ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

Université Paris Cité

Contraception, Fertility in Men and Women with Rare and Vascular Liver Diseases

Pierre-Emmanuel RAUTOU

Inserm U1149, Centre de recherche sur l'inflammation, Paris

Service d'hépatologie, Hôpital Beaujon, Clichy, France

pierre-emmanuel.rautou@inserm.fr

MVF CENTRE DE RÉFÉRENCE MALADIES VASCULAIRES DU FOIE

Instituts thématiques Inserm Institut national de la santé et de la recherche médicale

CRI CENTRE de RECHERCHE sur l'INFLAMMATION

Fertility and contraception in rare liver diseases

- Fertility
- Medically assisted reproduction
- Contraception

Fertility in rare liver diseases

	Fertility
Portal vein thrombosis	No data
PSVD	No data
Budd-Chiari	

Fertility in Budd-Chiari syndrome

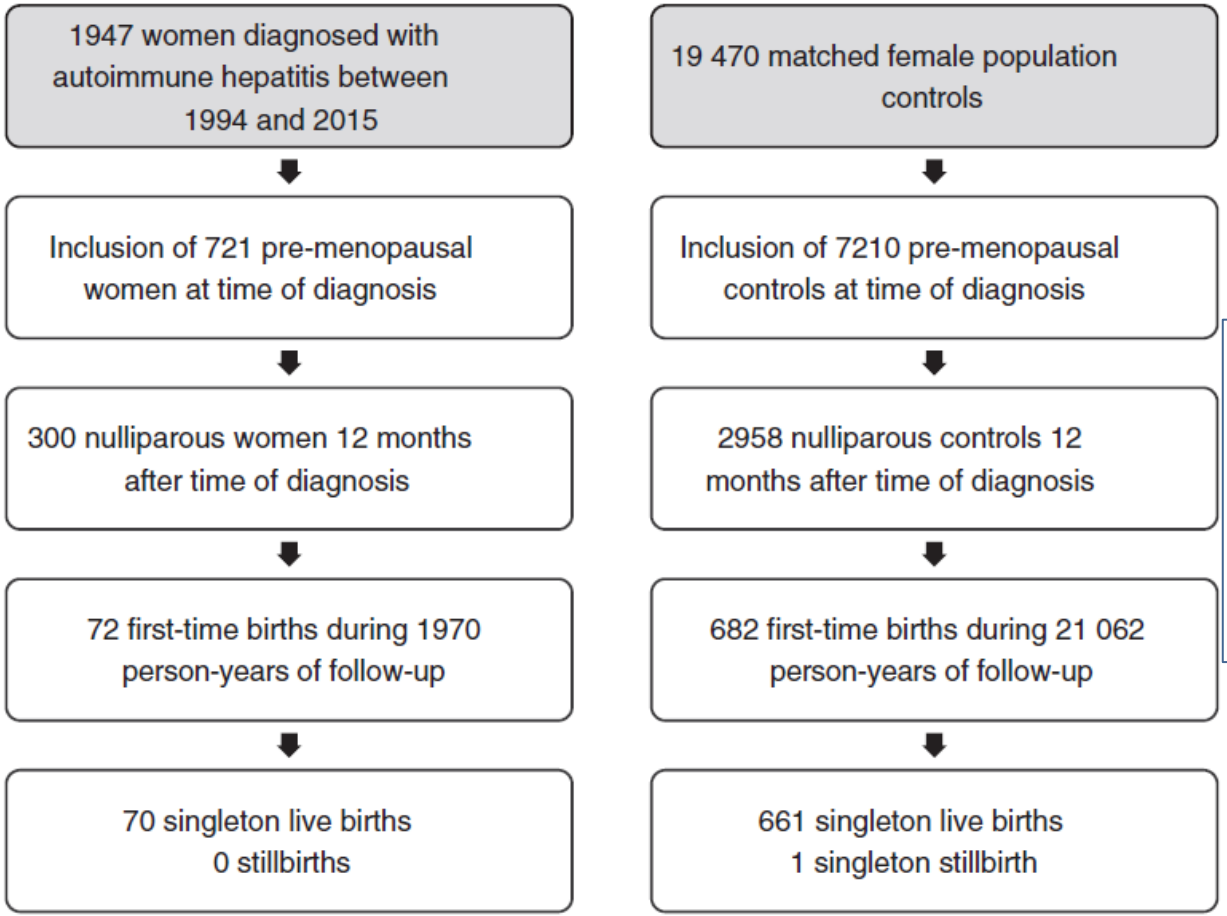
	Impaired before treatment	Impaired in the general population
Women: infertility	25 %	6 %
Men -erectile dysfunction -hypogonadism	 31 % 50 %	 15-30 % 2-13 %

Shukla, et al. Liver Int 2018; Ramani et al., Hepatol Int 2022
Biswas, *et al.* Indian J Gastroenterol 2023, Mukund, *et al.* J Clin Exp Hepatol 2024

Fertility in rare liver diseases

	Fertility
Portal vein thrombosis	No data
PSVD	No data
Budd-Chiari	Impaired
Autoimmune hepatitis	
PSC	
PBC	

Fertility in autoimmune hepatitis: unaffected



Danish healthcare registries

- **Miscarriage:**
  OR 1.17 (95% CI 0.8-1.7)
- **First-time birth rate:**
  37 *vs.* 32 /1000 pers.yr (ns)

Grønbaek, *et al.* APT 2018

Fertility in PSC: unaffected

	PSC (N= 229)	Healthy controls (N= 569)	P=
Women	38%	41%	n.s.
With Children	53%	53%	n.s.

- The population-based recruitment of patients and controls
- Risk factor for miscarriage: active inflammatory bowel disease

Wellge *et al.* Gut 2011 ; Zakharia, *et al.* Liver International 2017

Fertility in PBC: unaffected

	PBC (N= 186)	Aged matched controls (N= 367)	P=
Age when pregnant	29.5 yrs	28.9 yrs	n.s.
Number of pregnancies	2.7	1.9	<0.05
Miscarriages	17 %	22 %	n.s.
Voluntary interruptions of pregnancy	2.2 %	2.3 %	n.s.

Boonstra, *et al.* Liver International 2014; Floreani, *et al.* Clinic Rev Allerg Immunol 2015; Poupon, *et al.* J Hepatol. 2005; Zakharia, *et al.* Liver International 2017

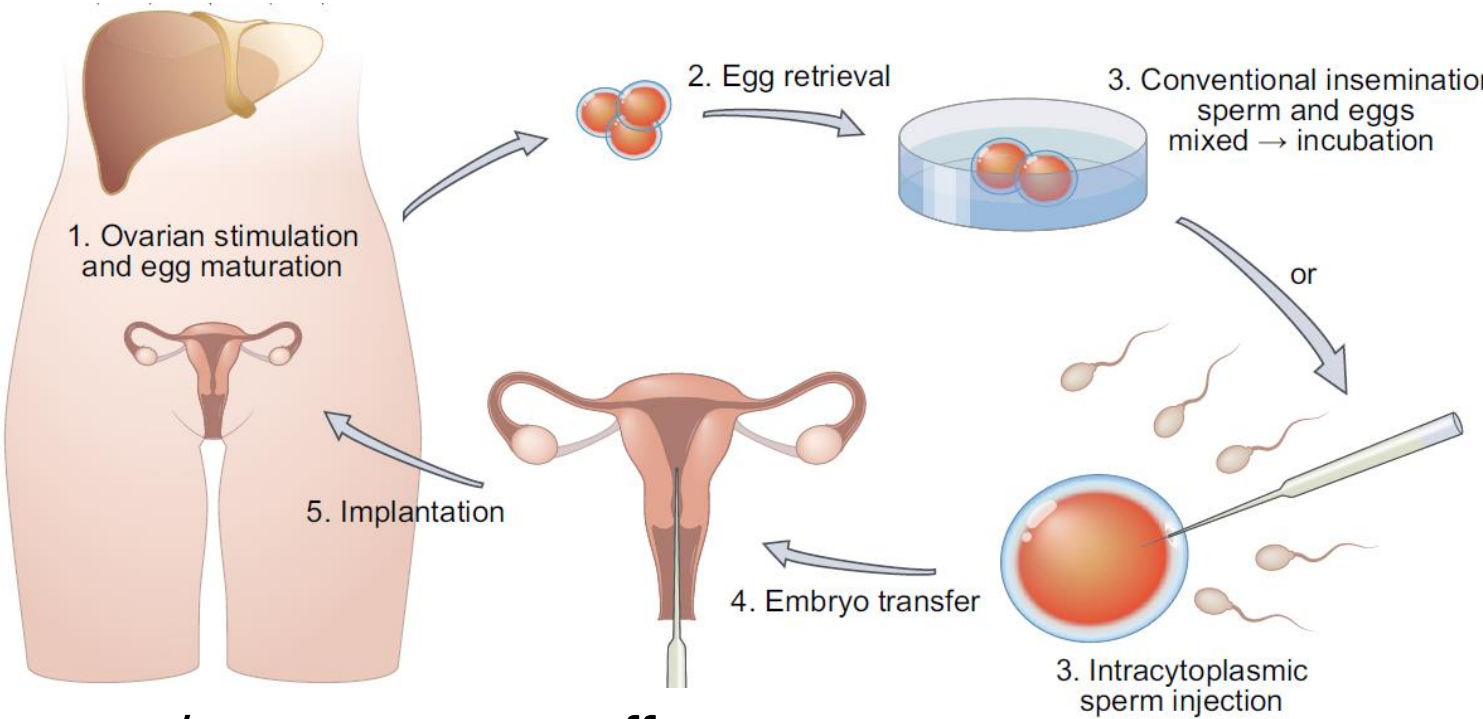
Fertility in rare liver diseases

	Fertility
Portal vein thrombosis	No data
PSVD	No data
Budd-Chiari	Impaired
Autoimmune hepatitis	Unaffected
PSC	Unaffected
PBC	Unaffected

Fertility and contraception in rare liver diseases

- Fertility
- Medically assisted reproduction
- Contraception

Medically assisted reproduction in liver diseases



- Direct oestrogen/progesterone effects
- Hypercoagulability
- Invasive procedure

Rahim J, *et al.* Hepatol 2021

Medically assisted reproduction in chronic liver diseases

- **42 women, median age 33:**
  - No cirrhosis n=25
  - Cirrhosis n=6
  - Post LT n=11

  } 15 cholestatic / autoimmune

- **57 in vitro fertilization** cycles

- **Liver outcome:**
  - ↑ liver enzyme: 16%; all improved within 1 month
  - 1/6 cirrhosis decompensation

Rahim J, *et al.* Hepatol 2021

Medically assisted reproduction in chronic liver diseases

- **Success of similar to general population**
  - Pregnancy: 75% of cycles
  - Live birth occurring: 56% of cycles

- **Complications:**
  - Ovarian hyperstimulation syndrome: 3/42 (7%)
  - Hypertensive complications: 3/42 (7%)
  - Intrahepatic cholestasis of pregnancy: 6/42 (14%)
  - Premature: 16/32 (50%)

Rahim J, *et al.* Hepatol 2021

Medically assisted reproduction in VLD

- **10 women, median age 33:**
  - PSVD n=5; cavernoma n=5
  - Risk factor for thrombosis, n=7
  - Duration since VLD diagnosis: 9 years
  - High risk varices: 46%
  - Serum bilirubin: 14 µmol/L (8 - 40)
  - Anticoagulation: n=6

Payancé, et al. In preparation

Medically assisted reproduction (MAR) in VLD

- **Success:** 8 pregnancies / 13 attempts
- **Complications during MAR and pregnancy:**

Maternal complications	During MAR	During pregnancy
Liver related	0	0
Non liver related	1 intraperitoneal bleeding	0

Payancé, *et al.* In preparation

Medically assisted reproduction (MAR) in VLD

Outcome of the 8 pregnancies:

Miscarriage

Preterm
(32 to 34 gestation weeks)

Term

No thrombosis
No decompensation
No death

Payancé, *et al.* In preparation

Medically assisted reproduction (MAR) in VLD

Outcome of the 8 pregnancies:

Miscarriage

Preterm
(32 to 34 gestation weeks)

Term

- 1 gut malformation
- 1 with ulcero-necrotizing enterocolitis

Payancé, *et al.* In preparation

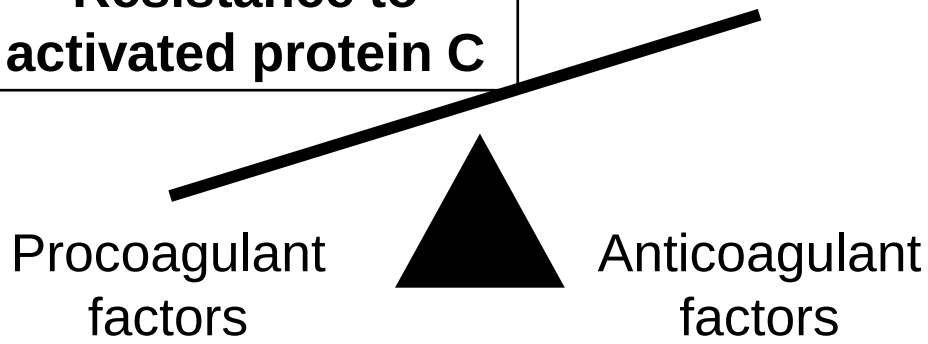
Fertility and contraception in rare liver diseases

- Fertility
- Medically assisted reproduction
- Contraception

Oral contraception and venous thromboembolism

↑ Fibrinogen ↑ Factors II, VII, VIII and X
↓ Protein S Resistance to activated protein C

↓ Factor V
↑ Fibrinolysis



- Risk ratio oestro+Prog ≈ 2
- ↓ with:
  - ✓ dose of oestrogen
  - ✓ duration

Lidegaard BMJ 2009; Dragoman, et al Intl J Gynecology Obste 2018

Is oral contraception a risk factor for vascular liver diseases?

Budd-Chiari	
Portal vein thrombosis	
PSVD	

Is oral contraception a risk factor for Budd-Chiari syndrome?

	In the 70^{ies} and 80^{ies}	In the 90^{ies}
Type of pills	1st and 2nd generation	Likely 2nd and 3rd generation
Odds Ratio (95% CI)	2.4 (1.05-5. 4)	2.4 (0.9-6.2)
Reference	Valla, Gastroenterology 1986	Janssen, Blood 2000

Yes

(likely, and other risk factors frequently associated)

Oral contraception: risk factor for PVT?

- Prevalence of oral contraception varies:

Reference	Prevalence among child-bearing aged women
Janssen, Blood 2000	48%
Mohanty, Hepatology 2001	0%
Plessier, Hepatology 2009	44%
Wiegers, BJOG 2022	30%

- One case-control study:

  odds ratio 1.5 (95% CI 0.6-3.4)

Is oral contraception a risk factor for rare liver diseases?

Budd-Chiari	**Yes (likely)**
Portal vein thrombosis	Unclear
PSVD	Not assessed
Autoimmune hepatitis	
PSC	
PBC	

Oral contraception more common in AIH

	Controls (N= 563)	AIH (N= 358)	P=
Ever oral contraceptives	74%	83%	0.006
Age OC start	21 yrs	19 yrs	< 0.001

- Prospective collection of questionnaires at Mayo clinic
- Controls: annual visits for preventive medical examination

Lammert, *et al.* Liver International 2021

Oral contraception does not favor PSC

	Controls (N= 73)	PSC (N= 69)	P=
Ever oral contraceptives (OC)	85%	51%	< 0.001
Duration of OC	9	8	ns

- Prospective collection of questionnaires in Norway
- Controls: Bone Marrow Donor Registry

Andersen, *et al.* Clinical Gastroenterology and Hepatology 2014

Oral contraception does not favor PBC

	Controls (N= 430)	PBC (N= 197)	P=
Ever oral contraceptives (OC)	66%	56%	0.02

- Controls: randomly selected in the general population and matched for age, gender, and residential location

Corpechot, *et al.* J Hepatol 2010

Is oral contraception a risk factor for rare liver diseases?

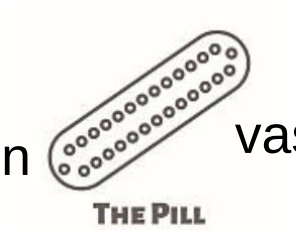
Budd-Chiari	**Yes (likely)**
Portal vein thrombosis	Unclear
PSVD	Not assessed
Autoimmune hepatitis	Maybe
PSC	No (protective)
PBC	No (protective)

Contraception: what modality in VLD

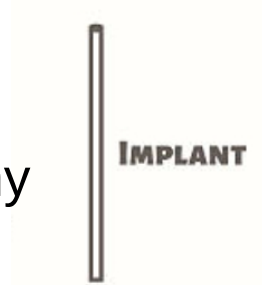
Pearl Index*

natural methods

Tubal occlusion



vasectomy



Less effective → More effective

15	6	1 to 9	2	0.2 – 0.6	0.5	0.3	0.05	0.1

* = mesures the number of pregnancies that occur for each contraceptive method if used by 100 women for one year **of perfect use**

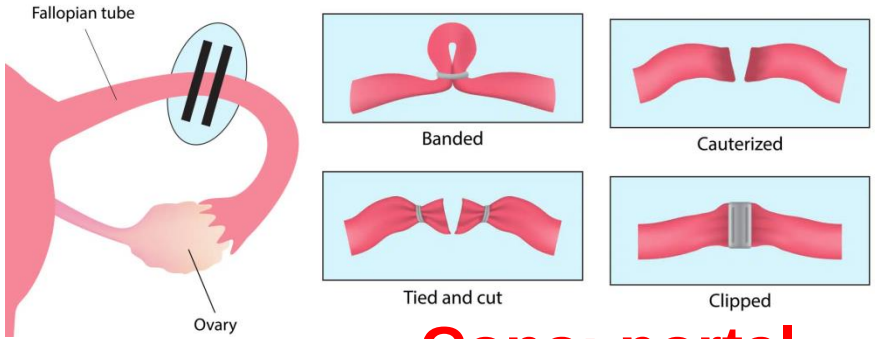
Contraception: what modality in VLD

(micro)**progestatif:**
desogestrel
levonorgestrel
Cons: compliance

Intrauterine device
levonorgestrel > copper

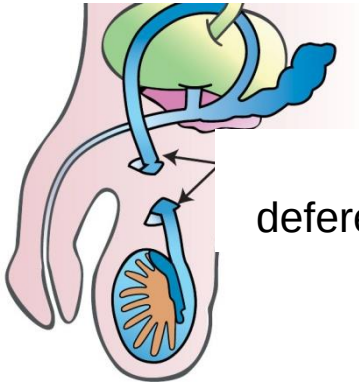
Implant
Cons: anticoagulant thrombopenia

Bilateral tubal occlusion



Cons: portal hypertension !

Partner surgery: vasectomy



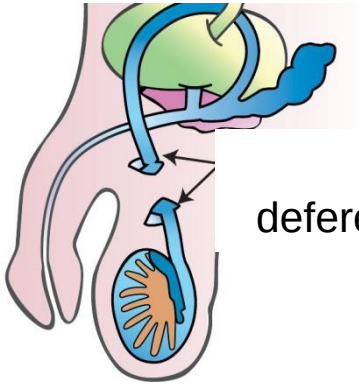
Vas deferens occlusion

Contraception: what modality in VLD

(micro)**progestatif:**
desogestrel
levonorgestrel
Cons: compliance

Intrauterine device
levonorgestrel > copper

Partner surgery: vasectomy



Vas deferens occlusion

Fertility and contraception in rare liver diseases: conclusion

- **Fertility:**
  - ✓ Impaired in Budd-Chiari
  - ✓ Unknown in PVT and PSVD
  - ✓ Unaffected in AIH, PBC, PSC
- **Medically assisted reproduction:** possible
- **Contraception:**
  - ✓ (micro)progestatif, intrauterine device, vasectomy

Networks for vascular liver diseases

European Reference Network | Hepatological Diseases (ERN RARE-LIVER)

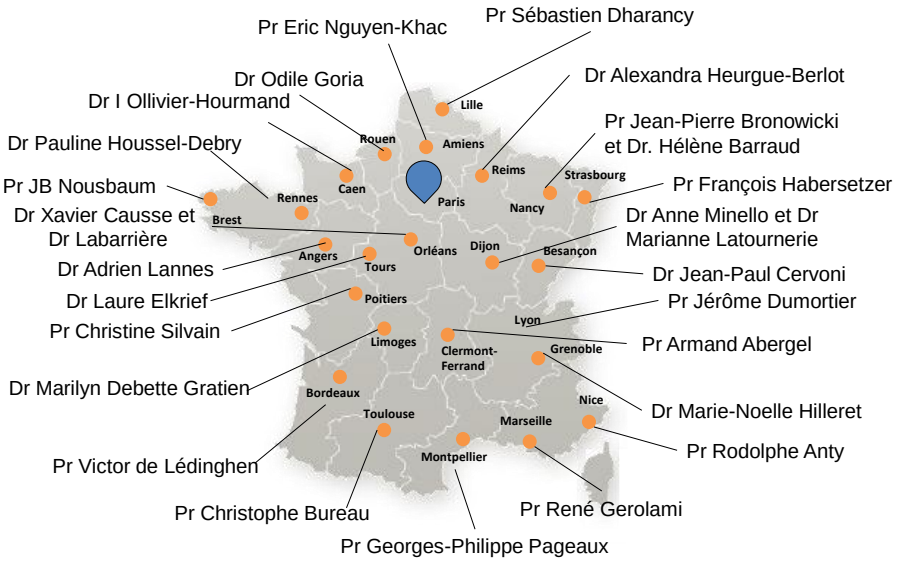
VALDIG

VASCULAR LIVER DISEASE GROUP

French network for vascular liver diseases

MVF

CENTRE DE RÉFÉRENCE MALADIES VASCULAIRES DU FOIE



Instituts thématiques

Inserm
Institut national
de la santé et de la recherche médicale

Université Paris Cité

CRI
CENTRE de RECHERCHE sur l'INFLAMMATION

Hepatology unit, Beaujon Hospital
Reference center for vascular liver diseases

Inserm U1149 www.rautoulab.com/
Team "*vessels in liver diseases*"

anr agence nationale de la recherche

EF Clif
EUROPEAN FOUNDATION FOR THE STUDY OF CHRONIC LIVER FAILURE

Get these slides there:

France 2030 Lauréat

AFEF

Association des Malades des Vaisseaux du Foie AMVF

Société Nationale Française de Gastro-Entérologie SNFGE

FONDATION ARC POUR LA RECHERCHE SUR LE CANCER

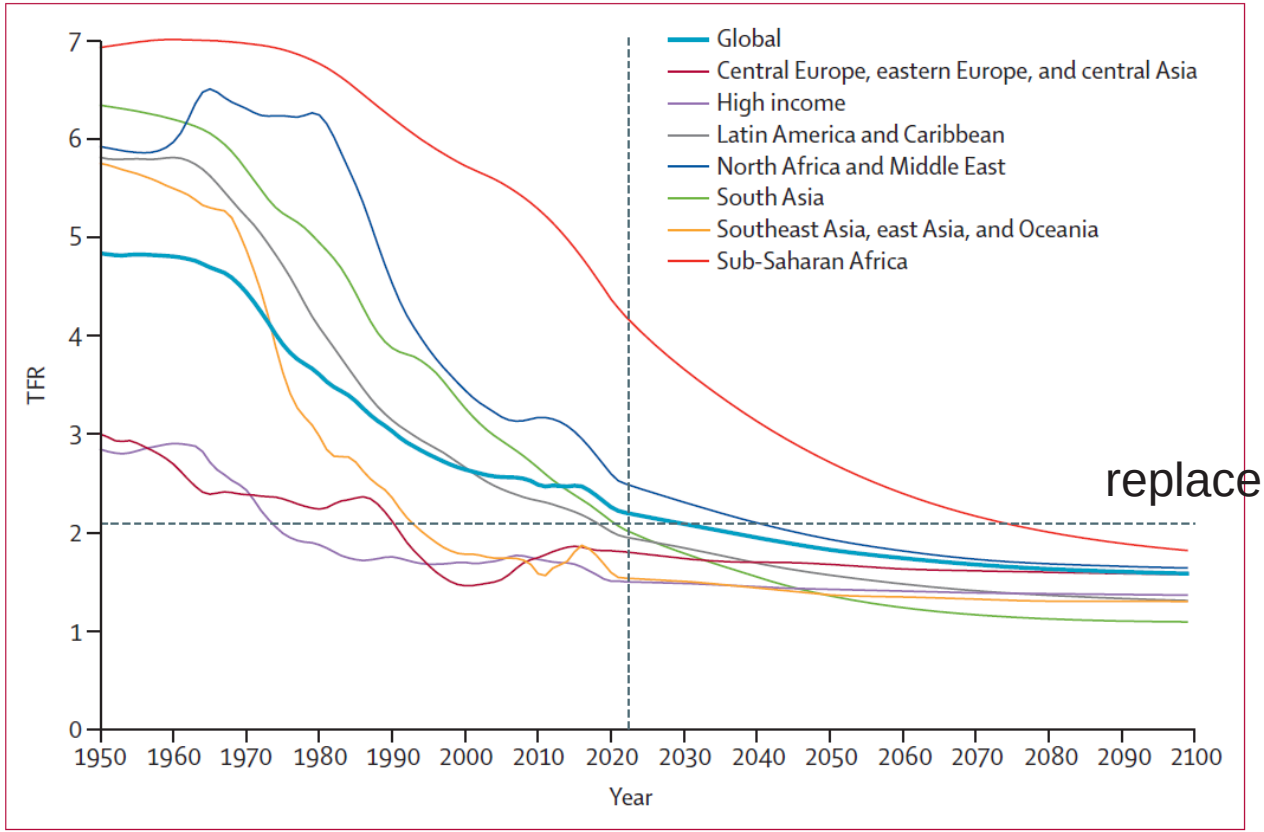
FRM FONDATION RECHERCHE MÉDICALE

HORIZON 2020

Les Programmes Hospitaliers de Recherche Clinique (PHRC)

Fertility in rare liver diseases

Total fertility rate



replacement fertility rate

Lancet 2024