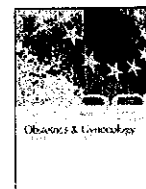




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Review

Turner syndrome and pregnancy: clinical practice. Recommendations for the management of patients with Turner syndrome before and during pregnancy[☆]

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ABSTRACT

Following the death in France by acute aortic dissection of two women with Turner syndrome who were pregnant following oocyte donation, the Director of the French Biomedicine Agency (*Agence de la biom decine*) sent a letter to the President of the French College of Obstetricians and Gynaecologists (FCOG). He requested the College's expertise in reviewing point-by-point the cases and risk factors and in determining whether there are grounds to propose additional measures complementary to the recommendations made by the *Haute autorit  de sant * or French National Authority for Health (HAS) in 2008 in terms of indication and monitoring of patients. A joint practice committee of the FCOG, the French Cardiologic Society, the French Chest and Cardiovascular Surgery Society, the French Society of Anaesthesia and Intensive Care, the French Endocrine Society, the French study group for oocyte donation, and the Biomedicine Agency defined the exact questions to be put to the experts, chose these experts, followed them up and drafted the synthesis of recommendations resulting from their work.

The questions concerned the check-up before pregnancy of Turner patients, contraindication and acceptance of pregnancy, information for the patients, and recommendations for antenatal care, delivery and postnatal follow-up.

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[☆] On behalf of the joint practice committee of the French College of Obstetricians and Gynaecologists, the French Cardiologic Society, the French Chest and Cardiovascular Surgery Society, the French Society of Anaesthesia and Intensive Care, the French Endocrine Society, the French study group for oocyte donation, and the Biomedicine Agency.

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1. Introduction

Turner syndrome is associated with monosomy X (45X and mosaic) in 50% of cases and with rearrangements of the short arms of chromosome X in the remaining 50%. Along with short stature, primary amenorrhoea is the cardinal sign of Turner syndrome. Spontaneous pregnancies are very rare (2%) in women with Turner syndrome [1], and primarily occur when the syndrome is associated with an X anomaly (number or structure) or mosaicism. For the vast majority of such women, oocyte donation represents the only way to become pregnant.

These pregnancies carry particular risks since as many as 5–50% of women with Turner syndrome have a cardiovascular malformation [2–5] such as aortic coarctation (10% of cases) and bicuspid aortic valve (25% of cases) [6]. The most serious maternal complications are therefore cardiovascular, such as worsening of pre-existing hypertension or aortic dissection which, as in Marfan syndrome [19], may be life-threatening [7]. Among the patients with Turner syndrome, 2% are at risk of death caused by aortic dissection or rupture, a rate 100× higher compared with women in the general population [17]. The risk factors for dissection are bicuspid aortic valve, coarctation and hypertension [7,8]. In reported cases of dissection, aortic diameter measured by magnetic resonance imaging (MRI) at the right pulmonary artery was above 25 mm/m² or 35 mm on average 3 years before the dissection [17]. Values much above these were reported in the two French cases. The risk of dissection during pregnancy is unclear, but all cases reported in the literature so far suggest that it could reach 10%, bearing in mind the bias of such retrospective studies. This risk is increased at the end of pregnancy since 50% of aortic dissections reported in the literature occur in the third trimester [8] or during the puerperium.

A review of the literature between 1961 and 2006 revealed 85 cases of aortic dissection in women with Turner syndrome. In the seven cases of aortic dissection reported after assisted reproductive technologies (ART), six patients died [9–11]. Severe hepatic

steatosis or cholestasis, and pregnancy-induced hypertension have also been reported [12–14]. In 2008 the HAS published a national protocol for the diagnosis and care of patients with Turner syndrome [15]. It includes a section on pregnancy, which needs to be updated in view of the possibility of pregnancy through egg donation and recent publications on the complications of Turner syndrome during pregnancy [16,18,20,23–26]. Given the rarity of pregnancy in Turner syndrome patients, the published data provide a low level of proof and the following recommendations are essentially based on expert opinions.

2. Method

Following the death in France by acute aortic dissection of two women with Turner syndrome who were pregnant following oocyte donation, the Director of the French Biomedicine Agency (*Agence de la biomédecine*) sent a letter on 2nd of July 2008 to the President of the French College of Obstetricians and Gynaecologists (FCOG). He requested the College's expertise in reviewing point-by-point the cases and risk factors and in determining whether there are grounds to propose additional measures complementary to the recommendations made by the French National Authority for Health (*Haute autorité de santé* or HAS) in 2008 in terms of indication and monitoring of patients. The main goal was to improve healthcare safety.

The French College of Gynaecologists and Obstetricians (CNGOF) appointed a joint practice committee of the French College of Obstetricians and Gynaecologists, the French Cardiologic Society, the French Chest and Cardiovascular Surgery Society, the French Society of Anaesthesia and Intensive Care, the French Endocrine Society, the French study group for oocyte donation, and the Biomedicine Agency. This committee defined the exact questions to be put to the experts, chose these experts, followed them up and drafted the synthesis of recommendations resulting from their work.

The questions concerned the check-up before pregnancy of Turner patients, contraindication and acceptance of pregnancy, information for the patients, and recommendations for antenatal care, delivery and postnatal follow-up.

The experts analysed the scientific literature on the subject in order to answer the questions raised. For each question, each overview of validated scientific data was associated with a level of evidence established according to the quality of available data, using the working framework defined by the HAS (LE1: Very powerful randomised comparative trials, meta-analysis of randomised comparative trials; LE2: Not very powerful randomised trials, well-run non-randomised comparative studies, cohort studies; LE3: case-control studies; LE4: nonrandomized comparative studies with large biases, retrospective studies, transversal studies, series of cases). Concerning questions of prevalence, diagnosis and prognosis, the levels of evidence were set according to the working framework proposed by the University of Oxford Centre for Evidence Based Medicine (www.cebm.net).

The synthesis of recommendations was drafted by the organising committee based on the replies given by the expert authors. Each recommendation for practice was allocated a grade which depends not only on the level of evidence but also on the feasibility and ethical factors. Grade A represents the scientifically established evidence; grade B represents a scientific presumption; grade C is based on a low level of evidence, generally founded on LE3 or LE4. In the absence of any conclusive scientific evidence, some practices have nevertheless been recommended on the basis of agreement between all the members of the working group (professional consensus, PC). Cases of professional consensus have been kept to the strict minimum.

All the texts along with the synthesis of recommendations were reviewed by persons not involved in the work, i.e. practitioners in the various specialities concerned and working in varying situations (public, private, university, or non-university establishments). Once reviewing had been completed, changes were made. The methods, texts by the expert authors and synthesis of recommendations, together with the introduction by the President Jacques Lansac, have already been published in French on the website of the CNGOF.

3. Recommendations

3.1. Check-up before pregnancy

A check-up should be done in every patient who wishes to become pregnant, whatever her karyotype (mosaic or 45X), and whether pregnancy is sought naturally (if ovarian function is conserved, as is possible in patients with a mosaic karyotype) or after oocyte donation. The check-up should be multidisciplinary and involve different specialists especially in cardiology, endocrinology, nephrology, hepatology, and so forth.

3.1.1. General examination

Weight, height, body mass index.

3.1.2. Cardiovascular examination

One should remember that hypertension, bicuspid aortic valve, aortic dilatation and coarctation are aortic dissection risk factors in women with Turner syndrome.

3.1.3. Blood pressure

Measured while resting, possibly completed by ambulatory blood pressure monitoring. If hypertension is found, a renal cause is sought, using Doppler ultrasonography of the renal arteries (see below).

Two-dimensional transthoracic ultrasound with colour Doppler imaging, left parasternal long-axis view during end-diastole

(recommendations of the cardiologists of the HAS working group on Turner syndrome; normal values of Roman et al. related to body surface area [24]), is used to search for aortic malformations (bicuspid aortic valve: 25% of the patients, coarctation: 10%, abnormalities of the aorta structure) and anomalies of venous return, to screen for acquired aortic disease (aneurysm, dilatation), and during follow-up. The four characteristic diameters of the aortic root should be measured (the largest is used) and screening for bicuspid aortic valve should be performed. These ultrasound examinations should be done by an ultrasonographer-cardiologist according to the standardised methodology proposed in Appendix I.

Magnetic resonance angiography of the heart and aorta [18–23] is mandatory. It has the advantage of not exposing the patient to radiation and can be used to:

- analyse the whole of the thoracic and abdominal aorta and a part of abdominal aorta depending of the acquisition field of view;
- measure the four diameters of the aortic root;
- screen for or confirm coarctation to estimate pressure gradient across aortic coarctation;
- diagnose bicuspid aortic valve;
- perform successive comparative analyses with reproducibility of measurement;
- observe the renal arteries if the acquisition field of view allows this procedure;
- and with cardiac MRI, to assess cardiac function and wall motion.

The ascending aortic diameter indexed for body surface area is measured by MRI at the right pulmonary artery level. The 50th percentile is 17 mm/m² in patients with Turner syndrome and the 95th percentile is 20 mm/m² [17]. An indexed aortic diameter greater than or equal to 25 mm/m² or above 35 mm should be considered as a dilated ascending aorta with risk of dissection. Appendix II describes a protocol for MRI of the thoracic aorta. When MRI cannot be performed (pacemaker, defibrillator, catheter or other equipment), aorta CT angiography should be considered.

3.2. Endocrine tests

3.2.1. Blood tests

- thyroid stimulating hormone, free thyroxine, antithyroid antibodies (anti-TPO);
- fasting blood glucose, and HbA1c in cases of diabetes.

Possibly, plasma lipid profile to check for dyslipidaemia, other vascular risk factors.

3.2.2. Liver function tests

- blood tests: aspartate transaminase, alanine transaminase, gamma glutamyl transpeptidase and alkaline phosphatase;
- liver ultrasound when laboratory tests 6 months apart show anomalies: notably testing for portal hypertension. If any abnormality is noted, special advice from a hepatologist should be sought regarding aetiology.

3.2.3. Gynaecological evaluation

- a gynaecological examination;
- smear test if the last one was over 2 years ago;
- pelvic ultrasound with Doppler imaging of the uterine arteries, measurement of the uterus and of endometrial thickness and its echogenicity, search for uterine malformation;
- if malformation is suspected, 3D ultrasound and hysteroscopy.

3.2.4. Kidney function tests

- renal ultrasound to check for:
 - malformation (30% of cases): horseshoe kidney, ectopic kidney, renal agenesis, duplication hydronephrosis
 - cause of secondary hypertension (stenosis of renal arteries);
- laboratory tests in cases of hypertension or renal anomaly: blood urea nitrogen, blood creatinine, blood electrolytes, urine electrolytes;
- urine culture to check for urinary infection.

3.3. Contraindications to pregnancy

3.3.1. Cardiovascular

Pregnancy is contraindicated in cases of:

- a history of aortic surgery;
- a history of aortic dissection;
- aortic dilatation: with the largest aortic diameter is above 25 mm/m² or 35 mm. Those measurements represent an extrapolation of measurements made at the tubular aorta [18];
- aortic coarctation;
- uncontrolled hypertension despite treatment.

Even if surgery of the valves or aorta has been performed, the patient is still at risk of aortic dissection during pregnancy, therefore pregnancy remains contraindicated. Isolated bicuspid aortic valve (without aortic dilatation) is not a contraindication to pregnancy, but is a risk factor.

3.3.2. Hepatic

Portal hypertension with oesophageal varicose veins.

3.4. Information for the patient

If there are no contraindications and if a pregnancy is envisaged, the gynaecologist-obstetrician, cardiologist and endocrinologist should work together to inform the patient and if possible the couple, who will be given a written document (Appendix III).

The patient and where possible the couple should be informed that:

- there is an increased risk of miscarriage and chromosomal abnormalities in a spontaneous pregnancy (without oocyte donation). An interview with a doctor specialised in genetics should be proposed, along with the possibility of prenatal diagnosis;
- pregnancy carries a high risk of potentially life-threatening (mother and child) cardiovascular complications (hypertension, pre-eclampsia, aortic dissection), and metabolic complications (diabetes);
- in cases of oocyte donation only one embryo will be transferred to avoid multiple pregnancies;
- there is an increased risk of caesarean section because of a small pelvis and possible medical complications (85% of births are caesarean);
- the patient must be followed up by a specialised multidisciplinary team that includes at least a gynaecologist-obstetrician, a cardiologist and an anaesthetist. The anaesthetist will study specific problems concerning control of blood pressure and blood glucose during the peripartum period and regarding the airways

because of a greater likelihood of difficult intubation. Spinal examination is also necessary because of the possibility of spinal anaesthesia or epidural anaesthesia. Vaginal delivery or caesarean section must take place in a medical facility³ staffed by a team of cardiologists and a heart surgery team;

- risks for the unborn child because of obstetrical or cardiovascular complications: prematurity, intrauterine growth retardation requiring neonatal intensive care.

When there is a combination of diseases or failure to observe medical instructions, the multidisciplinary team has the right to refuse ART with oocyte donation, or in cases of persistent ovarian dysfunction the team can formally advise against pregnancy, after having informed the patient.

3.5. Conditions for medical acceptance of pregnancy

3.5.1. Cardiovascular

If the aortic diameter is less than 25 mm/m² or 35 mm and if there is no associated coarctation:

- the pregnancy can be authorised;
- pending egg donation, ultrasonography is repeated yearly by the same sonographer. If aortic dilatation increases by 10% or more, this must be confirmed with a second imaging technique (MRI, computed tomography or transoesophageal ultrasound). If confirmed, progression of aortic dilatation becomes a contraindication to pregnancy.

3.5.2. Liver function tests

Pending egg donation, liver function tests are repeated every year if the initial findings were normal or on the advice of a hepatologist.

3.5.3. Recommendations in cases of ART

In ART with oocyte donation a single embryo transfer is strongly recommended to avoid multiple pregnancies. While the embryo transfer is performed, the patient must be reminded of the risks of pregnancy and the need for a close follow-up. In case of incident or adverse event, it must be reported to the *Agence de la biomédecine* by the local correspondent of the health vigilance for ART, or by any health professional aware of the occurrence of such an incident or adverse event (*Journal officiel* no. 0301 of 27 December 2008, page 20184, text no. 69, NOR: SJSP0830456A).

3.6. Recommendations for antenatal care and delivery

Antenatal care should be multidisciplinary and co-ordinated. Cardiovascular monitoring
Echocardiography (Appendix I):

- at the end of the first and second trimesters;
- every month during the third trimester;
- an increase in aortic diameter greater than or equal to 10% between two examinations should be confirmed by MRI.

In cases of acute dissection of the aortic root during pregnancy (Appendix II):

Medical management will depend on the stage of pregnancy:

- before 25 weeks of gestation, emergency aortic root surgery with extracorporeal circulation, fetus in utero, with cardiocotography. The risk of maternal and/or fetal death is high;

³ In the legal sense of the term, in France, such a facility could include several hospitals (examples: the public hospitals of major cities, like Paris, Lyon or Strasbourg).

- after 25 weeks of gestation, emergency caesarean section, immediately followed by aortic root surgery.

If the aortic diameter becomes greater than 25 mm/m² or 35 mm or if it increases by >10% between two examinations or in comparison with the reference examination before the pregnancy:

- hospitalisation in a facility with a medical-surgical cardiology team and a maternity centre with a department of neonatology and/or neonatal intensive care if delivery before 32 weeks of gestation;
- cardiological and surgical advice is required in a reference centre;
- acceleration of fetal lung maturation if delivery occurs 25 and 34 weeks of gestation;
- planned caesarean section.

If the aortic diameter remains unchanged and below 25 mm/m² and 35 mm:

Delivery can take place in a facility involving a team of cardiologists and a team of heart surgeons. Caesarean section is necessary in 85% of cases because of narrowness of the pelvis. The timing of the caesarean after 34 weeks of gestation will depend on the mother's cardiovascular status. Vaginal delivery with close blood pressure monitoring can be envisaged if there is no fetal-pelvic disproportion or associated disease. Assisted delivery (vacuum extractor or forceps) is recommended.

3.6.1. Hypertension

Hypertension should be treated with a beta-blocker and treatment efficacy checked by ambulatory blood pressure monitoring. Even if there is no hypertension, beta-blocker treatment during pregnancy can be considered.

3.6.2. Liver function tests

Liver function tests are needed only in the event of a clinical sign, such as pruritus or jaundice. In cases of cholestasis, management is identical to that of a pregnant woman without Turner syndrome.

3.6.3. Screening for gestational diabetes

An O'Sullivan test is done at 24 weeks of gestation.

3.6.4. Kidney function tests

Blood creatinine level is determined every month in cases of renal malformation.

3.7. Postnatal follow-up

3.7.1. Cardiovascular

As cardiovascular risk persists after delivery, there should be an ultrasound monitoring of the aortic root diameters between 5 and 8 days after the delivery by a specialised ultrasonographer and according to the protocol in Appendix I.

3.7.2. Hepatic

No liver function tests in the absence of previous abnormal laboratory findings or clinical manifestations.

3.7.3. Obstetrical

As for any woman who has given birth vaginally or by caesarean section, at 6 weeks post-partum.

3.7.4. Examination of the infant

For a pregnancy not involving egg donation, the paediatric examination checks for chromosomal abnormalities: Turner syndrome for a girl, trisomy 21. For a pregnancy after oocyte donation, the paediatric examination does not include any specific test.

3.8. Reporting to the Turner Syndrome Registry

Any pregnancy with or without oocyte donation in a woman with Turner syndrome must be reported to the Turner Syndrome Registry at the email address: crmerc.turner@rdb.aphp.fr.

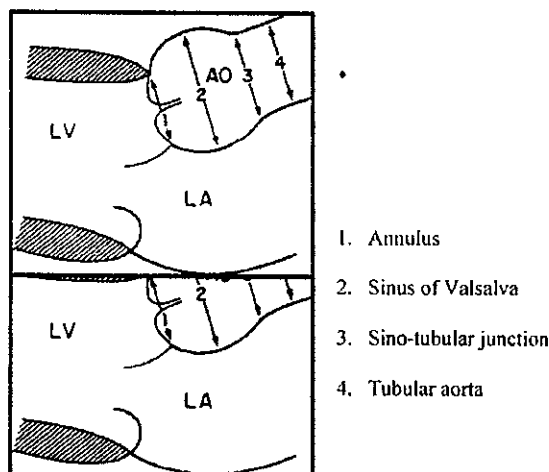
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Appendix A

Transthoracic cardiac ultrasound



Dilated Aorta > 20 mm/m² of body surface area
High risk of dissection > 25 mm/m² of body surface area

Measurements	Before pregnancy	1st trimester	2nd trimester	3rd trimester			15 days after delivery	8 weeks after delivery
				1st month	2nd month	3rd month		
Date								
Diameter of aortic annulus (mm/m ²)								
Diameter at sinus of Valsalva (mm/m ²)								
Diameter at sinotubular junction (mm/m ²)								
Subcoronary diameter of ascending aorta (mm/m ²)								
Aortic regurgitation (grade 0, I, II, III, IV)								
Bicuspid aortic valve								
Coarctation of the aorta								
Pericardial effusion								

Appendix B

Magnetic resonance imaging of the ascending aorta

Magnetic resonance system (1.5 T)

Antenna in phase network: cardiac or thoracic, preferred to the machine's antenna.

Whole magnetic resonance imaging (MRI) of the aorta recorded on a CD-ROM.

B.1. Examination before pregnancy

Morphology of the aorta

- Black blood technique in axial thoracic sections: T1- or T2-weighted fast spin-echo sequence, synchronised with the ECG

Magnetic resonance angiography

Gadolinium-enhanced three-dimensional magnetic resonance angiography (gadolinium 0.2 mmol/kg)

Acquisition in the coronal plane with centring between the ascending and descending aortas

Coverage of renal arteries if possible (patients of short stature): look for stenosis NB: Possible to use acquisition in the oblique parasagittal plane centred on the arch of the aorta.

- Multiplanar reconstructions in the plane perpendicular to the aortic axis centred on:
 - 1: the aortic root
 - 2: the sinus of Valsalva
 - 3: the sinotubular junction
 - 4: the tubular aorta with measurement of the aortic diameters at these different levels

Volume rendering of the thoracic aorta

B.1.1. Additional sequences

Steady-state free precession sequences centred on the aortic valve (axial sections ± phase-contrast MRI and velocimetry) to screen for a bicuspid aortic valve. In coarctation of the aorta: velocimetry and phase-contrast MRI centred on the coarctation to check for a trans-stenotic pressure gradient.

B.2. During pregnancy

Morphology of the aorta

Black blood technique in axial thoracic sections: T1- or T2-weighted fast spin-echo sequence, synchronised with the ECG

Steady-state free precession sequences (true fast imaging with steady-state precession [true FISP] – fast imaging employing steady-

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