

Case Reports

PATIENT WITH PRIMARY OVARIAN FAILURE DUE TO INTERMEDIATE PREMUTATION OF THE FMR1 GENE USING TRANSDERMAL TESTOSTERONE IN IVF TREATMENT, CASE REPORT AND LITERATURE REVIEW

Fernando Mancilla Hernández^{1a}, Jorge L. Lezama Ruvalcaba², Ricardo Rodríguez Calderón³, Carlos G. Salazar López-Ortiz⁴, Paola R. Becerril Rodríguez⁵, Julio C. Rodríguez Verduzco⁶

¹ Biología de la Reproducción Humana, Hospital Español, ² Biología de la reproducción, Hospital Español, ³ Biología de la reproducción, Hospital Español, ⁴ biología de la reproducción, Hospital Español, ⁵ Ginecología, Hospital 20 de Noviembre, ⁶ Ginecología, Hospital Civil de Morelia

Keywords: Ovarian insufficiency, FXPOI, FMR1, Female reproductive health, CGG repetition.

<https://doi.org/10.46989/001c.117352>

Journal of IVF-Worldwide

Vol. 2, Issue 2, 2024

Background

Fragile X syndrome (FXS) is a condition of non-Mendelian nucleotide repeats, which is due to the loss of function of the FMR1 gene (Fragile X Mental Retardation 1); it is caused by the hypermethylation of the repetitions of CGG (cytosine-guanine-guanine triple), expanded adjacent to exon 1 of the FMR1 gene; this mutation affects more than 98% of people with SXF.

Clinical Case

35-year-old patient. Consulted for primary infertility of 1 year of evolution, relevant biochemical studies were requested, among which he highlighted the result of Anti-Mullerian Hormone of 0.40 ng/mL. By age and diagnosis of low ovarian reserve, it is decided to perform FMR1 mutation analysis in search of the cause of the probable primary ovarian failure, resulting in a premutation with repetition of 49 CGG. It is decided to perform a cycle of controlled ovarian stimulation, with menotropins 300 IU every 24 hours + dydrogesterone 30mg orally to inhibit LH peak, as well as the use of transdermal testosterone 50 mg every 24 hours to improve the ovarian response, obtaining 2 MII oocytes, which are vitrified. It is decided to perform a 2nd cycle of ovarian stimulation with menotropins 300 Units + GnRH antagonist to be able to make embryo transfer. The use of 50mg of transdermal testosterone to improve the result, obtaining 4MII, a total of 6 MII oocytes for the two cycles, ICSI (intracytoplasmic sperm injection) is performed at the 6 oocytes of which 4 embryos were obtained in the blastocyst stage, transferring 1 embryo in fresh, and vitrifying 3, quantification of hCG beta-positive fraction is performed at 10 days post-transfer, obtaining a live newborn, male with a weight of 4,010 kg, Size: 58 cm without complications.

Conclusions

FMR1 premutation is associated with a risk of reduced ovarian function and premature ovarian failure with the early loss of fertility in 20% of carrier women due to the reduced number of follicles in the ovaries. Transdermal pretreatment of testosterone seems to increase pregnancy and the rates of live births in people considered deficient who undergo ovarian stimulation for IVF.

^a Corresponding Author
Fernando Mancilla, fmancilla21@outlook.com

BACKGROUND

Fragile X syndrome (FXS) is a non-Mendelian nucleotide repeat condition, which is due to the loss of function of the FMR1 (Fragile X Mental Retardation 1) gene. The FMR1 gene is found on the Xq27.3 chromosome and encodes the FMRP protein, which controls the translation of specific messengers. The repetition of CGG triplets (> 200 repetitions) and the promoter's methylation lead to the gene's silencing. However, the biological mechanism responsible for the presentation of the SXF is still unknown.¹

This syndrome is caused by the hypermethylation of CGG (cytosine-guanine triplet-guanine) repeats, expanded adjacent to exon 1 of the FMR1 gene; this mutation affects more than 98% of people with FXS.² It is estimated that the disorder affects 1/4,000 men and 1/8,000 women in the general Caucasian population, with 60% of individuals with the complete mutation also having autism spectrum disorders.³ Carriers of fragile X premutation (55-200 CGG repeats) are relatively common in the general population.⁴

As mentioned above, the FMR1 gene is mapped on the X chromosome at the q27.3 position and encompasses approximately 40 kb of genomic sequence. This gene contains 17 exons, and its mRNA is 4 kb long. Exons 12, 14, 15, and 17 can be spliced alternately, resulting in different mRNA and protein isoforms.⁵

Fragile X premutation is associated with two clinical disorders: fragile X-associated tremor/ataxia syndrome (FX-TAS) and fragile X-associated primary ovarian insufficiency disorder (FXPOI).⁶ Women who are carriers of premutation may have a spectrum of ovarian dysfunction and may also have normal menstruation with normal or high FSH but with reduced fertility.⁷

CLINICAL CASE

35-year-old patient. Consulted for primary infertility of 1 year of evolution, relevant biochemical studies were requested, among within the result of Anti-Mullerian Hormone of 0.40 ng/mL, by age and diagnosis of low ovarian reserve it is decided to perform FMR1 mutation analysis in search of the cause of the probable primary ovarian failure, resulting in a premutation with repetition of 49 CGG.

We decide on high-complexity treatment (IVF/ICSI) to increase the chances of pregnancy, using menotropins 300 IU every 24 hours plus dihydrogesterone 30mg orally, as well as the use of testosterone 50 mg transdermal every 24 hours to improve the ovarian response starting from 3rd day of the menstrual cycle. An endocavitary ultrasound was performed on day 11 of the cycle (**IMAGE 1**). Subsequently, a serum sample of estradiol and progesterone was taken, resulting in 1010.14 pg/ml and 0.63 ng/ml, respectively. Final oocyte maturation was performed with hCG 10,000 IU. Oocyte capture is carried out at 34 hours after day 13 of the cycle, obtaining 4 oocytes being 2 MII; due to the poor response, vitrification of the oocytes obtained was proposed (**IMAGE 2**), and carrying out from another cycle of ovarian stimulation controlled to obtain more mature oocytes and perform ICSI.

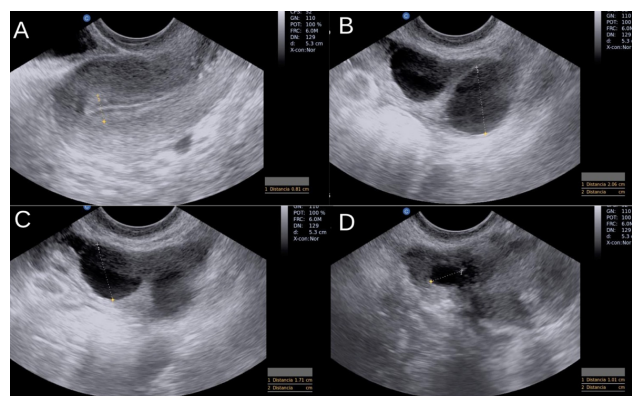


IMAGE 1. Endocavitary ultrasound on day 11 of the cycle. A) endometrial thickness 8 mm with a trilaminar appearance, B) Right ovary with a 20 mm follicle, C) Right ovary with a 17 mm follicle, D) Left ovary with a follicle larger than 10 mm.



IMAGE 2. Mature oocytes obtained (300X)

The use of testosterone 50 mg transdermal every 24 hours was continued without suspending it for 2 months, during which the ovarian stimulation cycles were performed, a change of controlled ovarian stimulation was decided because of the patient's desire and reasons she had to leave the country, a fresh transfer was decided, a second controlled ovarian stimulation was performed with flexible GnRH antagonist protocol, starting on the 3rd day of the cycle using menotropins 300 IU every 24 hours, with GnRH antagonist to inhibit LH peak starting on day 7 of the cycle, on day 10 of the cycle, estradiol and progesterone were taken with the following result Estradiol: 878.82 pg/ml Progesterone: 0.71 ng/ml. Oocyte maturation with hCG 10,000 IU, oocyte capture was carried out on the 14th of the cycle, 34 hours after the trigger, obtaining 4 oocytes being the 4 MII, ICSI was carried out to 6 oocytes in total MII and developing 4 embryos in blastocyst stage (**IMAGE 3** and **4**), complying with the criteria of Gardner's classification according to which a fresh embryo transfer of 1 embryo with BHi AA quality was carried out (**IMAGE 5**), vitrifying 3 embryos, 2 with BHi AA quality and one embryo with BHi BA quality (**TABLE 1**).

Quantification of hCG beta fraction 10 days after embryo transfer, which was 50 mIU/mL, 3 weeks after, endovaginal ultrasound was performed, finding a fetal heart rate of 170 beats per minute. Fetal DNA at 10 weeks of gestation re-



IMAGE 3. A) hatching blastocyst. B) Cavitated blastocyst of the devitrified oocyte cycle (300X)



IMAGE 4. Fresh cycle vitrified cavitated blastocyst (300 X)



IMAGE 5. Hatching blastocyst transferred from fresh cycle (300X)

sults negative for chromosomal alterations such as trisomy 21, 18, and 13, reporting male sex.

The first-trimester ultrasound was performed by a maternal-fetal doctor, with a screening report for structural alterations without pathological findings; the calculation of risks for chromosomopathies (T.21, T.18, T.13) was considered out of range by caudal skull length (CN) >84 mm. Emerging markers were evaluated, finding them normal, the calculation of risk of placental ischemic syndrome (preeclampsia 1:516, fetal growth restriction 1:587) was considered low, risk of preterm birth of 1:2.965 before the 34 weeks, the calculation of risks of gestational diabetes was counted at 1:24, so from the 24- 28 weeks it was recommended to perform an oral glucose tolerance curve of 75 (CTOG 75). Likewise, organ structural ultrasound was performed by a maternal-fetal doctor at 22 weeks, finding exposed in [TABLE 2](#).

The pregnancy was resolved by cesarean section at 39 weeks of gestation. This resulted in a live male newborn weighing 4,010 kg and a height of 58 cm. Apgar was born on 9/9 without complications.

MATERIALS AND METHODS

A search was carried out in the Medline database via PubMed using the following terms: "Ovarian insufficiency," "FXPOI," "FMR1," "Female reproductive health," and "CGG repeat." The following filters limited the search: "Case Reports," "Review," "Systematic Reviews", and "Books and Documents," "Spanish and English", from 1981 to 2021, in total 1,978 studies were found, editorials, reviews, duplicate articles were excluded, and 33 studies were selected that included women with primary ovarian insufficiency associated with the premutation of the FMR1 gene.

DISCUSSION

Transcriptional silencing of FMR1 results in the loss of the fragile mental retard protein X (FMRP), which is necessary for neuronal development and cognition. Carriers of FMR1 premutation also have disorders associated with ovarian function, including loss of fertility and hypoestrogenic (FX-POI), as well as neurodegeneration with associated memory loss and general Parkinsonism (FXTAS).⁸

BIOLOGICAL BASES OF FRAGILE X SYNDROME

The exact biological mechanism responsible for the presentation of SXF is unknown; however, it is known to lie in the ability of the FMRP protein to bind to RNA and proteins. Specifically, FMRP joins ribosomes and is present in the synaptic compartments, which control the translation of specific messengers. The loss of FMRP causes alterations in synaptic connectivity in neurons, translating into the specific symptoms of SXF. These synaptic connectivity alterations manifest in the brain with the decrease in the number of dendrites and spines in the neurons of patients with FXS.¹

Table 1. Morphological description of the blastocyst.

INNER CELL MASS	TROPHOECTODERM
A: Compact, with many cells and well defined	A: complete, made up of many cells
B: Several cells grouped together and with a loose appearance	B: incomplete presents some liner zone
C: a few cells	C: made up of a few cells
D: absent or degraded	D: with degenerated cells.

TABLE 2. ORGANOSTRUCTURAL ULTRASOUND RESULTS

PARAMETER	MEASURE	WEEKS
BD	5.51 cm	22.6 sdg
HC	19.97 cm	22.1 sdg
AC	17.66 cm	22.4 sdg
FL	3.89 cm	22.3 sdg
TIB	3.44 cm	22.6 sdg
HL	3.69 cm	22.6 sdg
RAD	3.14 cm	22.3 sdg
EFW	509.61 g	22.2 sdg p.26
Ultrasonographic evaluation was performed with Vino E.35 equipment qith volumetric transducer, finding the following findings: Single live fetus.		
Skull	Presence of midline, cavum septum pellucidum, separated thalami, without third ventricle dilation. Lateral ventricles with normal characteristics, with left atrium (posterior) measurement of 5.4 mm. Posterior fossa without alterations. Cerebellum with normal characteristics of 26.0 mm.	
Face	Integrity of the midline and upper lip is observed, with the presence of orbital lenses. Nasal bone present of 7.2 mm.	
Chest	Symetrical with four-chamber section with heart in levocardia, levoapex, AV and VA concordance, perforated mode, normal AV valve offset, integrity of the interventricular septum. Outflow tracts without alterations, with crossover of the great vessels without alterations. Section of three normal vessels and three normal trachea vessels. Normal aortic arch in sagittal assessment.	
Abdomen	Abdominal situs solitus is found, adequate closure of the abdominal wall. It is noted presence of gastric chamber. Renal pelvises within normal ranges. Two umbilical arteries and two renal arteries are observed. Bladder present, with normal characteristics.	
Spine	Íntegrates, without alterations.	
Extremities	Whole, symetrical, with normal motility. 12 tubular bones of dimensions according to gestational age. Complete finger count.	
Amniotic fluid	Qualitatively normal, maximum pool of 5.13 cc.	
Placenta	Anterior body grade I. With mean IP of uterine arteries of 1.3 (1.4 MoM) without data of placental resistance. With central cord insert.	
Cervix:	Closed 44 mm long, without funneling or sludge data.	

Pregnancy of 22.6 weeks by LMP – **BD:** Biparietal diameter, **HC:** Head circumference, **AC:** Abdominal circumference, **FL:** Femoral length, **TIB:** tibia, **LH:** Humerus length, **RAD:** radius, **EFW:** Estimated fetal weight

The lack of FMRP in neurons leads to an exacerbated expression of glutamate receptors, both metabotropic (mGluR5) and ionotropic (AMPA and NMDA).⁹ The synthesis, degradation, and transport proteins of g-aminobutyric acid (GABA) and GABA receptors are also reduced.¹⁰ It is not known exactly how these changes in neurotransmitter systems affect the morphology of dendrites and spines in neurons, but it is suspected that they are related. The role of the FMRP protein in glial cells is less known, but it is known that in FXS, the FMRP protein regulates the translation of mGluR5 into astrocytes¹¹ and the production

of myelin in oligodendrocytes.¹² During prenatal development, radial glial cells contain FMRP, which is involved in the active transport of mRNA along the glial fiber.¹³ A change in any of these mechanisms can contribute to the development of cognitive disorders in patients with SXF.

Expanded CGG repetitions are common, intermediate, premutation, and complete mutation alleles. The common alleles in the general population generally contain 6 to 40 repetitions of CGG that are stable and generally do not expand in the transmission from the parents to the offspring. Intermediate alleles containing 41-60 CGG repeats

have variable expansion risks, while premutation alleles (i.e., 55-199 CGG repeats) are generally not methylated.¹⁴ Repetition can become unstable after maternal transmission, which usually results in the expansion of repetition in the next generation. When repetition expands and ranges between 55 and 200, individuals are considered carriers of premutation. In patients with FXS, the repetition of CGG has expanded to more than 200 units.¹⁵

The mechanism underlying the increase in transcriptional activity of the alleles of the premutation range is unknown. However, a recent study reported the differential use of transcriptional initiation sites and polyadenylation sites in FMR1 premutation alleles, leading to different expressions in expanded premutation alleles compared to normal alleles.¹⁶

PRIMARY OVARIAN INSUFFICIENCY (POI) IN PATIENTS WITH FMR1 GENE MUTATION

Only 1% of women experience menopause before the age of 40, called POI. This is the “final stage” of continuous ovarian dysfunction, and despite its clinical importance, the etiology of the POI is often not identified. Women with premutation are at risk of premature ovarian insufficiency (primary ovarian insufficiency associated with fragile X; FXPOI). It has been shown that women with a certain premutation through families with FXS have a POI rate of up to 23% and, as a group, experience a previous menopause in approximately 5 years.¹⁷ Currently, there is no consensus on estimating the absolute risk of POI when a woman has normal or high intermediate repetition alleles. Several studies have been estimated at between 15% and 27% in premutation carriers, compared to a background risk of 1%.¹⁸

Regardless of the cause, in women with established POI, the opportunity to preserve fertility is lost due to the loss of most of the reproductive material. In this case, recent guidelines still report oocyte donation as the only realistic option for pregnancy.¹⁹

This type of treatment must also be cryopreserved to preserve a couple's or a woman's fertility. If premature ovarian insufficiency is predicted long before the onset of early menopause, patients at risk of this condition could benefit from the preservation of fertility due to cryopreservation of reproductive material.²⁰

A pre-implantation genetic diagnosis should be suggested to prevent the birth of offspring affected by the complete FMR1 mutation. In this case, PGT-M is the preferred method for selecting and cryopreserving suitable embryos or using them in IVF programs.²⁰

CLINICAL PRESENTATION OF PATIENTS AFFECTED WITH COMPLETE MUTATION OF THE FMR1 GENE

Patients affected by the complete mutation of the FMR1 gene have special phenotypic characteristics, including an elongated face, large and prominent ears, joint hypermobility, and macroorchidism.²¹

More than 90% of affected children have developmental delays, and approximately 50-60% are diagnosed with

Autism Spectrum Disorder (ASD).²² Throughout their lives, both men and women have behavioral alterations commonly associated with the syndrome, usually beginning during childhood: anxiety and attention and hyperactivity disorder (ADHD) are the most prevalent. However, compulsive disorders such as hyperphagia and aggressiveness are also common. Some characteristics reported in patients with a complete mutation of the FMR1 gene are summarized in [TABLE 3](#).

USE OF ANDROGENS IN PATIENTS WITH LOW RESPONSE UNDERGOING IN VITRO FERTILIZATION

The poor ovarian response results from inadequate ovarian stimulation, generally defined by a low number of recovered oocytes or a low number of developing follicles and a low concentration of estradiol in a previous or functioning IVF cycle.²³

It has been suggested that the accumulation of androgens in the microenvironment of the ovary plays a fundamental role in early follicular development and the proliferation of granulosa cells.²⁴ Excess androgens have been shown to stimulate the early stages of follicular growth²⁵ and increase the number of preantral and antral follicles.²⁶ In addition, the increase in the intraovarian concentration of androgens seems to increase the expression of the follicle-stimulating hormone (FSH) receptor in the granulosa cells²⁷ and, therefore, potentially lead to a greater response of the ovaries to FSH.²⁸

Low ovarian reserve is considered one of the most frequent causes of infertility and is considered one of the main challenges in reproductive medicine. Numerous studies have suggested that androgens (dehydroepiandrosterone and testosterone) play an important role in follicular development by increasing the number of oocytes, thus increasing the pregnancy rate. Testosterone is a sex steroid hormone that originates from cholesterol and is considered a precursor of estradiol biosynthesis.²⁹

Previous treatment with transdermal testosterone has been suggested as a safe and effective way to increase the intraovarian concentration of androgens.³⁰

Recently published randomized controlled trials (RCTs) have evaluated transdermal testosterone³¹ or the pre-treatment of DHEA.³² In people with poor response who undergo ovarian stimulation for IVF, with inconclusive results and others with notable benefits in a number of oocytes, embryo development, and pregnancy rates.

CONCLUSIONS

FMR1 premutation is associated with the risk of reduced ovarian function and premature ovarian failure with early loss of fertility in 20% of women carriers due to the reduced number of follicles in the ovaries.

Patients with POI have lower levels of E2 and lower levels of AMH and undergo menopause, on average, 5 years earlier than non-carrier women. Suppose an early diagnosis of a genetic alteration related to POI is made. In that case, precise genetic advice is required for the patient and her

TABLE 3. Clinical characteristics of the patients with complete mutation of the FMR1 gene²²

PHYSICAL	Long face
	Macrocephaly
	Prominent ears
	Prominent jaw
	Flatfoot
	Joint hypermobility
PSYCHOLOGICAL	ASD
	AHD
	Anxiety
	Aggressiveness
DEVELOPMENT	Intellectual disability
	Language deficit
OTHERS	Squint
	Recurrent Otitis
	Gastrointestinal disorders
	Obesity
	Seizures

AHD: Attention and hyperactivity disorder, ASD: Autism spectrum disorders.

family, as well as an evaluation for the preservation of fertility, as soon as possible.

It is necessary to consider specific clinical and ethical issues regarding the possible association with syndromic clinical conditions, as well as the different mechanisms that led to a poor ovarian response, which increases the complexity of choosing the most appropriate fertility preservation techniques.

In this case, the patient did not want to carry out a pre-implantation genetic study due to the low risk of aneuploidy according to age; she does not accept PGTm either. It is considered to make a fresh transfer since its hormonal levels allow an adequate endometrial thickness.

According to the limited available evidence, transdermal testosterone pretreatment seems to increase pregnancy and the rates of live births in people considered as low responders who undergo ovarian stimulation for IVF. We consider that having been with greater exposure to transdermal testosterone before and during the second controlled ovarian stimulation can improve the number of mature oocytes obtained in the second cycle and thus increase the chances of having embryos developed for embryo transfer. Although several studies suggest the use of testosterone as a safe treatment to increase the number of mature oocytes in fertility treatments, more studies are required to validate the effectiveness and safety of this treatment.

AUTHORS' CONTRIBUTION - [CREDIT](#)

Conceptualization: Fernando Mancilla Hernández (Lead). Resources: Fernando Mancilla Hernández (Lead). Writing – review & editing: Fernando Mancilla Hernández (Lead). Data curation: Jorge L. Lezama Ruvalcaba (Lead). Project administration: Jorge L. Lezama Ruvalcaba (Lead). Supervision: Jorge L. Lezama Ruvalcaba (Lead). Writing – original draft: Jorge L. Lezama Ruvalcaba (Lead). Formal Analysis: Ricardo Rodríguez Calderón (Lead). Software: Ricardo Rodríguez Calderón (Lead). Funding acquisition: Carlos G. Salazar López-Ortiz (Lead). Validation: Carlos G. Salazar López-Ortiz (Lead). Methodology: Paola R. Becerril Rodríguez (Lead). Investigation: Julio C. Rodríguez Verduzco (Lead). Visualization: Julio C. Rodríguez Verduzco (Lead).

COMPETING OF INTEREST – COPE

No competing interests were disclosed.

INFORMED CONSENT STATEMENT

All authors and institutions have confirmed this manuscript for publication.

DATA AVAILABILITY STATEMENT

All are available upon reasonable request.

Submitted: March 10, 2024 CDT, Accepted: May 04, 2024 CDT



This is an open-access article distributed under the terms of the Creative Commons Attribution 4.0 International License (CCBY-NC-SA-4.0). View this license's legal deed at <https://creativecommons.org/licenses/by-nc-sa/4.0> and legal code at <https://creativecommons.org/licenses/by-nc-sa/4.0/legalcode> for more information.

REFERENCES

1. Salcedo-Arellano MJ, Hagerman RJ, Martínez-Cerdeño V. Síndrome X frágil: presentación clínica, patología y tratamiento. *Gaceta médica de México*. 2020;156(1):60-66. doi:10.24875/gmm.19005275
2. Fu YH, Kuhl DP, Pizzuti A, et al. Variation of the CGG repeat at the fragile X site results in genetic instability: resolution of the Sherman paradox. *Cell*. 1991;67(6):1047-1058. doi:10.1016/0092-8674(91)90283-5
3. Crawford DC, Acuña JM, Sherman SL. FMR1 and the fragile X syndrome: human genome epidemiology review. *Genetics in medicine: official journal of the American College of Medical Genetics*. 2001;3(5):359-371. doi:10.1097/00125817-200109000-00006
4. Hagerman PJ. The fragile X prevalence paradox. *Journal of medical genetics*. 2008;45(8):498-499. doi:10.1136/jmg.2008.059055
5. Verkerk AJ, Pieretti M, Sutcliffe JS, et al. Identification of a gene (FMR-1) containing a CGG repeat coincident with a breakpoint cluster region exhibiting length variation in fragile X syndrome. *Cell*. 1991;65(5):905-914. doi:10.1016/0092-8674(91)90397-h
6. Willemsen R, Levenga J, Oostra BA. CGG repeat in the FMR1 gene: size matters. *Clinical genetics*. 2011;80(3):214-225. doi:10.1111/j.1399-0004.2011.01723.x
7. Wheeler AC, Bailey DB Jr, Berry-Kravis E, et al. Associated features in females with an FMR1 premutation. *Journal of neurodevelopmental disorders*. 2014;6(1):30. doi:10.1186/1866-1955-6-30
8. Peprah E. Understanding decreased fertility in women carriers of the FMR1 premutation: a possible mechanism for Fragile X-Associated Primary Ovarian Insufficiency (FXPOI). *Reproductive health*. 2014;11:67. doi:10.1186/1742-4755-11-67
9. Danesi C, Achuta VS, Corcoran P, et al. Increased Calcium Influx through L-type Calcium Channels in Human and Mouse Neural Progenitors Lacking Fragile X Mental Retardation Protein. *Stem cell reports*. 2018;11(6):1449-1461. doi:10.1016/j.stemcr.2018.11.003
10. Pizzo L, Lasser M, Yusuff T, et al. Functional assessment of the “two-hit” model for neurodevelopmental defects in *Drosophila* and *X. laevis*. *PLoS genetics*. 2021;17(4):e1009112. doi:10.1371/journal.pgen.1009112
11. Higashimori H, Morel L, Huth J, et al. Astroglial FMRP-dependent translational down-regulation of mGluR5 underlies glutamate transporter GLT1 dysregulation in the fragile X mouse. *Human molecular genetics*. 2013;22(10):2041-2054. doi:10.1093/hmg/ddt055
12. Wang H, Ku L, Osterhout DJ, et al. Developmentally-programmed FMRP expression in oligodendrocytes: a potential role of FMRP in regulating translation in oligodendroglia progenitors. *Human molecular genetics*. 2004;13(1):79-89. doi:10.1093/hmg/ddh009
13. Pilaz LJ, Lennox AL, Rouanet JP, Silver DL. Dynamic mRNA Transport and Local Translation in Radial Glial Progenitors of the Developing Brain. *Current biology: CB*. 2016;26(24):3383-3392. doi:10.1016/j.cub.2016.10.040
14. Verkerk AJ, Pieretti M, Sutcliffe JS, et al. Identification of a gene (FMR-1) containing a CGG repeat coincident with a breakpoint cluster region exhibiting length variation in fragile X syndrome. *Cell*. 1991;65(5):905-914. doi:10.1016/0092-8674(91)90397-h
15. Yu S, Pritchard M, Kremer E, et al. Fragile X genotype characterized by an unstable region of DNA. *Science (New York, NY)*. 1991;252(5009):1179-1181. doi:10.1126/science.252.5009.1179
16. Tassone F, De Rubeis S, Carosi C, et al. Differential usage of transcriptional start sites and polyadenylation sites in FMR1 premutation alleles. *Nucleic acids research*. 2011;39(14):6172-6185. doi:10.1093/nar/gkr100
17. Manor E, Jabareen A, Magal N, Kofman A, Hagerman RJ, Tassone F. Prenatal Diagnosis of Fragile X: Can a Full Mutation Allele in the FMR1 Gene Contract to a Normal Size. *Frontiers in genetics*. 2017;8:158. doi:10.3389/fgene.2017.00158
18. Sherman S, Pletcher BA, Driscoll DA. Fragile X syndrome: diagnostic and carrier testing. *Genetics in medicine: official journal of the American College of Medical Genetics*. 2005;7(8):584-587. doi:10.1097/01.gim.0000182468.22666.dd
19. European Society for Human Reproduction and Embryology (ESHRE) Guideline Group on POI, Webber L, Davies M, et al. ESHRE Guideline: management of women with premature ovarian insufficiency. *Human reproduction (Oxford, England)*. 2016;31(5):926-937. doi:10.1093/humrep/dew027

20. La Marca A, Mastellari E. Fertility preservation for genetic diseases leading to premature ovarian insufficiency (POI). *Journal of assisted reproduction and genetics*. 2021;38(4):759-777. [doi:10.1007/s10815-021-02067-7](https://doi.org/10.1007/s10815-021-02067-7)
21. Hagerman RJ, Berry-Kravis E, Hazlett HC, et al. Fragile X syndrome. *Nature reviews Disease primers*. 2017;3:17065. [doi:10.1038/nrdp.2017.65](https://doi.org/10.1038/nrdp.2017.65)
22. Bailey DBJ, Raspa M, Olmsted M, Holiday DB. Co-occurring conditions associated with FMR1 gene variations: findings from a national parent survey. *American journal of medical genetics Part A*. 2008;146A(16):2060-2069. [doi:10.1002/ajmg.a.32439](https://doi.org/10.1002/ajmg.a.32439)
23. Tarlatzis BC, Zepiridis L, Grimbizis G, Bontis J. Clinical management of low ovarian response to stimulation for IVF: a systematic review. *Human reproduction update*. 2003;9(1):61-76. [doi:10.1093/humupd/dmg007](https://doi.org/10.1093/humupd/dmg007)
24. Weil SJ, Vendola K, Zhou J, et al. Androgen receptor gene expression in the primate ovary: cellular localization, regulation, and functional correlations. *The Journal of clinical endocrinology and metabolism*. 1998;83(7):2479-2485. [doi:10.1210/jcem.83.7.4917](https://doi.org/10.1210/jcem.83.7.4917)
25. Vendola KA, Zhou J, Adesanya OO, Weil SJ, Bondy CA. Androgens stimulate early stages of follicular growth in the primate ovary. *The Journal of clinical investigation*. 1998;101(12):2622-2629. [doi:10.1172/JCI2081](https://doi.org/10.1172/JCI2081)
26. Hillier SG, Tetsuka M, Fraser HM. Location and developmental regulation of androgen receptor in primate ovary. *Human Reproduction*. 1997;12(1):107-111. [doi:10.1093/humrep/12.1.107](https://doi.org/10.1093/humrep/12.1.107)
27. Weil S, Vendola K, Zhou J, Bondy CA. Androgen and follicle-stimulating hormone interactions in primate ovarian follicle development. *The Journal of clinical endocrinology and metabolism*. 1999;84(8):2951-2956. [doi:10.1210/jcem.84.8.5929](https://doi.org/10.1210/jcem.84.8.5929)
28. Hillier SG, De Zwart FA. Evidence that granulosa cell aromatase induction/activation by follicle-stimulating hormone is an androgen receptor-regulated process in-vitro. *Endocrinology*. 1981;109(4):1303-1305. [doi:10.1210/endo-109-4-1303](https://doi.org/10.1210/endo-109-4-1303)
29. Esparza MEE, Ruvalcaba JLL, Salazar Lopez Ortiz CG, Salazar JC. Use of transdermal testosterone in women Poseidon IV group under high complexity assisted reproduction treatment. *Journal of IVF-Worldwide*. 2024;2(1). [doi:10.46989/001c.92149](https://doi.org/10.46989/001c.92149)
30. Casson PR, Lindsay MS, Pisarska MD, Carson SA, Buster JE. Dehydroepiandrosterone supplementation augments ovarian stimulation in poor responders: a case series. *Human reproduction (Oxford, England)*. 2000;15(10):2129-2132. [doi:10.1093/humrep/15.10.2129](https://doi.org/10.1093/humrep/15.10.2129)
31. Massin N, Cedrin-Durnerin I, Coussieu C, Galey-Fontaine J, Wolf JP, Hugues JN. Effects of transdermal testosterone application on the ovarian response to FSH in poor responders undergoing assisted reproduction technique--a prospective, randomized, double-blind study. *Human reproduction (Oxford, England)*. 2006;21(5):1204-1211. [doi:10.1093/humrep/dei481](https://doi.org/10.1093/humrep/dei481)
32. Wiser A, Gonen O, Ghetler Y, Shavit T, Berkovitz A, Shulman A. Addition of dehydroepiandrosterone (DHEA) for poor-responder patients before and during IVF treatment improves the pregnancy rate: a randomized prospective study. *Human reproduction (Oxford, England)*. 2010;25(10):2496-2500. [doi:10.1093/humrep/deq220](https://doi.org/10.1093/humrep/deq220)