

Characteristic of The Main Causal Factors of Infertility

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Keywords	Abstract
<i>Causes of infertility;</i> <i>Gynaecological diseases;</i> <i>Hormonal disorders;</i> <i>Infertility;</i> <i>Miscarriage;</i>	This article dedicated to fertility impairment, which is one of the most important problems in reproductive medicine, and solving ways for timely diagnosis and adequate therapy of couples suffering from infertility in order to not only to prevent the development of complications such as miscarriage, ectopic pregnancy, intrauterine infection, fetal hypoxia, fetal-placental dysfunction, etc. but also help to reduce reproductive losses and the birth of healthy progeny. It should be noted that works devoted to the problem of infertility in the region of Uzbekistan, where information on its frequency and structure is insignificant. In the population, such studies had not been conducted, and at the same time, judging by the appeal statistics, the number of infertile marriages had increased in recent years. During the experiment, there were determined main reasons, which straightforwardly lead to infertility, such as inflammatory diseases of the genital organs, hormonal disorders, man role in sterility, relative marriage etc.

1. Introduction

According to the literature, the prevalence of infertility in marriage in recent years varies considerably - from 8 to 17.8% and more (Mascarenhas et al., 2012; Thoma et al., 2013). In the development of fertility disorders, one of the leading roles is played by inflammatory diseases of the genital organs, the frequency of which continues to increase (Pushkarev, 2013; Agarwal et al., 2015). At the same time, almost every fourth married couple has a combination of male and female factors of infertility and pathological conditions caused by Sexual Transmitted Infections are the leading ones, they represent the most severe contingent. Diagnostics and therapy of inflammatory processes of the genital organs at the present stage are difficult (Frobenius & Bogdan, 2015). Due to the polyetiology of pathogens, it becomes necessary to study the structure, role of urogenital infections, their relationship with opportunistic microorganisms, saprophytes, and develop clear tactics for managing married couples with inflammatory diseases of the genital organs and infertility, depending on the type of infections (Greil, 1997). Moreover, Ruz et al. (2012) state that the role of urogenital infections in the development of reproductive disorders has been proven.

However, diagnostic and therapeutic measures in spouses with a co-infection require further development.

A certain role in the aetiology of infertility is played by hereditary pathology - both monogenic diseases and genomic disorders (Aitken et al., 2003; Tournaye et al., 2017). In the other side, Arnold & Chen (2009) reveal that the presence of sex chromosome abnormalities in the genotype leads to dysfunctions of the reproductive organs of varying degrees - from agenesis of the gonads in women and aplasia of epithelial cells of spermatozoa in men to partial preservation of fertility in mosaicism. At the same time, the role of closely related marriages as one of the factors of impaired fertility remains unexplored.

2. Materials and Methods

Clinical and statistical analysis (Meehl, 1954) of the causes of infertility in 800 married couples with impaired fertility was carried out. When studying the gynaecological status of 800 patients in infertile marriages, it was found that inflammatory diseases of the pelvic organs (40.3%) and endocrine disorders (44.8%) were observed with equal frequency. However, a more detailed analysis showed that if the inflammatory process of the genitals prevailed in women with secondary infertility (52.3%), then in patients with primary infertility, endocrine disorders were more often detected (49.4%). There were 300 married couples under supervision, who underwent an in-depth complex examination and treatment. Three hundred infertile couples with inflammatory diseases of the genital organs were examined for urogenital infections (*Gardnerella vaginalis*, *Trichomonas vaginalis*, *Mycoplasma hominis*, *Ureaplasma urealyticum*, *Chlamydia trachomatis*, *Herpes simplex*, *Cytomegalovirus*), and with microscopy by smear. The division of infertile married couples with inflammatory diseases of the genital organs was carried out depending on the type of mono- or mixed infection.

To identify violations of hormonal activity in the pituitary-ovarian system in 200 women in infertile marriages, the content of FSH, LH, prolactin, testosterone, estradiol, TSH, T3, T4 in the peripheral blood plasma was studied. The control group consisted of 20 healthy women. Clinical examination of women included an ultrasound of the pelvic organs with a vaginal probe. In the absence of genital tract infection, 344 women underwent hysterosalpingography (HSG). The study of ejaculate was carried out in 598 men in infertile marriages.

3. Results and Discussions

To determinate the structure of infertility, data from 800 infertile married couples were analyzed, of which 496 (62%) with primary infertility, 304 (38%) secondary, that is, the appeal of spouses with primary fertility disorders was 1.6 times higher than that of secondary infertility. In 40.2% of the examined patients, inflammatory diseases of the pelvic organs were found, in 44.8% - endocrine disorders. The malefactor in the development of primary and secondary infertility was 37.6 and 19.5%, respectively. In 17.2% of cases, both spouses had violations. Primary infertility was more often observed at the age of 21 - 25 years (48.2-2.2%), less often in age groups over 30 years. Secondary infertility was more often registered in women aged 26-30 years (43.1-2.8%) and less often in patients over 31 years old.

Of the previous surgical interventions in women, both with primary and secondary infertility, appendectomy was most often noted as (7.12 and 10.3%), laparoscopy (6.5 and 7.0%) and operations on the uterine appendages (4.2 and 6.6%). 11.1% of women with secondary infertility have undergone surgery for ectopic pregnancy in the past. A detailed analysis of the majority of women with secondary infertility revealed chronic adnexitis (52.3%). Endocrine disorders were more common in patients with primary impairment of fertility (49.4%) than in women with a

secondary pathology (37.5%). It should be noted that in women with impaired fertility, in addition to inflammatory processes in the genitals, endometriosis and endocrine disorders in the reproductive system, a combination of these factors is often observed. Thus, among the women surveyed by us with primary impairment of fertility, the combination of factors took place in 16.1%, and with secondary infertility - in 19.1%.

When analyzing the ejaculate of men in a sterile marriage, oligozo-, azo- and aspermia was detected in 31.2% of cases. At the same time, primary infertility occurred in 37.6%, secondary in 19.5% of men. It should be noted that the improvement of the ejaculate examination technique makes it possible to identify impaired fertility even in men with normal sperm analysis. When determining the motility of spermatozoa within 24 hours, dynamic asthenozoospermia with normospermia was found in 20% of men with primary infertility and in 17.7% with secondary infertility. Thanks to modern methods, it is possible to accurately determine the cause of impaired fertility in men during the initial visit and examination. Of 411 men with normospermia, 323 (78.6%) had dynamic asthenospermia and sperm agglutination phenomena, and only 21.4% of the examined did not have pathological abnormalities. A decrease in the number of actively motile spermatozoa within 24-48 hours, an increase in ejaculate viscosity and the phenomenon of auto immunization (Sperma agglutination), even with normospermia, lead to a decrease in the fertilizing ability of spermatozoa.

However, if we take into account the changes (Sperma agglutination, increased viscosity, dynamic asthenozoospermia, observed during inflammatory processes) in the analysis of ejaculate in men with normospermia, then infertility in men reaches 78.6%, which indicates a significant role of the malefactor in the formation of infertility in marriage.

Literature data show that one of the first places among the causes of infertile marriage is occupied by inflammatory processes of various etiologies. According to our data, inflammatory processes in the genitals were observed in 32.9% with primary and 52.3% of women with secondary impairment of fertility. Examination of patients with inflammatory diseases of the genital organs and infertility for urogenital infections in 65.2% of married couples revealed mono- or mixed infection. Of these, 60.3% of couples had a primary, and 74.2% of spouses had a secondary impairment of fertility.

It is known that inflammatory diseases of the uterine appendages, as a rule, are caused by mixed polymicrobial infections, the most important causative agents of which are anaerobic-aerobic microorganisms (25-60%), gonorrhoea (25-50%), chlamydia (25-30%), mycoplasma (up to 15 %). Chlamydia was diagnosed in 70% of women suffering from infertility, of which only one third was found as mono-infection.

We found that if chlamydia and ureaplasma were more common in women with primary infertility, then in patients with a secondary disorder, Gardnerella and herpes prevailed. Mixt infection was detected in 35.3% of women. A detailed analysis of the incidence of infections showed that in patients with impaired fertility, the dominant infection was chlamydia - 50.6%, Gardnerella - 32.3%, ureaplasma - 28.6% and herpes - 23.3%. At the same time, chlamydia was found in 56.4% of patients with primary and 42.1% with secondary infertility, and gardnerella, ureaplasma and herpes were found equally often in women with both primary and secondary impairment of fertility. If in women with primary infertility chlamydia and ureaplasma were more often detected, then in patients with secondary impairment of fertility, as a rule, chlamydia, Gardnerella and herpes were sown. In women with primary infertility, the most frequent combination was chlamydia with ureaplasma (6.6%) and chlamydia with mycoplasma (5%). Mixt infection was found in 53%, and mono-infection - in 47% of women with infertility. It should be noted that the combination of infection in women with both primary and secondary impairment of fertility (51.4 and 55.4%) was the same. In a bacteriological study conducted in patients with infection, 78.6% of them found one of the opportunistic microorganisms: as a rule, these were gram-positive Staphylococcus epidermidis (36%), Streptococcus viridans (8.4%) Enterococcus faecalis (5, 6%), Staphylococcus

aureus (4.6%) and gram-negative *Escherichia coli* (6.5%) and *Proteus mirabilis* (2.8%). In 21.4% of patients, pathogenic growth was not detected in the analyzes. *S.epidermidis* occurred with almost every detected infection, but more often, it was combined with chlamydia (43.6%), ureaplasma (38.9%) and *Gardnerella* (30.7%). Ureaplasma, as a rule, was inoculated with *E. coli* (71%), and *gardnerella* was often detected even in the absence of pathological growth (34.7%). At the same time, urogenital infections were combined not only with opportunistic microorganisms and saprophytes, but were encountered even in the absence of pathological growth.

In the study of the ejaculate of spouses (89) with primary infertility, azoospermia was detected in 7 (7.9%), oligozoospermia - in 23 (25.8%), dynamic asthenozoospermia, increased viscosity and sperma agglutination - in 35 (39.3%), with 24 (27.0%) men had normozoospermia. Of 49 men with secondary infertility, oligozoospermia was observed in 10 (20.4%), dynamic asthenozoospermia in 28 (57.1%) and normozoospermia in 11 (22.4%). Chronic prostatitis occurred in 29 (32.6%) men with primary and 18 (36.7%) with secondary infertility. Increased viscosity, sperm agglutination and pronounced autoimmune changes in the ejaculate were found in 63 (45.6%) of the examined

To determine the depth of damage in the reproductive system in order to develop tactics for managing women with endocrine infertility, we used the classification, WHO (2003). The patients were divided into four groups depending on the level of gonadotropic hormones. The first group included 97 women with hypothalamic-pituitary dysfunction; the second group consisted of 48 patients with hypothalamic-pituitary insufficiency (LH <5 IU / L, FSH <3 IU / L, estradiol <70 nmol / L); the third group included 30 women with hyperprolactinemia; the fourth group included 25 patients with ovarian insufficiency (FSH > 20 IU / L, LH > 30 IU / L). As can be seen from Table 1, the level of LH and FSH in patients with hypothalamic-pituitary and ovarian insufficiency significantly differs from the control.

In women with pituitary-ovarian dysfunction and hyperprolactinemia, the LH content does not significantly differ from that of the control group, while the FSH concentration significantly differs in all groups, which indicates dysfunction of the hypothalamic-pituitary system.

In patients with pituitary-ovarian insufficiency, the level of LH and FSH was significantly reduced, respectively, by 3.8 and 1.5 times, while in women with ovarian insufficiency these indicators were significantly (5.6 and 8.2 times) higher than in healthy ...

The prolactin level in patients with hyperprolactinemia ($P < 0.01$) and ovarian failure ($P < 0.05$) was significantly higher than in the control group. At the same time, in women of the third group, this indicator significantly exceeded its values in other groups.

The testosterone level in the group of patients with hypothalamic-pituitary dysfunction significantly exceeded the control indicator ($P < 0.05$), which indicated a high frequency of hyperandrogenism in them. As for the level of progesterone, its reliably low values in all groups of the examined ($P < 0.05$) indicate a violation of the ovulation process in endocrine infertility, regardless of the level of gonadotropic hormones.

The level of estradiol ($P < 0.05$) was significantly reduced in all groups, but most significantly (5.9 times) in patients with pituitary insufficiency.

Analysis of the data obtained showed that all the studied parameters, except for prolactin and LH, in patients with pituitary-ovarian dysfunction significantly differed from the control values ($P < 0.05$). And in the patients of the second group, the levels of LH and FSH and other hormones were significantly lower ($P < 0.05$) than in control, while the levels of prolactin and testosterone did not differ significantly from those of healthy women. In patients of the third group, the content of FSH, prolactin, TSH was significantly increased, and the level of progesterone and estradiol, T3, T4, and the level of progesterone and estradiol, T3, T4 was reduced with normal fluctuations in LH and testosterone. The levels of LH, FSH and prolactin in the patients of the fourth group were higher, and the levels of progesterone and estradiol, lower than in control, which indicated ovarian failure accompanying the violation of ovulation. The level of thyroid-stimulating hormones, while remaining within the normative fluctuations, in patients of all groups significantly decreased, which

also indicates the defeat of the hypothalamic-pituitary system. Only in women with hyperprolactinemia, the TSH level was higher than the control values, with a decrease in the amount of T4 (1.4 times), which indicates the presence of primary hypothyroidism in these patients.

Correspondingly to the decrease in the thyroxine level in women of this group, a compensatory increase in the thyroid-stimulating hormone content occurs. The data obtained indicate the role of thyroid hormones in the development of anovulation and infertility in women.

Analysis of clinical manifestations depending on the state of the hypothalamic-pituitary system showed that menstrual irregularities and hypoplasia of the genitals with infertility were more often observed in the group of patients with hyperprolactinemia (43.3 and 33.3%) and ovarian insufficiency (60 and 52%), which indicates deep lesions in the hypothalamic-pituitary-ovarian system. In most patients with hypothalamic-pituitary dysfunction, hirsute syndrome was observed in 26.8%, and polycystic ovary syndrome was most often found in women with ovarian insufficiency (20%) and hypothalamic-pituitary dysfunction (18.5%). Galactorrhea was common in women with hyperprolactinemia (30.0%) and ovarian failure (24%).

A genealogical study of infertile married couples according to the generally accepted method using the international notation system and subsequent study of genealogical tables showed that the parents of 12% of women and 8.3% of men were closely related, and 13% of those surveyed were themselves, close relatives. The cytogenetic study revealed 7.1% of women with karyotype abnormalities. These results indicate that genetic disorders can lead to absolute infertility in both men and women. Family marriages between parents and spouses themselves can become one of the causes of infertility.

Of 300 married couples with impaired fertility, inflammatory processes in the genitals and urogenital infection, 156 spouses underwent specific anti-inflammatory therapy. Of these couples, primary infertility occurred in 67.3%, secondary in 32.7%. In women with inflammatory diseases of the genital organs, the predominant mono-infection was chlamydia and Gardnerella. If mono-infection was found in 73 (46.8%) spouses, then two types of infection were observed in 57 (36.5%) examined, and a combination of more than two types of urogenital infection was in 26 (16.7%) married couples.

Among the surveyed married couples, the infection was found in 84.8% of men. Of these, 7 had azoospermia, 23 had oligozoospermia. Autoimmune process and dynamic asthenozoospermia were observed in 39.3% of men with primary and 57.1% with secondary infertility. Chronic prostatitis was diagnosed in 32.6% of men with primary and 36.7% with secondary infertility. These data indicate the role of the studied infections in the development of infertility in men, especially with secondary infertility.

4. Conclusion

The comprehensive, in-depth examination made it possible to establish that the male factor prevails over the female factor in the structure of infertile marriage and amounts to 78.6%. Next, among the causes of female infertility, inflammatory diseases of the genitals account for 40.3%, endocrine disorders of the pituitary-ovarian system - 44.8%.

Bacteriological studies of seven types of causative agents of urogenital infections identified in married couples with infertility, as well as comparing them with opportunistic microorganisms and saprophytes, showed that 65.2% of women with infertility have mono- or mixed infections. Of these, 60.3% of women had primary and 76.7% secondary infertility. Among men, these indicators were 39.6% and 60.3%, respectively.

As possible risk factors for impaired fertility in patients with small developmental anomalies, one can consider not only twin pregnancy and increased age of parents, but also closely related marriages.

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