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CELL-BASED DRUG DEVELOPMENT, SCREENING, AND TOXICOLOGY

First-in-Human Case Study: Pregnancy in Women With Crohn's Perianal Fistula Treated With Adipose-Derived Stem Cells: A Safety Study

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ABSTRACT

The aim of this study was to determine whether treatment with adipose-derived stem cells (ASCs) had any influence on fertility, course of pregnancy, newborn weight, or physical condition of newborns. We performed a retrospective study of patients with a desire to become pregnant after having received intralesional injection of autologous ASCs for the treatment of perianal or rectovaginal fistula associated with Crohn's disease. We collected data on the resulting pregnancies, deliveries, and newborns of these patients. ASCs were expanded in vitro and characterized according to the international guidelines for cell surface markers (clusters of differentiation) and differentiated to adipocytes, chondrocytes, and osteocytes prior to implantation (except first implant in 2002). We analyzed five young women with Crohn's disease treated with ASCs, one for rectovaginal and perianal fistula, two for rectovaginal fistula, and two for perianal fistula only. All patients received 2 doses of 20 million and 40 million cells at an interval of 3–4 months. Another patient received 2 doses of 6.6 million and 20 million ASCs with 9 months between each dose. Fertility and pregnancy outcomes were not affected by cell therapy treatment. No signs of treatment-related malformations were observed in the neonates by their respective pediatricians. In the patients studied, cell therapy with ASCs did not affect the course of pregnancy or newborn development. STEM CELLS TRANSLATIONAL MEDICINE *2015;4:1–5*

SIGNIFICANCE

Local treatment with mesenchymal stem cells derived from adipose tissue seems not to affect the ability to conceive, the course of pregnancy, pregnancy outcomes, or newborns' health in female patients. This is the first publication about pregnancy outcome in women with perianal fistula and Crohn's disease treated with stem cell therapy, and could be of interest for doctors working in cell therapy. This is a very important question for patients, and there was no answer for them until now.

INTRODUCTION

Mesenchymal stem cells (MSCs) are nonhematopoietic progenitor cells that are defined by their ability to adhere to plastic surfaces and their capacity to differentiate toward different mesodermic lineages [1]. An important feature of MSCs is their immunomodulatory and anti-inflammatory capacity [2]. Adipose tissue is a readily accessible and rich supply of adult MSCs [3, 4]. Adipose-derived stem cells (ASCs) are prepared as a suspension of living adult mesenchymal stem cells extracted from the stromal vascular fraction (SVF) of the subdermal adipose tissue, which is obtained by liposuction. The SVF has a heterogeneous cell component comprising mast cells, endothelial cells, pericytes, fibroblasts, and stem cells with multilineage capacity. After the SVF is isolated by digestion of adipose tissue with collagenase type I, differential centrifugation, and erythrocytes lysis, MSCs can be isolated thanks to their ability to adhere to tissue culture plates. Finally, they are cultured under controlled conditions to get expanded ASCs (eASCs) [5].

The potential therapeutic application of eASCs has been the subject of a significant number of studies. Their use to treat perianal fistulas in patients with Crohn's disease is being explored because these cells deliver immunoregulatory signals that suppress inflammation, allowing fistula tracts to heal. The incidence of perianal fistulizing disease in patients with inflammatory bowel disease (IBD) is near 50% [6], and perianal fistulizing disease greatly affects patients' quality of life because often they do not respond to current treatments [7–9] and recurrence and complications are frequent [10, 11]. Since 2001, our team has participated in several clinical trials intended

to study the use of eASCs to treat fistulizing disease in patients with Crohn's disease [12–15]. These studies have shown promising efficacy levels and a good safety profile in patients from both autologous and allogeneic settings.

Women with IBD and their treating physician must make difficult decisions about issues of conception and pregnancy, with very limited and often contradictory information [16]. Although published studies indicate that patients with IBD may have overall fertility rates similar to the general population [16–19], infertility and poor pregnancy outcomes (e.g., increased rates of preterm birth, low birth weight, and miscarriage) have been reported in patients with active Crohn's disease and in patients with Crohn's disease with previous surgical intervention [18–20]. Within this context, the aim of this study was to examine fertility, course of pregnancy, and newborn development in patients with fistulizing Crohn`s disease previously treated with eASCs. No information in this regard is currently available, although patients screened for clinical trials involving cell-based therapies frequently have questions about these issues.

Patients and Methods

We performed an observational, retrospective, and descriptive study including those patients who expressed a desire to become pregnant after participating in the clinical trials for the treatment of fistulizing Crohn's disease with ASCs, carried out by the Colorectal Surgery Service of Hospital La Paz in Madrid, Spain. During the development of these trials, 23 women were treated with eASCs in a proof-of-concept study with autologous eASCs [13]: 2 in phase I with autologous eASCs [14], 6 in phase II with autologous eASCs for perianal fistula [15], 4 in phase I/II with allogeneic eASCs for perianal fistula [12], 10 in phase I using allogeneic eASCs for rectovaginal fistula (Herreros, MD, González-Gómez, C, De la Quintana, P et al., manuscript in preparation), and 1 with compassionate use [21]. Most of these patients were young women of childbearing age. Six who entered remission after stem cell treatment decided to become pregnant after completion of the trial. Data collection forms were filled out based on computer records, clinical documentation, and direct or telephone interviews. All patients provided signed consent to participate in the study, and data collection was reviewed and approved by the clinical research ethics committee of La Paz University Hospital. Recorded data included relevant clinical history, including gynecological history; age at the time of cell implantation; injected dose; time from treatment to pregnancy; number of pregnancies after treatment and outcome (miscarriages, term and preterm deliveries); method of conception (spontaneous, assisted reproduction); obstetric history of each pregnancy; disease activity before pregnancy, during pregnancy, and in the postpartum period; treatment of Crohn's disease during pregnancy; mode of delivery; newborn birth weight; and pediatric data for the first 3 months of life.

The results were analyzed using the statistical package SPSS version 11.5 (IBM Corp., Armonk, NY, http://www-01.ibm.com/software/analytics/spss/).

Results

All six women who expressed a desire to become pregnant after completion of the clinical trial were successful. Five provided information for this study. One patient could not be contacted to provide information.

The average age was 34.4 years at cell therapy and 36.6 years at gestation.

Results corresponding to the different patients are described below and summarized in Table 1.

Patient 1

This patient had recurrent rectovaginal fistula for which she received seton drainage in 2001. She received cell therapy twice. The first time was in 2002, when she was aged 35 years. She was successfully treated with intralesional injection of autologous ASCs (6.6 million cells). Nine months later she received a second treatment, consisting of an injection of 20 million cells, for a new rectovaginal fistula. The patient had no previous child. Six years after the second treatment, when she was aged 41 years, she became pregnant by artificial insemination because of low ovarian reserve. During the course of pregnancy, the patient had normal weight gain (13 kg) and no fetal or obstetric complications. An elective cesarean delivery was performed at 38.4 weeks of gestation to provide perineal protection and did not cause any complications. She gave birth to a healthy male newborn with normal weight (3,280 g, 61st percentile). During pregnancy, the patient was treated with azathioprine and olsalazine because of increased activity of Crohn's disease.

Patient 2

This patient had previously undergone conventional surgery to treat rectovaginal fistula. In 2005, at the age of 34 years, she had received successful treatment for a perianal fistula with autologous ASCs (20 million and 40 million cells). She became pregnant spontaneously 6 months after the end of trial follow-up (18 months after cell application), when she was aged 35 years. The patient had normal weight gain for a multiple pregnancy (15 kg) with no obstetric complications. An elective cesarean delivery was performed at 37 weeks of gestation to provide perineal protection and support for twin pregnancy; the patient did not suffer any complications. She gave birth two healthy female newborns with low weight but no significant weight discordance (2,400 g, ninth percentile; 2,080 g, first percentile). During pregnancy, the patient received azathioprine to control her Crohn's disease. Four years later she had a rectovaginal relapse treated with adalimumab.

Patient 3

This patient had previously undergone conventional surgery to treat rectovaginal fistulas (three times). She was successfully treated with 2 doses of allogeneic ASCs (20 million and 40 million cells) obtained from a healthy donor. The cells were administered to treat a rectovaginal fistula in 2010, when the patient was aged 33 years, at an interval of 4 months. The patient had no previous children, and she became pregnant spontaneously 6 months after the end of trial follow-up (18 months after cell treatment), when she was aged 34 years. The patient had normal weight gain (15 kg) with no fetal or obstetric complications. An elective cesarean delivery was performed at 39 weeks of gestation to provide perineal protection; the patient did not suffer any complications. She gave birth to a healthy male newborn with normal weight (3,450 g, 71st percentile). During pregnancy, the patient received azathioprine to control her Crohn's disease. During the postpartum period, she

Table 1. Patients information and reproductive outcomes

Patient	Type of fistula	Cell therapy	Dose (million cells)	Age at cell therapy (years)	Gestation	Age at gestation (years)	Time elapsed between cell treatment and gestation	Gestational complications	CD treatment during pregnancy	Gestational age at birth (weeks)	Delivery	Fetal weight (g)	Newborn malformations
1	Rectovaginal/ rectovaginal	Autologous/ autologous[a]	6.6/20[a]	35	Yes	41	6 years	No	Azathioprine, olsalazine	38.4	CS	3,280	No
2	Rectovaginal	Autologous	20 + 40	34	Yes	35	18 months	FGR, SGA	Azathioprine	37	CS	2,400/2,080	No
3	Rectovaginal	Allogeneic	20 + 40	33	Yes	34	18 months	No	Azathioprine	39	CS	3,450	No
4	Perianal	Allogeneic	20 + 40	37	Yes	38	17 months	No	Azathioprine	37.3	CS	3,110	Syndactyly, clinodactyly
5	Perianal	Allogeneic	20 + 40	33	Yes	35	2 years	2 FTA	No				

[a]Two treatments.
Abbreviations: CD, Crohn's disease; CS, cesarean section; FGR, fetal growth restriction; FTA, first-trimester abortion; SGA, small for gestational age.

developed a rectovaginal fistula during a new episode of Crohn's disease.

Patient 4

In addition to Crohn's disease, this patient had a previous history of ankylosing spondylitis, tonsillectomy, appendectomy, eye surgery, myomectomy, and cesarean section. In 2010, at the age of 37 years, she received successful treatment for a perianal fistula with allogeneic ASCs (20 million and 40 million cells). The patient had three pregnancies before cell therapy (two miscarriages and one full-term birth by cesarean delivery). Five months after completing the treatment and follow-up period of the trial (17 months after cells application), the patient became pregnant spontaneously and experienced normal weight gain (15 kg) without obstetric complications. An elective cesarean delivery was performed at 37.3 weeks of gestation to provide perineal protection and because of previous uterine surgeries; the patient did not experience any complications. She gave birth to a female newborn with normal weight (3,110 g, 77th percentile). The newborn had bilateral syndactyly of toes 2 and 3 and, like her father, bilateral clinodactyly of the fifth fingers. At the time of writing, no other abnormalities had been observed during her first 6 months of life. The mother required medical treatment with azathioprine during the first and second trimesters of the pregnancy to control her Crohn's disease.

Patient 5

In 2010, when the patient was aged 33 years, she was treated successfully for perianal fistula, receiving 2 doses of allogeneic ASCs (20 million and 40 million cells). The ASCs were obtained from a healthy donor and were administered at an interval of 4 months. The patient had no previous child. At 35 years of age, 2 years after cell therapy, she had two first-trimester miscarriages. No pathologic or genetic study was performed following either of the abortions. She did not receive any medical treatment during the pregnancies.

Discussion

Fertility, pregnancy, and childbirth are important issues for young women affected by Crohn's disease because active disease is associated with an increase in the risk of antepartum hemorrhage, stillbirth, spontaneous abortion, low birth weight, and premature delivery [18, 22–26]. Patients who conceive when their disease is active are more likely to have active disease during pregnancy, so it is advisable to conceive during remission [22, 27]. Patients with quiescent IBD are as fertile as the general population; however, it is suggested that active Crohn's disease reduces fertility in women by several mechanisms, including inflammation involving the fallopian tubes and ovaries and perianal disease causing dyspareunia [28].

In terms of treatment of the disease, no evidence shows that medication affects fertility in women [28]. Based on our studies and on the results published by other groups, eASCs seem to be a successful approach to treating perianal fistula in patients with Crohn's disease. In addition, the biosafety profile of ASCs demonstrated in numerous clinical trials and experimental models appears to be good. However, data on fertility, pregnancies, and newborns after eASC administration are not available, despite patients who are going to be treated with cell-based

products having questions about the influence on reproduction. This article is an attempt to explore this issue and to provide initial data to these patients.

Fertility

All five patients who participated in this study succeeded in becoming pregnant, indicating that cell therapy with eASCs did not seem to have a negative affect in this regard. In addition, the fact that all women finally became pregnant suggests that the successful treatment of fistulas may have helped them pass the psychological barrier that this type of patient frequently has in relation to the decision to become pregnant.

In this study, 1 of the 5 women (20%) reported infertility before treatment. This rate is somewhat higher than that described in the literature for patients with Crohn's disease [29]. In this case, pregnancy took place when the patient was aged 41 years (i.e., 6 years after eASC therapy) and after artificial insemination was indicated because of low ovarian reserve.

Pregnancies

In the general population, miscarriage in the first 12 weeks of gestation is the most common complication of pregnancy and affects 12%–24% of all pregnancies. The miscarriage rate associated with Crohn's disease is close to 40% [30]. Among the five patients that provided information for the study, four had full-term pregnancies, whereas the fifth had two first-trimester abortions. The miscarriage rate was in line with that found in the general population (1 in 5 patients, 20%); therefore, treatment with eASCs does not appear to be associated with an increase in miscarriages. Moreover, the patient with the history of miscarriages succeeded in becoming pregnant.

It is well known that 90% of first-trimester miscarriages are caused by chromosomal abnormalities; however, no genetic studies of the fetuses were performed.

Women with IBD and, in particular, with Crohn's disease may have an increased risk of adverse pregnancy outcome in terms of low birth weight, preterm delivery, and increased frequency of cesarean section, regardless of disease activity; however, in Crohn's disease, the rate of preterm delivery correlates with the severity of the disease [28].

Deliveries

The cesarean rate among patients with Crohn's disease and fistulizing perianal and rectovaginal disease is higher than that in the general population [31], although in patients with established perianal disease, vaginal delivery and cesarean section seem to have similar results [32]. Patients with uncomplicated disease should be treated like the general population when deciding on delivery [22]. In our series, all births were carried out by elective cesarean section to protect the perianal area, in line with what is reported in previous studies [25, 30].

Newborns

Although Crohn's disease is often associated with low birth weight [22, 33], at the time of delivery, all newborns in this study had normal weight for their gestational age, except the twins. One of the twins was small for gestational age (ninth percentile) and the other had an intrauterine growth limitation (first percentile) with no existing significant discordant growth (weight difference between the twins was $<$20%). Although the global "fetal mass" in multiple pregnancies is much higher than that of a singleton of the same gestational age, both growth restriction and discordant growth are increased compared with singletons [34], and multiple newborns being smaller than singletons is not always pathologic [35], as occurred in this case. In addition, low prepregnancy weight is related to low birth weight, and it must be noted that the patient with the twin pregnancy had a body mass index <20 kg/m^2 at the time of conception [36].

The only abnormalities were seen in one of the babies, who was born with syndactyly of toes 2 and 3 on both feet (subsequently resolved without surgery) and clinodactyly of the fifth finger of both hands. It is important to note that her syndactyly and clinodactyly are congenital diseases and that the father also had clinodactyly. Consequently, any relationship with the administration of eASCs is ruled out. None of the other babies presented important health conditions during their first 6 months of life.

Disease Activity During Pregnancies

It has been published that when conception occurs during a quiescent state, 70%–80% of ulcerative colitis patients will remain in remission. In this situation, relapse rates in pregnant women are similar to general population [22]. Before pregnancy, our 5 patients each experienced at least 1 outbreak annually, and 4 patients (80%) required treatment for an outbreak during pregnancy (1 only during the first trimester). Consequently, local cell therapy with eASCs does not appear to have a significant effect on the evolution of Crohn's disease. In addition, we have not observed that pregnancy affected closure of the fistula achieved during treatment with eASCs.

Conclusion

To our knowledge, this publication is the first to report data on reproduction outcomes for women with Crohn's disease treated with stem cells for their fistulas.

In the patients analyzed in this study, the local injection of eASCs did not seem to be associated with deleterious effects on the ability of patients to conceive or with the course of pregnancy or newborn health.

Despite the low number of patients included in this study, we believe that these data may be of interest to doctors working with stem cell-based products because the information addresses aspects of concern to patients with fistulizing Crohn's disease who undergo cell therapies. Studies in larger groups of patients are needed to reach more definite conclusions.

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Author Contributions

R.S.-B. and M.G.-A.: conception and design, assembly of data and interpretation, manuscript writing; H.G. and P.d.l.Q.: collection of data and interpretation, final approval of manuscript; D.G.-O. and M.D.H.: interpretation, financial support and final approval of manuscript.

Disclosure of Potential Conflicts of Interest

M.G.-A. has uncompensated employment and uncompensated intellectual property rights. D.G.-O. has uncompensated intellectual property rights and is an uncompensated consultant. The other authors indicated no potential conflicts of interest.

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