



SARCOMA/GIST AND FERTILITY

Christine Rousset-Jablonski

Medical Gynecologist

Léon Bérard Cancer Center, Lyon



SPAEN conference, Milan 2018

Fertility/ Pregnancy after cancer

A major concern for patients surviving a cancer

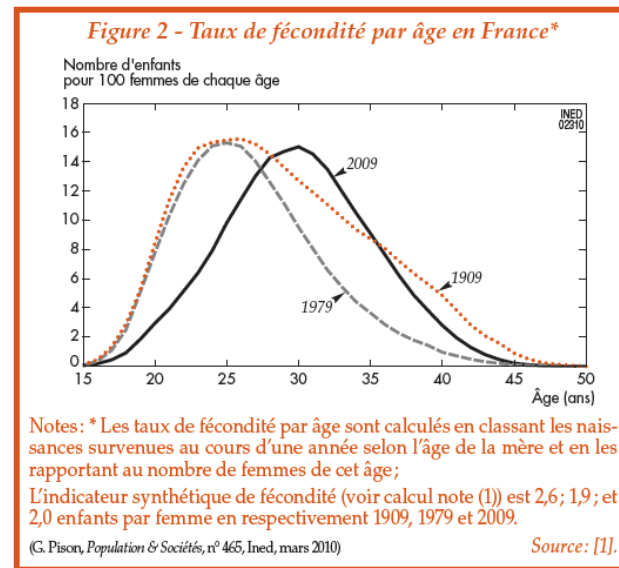
Improvement in treatments → quality of life

Major concern for patients surviving a cancer
« could impact the therapeutic choices »

Howard-Anderson, JNCI 2012, Partridge JCO 2004

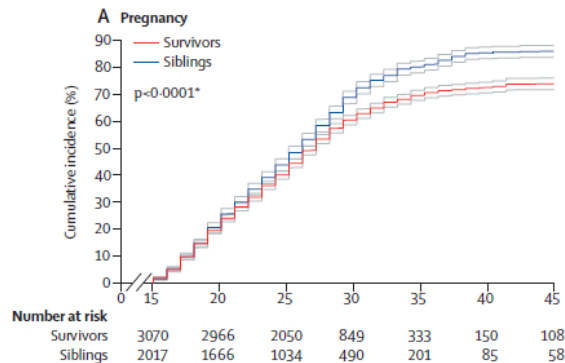
Who is concerned ?

- Survivors of childhood cancer
- Adolescents and Young Adults treated for cancer



Mean age at delivery : 30 years

Reduced likelihood of pregnancy among survivals of childhood cancer



Chow EJ, Lancet Oncol 2016

10938 survivals / 3949 siblings

Mean follow up : 8 years

38% attempted pregnancy– 83% achieved
(siblings : 62% attempted – 90% achieved)

Reduced likelihood of pregnancy

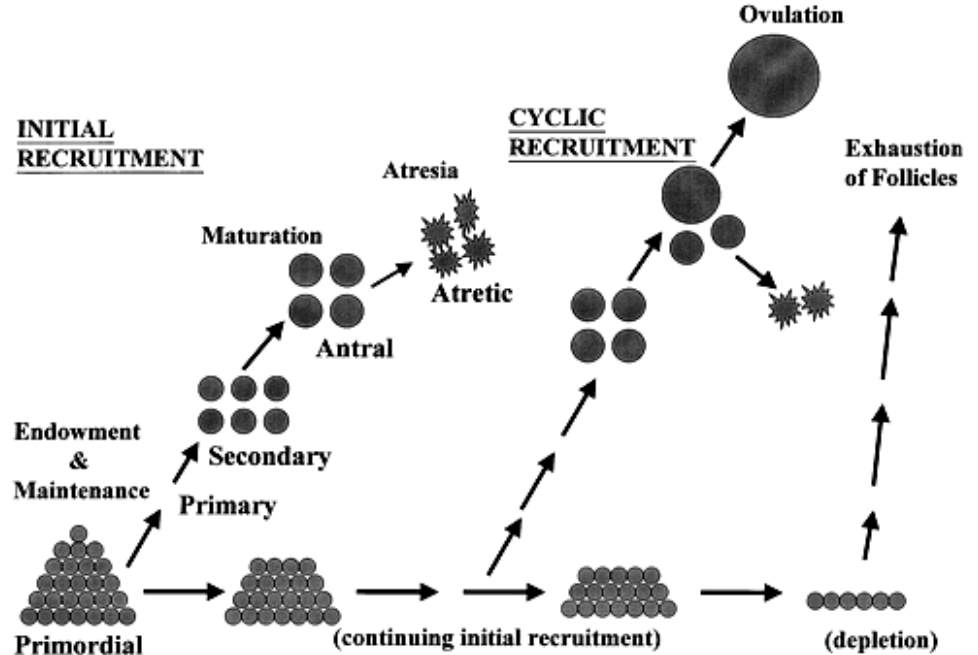
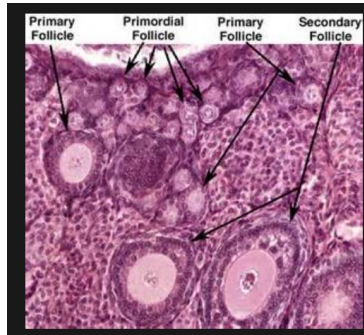
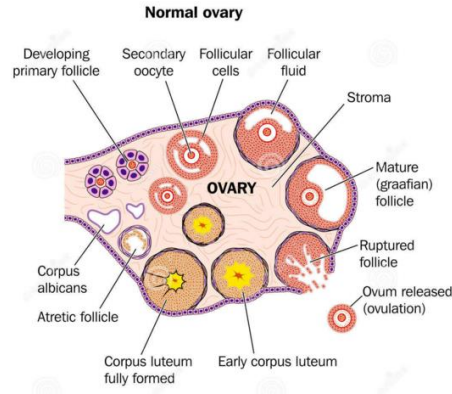
Upper doses of alkylating agents

Pelvic / TB Irradiation

Sarcoma / GIST and fertility

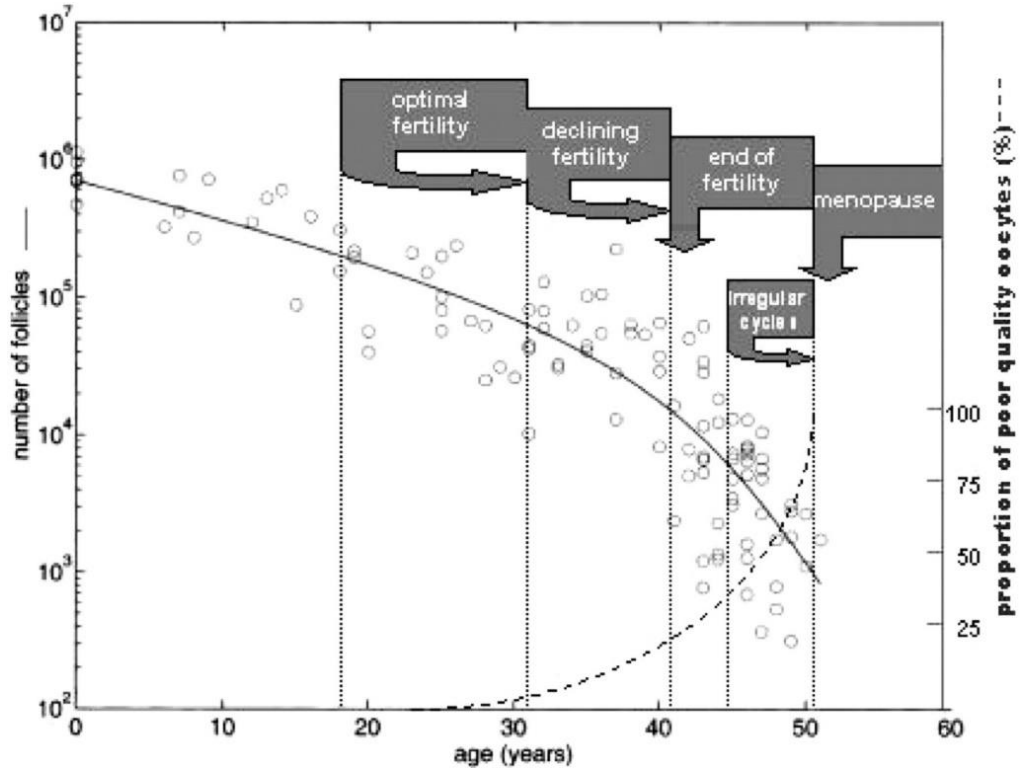
- Impact of treatments on fertility (female / male)
- Fertility preservation strategies
- How to decide ? Different diseases / different situations
- Fertility preservation organization

OVARIAN RESERVE

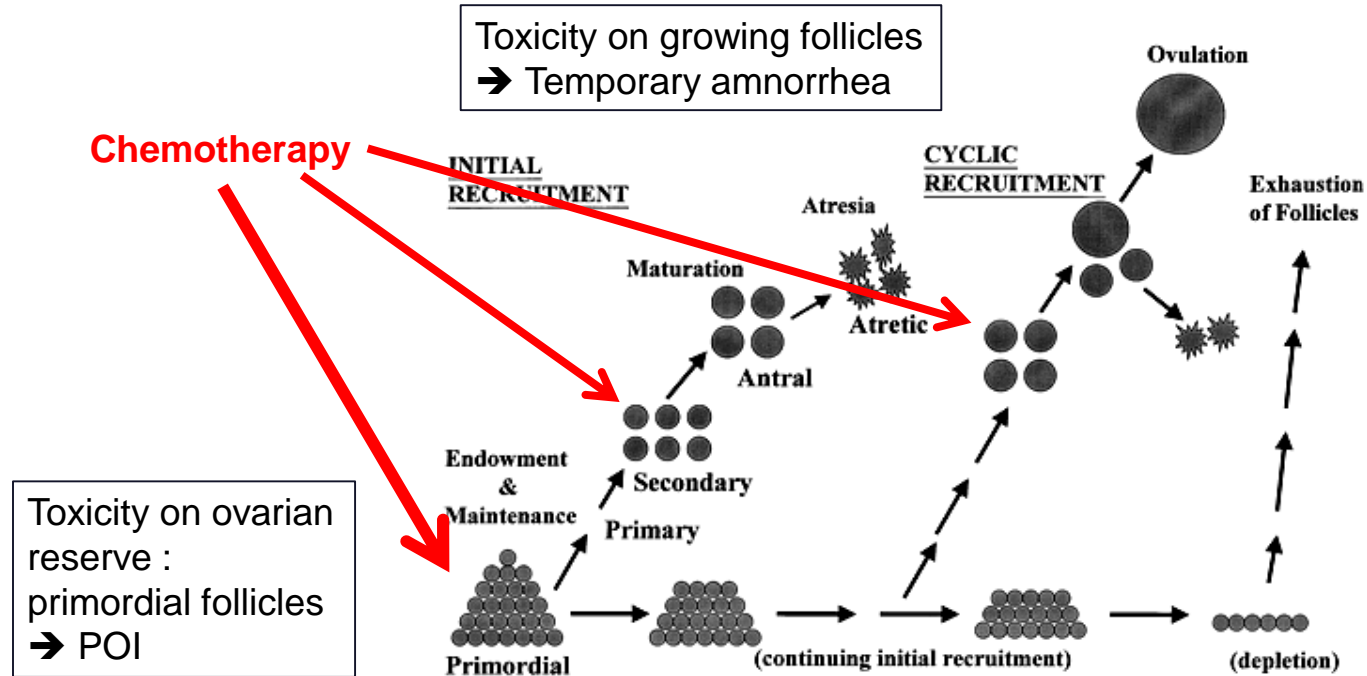


OVARIAN RESERVE

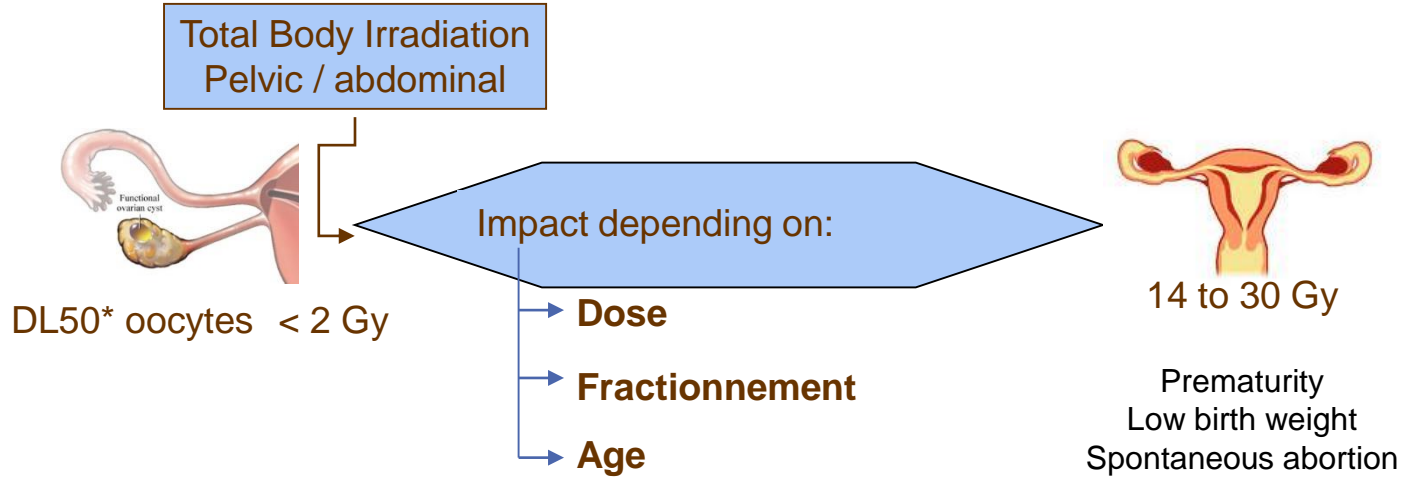
- ~13, 5 years between fertility decline and menopause



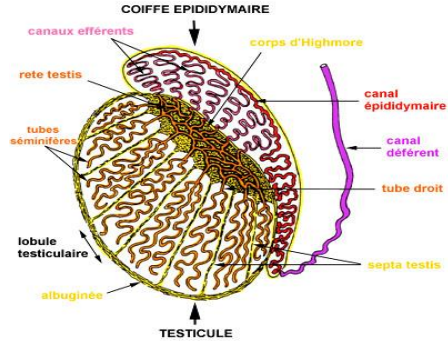
Impact of chemotherapy on ovarian reserve



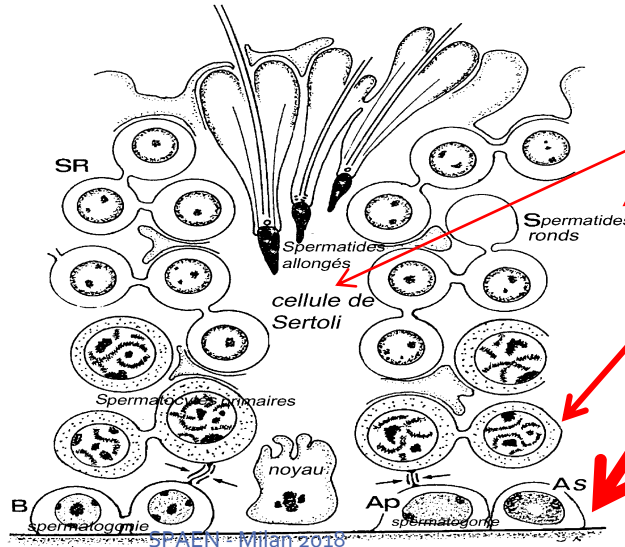
Impact of radiotherapy



Impact of treatment on spermatogenesis



Low toxicity on cells producing testosterone



Radiotherapy
Chemotherapy

Risk of amenorrhea	Age at treatment	Treatment
High risk (>80%)	Adult	Abdominal or pelvic radiation
	Any age	Total Body Irradiation
		Alkylating chemotherapy conditioning for transplantation
	≥40 years	Cyclophosphamide 5g/m ²
	<20 years	Cyclophosphamide 7,5 g/m ²
Intermediate risk (30 à 70%)	prepubertal	Abdominal or pelvic radiation doses 10 - 15 Gy
	postpubertal	Abdominal or pelvic radiation doses 5 -10 Gy
Low risk (<20%)	Any age	Non-alkylating chemotherapy (ABVD, CHOP, COP)
		Anthracycline + cytarabine
Very low risk	Any age	Methotrexate + fluorouracil
		Vincristine
		Iodine Radioactive
Unknown risk		oxaliplatin, irinotecan, bevacizumab, cetuximab, trastuzumab, erlotinib, imatinib

Targeted therapies / Tyrosine Kinase Inhibitors

- Recent treatments
- **Conception not recommended under treatment**
 - Mutagenic effect on oocyte / sperm
- **Pregnancy not recommended under treatment** : Teratogenic effect
- **Few data on fertility/gonadotoxicity of TK**
 - No data found about pazopanib
 - Imatinib
 - In mouse : No effects on folliculogenesis or spermatogenesis (*Schultheis B, Leuk Res 2012*)
 - In human : reduced sperm density, counts, survival rates, and activity (*Chang X, Target Oncol 2017*)
 - Sunitinib : in rats : Impact on folliculogenesis but no impact on ovarian reserve. No effects on male reproduction (*Coburn AM, Birth Defects Res B Dev Reprod Toxicol 2012*)

Consequences of delaying childbearing

Fecondability mainly depends on age



- Léridon H. *Hum Reprod* 2004 ; 19 : 1548-1553

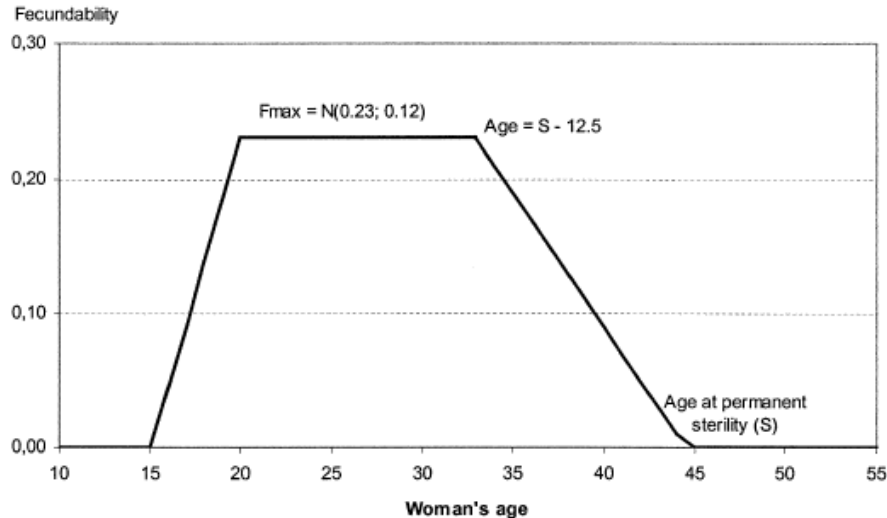
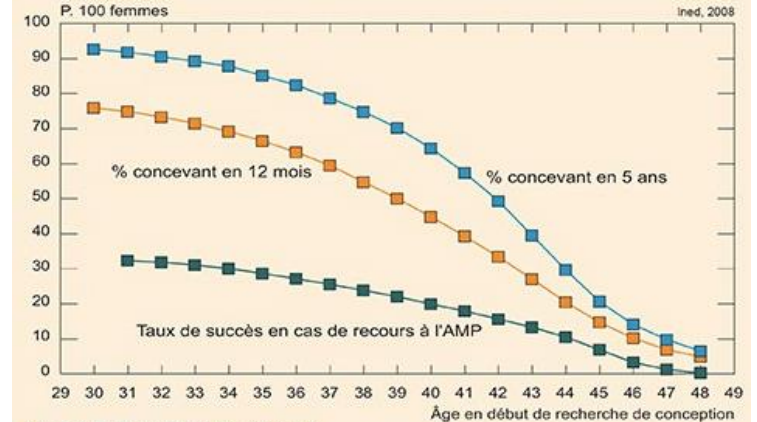


Figure 1. Probabilité d'obtenir une grossesse (conduisant à une naissance vivante) selon l'âge en début de tentative : spontanément en 12 mois ou en 5 ans, au moyen d'un traitement d'aide médicale (deux tentatives de FIV)



Source : modèle de simulation (Léridon, 2004 et 2005).

Fertility preservation : guidelines

French bioethics law

Lois de Bioéthique, de 2004 et 2011 (décret d'application du 22 décembre 2006)

« toute personne peut bénéficier du recueil et de la conservation de ses gamètes ou de tissu germinale [...] lorsqu'une prise en charge médicale est susceptible d'altérer sa fertilité ou lorsque sa fertilité risque d'être prématurément altérée ».

- Expert consensus / guidelines
- Oncology : ASCO (2013)
- Reproductive medicine
 - *European Society of Human Reproductive Endocrinology ESHRE*
 - *American Society of Reproductive Medicine ASRM*
 - *International Society of Fertility Preservation ISFP*
 - *FeetiProtekt*



Fertility preservation : how to preserve ?

How to decide ?

Gonadotoxicity of the treatment

Delayed childbearing

« Rentability » :
clinical outcomes of
FP technique



Risks induced by FP

Cost

Feasibility

- Delay before starting treatment
- Communication with reproductive medicine team



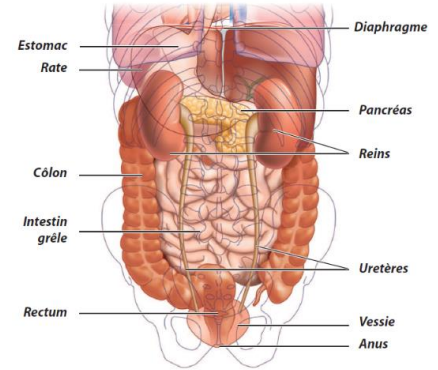
GnRH agonists

- Efficiency still debated -Seems to be efficient in breast cancer
 - *Del Mastro L, Cancer Treat Rev 2014 - Lambertini, SABCS 2017*
- Subcutaneous / Intramuscular injections during chemotherapy
- Compatible with other techniques

• ASCO Clinical Practice Guidelines 07/2013 : «insufficient evidence regarding effectiveness » «should not be relied on to preserve fertility »

Ovarian transposition

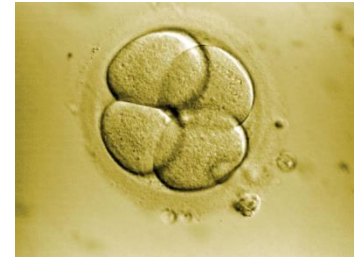
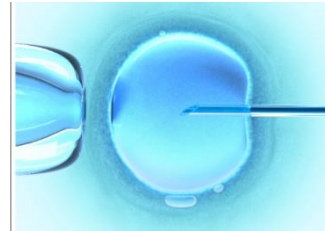
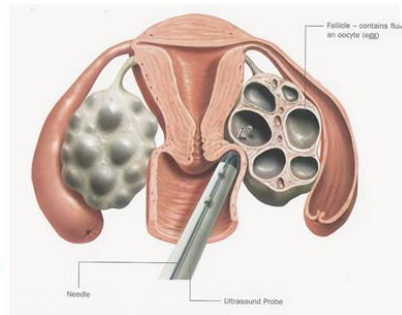
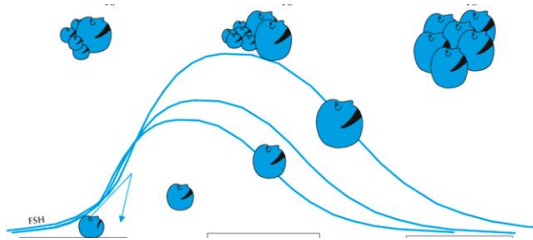
- Protect ovaries from irradiation
- *Irtan S, Lancet Oncol 2013*



Ovarian stimulation followed by oocyte retrieval

Oocyte or embryo vitrification

- Before any treatment
- Pubertal patients
- Technique :
 - Hormonal stimulation(needs 15 days)
 - Oocyte retrieval
 - Oocyte vitrification or Oocyte fertilization and embryo vitrification



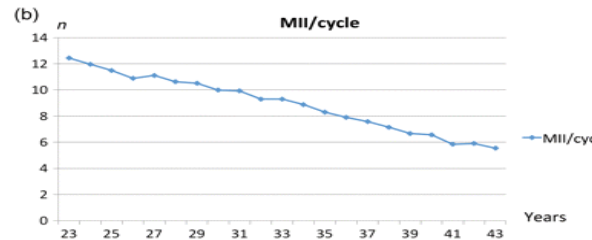
Success rates/Outcomes after Embryo / Oocyte vitrification

● Embryo vitrification

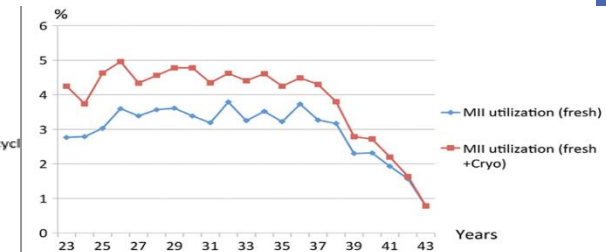
- Similar live birth rate (LBR) per patient to that achieved in non-cancer patients has been reported

● Oocyte vitrification

- 16 oocytes → 1 pregnancy
- 5 - 7% oocyte –to-baby-rate
- **FP in cancer patients**
 - Still few data



SPAEN - Milan 2018



Stoop D, Human Reprod 2012

Ovarian stimulation followed by oocyte retrieval Oocyte or embryo vitrification

ASCO Clinical Practice Guideline 07/2013

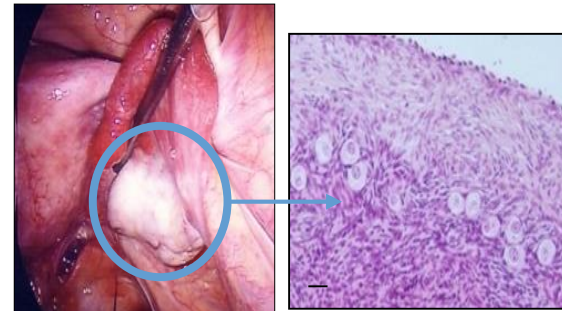
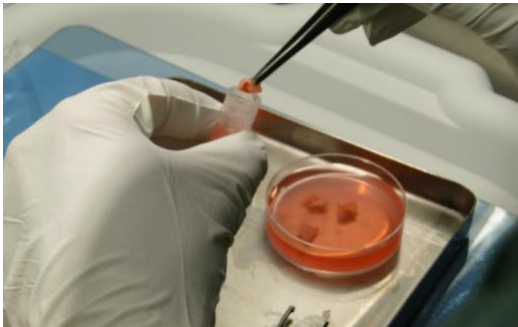
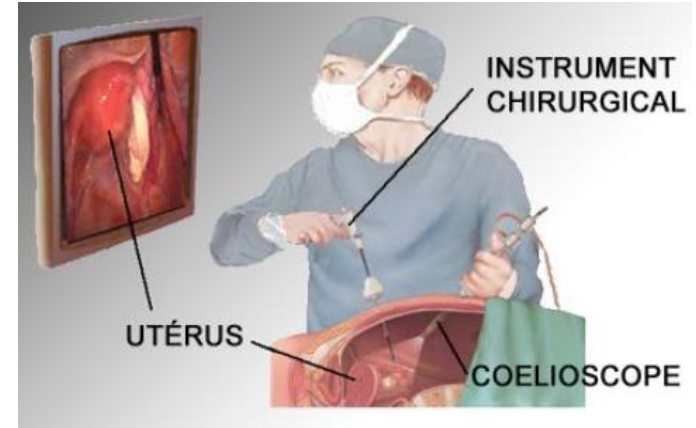
« present both embryo and oocyte cryopreservation as established fertility preservation methods »

- **ISFP – ESHRE – ASRM Expert Meeting 2015 (Martinez F, Fertil steril 2017)**
 - Embryo and oocyte cryopreservation are first-line FP methods in postpubertal women.
 - Metaphase II oocyte cryopreservation (vitrification) is the preferred option.

Ovarian tissue cryopreservation

Technique

- Laparoscopic ovarian harvesting
- Fragmentation
- Use : Reimplantation of frozen-thawed ovarian tissue (pelvic cavity)



Ovarian tissue cryopreservation

- Published live birth
- 29% live birth rate per patient (111 women)
- *Donnez, Fertil Steril 2015*



Feasability : 48-72h

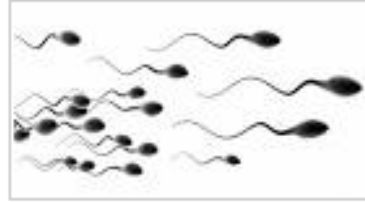
- Surgery
- Consequences on ovarian reserve ?
- Ovarian localisation of the disease ?
 - Low risk (no MDD in 14 Ewing + 12 STS)
 - *Dolmans MM, Hum Reprod 2016*

ASCO Clinical Guidelines 07/2013 : « *inform patients that ovarian tissue cryopreservation is still experimental* »

ISFP – ESHRE – ASRM Expert Meeting 2015 “*Cumulative evidence of restoration of ovarian function and spontaneous pregnancies after ART following orthotopic transplantation of cryopreserved ovarian tissue supports its future consideration as an open clinical application*”

Fertility preservation in male

Semen Cryopreservation



- **Semen Cryopreservation:**

- Procurement of semen samples by masturbation
- Alternatives: assisted ejaculation methods such as penile vibratory stimulation or electroejaculation.

- **Clinical outcomes**

- With ICSI : reported a LBR of 62.1% in a cohort of 272 men with cancer
- significantly higher than that of the comparative normospermic non-cancer population.
- *Garcia A, J Can Surv 2015*

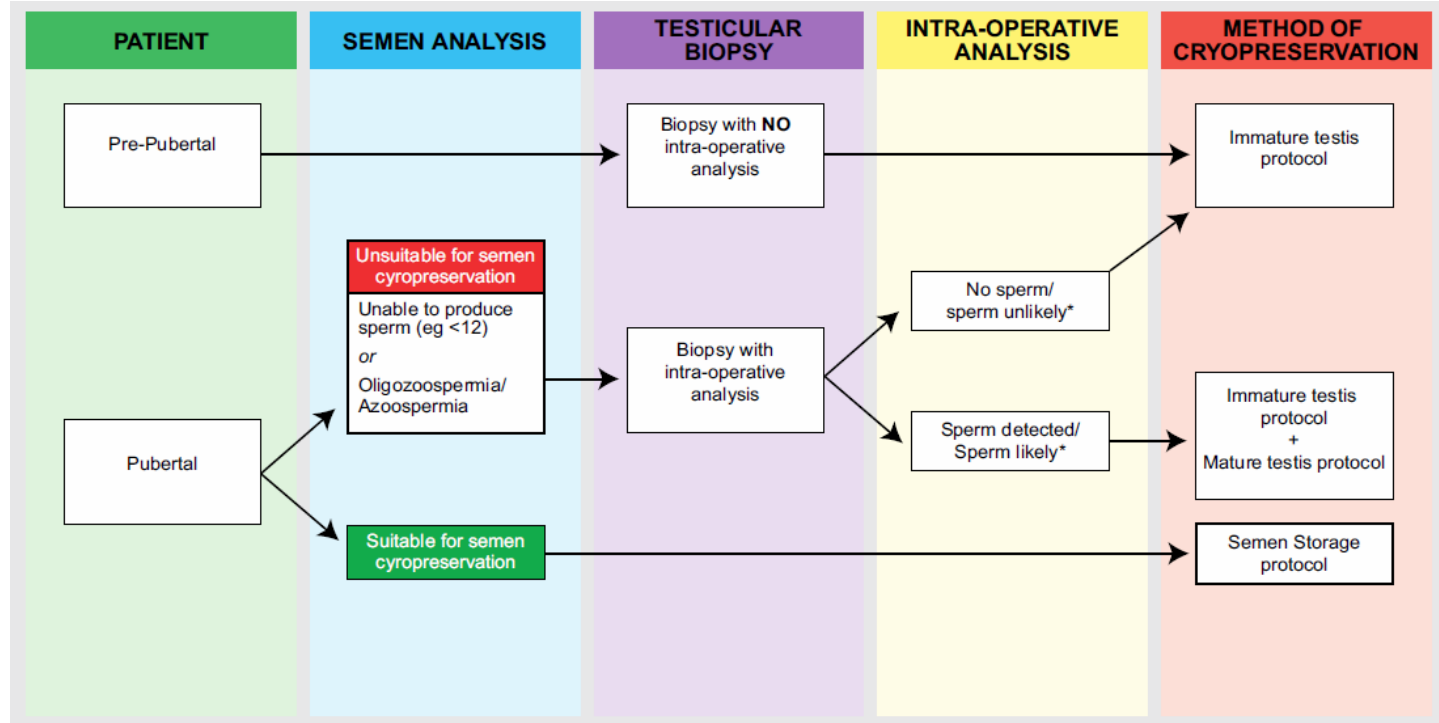
ISFP – ESHRE – ASRM Expert Meeting 2015

Semen cryopreservation is the only established method for FP in men.

SPAFN - Milan 2018

Fertility preservation in male

Prepubertal / unsuitable for semen preservation



Alternatives to « natural » conception

- Assisted reproductive techniques
 - IVF / ICSI
- Oocyte donation / sperm donation
- Gestational surrogacy
- Adoption

Different diseases – different situations

- Bone sarcoma

**Gonadotoxicity of
treatments**



- Ewing sarcoma
 - Alkylating agents
 - Pelvic radiotherapy
 - Autologous Stem Cell Transplantation
- Osteosarcoma
 - Alkylating agents



Fertility preservation before treatment

Oocyte / embryo vitrification
Ovarian tissue
cryopreservation
Semen / testicular tissue
cryopreservation

Different diseases – different situations

- Soft tissue sarcoma

- Alkylating agents
- Giant cell tumor of soft tissue : Long duration treatment (denosumab)
- Dermatofibrosarcoma : long duration treatment Imatinib

Gonadotoxicity of treatments



Delaying childbearing



- GIST

- Long duration treatments Imatinib/ Sorafenib / Regorafenib
- Transient interruption Imatinib ? BFR 14 Study

Fertility preservation before treatment ??

Oocyte / embryo
vitrification
Semen cryopreservation

Different diseases – different situations

Delaying
childbearing



- Desmoid tumors

- Chemotherapy : low gonadotoxicity
- Tyrosine Kinase Inhibitors : duration
- Estrogen sensitivity
 - Ovarian stimulation ?



Targeted therapies / Tyrosine Kinase Inhibitors

- **Fertility preservation before starting TT**

- Male : sperm cryopreservation
- Female : oocyte vitrification
- Transient interruption of TT for a pregnancy project ?

- **During TT : preservation not recommended**

- *Su HJ, Fertil Steril 2016*
- *2 Female patients treated with long term crizotinib / denosumab*
- *Extensive counseling to consider: her limited lifespan; risks of cancer progression off crizotinib prior to and during ovarian stimulation; unknown risks of crizotinib exposure on oocyte and embryo; known fetotoxic effects of crizotinib;*
- *They were counseled on adoption or surrogacy with oocyte donation, but they strongly wished to have a biologic child.*
- *Following several months of information gathering, counseling and care coordination, the couple decided to pursue autologous ovarian stimulation, preimplantation genetic screening (PGS), and pregnancy via gestational surrogacy.*

47 centres pratiquant la préservation de la fertilité en 2015. Bonne répartition globale des centres pour une activité qui ne se veut pas de « proximité ». Certains territoires sont néanmoins classiquement en marge :

- Sud du Massif-Central et Cévennes
- Massif des Alpes et Pyrénées
- Massif Armoricain

Difficultés liées à l'insularité :

- Aucun centre en Corse (→ PACA), Guyane et Mayotte
- Pas d'activité de congélation d'ovocytes à la Réunion et à la Martinique (→ Guadeloupe)
- Pas d'activité de congélation de tissus gonadiques dans les Antilles

Si le manque d'offre du sud de la Champagne-Ardenne au Morvan est « classique » pour ce type de soins, l'absence de centre dans le Nivernais ou le Berry laisse présager des difficultés d'accès aux soins pour ces espaces. La seule activité de congélation de spermatozoïdes à Orléans ne fait que renforcer cette supposition. D'important flux de patients vers Paris, Tours, Clermont Ferrant et Limoges sont à prévoir.

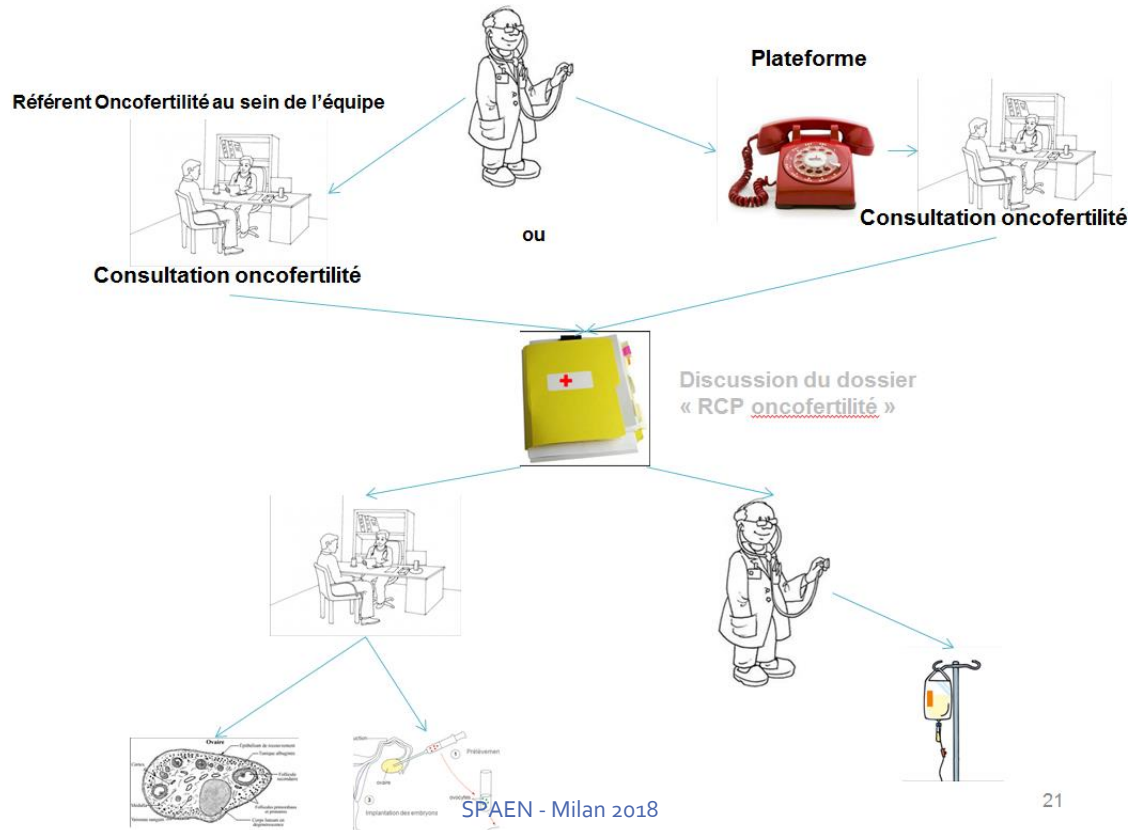
Les autres principales difficultés qui apparaissent sur la carte sont donc l'absence de centres en Poitou-Charentes (ouverture prévu à Poitiers) et dans le Pays Basque

Centres autorisés pour la préservation de la fertilité en 2015



SPAEN - Milan 2018

Communication with Assisted Reproductive Techniques Team



Conclusion / Take home messages

- Major concern for patients / family
- Lack of data
 - ➔ The establishment of international registries on the short- and long-term outcomes of FP techniques is strongly recommended.
- Information on consequences of treatment on fertility
- Fertility preservation when needed / possible



SOLEDAD