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SCIENTIFIC LETTER

Familial hypercholesterolaemia in twin brothers born using *in-vitro* fertilisation with donor semen and ovules☆

Hipercolesterolemia familiar en 2 hermanos mellizos nacidos por fecundación *in vitro* con semen yóvulos de donante

To the editor:

Assisted reproductive technology (ART) accounts for approximately 8% of births in Spain. The relative obscurity of these pregnancies and the anonymity of gamete donors, established by Spanish law on ART (in contrast with neighbouring countries), have given rise to new dilemmas in paediatric practice.[1] The group of experts that reviewed the current situation of ART in Europe questioned the actual anonymity of gamete donors.[2]

We present 2 clinical cases that we consider of interest on account of the ethical aspects that it brought up following diagnosis of a genetic disorder in 2 siblings conceived through ART with donor sperm and eggs, and therefore with an unknown family history.

The patients were twins, one boy and one girl, referred to the paediatric endocrinology unit of tertiary care hospital after chance finding of high total cholesterol and low-density lipoprotein (LDL) levels. The relevant personal history included birth at 35 weeks with a weight adequate for gestational age following conception by *in vitro* fertilization (IVF) and a bichorial-diamniotic twin gestation. Neither patient had xanthomas. The girl was obese (body mass index z-score, +2.11). During the follow-up, the patient had sustained LDL levels of more than 190 mg/dL despite implementation of dietary measures and daily physical activity. Suspicion of familial hypercholesterolaemia (FH) led to genetic testing with second-generation sequencing of LDL receptor, apolipoprotein B and proprotein convertase subtilisin/kexin type 9 genes. Testing detected a heterozygous pathogenic variant in exon 13 of the LDL receptor gene (p.Leu658Pro, c.1973 T > C) in both patients, confirming the diagnosis of FH.

Familial hypercholesterolaemia is a genetic disorder that affects approximately 1 out of every 300 individuals in the general population. It is characterised by elevation of LDL levels from birth, the development of xanthomas and premature cardiovascular disease.[3] It has an autosomal dominant pattern of inheritance, so that half of the offspring of an affected individual may develop the disorder. Most cases are caused by mutations in the LDL receptor gene, and de novo mutations in this gene are extremely rare.[4] Since early diagnosis and treatment mitigate mitigating cardiovascular morbidity and mortality risk, diagnosis between ages 2 and 10 years is recommended.[5] Despite the high risk of cardiovascular disease in these patients, most are undiagnosed and untreated.

Sperm and egg donors undergo a confidential evaluation that includes a physical examination and laboratory tests for detection of infectious and genetic diseases that could be transmitted to the offspring. Given the exponential growth in our knowledge of genetic changes, there is an ongoing debate as to the genetic screens that should be performed in gamete donors.[2] Despite the high prevalence of FH and that it may be asymptomatic, current law does not mandate or contemplate genetic testing for this disease.

The diagnosis of FH in 2 siblings conceived through IVF from donor gametes posed a series of ethical dilemmas.

First, there is the harm caused to both patients through transmission of this disease, who will require lifelong treatment with dietary measures and lipid-lowering drugs.

Second, while the donation process is anonymous and confidential, Law 14/2006, of 26 May, on ART, establishes 2 situations in which the identity of the donor can be exceptionally revealed, with restrictions and without publicity: ''certain danger to the life or the health of the child'' and ''as appropriate according to the law of criminal procedure''.[6] Despite the risk of early cardiovascular disease of affected donors, the law does not contemplate disclosure of the identity of the donor on account of a health risk to the donor. We do not know whether the donor intentionally concealed the diagnosis of FH and chose not to provide truthful information about their health or was unaware of the condition. Either way, in this case, searching for the donors to inform them was not indicated.

On the other hand, there is the possibility that the gamete donor will transmit the disease to other offspring, although the law limits donation to a maximum of 6 offspring, including those conceived naturally or with ART.

In short, the situation presented here requires careful consideration of how we can prioritise the wellbeing of children conceived by ART.

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References

1. Gallego Riestra S, Riaño Galán I. ¿Quién decide qué datos deben constar en la historia clínica en relación con el origen biológico? Aten Primaria. 2018;50:74–8.
2. Harper JC, Geraedts J, Borry P, Cornel MC, Dondorp WJ, Gianaroli L, et al. Current issues in medically assisted reproduction and genetics in Europe: Research, clinical practice, ethics, legal issues and policy: European Society of Human Genetics and European Society of Human Reproduction and Embryology. Hum Reprod. 2014;29:1603–9.
3. Akioyamen LE, Genest J, Shan SD, Reel RL, Albaum JM, Chu A, et al. Estimating the prevalence of heterozygous familial hypercholesterolaemia: a systematic review and meta-analysis. BMJ Open. 2017;7:e016461.
4. Tada H, Hosomichi K, Okada H, Kawashiri MA, Nohara A, Inazu A, et al. A de novo mutation of the LDL receptor gene as the cause of familial hypercholesterolemia identified using whole exome sequencing. Clin Chim Acta. 2016;453:194–6.
5. Goldberg AC, Hopkins PN, Toth PP, Ballantyne CM, Rader DJ, Robinson JG, et al. Familial hypercholesterolemia: screening, diagnosis and management of pediatric and adult patients: clinical guidance from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. J Clin Lipidol. 2011;5 Suppl 3:S1–8.
6. Enguer P, Ramón F. Dilemas bioéticos y jurídicos de la reproducción asistida en la sociedad actual en España. Revista Latinoamericana de Bioética. 2017;18:104–35.

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Rapid desensitisation to tocilizumab in systemic idiopathic juvenile arthritis☆

Desensibilización rápida a tocilizumab en artritis idiopática juvenil sistémica

To the Editor:

Systemic juvenile idiopathic arthritis (SJIA) accounts for 10%–15% of cases of juvenile idiopathic arthritis (JIA), with a similar incidence in individuals of either sex. In 66% of patients, it has onset before age 5 years, a subset that includes the most severe cases and in which extraarticular manifestations are particularly important.[1]

The advent of monoclonal antibodies against human interleukin 1 (IL-1) and 6 (IL-6) (tocilizumab) revolutionized the treatment of SJIA, achieving remission in cases refractory to conventional treatment.[2] Tocilizumab is a well-tolerated drug. Adverse reactions following its administration have been described in 8% of patients treated with the drug, of which 0.13% were hypersensitivity reactions.[3,4]

We present the case of a female patient aged 2 years with a body weight of 10 kg that presented with persistent high-grade fever of up to 40 °C of 3 weeks' duration, a generalised erythematous maculopapular rash that worsened during febrile episodes and resolved spontaneously, axillary, inguinal and cervical lymph enlargement with mobile, soft and painless enlargement to 2 cm, arthritis in the knees, elbows and hands manifesting with pain and impaired gait and hepatosplenomegaly. Blood tests revealed hypoalbuminaemia, hypochromic microcytic anaemia, leucocytosis and elevation of liver enzymes, and after exclusion of underlying infection or blood or solid tumours, SJIA was diagnosed based on the criteria established by the International League of Associations for Rheumatology.

The patient started treatment with methotrexate, oral prednisone and intravenous boluses of methylprednisolone, but subsequently developed macrophage activation syndrome, with elevation of serum ferritin levels (14 060 ng/mL), a sharp decrease in the erythrocyte sedimentation rate, thrombocytopenia, anaemia and elevation of transaminases and lactate dehydrogenase, which required initiation of treatment with tocilizumab, administered in doses of 12 mg/kg for a total dose of 120 mg every 15 days. The patient did not exhibit hypersensitivity reactions to the first cycle of tocilizumab, but she continued to exhibit clinical and laboratory features suggestive of persistent disease activity. Following consultation with the department of haematology, etoposide was administered, but it did not achieve clinical improvement.

In the first 5 min of infusion of the second cycle of intravenous tocilizumab, the patient developed a rash, facial swelling, tachycardia, tachypnoea, difficulty breathing, oxygen desaturation to 88%, abdominal pain, fever and piloerection, leading to discontinuation of the bolus of tocilizumab and administration of intramuscular

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