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ORIGINAL ARTICLE

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

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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 fluorescence in situ hybridization (FISH) of 500 maternal lymphocytes. Following a detailed medical, including cardiac, evaluation, donor oocyte *in vitro* fertilization (IVF) 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

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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.

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## 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 led to 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-Mosaics. 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

by administration of progesterone, methylprednisolone, and doxycycline per protocol. Clinical outcomes (embryo transfer, clinical pregnancies and delivery rates) of these cycles were determined. Clinical pregnancy was defined as a positive test for beta human chorionic gonadotropin ( $\beta$ HCG) level 2 weeks following embryo transfer (ET) with subsequent development of a fetal heartbeat at 6–7 weeks gestation on transvaginal ultrasound. A chi square analysis with Yates correction was employed to determine the significance ( $p < 0.05$ ).

### 3. Results

Fourteen couples were enrolled in the study. The average age of the TS-Mosaic women was 33 (range of 28–37). Following WBC evaluation to determine the degree of X chromosome mosaicism via FISH analysis, 13 women were confirmed to have TS-Mosaic status (Table 1). Of these 13 women, the percentage of abnormal cells (X or XXX) ranged from 1% to 99% with an average of 20%. Six (46%) couples, with rates of mosaicism ranging from 1% to 99%, were excluded from proceeding with IVF due to medical indications or a personal decision to delay fertility treatment. Of note, all women who ultimately completed an IVF cycle had relatively low levels of TS-mosaicism (3–12%) compared with other women in the study who were excluded for medical indications (64%, 99%, 100%, 18%).

There were no significant differences among the oocyte donors regarding serum hormone profiles. No difference was found in baseline laboratory values, including follicle stimulating hormone (FSH) and E2 levels on CD#2, or the total injectable medications. Peak serum E2 levels ranged from 1817 pg/ml to 2547 pg/ml. No difference was noted in the number of oocytes retrieved (range of 14–19). Per donor cycle, an average of 12 (range of 8–15) oocytes achieved fertilization. Of these, each cycle yielded an average of 8 blastocyst embryos. All IVF cycles underwent the transfer of 2 blastocysts of very high quality (grade 4 using our grading system). All semen analysis results from the male partners of the TS-Mosaic women were within normal limits as defined by world health organization (WHO) parameters.

The seven remaining couples, with rates of maternal X chromosome mosaicism ranging from 3% to 12%, that obtained

medical clearance to proceed with IVF underwent a total of 13 ET cycles which resulted in six (46% of cycles) clinical pregnancies (Fig. 1). Of these pregnancies, four (67% of pregnancies) resulted in spontaneous first trimester pregnancy loss and two (33% of pregnancies) resulted in the delivery of a healthy infant at term. The rates of maternal X chromosome mosaicism noted in cycles from women with miscarriages (3%, 4%, 4%, and 6%) were not statistically different from cycles in TS-Mosaic women with normal deliveries (3% and 11%). One woman with an X chromosome mosaicism rate of 4% underwent two separate embryo transfers and subsequently experienced two first trimester miscarriages. For the purposes of statistical evaluation, each cycle was considered separately. No adverse maternal health events were experienced in any of the women enrolled in this study. Of the four first trimester pregnancy losses, two cytogenetic evaluations were performed and both revealed normal karyotypes. As all women enrolled in this study had been diagnosed with premature ovarian failure, the degree of ovarian function was not able to be correlated to pregnancy or miscarriage rates. Maternal age was not correlated to women undergoing IVF cycles or pregnancy/miscarriage results.

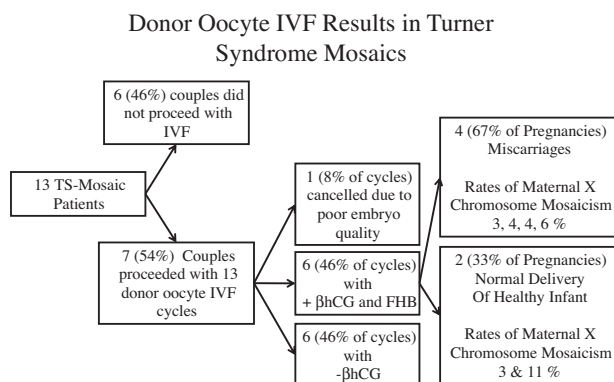
### 4. Discussion

Numerous challenges exist for TS or TS-Mosaic women in achieving pregnancy either spontaneously or through IVF. These include premature ovarian failure, low pregnancy rates, maternal morbidity, high rates of fetal loss, and significant chromosomal or developmental abnormalities (5,7,19). Donor oocyte IVF was introduced as a therapy that may overcome some of these concerns (8,21). TS-Mosaic women have been shown to have lesser degrees of ovarian dysfunction compared with TS non-mosaics (16,27). Indeed, pregnancy is much more likely to be achieved in TS-Mosaic women compared with non-mosaic TS women (11–14).

Conflicting data exist regarding the miscarriage rates seen in TS-Mosaic women undergoing donor oocyte IVF (2,22–26). One theory as to why an increased miscarriage rate may exist in TS patients is that TS and TS-Mosaic patients are more likely to possess a hypoplastic uterus with compromised uterine blood flow (8,23). Other theories purport that defects

**Table 1** Patient karyotype and success in achieving pregnancy.

Patient #	Maternal FISH sex chromosome mosaic karyotype	Percent abnormal (%)	Proceed with IVF	Age of embryo recipient	Total fresh embryo transfer (max 2 blasts/cycle)	Total frozen embryo transfer (max 2 blasts/cycle)	Clinical pregnancy	Live birth
1	X [25]/XXX [8]/XX [467]	7	N	28				
2	X [6]/XX [494]	1	N	37				
3	X [32]/XX [468]	6	Y	33	2	2	Y	N
4	X [59]/XXX [1]/XX [440]	12	Y	35	2	2	N	N
5	X [291]/XXX [30]/XX [179]	64	N	30				
6	X [16]/XX [484]	3	Y	31	2		Y	Y
7	X [453]/XXX [41]/XX [6]	99		33				
8	X [13]/XX [487]	3	Y	36	2	2	Y	N
9	X [498]/XXX [2]/XX [0]	100		31				
10	X [32]/XXX [2]/XX [466]	7	Y	29	2	2	N	N
11	X [57]/XX [443]	11	Y	34	2	2	Y	Y
12	X [88]/XX [412]	18		32				
13	X [19]/XX [481]	4		34				
14	X [22]/XX [478]	4	Y	33	2	2	Y	N



**Figure 1** Donor oocyte IVF results in Turner syndrome mosaics.

in endometrial function or hormonal receptivity exist that may affect implantation (25,28,29). Others have suggested that these deficiencies may be overcome by hormonal supplementation protocols (22–24,26).

Our overall high pregnancy and miscarriage rates per cycle were comparable with other studies evaluating TS-Mosaic women undergoing donor oocyte IVF (23,24). Of the six pregnancies that were observed in this study, two resulted from fresh ET and four resulted from thawed blastocyst embryo transfers. However, to our knowledge this study is the first to evaluate if varying degrees of maternal X/XX mosaicism are correlated to pregnancy loss. Our data suggest that the level of maternal X chromosome mosaicism in somatic lymphocytes is not correlated with the rate of pregnancy loss in TS-Mosaic women undergoing donor oocyte IVF. This observation is potentially valuable in counseling patients who are known TS-Mosaic women and wish to pursue donor oocyte IVF.

One limitation of this study is the small sample size of 13 IVF cycles. In our center, concern over maternal morbidity required an exhaustive medical, including cardiac, workup of all TS and TS-Mosaic women interested in undergoing donor oocyte IVF. This placed the limitations both on the number of women entering this study and the number of women who ultimately were allowed to proceed with an IVF cycle. It is possible that the low numbers of women enrolled in the study precluded the ability to accurately detect differences that would be appreciated with larger sample sizes. The maternal mosaicism rates in this study ranged from 1% to 99%. However, all of the women who underwent IVF cycles in this study had relatively low levels of TS-Mosaicism (3–12%). Indeed, women with higher levels of mosaicism were excluded for medical indications prior to initiating a donor oocyte IVF cycle. Therefore, it is possible that higher rates of TS-mosaicism could be more deleterious on pregnancy outcomes. Therefore, we cannot comment, based on these data, how higher percentages of maternal X chromosome mosaicism might affect pregnancy loss rates. However, we have not observed any trends that would suggest such a difference.

A central focus of treatment for TS and TS-Mosaic women seeking care for infertility must always include a thorough medical evaluation prior to initiating any treatment. Concerns of cardiovascular compromise during pregnancy are especially warranted due to the high prevalence of congenital cardiac or vascular abnormalities in at least 25–50% of TS patients (3,26,30–33). These and other cardiovascular maternal abnormalities lead to an overall 2% maternal mortality rate during

pregnancy in TS women (34). This mortality rate is more than 100 times greater than that of the general population of age matched women (34). These cardiac abnormalities are found at a higher rate in non-mosaic TS compared TS-Mosaic women (30,35). However, TS-Mosaic women still have cardiac abnormalities at a rate far higher than the general population (30). As was done in this study, prior to initiating fertility treatment in all TS or TS-Mosaic women, a detailed cardiac evaluation, including cardiac imaging, is required (34,36).

Furthermore, patients who have been cleared medically to proceed with IVF need detailed counseling as their chances for pregnancy success and pregnancy related morbidity do not mirror that of the general population. For example, in our study, for those women who achieved pregnancy, the observed miscarriage rate was 67%. This is more than 6 times higher than the average miscarriage rate of 10% experienced in non-TS donor oocyte IVF cycles performed in our center (Internal Data). This difference in miscarriage rate as well as the serious underlying cardiovascular risk in all TS patients, TS and TS-Mosaic, needs to be a paramount consideration during the counseling and treatment process.

## 5. Conclusions

Women with a diagnosis of TS or TS-Mosaicism have a complicated medical picture. It is incumbent upon medical professionals considering the administration of infertility treatment in this patient population to take the proper steps to ensure that the risks of pregnancy are adequately evaluated, including a cardiology consultation, and provide detailed counseling regarding the chances of success and potential for maternal morbidity. Donor oocyte IVF has emerged as a treatment option for women with TS or TS-Mosaicism wishing to proceed with pregnancy. While loss rates are known to be higher in this population, it has not been previously established if the rate of X chromosome mosaicism in TS-Mosaic women correlates with the rate of miscarriage. Our preliminary data suggest that knowing this rate of mosaicism may not affect pregnancy loss rates. Given the low rate of pregnancy success and significant maternal morbidity and mortality risks associated with TS and TS-Mosaic women carrying a pregnancy, increased utilization of gestational carriers for these women may be considered.

## Conflict of interest

None declared.

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