



HHT AND PREGNANCY

Pr Olivier Dupuis Lebreton
Obstetrics and Gynecology, Lyon
MD, PhD



B.E.E Meeting
Copenhagen, May 25, 2023



Conflict of interest ?

None

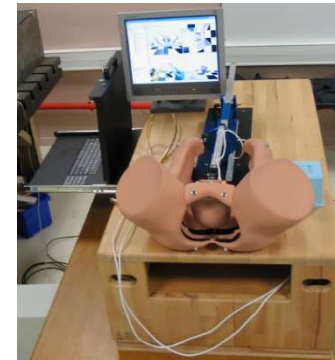
Can we improve obstetrics safety ?

Civilian Aviation
One casualty
Fly 438 years ,
24 hours a day

Mortality Risk
=
1 / 8 000 000 flights



x 800



Obstetrics
France
800 000 births / year

Mortality Risk
=
1 / 10 000 pregnancies

Methods

- ✓ **Pubmed review : « HHT and Pregnancy »**
Access May 23 2023, 67 papers
- ✓ **Our retrospective study through a phone questionnaire** *Delagrang L et al BJOG. 2023;130(3):303-311.*
- ✓ **My work on Birth Safety**

Q1 : Are woman with HHT at higher risk during pregnancy ?

Ref	Women (n) / Pregnancies = P (n)	Results	Maternal Death	Known diagnosis (%) / rate of patients screened for PAVM / CAVM	Obstetrics events (% of LB)	Route of delivery Vaginal D / C S
Goodman et al. 1967	40 / 32 + 80 controls 19 LB	no statistically significant difference between the 2 groups	NA	100 / - / -	Miscarriage 14,4 vs 10% Abnormal outcome 50 vs 42% Prematurity 9,4 vs 10,3% Stillbirth 3,1 vs 2,6%	
Shovlin et al. 1995	47 / 161 LB ?	Severe events = 6,8% of P PAVM shunt deterioration n=6 Cerebro vascular accident* n=3 (1 fatal ischaemic type) Fatal Pulmonary hemorrhage n=2 10/11 events in the « PAVM + » gp	3 (1,9% of P)	100 / - / -	No Significant difference In the Miscarriage rate between the « PAVM + » and « PAVM - » group	
Shovlin et al. 2008	199 / 484 LB ?	Severe events = 2,7% of P Myocardial infarction n=1 (<i>died</i>) Cerebro vascular accident n=6 (2 <i>died</i> // 2 <i>ischaemic</i> , 3 <i>haemorrhagic</i> , 1 ?) Pulmonary hemorrhage n=6 (2 <i>died</i>)	5 (1% of P)	26 / - / -		
Wain et al. 2012	226 / 560 457 LB	<i>Survey Response Rate 49%</i>	ND	100 / - / -	T1 Miscarriage 14,3 % Preeclampsia 0,6% PPH 6,2% Prematurity 13,8% LBW 10,7%	73,5 / 20,6 %
De Gussem et al. 2014	87 / 244 185 LB	Severe events = 4,9% of P Heart failure n=1 Hemothorax n=5 (4 undiagnosed PAVMS) Transient Ischaemic attack n=2 Deep veinous thrombosis n=1 Pulmonary embolism n=1 Myocardial ischemia n=2	ND	100 / 13 / 17	Miscarriage 20 % Gestational hypertension 2,7% Preeclampsia 7% Eclampsia 0,5% Diabetes 3,2% PPH 2% Prematurity 12%	70 / 30%

		Treatment T Transfusion S Surgery E Embolisation D Drain	Date of events	Clinical presentation	Term of Delivey	Maternal outcome	Foetal outcome
Haemothorax N=10							
Texier	2018	T + S / HHT -	26 wg	Chest pain	40	Well	Live infant
Md Noh	2018	E / HHT -	20 wg	Dyspnea	20	Small bowell active hge	foetal death
Raiya	2017	D + E / HHT -	23 wg	Dyspnea Chest pain	40	Well	Live infant
Jakobi	2001	S / HHT +	26 wg	?	40	Hypoxemia PP embolisation	SGA infant
Adegboyega	1996	D / HHT -	29 wg	Dyspnea Chest pain	40	Discharged no sequelae	Live infant
Freixinet	1995	D + S / HHT ?	27 wg	Dyspnea	?	Severe mitral regurgitation	Live infant
Bevelaqua	1992	D + E / HHT -	26 wg	Dyspnea Chest pain	40	diagnosed 6 wk	Live infant
Laroche	1992	D + S / HHT +	29 wg	Dyspnea Chest pain	37	postembolotherapy.	Live infant
Gammon	1990	D + E / HHT -	24 wg	Dyspnea Chest pain	30	Heart failure resolved	Live infant
Waring	1990	D + E / HHT +	26 wg	Dyspnea	32	heart failure resolved.	Live infant
Hemoptysis							
Tandon	2017	reE of PAVM/HHT+	32 wg	Unconscious and hypoxia	37	Well	Live infant(VD)
Yaniv-Salem	2017	reE of PAVM/HHT+	35 wg	Massive hemoptysis	37	Well	Live infant(VD)
Severe Hypoxemia							
Sugiyama	2006	E / HHT +	-	Hypoxemia	36	Clinically improved	IUGR (CS)
Jakobi	2001	- / HHT +	25 wg	Hypoxemia IUGR	25	-	foetal death
Swinburne	1986	- / HHT +	35 wg	Dyspnea, cyanosis	35	Post partum PAVM surgery Active limited live	Live infant (CS)
Cerebral Ischemic stroke							
Swietlik	2008	Craniotom / HHT +	35 wg	Headache and dyspnea Brain abscess + PAVM	35	Post partum Hemothorax requiring re Embolisation	Live infant (CS)

	Treatment	Date of events	Clinical presentation	Term of delivery	Maternal outcome	Foetal outcome
Intracranial hemorrhage Gillard 1996 Neau 1988	CAVM surgery/HHT-	21 wg	right hemiplegia, aphasia	38,5	Post partum epilepsy Right hemiparesis	Live infant (CS)
	Brain surgery/HHT-	30 wg	right hemiplegia with aphasia violent headache and vomiting	30	Fatal (multiple CAVM, 5 hematomas)	fetal death (VD)
High output heart failure All related to x liver AVM	Diuretics /HHT-	25 wg	Dyspnea	33	At day 16 post partum complete regression of congestive signs	Live infant (CS)
	?/ HHT+	36 wg	Rest Dyspnea	36	well	Live infant (CS)
	? / HHT-	29 wg	Right sided heart failure and preterm labor		On post partum day 2 : dyspnea and lower extremity edema	? (CS°)
Berthelot 2015 Lai 2010 Goussous 2009	Diuretics / HHT+	26 wg	Weakness, dyspnea	35 (?)	At 4 months Post partum no more heart failure	Live infant
Livneh 1988 (2 cases)	Diuretics / HHT-	26 wg	Dyspnea	40	At 4 months Post partum no more heart failure	Live infant
Hepatobiliary necrosis McInroy 1998 Bauer 1995	Post partum Liver transplantation HHT+	30 wg	Abdominal pain + fever	30	Biliary necrosis, liver transplant postdelivery	Live infant
	Liver transplant HHT-	-	Abdominal pain dyspnea, Melaena	-	Liver transplant	-

	Treatment	Date of events	Clinical presentation	Term of delivery	Maternal outcome	Foetal outcome
Branch retinal artery occlusion Askim 2017	Subcutaneous Heparin + PAVM embolization / HHT -	12 wg	Sudden painless scotoma in left eye.	40 wg	Well	Live infant (VD)
Gastrointestinal bleeding Hillert 2001	Liver transplantation / HHT +	27 wg	Diffuse abdominal pain	29 wg	Well	Live infant (CS)

When we deal with maternal or neonatal mortality or morbidity :

We need to differentiate :

- ❖ **Definitely avoidable cases (72% of neurological damage ++)**
- ❖ **Unavoidable cases where medicine could not help**
- ❖ **The cases in between**



Available online at www.sciencedirect.com

ScienceDirect

European Journal of Obstetrics & Gynecology and
Reproductive Biology 134 (2007) 29–36



Is neonatal neurological damage in the delivery room avoidable?
Experience of 33 levels I and II maternity units
of a French perinatal network

O. Dupuis^{a,*}, C. Dupont^b, P. Gaucherand^a, R.-C. Rudigoz^c,
M.P. Fernandez^d, E. Peigne^e, J.M. Labaune^f

^a Cellule des Transferts Périnataux de la Région Rhône-Alpes, Hôpital Edouard Herriot,
Hospices Civils de Lyon, Place d'Arsonval, 69008 Lyon, France

^b Département d'Information Médicale, Hospices Civils de Lyon, 62 Avenue Lacassagne, 69003 Lyon, France

^c Service de Gynécologie-Obstétrique, Hôpital de la Croix Rousse, Hospices Civils de Lyon,
103 Grande rue de la Croix Rousse, 69317 Lyon Cedex 04, France

Q2 : During pregnancy do we know that the woman has HHT ?

Reference	Rate of pregnant woman with HHT diagnosis done before their first pregnancy ?
Shovlin CL 2008 (n=111 woman)	26%
Delagrance L 2022 (n=207 woman)	29%
Andorfer KEC 2022 (n=45 woman)	11%

Shovlin CL et al BJOG 2008;115:1108

Delagrance L et al BJOG 2023;130(3):303

Andorfer KEC et al J Clin Med 2022;11(8):2178

- **71% of affected individuals show some evidence of the condition by the age of 16 years.**

Begbie ME, Shovlin CL Postgrad Med J 2003;79:18-24

- **Half the patients have cutaneous telangiectases at the age of 30 years**

Plauchu H et al, Am J Med Genet 1989;32:291

- **Epistaxis > 4 per year with no other cause , typically develop in the second decade**

We need to

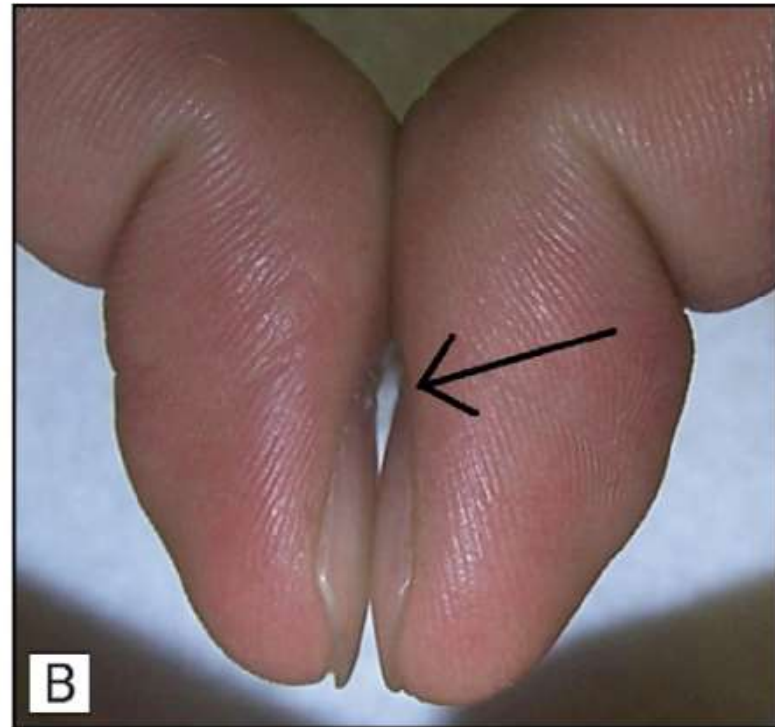


- improve medical teaching,**
- use appropriate tools,**
- increase awareness of GP to increase the rate of diagnosis in woman of childbearing age (15-45 years old)**

What is the « Shamroth » sign ?
(ie the « diamond shaped gap » sign)



Clubbing = lack of diamond shaped gap



**Normally
When the nail of two fingers
are apposed there is a diamond shaped gap**

*Jean Capron, Olivier Steichen Quantification of finger clubbing
Presse Med 2008;37(10):1520-1*

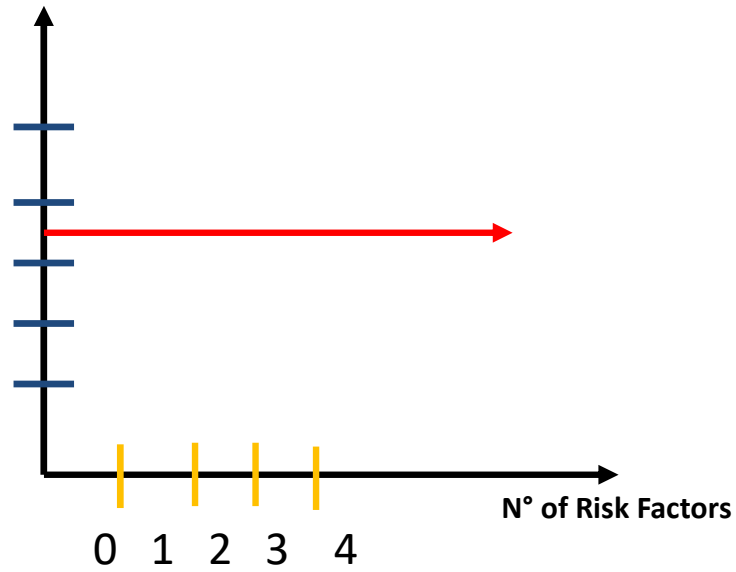
Shunt of at least 20% is required for chronic hypoxia to induce clubbing

Lomax S Can J Anesth J 2009;56:374

**Q 3 : « HIGH RISK
PREGNANCIES »**

What does that mean ?

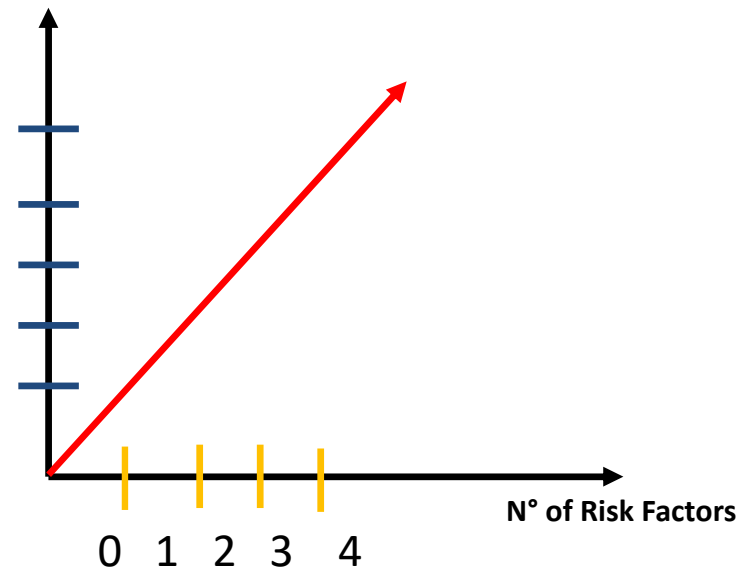
Number of US exams performed during pregnancy



« Middle Ages »
« Therapeutic Obstetrics »



Number of US exams performed during pregnancy



« Modern Medicine »
« Prevention Obstetrics »

**Q 4 : Is hemorrhage from spinal AVM
a problem during delivery of
pregnant woman with HHT?**

Red arrows show dilated draining veins



Kamimura Y et al JA Clinical Reports 2021;7(1):19

Japan – Nagoya - 27-year-old woman 30th WG, second pregnancy, suddenly felt severe back pain and dyspnea - Chest CT showed a ruptured pulmonary AVM (36x21mm) Embolization then referred to a tertiary perinatal center – Then diagnosed with HHT – Spinal and cerebral MRI at 32 WG : Spinal AVM from the thoracic to lumbar levels CS under general anesthesia – Healthy baby .

Référence	n° of epidural analgesia performed	n° of patients Screened for SAVM	n° of Spinal Haemorrhage	Rate of Régional anesthesia
Shovlin CL 2008	NA	NA 2008 <<100% since 2008 for NHS>>	0	NA
Gussem EM 2014	92	0	0	50% (92/185)
Delagrange L 2022	139	27	0	31% (139/452)
	231	27	0	-

Shovlin CL et al BJOG 2008;115:1108

Gussem EM Obstet Gynecol 2014;0:1-7

Delagrange L et al BJOG 2023;130(3):303

- Rate of Spinal AVM are < 0,5%
- No cases of Spinal Haemorrhage following epidural analgesia in HHT patients
- Spinal AVM are located in the SUB ARACHNOIDAL SPACE

During epidural analgesia the needle does not enter the SUB ARACHNOIDAL SPACE

- **Screening for Spinal AVM seems UNNECESSARY but . . .**

- **EPIDURAL ANALGESIA CAN BE PERFORMED**

- * ***Avoid blind intubation techniques to avoid oro-pharyngeal trauma that may occur with laryngoscopy and endo tracheal tube manipulation during general anesthesia***

Plosker H et al Mt Sinai J Med 1984;51:610-3

Q 5 : Are complications of pulmonary AVM a problem during pregnancy of HHT pregnant woman ?

❑ **Pulmonary AVM can lead to**

❖ **Rupture**

Intra bronchial rupture lead to hemoptysis

Intra pleural rupture lead to hemothorax

8% risk in a series of 143 patients (Ference BA , Chest 1994;106:1387)

❖ **Cerebral Abscess (paradoxical emboli)**

5-17% risk

1% of HHT patient will have during their life time

❖ **Other Abscess : kidney, knee, spinal cord, arm, hip, liver, endocarditis....**

❖ **Severe Hypoxemia ...IUGR and foetal death**

❖ **Ischemic cerebral stroke, transient cerebral ischemic attack**

❖ **Ocular ischaemia**

- Rate of pulmonary AVM in HHT patients = 50%
- Reported maternal and foetal deaths and severe events :
 - Shovlin 1995 study : **91% of severe events are PAVM related**
(10/11 ; 3 maternal deaths)
 - Our study 2023 : **89% of severe events are PAVM related**
(8/9 = 2 Haemoptysis + 4 Hypoxemia + 2 cerebral stroke)
- **No respiratory symptoms in 78% of PAVMS**

Normal arterial blood gases on room air do not exclude PAVM

Despite enlarging PAVM during pregnancy **oxygen saturation may be higher than pre pregnancy levels due to the gravid uterus decreasing the blood flow to the lower lung when supine** (*Lomax S et al Can J Anesth J 2009;56:374-84*)

- **No data exist on which PAVM is most likely to rupture based on size or location**

Rupture is described **as soon as 19 WG** (*Ference BA et al Chest 1994;106:1387-90*)

29% of Hemothorax associated with PAVM have occurred **during pregnancy**
(*Ference BA et al Chest 1994;106:1387-90*)

Screen woman (15-45 years old) with HHT even if asymptomatic before pregnancy for PAVMs

Chest CT with 3 mm cuts

Cottin V et al Medicine 2007;86(1)

TransThoracic Contrast Echocardiography (TTCE)

Diagnostic sensitivity up to 97%

Negative Predictive Value of 99%

Parra JA Eur Resp J 2010;35:1279

Q 6 : In HHT pregnant woman is it safe to perform a pulmonary embolization ?

From 16 WG – Term

Performed by an expert team*

Estimated foetal dose of radiation is <50 to 220 mrad

Time of fluoroscopy 20 to 49 mn

Maximum recommended exposure for pregnant worker is 500 mrad

**Gherson AS Chest 2001;119:470*

7 cases at Yale University and Toronto

embolization was 100% successful

all delivered vaginally at term of healthy babies

Q 7 : Are Hepatic AVM dangerous during pregnancy ?

- Rate of hepatic AVM in HHT patients = 30%
- Reported severe events :
 - Shovlin 1995 study : **0% of severe events are HAVM related**
 - Our study 2023 : **11% of severe events are HAVM related**
(1/9 = Hepato biliary necrosis requiring liver transplant , unknown HHT)
- **95% of HAVMS are asymptomatic** (*Mc Donald J Gene Reviews 2012*)

Screen asymptomatic woman with Doppler Liver Ultrasonography before pregnancy

Measure the Hepatic artery diameter and use the E Buscarini grading system

(*Buscarini E Ultraschall in Med 2004;25:1-9*)

Grade 1 and 2 : periodic liver doppler US

Grade 3 and 4 : avoid pregnancy ...

evaluate cardiac function and
pulmonary pressure

Q 8 : Are Cerebral AVM dangerous during pregnancy ?

➤ Rate of cerebral AVM in HHT patients = 10%

➤ Reported severe events :

Our study 2023 : **207 woman 562 pregnancies zero cerebral haemorrhage**

➤ **3,5% risk of primary haemorrhage from a CAVM of any etiology during pregnancy did not differ from the annual bleeding rate of non gravid woman**

Retrospective analysis of 451 woman

Horton JC et al Neurosurgery 1990;27:867-71

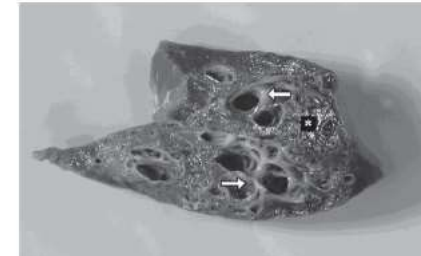
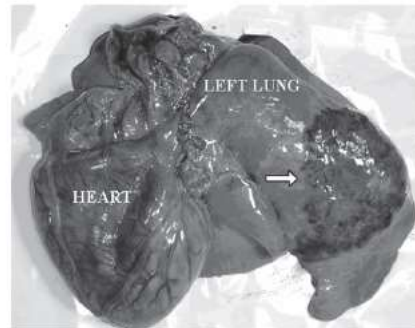
Robinson JL J Neurosurg 1974;41:63-70

**During delivery of every HHT woman
Avoid prolonged second stage
Avoid Valsalva manoeuvres**

Q 9 : During pregnancy which clinician should perform foetal ultrasonography ?

- 6 cases of foetal PAVM diagnosed during pregnancy (n=1) or during the first week of life in HHT patients (n=5)
- 2 neonate died / 4 survived
- **The 2 neonate who died were not diagnosed prenatally +++**
- 30 year old - 39WG – HHT Known PAVM – T3 US « normal »
FHR abnormalities – Emergency CS – Umbilical cord pH 7.05 and 7.20
Autopsy large PAVM and cardiomegaly

*(J Matern Fetal Neonat Med
2012;25(8):1494)*



**During pregnancy of HHT patients
perform foetal ultrasonography
at an expert US center**

In Obstetrics :

➤ Make unseen anatomy visible

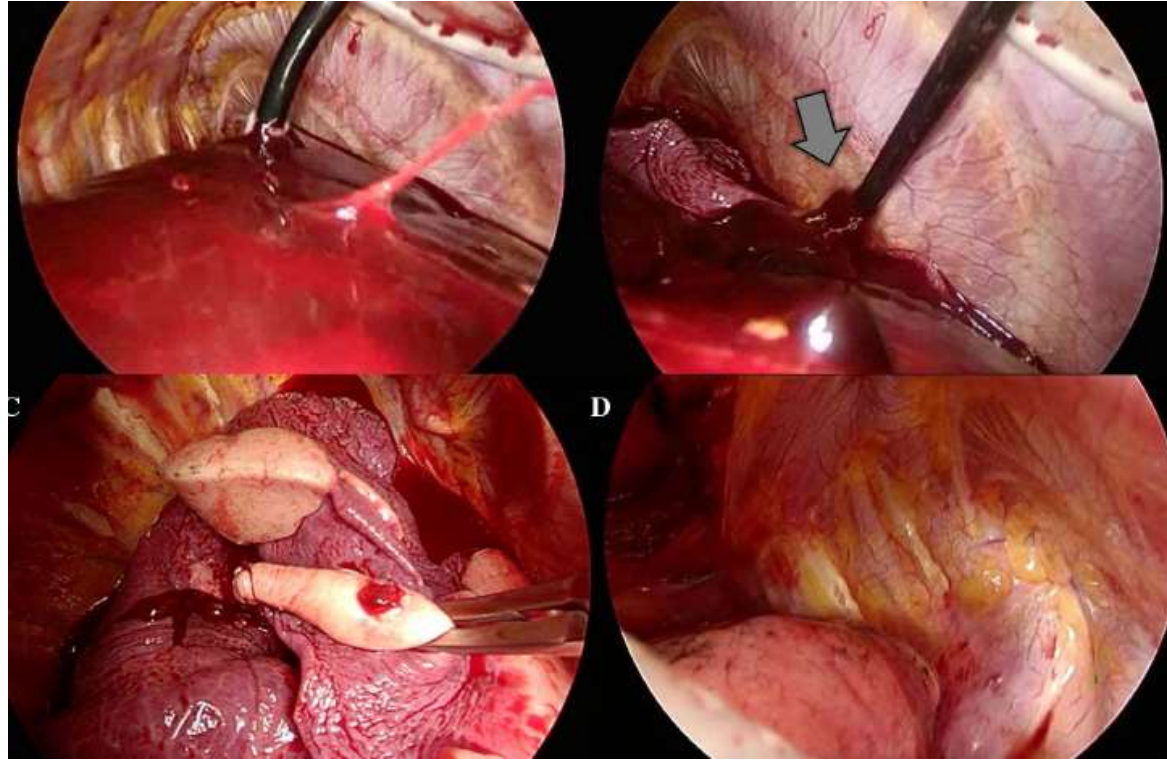
- Screening for PAVM with TTCE or CT scan and screening for hepatic AVM before pregnancy*
- In case of symptoms suggestive of brains AVM performed unenhanced Brain MRI during T2*

➤ In case of red-flag symptoms :

- In Utero transfer in hospitals with surgery units (thoracic ++)
transfusion facility
24:7 ObGyn and Anesthesiologists*

➤ In case of untreated PAVM or Brain VM or unscreened patients

- Follow up in tertiary centers by high-risk team with HHT expertise*



Jun Naito et al GenThorac and Cardiovasc Surg 2020; 68(12): 1528-31

Japan – Chiba city – Undiagnosed HHT - 34-year-old woman 28th WG, first pregnancy, suddenly felt right chest pain - Non contrasted Chest CT - Exploratory Thoracoscopy – Emergency Thoracotomy - Total blood loss 5120 gr – CS at 38th week – Healthy baby .

➤ **Improve communication skills**

- *Between MDs, Nurses, MWs, Patients*
- *Implement therapeutic workshops and give training on Red-flag symptoms...(sudden chest pain, severe dyspnea, hemoptysis, severe headaches, neurological signs)*

➤ **Let's improve our ability for change and innovation**

- *Multigene panel testing in case of severe epistaxis in woman of child bearing age and normal coagulation test ..
(ENG, ACVRL1, SMAD4 / GDF2 / RASA1, EPHB4)*

➤ **Be aware of the patient soul ...**

- *Involve the psychologist*

When a woman delivers her first baby which change does she feel ?

She was a **woman**she become a **Mother**

She had a **husband**he become a **Father**

**In every pregnancy the first delivery Induce an « Identity Switch »
that recall the Family History**

This can lead to a psychic storm

This is of course boosted in case of genetic disease with a **50% risk of inheriting
the condition.**

Can induce a major stress leading to depression / suicide / even neonatal crime



**Involve the psychologist during
the second trimester and after**

Conclusion

- **Lack of Information on symptoms of HHT for MD**
- **Lack of HHT diagnosis in woman of child bearing age ...**
- **Lack of Pulmonary AVM screening before pregnancy**
- **HHT pregnancies are High Risk Pregnancies they need
a reinforced follow up
from a maternal as well as
from a foetal point of view**

✓ Before Pregnancy

- Diagnose HHT
- Screen HHT patients for
PAVM + + + and treat PAVM + + +

Hepatic AVM
- Informed of the High Risk Situation
- Arrange a follow up by an Obstetrician
- Teach the red-flag symptoms
- In case of red-flag symptoms In Utero Transfer in an Hospital with
a surgery unit
a transfusion facility
an on call on site Obgyn and Anesthesiologists

✓ During Pregnancy

- In patients with Pulmonary AVM **Monitor SaO₂**
- In patients with Hepatic AVM **Monitor the Cardiac output with cardiac US**
- In case of **Ischaemic Cerebral or ocular Stroke** look for paradoxical embolization and perform Cardiac US and PAVMS screening (Chest CT Scan)
- In case of bleeding of PAVM perform **pulmonary embolization** to allow the pregnancy to continue for weeks or months
- In case of dental procedures **use prophylactic antibiotics** to avoid infections (brain abscess, endophthalmitis.....)
- Involve the **anesthesiologist** during the second trimester
- Involve the **psychologist** during second trimester

✓ **During Delivery**

- **Antibiotic prophylaxis in case of PAVM (TTCE+) or if not screened for PAVM (amoxicillin + clavulanic acid or clindamycin)**
- **No prolonged second stage, after 20 mins forceps delivery**
- **Avoid Valsava maneuver (would increase venous pressure)**
- **If General anaesthesia is required avoid PEEP and use small tidal volume**

Follow the 2020 Clinical Guideline

Annals of Internal Medicine

CLINICAL GUIDELINE

Second International Guidelines for the Diagnosis and Management of Hereditary Hemorrhagic Telangiectasia

Marie E. Faughnan, MD, MSc; Johannes J. Mager, MD, PhD; Steven W. Hetts, MD; Valerie A. Palda, MD, MSc; Kelly Lang-Robertson; Elisabetta Buscarini, MD; Erik Deslandres, MD; Raj S. Kasthuri, MD; Andrea Lausman, MD; David Poetker, MD, MA; Felix Ratjen, MD; Mark S. Chesnutt, MD; Marianne Clancy, RDH, MPA; Kevin J. Whitehead, MD; Hanny Al-Samkari, MD; Murali Chakinala, MD; Miles Conrad, MD; Daniel Cortes, BscPhm; Claudia Crocione; Jama Darling, MD; Els de Gussem, MD; Carol Derksen; Sophie Dupuis-Girod, MD, PhD; Patrick Foy, MD; Urban Geisthoff, MD; James R. Gossage, MD; Adrienne Hammill, MD; Ketil Heimdal, MD; Katharine Henderson, MS, CGC; Vivek N. Iyer, MD, MPH; Anette D. Kjeldsen, MD; Masaki Komiyama, MD; Kevin Korenblatt, MD; Jamie McDonald, MS, CGC; Jack McMahon; Justin McWilliams, MD; Mary E. Meek, MD; Meir Mei-Zahav, MD; Scott Olitsky, MD, MBA; Sara Palmer, PhD; Rose Pantalone, RN; Jay F. Piccirillo, MD; Beth Plahn, RN, MHA; Mary E.M. Porteous, MD; Marco C. Post, MD, PhD; Ivan Radovanovic, MD; Paul J. Rochon, MD; Josanna Rodriguez-Lopez, MD; Carlo Sabba, MD; Marcelo Serra, MD; Claire Shovlin, PhD, MA; Dennis Sprecher, MD; Andrew J. White, MD; Ingrid Winship, MBChB, MD; and Roberto Zarrabeitia, MD



**Thank you for your
Attention**



olivier.dupuis@chu-lyon.fr