## Autoimmune Factors Evaluation Questionnaire

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|---|---|
| Do you have Hashimoto's thyroiditis? | |
| Do you have diabetes? | |
| Do you suffer from migraines? | |
| Do you have an allergic predisposition? | |
| Do you have unresolved skin rashes (such as acne on your shoulders or itchy, sensitive reactions on your hands)? | |
| Do you frequently develop mouth ulcers (aphthous ulcers)? | |
| Do you experience bloating after certain meals? | |
| Do you feel discomfort particularly after consuming bread or bulgur? | |
| Do you have vitiligo (white patches on your skin)? | |
| Do you wake up feeling tired? | |
| Do you have fibromyalgia (pain in the neck region)? | |
| Do you often think, "Everything hurts"? | |
| Do you experience easy fatigue? | |
| Does your skin react when you wear jewelry other than gold? | |
| Do you experience joint pain (arthritis/arthralgia)? | |

## What is infertility?

Infertility is defined as the inability to achieve pregnancy within 12 months despite regular, unprotected sexual intercourse.

In women aged 35 years and older, this period is evaluated as 6 months.

Infertility may arise from problems in either the female or the male partner, and genetic factors play an important role among the causes of infertility.

It is a condition that can develop due to many factors and may present with different clinical scenarios, ranging from impaired sperm production to decreased ovarian reserve and premature menopause, from recurrent pregnancy losses to repeated IVF failures. Certain disease variants carried by the partners may affect embryo formation, implantation, and placental development, leading to an inability to have children.

**Why is genetic evaluation performed?**

Genetic tests are performed to clarify the cause of infertility, to determine treatment approaches based on the underlying cause, and to help families identify which method will enable them to achieve pregnancy and take home a healthy baby. Everyone's genetic makeup is different. Even identical (monozygotic) twins do not have exactly the same genetic structure. Since each individual's genetic profile is unique, treatments that aim to improve success should also be tailored accordingly. This approach is called personalized medicine. For this reason, knowing in advance our genetic predispositions, the conditions we carry, and how we may respond to medications before starting treatment will increase treatment success.

**In whom should we perform genetic testing?**

- In men: Azoospermia; severe oligozoospermia (very low sperm count); a high proportion of abnormal sperm (morphological abnormalities); delayed puberty; small testes; gynecomastia.
- In women: Primary ovarian insufficiency / premature menopause; menstrual irregularities.
- A family history of infertility.
- A family history of any genetic disorder.
- Delayed puberty, small testes, gynecomastia.
- A history of pregnancy loss in the family.
- A history of failed IVF attempts.
- A previous pregnancy or child with a known genetic abnormality.
- Consanguinity (the partners being related).

In the situations listed above, couples should receive genetic counseling and appropriate tests should be planned.

# INFERTILITY
## AND ITS GENETIC CAUSES

İNTERGEN | Genetics and Rare Diseases Diagnosis Center

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## What are the genetic causes of infertility?

Different genetic factors may lead to infertility.

### 1) Chromosomal abnormalities

Changes in the number or structure of chromosomes:

Healthy women and men have 46 chromosomes (23 pairs). Half are inherited from the mother and half from the father. Approximately 20,000 genes are located on these chromosomes, and each chromosome carries a different number of genes. Certain changes in the number or structure of these chromosomes may create risks for pregnancy. For this reason, anyone planning a pregnancy should ideally undergo this test. It is a simple but very important test, and it can be performed in many genetic centers in our country.

**Commonly observed abnormalities: Detection of 47,XXY in males (Klinefelter syndrome):**

Klinefelter syndrome is one of the most common genetic causes of male infertility and is strongly associated with non-obstructive azoospermia. In individuals with XXY karyotype, the testes are usually small and reduced in volume, and over time seminiferous tubule damage and germ cell loss develop. As a result, spermatogenesis is impaired. Most patients present with azoospermia or very severe oligozoospermia. The hormonal profile typically reflects hypergonadotropic hypogonadism (elevated FSH/LH, low–normal testosterone).

The prevalence of Klinefelter syndrome in azoospermic men is reported to be approximately 10–12% (higher in some series). In some XXY cases, focal areas of sperm production may be present in the testes; therefore, in selected patients, fatherhood may be possible through microTESE combined with ICSI.

**Detection of Turner syndrome in females (45,X / Mosaic Turner):** Turner syndrome occurs when a woman has only one X chromosome (45,X) or when some cells are normal while others are missing one X chromosome (mosaic Turner). In Turner syndrome, ovarian tissue is usually lost at an early stage, and the ovaries may develop as “streak gonads.” Ovarian reserve is depleted prematurely. Primary amenorrhea or premature ovarian insufficiency (POI) may develop, and therefore it is strongly associated with infertility.

In mosaic Turner cases, ovarian function may be better preserved, allowing spontaneous menstruation and, rarely, spontaneous pregnancy; however, the risk of early ovarian reserve depletion remains high.

D**etection of a structural chromosomal abnormality in one of the partners:** Certain structural chromosomal alterations (e.g., balanced translocations, inversions) may not cause any apparent health problems in the individual, and the person may appear completely healthy. However, these abnormalities may lead to problems during the formation of reproductive cells (egg/sperm). In such individuals, some of the reproductive cells may develop with unbalanced chromosomal content. As a result, this condition may lead to failure to achieve pregnancy (infertility), recurrent miscarriages, impaired embryo development or repeated IVF failure, and in some cases, the birth of a child with chromosomal imbalance associated with intellectual disability and developmental delay.

**What is done when a structural chromosomal abnormality is detected?** The potential pregnancy-related risks are determined according to the specific chromosomal alteration identified. If natural conception is desired, the prenatal diagnostic tests to be performed during pregnancy, as well as their success rates and limitations, are explained. If the couple prefers in vitro fertilization (IVF) with preimplantation genetic testing for structural rearrangements (PGT-SR), the details of these procedures should be discussed comprehensively. For this reason, karyotype analysis is recommended for couples diagnosed with infertility or those with a history of ≥2 recurrent miscarriages. However, today it is recommended that couples planning to have children receive appropriate genetic counseling and undergo certain genetic tests proactively, in order to prevent encountering these problems.

### 2) Single-gene alterations

There are approximately 20,000 known genes in humans. More than 1,000 genes are thought to be directly related to reproduction. About half of these are associated with female reproductive function and the other half with male reproductive function. These genes affect sperm production, ovarian function, and oocyte/embryo development. Currently, numerous candidate genes are known to be associated with reproductive disorders. In addition to these genes, many genetic variations related to inflammation and autoimmune factors are directly associated with reproductive function.

Previously, cystic fibrosis testing in men and FMR1 premutation (Fragile X) testing in women were prioritized. However, it is now clear that these tests alone are insufficient, and comprehensive genetic panels are necessary. Of course, in cases of congenital absence of the vas deferens and obstructive azoospermia in men, cystic fibrosis is strongly suspected. Nevertheless, performing this test alone is not recommended. Genetic testing should be recommended to all couples with pregnancy losses, implantation failure, or infertility due to various causes. Within the infertility panel exome analysis, genes associated with inflammation and autoimmune factors are also evaluated, and a treatment plan is established in collaboration with the clinician.

**Male Infertility – Basic Panel**

- Chromosome analysis (karyotype)
- Y-chromosome microdeletion analysis
- TUNEL test (Sperm DNA fragmentation test)
- Sperm aneuploidy test
- Infertility panel exome analysis

**Female Infertility – Basic Panel**

- Chromosome analysis (karyotype)
- Infertility panel exome analysis
- FMR1 premutation analysis

### 3) Carrier Status

The primary goal of infertility treatment is to achieve the birth of a healthy baby. When performing genetic testing, the aim is not only to determine the cause of infertility and plan treatment accordingly, but also to ensure the health of the baby. Genetic variants carried by either partner, even if not directly related to infertility, may pose a disease risk to the baby. For this reason, we recommend evaluating carrier status in both partners during infertility treatment planning.

Therefore, our recommendation is that couples undergo an expanded genetic panel. For women, this includes the Pregnarisk Panel 3. For men, this includes Y-chromosome microdeletion analysis and sperm tests together with the Pregnarisk Panel 3.

**Male Infertility – Expanded Panel**

- Y-chromosome microdeletion analysis
- TUNEL test (Sperm DNA fragmentation test)
- Sperm aneuploidy test
- Pregnarisk Panel 3

**Female Infertility – Expanded Panel**

- Pregnarisk Panel 3

To increase the diagnostic and clinical value of these tests, detailed clinical findings are extremely important. Along with these tests, you are kindly requested to complete the Autoimmune Factors Evaluation Questionnaire found on the first page in full and share it with your physician. Particularly in the female partner, the presence of these findings may require specific modifications in the treatment plan.

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