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# Pregnancy outcome in Turner syndrome: A French multi-center study after the 2009 guidelines

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ABSTRACT

*Objective:* This study aimed to assess the application of the French guidelines for pregnancies in Turner syndrome (TS) and their impact on perinatal prognosis.
*Study design:* We performed a French multi-center retrospective study (14 centers), including TS pregnant patients (spontaneously or by Assisted Reproductive Technology (ART)) between January 2006 and July 2017. Only clinical pregnancies were analyzed. The adjustment of medical follow-up modalities to French guidelines was evaluated for all pregnancies after 2009. Pregnancies from oocyte donation (OD) after 2009 were compared to those of a cohort of TS pregnancies obtained by OD before 2009, which were reported by the French Study Group for Oocyte Donation.
*Results:* One hundred seventy pregnancies in 103 patients were included: 35 spontaneous, 5 by means of intra-conjugal ART, and 130 with OD. No serious maternal complications were observed. We reported two stillbirths and one intra uterine fetal death.
The French guidelines were partially respected. The preconceptional assessment was carried out in 74% of cases. Cardiology follow-up during pregnancy was performed in accordance with guidelines in 74% of patients. Postpartum cardiac ultrasonography was performed in 45% of pregnancies but only in 11% within 8 days post-partum.
When compared to the 2009 historical cohort, the rates of high blood pressure (19% vs. 38%; $p < 0.005$) pre-eclampsia (8% vs. 21%; $p < 0.005$) and prematurity <35 weeks (15% vs 38%; $p < 0.0001$) were lower.
*Conclusions:* The implementation of guidelines has allowed the standardization of TS pregnancy care and improved perinatal indicators for both mothers and children. However, an effort must be done, in a postpartum survey.



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## Introduction

Turner Syndrome (TS) represents 1/2000–1/2500 of female newborns [1,2]. It corresponds to the partial or total absence of one X chromosome in a fetus with 46, XX or the loss of the Y chromosome in a fetus with 46, or XY giving rise to monosomy.

Turner Syndrome can have variable forms [3]. The cardinal signs are the growth restriction and primary ovarian failure due to gonadal dysgenesis. The ovarian failure is sometimes relative, with 5–20% of patients having spontaneous menarche [4–6] and 2–5% of patients having spontaneous pregnancies [5,7–10]. Spontaneous pregnancies are more frequent in patients with mosaic TS [9], and rare in patients with monosomy. These patients have an increased rate of spontaneous miscarriage [1,5]. The risk of chromosomal abnormalities (mainly Turner Syndrome) is higher than in the general population [9,11,12]. In most cases, the only solution for patients to become pregnant is oocyte donation [13].

Cardiac abnormalities (coarctation of the aorta, valvulopathy, high blood pressure (HBP)) affect 20–40% of TS patients [11,14–17]. They are the main factors to allow assisted reproductive technologies (ART) and to survey the pregnancies. Renal, endocrine, and autoimmune abnormalities are also more frequent than in the general population and can impact the pregnancy prognosis.

The cohort of 93 patients published in 2011 by Chevalier et al. has shown that only 40.2% were uncomplicated pregnancies. Indeed, 37.8% of pregnancies had HBP, including 54.8% with pre-eclampsia, 27.5% had intra uterine growth retardation (IUGR); and 2 resulted in maternal death due to aortic dissection [18]. The most severe maternal complications are cardiovascular, such as the aggravation of preexisting HBP, or an aortic dissection that may lead to death. The risk of death from aortic rupture in these patients is estimated to be 100 times greater than the risk for women in the general population [19–21].

These pregnancies require special monitoring, as described in the French guidelines established in 2009 [12,22–24]. The recommendations concern first check-up before pregnancy to assess the conditions for medical acceptance of pregnancy: aortic diameter less than 25 mm/m$^2$ or 35 mm without coarctation, normal liver function. The aortic diameter must be carefully monitored during pregnancy at the end of the first and second trimesters, every month during the third trimester and between 5 and 8 days after the delivery by a specialised ultrasonographer. During the pregnancy, it is also recommended to check blood pressure, liver and kidney functions.

The aim of our study was to evaluate the application of these guidelines. We also observed the characteristics of spontaneous, induced or by oocyte donation (OD) pregnancies in patients with Turner Syndrome and assessed the improvement of perinatal prognosis by the use of the guidelines.

## Materials and methods

### *Study design*

This is a multi-center retrospective study including all TS pregnancies whatever their origin. The participating centers were the University Hospitals of Angers, Bordeaux, La Réunion, Lille, Metz, Nantes, Nice, Paris Tenon Hospital, Rennes, Rouen, Saint Étienne, Strasbourg, and Toulouse and the Paris Institut Mutualiste Monsouris.

### *Patients*

We included pregnant patients with Turner Syndrome between January 2006 and July 2017.

When at least 5% of peripheral blood cells were 45,X0 patients were considered to have mosaic Turner Syndrome [8,25].

All spontaneous pregnancies or resulting from oocyte donation, intra-conjugal Assisted Reproductive Technology (ART) were included. Pregnancies were defined by the presence of yolk sac visualized by ultrasonography examination.

To define small for gestational age (SGA) children, individual curves were used for spontaneous pregnancies; however, for pregnancies resulting from OD, since the anthropometric parameters of the donors were not available, we used a standardized curve (Hadlock's curve) [26].

### *Data collection*

Data were collected anonymously from patient databases.

### *Statistical analysis*

Results were given as means ± standard deviations or as percentages. Qualitative data were compared using the $\chi^2$ test, and quantitative data were compared using the *t*-test or Mann-Whitney according to data distribution. A *P*-value < 0.05 was considered to be statistically significant. The data were analyzed with Stat-View software (SAS Institute, Cary NC, USA).

The characteristics of pregnancies from OD since 2009 were compared to those of a cohort of 93 TS pregnancies obtained by OD before 2009, reported by the French Study Group for Oocyte Donation [18].

We also compared the characteristics of pregnancies after 2009 for our population to those of pregnancies from the general population of France, relying on the results of the National Perinatal Survey of 2016, published by the Ministry of Health [27].

## Results

### *Demographic data*

When compared to spontaneous pregnancies, the age of first pregnancy (33.4 ± 4.4 vs 28.7 ± 6.8; P < 0.01) was higher and the percentage of mosaic karyotype was lower (17% vs 71%; P < 0.001) in OD pregnancies.

Before pregnancy, the HBP and diabetes rates prior to pregnancy were low, but we found a high preconception rate of hypothyroidism (Table 1).

### *Description of the pregnancies and their outcomes*

Fig. 1 reports the evolution of the pregnancies (5 pregnancies were obtained through In Vitro Fertilization (IVF), resulting in 3 spontaneous miscarriages, 1 EP, and one birth that have been classified with the spontaneous pregnancies for the analysis of ongoing pregnancies).

One twin pregnancy, obtained by OD, required a cesarean section at 35 WG due to an IUGR on one twin associated to a pre-eclampsia with HELLP Syndrome. The 2 male newborns weighed 2075 g and 1780 g.

There was also one pregnancy termination at 36 WG for severe heart disease due to Ebstein's anomaly, which was discovered by ultrasound during the third trimester, and 1 pregnancy termination at 33 WG within a context of severe pre-eclampsia.

During pregnancy, the HBP rate was 18% and prematurity occurred in 43% of pregnancies, but only 4% were severe (<32 WG).

The rate of cesarean sections was high (68%) and trended to be higher in OD pregnancies compared to spontaneous pregnancies (74% vs 45%; NS). The main causes were feto-pelvic disproportion (35%), failure to progress or presence of abnormalities of fetal heart