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Special Article

Contraception, Pregnancy and Rare Respiratory Diseases☆

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ABSTRACT

Three percent of rare diseases are pneumopathies. Improvements in survival and quality of life have led to a new situation where patients with rare respiratory diseases want to plan their reproductive lives. The intention of this review is to present the experience accumulated in the field of reproductive health of these women.

In several rare respiratory diseases, a genetic base has been identified. The combination of preimplantation genetic diagnosis, assisted reproduction and molecular biology techniques enable embryos to be studied genetically before being transplanted into the uterus. Therefore, the risk for transmitting a certain disease or chromosome alteration may be avoided in high-risk couples, and prenatal diagnoses may be done by chorionic villus sampling or amniocentesis.

As a general rule, contraceptive methods should be personalized by evaluating the general state of female patients as well as their possibilities for pregnancy, complications and the future possibility of lung transplantation.

In lymphangioleiomyomatosis and primary pulmonary hypertension, pregnancy is considered a contraindication. In the former, there is a very high risk for pneumothorax and loss of lung function. In the latter, mortality reaches 33%. In cystic fibrosis, it is estimated that each year 4% of patients become pregnant and there is no observed loss in lung function.

There are special circumstances in childbirth that should be considered as well as specific anesthesia risks.

The present review suggests that while taking decision about contraceptive methods, pregnancy as a contraindication or conditions for managing a pregnancy should be both individualized and multidisciplinary.

Anticoncepción, embarazo y enfermedades respiratorias minoritarias

Palabras clave:
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Embarazo
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RESUMEN

El 3% de las enfermedades raras son neumopatías. Las mejoras en la supervivencia y en la calidad de vida hacen que las pacientes con enfermedades respiratorias minoritarias deseen planificar su vida reproductiva. Esta revisión intenta presentar la experiencia acumulada en el campo de la salud reproductiva en estas mujeres.

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Fibrosis quística
Linfangioleiomiomatosis
Hipertensión pulmonar primaria

En diversas enfermedades respiratorias minoritarias se ha identificado una base genética. La combinación del diagnóstico genético preimplantacional, la reproducción asistida y las técnicas de biología molecular permite realizar el estudio genético de los embriones, antes de ser transferidos al útero; por tanto, puede evitarse el riesgo de transmitir una determinada enfermedad o alteración cromosómica en las parejas de elevado riesgo y se puede, también, realizar un diagnóstico prenatal mediante biopsia corial o amniocentesis.

Como norma general, debemos personalizar el método anticonceptivo evaluando el estado general de la mujer y las posibilidades de embarazo, complicaciones y la posibilidad futura de trasplante pulmonar.

En la linfangioleiomiomatosis y la hipertensión pulmonar primaria el embarazo se considera contraindicado. En la primera existe un riesgo muy elevado de neumotórax y de pérdida de función pulmonar. En la segunda, la mortalidad alcanza el 33%. En fibrosis quística se estima que cada año un 4% de las pacientes se quedan embarazadas y no se observa un deterioro de la función pulmonar.

Existen circunstancias especiales en el parto a tener en cuenta y riesgos anestésicos específicos.

La presente revisión sugiere que tanto la decisión sobre la anticoncepción como la contraindicación de un embarazo o las condiciones de su seguimiento deben ser individualizadas y multidisciplinares.

Introduction

Rare or uncommon diseases are defined as those that have a prevalence of fewer than 5 cases per 10 000 inhabitants. This definition was adopted by the "Programme of Community Action on Rare Diseases (1999–2003)" and has been accepted by most member-states of the European Union. It is also used by the European Medicines Agency for declaring orphan drugs. There are close to 6000 diseases that are classified as rare, and 181 (3%) of them are pneumopathies. Table 1 demonstrates the prevalence of several of them.

What rare lung diseases (RLD) frequently have in common is that they affect young patients, are chronic in character, entail severe prognoses and are complex to diagnose and treat.

Spectacular improvements have been made in survival and quality of life in some of these diseases, such as cystic fibrosis (CF) or primary pulmonary hypertension (PPH), and the accumulated experience in lung transplantation guarantees optimal survival when other therapeutic options have been exhausted. These factors mean that pulmonologists and other specialists now have to face questions and patient situations that we did not have to face several years ago. A prime example of this is reproductive life planning which, in addition to being a key intervention in improved patient health, is a human right, as has been established by Spanish legislation and several international documents.[1]

This review presents the multidisciplinary experience accumulated in the area of reproductive health of women with RLD, in a practical, integrated manner.

Reproductive Counseling for Patients Affected by Rare Lung Diseases

In most rare lung diseases, a genetic origin has been identified.[2] Genetic counseling is necessary for parents whose first child is affected by one of these diseases and who may plan another pregnancy. Counseling is also needed for couples with a member who is either affected by the disease or is a carrier of the mutation.

Table 1
Prevalence of Main RLDS.

	No. of Cases/ 10 000 Inhabitants
Alpha-1 antitrypsin deficiency	3.3
Idiopathic pulmonary fibrosis	1.67
Cystic fibrosis	1.26
Idiopathic and/or familial primary pulmonary hypertension	0.15
Lymphangioleiomyomatosis	0.056
Sarcoidosis	1.5
Wegener's disease	0.66

Taken from: http://www.orpha.net/orphacom/cahiers/docs/ES/prevalencia_de_las_enfermedades_raras_por_orden_alfabetico.pdf.

Currently, by means of the combination of advances made in the fields of pre-implantation genetic diagnosis (PGD), assisted reproduction, and molecular biology techniques such as fluorescence *in situ* hybridization and polymerase chain reaction, embryos can be studied genetically before being implanted in the uterus. Therefore, the risk for transmitting a certain disease or chromosomal alteration may be avoided in high-risk couples. In those cases requiring urgent genetic counseling (unplanned pregnancy), prenatal diagnosis may be performed by either chorionic biopsy or amniocentesis.

PGD consists of the biopsy of one or two cells of the embryo (blastomeres) on the third day of *in vitro* development. It is able to detect chromosomal anomalies, mutations or genetic variations associated with monogenic diseases. In each *in vitro* fertilization procedure, only those embryos that are determined to be healthy, chromosomally normal or, in recessive diseases, and non-diseased (although they may be carriers of the disease) are chosen to be transferred to the maternal uterus.

The first pregnancy of a CF-free fetus achieved by PGD in the world was published in 1992, and ten years later this was achieved in Spain.[3] Although there are many CFTR mutations identified, and some have no clinical significance, it is advisable to carry out the gene study in patients with CF and in their families in order to identify the specific mutations in each case and to adjust the technique.

The European Society of Human Reproduction and Embryology (ESHRE consortium) has compiled a list of monogenic diseases that are analyzable with PGD. Briefly, they have identified mutations that provide genetic diagnoses for: alpha-1-antitrypsin deficiency (AAT) (E264V allele S, E343K allele Z in the PI gene); familial primary pulmonary hypertension (PPH), and lymphangioleiomyomatosis (LAM) associated with tuberous sclerosis. PPH (BMPR2 gene) is a dominant autosomal disease with reduced penetrance (20%), which means that, despite the fact that the risk of inheriting the mutation from an affected parent is 50%; the probability of developing the clinical disease may only be 10%. LAM associated with tuberous sclerosis presents a dominant autosomal inheritance in which mutations have been identified in two TSC1 and TSC2 genes for which there are DNA tests available for the PGD.

In the cases in which genetic tests are not predictive of disease but instead of risk, performing PGD requires the express authorization of health authorities and a report from the National Commission of Assisted Human Reproduction, which individually evaluates each case. The report of the Health Technologies Evaluation Agency of the Carlos III Health Institute and the Spanish Health Ministry ("*Investigación priorizada en Evaluación de Tecnologías*