28 - 30 Juin 2017

Antibes Juan-Les-Pins

GynAzur

L'insuffisance ovarienne précoce

Dr Christophe Sifert

Dr Samir Boukaidi

Définitions

L'insuffisance ovarienne

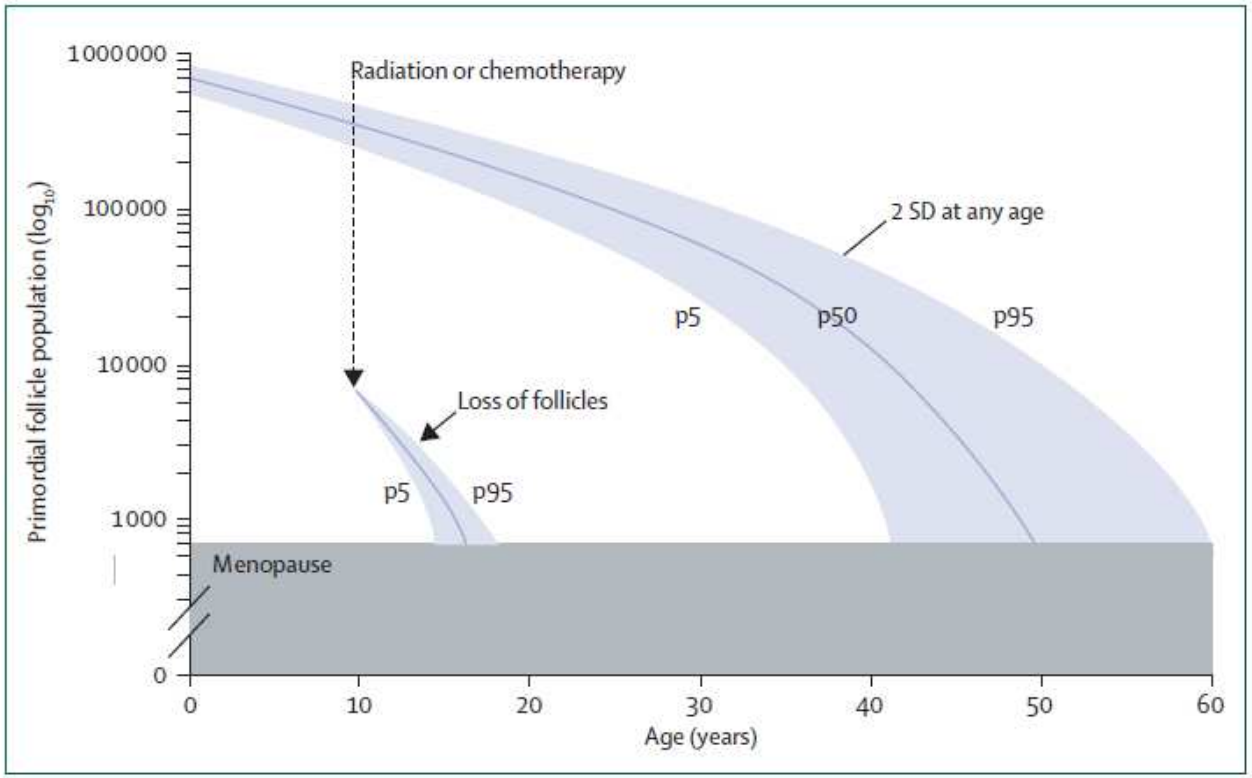
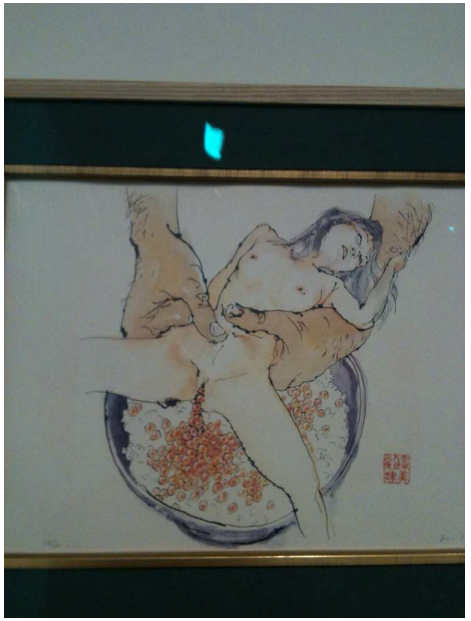


Figure 1: **Decline of ovarian follicular reserve**
Biexponential decline of primordial follicles in the ovaries, first reported by Faddy and colleagues,[8] and the loss of follicles in women undergoing chemotherapy. p5=5th percentile. p50=median. p95=95th percentile.



De Vos et al. Lancet 2010

L'insuffisance ovarienne

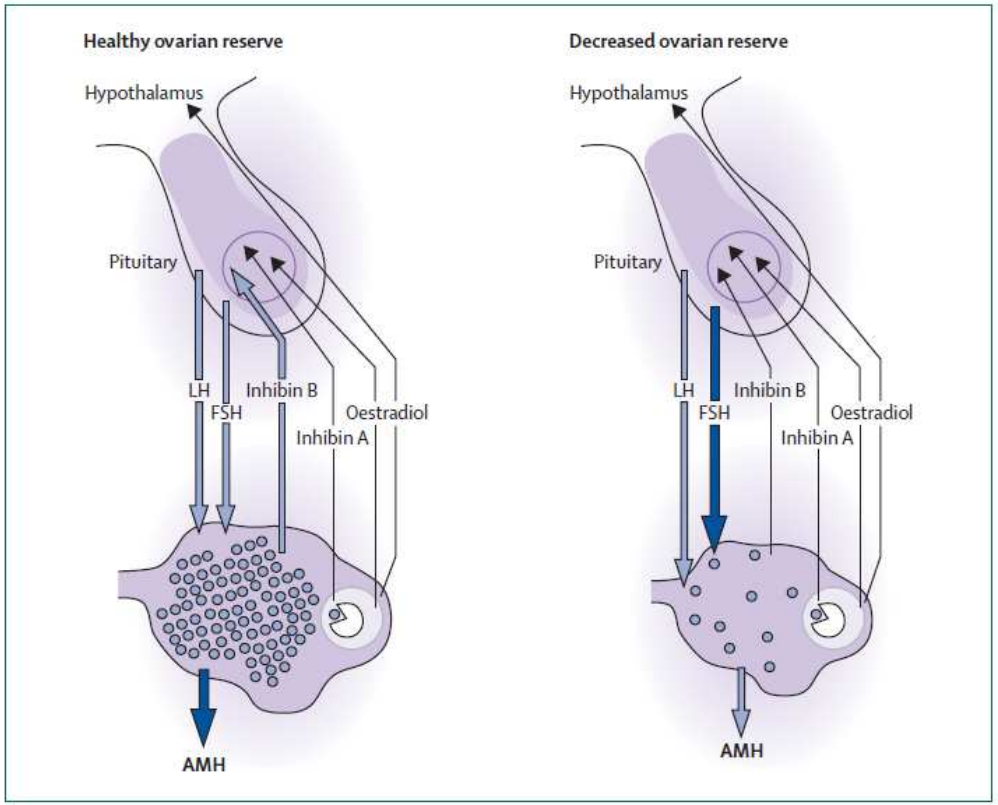


Figure 2: **Healthy and decreased ovarian follicular reserve with increased age and changes in concentrations of ovarian and hypothalamopituitary hormones**

Thickness of arrows shows concentration of hormone secretion. Adapted with permission from Soules and colleagues.[35] AMH=anti-Mullerian hormone. FSH=follicle-stimulating hormone. LH=luteinising hormone.

De Vos et al. Lancet 2010

L'insuffisance ovarienne

- Physiologique: Déclin avec l'âge (- 15% potentiel de fertilité par an; ≥ 35 ans)
  Ménopause: 51 ans [40-60 ans] *Morabia et al. Am J Epidemiol 1998*

- Pathologique:
  - Aménorrhée I (25%) / II >4 mois (75%)
    (Déficit des hormones stéroïdes)
  - <40 ans (> 2 SD âge de la ménopause)
  - FSH x2 > 20-40 mUI/ml

- Fréquence:

1/100	<40 ans
1/1000	<30 ans
1/10000	<30 ans
15%	Formes familiales
1,5/1/0,5%	Afrique/Caucase/Asie

Goswami et al. HRU 2005

- POI = Primary Ovarian Insufficiency
- POF = Premature Ovarian Failure

≠ Mauvaises répondeuses

POR (Poor Ovarian Response)

Human Reproduction, Vol.26, No.7 pp. 1616–1624, 2011
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human reproduction

ESHRE PAGES

ESHRE consensus on the definition of 'poor response' to ovarian stimulation for *in vitro* fertilization: the Bologna criteria†

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Table I Criteria used to define poor ovarian response (POR).

Reference	Criteria
Garcia-Velasco *et al.* (2000)	At least one previous cycle cancelled because of ≤3 follicles ≥18 mm
Ferraretti *et al.* (2000)	At least two previous cycles concelled or with ≤3 oocytes
Akman *et al.* (2001)	Two failed IVF attempts for one of the following reasons: Day 3 FSH >15 mIU/ml E_2 <500 pg/ml at hCG <4 mature oocytes
Weissman *et al.* (2003)	One previous cycle with at least one of the following characteristics: <5 oocytes ≤3 follicles 16 mm or larger E_2 <500 pg/ml at hCG
Marci *et al.* (2003)	One previous POR in a standard treatment
Goswami *et al.* (2004)	One to three failed IVF attempts due to POR to conventional long-agonist protocol
Kolibianakis *et al.* (2004)	One or more failed IVF cycles in which ≤5 oocytes were retrieved and Day-3 FHS level >12 mIU/ml
Morgia *et al.* (2004)	One previous IVF cycle with ≤3 oocytes
Detti *et al.* (2005)	One or more of the following criteria present: age >38 years previous cancelled cycle previous POR (≤3 oocytes or E_2 <500 g/ml) Day-3 FSH >13 mIU/ml
Cheung *et al.* (2005)	One previous POR with ≤3 oocytes on a long-agonist protocol or repeated Day-3 FSH >10 IU/l
Garcia-Velasco *et al.* (2005)	At least one previous cancelled cycle due to ≤4 follicles >16 mm and/or E_2 level ≤500 pg/ml
Massin *et al.* (2006)	Two of the following criteria present: previous POR (E_2 <1200 pg/mo at hCG and ≤5 oocytes) Day-3 FSH >12 Day-3 inhibin B <45 pg/ml
Aletebi (2007)	POR in previous cycle(s): ≤4 oocytes following stimulation for ≥15 days involving 300 IU of gonadotrphins daily
Schoolcraft *et al.* (2008)	At least one of the following criteria: Day-3 FSH >10 mIU/ml age >41 years AFC <6 one previous cycle cancelled one previous POR (E_2 <500 pg/ml and/or <6 oocytes)
Frattarelli *et al.* (2008a)	One or more of the following characteristics: Day-3 FSH >12 mIU/ml AFC ≤3 history of POR (≤5 oocytes, poor quality oocyte and/or poor quality embryos)
Frattarelli *et al.* (2008b)	Two previous POR (criteria not defined)
Barrenetxea *et al.* (2008)	Age ≥40 years and Day-3 FSH ≥10 mIU/ml
Tazegul *et al.* (2008)	Previous POR: E_2 <500 pg/ml or ≤3 mature follicles or <3 oocytes
Fábregues *et al.* (2009)	First IVF cycle cancelled because of POR (criteria not defined)
Kahraman *et al.* (2009)	One or more of the following criteria present in at least one previous cycle: cycle cancelled ≤3 oocytes E_2 >500 pg/ml
Yarali *et al.* (2009)	Abnormal ORTs (FSH >10 mIU/ml or AFC <6) or previous POR (cycle cancelled or E_2 >500 pg/ml or ≤3 oocytes)
Weitzman *et al.* (2009)	One or more of the following criteria: age ≥40 years Day-3 FSH ≥10 mIU/ml previous cycle cancelled:previous cycle with ≤4 oocytes collected
Demirol and Gurgan (2009)	At least two previous POR (E_2 <500 pg/ml or ≤3 oocytes) and Day-3 FSH >15 IU/l
Tehraninejad *et al.* (2009)	At least one previous cycle cancelled because of <3 mature follicles

AFC, antral follicle count; E_2, estradiol; FSH, follicle stimulating hormone; HCG, human chorionic gonadotrophin; IVF, *in vitro* fertilization; ORTs, ovarian reserve tests.

Les critères de Bologne

At least two of the following three features must be present:

(i) Advanced maternal age (≥40 years)

(ii) A previous POR (≤3 oocytes with a conventional stimulation protocol);

(iii) An abnormal ovarian reserve test (i.e. AFC <5–7 follicles or AMH <0.5–1.1 ng/ml).

Two episodes of POR after maximal stimulation are sufficient to define a patient as poor responder in the absence of advanced maternal age or abnormal ORT.

➢ *L'IOP n'est pas la mauvaise réponse ovarienne*

- Femmes (âgées ++) consultant pour infertilité
- Cycles souvent réguliers
- FSH légèrement élevée (10-15 mUI/ml)
- AMH diminuée
- compte de follicules ovariens bas

Causes de l'IOP

- Inconnue: 85% des cas
- Génétiques
- Immunologiques
- Infectieuses
- Iatrogènes

De Vos et al. Lancet 2010

Panel 1: Disorders leading to ovarian insufficiency*

Ovarian follicle dysfunction

Signalling defect
- Follicle-stimulating-hormone-receptor mutation (*FSHR*)
- Luteinising-hormone-receptor mutation (*LHR*)
- Pseudohypoparathyroidism type 1a (*GNAS*)

Enzyme deficiency
- Isolated 17-α-hydroxylase or 17,20-lyase deficiency (*CYP17A1*)
- Aromatase deficiency (*CYP19*)

Autoimmunity
- Autoimmune lymphocytic oophoritis
- Polyglandular autoimmune syndrome, including adrenal, thyroid, or thymic disease
- Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (*AIRE*)

Associated with insufficient follicle number
- Luteinised graafian follicles

Ovarian follicle depletion

Insufficient initial follicle number
- Blepharophimosis, ptosis, and epicanthus inversus syndrome (*FOXL2*)
- 46,XY gonadal dysgenesis (*SRY* and others)
- Other syndromes and genes associated with an insufficient initial follicle number that have not been described

Spontaneous accelerated follicle loss
- Turner's syndrome: full blown and mosaic variants (unknown)
- Trisomy or polysomy X, or mosaic variants
- Macrodeletions Xp or Xq
- Autosomal or X translocations

Adapted from Nelson.[28] *Genes associated with primary ovarian insufficiency are shown in parenthesis.

Panel 2: Genes associated with primary ovarian insufficiency

Known human X chromosome-located functionally relevant genes
- Basic helix-loop-helix protein (*BHLHB9*)
- Bone morphogenetic protein 15 (*BMP15*)
- Homologue of the *Drosophila* dachshund gene (*DACH2*)
- Second human homologue of the *Drosophila* diaphanous gene (*DIAPH2*)
- Fragile X mental retardation syndrome (*FMR1*)
- X-linked mental retardation, associated with fragile site FRAXE (*FMR2*)
- Premature ovarian failure 1B (*POF1B*)
- X-inactivation-specific transcript (*XIST*)
- X-prolyl aminopeptidase 2 (*XPNPEP2*)

Known human autosomal functionally relevant genes
- Autoimmune regulator (*AIRE*)
- Deleted in azoospermia-like (*DAZL*)
- Homologue of yeast disrupted meiotic cDNA 1 (*DMC1*)
- Eukaryotic translation initiation factor 5B (*EIF5B*)
- Oestrogen receptor 1 (*ESR1*)
- Homologue of murine factor in germline α (*FIGLA*)
- Forkhead transcription factor (*FOXL2*)
- Forkhead box O1A (*FOXO1A*)
- Forkhead box O3A (*FOXO3A*)
- β chain of follicle-stimulating hormone (*FSHB*)
- Follicle-stimulating-hormone receptor (*FSHR*)
- Galactose-1-phosphate uridyltransferase (*GALT*)
- Growth-differentiation factor 9 (*GDF9*)
- G protein-coupled receptor 3 (*GPR3*)
- Type II 3-β-hydroxysteroid dehydrogenase deficiency (*HSD3B2*)
- Inhibin alpha (*INHA*)
- Luteinising hormone, β polypeptide (*LHB*)
- LIM homeobox gene 8 (*LHX8*)
- Homologue of *Escherichia coli MutS*, 5 (*MSH5*)
- Homologue of *Drosophila Nanos3* (*NANOS3*)
- Homologue of murine newborn ovary homeobox (*NOBOX*)
- Homologue of murine noggin (*NOG*)
- Nuclear receptor subfamily 5, group A, member 1 (*NR5A1*)
- Progesterone receptor membrane component 1 (*PGRMC1*)
- DNA polymerase γ (*POLG*)
- Transforming growth factor-β receptor, type 3 (*TGFBR3*)
- Y box-binding protein 2 (*YBX2*)

Causes génétiques

1- Liés au Chromosome X (10-15% des IOP):

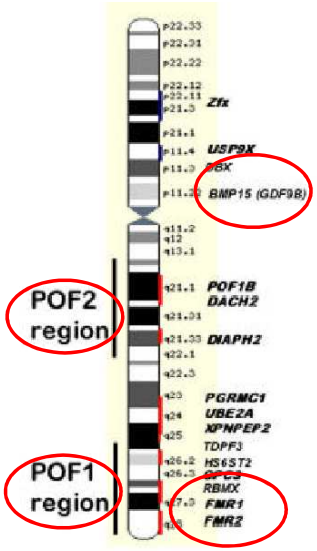
Anomalies de Nombre (+++):

- Monosomie du X +++ (Syndrome de Turner) totale / partielle (Mosaïque: 45X/46XX et 45X/47XXX): 1 / 2500 filles
  - Atrésie folliculaire accélérée (à partir de 26 SA) par effet dose de gènes d'intérêt (haplo-insuffisance)
  - Impubérisme (>60%), Aménorrhée II (<30%), Cycles spontanés (<10%), Grossesse exceptionnelle
  - Retard de croissance constant, IOP >95%.

- Trisomie partielle ou totale du X: 1 femme / 900

Anomalies de Structure (-): (effet de positionnement)
- Xq26-28; Xq13-21(régions POF 1, POF 2)
- Xp11 (BMP 15), aménorrhée I (50%) II (50%)

- Xq27.3 (FMR1 +++)

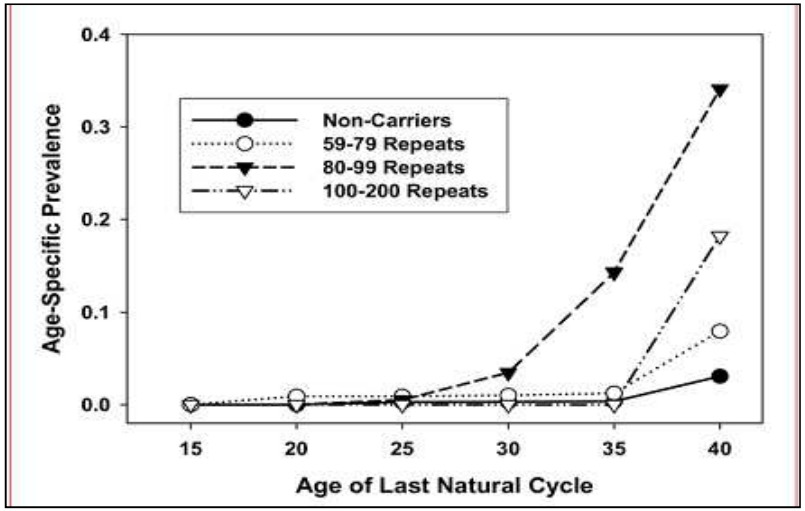


Goswani et al. Human Reprod Update 2005

Causes génétiques

- Mutation du gène FMR-1: (Fragile Mental Retardation type), 1 / 590 garçons
- Xq27.3
- Syndrome de l'X fragile = 1ère cause de retard mental chez le garçon
- Répétitions d'un trinucléotide CGG en 5' du gène:

< 50	Normal
50 – 199	Prémutation



- (20% des IOP: 5% IOP sporadique, 15% IOP Famille Xfra)
- Risque +++ entre [80-100] répétitions
- Mécanisme inconnu (Dysrégulation métabolisme ARNm?)

Wittenberger et al. Fertil Steril 2007

> 200	Mutation complète (Pas d'IOP)

Causes génétiques

2- Liés à d'autres Chromosomes:

- **Chromosome 3:** Blepharophimosis/ptosis/epicanthus inversus syndrome (BPES-1)
  Région 3q23, gène FOXL2 muté, transmission dominante
  Forme familiale

EVAR WorkShop Group. Human Reprod Update 2011 (33 gènes identifiés)

Table I. Genes implicated in POF *Goswani et al. Human Reprod Update 2005*

Categories	Chromosome	Gene	Gene locus
Mutations identified	X chromosome genes	*FMR1*	Xq27.3
		FMR2	Xq28
		BMP15	Xp11.2
	Autosomal genes	*FOXL2*	3q22–q23
		FSHR	2p21–p16
		LH receptor	2p21
		FSH beta variant	11p13
		LH beta	19q13.32
		Inhibin A	2q33–q36
		GALT	9p13
		AIRE	21q22.3
		EIF2B2, -4, and -5	14q24.3, 2p23.3, 3q27
		NOGGIN	17q22
		POLG	15q25

Table II Human genes associated with ovarian insufficiency/failure.

Acronym	Name
AIRE (Ahonen *et al.*, 1990)	Autoimmune regulator
ATM (Miller and Chatten, 1967)	Ataxia telangiectasia mutated
BHLHB9 (De Vos *et al.*, 2010)	Basic helix–loop–helix domain-containing, class B, 9
BMP15 (Di Pasquale *et al.*, 2004)	Bone morphogenetic protein
DACH2 (Prueitt *et al.*, 2002)	*Drosophila* dachsund
DIAPH2 (Bione *et al.*, 1998)	Homologue *Drosophila* diaph
FMR1 (Murray *et al.*, 1999)	Fragile X mental retardation 1
FMR2 (Murray *et al.*, 1999)	Fragile X mental retardation 2
XIST (Sato *et al.*, 2004)	X inactivation transcript
XPNPEP2 (Prueitt *et al.*, 2000)	Propyl aminopeptidase
DAZL (Tung *et al.*, 2006)	Deleted azoospermia
DCM1 (Mandon-Pepin *et al.*, 2008)	Disrupted meiotic cDNA 1
EIF2B (Fogli *et al.*, 2004)	Eukaryotic translation initiation
ESR1 (Tung *et al.*, 2006)	Oestrogen receptor
FIGLA (Zhao *et al.*, 2008)	Murine factor germline alpha
FOXL2 (Crisponi *et al.*, 2001)	Forkhead transcription factor
FOXO1A (Watkins *et al.*, 2006)	Forkhead box O1A
FOXO3a (Vinci *et al.*, 2008)	Forkhead box O3a
FSHR (Aittomaki *et al.*, 1995)	FSH receptor
GALT (Leslie *et al.*, 1992)	Galactose phosphate transferase
GDF9 (Dixit *et al.*, 2005)	Growth differentiation factor 9
GPR3 (Kovanci *et al.*, 2008)	G protein-coupled receptor
INHA (Dixit *et al.*, 2004)	Inhibin A
LHB (Takahashi *et al.*, 1999)	LH beta
MSH5 (Mandon-Pepin *et al.*, 2008)	MutS homolog 5
NOBOX (Qin *et al.*, 2007)	Murine newborn ovary box
NOGGIN (Laissue *et al.*, 2007)	Binds and inactivates members of the transforming growth factor-β superfamily signalling proteins
NR5A1 (SF-1) (Lourenco *et al.*, 2009)	Nuclear receptor subfamily 5 A1
NSB1 (Chrzanowska *et al.*, 2010)	Nijmegen breakage syndrome 1
PGRMC1 (van Dooren *et al.*, 2009)	Progesterone receptor membrane component-1
POLG (Luoma *et al.*, 2004)	Mitochondrial DNA polymerase gamma mutations
TGFBR3 (Dixit *et al.*, 2006)	Tumour growth factor receptor
WT1 (Chun *et al.*, 1999)	Wilms Tumor 1

Importance du caryotype +++, de l'analyse moléculaire (+++ dans contexte familiale)

Causes auto-immunes

- 10 à 30% des IOP: présence d'un terrain auto-immun *Christin-Maître . Mise à jour en Gyn Med, CNGOF 2009*

  - hypothyroïdie ou présence d'anticorps anti-TPO
  - insuffisance surrénalienne
  - lupus, polyarthrite rhumatoïde
  - Crohn

- Aucun intérêt des Anticorps Anti-Ovaires (Difficultés de dosages, très peu spécifique)

- Corrélation entre l'infiltration lymphocytaire ovarienne et présence des anticorps anti-StCA à la biopsie ovarienne

- Pathologies thyroïdiennes

  39% des IOP à caryotype normal

  Bilan: Anticorps anti-thyroperoxydase et/ou thyroglobuline +++

- Pathologies surrénaliennes

  2 à 10% des IOP

  Bilan: Anticorps Anti-Surrénalien

  L'IOP précéderait de 8 à 14 ans la maladie d'Addison (prev: 1/10 000)

Causes auto-immunes

Table II. Autoimmune polyglandular syndromes and POF

autoimmune-polyendocrinopathycandidiasis-ectodermal dystrophy (APECED)

APS type	Inheritance	Autoimmune involvement	Age group	Incidence of POF
APS I	Autosomal recessive caused by a mutation in the autoimmune regulator (*AIRE*) gene on chromosome 21	Chronic mucocutaneous candidiasis, adrenal and parathyroid failure	Children age 3–5 years or in early adolescence	17–50% (Ahonen *et al.*, 1990)
APS II (more common)	Polygenic, characterized by dominant inheritance and association with HLA DR3	Primary adrenal failure (Addison's disease) with autoimmune thyroid disease (Schmidt's syndrome) and/or type 1 diabetes (Carpenter's syndrome)	Adults in the third or fourth decade	3.6–10% (Betterle *et al.*, 2004)
APS III	Apart from the absence of adrenal failure, no clinical differences between types II and III have been described	Thyroid failure and other immunological syndromes with exclusion of Addison's disease	Adults	

Goswani et al. Human Reprod Update 2005

Causes infectieuses

- Tuberculose
- Oreillons
- Malaria
- Varicelle
- Shigella

Causes métaboliques

- Diabète mal équilibré

De Vos et al. Lancet 2010

Causes iatrogéniques

- Chimiothérapie
- Radiothérapie:
  - 9 grays: détruit les ovaires
  - Dépend de l'âge: relative résistance avant la puberté
    - Beerendonk and Braat, 2005
- Ovariectomie partielle ou totale
- Embolisation des artères utérines

Panel 3: Estimated risk of gonadal dysfunction with cytotoxic drugs

High risk
- Cyclophosphamide
- Ifosfamide
- Chlormethine
- Busulfan
- Melphalan
- Procarbazine
- Chlorambucil

Medium risk
- Cisplatin
- Carboplatin
- Doxorubicin

Low risk
- Vincristine
- Methotrexate
- Dactinomycin
- Bleomycin
- Mercaptopurine
- Vinblastine

Data from reference 59.

Panel 4: Ovarian insufficiency risk assessment

High risk
- Total body irradiation or radiation of the pelvis
- Chemotherapy conditioning for bone marrow transplant
- Hodgkin's disease (alkylating agent-based treatment)
- Soft tissue sarcoma (metastatic disease)
- Breast cancer

Medium risk
- Acute myeloblastic leukaemia
- Hepatoblastoma
- Osteosarcoma or Ewing sarcoma
- Soft-tissue sarcoma
- Non-Hodgkin lymphoma or Hodgkin's disease
- Brain tumour: craniospinal irradiation or cranial irradiation of >24 Gy

Low risk
- Acute lymphoblastic leukaemia
- Wilms' tumour
- Soft-tissue sarcoma (stage 1)
- Germ-cell tumours (with no radiation therapy)
- Retinoblastoma
- Brain tumour: surgery only, cranial irradiation <24 Gy

Adapted from Wallace and colleagues.[60]

De Vos et al. Lancet 2010

Bilan de l'IOP

- Tableau clinique et Interrogatoire

- ATCDs Chirurgicaux/Médicaux/Infectieux/Familiaux
- Aménorrhée I, II (> 4 mois) avec symptômes de la ménopause (syndrome climatérique)
- Petite taille ? (Turner)
- ATCD de retard mentaux chez les garçons de la famille ? (X Fra)
- Malformation des paupières (BPES-1)
- ATCD d'ambiguïté sexuelle dans la famille (Mutation SF-1)
- Auto-immunité (APECED,…)
- Surdité (Peyrault: Mutation HARS2, 2% IOP)

Bilan de l'IOP

- Bilan

- AMH, FSH (x2), LH, Œstradiol, Echographie pelvienne: Insuffisance gonadotrophique
- Caryotype (Aménorrhée I: 50% anomalies caryotype; II: Nle)
- Recherche de mutation FMR-1 + prélèvement d'ADN
- Cortisol et test au Synacthène simple, ACTH si besoin
- Auto Immunité: TSH, Ac Anti TPO/Thyroglobuline, Ac Anti Surrénalien (anti 21 Hydroxylase); Ac Anti Ovaire? (Anti St CA)
- Glycémie
- Ostéodensitométrie (retentissement osseux et suivi efficacité du THS)
- Sur prélèvement ADN: Recherche (i) de mutations de gènes connus ou (ii) de gènes candidats (cas familiaux et ADN Satellites)

Conséquences de l'IOP

Podfigurna –Stoppa et al. J Endocrinol Invest 2016

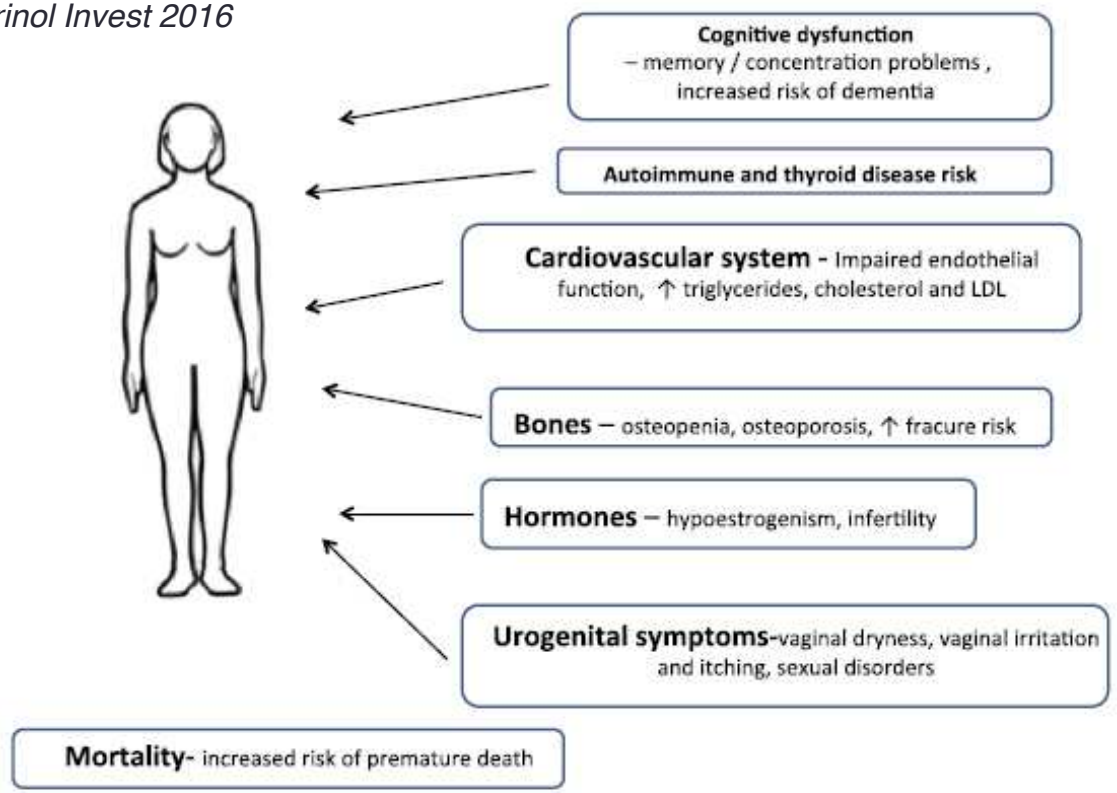


Fig. 1 Long-term consequences of premature ovarian insufficiency–schematic summary

Prise en charge de l'IOP

- Traitement Hormonal Substitutif:

  Effets Cardio-vasculaires / Utérins / Osseux

- Fertilité:

- Préservation de la fertilité féminine:

- PEC Psychologique

Prise en charge de l'IOP

Table III. Issues in the management of women with POF

Education and counselling
Remission: The likelihood of recovery of ovulation is not possible to predict
There is no proven effective treatment for infertility
Adoption and oocyte donation are among the available options but require guidance and counselling
Access to follow-up counselling is important as issues return with life events such as pregnancy in family
Investigations
Thyroid function tests are useful as thyroid involvement is a common association
Autoantibody screen including thyroid and adrenal antibodies
Karyotype for early onset POF and genetic screen for *FRAXA* premutation
Pelvic ultrasound and ovarian biopsy do not alter the management
Treatment
Estrogen and progesterone replacement is usually indicated
There is no comparative data to guide estrogen use in young women as most studies on HRT involve post-menopausal women
Inform on all estrogen preparations—oral, transdermal and implants
Inform on media HRT scares and relevance to young women
Consider vaginal estrogen and testosterone supplements

Goswani et al. Human Reprod Update 2005

Prise en charge de l'IOP

- Traitement Hormonal Substitutif: **UTERUS**
  - Physiologique > Standard *(O Donnell et al. HR 2012)*

Table I 'Physiological' and 'standard' sex steroid regimens.

	Product	Component	Dose				Dosing freq.
			Week 1	Week 2	Week 3	Week 4	
pSSR	Patches Vaginal pessaries	Estradiol Progesterone	100 μg	150 μg	150 μg 200 mg	150 μg 200 mg	/24 h /12 h
sSSR	Pill	Ethinylestradiol 30 μg Norethisterone 1.5 mg	Pill-free	1 pill	1 pill	1 pill	/24 h

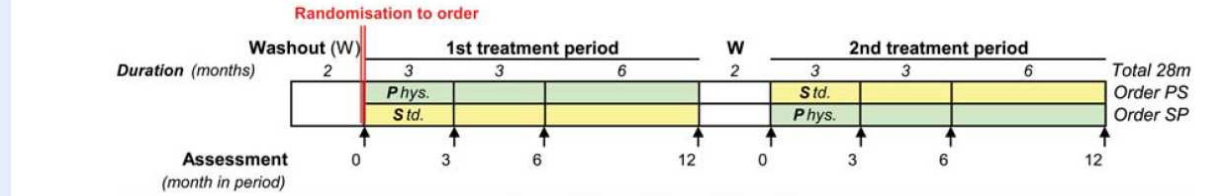
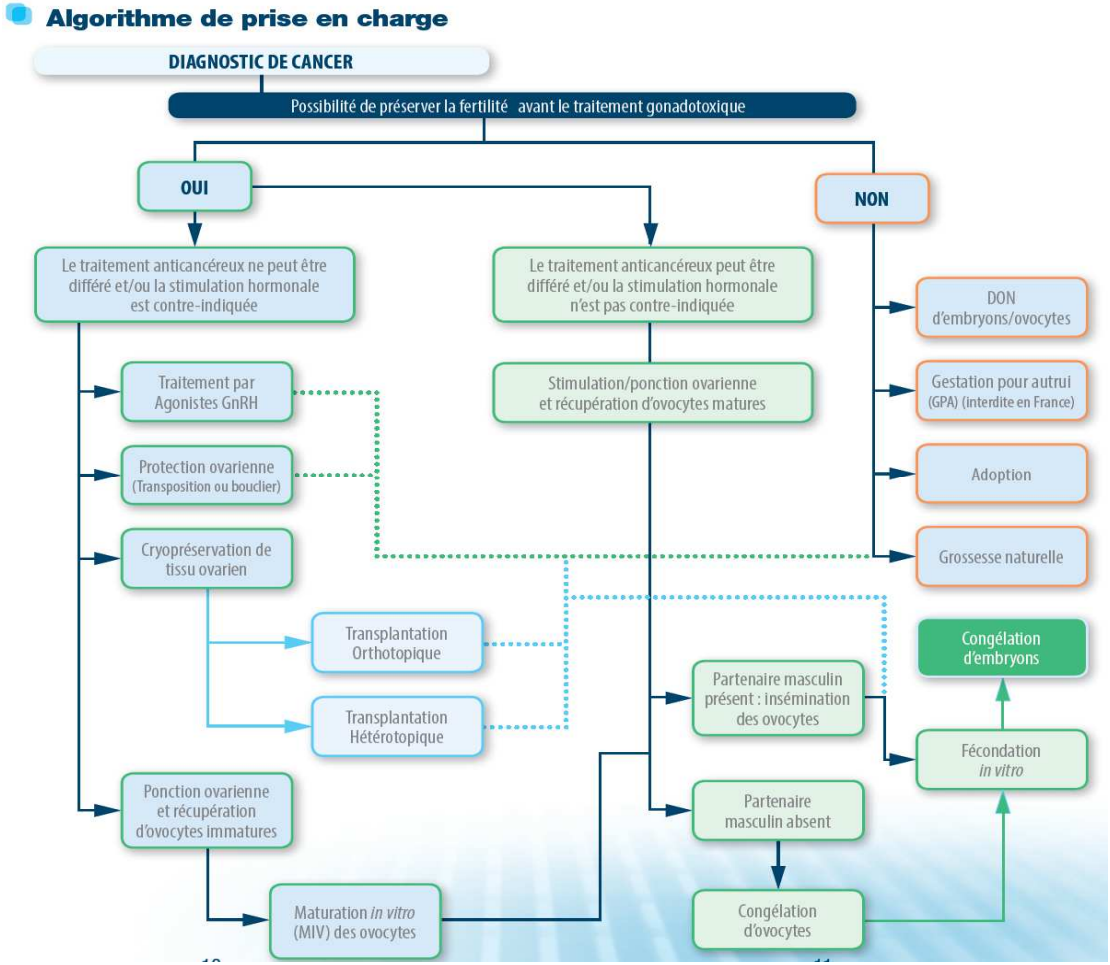


Figure 1 Time-course of study showing wash-out and treatment periods, plus timing of randomization and assessments.

17 completed (out of 29 who were randomised *and* could contribute data to uterine sub-study)
25 patients had at least one assessment on treatment (ie continued to 3 month assessment of 1st treatment period) & all 25 were included in the analysis (P then S, n=10; S then P, n=15)

Prise en charge de l'IOP

- Préservation de la fertilité:



Prise en charge de l'IOP

- Préservation de la fertilité:

Salama et al. Ann Oncol 2013

Table 2. Different options for fertility preservation, third-party reproduction, and adoption that can be offered to female patients with cancer adapted from the American Society of Clinical Oncology (ASCO) guidelines on fertility preservation in female patients with cancer [16, 78]

Characteristic	Ovarian protection			Embryo freezing	Oocytes cryopreservation	Ovarian tissue cryopreservation and autotransplantation	Oocyte in vitro maturation (IVM)	Third party reproduction			Adoption
	Ovarian transposition (oophoropexy)	Gonadal shielding	Ovarian suppression					Embryo donation	Oocytes donation	Gestational surrogacy	
Definition	Surgical repositioning of ovaries away from the radiation field	Use of shielding to reduce scatter radiation to the reproductive organs	Use of GnRH analogs to suppress ovaries	Ovarian stimulation, harvesting oocytes, IVF, and freezing of embryos for later implantation	Ovarian stimulation, harvesting and freezing of unfertilized oocytes	Freezing of ovarian tissue and reimplantation after cancer treatment	Harvesting of immature oocytes, IVM and oocyte or embryo freezing	Embryos donated by a couple	Eggs donated by a woman	Woman carries a pregnancy for another woman or couple	Process that creates a legal parent–child relationship
Is it established or still experimental?	Established	Established	Experimental	Established	Experimental	Experimental	Experimental	Established	Established	Established	Established
Is it suitable for prepubertal girls?	Suitable	Suitable	Not suitable	Not suitable	Not suitable	Suitable	Not suitable	Not suitable	Not suitable	Not suitable	Not suitable

Mature oocyte cryopreservation: a guideline

The Practice Committees of the American Society for Reproductive Medicine and the Society for Assisted Reproductive Technology

Society for Reproductive Medicine and Society for Assisted Reproductive Technology, Birmingham, Alabama

There is good evidence that fertilization and pregnancy rates are similar to IVF/ICSI with fresh oocytes when vitrified/warmed oocytes are used as part of IVF/ICSI for young women. Although data are limited, no increase in chromosomal abnormalities, birth defects, and developmental deficits has been reported in the offspring born from cryopreserved oocytes when compared to pregnancies from conventional IVF/ICSI and the general population. Evidence indicates that oocyte vitrification and warming should no longer be considered experimental. This document replaces the document last published in 2008 titled, "Ovarian Tissue and Oocyte Cryopreservation," Fertil Steril 2008;90:S241-6. (Fertil Steril® 2013;99:37–43.

Use your smartphone to scan this QR code

Prise en charge de l'IOP

- Préservation de la fertilité:

Salama et al. Ann Oncol 2013

Table 1. Risks of permanent amenorrhea with modern chemotherapy and radiotherapy adapted from the American Society of Clinical Oncology (ASCO) guidelines on fertility preservation in female patients with cancer [16]

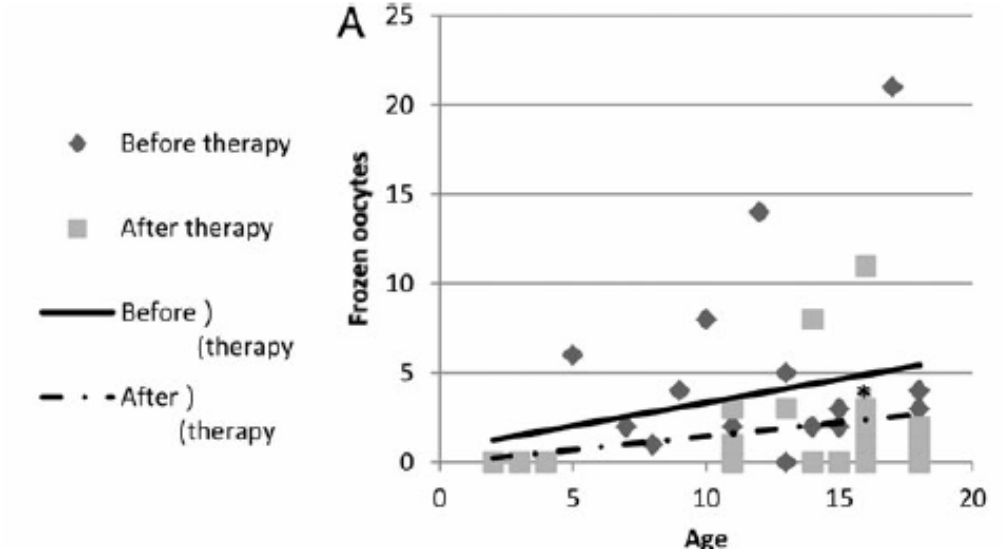
Degree of risk	Treatment
High risk (>80%)	
	- Hematopoietic stem cell transplantation with cyclophosphamide/total body irradiation or cyclophosphamide/busulfan - External beam radiation to a field that includes the ovaries - CMF, CEF, CAF × six cycles in women age 40 and older (adjuvant breast cancer therapy with combinations of cyclophosphamide, methotrexate, fluorouracil, doxorubicin, and epirubicin)
Intermediate risk	
	- CMF, CEF, CAF × six cycles in women age 30–39 (adjuvant breast cancer therapy with combinations of cyclophosphamide, methotrexate, fluorouracil, doxorubicin, and epirubicin) - AC × four cycles in women age 40 and older (adjuvant breast cancer therapy with doxorubicin/cyclophosphamide)
Lower risk (<20%)	
	- ABVD (doxorubicin/bleomycin/vinblastine/dacarbazine) - CHOP × four to six cycles (cyclophosphamide/doxorubicin/vincristine/prednisone) - CVP (cyclophosphamide/vincristine/prednisone) - Acute myeloid leukemia (AML) therapy (anthracycline/cytarabine) - Acute lymphoblastic leukemia (ALL) therapy (multi-agent) - CMF, CEF, CAF × six cycles in women less than 30 (adjuvant breast cancer therapy with combinations of cyclophosphamide, methotrexate, fluorouracil, doxorubicin, epirubicin) - AC × four cycles in women less than 40 (adjuvant breast cancer therapy with doxorubicin/cyclophosphamide)
Very low or no risk	
	- Methotrexate, fluorouracil, vincristine, bleomycin, dactinomycin
Unknown risk (examples)	
	- Taxanes, oxaliplatin, irinotecan, monoclonal antibodies, tyrosine kinase inhibitors

Prise en charge de l'IOP

- Préservation de la fertilité:

Cryopreservation of *in vitro* matured oocytes in addition to ovarian tissue freezing for fertility preservation in paediatric female cancer patients before and after cancer therapy

R. Abir[1,*], I. Ben-Aharon[2], R. Garor[1], I. Yaniv[3], S. Ash[3], S.M. Stemmer[2], A. Ben-Haroush[1], E. Freud[4], D. Kravarusic[4], O. Sapir[1], and B. Fisch[1]

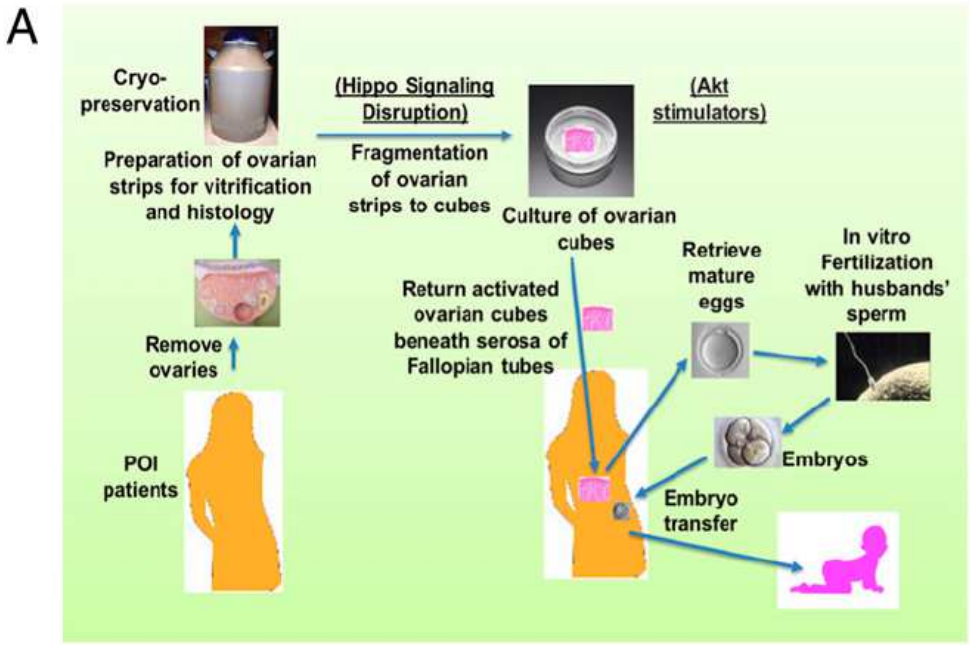


MAIN RESULTS AND ROLE OF CHANCE: Ovarian tissue was successfully collected from 78.7% of the 42 patients. Oocytes were obtained from 20 patients before chemotherapy and 13 after chemotherapy. The youngest patients from whom oocytes were retrieved were aged 2 years (two atretic follicles) and 3 years. Of the 395 oocytes collected, ~30% were atretic (29.6% in the pre-chemotherapy group, 37% in the post-chemotherapy group). One hundred twenty-one oocytes (31%) were matured *in vitro* and vitrified: 67.8% from patients before chemotherapy, the rest after chemotherapy. Mature oocytes suitable for vitrification were obtained from 16/20 patients before chemotherapy and from 12/13 patients after chemotherapy (maturation rate, 32 and 26.4%, respectively). There were significant correlations of the number of vitrified oocytes with patient age (more matured oocytes with older age) ($P = 0.001$) and with pre-oophorectomy AMH levels ($P = 0.038$ pre-chemotherapy group, $P = 0.029$ post-chemotherapy group). Oocytes suitable for vitrification were obtained both by manual aspiration of antral follicles

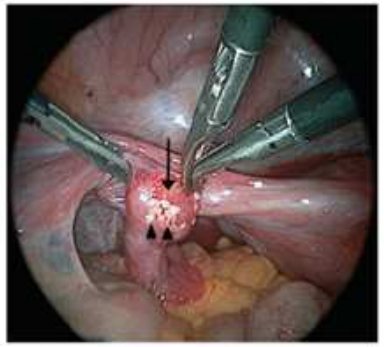
Abir et al. HR 2016

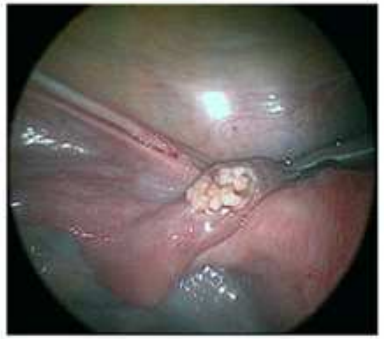
Prise en charge de l'IOP

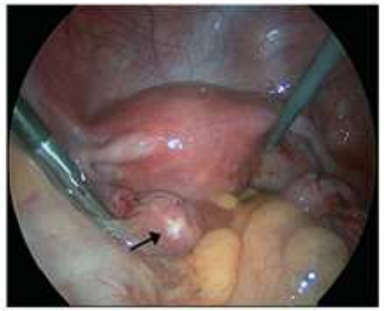
- Stimulation de la folliculogénèse:
  (n=27 patients POI)

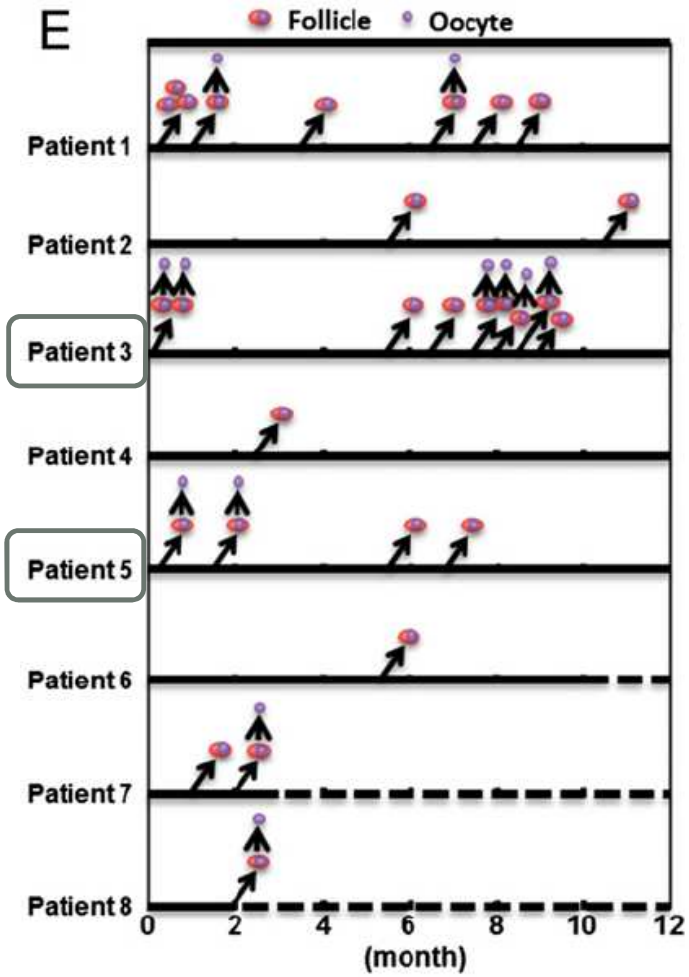


Kawamura et al. PNAS 2013









Prise en charge de l'IOP

- Fertilité:

  1- Don d'ovocytes +++

- Indications du don d'ovocytes en France (Données ABM 2010)

  - 60% IOP/POR
  - 20% Echec PMA
  - 10% Cause génétique non éligible au DPI,

  2- Accueil d'embryons

  3- Adoption

Prise en charge des POR

J Assist Reprod Genet
DOI 10.1007/s10815-015-0476-4

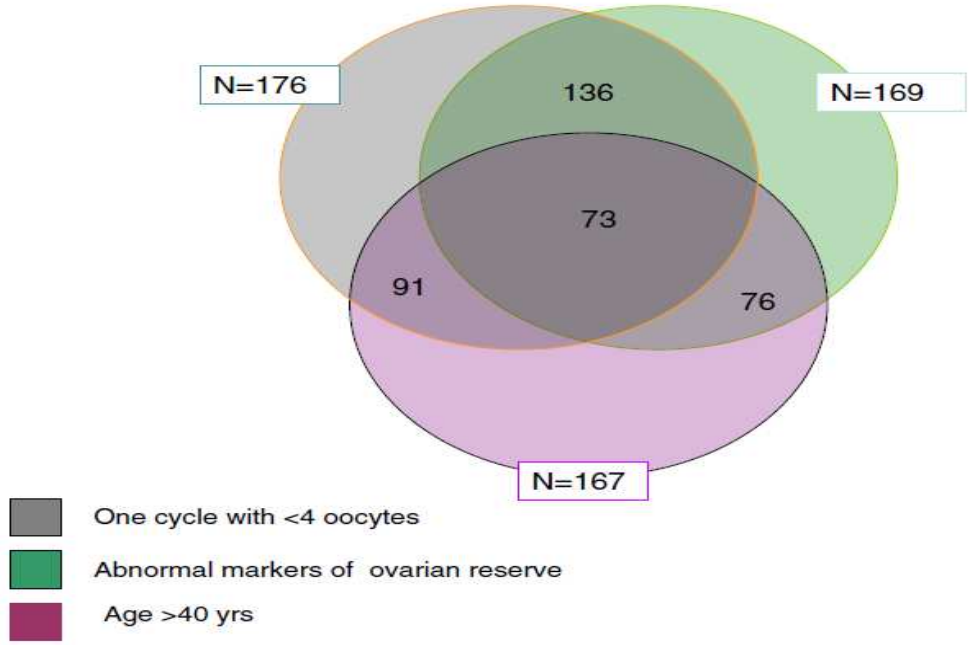
ASSISTED REPRODUCTION TECHNOLOGIES

Live birth rates in the different combinations of the Bologna criteria poor ovarian responders: a validation study

Antonio La Marca[1] · Valentina Grisendi[1] · Simone Giulini[1] · Giovanna Sighinolfi[1] · Alessandra Tirelli[1] · Cindy Argento[1] · Claudia Re[1] · Daniela Tagliasacchi[1] · Tiziana Marsella[1] · Sesh Kamal Sunkara[2]

Received: 23 November 2014 / Accepted: 6 April 2015

Fig. 1 According to the Bologna Criteria for poor response, two out of three criteria need to be present in order to formulate the diagnosis of poor response. Of the 176 women with less than 4 oocytes, 91 were older than 40. An abnormal ORT was found in 169 women and 136 of them had an oocyte yield lower than 4. Seventy-six women were expected poor responders, having had an abnormal ORT and age >40. Seventy-three women met all three Bologna criteria of poor response



Prise en charge des POR

Table 3 Outcome of IVF/ICSI cycles in different categories of women diagnosed as poor responders according to Bologna criteria

Variables	Poor ovarian response categories				
	1 Two cycles with <4oocytes	2 Age >40+cycle with <4oocytes	3 Age>40+abnormal markers of ovarian reserve	4 Cycle with <4oocytes+abnormal markers of ovarian reserve	5 Cycle with <4oocytes+age> 40+abnormal markers of ovarian reserve
Number of patients	76	91	76	136	73
Age (years) (mean, SD)	39±4.7	41.4±1.1	41.3±0.9	38±3.9	41.8±1.7
BMI (kg/m2), (mean, SD)	22.1±2.2	22.3±1.8	23.0±2.3	21.9±2.7	22.1±2.4
Smokers, %	20.3	19.6	19.6	20.1	19.9
Duration of infertility, months (mean,SD)	45±21	44±22	47±26	43±24	46±20
AFC (n) (mean, SD)	4.1±0.9	3.9±1.1	3.7±0.87	3.7±1.2	3.9±1.1
AMH (ng/ml) (mean,SD)	0.6±0.29	0,5±0,32	0,65±0,29	0,5±0,3	0,57±0,31
No. of oocytes (mean, SD)	1.98±1.1	1.93±1.23	1.76±1.02	2.1±1.3	1.6±1.1
No. of embryos transferred (mean, SD)	1.3±0.15	1.1±0.2	1.2±0.13	1.2±0.17	0.9±0.2
Cycles with oocyte retrieval (%)	79.5	75.6	71.1	81.1	70.1
Cycles with embryo transfer (%)	69.1	63.2	66.3	70.6	60.4
Clinical pregnancy rate (per started cycle) (%)	13.7	12.5	14.3	13.4	12.5
Live birth rate (per started cycle)	7.4	6.6	5.9	6.7	5.5

Prise en charge des POR

N=160 cycles, 142 fresh ET, 134 patients who had completed ET with all available embryo

Table 3. Reproductive outcomes in EPOR by ovarian response.

	> 3 oocytes retrieved	≤ 3 oocytes retrieved	P value
Live birth in fresh cycle	30/97 (30.9%)	8/45 (17.8%)	NS
Cumulative live birth	40/91 (44.0%)	8/43 (18.6%)	0.006

Chai *et al.*, Plos One 2015

Live birth rates in Bologna poor responders treated with ovarian stimulation for IVF/ICSI

Nikolaos P Polyzos *, Milie Nwoye, Roberta Corona, Christophe Blockeel, Dominic Stoop, Patrick Haentjens, Michel Camus, Herman Tournaye

Abstract This retrospective study determined the efficacy of ovarian stimulation for IVF/intracytoplasmic sperm injection (ICSI) in poor ovarian responders fulfilling the Bologna criteria for poor ovarian response and identified predictors of live birth rates. Overall, 485 patients undergoing 823 ovarian stimulation cycles for IVF/ICSI with maximum gonadotrophin dose (≥300 IU) between January 2009 and December 2011 were included. Patients were considered eligible, irrespective of the treatment protocol, if they were classified as poor responders based on the recently developed definition for poor ovarian response by the European Society of Human Reproduction and Embryology, the Bologna criteria. Live birth rates did not significantly differ between women aged <40 and women aged ≥40 years either per cycle (7.1 versus 5.2%, OR 1.38, 95% CI 0.77–2.46) or per patient (11.6 versus 8.8%, OR 1.36, 95% CI 0.75–2.46). In logistic regression analysis, the number of oocytes retrieved was the only variable significantly associated with live births (OR 1.92, 95% CI 1.03–3.55 for >3 versus 1–3 oocytes). Bologna poor responders demonstrate very low live birth rates, irrespective of age and treatment protocol used. An increase in the number of oocytes retrieved is an independent variable related to live birth rates.

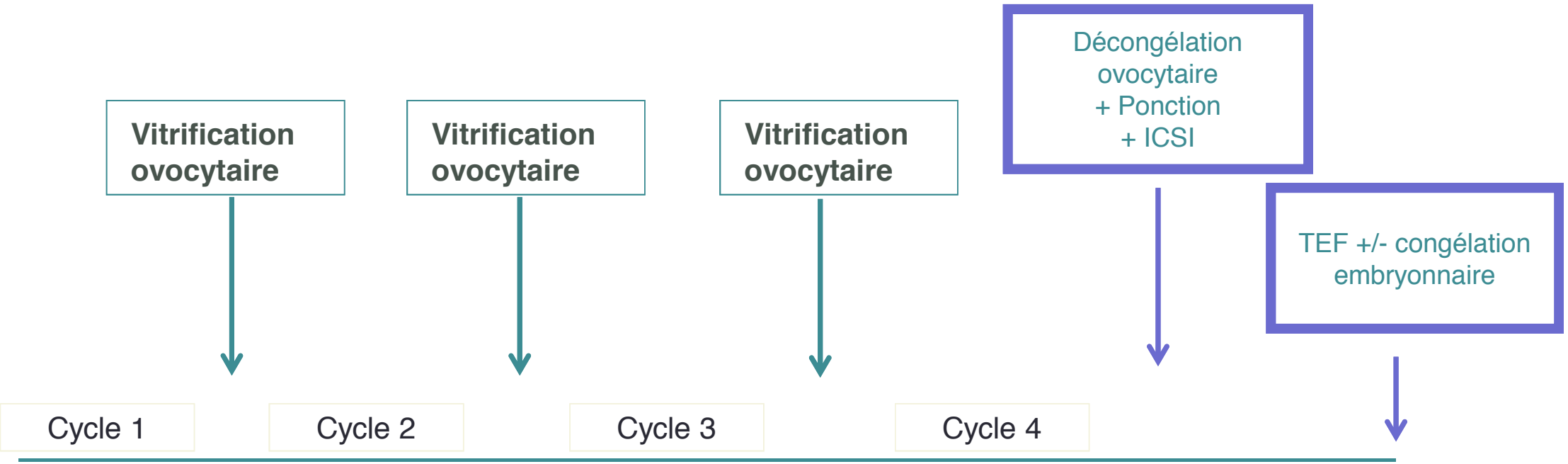
Prise en charge des POR

Poor Ovarian Responder et Taux de succès après AMP?

- **Très faible** (Consensus à +/- 6%)
- **Coute cher** (87 748 euros/Birth (Busnelli et al., HR 2015))
- **Augmente avec le nombre d'ovocytes**

Prise en charge des POR

Le cumul ovocytaire: Le concept



Prise en charge des POR

Arguments pour le cumul ovocytaire

- Recherche de l'ovocyte au meilleur potentiel implantatoire?
- Augmentation globale de l'exposition à la grossesse?
- Aspects psychologiques (vécu, drop out…)?
- Préservation de la fertilité?

Trop peu de données…..

Prise en charge des POR

- Impact sur la parcours des patientes
  - Moins de drop-out
    - 75% pour les cycles frais

Cobo *et al.*, RBO, 2012

  - Moins d'échecs répétés
  - Meilleur vécu?

- « Préservation de la fertilité » si embryons surnuméraires

Prise en charge des POR

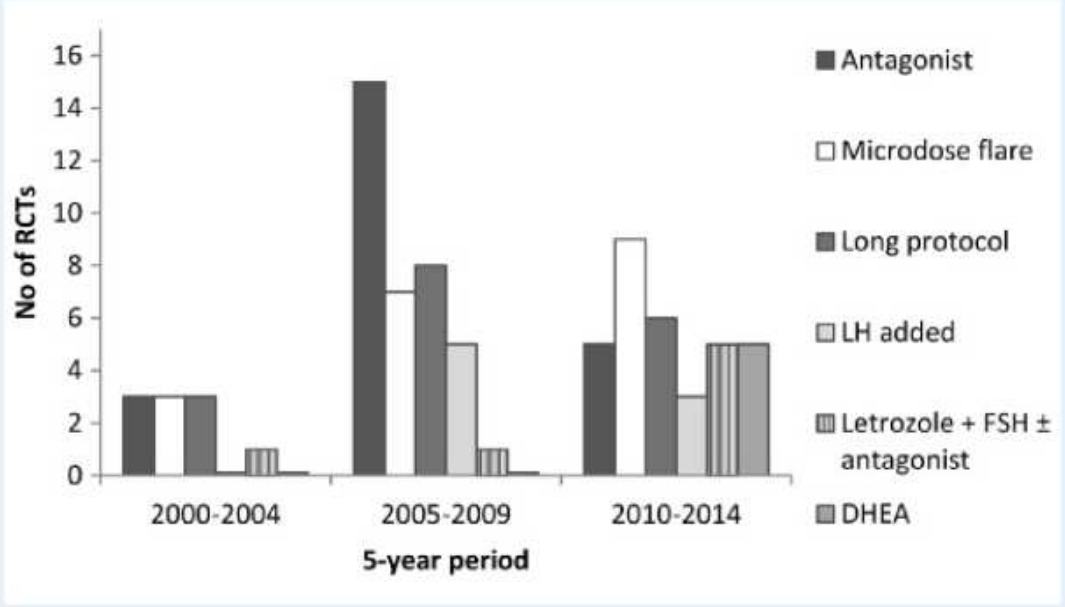


Figure 4 Most popular interventions in 'poor responder' randomized trials (presented in three 5-year intervals to display trends). DHEA, dehydroepiandrosterone.

Papathanasiou et al. HRU 2016

Table II Interventions investigated by RCTs in 'poor responders' (most popular intervention first).

Antagonist
Microdose flare
Long protocol
LH added
Letrozole + FSH ± antagonist
DHEA
Short protocol
Transdermal testosterone
Growth hormone
HCG added at stimulation
Increase of FSH dose
Clomiphene citrate + FSH/HMG +/- antagonist
Luteal FSH start
Estrogen for luteal support
Follicular flushing
Long-stop protocol
FSH/HMG only (no agonist or antagonist)
FSH dose 300 IU
Late FSH start
Metformin
Ultrashort agonist-antagonist
Modified flare
Low-dose aspirin
Natural cycle
Mini-long protocol
Step-down of FSH dose
Luteal phase antagonist
Gamete intrauterine transfer
Day of embryo transfer
Early (Day 1) FSH start
FSH dose 450 IU
FSH dose 600 IU
Clomiphene citrate only

DHEA, dehydroepiandrosterone.

Prise en charge des POR

Table III Interventions with at least one RCT indicating benefit in reproductive outcomes.

Intervention	Significant outcome	Number of RCTs showing benefit	Number of RCTs showing no benefit
Estrogen add-back for luteal support	Live birth	**1 RCT** Kutlusoy *et al.* (2014)	**1 RCT** Aghahosseini *et al.* (2011)
rLH 4-day treatment followed by rFSH treatment during long protocol	Live birth	**1 RCT** Ferraretti *et al.* (2014)	**None**
DHEA supplementation	Ongoing pregnancy	**1 RCT** Moawad and Shaeer (2012)	**4 RCTs** Wiser *et al.* (2010) Artini *et al.* (2012) Kara *et al.* (2014) Yeung *et al.* (2014)
Antagonist flexible protocol (compared with microdose flare protocol)	Ongoing pregnancy	**1 RCT** Lainas *et al.* (2008)	**8 RCTs** Akman *et al.* (2001) Martinez *et al.* (2003) Malmusi *et al.* (2005) Schmidt *et al.* (2005) De Placido *et al.* (2006) Demirol and Gurgan (2009) Kahraman *et al.* (2009) Davar *et al.* (2013)
Day 2 embryo transfer (compared with Day 3)	Ongoing pregnancy	**1 RCT** Bahceci *et al.* (2006)	**None**
Long protocol (compared with antagonist protocol)	Clinical pregnancy	**1 RCT** Prapas *et al.* (2013)	**7 RCTs** Cheung *et al.* (2005) Marci *et al.* (2005) Tazegul *et al.* (2008) Kim *et al.* (2009) Shahrokh Tehrani Nejad *et al.* (2008) Kim *et al.* (2011) Sunkara *et al.* (2014)
Follicular flushing	Clinical pregnancy	**1 RCT** Mok-Lin *et al.* (2013)	**1 RCT** Levens *et al.* (2009)
Day 4 FSH start (compared with Day 1 FSH start) during antagonist protocol	Clinical pregnancy	**1RCT** Baerwald *et al.* (2012)	**None**
Transdermal testosterone	Clinical pregnancy	**1 RCT** Kim *et al.* (2011)	**2 RCTs** Massin *et al.* (2006) Fabregues *et al.* (2009)
Luteal phase FSH start	Clinical pregnancy	**1 RCT** Kucuk *et al.* (2008)	**2 RCTs** Kucuk and Sozen (2007) Kansal Kalra *et al.* (2008)
Addition of rLH mid-stimulation (compared with FSH dose increase)	Clinical pregnancy	**1 RCT** Ruvolo *et al.* (2007)	**2 RCTs** De Placido *et al.* (2001) De Placido *et al.* (2005)
High FSH dose (300 IU/day) (compared with 150 IU/day)	Clinical pregnancy	**1 RCT** Klinkert *et al.* (2005)	**None**

rLH/rFSH, recombinant LH/FSH.

Conclusions générales

- IOP:
  - Bilan simple disponible
  - PEC: Symptomatique: THS, Psychologique
    Préservation de la fertilité: Vitrification ovocytaire?
    Fragments ovariens?
    Fertilité: Don d'ovocytes +++

- Mauvaises répondeuses:
  - PEC médicale type « recette de cuisine » non fondée sur la preuve scientifique

Merci pour votre attention