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ORIGINAL ARTICLE

Maternal XX/X chromosome mosaicism in donor oocyte *in vitro* fertilization (IVF)

Paul R. Brezina [a,*], Mindy S. Christianson [a], Khanh-Ha D. Nguyen [b], Andrew Siegel [c], Andrew T. Benner [d], William G. Kearns [a,d,1]

[a] *Department of Gynecology and Obstetrics, Johns Hopkins Medical Institutions, Baltimore, MD 21287, United States*
[b] *Beth Israel Deaconess Medical Center, Harvard Medical School, Cambridge, MA, United States*
[c] *Medical College of Virginia, Richmond, VA, United States*
[d] *Center for Preimplantation Genetics, LabCorp., Rockville, MD 20850, United States*

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KEYWORDS

Turner syndrome;
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Abstract *Objective:* To evaluate if the degree of maternal X chromosome mosaicism is correlated to the pregnancy loss rate in donor oocyte IVF in women with a Turner syndrome mosaic (TS-Mosaic) diagnosis.
Design: Prospective trial.
Patients and methods: Women with X chromosome Turner syndrome mosaicism and infertility were enrolled in a clinical trial. The rate of mosaicism was determined through florescence in situ hybridization (FISH) of 500 maternal lymphocytes. Following a detailed medical, including cardiac, evaluation, donor oocyte *in vitro* fertilization (IFV) was performed and pregnancy and pregnancy loss rates were observed.
Results: The rates of maternal X chromosome mosaicism noted in the cycles from women with miscarriages (3%, 4%, 4%, and 6%) were not statistically different from cycles in TS-Mosaic women

* Corresponding author. Address: Division of Reproductive Endocrinology and Infertility, Phipps 264, 600 N, Wolfe Street, Baltimore, MD 21287, United States. Tel.: +1 410 583 2750; fax: +1 410 583 2767.
E-mail address: pbrezin1@jhmi.edu (P.R. Brezina).
[1] Tel.: +1 301 251 2804; fax: +1 301 251 2857.

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with normal deliveries (3% and 11%). These data suggest that the rate of maternal X chromosome mosaicism does not affect pregnancy loss rates in TS-Mosaic women undergoing donor oocyte IVF.

1. Introduction

Turner syndrome (TS) is diagnosed in any phenotypic female found to have complete or partial absence of one X chromosome with growth failure or pubertal delay and/or a spectrum of typical clinical features involving the cardiac, skeletal, lymphatic, skin, gonadal, and auditory systems (1,2). Although most 45,X conceptuses end in spontaneous abortions, it is a common genetic disorder comprising approximately 1 in 2500 live births (3,4). Most patients with TS have premature ovarian failure and subsequent infertility (5–7). Though TS patients may not experience puberty, menarche and even pregnancy occur and are more common in women with some forms of X chromosome mosaicism (TS-Mosaic) (5–8).

Among all patients exhibiting clinical features of TS, up to 70% carry some form of X chromosome mosaicism and about 30% of patients initially diagnosed as pure 45,X may be found later to have mosaic karyotypes upon extensive cellular analysis (9,11). To determine the true rate of TS-Mosaicism present in an individual requires that a significant number of cells, greater than or equal to 500, must be individually analyzed by FISH. This determination is not often described is not surprising as the determination of the degree of TS-Mosaicism is a comprehensive and involved process. Most of TS pregnancy cases are from TS-Mosaic women, suggesting the presence of some 46,XX cell lines that positively affects the likelihood of ovulating and achieving a live birth (1,11–14).

Exploring ways to optimize the ovarian potential of TS patients has been an area of ongoing interest including IVF and oocyte cryopreservation (5,15–18). However, data exist that suggest that even when pregnancy is spontaneously achieved in TS-Mosaic women, there is a marked increase in adverse outcomes (6,19,20). Nielsen et al. reviewed 56 pregnancies from TS-Mosaic women and found a first trimester loss rate of 27%, a stillbirth rate of 7%, a TS rate of 9%, a Down syndrome (trisomy 21) rate of 5%, and a rate of significant physical or mental handicap of 22% (19).

These concerns coupled with the inherently poor ovarian reserve in TS and TS-Mosaic patients have lead the emergence of donor oocyte IVF as a viable treatment option for TS and TS-Mosaic women who wish to proceed with pregnancy (8,21–23). However, a marked increase in subsequent miscarriage rates exists in TS and TS-Mosaic women who achieved pregnancy through donor oocyte IVF (23–25). This observation is surprising as women undergoing donor oocyte IVF for other reasons, such as diminished ovarian reserve, are generally found to have extremely low miscarriage rates, 10% in our center (Internal data). These trials, however, failed to comment on whether TS-Mosaic women were separated in their analyses from pure TS patients or failed to describe the actual rate of X chromosome mosaicism in these TS-Mosaic women (23–25).

Other more recent studies conflict with this older data and have cast doubt on whether women with TS actually do have decreased pregnancy potential when undergoing donor oocyte IVF. A study by Karnis et al. reported 101 of 146 patients with a diagnosis of Turner syndrome who attempted donor oocyte IVF achieved pregnancy with a miscarriage rate of only 7% (26). Furthermore, this study relied on the responses from surveys mailed to over 258 centers rather than directly evaluated patient records (26). Multiple biases could have been introduced using this methodology. As with other studies, this research did not distinguish between pure TS and TS-Mosaic women (26).

It is well documented that TS-Mosaic women are more likely to have pubertal development compared with pure TS women (5–8). This suggests that certain physiological deleterious effects seem to be blunted in TS-Mosiacs. The goal of this study is to determine if a significant difference exists in terms of degree of X chromosome mosaicism in women with a TS-Mosaic diagnosis who experienced donor oocyte IVF and achieved normal deliveries as compared to women who achieved miscarriages. To our knowledge, this is the first study, although with a limited sample size due to the number of patients treated with TS in our center, to address this question. Using a Pubmed literature review we were unable to identify a study that correlated pregnancy success to rate of X chromosome mosaicism in TS-Mosaic women undergoing donor oocyte IVF.

2. Materials and methods

Institutional review board (IRB) approval was obtained. Prior to being enrolled in the study all participants signed the informed consent. All patients seeking treatment for infertility with a diagnosis of premature ovarian failure and a clinical suspicion, including short stature, shield chest, webbing of the neck, or other typical TS physical characteristics, of TS-Mosaicism over a period of 12 months were enrolled in the study.

Prior to proceeding with IVF, the diagnosis of TS-Mosaicism in these women was confirmed and the ratio of XX to X or XXX sex chromosome mosaicism was established. To accomplish this, peripheral blood samples were obtained from enrolled women and white blood cells (WBC) were isolated using a modified microspin/phosphate buffered saline (PBS) wash. WBCs were fixed using a modified Carnoy's method and fluorescence in situ hybridization (FISH) was performed for chromosomes X and Y. Five-hundred cells were scored to determine the actual percentage of sex chromosome mosaicism in each woman. The FISH interpretation was verified by the laboratory director. The accuracy of FISH in our laboratory as determined by the internal validation studies and over ten years of clinical experience is approximately 99%.

Prior to proceeding with IVF, all TS-Mosaic couples received counseling regarding the possible medical risks of ovarian stimulation or pregnancy with a donor oocyte IVF cycle. All women required a cardiology release for potential cardiac and aortic risks. Controlled ovarian stimulation using standard methods in oocyte donors were performed using gonadotropins and an agonist trigger with uncomplicated retrievals. All oocytes were fertilized with standard fertilization. All TS-Mosaic patients underwent standard endometrial stimulation followed