Turner syndrome and pregnancy
Clinical practice recommendations

Mission
Following the death by acute aortic dissection of two women with Turner syndrome who were pregnant following egg donation, the Director General of the Agence de la biomédecine sent a letter on 2 July 2008 to the President of the French National College of Gynaecologists and Obstetricians (CNGOF) requesting the College’s expertise in reviewing point by point the cases and risk factors and in determining whether there are grounds to propose measures complementary to the recommendations made by the Haute autorité de santé (HAS) in 2008 in terms of indication and monitoring of patients, with a view to improving healthcare safety.

Working group

<table>
<thead>
<tr>
<th>Organisation</th>
<th>Speciality</th>
<th>Name and email address</th>
<th>Observation</th>
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Introduction

Turner syndrome is associated with monosomy X (45 X 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) and mosaicism. For the vast majority of such women, being an egg recipient is the only way to become pregnant (Appendix VII lists the accredited centres).

These pregnancies carry particular risks inasmuch as 5 to 50% of women with Turner syndrome have a cardiovascular malformation [2, 3, 4, 5]: coarctation of the aorta (10% of cases), 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]. An estimated 2% of women with Turner syndrome are at risk of death caused by aortic dissection or rupture, a rate 100 times that of 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 well above these were reported in the two French cases. The risk of dissection during pregnancy is unclear, but all literature cases to date suggest it may be about 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 post-partum.
A review of the literature between 1961 and 2006 revealed 85 cases of aortic dissection in women with Turner syndrome. In the 7 cases of aortic dissection reported after assisted reproductive technologies (ART), 6 patients died [9, 10, 11]. Severe hepatic steatosis or cholestasis, and pregnancy-induced hypertension have been reported [12, 13, 14]. In 2008 the HAS published a national protocol for diagnosis and care of Turner syndrome [15] that 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, 20-24]. Given the rarity of pregnancy in Turner syndrome patients, the literature data are of a low level of proof and the following recommendations are essentially based on expert opinions.

**Work-up before pregnancy**

A work-up should be done in every patient who wishes to become pregnant, whatever her karyotype (mosaic or 45 X), and whether pregnancy is sought naturally (if ovarian function is conserved, as it generally is in patients with a mosaic karyotype) or through third-party reproduction (egg donation). The work-up should be multidisciplinary and involve specialists in cardiology, endocrinology, nephrology, hepatology, and so forth.

**General examination**

Weight, height, body mass index.

**Cardiovascular examination**

Hypertension, bicuspid aortic valve, aortic dilatation and coarctation are aortic dissection risk factors in women with Turner syndrome.

**Blood pressure:** measured at rest, 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 [25]), is used to search for aortic malformations (bicuspid aortic valve: 25% of patients, coarctation: 10%, anomalies of the structure of the aorta) and anomalies of venous return, to screen for acquired aortic disease (aneurysm, dilatation), and during follow-up. The four diameters characteristic of the aortic root are measured (the largest is used) and screening for bicuspid aortic valve is 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 [18-24] 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;
- measure the four diameters of the aortic root;
- screen for or confirm coarctation, bicuspid aortic valve;
- do successive comparative analyses;
- observe the renal arteries if the acquisition area allows.

The aortic diameter indexed for body surface area is measured by MRI at the right pulmonary artery. 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 to indicate a dilated aorta at risk of dissection.

Appendix II describes a protocol for MRI of the ascending aorta.

When MRI cannot be performed (pacemaker, defibrillator, catheter or other equipment), computed tomography of the aorta should be considered.

**Endocrine tests**

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.
Liver function tests
- blood tests: aspartate transaminase, alanine transaminase, gamma glutamyl transpeptidase and alkaline phosphatase;
- liver ultrasound when laboratory tests six months apart show anomalies: notably testing for portal hypertension.
If there are anomalies, specialist advice should be sought regarding aetiology.

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

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.

Contraindications to pregnancy

Cardiovascular
Pregnancy is contraindicated if there is:
- a history of aortic surgery;
- a history of aortic dissection;
- aortic dilatation: the largest aortic diameter is above 25 mm/m² or 35 mm. This is an extrapolation of measurements made at the tubular aorta [18];
- coarctation of the aorta;
- hypertension uncontrolled despite treatment.
Even if surgery of the valves or aorta has been performed, the patient is still at risk of aortic dissection in pregnancy, which remains contraindicated. Isolated bicuspid aortic valve (without aortic dilatation) is not a contraindication to pregnancy, but is a risk factor.

Hepatic
Portal hypertension with œsophageal varices.

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 spontaneous pregnancy (without egg 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 egg donation only one embryo will be transferred to avoid multiple pregnancies;
- there is an increased risk of caesarean delivery 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 gynaecologistobstetrician, 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 delivery must take place in a medical facility 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 egg donation, or in cases of persistent ovarian dysfunction the team can formally advise against pregnancy, after having informed the patient.

**Conditions for medical acceptance of pregnancy**

**Cardiovascular**

If the aortic diameter is less than 25 mm/m² and 35 mm and 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 using a second imaging technique (MRI, computed tomography or transoesophageal ultrasound). If confirmed, progression of aortic dilatation becomes a contraindication to pregnancy.

**Liver function tests**

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

**Recommendations in the case of ART**

In ART with egg donation (Appendix VII lists centers accredited for egg donation), it is strongly recommended to transfer a single embryo to avoid multiple pregnancies. When embryo transfer is done, the patient must be reminded of the risks of pregnancy and the need for close follow-up. If there is an incident or adverse event, it must be reported to the *Agence de la biomédecine* by the local correspondent of the health watchdog for ART, or by any health professional who knows 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). Appendix V outlines the reporting procedure.

**Recommendations for pregnancy follow-up**

Pregnancy follow-up should be multidisciplinary and concerted.

**Cardiovascular monitoring**

**Echocardiography (Appendix I):**
- at the end of the first and second trimesters;
- every month during the third trimester;
- a increase in aortic diameter greater than or equal to 10% between two examinations should be confirmed by MRI (Appendix II).

**In the case of acute dissection of the aortic root during pregnancy:**

Medical management will depend on the stage of pregnancy:
- before 25 weeks of gestation, emergency aortic root surgery with extracorporeal circulation, foetus in utero, with cardiotocography. The risk of maternal and/or foetal death is high;
- after 25 weeks of gestation, emergency caesarean section, immediately followed by aortic root surgery.

*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)*
If the aortic diameter becomes greater than 25 mm/m² or 35 mm or if it increases by >10% between two examinations or with respect to 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 sought in a reference centre (Appendix IV)
- acceleration of foetal lung maturation if delivery is between 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 staffed by a team of cardiologists and a heart surgery team.
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 foetal-pelvic disproportion or associated disease. Assisted delivery (vacuum extractor or forceps) is recommended.

**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.

**Liver function tests**
Liver function tests are only needed 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.

**Screening for gestational diabetes**
The O'Sullivan test is done at 24 weeks of gestation.

**Kidney function tests**
Blood creatinine level is determined every month in cases of renal malformation.

**Postnatal follow-up**

**Cardiovascular**
As cardiovascular risk persists after delivery, there should be 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.

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

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

**Examination of the infant**
For pregnancy not involving egg donation, the paediatric examination is used to check for chromosomal abnormalities: Turner syndrome for a girl, trisomy 21.
For pregnancy after egg donation, the paediatric examination does not include any special tests.

**Reporting to the Turner Syndrome Registry**
Any pregnancy with or without egg donation in a woman with Turner syndrome must be reported to the Turner Syndrome Registry at the email address: crmerc.turner@rdb.aphp.fr. The reporting form is given in Appendix VI.

1 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)
References

## Appendix I – Transthoracic cardiac ultrasound

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

<table>
<thead>
<tr>
<th>Measurements</th>
<th>Before pregnancy</th>
<th>1st trimester</th>
<th>2nd trimester</th>
<th>3rd trimester</th>
<th>15 days after delivery</th>
<th>8 weeks after delivery</th>
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<tr>
<td>Date</td>
<td></td>
<td>1st month</td>
<td>2nd month</td>
<td>3rd month</td>
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<td>Diameter of aortic annulus (mm/m²)</td>
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<td>Diameter at sinus of Valsalva (mm/m²)</td>
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<td>Diameter at sinotubular junction (mm/m²)</td>
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<td>Subcoronary diameter of ascending aorta (mm/m²)</td>
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<td>Aortic regurgitation (grade 0, I, II, III, IV)</td>
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<tr>
<td>Bicuspid aortic valve</td>
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<td>Coarctation of the aorta</td>
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Appendix II - Magnetic resonance imaging of the ascending aorta

Magnetic resonance system (1.5 Tesla)
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.

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

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.

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-state acquisition [FIESTA] – balanced turbo field echo [b-TFE]) centred on the ascending aorta
  (coronal plane, oblique parasagittal plane, plane perpendicular to the aortic valve…)

Measurement of aortic diameters at the:
1: aortic root
2: sinus of Valsalva
3: sinotubular junction
4: tubular aorta
Appendix III - Information document for the patient and her partner

Madam, Sir,

Madam, as you know, you have a chromosomal abnormality called Turner syndrome, which is characterised by the partial or complete absence of one of the two X chromosomes normally observed.

Spontaneous pregnancies in cases of preserved ovarian function are rare (2%) and carry an increased risk of miscarriage and chromosomal abnormalities. You are advised to agree to an appointment with a doctor specialised in genetics to determine the risk of transmission to the child of a genetic abnormality, and to discuss the possibility of prenatal diagnosis.

In most cases of Turner syndrome, being an egg recipient is the only way to become pregnant.

Whether the pregnancy is spontaneous or medically assisted through egg donation, it is at high risk of complications:
- cardiovascular (hypertension, dilatation even rupture of the aorta): life-threatening for both mother and child;
- metabolic: diabetes;
- hepatic: bile retention;
- obstetrical: hypertension, pre-eclampsia. In 85% of cases, caesarean delivery is necessary, notably because of a narrow pelvis.

Before considering pregnancy, a review by a specialised medical team is essential. This review involves:
- a consultation with a cardiologist to measure blood pressure and for ultrasound examination or magnetic resonance imaging (MRI) of the heart;
- a consultation with an endocrinologist to test for diabetes, thyroid gland disease, liver disease and kidney disease;
- a consultation with a gynaecologist-obstetrician to assess the condition of the womb and to measure the pelvis. It may be necessary to examine the pelvis by ultrasound or MRI or both.

After this medical review, the specialised multidisciplinary team may formally advise against pregnancy, particularly if you have had surgery on the aorta or if testing has revealed hypertension or if ultrasound examination of the heart gives abnormal findings.

If pregnancy is not contraindicated and you are awaiting egg donation, an annual appointment with the cardiologist will be necessary. Liver function tests will also be done every year.

With egg donation or other techniques of ART procreation, you will receive a single embryo to avoid a multiple pregnancy, which would increase the risk of complications.

During pregnancy, apart from the usual follow-up by the gynaecologist-obstetrician, it will be necessary to see the cardiologist for further ultrasound scans at the end of the first and second trimesters, and also every month of the last trimester of the pregnancy.

If during pregnancy the aorta dilates by more than 10% compared with the measurement at the start of pregnancy, it may be necessary to deliver your baby by caesarean before term and to operate on your aorta. If hypertension occurs, treatment may be necessary. There may also be a liver complication that causes itching and jaundice and which will require treatment or even premature delivery of the baby.

If the pregnancy goes well and reaches term, the delivery should take place in a centre with, in addition to a maternity department and a paediatric department, a team of cardiologists and heart surgeons, as emergency cardiac intervention may be necessary. The route of delivery will be discussed with the obstetrician, but most often (available data suggest 85% of cases) it will be necessary to perform a caesarean section.

After the delivery, cardiac monitoring by the same team will be needed, and ultrasound scans should be done 2 and 8 weeks after the birth, and then every year.

Yours is a high-risk pregnancy, particularly because of the possibility of dilation or even rupture of the aorta, which requires emergency cardiac intervention. In the absence of suitable care and multidisciplinary monitoring by a specialised team, complications may be life-threatening for you and your child. On the basis of available information, notably after recommendations from the team in charge of your treatment, it is therefore necessary, with your partner and the team, to weigh up the difficulties and risks of such a pregnancy and of possible alternatives. The team is there to help you make a decision. If you decide to have a child, your close collaboration is essential if the pregnancy is to be completed successfully.
### Reference endocrinology centres

<table>
<thead>
<tr>
<th>Reference centres</th>
<th>City</th>
<th>Hôpital</th>
<th>Names of coordinators at each site</th>
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<tr>
<td>Rennes</td>
<td>Dr Sylvie NIVOT-ADAMIAK, Prof Brigitte DELEMER</td>
<td><a href="mailto:sylvie.nivot-adamiak@chu-rennes.fr">sylvie.nivot-adamiak@chu-rennes.fr</a>, <a href="mailto:bdelemer@chu-rennes.fr">bdelemer@chu-rennes.fr</a></td>
</tr>
<tr>
<td>Tours</td>
<td>Dr François DESPRET, Prof Pierre LECOMTE</td>
<td><a href="mailto:despret@med.univ-tours.fr">despret@med.univ-tours.fr</a>, <a href="mailto:lecomte@med.univ-tours.fr">lecomte@med.univ-tours.fr</a></td>
</tr>
<tr>
<td>Reims</td>
<td>Dr Véronique SULMONT, Prof Brigitte DELEMER</td>
<td><a href="mailto:vsulmont@chu-reims.fr">vsulmont@chu-reims.fr</a>, <a href="mailto:bdelemer@chu-reims.fr">bdelemer@chu-reims.fr</a></td>
</tr>
<tr>
<td>Besançon</td>
<td>Dr Anne-Marie BERTRAND, Prof Alfred PENFORNIS</td>
<td><a href="mailto:anne-marie@wanadoo.fr">anne-marie@wanadoo.fr</a>, <a href="mailto:alfred.penfornis@univ-fcomte.fr">alfred.penfornis@univ-fcomte.fr</a></td>
</tr>
<tr>
<td>Montpellier</td>
<td>Prof Charles SULTAN, Prof Jacques BRINGER</td>
<td><a href="mailto:c-sultan@chu-montpellier.fr">c-sultan@chu-montpellier.fr</a>, <a href="mailto:j-bringer@chu-montpellier.fr">j-bringer@chu-montpellier.fr</a></td>
</tr>
<tr>
<td>Nancy</td>
<td>Dr Bruno LEHEUP, Prof Georges WERYHA</td>
<td><a href="mailto:b.leheup@chu-nancy.fr">b.leheup@chu-nancy.fr</a>, <a href="mailto:g.weryha@chu-nancy.fr">g.weryha@chu-nancy.fr</a></td>
</tr>
<tr>
<td>Lille</td>
<td>Dr Jacques WEILL, Prof Jean-Louis WEMEAU</td>
<td><a href="mailto:jweill@chu-lille.fr">jweill@chu-lille.fr</a>, <a href="mailto:j-l-wemeau@chu-lille.fr">j-l-wemeau@chu-lille.fr</a></td>
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<tr>
<td>Nantes</td>
<td>Dr Sabine BARON, Prof Bernard CHARBONNEL</td>
<td><a href="mailto:sabine.baron@chu-nantes.fr">sabine.baron@chu-nantes.fr</a>, <a href="mailto:bernard.charbonnel@univ-nantes.fr">bernard.charbonnel@univ-nantes.fr</a></td>
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<tr>
<td>Amiens</td>
<td>Dr Hélène BONY TRIFUNOVIC, Dr Rachel DESAILLOUD</td>
<td><a href="mailto:bony.helene@chu-amiens.fr">bony.helene@chu-amiens.fr</a>, <a href="mailto:r.desailoud@chu-amiens.fr">r.desailoud@chu-amiens.fr</a></td>
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<tr>
<td>Nice</td>
<td>Dr Kathy WAGNER MAHLER, Dr Elisabeth BAECHLER, Prof Patrick FENCHEL</td>
<td><a href="mailto:wagner.k@chu-nice.fr">wagner.k@chu-nice.fr</a>, <a href="mailto:elisabeth.baechler@lenval.com">elisabeth.baechler@lenval.com</a>, <a href="mailto:fenichel.p@chu-nice.fr">fenichel.p@chu-nice.fr</a></td>
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<tr>
<td>St Etienne</td>
<td>Dr Odile RICHARD</td>
<td><a href="mailto:odile.richard@chu-st-etienne.fr">odile.richard@chu-st-etienne.fr</a></td>
</tr>
<tr>
<td>Grenoble</td>
<td>Prof Olivier CHABRE</td>
<td><a href="mailto:olivierchabre@chu-grenoble.fr">olivierchabre@chu-grenoble.fr</a></td>
</tr>
</tbody>
</table>
Reference centres and knowledge centres for Marfan syndrome and related diseases with links to a centre specialised in development (the correspondents are coordinators in touch with cardiologists)

### Reference centres

<table>
<thead>
<tr>
<th>District</th>
<th>Location</th>
<th>Contact Person</th>
<th>Address</th>
<th>Email</th>
</tr>
</thead>
<tbody>
<tr>
<td>14th district</td>
<td>Paris</td>
<td>Dr Daniel Czitröm</td>
<td>Institut mutualiste Montsouris, Service de cardiologie du Pr Laborde, 42 boulevard Jourdan, 75014 Paris</td>
<td><a href="mailto:daniel.czitrom@imm.fr">daniel.czitrom@imm.fr</a></td>
</tr>
<tr>
<td>15th district</td>
<td>Paris</td>
<td>Dr Laurence Iserin</td>
<td>Hôpital européen Georges Pompidou, Service de cardiologie du Pr Le Heuzet, 22 rue Leblanc, 75015 Paris</td>
<td><a href="mailto:laurence.iserin@egp.aphp.fr">laurence.iserin@egp.aphp.fr</a></td>
</tr>
<tr>
<td>18th district</td>
<td>Paris</td>
<td>Dr Guillaume Jondeau</td>
<td>Centre de référence pour le syndrome de Marfan et apparentés, Hôpital Bichat, 46 rue Henri Huchard, 75018 Paris</td>
<td><a href="mailto:Consultation.marfan@bch.aphp.fr">Consultation.marfan@bch.aphp.fr</a>, <a href="http://www.marfan.fr">www.marfan.fr</a></td>
</tr>
</tbody>
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### Knowledge centres

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<th>Address</th>
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<tbody>
<tr>
<td>Lyon</td>
<td>Prof Henri Plauchu</td>
<td>Hôtel Dieu, 69228 Lyon 02</td>
<td><a href="mailto:henri.plauchu@chu-lyon.fr">henri.plauchu@chu-lyon.fr</a></td>
</tr>
<tr>
<td>Dijon</td>
<td>Prof Laurence Faivre</td>
<td>Hôpital d'enfants, 10 boulevard Maréchal de Lattre de Tassigny, 21034 Dijon</td>
<td><a href="mailto:laurence.faivre@chu-dijon.fr">laurence.faivre@chu-dijon.fr</a></td>
</tr>
<tr>
<td>Marseille</td>
<td>Dr Patrick Collignon</td>
<td>Hôpital de la Timone, 13385 Marseille</td>
<td><a href="mailto:patrick.collignon@ch-toulon.fr">patrick.collignon@ch-toulon.fr</a></td>
</tr>
<tr>
<td>Rennes</td>
<td>Prof Sylvie Odent</td>
<td>Hôpital Sud, 16 boulevard de Bulgarie, BP 90347, 35203 Rennes</td>
<td><a href="mailto:sylvie.odent@chu-rennes.fr">sylvie.odent@chu-rennes.fr</a></td>
</tr>
<tr>
<td>Toulouse</td>
<td>Dr Yves Dulac</td>
<td>Hôpital des enfants, 330 avenue de Grande-Bretagne, TSA 70034, 31059 Toulouse cedex</td>
<td><a href="mailto:edouard.1@chu-toulouse.fr">edouard.1@chu-toulouse.fr</a></td>
</tr>
<tr>
<td>Bordeaux</td>
<td>Dr Marie-Ange Delrue</td>
<td>Hôpital Pellegrin enfants, Place Amélie Raba Léon, 33076 Bordeaux cedex</td>
<td><a href="mailto:marie-ange.delrue@chu-bordeaux.fr">marie-ange.delrue@chu-bordeaux.fr</a></td>
</tr>
<tr>
<td>Nancy</td>
<td>Prof Bruno Leheup</td>
<td>CHU Nancy, Hôpital d'enfants, 54500 Vandœuvre les Nancy</td>
<td><a href="mailto:b.leheup@chu-nancy.fr">b.leheup@chu-nancy.fr</a></td>
</tr>
</tbody>
</table>
Appendix V – Reporting incidents or adverse events related to ART to the Agence de la biomédecine

Doctors involved in questions of fertility and human reproduction (gynaecologists-obstetricians, endocrinologists, medical laboratory technologists) are under obligation to report immediately (see part A) or after its conclusion (see part B) an incident or adverse event related to or likely to be related to procedures concerning gametes, germinal tissue or embryos used in ART. The report is sent in writing to the Agence de la biomédecine by the local correspondent of the health watchdog for ART or by any professional who knows of the occurrence of such an incident or adverse event.

The reporting procedure is detailed in the appendices of the Journal officiel no. 0301 of 27 December 2008 (page 20184, text no. 69, NOR: SJSP0830456A), and below.

PART A: immediate reporting of the incident or adverse event

Institute or body concerned.
Person submitting the report.
Material involved: gametes, germinal tissue or embryos.
Where relevant, the donation identification number.
Details on the person or persons involved in cases of an adverse event.
ART procedures concerned.
Date of the incident or adverse event.
Date the incident or adverse event was observed.
Where relevant, date and place of:
— collection or sampling of gametes or germinal tissue;
— artificial insemination;
— embryo transfer.
Stage at which the incident or adverse event occurred.
Description of the event:
— type of incident or adverse event according to the Agence de la biomédecine classification;
— seriousness of the incident or adverse event according to the Agence de la biomédecine classification;
— details of the incident or adverse event;
— flaw in gametes, germinal tissue, embryos;
— defective equipment;
— human error;
— other.
Consequences of the incident or adverse event.
Preventive or corrective measures implemented, including a procedure to stop use of gametes, germinal tissue or embryos.
Has another health watchdog also been informed?

PART B: reporting after conclusion of the incident or adverse event

Confirmation of the incident or adverse event and date of confirmation.
Reclassification of type, if necessary.
Reclassification of seriousness, if necessary.
Preventive or corrective measures implemented.
Clinical outcome, where necessary.
Control of the incident or adverse event.
Avoidability of the incident or adverse event.
Description of the cause of the incident or adverse event.
Results of the investigation and final conclusion.
Appendix VI – Turner Syndrome Registry reporting form

Email to the following address: crmerc.turner@rdh.aphp.fr

Name: 
First name: 
Date of birth: (Turner syndrome) 

**Cardiac monitoring**

Date of evaluation: 
Cardiologist: Dr 
Hospital: 

Weight (kg): 
Blood pressure (mmHg): 
Height (cm): 
Body surface area (m²): 
Antihypertensive treatment: NO YES 

Electrocardiogram: normal abnormal, specify: prolonged QT interval other: 

**Known history before the last imaging examination:**

- Cardiovascular surgery NO YES Indicate type: Date: 
- Hypertension NO YES 

- Bicuspid aortic valve NO YES Undetermined 
- Coarctation of the aorta NO YES Maximum gradient: mmHg 
- Aortic regurgitation NO YES 
- Aortic valve stenosis NO YES 

- Mitral regurgitation NO YES 
- Mitral valve stenosis NO YES 
- Malformation NO YES Undetermined Specify: 

**Results of the last imaging examination:**

**Ultrasound of the heart / aorta:** Date of last exam: / / 
**Magnetic resonance imaging of the heart / aorta:** Date of last exam: / / 
**Computed tomography of the heart / aorta:** Date of last exam: / / 

**IMAGING 1: ULTRASONOGRAPHY**

<table>
<thead>
<tr>
<th>AORTA</th>
<th>Measurement (mm)</th>
<th>AORTA</th>
<th>Measurement (mm)</th>
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<tbody>
<tr>
<td>1-Aortic annulus</td>
<td>Arch</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-Sinus of Valsalva</td>
<td>Proximal descending</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-Sinotubular junction</td>
<td>Thoracic descending</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-Ascending aorta 1 cm from the sinus of Valsalva</td>
<td>Abdominal</td>
<td></td>
<td></td>
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</tbody>
</table>

Measurements done according to the recommendations of the American Society of Cardiology (leading edge to leading edge, including the anterior wall and excluding the posterior wall). Left parasternal long-axis view (perpendicular to the long axis of the aorta, at end-diastole, averaging over at least 3 cycles).
Cardiac and aortic abnormalities found at last imaging examination:

- Bicuspid aortic valve  NO  YES  Undetermined
- Coarctation of the aorta  NO  YES  Maximum gradient: ..... mmHg
- Aortic regurgitation  NO  YES  Slight / moderate / severe
- Aortic valve stenosis  NO  YES  Aortic surface area: ..... cm²
  Average gradient: mmHg
- Mitral regurgitation  NO  YES  Slight / moderate / severe
- Mitral valve stenosis  NO  YES  Mitral surface area: ..... cm²
- Left ventricular hypertrophy  NO  YES
- Left ventricular end-diastolic volume: ..... mm  Left ventricular posterior wall (diastole): ..... mm
- Left ventricular end-systolic volume: ..... mm  Septal thickness (diastole): ..... mm
- Left ventricular fractional shortening (%): .....%:
- Left ventricular ejection fraction (%): .....%
- Malformation  NO  YES  Undetermined
  Specify:

Cardiologist’s conclusions:

Management:

Next cardiovascular consultation should be scheduled in .................................................................

Next cardiovascular imaging should be scheduled in .................................................................

and should involve: ultrasonography  magnetic resonance imaging of the aorta

Need for perioperative antibiotic prophylaxis for high-risk valve disease  □ NO  □ YES
APPENDICES:

More frequent cardiological examinations if the largest diameter of the ascending aorta is:
- 2 cm/m² (magnetic resonance imaging: Matura LN. Circulation 2007)
- or 2.1 cm/m² (ultrasonography: Roman MJ. Am J Cardiol 1989)

Seek specialised surgical advice if the largest diameter of the ascending aorta is > 2.5 cm/m²

Calculation of the body surface area according to Dubois (Matura LN. Circulation 2007;116:1663):

Surface area = 0.007184 x height (cm) to the power 0.725 x weight (kg) to the power 0.425 Surface area (m²) - height (cm) - weight (kg)

or simplified if < 30 kg (paediatrics): Surface area = (4 x weight + 7) / (weight + 90 )

Monitoring of aortic diameters:

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<td>1-Aortic annulus</td>
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<tr>
<td>2-Sinus of Valsalva</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-Sinotubular junction</td>
<td></td>
<td></td>
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<tr>
<td>4-Ascending aorta at 1 cm from the sinus of Valsalva</td>
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<tr>
<td>Sinus of Valsalva/body surface area and/or</td>
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<tr>
<td>Sinus of Valsalva (DS???)</td>
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Morphologie basée sur la coupe parasternale petit axe

Raphé visualisé

OUI «pseudo bicuspid »

Raphé = 1

Fusion: Droite-Gauche

NON «vraiment bicuspid »

Raphé = 2

Gauche - Droite

Antero- Posterior

Cocher la case correspondante

Morphologie basée sur la coupe parasternale petit axe = Morphology based on parasternal short-axis view Raphé visualisé = Raphe visualised OUI “pseudo bicuspid” = YES “pseudo bicuspid valve” NON “vraiment bicuspid” = NO “true bicuspid valve” Raphé = Raphe Fusion: Droite-Gauche = Fusion: Right-Left Fusion: Droite-NC = Fusion: Right-??

Gauche-Droite = Left-Right Antero-Postérieur = Anteroposterior Cocher la case correspondante = Tick the appropriate box
Aortic root dimensions/body surface area in normal children and adults (Roman et al. 1989)
<table>
<thead>
<tr>
<th>Name</th>
<th>Address</th>
<th>Telephone</th>
<th>Email</th>
<th>Website</th>
</tr>
</thead>
</table>
| CH des Quatre Villes S
te de Sévres           | 141 grande rue 92310 Sévres    | 01 41 14 75 50     | martine.lescombes@chi-sevres.fr           | www.chi-sevres.fr                           |
<p>| CH des Quatre Villes Site de Sévres            | 141 grande rue 92310 Sévres    | 01 41 14 75 24     |                                            |                                              |
| CHI de Poissy-St Germain en Laye                | 10 rue du Champ Gaillard 78303 Poissy | 01 39 27 51 55 | <a href="mailto:ampcyto-poissy@hotmail.com">ampcyto-poissy@hotmail.com</a>                | <a href="http://www.chi-poissy-st-germain.fr">www.chi-poissy-st-germain.fr</a>                |
| CHRU de Lille Hôpital Jeanne de Flandre Gynécologie endocrinienne et médecine de la reproduction | 2 avenue Oscar Lambret 59037 Lille | 03 20 44 68 97 | <a href="mailto:c-valdes@chru-lille.fr">c-valdes@chru-lille.fr</a> <a href="mailto:h-drygierczyk@chru-lille.fr">h-drygierczyk@chru-lille.fr</a> | <a href="http://www.chru-lille.fr">www.chru-lille.fr</a> |
| CHRU de Rennes Hôpital sud Département d'obstétrique, gynécologie et médecine de la reproduction | 16 boulevard de Bulgarie 35064 Rennes | 02 99 26 67 09 |                                            | <a href="http://www.chu-rennes.fr">www.chu-rennes.fr</a>                          |
| CHRU de Tours Hôpital Bretonneau                | 2 boulevard Tonnelle 37044 Tours |                    |                                            | <a href="http://www.chu-tours.fr">www.chu-tours.fr</a>                            |
| CHU d’Amiens Centre de gynécologie obstétrique | 124 rue Camille Desmoulins 80054 Amiens | 03 22 53 36 75/77 | <a href="mailto:cecos@chu-amiens.fr">cecos@chu-amiens.fr</a>                       | <a href="http://www.chu-amiens.fr">www.chu-amiens.fr</a>                           |
| CHU de Besancon Hôpital St Jacques              | 2 place Saint Jacques 25030 Besançon | 03 81 21 88 04 | <a href="mailto:fiv@chu-besancon.fr">fiv@chu-besancon.fr</a>                      | <a href="http://www.chu-besancon.fr">www.chu-besancon.fr</a>                         |
| CHU de Clermont-Ferrand Hôtel Dieu              | 13 boulevard Charles de Gaulle 63058 Clermont-Ferrand | 04 73 75 01 15 | <a href="mailto:reproduction@chuclermontferrand.fr">reproduction@chuclermontferrand.fr</a>         | <a href="http://www.chuclermontferrand.fr/reproduction">www.chuclermontferrand.fr/reproduction</a>        |
| CHU de Montpellier Hôpital Arnaud de Villeneuve Département de médecine et biologie de la reproduction Unité d’AMP clinique | 371 avenue du Doyen Giraud 34295 Montpellier | 04 67 33 64 81 | <a href="mailto:gyneco-obst-pma@chumontpellier.fr">gyneco-obst-pma@chumontpellier.fr</a>          | <a href="http://www.chu-montpellier.fr">www.chu-montpellier.fr</a>                      |
| CHU de Nice Hôpital de l’Arche II               | 151 route St Antoine Ginestiere 06202 Nice | 04 92 03 64 03 |                                            | <a href="http://www.chu-nice.fr">www.chu-nice.fr</a>                             |
| CHU de Reims Hôpital Maison Blanche             | 45 rue Cognacq Jay 51092 Reims | 03 26 78 77 50 |                                            | <a href="http://www.chu-reims.fr">www.chu-reims.fr</a>                            |
| CHU de Toulouse Hôpital Paule de Viguier        | 330 avenue de Grande-Bretagne 31059 Toulouse | 05 67 77 10 05 |                                            | <a href="http://www.chu-toulouse.fr">www.chu-toulouse.fr</a>                         |
| CHU Pellegrin Centre clinico-biologique d’AMP-CEGOS | Place Amélie Raba Léon 33076 Bordeaux | 05 56 79 54 31 |                                            | <a href="http://www.chu-bordeaux.fr">www.chu-bordeaux.fr</a>                         |
| Clinique mutualiste la Sagesse                  | 4 place Saint Guénolé 35000 Rennes | 02 99 85 75 20 | j座<a href="mailto:re.degov@wanadoo.fr">re.degov@wanadoo.fr</a> <a href="mailto:jerome.degov@wanadoo.fr">jerome.degov@wanadoo.fr</a> | <a href="mailto:prav-laurent@wanadoo.fr">prav-laurent@wanadoo.fr</a>                      |
| Clinique St Jean Languedoc (Ifréres)            | 20 route de Revel 31077 Toulouse | 05 61 54 90 40 |<a href="mailto:.sec.med.sec-amp@jvr.aphp.fr">.sec.med.sec-amp@jvr.aphp.fr</a>                | <a href="http://www.aphp.fr">www.aphp.fr</a>                                 |
| Complexe hospitalier du Bocage                  | 2 boulevard de Lattre de Tassigny 21079 Dijon | 03 80 29 36 14 | <a href="mailto:amp@chu-dijon.fr">amp@chu-dijon.fr</a>                          | <a href="http://www.chu-dijon.fr">www.chu-dijon.fr</a>                            |
| Groupe hospitalier du Havre Hôpital Jacques Monod | Avenue Pierre Mendes France 76290 Montvilliers | 02 32 73 33 35 | <a href="mailto:sec.amp@ch-havre.fr">sec.amp@ch-havre.fr</a>                       | <a href="http://www.aphp.fr">www.aphp.fr</a>                                 |
| Hôpital Antoine Béclère Service de gynécologie obstétrique médecine de la reproduction | 157 rue de la Porte de Trivaux 92140 Clamart |                    |                                            | <a href="http://www.aphp.fr">www.aphp.fr</a>                                 |
| Hôpital Cochin                                  | 27 rue du Faubourg St Jacques 75014 Paris | 01 58 41 15 38 |                                            | <a href="http://www.aphp.fr">www.aphp.fr</a>                                 |
| Hôpital de la Conception                        | 147 boulevard Baille 13005 Marseille |                    |                                            | <a href="http://www.aphp.fr">www.aphp.fr</a>                                 |
| Hôpital Jean Verdier Service médecine de la reproduction | Avenue du 14 juillet 93143 Bondy | 01 48 02 68 56 | <a href="mailto:secmed.sec-amp@jvr.aphp.fr">secmed.sec-amp@jvr.aphp.fr</a>                | <a href="http://www.aphp.fr">www.aphp.fr</a>                                 |
| Hôpital St Vincent de Paul                      | 82 avenue Denfert Rochereau 75014 Paris | 01 40 48 81 44 | <a href="mailto:f.martinet@svp.aphp.fr">f.martinet@svp.aphp.fr</a>                    | <a href="http://www.aphp.fr">www.aphp.fr</a>                                 |</p>
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<tr>
<td>Hôpital Tenon Service de gynécologie obstétrique et médecine de la reproduction Secteur AMP clinique</td>
<td>4 rue de la Chine 75970 Paris</td>
<td>01 56 01 68 69 (morning)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Hôpital femme-mère-enfant Médecine de la reproduction</td>
<td>59 boulevard Pinel 69677 Bron</td>
<td>04 72 12 94 05</td>
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<td></td>
<td>Sperm donation:</td>
<td>04 72 11 66 66</td>
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<tr>
<td>Institut mutualiste Montsouris</td>
<td>42 boulevard Jourdan 75674 Paris</td>
<td>01 56 61 61 05/06</td>
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<td><a href="http://www.imm.fr">www.imm.fr</a></td>
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<tr>
<td>SIHCUS -CMCO</td>
<td>19 rue Louis Pasteur 67303 Shiltigheim</td>
<td>03 88 62 83 13</td>
<td></td>
<td><a href="mailto:martine.camaeti@sihcus.fr">martine.camaeti@sihcus.fr</a></td>
<td><a href="http://www.sihcus-cmco.fr">www.sihcus-cmco.fr</a></td>
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<tr>
<td>Syndicat inter-hospitalier femme-mère-enfant Site Sainte Croix</td>
<td>1-5 place Sainte Croix 57045 Metz</td>
<td>03 87 34 51 92</td>
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<td><a href="http://www.maternite-hopitalste-croix.fr">www.maternite-hopitalste-croix.fr</a></td>
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