gene Asn/Ser variants among fertile and infertile groups*

Items	Fertile (n=24)	Infertile (n=32)	X^2
Wild Asn/Asn (n = 24)	13 (54.2%)	11 (34.4%)	0.071
Heterozygous Asn/Ser (n=26)	11 (45.8%)	15 (46.8%)	
Mutant Ser/Ser (n=6)	0 (0.0%)	6 (18.8%)	

4.4. Spermatogenic potential of FSHR allele Polymorphism among the studied groups:

Sperm count was significantly decreased in mutant (Ser/Ser) FSHR allele compared to wild (Asn/Asn) FSHR allele. On the other hand, sperm motility showed no significant differences among various groups. Furthermore, there was a tendency of semen parameters to be decreased in FSHR gene variants Asn/Ser and Ser/Ser than Asn/Asn similar result was obtained by Zalata et al. (2008). In this context, Shimoda et al. (2009) reported that the combination of heterozygous FSHR variants might be responsible for male infertility in Japanese population. In Iranian population, study demonstrated that the genetic polymorphism in FSHR gene might increase the susceptibility to obstructive azoospermia in men (Gharesi-Fard et al., 2015).On the other hand, some studies showed no statistically significant associations between semen parameters and FSHR gene polymorphisms (Pengo et al., 2006, Balkan et al., 2010, Safarinejad et al., 2010, Ghirelli-Filho et al., 2012 and Grigorova et al., 2013).

Table 7 *FSHR polymorphism in relation to spermatogenic potential*

Items	Group Heterozygous Asn/Ser (n=26)	Wild Asn/Asn (n=24)	Mutant Ser/Ser (n=6)	F	P-value
Sperm countX10^6/milliliter (mini-max)	18.1±20.2 (0.00-60.0)	24.6±19.8 (0.0-56.0)	2.5±2.8* (0.0-7.0)	3.312	0.044
Active% (mini-max)	21.6±25.9 (0.0-65.0)	28.9±25.2 (0.0-70.0)	2.5±4.2 (0.0-10.0)	2.851	0.067
Sluggish% (mini-max)	18.5±12.1 (0.0-35.0)	22.5±10.0 (0.0-40.0)	18.3±11.3 (0.0-30.0)	0.913	0.408
Dead% (mini-max)	32.9±30.9 (0.0-80.0)	36.1±25.5 (0.0-80.0)	64.2±32.3 (0.0-90.0)	2.914	0.063

(*Significant, P<0.05): *compare wild group versus hetero, mutant group.

4.5. Hormonal level of FSHR allele polymorphism among the studied groups:

T testosterone was significantly decreased in mutant (Ser/Ser) FSHR allele compared to wild (Asn/Asn) FSHR allele and the LH was significantly increased in mutant (Ser/Ser) FSHR allele compared to wild (Asn/Asn) FSHR allele. However, there was no significant difference in FSH levels among various groups (Table 8). The findings of the present study

regarding significant association between the FSHR polymorphism and T testosterone are consistent with the findings obtained by Zalata et al. (2008)and Grigorova et al. (2013). However, this finding contrasts with the finding of Foresta et al. (2006), Safarinejad et al. (2010) and Ghirelli-Filho et al. (2012). Significant increased level of LH was also found in men carrying the Ser/Ser genotypes compared with men carrying Asn/Asn genotypes. Such result disagreed with the results of Safarinejad et al. (2010), Ghirelli-Filho et al. (2012) and Grigorova et al. (2013).

We concluded that the FSHR polymorphism at codon 680 did not result in significant differences in serum FSH levels in men. Similarly, Pengo et al. (2006)andForesta et al. (2006) evaluated the FSHR polymorphisms in Italian population, but the results disclosed that FSHR genotypes have no influence on FSH concentrations both in normal and infertile males. Similar results were found byAhda et al. (2005) in Germanpopulation, Zalata et al. (2008) in Egyptian population, Balkan et al. (2010) in Turkish, Safarinejad et al. (2010) in Iranian population,Ghirelli-Filho et al. (2012) in Brazilianpopulation and Song et al. (2013) in Chinese population. Conversely, Shimoda et al. (2009), Grigorova et al. (2013) and Gharesi-Fard et al. (2015) found that thegenetic variations, Asn680Ser of the FSHR gene are correlated with serum FSH levels in Japanese, Estonian and Iranian population, respectively.

Table 8 *FSHR polymorphism in relation to hormonal level*

Items	Group Heterozygous Asn/Ser (n=26)	Wild Asn/Asn (n=24)	Mutant Ser/Ser (n=6)	F	P-value
LH(mIU/ml) (mini-max)	5.5±3.2 (2.4-19.3)	4.7±1.6 (1.8-8.5)	8.1±3.4* (4.4-14.0)	3.942	0.025
FSH(mIU/ml) (mini-max)	11.0±11.9 (2.8-46.7)	8.3±7.2 (2.5-35.2)	11.7±5.8 (4.0-18.5)	0.613	0.545
Testosterone(ng/ml) (mini-max)	4.4±1.9 (1.5-7.2)	4.9±1.7 (0.93-8.2)	2.8±1.1* (1.6-4.4)	3.387	0.041

(*Significant, P<0.05): *compare wild group versus hetero, mutant group.

5. Conclusions:

Sperm count was significantly decreased in azoospermia and oligospermia compared to control. In sperm motility active sperm was significantly decreased in azoospermia and oligospermia compared to control. A sluggish sperm was significantly decreased in azoospermia compared to control and oligospermia. A dead sperm was significantly decreased in azoospermia compared to control. Conversely, a dead sperm was significantly increased in oligospermia compared to control and azoospermia. LH and FSH were significantly increased in azoospermia compared to controls and oligospermia. T testosterone was significantly decreased in azoospermia and oligospermia compared to control. FSHR gene variants showed no difference in distribution between azoospermia, oligospermia and fertile men. Sperm count was significantly decreased in mutant (Ser/Ser) FSHR allele compared to wild (Asn/Asn) FSHR allele. On the other hand, sperm motility showed no significant differences among various groups. LH was significantly increased in mutant (Ser/Ser) FSHR allele compared to wild (Asn/Asn) FSHR allele. However, there was no significant difference in FSH levels among various groups. T testosterone was significantly decreased in mutant (Ser/Ser) FSHR allele compared to wild (Asn/Asn) FSHR allele.

References:

Ahda, Y., Gromoll, J., Wunsch, A., Asatiani, K., Zitzmann, M., Nieschlag, E., & Simoni, M. (2005). Follicle-Stimulating Hormone Receptor Gene Haplotype Distribution in Normozoospermic and Azoospermic Men. *Journal of andrology*, *26*(4), 494-499.

Balkan, M., Gedik, A., Akkoc, H., Izci Ay, O., Erdal, M. E., Isi, H., & Budak, T. (2010). FSHR single nucleotide polymorphism frequencies in proven fathers and infertile men in Southeast Turkey. *Journal of Biomedicine and Biotechnology*, *2010*, 1-5. doi:10.1155/2010/640318

Ferlin, A., Arredi, B., & Foresta, C. (2006). Genetic causes of male infertility. *Reproductive Toxicology*, *22*(2), 133-141.

Ferlin, A., Raicu, F., Gatta, V., Zuccarello, D., Palka, G., & Foresta, C. (2007). Male infertility: role of genetic background. *Reproductive biomedicine online*, *14*(6), 734-745.

Foresta, C., Selice, R., Garolla, A., & Ferlin, A. (2008). Follicle-stimulating hormone treatment of male infertility. *Current opinion in urology*, *18*(6), 602-607.

Gharesi-Fard, B., Ghasemi, Z., Shakeri, S., Behdin, S., Aghaei, F., & Malek-Hosseini, Z. (2015). The frequency of follicle stimulating hormone receptor gene polymorphisms in Iranian infertile men with azoospermia. *Iranian journal of reproductive medicine*, *13*(11), 673-678.

Grigorova, M., Punab, M., Poolamets, O., Sober, S., Vihljajev, V., Žilaitienė, B., ... & Laan, M. (2013). Study in 1790 Baltic men: FSHR Asn680Ser polymorphism affects total testes volume. . *American Society of Andrology and European Academy of Andrology*, *1*(2), 293-300.

Holt, R. I., & Hanley, N.A. (2012). *Essential Endocrinology and Diabetes*. (6th ed.). United Kingdom: John Wiley & Sons, Ltd.

Laan, M., Grigorova, M., & Huhtaniemi, I. T. (2012). Pharmacogenetics of FSH action. *Current opinion in endocrinology, diabetes, and obesity*, *19*(3), 220-227.

Li, Y., Gu, A., Yang, H., Ding, X., Ji, G., Lu, C., ... & Wang, X. (2011). FSH receptor gene polymorphisms in fertile and infertile Han-Chinese males. *ClinicaChimicaActa*, *412*(11), 1048-1052.

Lubbad, A. M. (2015). Hormonal and Histological Aspects of Germ Cell Aplasia among a Group of Infertile Men in Gaza Strip. *IUG Journal of Natural Studies*, *23*(1), 55-62.

Meduri, G., Bachelot, A., Cocca, M. P., Vasseur, C., Rodien, P., Kuttenn, F., ... & Misrahi, M. (2008). Molecular pathology of the FSH receptor: new insights into FSH physiology. *Molecular and cellular endocrinology*, *282*(1), 130-142.

O'FlynnO'Brien, K. L., Varghese, A. C., & Agarwal, A. (2010). The genetic causes of male factor infertility: a review. *Fertility and sterility*, *93*(1), 1-12.

Pengo, M., Ferlin, A., Arredi, B., Ganz, F., Selice, R., Garolla, A., & Foresta, C. (2006). FSH receptor gene polymorphisms in fertile and infertile Italian men. *Reproductive biomedicine online*, *13*(6), 795-800.

Poongothai, J., Gopenath, T. S., & Manonayaki, S. (2009). Genetics of human male infertility. *Singapore Med J*, *50*(4), 336-347.

Safarinejad, M. R., Shafiei, N., & Safarinejad, S. (2010). Evaluating the role of the FSH receptor gene Thr307-Ala and Asn680-Ser polymorphisms in male infertility and their association with semen quality and reproductive hormones. *BJU international*, *108*(2b), E117-E125.

Shimoda, C., Eitetsu, K. O. H., YaMaMOtO, K., MatSui, F., SuGiMOtO, K., Sin, H. S., ... & Namiki, M. (2009). Single nucleotide polymorphism analysis of the follicle stimulating hormone (FSH) receptor in Japanese with male infertility: Identification of codon combination with heterozygous variations of the two discrete FSH receptor gene. *Endocrine journal*, *56*(7), 859-865.

Song, D., Zhang, Z., Zhang, H., Zhou, W., Zhang Y., Xu, Y., & Hui, N. (2013). Relationship of single nucleotide polymorphism of follicle-stimulating hormone receptor gene and severe oligoasthenozoospermia in yangtze river delta of China. *International Journal of Reproduction, Contraception, Obstetrics and Gynecology*, *33*(5), 294-299.

Wang, L., Huang, H., Jin, F., Zhou, C., Qian, Y., & Chen, J. (2014). High expression of follicle stimulating hormone receptor in testicular tissue of idiopathic azoospermic patients with severe spermatogenic defects. *Chinese medical journal*, *127*(3), 488-493.

World Health Organization. (2010). *WHO laboratory manual for the examination and processing of human semen*. (5th ed.). Retrieved June 15, 2016 from: http://apps.who.int/iris/bitstream/10665/44261/1/9789241547789_eng.pdf.

Wu, X. Q., Xu, S. M., Wang, Y. Q., Li, Q., Wang, Z. Q., Zhang, C. L., & Shen, Y. (2015). FSHR gene Thr307Ala and Asn680Ser polymorphisms in infertile men: an association study in North China and meta-analysis. *Genetics and Molecular Research*, *14*(2), 5592-5601.

Wunsch, A., Ahda, Y., Banaz-Yaşar, F., Sonntag, B., Nieschlag, E., Simoni, M., & Gromoll, J. (2005). Single-nucleotide polymorphisms in the promoter region influence the expression of the human follicle-stimulating hormone receptor. *Fertility and sterility*, *84*(2), 446-453.

Zalata, A. A., Hassan, A. H., Nada, H. A., Bragais, F. M., Agarwal, A., & Mostafa, T. (2008). Follicle-stimulating hormone receptor polymorphism and seminal anti-Müllerian hormone in fertile and infertile men. *Journal of Andrologia*, *40*(6), 392-397.

Zhang, S., Li, W., Zhu, C., Wang, X., Li, Z., Zhang, J., ... & Zhang, Y. (2012). Sertoli cell-specific expression of metastasis-associated protein 2 (MTA2) is required for transcriptional regulation of the follicle-stimulating hormone receptor (FSHR) gene during spermatogenesis. *Journal of Biological Chemistry*, *287*(48), 40471-40483.

تعدد الأشكال لمستقبل هرمون المنبه للجريب في الرجال الفلسطينيين العقيمين

هرمون المنبه للجريب (FSH) ضروري للتكاثر الجنسي. مستقبل هرمون المنبه للجريب (FSHR) يحفز على تكاثر خلايا السيرتولي ويحافظ على إنتاج الحيوانات المنوية. وتهدف الدراسة إلى البحث في تعدد الأشكال FSHR في الرجال الفلسطينيين العقيمين. ووجد أن كل 56 من الذكور ينقسموا إلى 24 طبيعي، و32 من العقيمين. وينقسم العقيمين إلى 11 انعدام في إنتاج الحيوانات المنوية، و21 ضعف في إنتاج الحيوانات المنوية. تم تحليل السائل المنوي، وتم قياس FSH، هرمون اللوتنين (LH) وهرمون التستوستيرون. تم تحديد أليل من جين FSHR بواسطة تقنية PCR-RFLP. عدد الحيوانات المنوية منخفض بشكل مهم في القلة والانعدام مقارنة بالضابطة. حركة الحيوانات المنوية أظهرت فروق ذات دلالة إحصائية بين المجموعات المختلفة. FSH وLH زادت بشكل ملحوظ في الإنعدام مقارنة مع الضابطة ومع القلة. التستوستيرون يكون منخفض بشكل كبير في الضعف والانعدام مقارنة مع الضابطة. لم تظهر أي اختلاف كبير في انتشار وحيدة النيوكلوتايدة لأليل FSHR بين المجموعات الثلاث. عدد الحيوانات المنوية انخفض بشكل كبير في طفرة FSHR (Ser/Ser) أليل مقارنة بالأصل FSHR (Asn/Asn) أليل. من ناحية أخرى، أظهرت حركة الحيوانات المنوية عدم وجود فروق ذات دلالة إحصائية بين المجموعات المختلفة. LH إزداد بشكل كبير في طفرة FSHR (Ser/Ser) أليل مقارنة بالأصل FSHR (Asn/Asn) أليل. بينما التستوستيرون انخفض بشكل كبير في طفرة FSHR (Ser/Ser) أليل مقارنة بالأصل(Asn/Asn)FSHR أليل. ومع ذلك، لم يكن هناك اختلاف كبير في مستويات FSH بين مختلف المجموعات. نستنتج أن وجود طفرة (Ser/Ser)FSHR أليل يكون سببا لانخفاض في عدد الحيوانات المنوية ومستوى التستوستيرون ويزيد من مستوىLH.

كلمات مفتاحية:
عقم الرجال،
هرمون المنبه للجريب،
هرمون اللوتنين،
هرمون التستوستيرون،
مستقبل هرمون المنبه للجريب.