



Préservation de la fertilité féminine

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Préservation de la fertilité féminine

Learning objectives: Y penser !!!



- Les techniques de préservation de la fertilité féminine
- Préservation de la fertilité dans le cadre du cancer
- Y penser pour toute pathologie risquant d'altérer la réserve ovarienne!



Préservation de la fertilité inscrite dans la Loi Française

«Toute personne dont la prise en charge médicale est susceptible d'altérer la fertilité, ou dont la fertilité risque d'être prématurément altérée, peut bénéficier du recueil et de la conservation de ses gamètes ou de ses tissus germinaux, en vue de la réalisation ultérieure, à son bénéfice, d'une assistance médicale à la procréation, ou en vue de la préservation et de la restauration de sa fertilité»

« Toute prise en charge susceptible d'altérer la fertilité »

« Toute personne dont la fertilité risque d'être prématurément altérée »

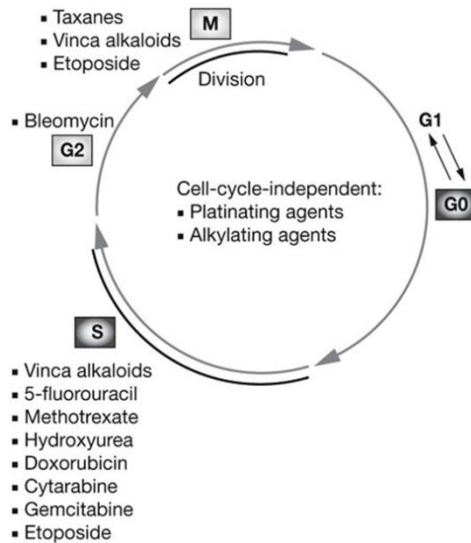
Indications TRES
TRES larges....



Traitement anti-cancéreux

Agents ovariotoxique (Alkylants +++)

Radiothérapie pelvienne

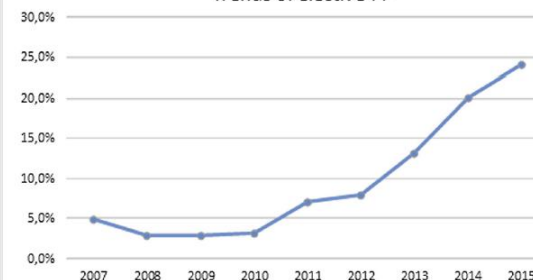


Seiwert *et al.* 2007

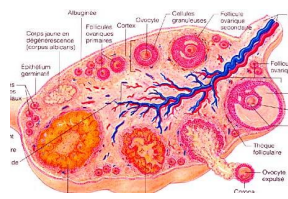
Pathologies bénignes

- Chirurgie itérative de kystes ovariens (endométriomes, tératomes...)
- Antécédents familiaux d'insuffisance ovarienne prématurée
- Pathologies génétiques à risque d'insuffisance d'ovarienne prématurée

Trends of elective FP



Cobo *et al.*, 2016

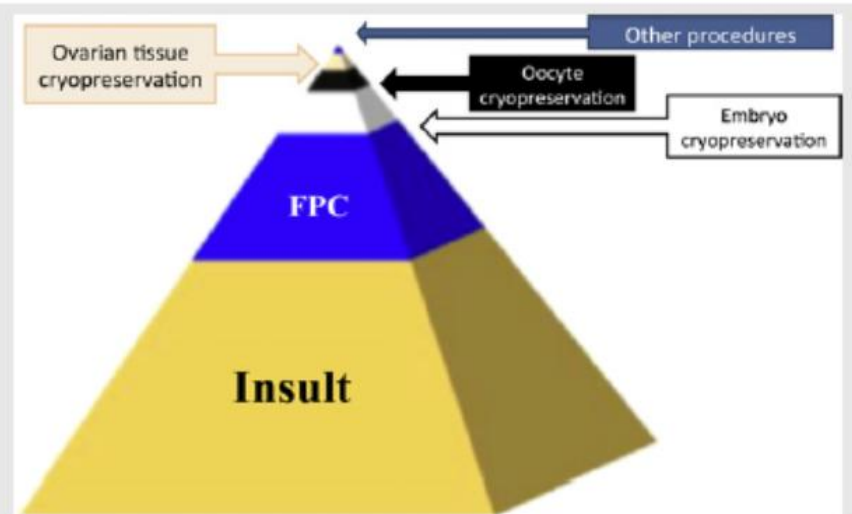


1 . Les techniques de préservation de la fertilité féminine

Fertility preservation in patients undergoing gonadotoxic therapy or gonadectomy: a committee opinion

The Practice Committee of the American Society for Reproductive Medicine
American Society for Reproductive Medicine, Birmingham, Alabama

2013



“Pyramid” of fertility preservation. Medical interventions including chemotherapy, radiotherapy, and surgery act as insults to ovarian reserve and may result in premature ovarian failure and infertility. However, of all the patients at risk for premature ovarian failure, only a fraction will be referred to fertility preservation consultation (FPC) (5). Of those even a smaller fraction will be undergoing fertility preservation due to social, economic, or technical hurdles. Of all techniques offered, embryo cryopreservation is most commonly used, followed by oocyte cryopreservation, ovarian tissue freezing, and other methods, in that order.

Bedaschi. Fertility preservation by embryo cryopreservation. Fertil Steril 2013.

Seules la vitrification ovocytaire et la congélation embryonnaire sont considérées comme des techniques « non expérimentales »

Vitrification ovocytes matures



Garcia-Velasco et al., 2013

Congélation embryonnaire



Courbiere et al., 2013
Barcroft et al., 2013

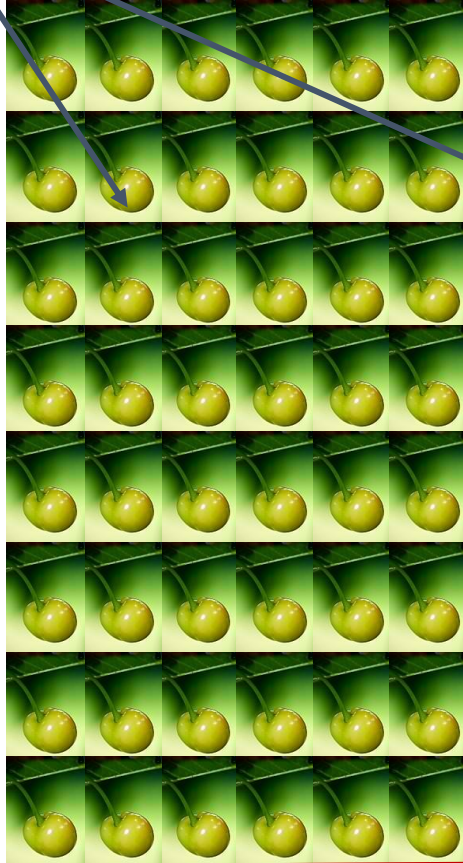
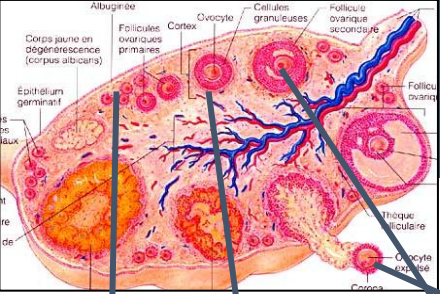
Cryoconservation tissu ovarien

Dolmans et al., 2013

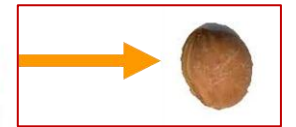
Maturation ovocytaire in Vitro

Grynberg et al., 2013

Comment expliquer la physiologie ovarienne et les techniques de préservation de la fertilité aux patientes? L'ovocyte n'est pas un spermatozoïde



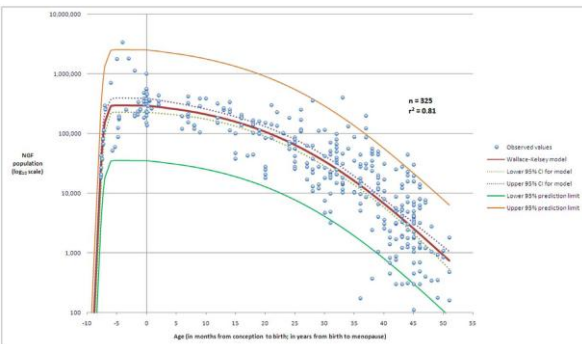
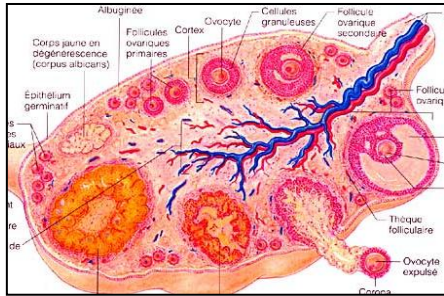
14 jours



1 seul ovocyte mature par mois

6 mois

La fertilité et la réserve ovarienne diminuent avec l'âge... Conditionnant les possibilités de préservation des gamètes...



20 ans



38 ans

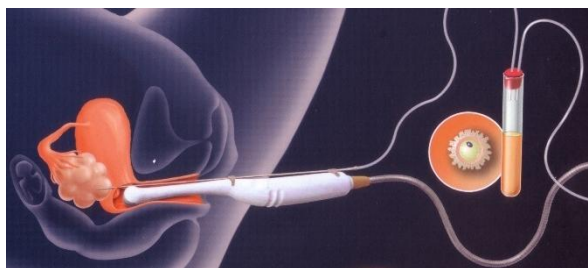
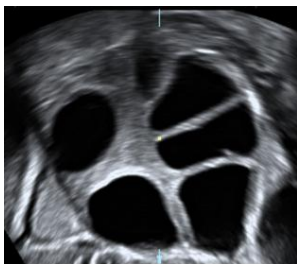


> 50 ans

Wallace et Kelsey, 2010

Autoconservation ovocytaire « raisonnable » jusqu'à 37 ans étant donné la diminution de la réserve ovarienne et l'augmentation du risque d'aneuploïdie...

Deux techniques de préservation de la fertilité qui donnent de « vraies » chances d'avoir un enfant



FIV

+ Congélation embryons

Live Birth Rate (LBR) = 30 % par transfert



Projet parental

Limites légales et éthiques

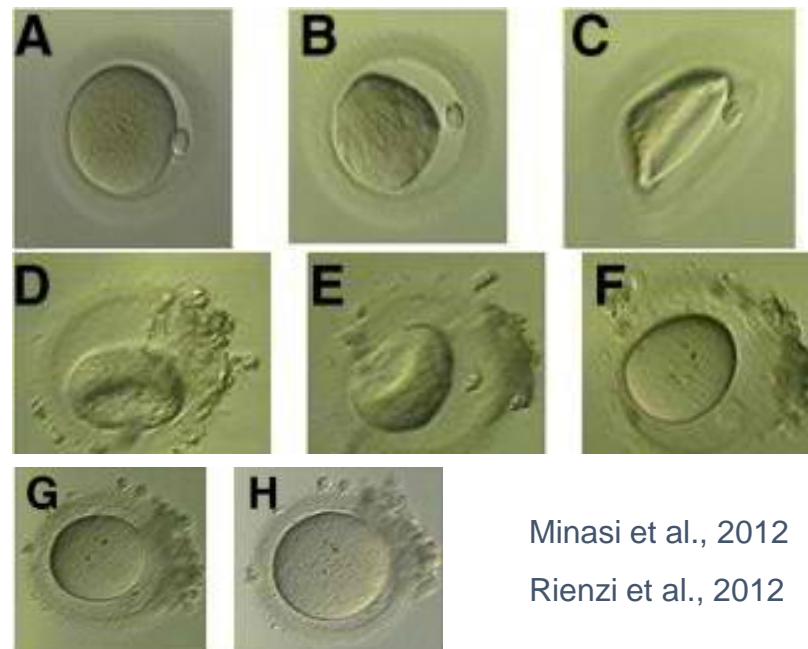
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Friedler et al., 2011

Courbiere et al., 2013

Vitrification ovocytes

LBR = 46,4 % si 8 ovocytes



Minasi et al., 2012

Rienzi et al., 2012



La congélation embryonnaire sera-t-elle obsolète dans le futur en biologie de la reproduction?

ARTICLE

Oocyte versus embryo vitrification for delayed embryo transfer: an observational study

Leyre Herrero ^a, Sandra Pareja ^a, Marina Aragonés ^a, Ana Cobo ^b, Fernando Bronet ^a, Juan Antonio Garcia-Velasco ^{a,c,*}

Table 2 Outcome per oocyte vitrification cycle and per embryo vitrification cycle.

<i>Group 1</i>	<i>First transfer (oocyte warming)</i>	<i>Second transfer (first cryopreserved embryo transfer)</i>	<i>Third transfer (second cryopreserved embryo transfer)</i>	<i>Total embryo transfers</i>
N	50	16	8	74
Biochemical pregnancy rate	26 (52.0)	6 (37.5)	4 (50.0)	36 (48.6)
Clinical pregnancy rate	22 (44.0)	5 (31.3)	4 (50.0)	31 (41.9)
Twin pregnancy rate	8 (36.4)	1 (20.0)	1 (25.0)	10 (32.2)
Clinical miscarriage rate	1 (4.5) ^a	0	2 (50.0)	3 (9.7) ^b
Implantation rate	30/92 (32.6)	6/28 (21.4)	5/14 (35.7)	41/134 (30.6)

<i>Group 2</i>	<i>First cryopreserved embryo transfer</i>	<i>Second cryopreserved embryo transfer</i>	<i>Third cryopreserved embryo transfer</i>	<i>Total embryo transfers</i>
N	46	19	3	68
Biochemical pregnancy rate <i>n</i> (%)	24 (52.2)	7 (36.8)	2 (66.7)	33 (48.5)
Clinical pregnancy rate <i>n</i> (%)	23 (50.0)	7 (36.8)	2 (66.7)	32 (47.1)
Twin pregnancy rate <i>n</i> (%)	5 (21.7)	2 (28.6)	0	7 (21.9)
Clinical spontaneous abortion rate <i>n</i> (%)	7 (30.4) ^a	0	0	7 (21.9) ^b
Implantation rate <i>n</i> (%)	28/80 (35.0)	9/33 (27.3)	2/5 (40.0)	39/118 (33.1)

^a*P* = 0.0007 (group 1).

^b*P* = 0.04 (group 2).

Oocyte vitrification achieved the same live birth rate as embryo

Oocytes vitrification as an efficient option for elective fertility preservation

Ana Cobo, Ph.D.,^a Juan A. García-Velasco, M.D.,^b Aila Coello, Ph.D.,^a Javier Domingo, M.D.,^c Antonio Pellicer, M.D.,^d and José Remohí, M.D.^a

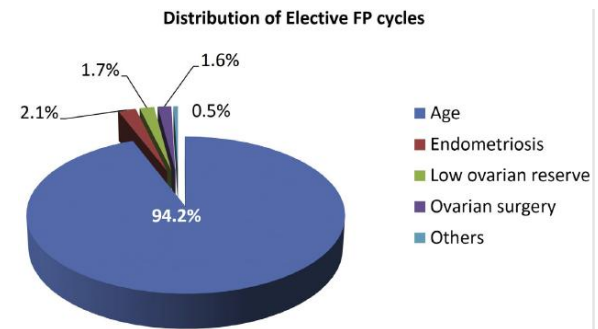
Fertil Steril, 2016

VITRIFICATION OVOCYTAIRE

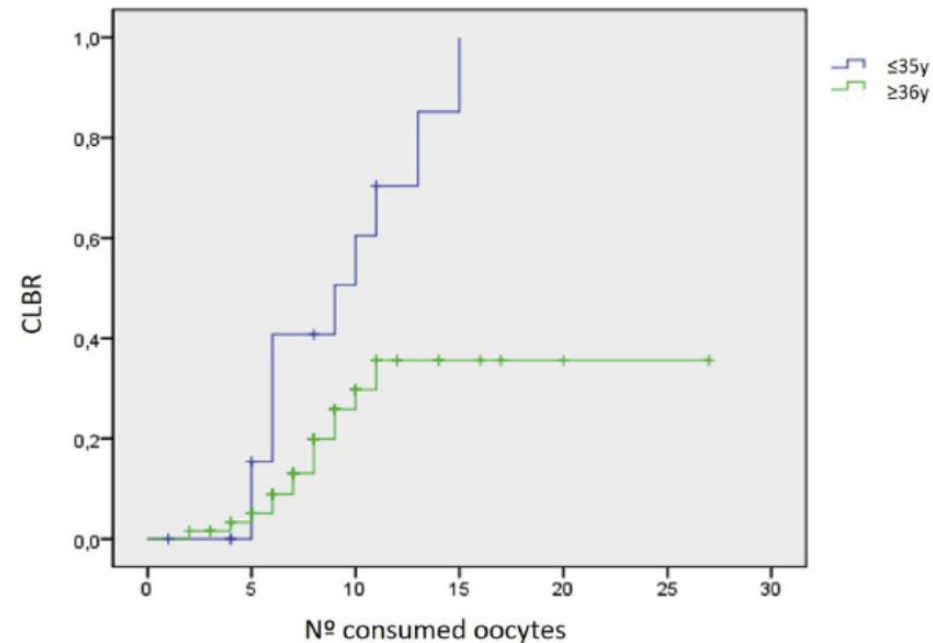
Bonne technique ... pour les femmes jeunes (< 35 ans) et si vitrification de « suffisamment » d'ovocytes !

→ si possible plusieurs cycles pour cumul ovocytaire

+++

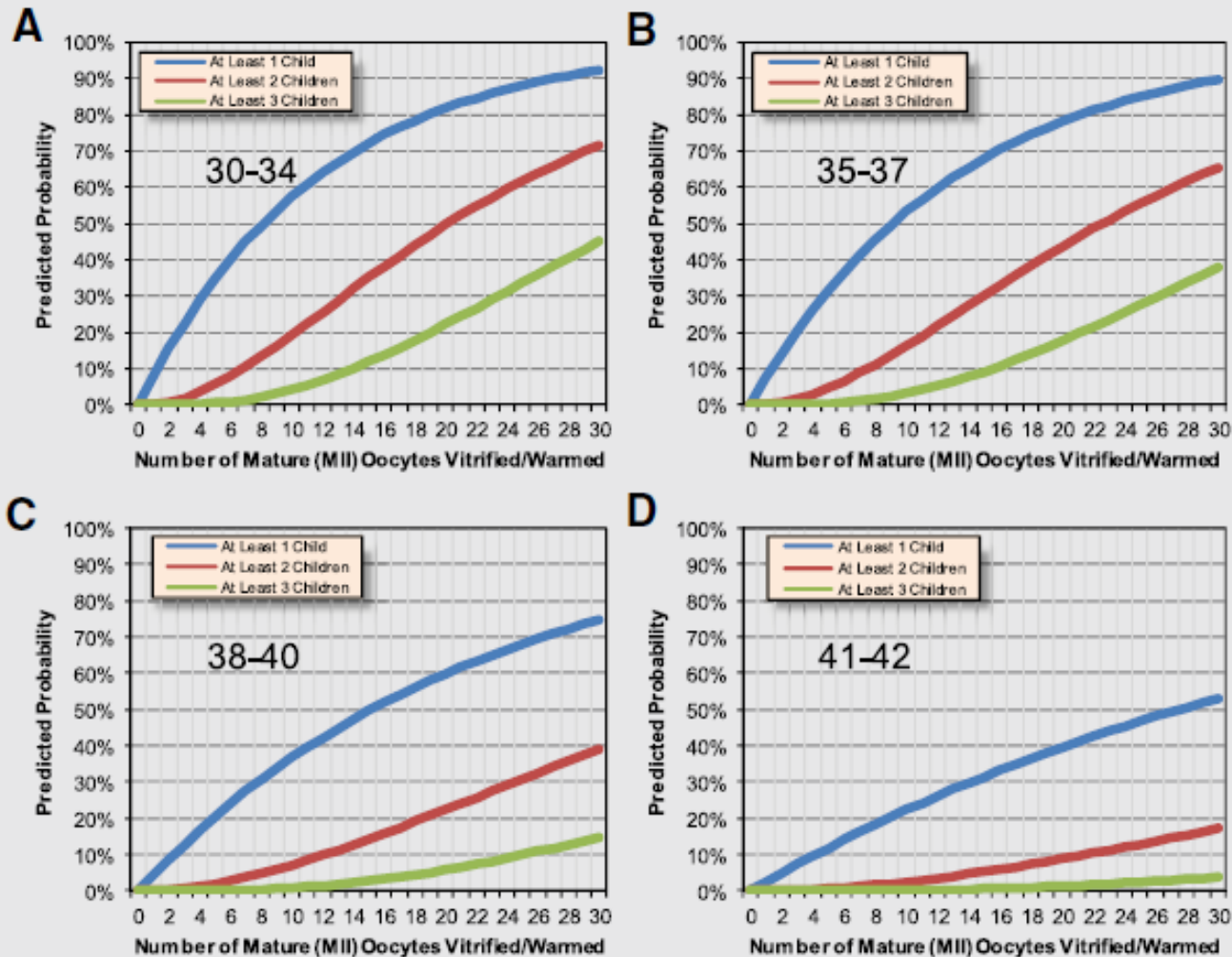


CLBR according to age (≤ 35 vs ≥ 36) and N° oocytes consumed



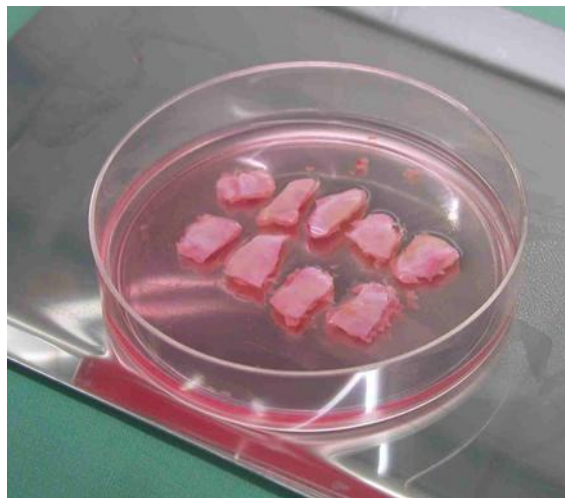
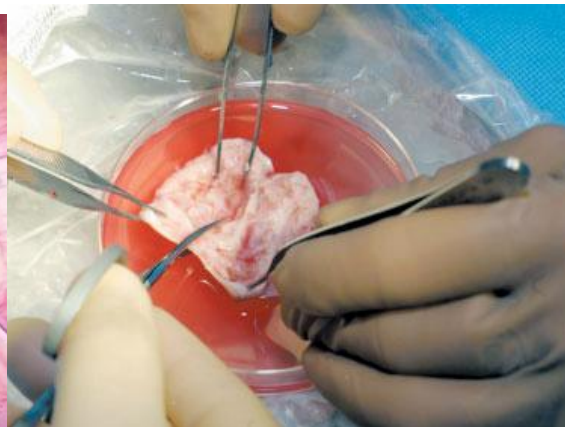
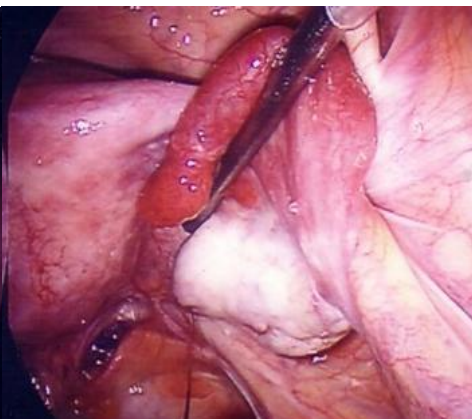
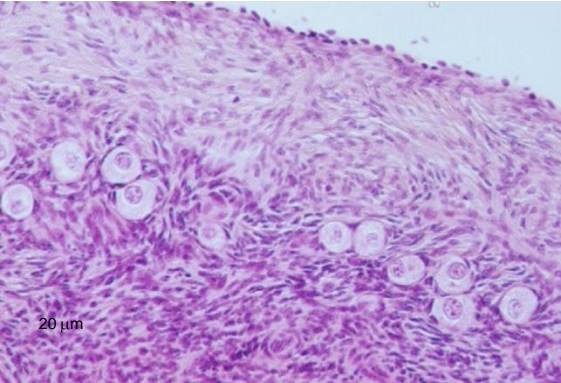
≤35 years old		≥36 years old	
N°oocytes	CLBR (IC95%)	N°oocytes	CLBR (95% CI)
5	15,4 (-4.2-35.0)	5	5,1 (-0.6-10.7)
8	40.8 (13.2-68.4)	8	19,9 (8.7-31.1)
9	50,6 (31.6-79.6)	9	25,8 (12.7-38.9)
10	60,5 (34.5-89.5)	10	29,7 (15.2-34.2)
15	85,2 (60.5-100)	11	35,6 (18.4-52.8)

Taux de naissance / transfert = 39 % 1 ovocyte vitrifié = 6,4 % de chances d'avoir une naissance

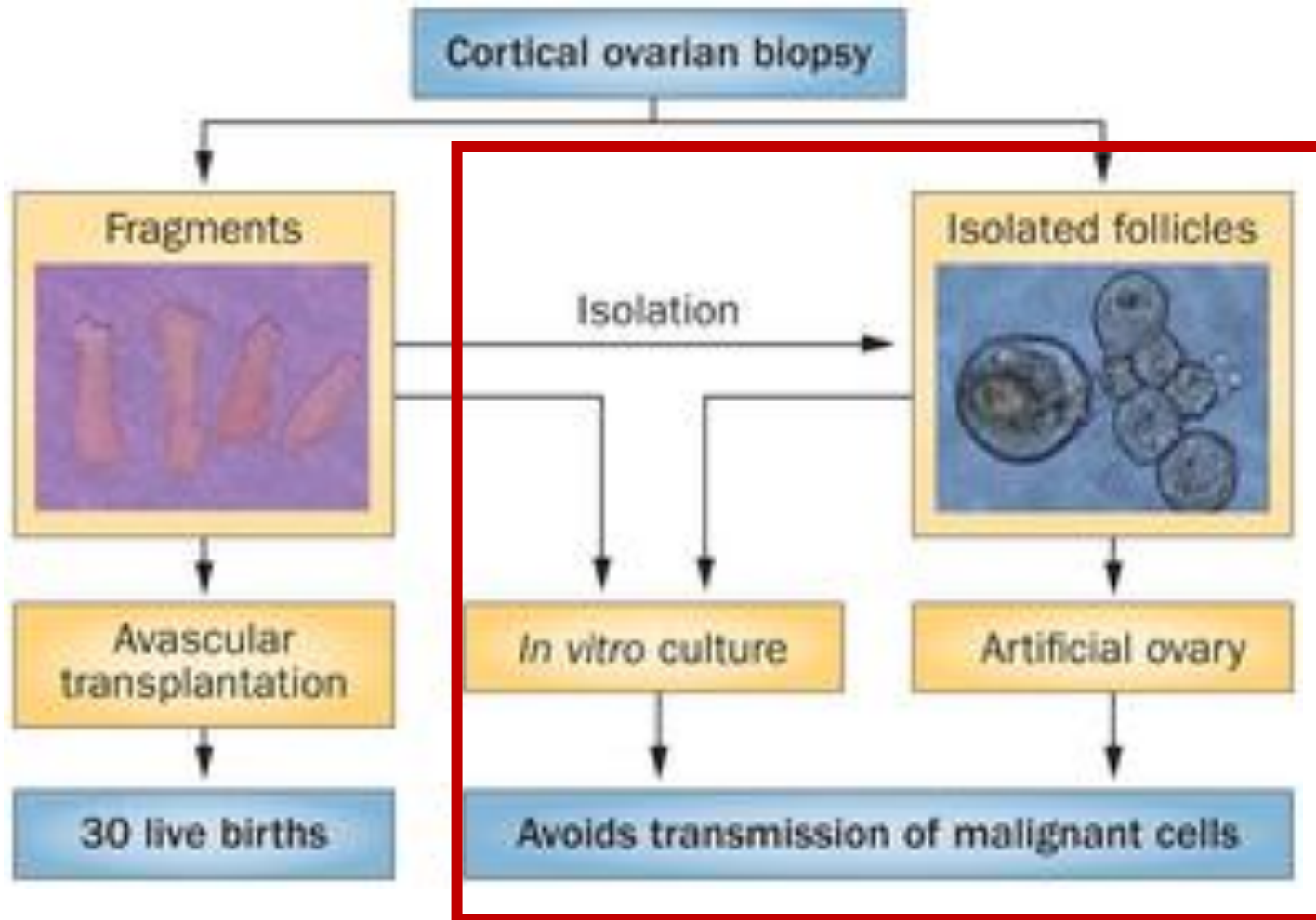


Predicted probabilities of having at least one, two, and three live-born children according to the number of mature oocytes cryopreserved for elective fertility preservation, according to age at oocyte retrieval and the associated oocyte to live-born child efficiency estimates: (A) 30–34 years, 8.2% efficiency; (B) 35–37 years, 7.3% efficiency; (C) 38–40 years, 4.5% efficiency; (D) 41–42 years, 2.5% efficiency.

Avant la puberté : Cryoconservation de tissu ovarien



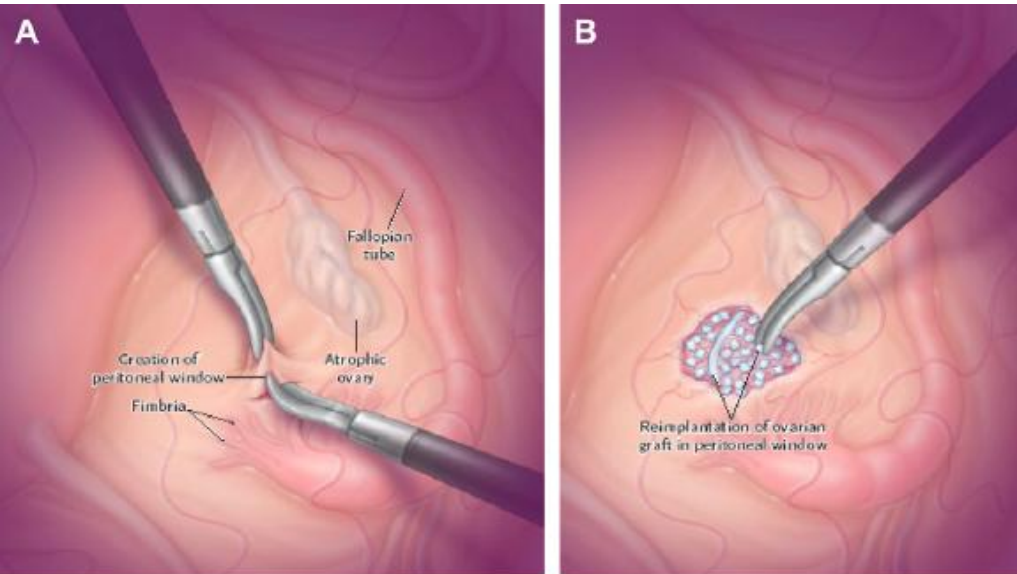
Quel devenir des fragments de cortex ovarien si désir de grossesse ?



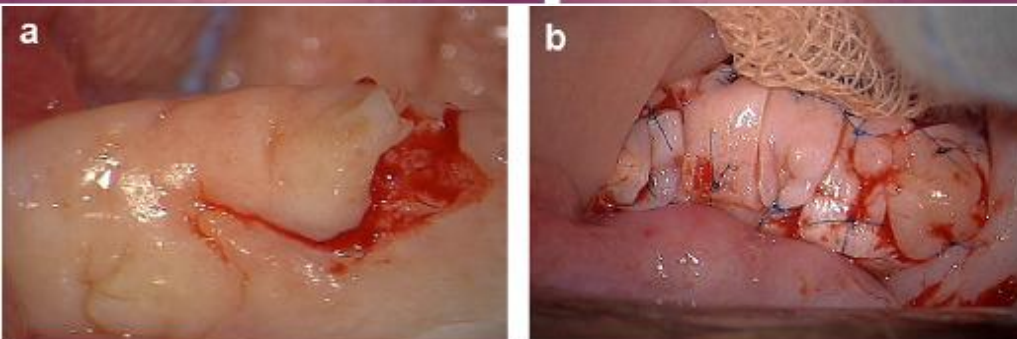
Recherche
fondamentale

Autogreffe orthotopique

Donnez et al., 2010



(1) Greffe de fragments au niveau d'une fenêtre péritonéale



(2) Greffe de fragments au niveau de l'ovaire restant controlatéral



Débat autour du risque théorique réintroduction de cellules malignes par autogreffe

Reimplantation of cryopreserved ovarian tissue from patients with acute lymphoblastic leukemia is potentially unsafe

Marie-Madeleine Dolmans,¹ Cristina Marinascu,¹ Pascale Saussoy,² Anne Van Langendonck,¹ Christiani Amorim,¹ and Jacques Donnaz¹

Dolmans et al. Blood. 2010; 116(16):2908-14

Cryopreserved ovarian cortex from patients with leukemia in complete remission contains no apparent viable malignant cells

Tine Greve,¹ Erik Clasen-Linde,² Morten T. Andersen,³ Mette K. Andersen,³ Stine D. Sørensen,¹ Mikkel Rosendahl,⁴ Elisabeth Ralfkiær,² and Claus Yding Andersen¹

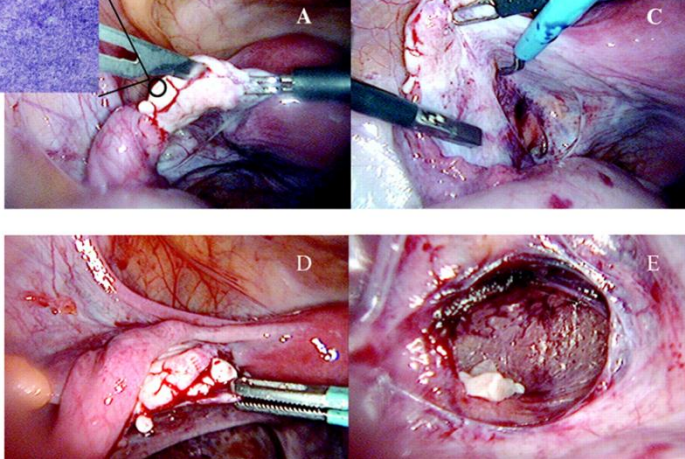
¹Laboratory of Reproductive Biology, Rigshospitalet–Copenhagen University Hospital, Copenhagen, Denmark; ²Department of Pathology, Rigshospitalet–Copenhagen University Hospital, Copenhagen, Denmark; ³Department of Clinical Genetics, Rigshospitalet–Copenhagen University Hospital, Copenhagen, Denmark; and ⁴Department Gynecology and Obstetrics, Rigshospitalet–Copenhagen University Hospital, Copenhagen, Denmark

Thus, the ovaries from patients in complete remission do not appear to contain viable malignant cells contrasting ovarian tissue retrieved before treatment. (*Blood*. 2012;120(22):4311-4316)

2017

13 ans après la première naissance après autogreffe de tissu ovarien

Demeestere et al. 2006



Ovarian cortex transplantation: time to move on from experimental studies to open clinical application

Jacques Donnez, M.D., Ph.D.^a
Marie-Madeleine Dolmans, M.D., Ph.D.^{b,c}
César Diaz, M.D., Ph.D.^d
Antonio Pellicer, M.D., Ph.D.^{d,e}

Fertil Steril 2015

TABLE 1

Results from five centers, allowing evaluation of pregnancy and live birth rates, because the number of transplants is known.

Team	Transplanted women	Women who conceived (%)	Women who gave birth	Live births (ongoing pregnancies)	Miscarriages
Donnez and Dolmans' team (2)	19	7	5	8 (+1) ^{a,b}	1
Andersen's team (4)	25	8	6	8 ^b	2
Pellicer's team (2)	33	8	4	6 ^{a,c} (+3)	3
Dittrich's team (3)	20	7	6	8 ^a	1
Rezen's team (5)	14	7	2	2 ^c	0
Total	111	32 (29)	23	33 (+4)	7

Note: Data from references 2-5. Values are number, except where noted.

^a One woman delivered twice.

^b One woman delivered three times.

^c One twin delivery.

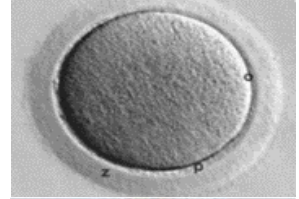
Donnez. Ovarian cortex transplantation. Fertil Steril 2015.

Fertility preservation in patients undergoing gonadotoxic therapy or gonadectomy: a committee opinion

The Practice Committee of the American Society for Reproductive Medicine
American Society for Reproductive Medicine, Birmingham, Alabama

Fertil Steril 2013

Transvaginal retrieval of immature oocytes with in vitro maturation (IVM) of oocytes. Transvaginal retrieval of immature oocytes with in vitro maturation (IVM) of oocytes has been advocated for patients with estrogen-sensitive tumors and for those who require urgent initiation of cancer therapy. This approach involves the retrieval of immature oocytes in unstimulated postpubertal ovaries and then maturation of the oocytes in the laboratory (IVM) for mature oocyte or embryo cryopreservation. While several live births have been reported using this technique, this technique still should be considered investigational because the efficacy and safety are unknown (63–65).



2. Les indications « faciles » d'autoconservation ovocytaire en oncologie

Table 1

Cytotoxic agents according to degree of gonadotoxicity.

High risk	Intermediate risk	Low/no risk
Cyclophosphamide	Adriamycin (Doxorubicin)	Methotrexate
Busulfan	Cisplatin	Bleomycin
Melphalan	Carboplatin	5-Fluorouracil
Cholarambucil		Actinomycin D
Dacarbazine		Mercaptopurine
Procarbazine		Vincristine
Ifosfamide		
Thiotepa		
Nitrogen mustard		

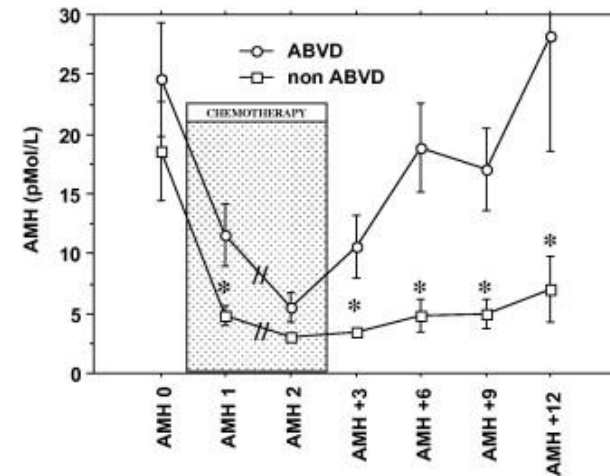
Donnez et al., 2010

Avant chimiothérapie avec alkylants ou si risque de rechute / intensification:

- Lymphomes +++++
- Sarcomes

A distance d'une chimiothérapie avec alkylants (1 an – 2 ans ?)

→ **Protocoles de cumul ovocytaire +++**



Decanter et al., 2010

3) Breast cancer

It is recommended that fertility preservation consultation is arranged at the time of initial diagnosis. In many cases, young breast cancer patients require adjuvant chemotherapy after surgery (mastectomy or lumpectomy). The best time for fertility preservation is after surgery and before adjuvant therapy.

Cryopreservation of embryos or cryopreservation of oocytes is recommended as a fertility preservation option before chemotherapy. As cryopreservation of embryos or oocytes requires controlled ovarian stimulation (COS), the risk of increased peak estradiol levels with COS in breast cancer patients (especially with ER+tumor) should be discussed before the procedure. The COS strategy using tamoxifen or letrozole in conjunction with gonadotropin may be safer for women with ER+tumor. For women who require urgent cancer treatment such as neo-adjuvant chemotherapy, cryopreservation of ovarian tissue should be considered. Alternatively, immature oocyte retrieval followed by IVM and cryopreservation of oocytes or embryos can be considered.

Pas d'augmentation des récurrences de cancer du sein après stimulation ovarienne avec Letrozole

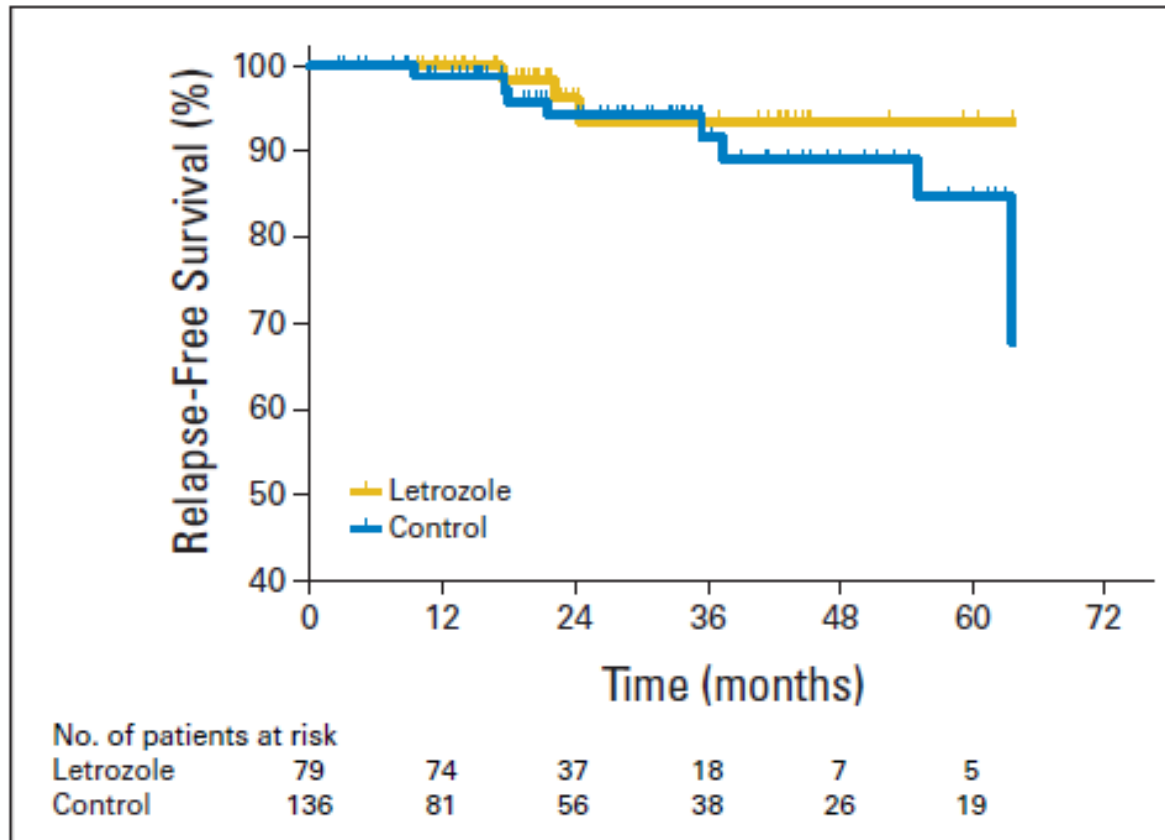
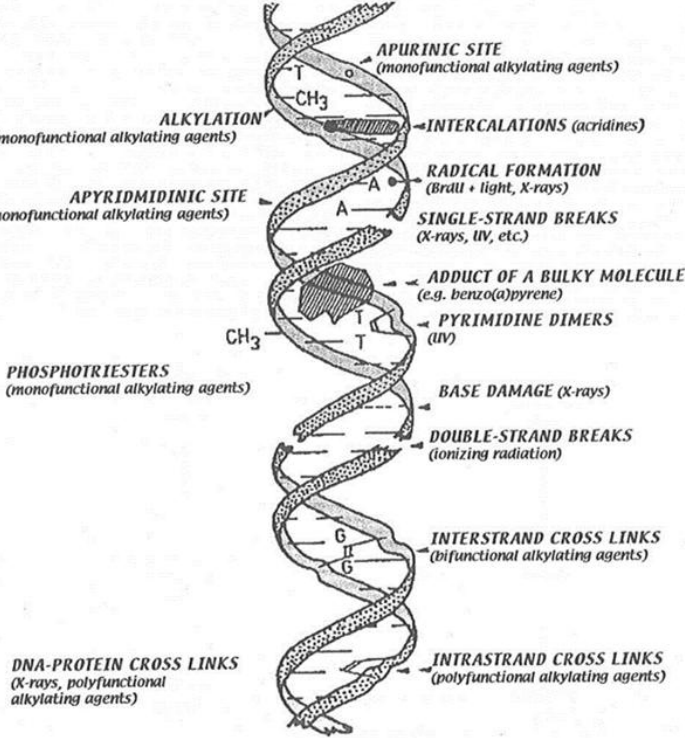


Fig 2. Relapse-free survival in ovarian stimulation and control groups. Kaplan-Meier plot for relapse-free survival in letrozole and control groups. $P = .36$ (log-rank test), hazard ratio = 0.56. The number of patients at risk at each year is shown below the graph.

Pas d'augmentation du risque de récurrence à 5 ans, RR = 0.77 (95% CI: 0.28, 2.13) Kim et al. JCEM 2016

Les indications difficiles: en cas d'atcd récent de chimiothérapie ex des leucémies aiguës



Class of agent	Name of drugs	Mechanism	Cell cycle
Alkylating agents	Cyclophosphamide, Nitrogen mustard, Chloroethyl nitrosurea, Busulfan, Chlorambucil, Melphalan, Thiotepa,	Cross-link DNA strand, interrupt RNA and protein synthesis	Non-specific
Cisplatin and analogues	Cisplatin, Carboplatin	Interferes with DNA synthesis without affecting normal RNA and protein synthesis	Possibly specific (G ₂ arrest)
Vinca alkaloids (aneuploidy inducers)	Vincristine, Vinblastine	Bind tubulin and cause dissociation of the microtubule apparatus	Specific: G ₁ and S phase
Antimetabolites	Methotrexate, Aminopterin, 5-Fluorouracil, Cytarabine	Inhibit cellular metabolites by acting as false substrates for reactions required in DNA or RNA synthesis.	Non- specific
Topoisomerase (top) interactive agents (radiomimetics)	Bleomycin, Actinomycin, Doxorubicin, Daunorubicin	Interact with enzyme-DNA complex. Prevents resealing of the top I-mediated DNA single strand breaks	Specific: G ₂ arrest/ S-phase apoptosis
Newer agents	Paclitaxel	Acts on microtubule system	Non-specific

Arnon et al., 2001

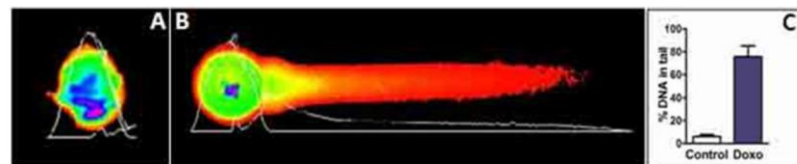


Figure 6. Comet assay with murine GV oocytes. Double strand DNA breaks were detected in murine GV oocytes using a single cell gel electrophoresis (Comet assay) after 24h culture with or without doxorubicin (10 µg/ml). Representative images of non-treated (A) and doxorubicin-treated (B) oocytes are shown. (C) Quantification of DNA damage in control versus doxorubicin treated oocytes; expressed as mean (± SD) % of DNA in the tail. P = 0.002 (t-test).

Soleimani et al., 2011

Leucémie aiguës: stimuler après un ligne de chimiothérapie (daunorubicine / aracytine)?

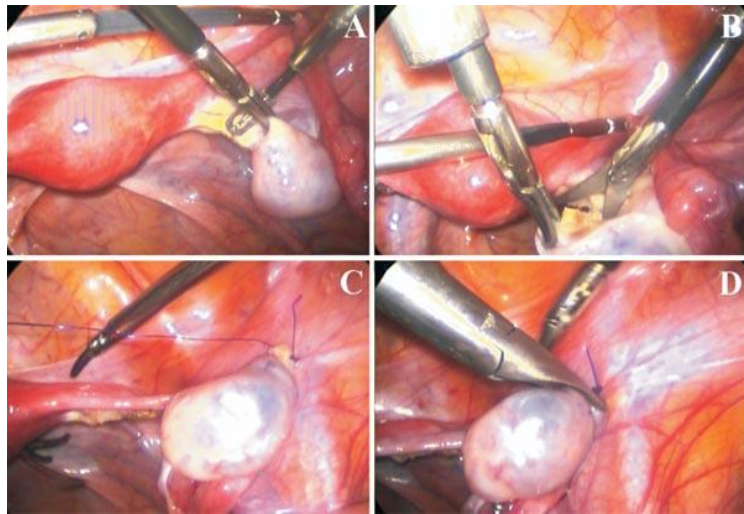
Quel risque génotoxique pour les ovocytes vitrifiés?

Difficultés en cas de radiothérapie pelvienne « surajoutée » car mauvais pronostic obstétrical même si autoconservation ovocytaire réalisée

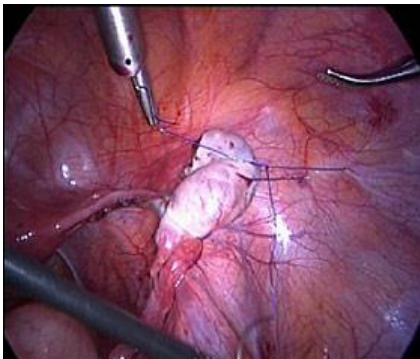
Transposition ovarienne dans les gouttières pariéto-coliques

↳ la dose reçue par les ovaires de 5 – 10 %

O'Neill et al., 2011



Furtado et
Kondo, 2008



Facteurs de mauvais pronostic pour la préservation de la fonction endocrine:

- Age > 25 ans
- Chimiothérapie gonadotoxique associée
- Dose reçue par les ovaires = 5 Gy

Haie-Meder et al., 1993

Kystes ovariens fonctionnels (30-40 %)

Douleurs abdominales

Métastases ovariennes Morice et al., 2001

Problèmes pour la fertilité future

Lésions radiques de l'utérus

Association between radiotherapy doses to uterus and ovaries and risk of stillbirth or neonatal death in offspring of survivors of childhood cancer

	Treatment before menarche		Treatment after menarche	
	Risk of stillbirth or neonatal death	Relative risk ^{††} (95% CI)	Risk of stillbirth or neonatal death	Relative risk ^{††} (95% CI)
No radiation	5/494 (1%)	Reference	13/447 (3%)	Reference
0.01–0.99 Gy	11/636 (2%)	1.3 (0.5–3.9)	7/599 (1%)	0.3 (0.1–1.0)
1.00–2.49 Gy	3/69 (4%)	4.7 (1.2–19.0)	2/70 (3%)	1.2 (0.2–6.4)
≥2.50 Gy	11/82 (13%)	12.3 (4.2–36.0)	1/85 (1%)	0.2 (0.0–1.4)

Data are n/N (%), unless otherwise indicated. Data are for the offspring of only 1481 (89%) of 1657 female survivors for whom timing of treatment in relation to menarche could be established. For the 160 women in whom age at menarche was missing and needed to be estimated, we assumed they were treated before menarche if they were treated at age 9 years or younger, and after menarche if they were treated at age 18 years or older.

* Adjusted for calendar year of birth and maternal age.

[†] p value for trend was 0.006.

^{††} p value for trend was 0.32.

- ↗ Fausses-couches
- ↗ Restriction de croissance, prééclampsie
- ↗ Hémorragies par anomalies insertion placentaire
- ↗ Prématurité
- ↗ Mort fœtale in utero et mortalité néonatale

Signorello, Lancet 2010; Teh et al., 2014

2. Pathologies bénignes & préservation de la Fertilité



Y PENSER!!!!

- **Après toute chirurgie ovarienne:**
Tumeurs border-line, endométriomes, kystes à risque de récurrence
- Pathologies à risque d'insuffisance ovarienne prématurée: syndrome de Turner, « ménopause précoce familiale »
- Attention aux indications limites voire mauvaises!

Une histoire malheureusement pas si rare...

Mme K., 32 ans, célibataire, pas d'enfants

2012: découverte d'un endométriose gauche sur dysménorrhée, coelioscopie pour kystectomie

09/2014: Deuxième coelioscopie pour endométriose droit

01/2015: Consulte en endocrinologie pour aménorrhée post-opératoire et bouffées de chaleur

FSH = 125, LH=69, E2=15



Endométriome: Kystectomie plutôt que destruction / drainage

Human Reproduction, Vol.29, No.3 pp. 400–412, 2014
 Advanced Access publication on January 15, 2014 doi:10.1093/humrep/det457

human reproduction ORIGINAL ARTICLE ESHRE pages

ESHRE guideline: management of women with endometriosis†

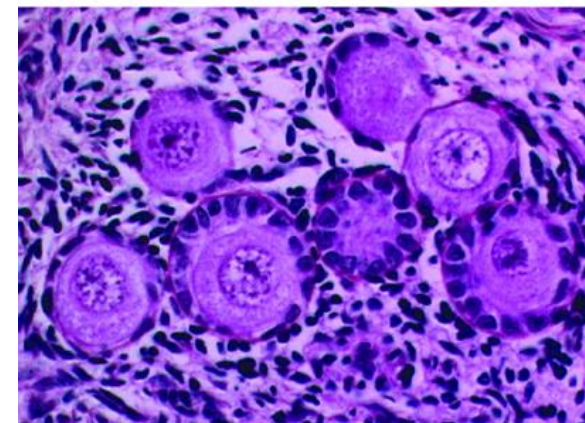
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Recurrence of signs and symptoms of endometriomas and rate of reoperation after 2 years.

	Cystectomy	Fenestration and coagulation	<i>P</i>
Recurrence of cyst (%)	9/52 (17.3)	15/48 (31.3)	.16
Recurrence of symptoms (%)	6/38 (15.8)	17/30 (56.7)	.001
Reoperation (%)	3/52 (5.8)	11/48 (22.9)	.003

Human ovarian tissue from cortex surrounding benign cysts: a model to study ovarian tissue cryopreservation

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Fresh tissue

Follicules primordiaux en regard des pièces de kystectomie

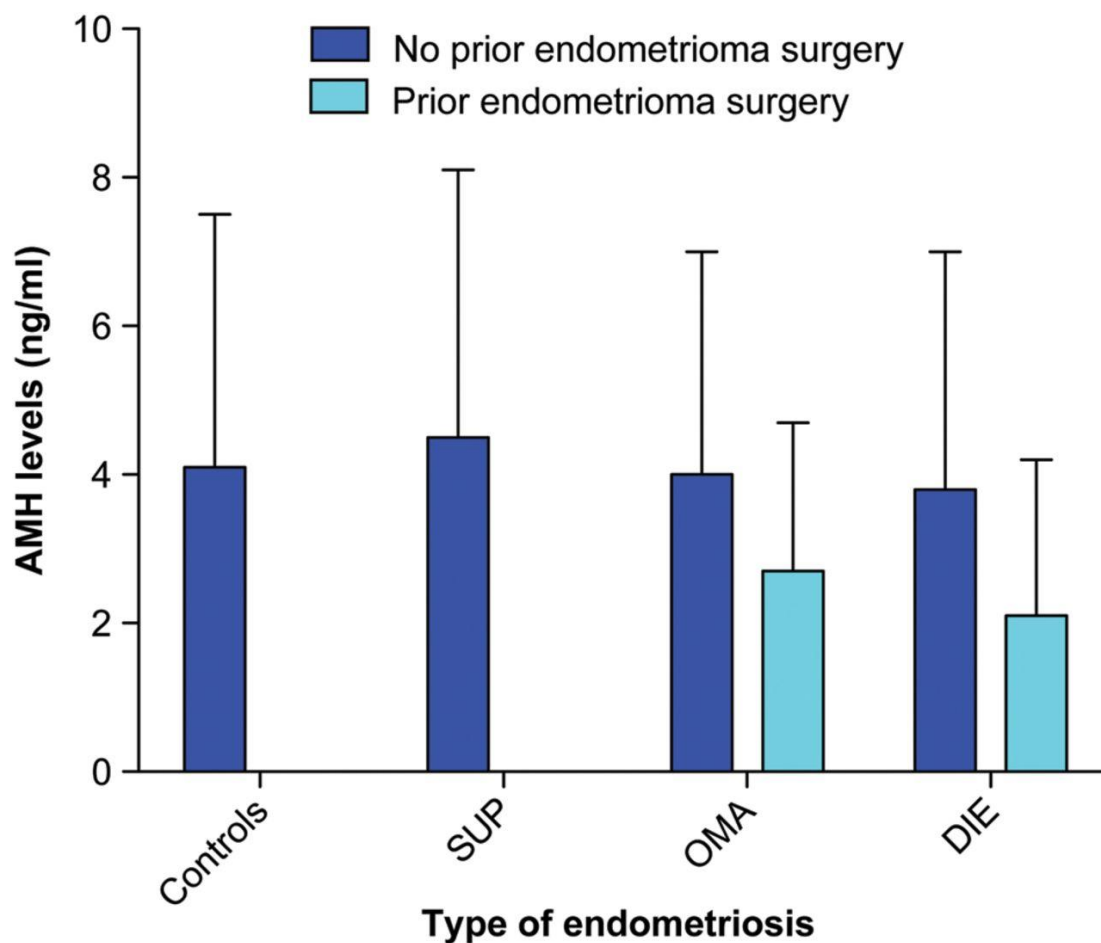
	Patient no.	Age (years)	Size of the cyst (mm)	Fresh tissue
				Primordial and primary follicles (no./mm ³)
Dermoid cysts	1	21	50	38.67
	2	26	41	13.04
	3	31	60	13.75
	4	35	nd	0.66
	5	28	40	53.70
	6 ^a	31	54	0.00
	7	20	42	4.50
		27.4 ± 2.1	47.8 ± 3.3	13.04
Endometriosis cysts	8 ^a	34	42	2.47
	9 ^a	33	55	0.64
	10 ^a	36	100	0.00
	11	30	51	0.12
	12 ^a	32	50	0.00
	13	26	40	0.00
	14 ^a	24	90	0.31
	15	30	48	2.78
	16 ^a	23	45	4.21
	17 ^a	27	76	0.00
	18 ^a	29	40	13.37
	19	24	60	3.06
	20 ^a	32	43	0.00
		29.2 ± 1.1	56.9 ± 5.4	0.31

In women with endometriosis anti-Müllerian hormone levels are decreased only in those with previous endometrioma surgery

Isabelle Streuli^{1,2}, Dominique de Ziegler¹, Vanessa Gayet¹, Pietro Santulli^{1,2}, Gérard Bijaoui¹, Jacques de Mouzon¹, and Charles Chapron^{1,3,*}

AMH levels according to the type of endometriosis and prior OMA surgery.

SUP, superficial peritoneal lesion; OMA, endometrioma; DIE, deep infiltrating endometriosis



Surgical diminished ovarian reserve after endometrioma cystectomy versus idiopathic DOR: comparison of *in vitro* fertilization outcome

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Une diminution de réserve ovarienne après kystectomie d'endométrïomes est de plus mauvais pronostic qu'une DOR « idiopathique »

Table IV IVF outcomes in women with DOR diagnosed after cystectomy(s) for endometrioma(s) (group A) and patients with idiopathic DOR (group B).

Characteristics	Group A (125 cycles)	Group B (243 cycles)	P-value
Implantation rate (%)	13/181 (7.2%)	49/364 (13.5%)	0.03
Clinical pregnancy rate per cycle (%)	14/125 (11.2%)	50/243 (20.6%)	0.02
Live birth rate (%)			
Per cycle	9/125 (7.2%)	41/243 (16.9%)	0.01
Per transfer	9/104 (8.7%)	41/216 (18.8%)	0.02
Spontaneous abortion rate (%) (before or after 12 weeks of gestation)	4/13 (30.8%)	8/49 (16.3%)	NS
Ectopic pregnancy rate (%)	1/14 (7.1%)	1/50 (2.0%)	NS
Multiple pregnancy rate (%)	2/13 (15.4%)	6/49 (12.2%)	NS



Penser à une autoconservation ovocytaire après kystectomie d'endométriome chez une femme sans enfants

Mme V., 26 ans,

Cœlioscopie à 25 ans pour endométriose sévère et dysménorrhée:
endométriome droit de 8 cm, endométriome gauche « drainé ».

AMH post-opératoire = 1,63 ng/mL (N > 2)

Malgré pilule en continu: récurrence endométriome gauche 5 cm un an plus
tard.



Protocole agoniste long – sclérothérapie des endométriomes
Stimulation ovarienne pour vitrification ovocytaire
Cumul ovocytaire (19 ovocytes en 3 cycles)

En pratique, consultations pour « préservation de la fertilité »
parfois compliquées....

→ Mauvaises indications et indications « limites »

- **Age > 38 ans**
- Réserve ovarienne déjà altérée au moment du diagnostic
- Quand risque élevé de mutations géniques transmissibles :
mutation BRCA, FMR1. Conseil génétique +++
- **Hystérectomie** → dans quel but? Gestation pour autrui ?
Transplantation utérine ?



Intégration de la problématique de la fertilité
dans toute prise en charge médicale susceptible de
l'altérer !!!

Avant et après un cancer

En cas de chirurgie ovarienne itérative / après une pathologie ovarienne à risque de récurrence (ex: endométrioses)

Dans les pathologies à risque d'insuffisance ovarienne (ex: syndrome de Turner mosaïque, Insuffisance ovarienne familiale)

Merci pour votre attention et votre accueil!

