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Case Report

Genetic Counseling in a Couple with Primary Infertility

Peter Ivan Hadiprajitno[1], Sultana MH Faradz[2*]

[1]Faculty of Medicine, Universitas Diponegoro, Indonesia
[2]Center for Biomedical Research, Faculty of Medicine, Universitas Diponegoro, Indonesia

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Abstract

Background: Couples unable to conceive and bear children could feel deep disappointment, often leading to depression. Infertility is one of the main reasons couples are not able to have children. Genetic counFig seling role in infertility ranges from explanation about possible genetic causes of infertility, pregnancy planning, and advice for treatment.

Case Presentation: A couple with 16 years of infertility was referred to the genetic clinic at National Diponegoro Hospital. Pre-test counseling was carried out to assess family history and explanation about the purpose and benefit of genetic testing. The 42 years old female had previous history of diabetes mellitus, obesity, and had treatment of epilepsy/seizure 15 years ago with routine carbamazepine therapy for 2 years, while her 42 years old husband had active hepatitis B infection for 15 years. This couple underwent insemination program twice and once completed In Vitro Fertilization (IVF), both management bearing no successful implantation or viable pregnancy. Recently, she underwent a laparoscopy procedure, which gave new diagnosis of endometriosis and adenomyosis. Chromosomal examination and Methylenetetrahydrofolate Reductase (MTHFR) C677T and A1298C alleles analysis were done in our laboratory. Both individuals carried normal karyotypes and *MTHFR* analysis was homozygote wild type allele. In Post-test counseling, we informed the finding of genetic testing, possible option, and psychosocial support. After the counseling, this couple has accepted their conditions. They still want to bear a child although she is at a crucial age.

Conclusion: The couple relieved after the explanation in genetic counseling session. After knowing the risk of conceiving pregnancy, the couple still attempt to bear a child. Infertility is a challenging and comprehensive problem. As healthcare professionals, we encounter problems not only in diagnosis and management, but also psychological and emotional dilemma. Genetic counseling is needed to solve the problems and avoid patient's psychological distress.

Keywords: *Genetic Counseling, Infertility, Chromosomal Examination, MTHFR*
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INTRODUCTION

Genetic counseling refers to the process of helping people understand and adapt to the medical, psychological, and familial implications of genetic contributions to disease.[1] The scope of genetic counseling encompasses the following four majors or areas of focus: cancer management, newborn screening, rare genetic disorders, as well as obstetrics and gynecology which include infertility.[2] The purpose of genetic counseling in cases of infertility is to encourage patients who are having trouble getting pregnant to use assisted reproductive technologies (ART), encourage preconception carrier screening, and support genetic testing of embryos.[3]

Infertility is a disorder of reproductive system that affects both male and female, characterized by the inability to conceive after 12 months or more of regular unprotected sexual intercourse.[4]

* Corresponding author:
E-mail: *sultanafaradz@gmail.com*
(Sultana MH Faradz)

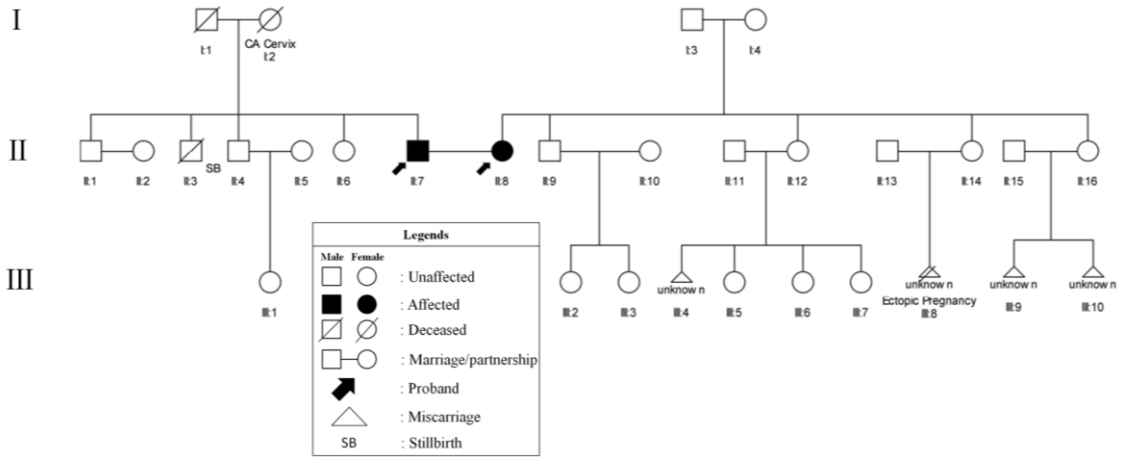

Figure 1. The pedigrees show three generations of the family. The probands (II.7 and II.8) are indicated with an arrow. II.8 siblings have pregnancy history with miscarriages (III.4, III.9, and III.10) and ectopic pregnancy (III.8).

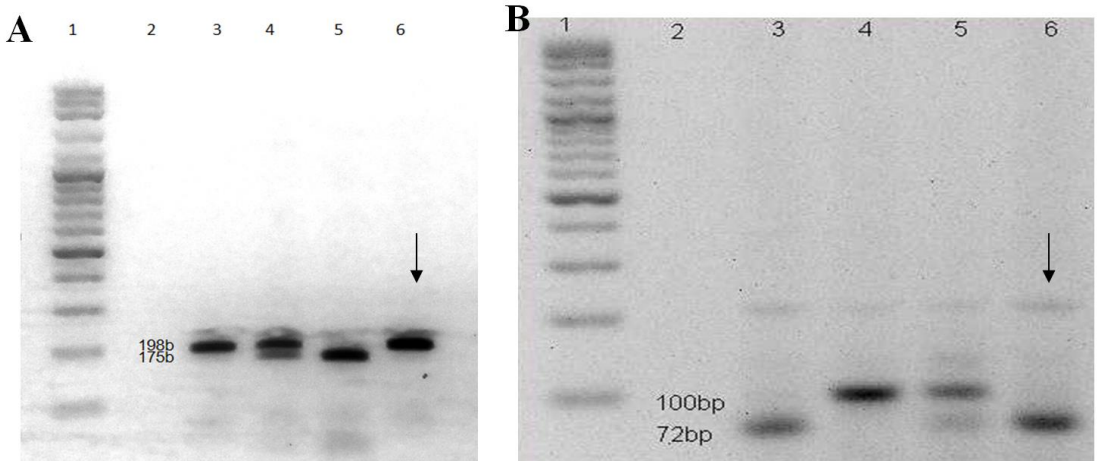

Figure 2. Methylenetetrahydrofolate reductase (MTHFR) analysis **(A)** C677T allele product. 1. Marker; 2. Blanco; 3. Normal Homozygote control (CC) :198 bp; 4. Heterozygote control (CT) : 198 bp and 175 bp ; 5. Mutation control (TT): 23 bp and 175 bp; 6. Patient (CC): 198 bp; **(B)** A1298C allele product. 1. Marker; 2. Blanco; 3. Normal control (AA) :72 bp; 4. Mutation control (CC) : 100 bp; 5. Heterozygote control (AC) : 72 bp and 100 bp; 6. Patient (AA): 72 bp

It is divided into two types which are primary infertility and secondary infertility. Primary infertility is when a couple has never experienced pregnancy, while secondary infertility is the failure to conceive after a prior pregnancy without the use of contraception, breastfeeding, or postpartum amenorrhea.[5]

The estimated incidence of infertility is 8-12% of reproductive-aged couples worldwide.[6] Infertility is found in one of every four couples in developing countries[7] and found in about 15-25% of Indonesian couples in 2013, gradually increasing every year.[8] Another literature reported that 9% of men and about 11% of women of reproductive age in the United States had fertility issues.[9] Both males and females have equal responsibility for the causes.[10]

Infertility can cause mental disorders in couples, including depression, mood disorders, anxiety, and bereavement, which could impair memory, focus, self-esteem, perceived control, interpersonal relationships, and overall quality of life. To enhance each patient's feelings, emotions, and treatment outcomes, genetic counseling is required.[11,12]

Building patient trust, understanding the patient's history and views, dealing with psychological concerns, and talking about delicate or private matters are difficult for genetic disorders.[13] In cases of infertility, difficulties having children (breaking bad news) quite often create a crisis in the couple and endangers the end of the marriage. In addition, partners can experience psychological reactions, including depression, anger, and frustration.[14] This article aims to find the causes and solve the problem of infertility, to minimize recurrence risk in failure of conception.

CASE REPORTS

A couple came to our genetic clinic in National Diponegoro Hospital to have a genetic counseling with a referral from an obstetrician with chief complaint of primary infertility. In pre-test counseling, we assess the patient's and family medical history. The husband and wife have the same age, about 42 years old. They were married for 16 years.

Table 1. Hormone Laboratory Result

Laboratory testing	Result	Reference range
Follicle-stimulating hormone (FSH)	7.42 mlU/ml	3.9 - 12 (follicular phase)
Prolactine	2.52 ng/ml	1.3 - 25 (follicular phase)
Estradiol	41.73 pg/ml	18 - 147 (follicular phase)
Anti Mullerian Hormone (AMH)	0.4 ng/ml	1.2 - 4.6
Human chorionic gonadotropin (hCG)	2.28 mlU/ml	<4 mlU/ml (cyclic women)

The husband had a medical history of ongoing hepatitis B infection since 2005. In 2007, he discontinued the consumption of Hepatitis B treatment of Telbivudine. His blood test of HBsAg was positive and HBeAg was reactive. After he underwent endoscopy and fibro scan examination, cirrhosis was identified and now treated with Tenofovir. He had already done a sperm analysis in 2011, with a result of oligoteratozoospermia and teratozoospermia in 2020. DNA fragmentation test for the sperm was done in 2022, found a normal result. His blood type is B with positive rhesus.

The wife reported that menarche had occurred when she was 13 years old. Her menstrual cycles were regular, with approximately a 32 days long cycle with a menstrual flow of 5 days' duration, and were associated with minimal dysmenorrhea. She had medical history of type 2 diabetes and pre-obese with BMI of 28,7 kg/m2. She had done treatment of carbamazepine for epilepsy 15 years ago. Her blood type is B with positive rhesus.

Her hormone blood level obtained during follicular phase is shown on Table 1. She underwent hysterosalpingogram examination 10 years ago, which found no blockage on the genital tract, followed by laparoscopy 1 year ago, which found endometriosis and adenomyosis and were immediately treated.

Insemination was carried out twice in 2012 and once In Vitro Fertilization (IVF) in 2021. Both procedures failed due to impaired implantation in the second week. There was a history of multiple miscarriages and one ectopic pregnancy on the family wife's side (shown in Figure1). After pre-test counseling, we suggested the couple undergo chromosomal examination and methylenetetrahydrofolate reductase (*MTHFR*) analysis for the wife to exclude folic acid metabolism disorder such as folat insufficiency and inadequate uterine vasculature.[15] Conventional chromosomal examinations of this couple were 46, XX and 46, XY respectively. The *MTHFR* analysis was wild types of homozygous C677T and A1298C allele (shown in Figure. 2)

DISCUSSION

The couple came to our genetic clinic with a chief complaint of primary infertility. We have already done two sessions of genetic counseling namely 1) pre-test counseling by collecting patient and family medical history, suggested genetic testing and 2) post-test counseling for delivering the result of genetic testing, giving an option for the next management, and overcome their psychosocial aspect.

Infertility can be caused by female, male, or due to unexplained reasons.[16] Female infertility caused by chromosomal anomalies accounted for 10%, whereas 15–30% of male infertility are caused by genetic abnormalities.[17] Unknown causes of infertility include immunological factors, uterine and/or fallopian tube issues, sperm or oocyte abnormalities, fertilization failure, embryo development arrest, and recurring embryo implantation failure.[16]

Active Hepatitis B viral infection in the husband may cause infertility via bloodstream to the testis and hematogenous spread. Hepatitis B virus (HBV) infections can spread sexually and vertically from mother to child.[18] HBV is present in human body fluid, specifically in serum, saliva, and semen. HBV in human semen induces the production of reactive oxygen species (ROS), which can cause lipid peroxidation (LPO) and subsequent sperm DNA fragmentation, increasing the rate of chromosome mutations.[19,20] Su *et al.* reported infertility incidence in patients with HBV was 1.59 times greater than in those without HBV infection (2.21 vs. 1.39 per 1,000 person-years).[21]

Metabolic syndrome forms a cluster of obesity, systemic hypertension, insulin resistance, and atherogenic dyslipidemia which are associated with the risk of infertility.[22] Obesity and insulin resistance in the wife, increase of leptin levels, and hyperandrogenemia. The reproductive system is impacted by changes in adipokine levels, the HPG axis, and steroidogenesis in obese women.[23] Hyperglycemia and insulin resistance cause delayed or absent preovulatory LH surges and ovulation in females.[24] In a cohort research, Tobias et al. found a statistically significant correlation between the risk of type 2 diabetes and past infertility (compared with no infertility).[25]

Epilepsy or seizure reduces the rate of fertility. The hypothalamus-pituitary-gonadal axis' release of the hormones GnRH, LH, and FSH is disrupted by epilepsy, which results in abnormal levels of estrogen and androgen.[26] Anti-epileptic drugs (AEDs) or anti-seizure medication have been linked to secondary endocrine diseases through increasing teratogenic risk and unfavorable effects on peripheral endocrine glands, which affect hormone metabolism and protein binding.[26,27] Long-term use of carbamazepine medication is linked to teratogenic effects, decreased sexual drive, and irregular menstrual cycles.[26]

Endometriosis and adenomyosis are closely related diseases with different conditions.[28] Dysmenorrhea, pelvic pain, and infertility are common complaints made by women with endometriosis and/or adenomyosis.[28,29] Progesterone and estrogen are influenced by endometriosis and mediated by an inflammatory environment. Resistance to progesterone caused by a failure in the activation of the receptor or the transcription of the target gene leads to impairment of ectopic implants. Increased levels of estrogen lead to aberrant endometriotic development and survival.[29] Pedachenko *et al.* also observed lower Anti Mullerian Hormone (AMH) levels in infertile women with endometriosis compared with infertile women without endometriosis.[30]

Adenomyosis-related infertility is linked to apical endometrial microvilli destruction, morphological pelvic adnexa distortion, aberrant steroid metabolism,

thickening of the junctional zone, altered uterine contractility, and an environment of oxidative stress.[28] The rate of implantation during an In-Vitro Fertilization (IVF) protocol is decreased by both endometriosis and adenomyosis.[30,31]

Advanced age in pregnancy is found in male and female. Advanced maternal age (AMA) is maternal age of ≥35 years at the time of delivery.[32] It is associated with higher risk of obstetric difficulties such as gestational diabetes, preeclampsia, fetal growth restriction and fetal mortality, preterm birth, and reproductive issues like infertility and miscarriage.[33,34] Age of the oocyte is impacted by AMA, which causes chromosomal segregation failure and raises the occurrence of aneuploidy. This process frequently occurs during first meiotic division, known as reverse segregation or premature separation of sister chromatids or meiosis I nondisjunction.[35]

Advanced paternal age (APA) is defined as the paternal age at conception of greater than 40 years, which is associated with the risk of infertility, reproduction failure, and risk of genetic disorders. Poor embryo quality, lower rates of fertilization and implantation, as well as lower rates of pregnancy and live birth, were all caused by APA. This condition is linked to an increase in miscarriage rates among pregnancies by IVF and ICSI. According to several studies, APA sperm had higher aneuploidy rates on chromosome 21 and the sex chromosomes, raising likelihood of trisomy 21 and sex aneuploidies.[34]

Chromosomal abnormalities account for 2–14% of male infertility and 10% of female infertility. Numerical and structural abnormalities are types of chromosome abnormalities that cause infertility. Examination of chromosomes is essential to distinguish the cause of infertility and proper management.[17] MTHFR gene is associated with homocysteine metabolic regulation in human reproduction. The maturing oocyte's follicular fluid contains folate and homocysteine. MTHFR mutation causes folic acid deficiency, which could compromise oocyte development, early embryogenesis, flow and prothrombotic impairment in the vessel wall, insufficient trophoblast invasion into the uterine vasculature, and placental hypoperfusion.[15,36]

Delivering on cases of infertility presents significant obstacles for genetic counselors. Counseling in infertility cases pays more attention in communication skills, decision-making, psychological impact of infertility, and concerning psychological help and support. Communication skills play a role in conveying information and breaking bad news. Use dialog such as "I'm so sorry to tell you..." to anticipate the bad news. Understanding the patient's background, culture, and beliefs are essential for choosing the effective decision. Personalized, sensitive, and caring character are needed to prevent emotional impact of infertility like depression, anger, and frustration. Providing access to professional psychological care or contacting other people with the same condition can help patient's psychological and emotional well-being.[14]

We delivered the genetic testing results, discussed the findings, made recommendations for future management, and provided psychosocial support and adjustment. Hepatitis B infection in the husband should be treated first to improve the semen quality, while his wife is recommended to get a screening as well. Treatment for obesity and diabetes mellitus must include a change in lifestyle. Miscarriages and ectopic pregnancy history in their family might be caused by small abnormalities on the chromosomal structure. Consequently, microarray analysis is advised to find minor deletions under 5 million base pairs.

We understand their speculative difficulties, listen to them without passing judgment, mention that they are not to blame for this problem, and encourage them. The couple relieved after the counseling but still insisted on bearing a child even though at crucial age. Our advice is against having children at this time due to the possibility of non-disjunction and adoption as a last resort.

CONCLUSION

The couple relieved after receiving genetic counseling about their situation and makes one last attempt to conceive even though they are at a crucial age. Comprehensive and thorough management of infertility is necessary. By gathering patient data, offering genetic testing to rule out any hereditary diseases, preparing for subsequent pregnancy, and providing subsequent therapy, the patient-centered approach in genetic counseling resolves infertility issues. Genetic counseling is vital in managing patients with infertility difficulties because genetics also have an impact on infertility. It supports their psychological issue, aids in decision-making, lowers the danger of having an abnormal pregnancy, and plans for future pregnancy.

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