# Devenir obstétrical des femmes guéries d'une leucémie aiguë dans l'enfance

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PARIS I 3 DÉCEMBRE 2024

SÉMINAIRE RECHERCHE EN PRÉSERVATION DE LA FERTILITÉ
CHEZ LES PATIENTS ATTEINTS D'UN CANCER

Introduction: traitement de la leucémie aigüe
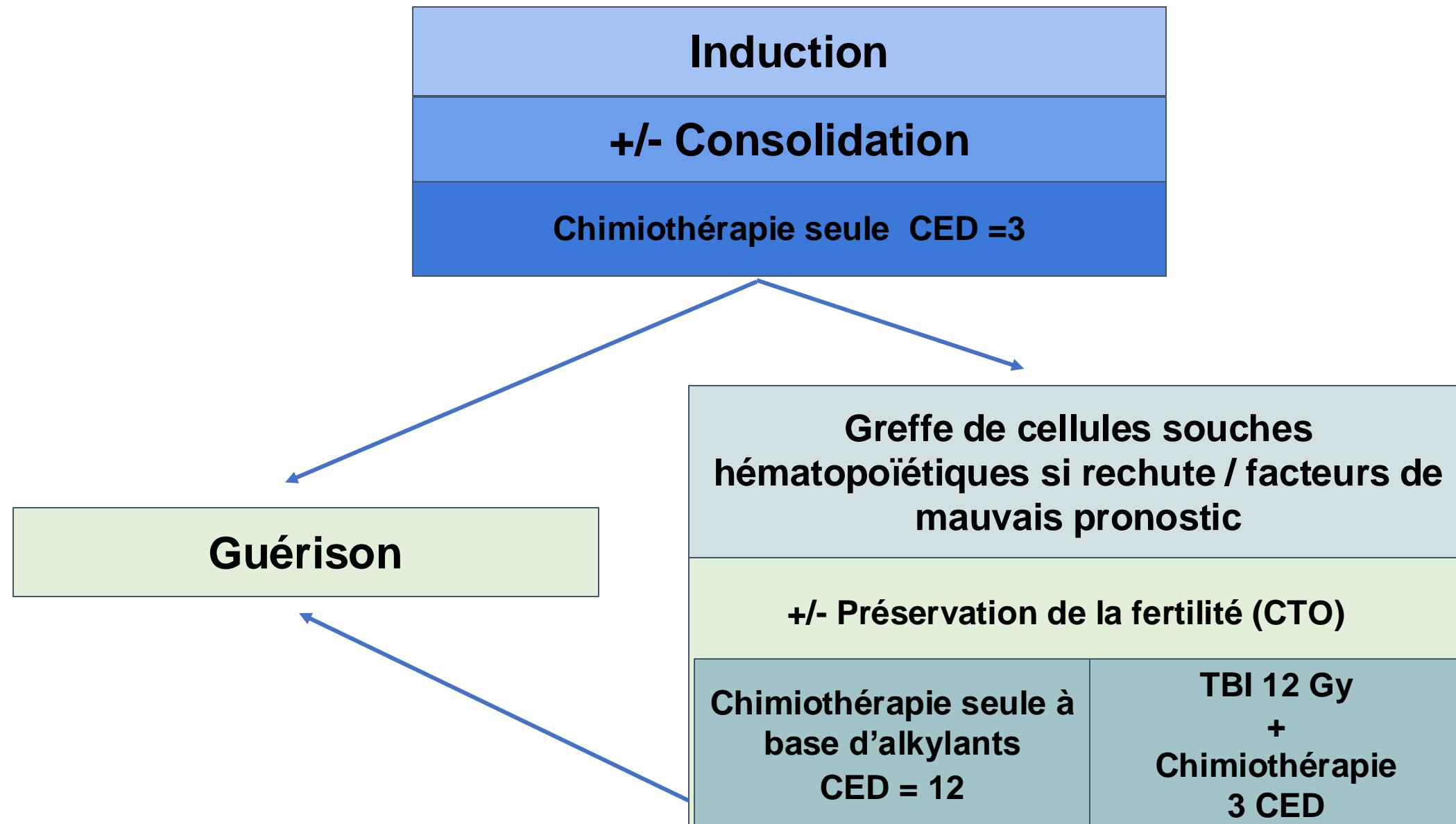
Fertility Preservation in Pediatric Leukemia and Lymphoma: A Report from the Children's Oncology Group. Close et al. 2023

Figure 1. – Level of risk for gonadal failure/infertility above that of the general population.

Female Risk Chart		Minimally Increased Risk	Significantly Increased Risk	High Level of Increased Risk
Alkylators CED g/m^2	Prepubertal	CED <8g	CED 8-12g	CED >12g
	Pubertal	CED <4g	CED 4-8g	CED >8g
Heavy Metal mg/m^2		Cisplatin Carboplatin		
Hematopoetic Stem Cell Transplant				Alkylator +/-total body irradiation Myeloablative and reduced intensity regimens
Radiation Exposure	Ovary Prepubertal		<15 Gy	≥15 Gy
	Pubertal		<10 Gy	≥10 Gy
	Hypothalamus	22-29.9 Gy	30-39.9 Gy	≥40 Gy

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update

Do cancer therapies damage the uterus and compromise fertility?

Meaghan J. Griffiths, Amy L. Winship[†], and Karla J. Hutt [iD]*,[†]

Nombreuses données sur l'impact de la radiothérapie (TBI ou radiothérapie pelvienne) sur l'utérus. Griffiths et al. 2019

Radiotherapy
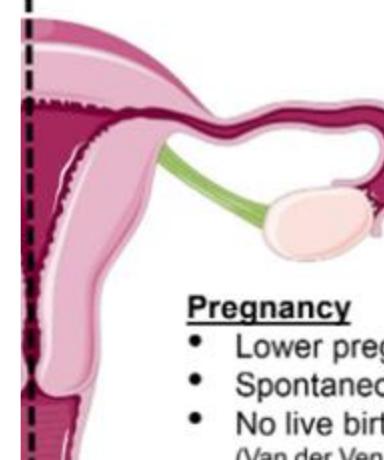
Structural/Functional
- Small uterine length and volume (Wallace et al. 1989; Critchley et al. 1992)
- HRT resistant (Bath et al. 1999; Critchley, Bath, and Wallace 2002; Critchley and Wallace 2005; Sudour et al. 2010)
- Absent uterine artery blood flow (Critchley, Bath, and Wallace 2002)
- Decreased uterine artery pulsatility (Critchley, Bath, and Wallace 2002; Critchley et al. 1992; Holm et al. 1999; Beneventi et al. 2015)
- Thin endometrium (Critchley et al. 1992)

Pregnancy
- Lower pregnancy rates (Anderson et al. 2018)
- Spontaneous abortions (Vernaeve et al. 2007)
- No live births following ovarian tissue cryopreservation (Van der Ven et al. 2016)
- Abnormal placentation (Hammer, Urnes, and Lurain 1996; Norwitz et al. 2001)

Birth outcomes
- Preterm birth (Green et al. 2002; Signorello et al. 2006; van de Loo et al. 2019)
- Low birth weight (Black et al. 2017)
- Small for gestational age (Signorello et al. 2006; van der Kooi et al. 2019)
- Thin, fibrotic uterus (Norwitz et al. 2001; Sudour et al. 2010)
- Risk of uterine rupture (Norwitz et al. 2001)
- Risk of stillbirth (Signorello et al. 2010)

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Meaghan J. Griffiths, Amy L. Winship[†], and Karla J. Hutt [iD] *,[†]

Chemotherapy

Structural/Functional
- Smaller uterine volume (Beneventi et al. 2015; van de Loo et al. 2019)
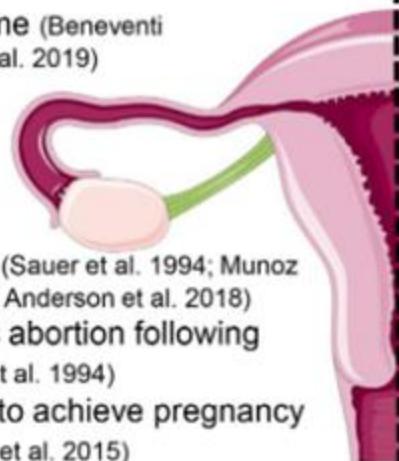
Pregnancy
- Lower pregnancy rates (Sauer et al. 1994; Munoz et al. 2015; Chow et al. 2016; Anderson et al. 2018)
- Increased spontaneous abortion following oocyte donation (Sauer et al. 1994)
- More embryo transfers to achieve pregnancy (Fujimoto et al. 2014; Munoz et al. 2015)

Birth outcomes
- Preterm birth (Black et al. 2017)
- Low birth weight (Black et al. 2017)
- Small for gestational age (Black et al. 2017)

Peu de données concernant l'impact des chimiothérapies sur l'utérus (Rodriguez-Wallberg and Olofsson, 2019)

Trois équipes ont rapporté une diminution du volume utérin après exposition aux agents alkylants à forte dose dans l'enfance
- **Beneventi et al., 2015; van de Loo et al., 2019)**
  - Population hétérogène
  - Volume utérin calculé par échographie

- **Courbiere et al 2023 :**
  - Population de femmes après leucémie aiguë dans l'enfance après HSCT.
  - Volume mesuré par IRM

Introduction

The uterine volume is dramatically decreased after hematopoietic stem cell transplantation during childhood regardless of the conditioning regimen

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2023

FONDATION ARC
POUR LA RECHERCHE
SUR LE CANCER
Reconnue d'utilité publique

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Comparison of magnetic resonance imaging parameters of the uterus according to the type of myeloablative conditioning regimen vs. the control group.

Control women	Control group (n = 88)	Alkylating agent–based regimen (n = 34)	TBI (n = 54)	Control vs. alkylating agents	Control vs. TBI	Alkylating agents vs. TBI
Uterine volume (mL)	79.7 ± 3.3	45.3 ± 5.6	19.6 ± 1.9	< .0001	< .0001	< .001
Uterine body-to-cervix ratio	1.7 ± 0.03	1.3 ± 0.06	1.3 ± 0.04	< .0001	< .0001	NS
ADC (10^{-3} mm²/s)	1.5 ± 0.02	1.2 ± 0.05	1.3 ± 0.03	< .001	< .001	NS

	Chemotherapy -only MAC regimen	TBI	Total	p
Total number of Pregnancies :	**10**	**19**	**29**	
				0,27
- Spontaneous pregnancy (%)	10 (100)	15 (79)	25 (86)	
- Oocyte donation (%)	0 (0)	3 (16)	3 (10)	
- Uterine insemination (%)	0 (0)	1 (5)	1 (4)	
Pregnancy outcome:				
				0,03
Medical abortion	0 (0)	4 (21)	4 (14)	
Early miscarriage	2 (20)	4 (21)	6 (21)	
Late Miscarriage	2 (20)	9 (47)	11 (38)	
Live-birth	6 (**60**)	2 (**11**)	8 (28)	

Etude OBSTLEA
Objectif

- Etudier le taux de naissance vivante et les issues de grossesses des patientes ayant conçu après une leucémie aigüe de l'enfance ou l'adolescence en fonction du traitement reçu
- Etudier le prognostic obstetrical et perinatal de cette même population en fonction du traitement reçu.

Etude OBSTLEA
Matériel et Méthodes

- Etude cas-témoin dans la cohorte LEA
- Recueil rétrospectif
- Critère d'inclusion :
  - Patientes issues de la cohorte LEA
  - >18 ans
  - Antécédent de Leucémie aiguë
  - Au moins un antécédent de grossesse quel que soit le mode de conception.

Matériel et Méthodes

CAS n=41	
Greffe de cellules souches hématopoïétiques	

CT seule (CED : 12g) n= 11 31 Grossesses	TBI + CT n= 30 55 Grossesses

Témoins n=76	

CT seule CED = 3g 180 Grossesses
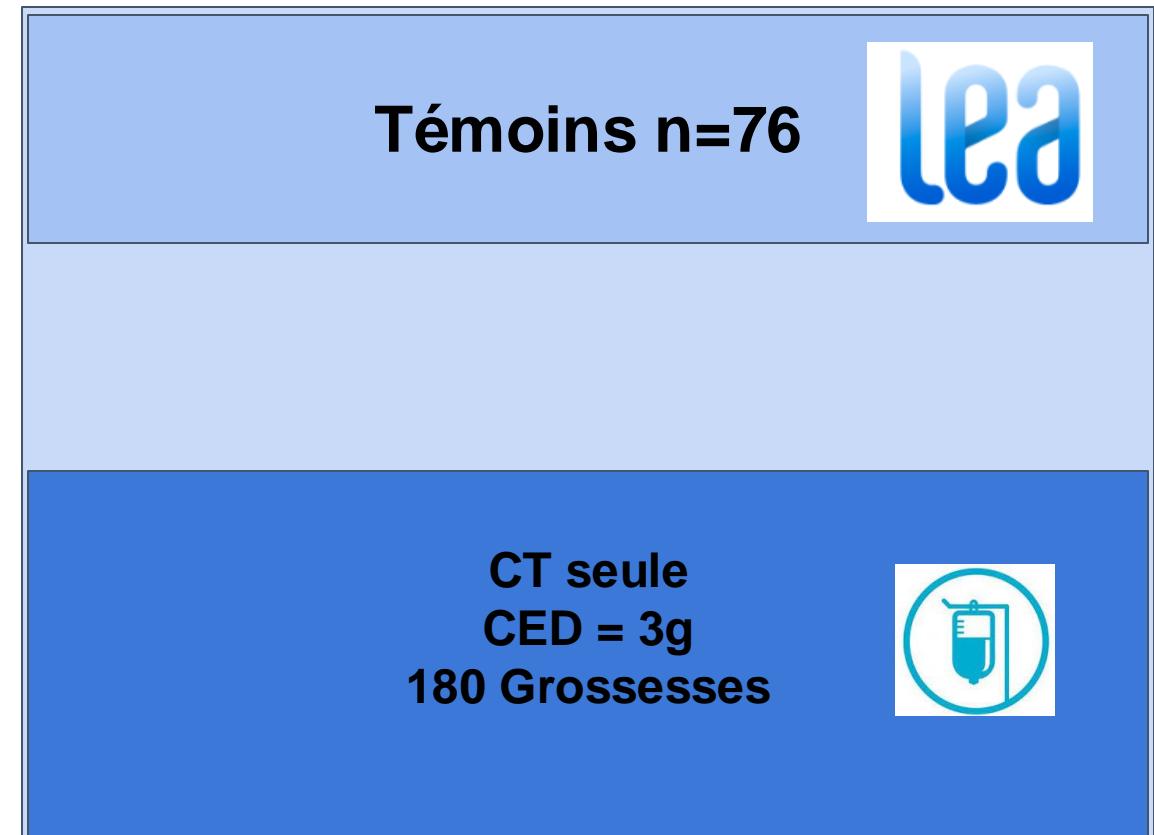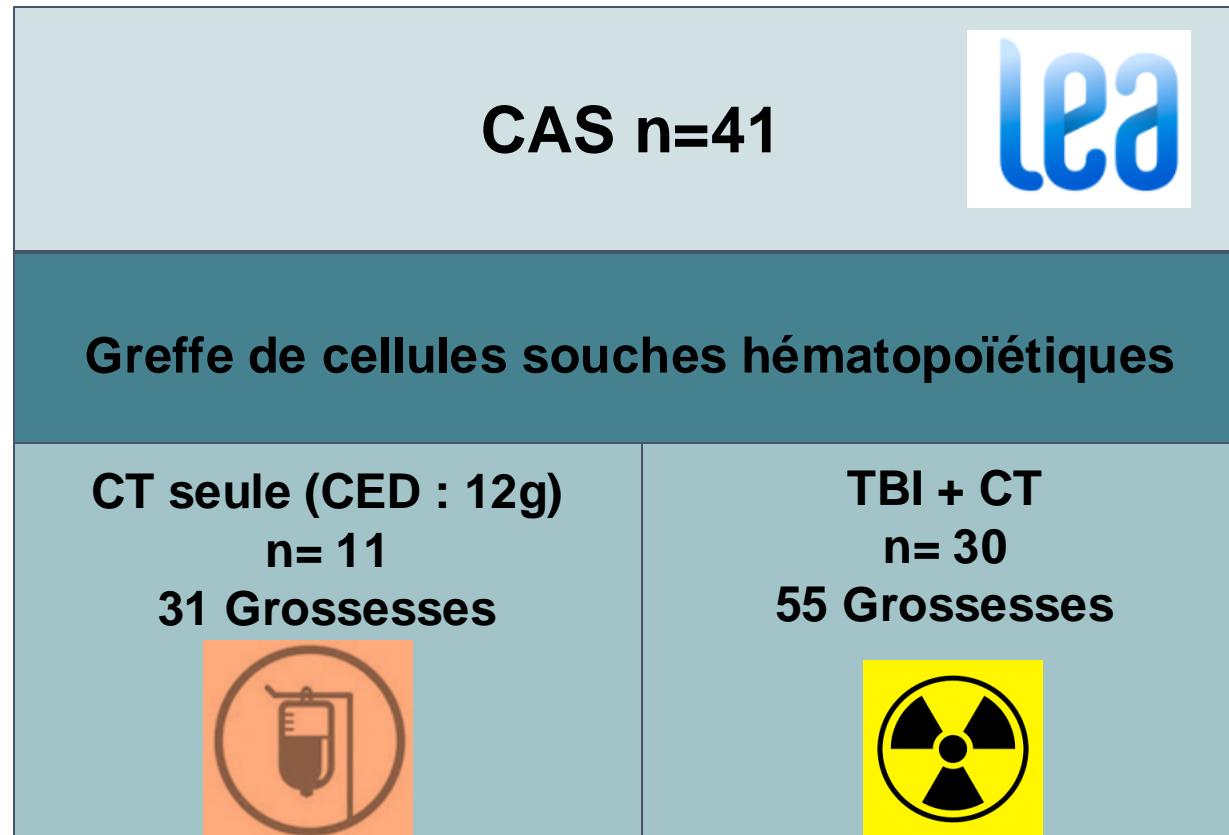
Table 1A

OBSTLEA population study: characteristics of the first pregnancy of female who conceived after childhood acute leukemia's treatment. n= 117 patients

Characteristics	Cases (n=41) HSCT group	Controls (n=76) Conventional chemotherapy	P value
Age (y) at acute leukemia diagnosis, mean (±SD)	8.66(±0.73)	7.98 (±0.56)	NS
Age (y) at last medical follow-up, mean (±SD)	32.89 (± 0.94)	33.15 (±0.71)	NS
Age (y) at first pregnancy, mean (±SD)	26.47(±0.61)	26.44(±0.56)	NS
Number of pregnancy per patient, mean (±SD)	2.10(±0.24)	2.37(±0.15)	NS
Type of leukemia			
Lymphoblastic acute leukemia	26 (63)	68 (90)	
Myeloid acute leukemia	15 (37)	8 (10)	<. 0001*
Total Body Irradiation	30 (73)	0 (0)	<. 0001*
Fertility preservation before treatment	2 (5)	0 (0)	
Oocyte vitrification	1 (2)	-	
Ovarian tissue preservation	1 (2)	-	NS
Diagnosis before menarche	32 (78)	59 (78)	NS
If diagnosed before menarche Normal progression of puberty	20 (63)	58 (98)	<. 0001*
Premature ovarian insufficiency	21 (51)	0 (0)	<. 0001*
If POI diagnosed, Supplied by HRT before pregnancy	19 (90)	-	

Table 1B

OBSTLEA population study: characteristics of the first pregnancy of female who conceived after childhood acute leukemia's treatment. n= 117 patients

Characteristics	Cases (n=41) HSCT group	Controls (n=76) Conventional chemotherapy	P value
Diabetes before first pregnancy	3 (7)	1 (1)	NS
Metabolic syndrome before first pregnancy	6 (15)	5 (7)	NS
BMI (kg/cm2) before first pregnancy mean (±SD)	21.08 (±0.50)	23.66 (±0.48)	<. 0001*
BMI>25 (kg/m2) at first pregnancy	5 (12)	20 (26)	NS
BMI<18.5(kg/m2) at first pregnancy	7 (17)	3 (4)	0.032*
Smoking at the beginning of the first pregnancy	8 (20)	22 (29)	NS
Smoking during pregnancy	5 (12)	13 (17)	NS
Intended first pregnancy	30 (73)	59 (79)	NS
Unintended first pregnancy	11 (27)	17 (21)	NS
Spontaneous first pregnancy	25 (61)	71 (93)	<. 0001*
After medical assisted reproduction	16 (39)	5 (7)	0.0003*
Ovulation simulation	0 (0)	3 (60)	
IUI	1 (6)	2 (40)	
Oocyte donation	15 (94)	0 (0)	

Table 2

OBST LEA population study: characteristics of pregnancies after childhood acute leukemia's treatment. Total pregnancies n=266			
Characteristics	**Pregnancies after HSCT (n=86)**	**Pregnancies after conventional chemotherapy (n=180)**	**P value**
Age (y) at beginning of pregnancy, mean (±SD)	27.44 (±0.43)	28.51 (±0.37)	NS
BMI (kg/cm2) at beginning of pregnancy, mean (±SD)	21.42 (±0.34)	23.22 (±0.27)	<. 0001*
BMI>25 (kg/cm2) at beginning of pregnancy,	12 (14)	38 (21)	NS
BMI<18.5(kg/cm2) at beginning of pregnancy,	13 (15)	5 (3)	0.0002*
Smoking at the beginning of pregnancy	21 (24)	56 (31)	NS
Smoking during pregnancy	13 (15)	27 (15)	NS
Intended pregnancies	71 (83)	143 (79)	NS
Unintended pregnancies	15 (17)	37(21)	
Spontaneous pregnancies	60 (70)	171 (95)	<. 0001*
After medical assisted reproduction	26 (30)	9 (5)	<. 0001*
Ovulation simulation	0 (0)	5 (56)	
IUI	1 (4)	2 (22)	
Oocyte donation	25 (96)	0 (0)	
IVF	0 (0)	1 (11)	
Double gamete donation	0 (0)	1 (11)	
Twin pregnancies	2 (2)	4 (2)	NS

Significativement plus de maigreur dans le groupe HSCT

70% de grossesses spontanées dans le groupe HSCT vs 95% pour le groupe témoin

29% de grossesses obtenue après don d'ovocytes

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Taux de naissance vivante (LBR) et issues de grossesse

Table 3

OBST LEA population study: Live-birth rate and pregnancy outcomes among childhood acute leukemia female survivors according to oncologic treatment. Cases = HSCT group composed by TBI-exposed cases and alkylating agent regimen and Controls with AL conventional chemotherapy.

Variables	Cases HSCT group	Cases TBI	Cases Alkylating agent regimen	Controls: Conventional CT	Cases vs. Controls	Cases TBI-exposed vs. Alkylating agent regimen	Alkylating-agent regimen cases vs. Conventional CT Controls
All pregnancies n=266	**n= 86**	**n= 55**	**n= 31**	**n= 180**			
Live birth rate (n=266)	38 (44)	19 (35)	19 (61)	128 (71)	<. 0001*	0,017*	0.272
Live birth rate without induced abortion (n= 235)	38 (48)	19 (37)	19 (70)	128 (82)	<. 0001*	0,004*	0.159
Ectopic pregnancy	2 (2)	2 (4)	0	0	0.104	0.534	-
Induced abortion	7 (8)	3 (6)	4 (13)	24 (13)	0.217	0.246	1.0
Early Miscarriage	22 (26)	17 (31)	5 (16)	27 (15)	0.037*	0.131	0.792
Late Miscarriage	14 (16)	13 (24)	1 (3)	0	<. 0001*	0.014*	0.147
Total pregnancy loss	36 (42)	30 (55)	6 (20)	27 (15)	<. 0001*	0.001*	0.592
Fetal death	0	0	0	0	-	-	-
Medical termination of pregnancy	3 (3)	1 (2)	2 (7)	1 (0.6)	0.101	0.294	0.057
Hemorrhage events	20 (23)	17 (31)	3 (10)	14 (8)	0.0004*	0.018*	0.721

LBR 37% chez les cas TBI vs 70% chez les cas CT alkylant et 82% chez les témoins

Augmentation du risque de de FCS , FCT d'hémorragie chez le groupe HSCT

Pas de différence entre Cas traité par CT et témoins

Taux de naissance vivante (LBR) et issues de grossesse

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IVG : 6% chez les cas TBI , 15% chez les cas traité par alkylants et chez les contrôles traité par CT convetionnelle

Complication obstétricales pré partum après leucémie aiguë

Table 4A

OBST LEA population study: obstetric and perinatal outcomes among childhood acute leukemia female survivors according to oncologic treatment. Cases = HSCT group composed by TBI-exposed cases and alkylating agent regimen and Controls with AL conventional chemotherapy.

Variables	Cases HSCT group	Cases TBI	Cases Alkylating agent regimen	Controls: Conventional CT	Cases vs. Controls	Cases TBI-exposed vs. Alkylating agent regimen	Alkylating agent regimen cases vs. Conventional CT Controls
Pre-partum outcomes n= 166	n= 38	n=19	n=19	n=128			
Gestational diabetes	2 (5)	0	2 (11)	8 (6)	1.0	0.486	0.619
Gestational hypertension	1 (3)	1 (5)	0	10 (8)	0.463	1.0	0.360
Pre-eclampsia	3 (8)	3 (16)	0	3 (2)	0.136	0.230	1.0
Fetal growth restriction	5 (13)	4 (21)	1 (5)	5 (4)	0.052	0.340	0.574
Threatened preterm labor	9 (24)	8 (42)	1 (5)	6 (5)	0.001*	0.019*	1.0
Placenta previa	0	0	0	1 (1)	1.0	-	1.0
Preterm premature rupture of membranes	2 (5)	2 (11)	0	4 (3)	0.622	0.486	1.0
Hospitalization during pregnancy	17 (45)	16 (84)	1 (5)	13 (10)	<. 0001*	<. 0001*	0.695
Pre partum obstetrical adverse outcome, composite criteria	20 (53)	16 (84)	2 (21)	30 (23)	0.0006*	0.0001*	1.0

42% de MAP chez les cas TBI

84% d'hospitalisation chez les cas TBI avec 84% de complication

Pas de différence entre Cas traité par CT et témoins

Complication obstétricales per partum et périnatales après leucémie aiguë

Table 4B

OBST LEA population study: obstetric and perinatal outcomes among childhood acute leukemia female survivors according to oncologic treatment. Cases = HSCT group composed by TBI-exposed cases and alkylating agent regimen and Controls with AL conventional chemotherapy.

Variables	Cases HSCT group	Cases TBI	Cases Alkylating agent regimen	Controls: Conventional CT	Cases vs. Controls	Cases TBI-exposed vs. Alkylating agent regimen	Alkylating agent regimen cases vs. Conventional CT Controls
Intra-partum outcomes n= 166	n= 38	n=19	n=19	n=128			
Singleton live birth	37 (97)	18 (95)	19 (100)	125 (98)	1.0	1.0	1.0
Caesarian section	11 (29)	9 (47)	2 (11)	27 (21)	0.312	0.012*	0.458
Post-partum hemorrhage	8 (21)	7 (37)	1 (5)	9 (7)	0.028*	0.042*	1.0
Perinatal outcomes of singleton live births n= 162	n= 37	n=18	n=19	n=125			
Prematurity	10 (27)	9 (50)	1 (5)	3 (3)	<. 0001*	0.003*	0.436
Low birth weight	6 (16)	6 (33)	0	8 (6)	0.091	0.008*	0.599
Small for gestational age	6 (16)	4 (22)	2 (11)	15 (12)	0.578	0.405	1.0
Birth weight (g) mean (±SD)	2921 (±141)	2444 (±220)	3373 (±102)	3242 (±42)	0.034*	0.0008*	0.253
Apgar Score at 5 minutes ≤7	1 (3)	1 (6)	0	4 (3)	1	0.406	1.0
Mechanic ventilation on new born	3 (8)	3 (17)	0	3 (2)	0.133	0.105	1.0
Transfer to an intense care unit for the new born	3 (8)	3 (17)	0	2 (2)	0.079	0.105	1.0
Perinatal complications composite criteria	14 (38)	11 (61)	3 (16)	21 (17)	0.006*	0.004*	1.0

37% d'hémorragie du post partum chez les cas TBI

50 % de prématurité, 33% de poids <2500g chez cas TBI

Pas de différence pour les petits poids pour l'âge gestationnel

61% des naissances compliquées chez les cas TBI

Complication obstétricales per partum et périnatales après leucémie aiguë

Table 4B

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Pas de différence significative pour le score d'Apgar , la ventilation mécanique ou le transfert en réanimation

Pas de différence entre Cas traité par CT et témoins

LBR , issues de grossesses , complication obstétricales et périnatales chez les patientes après HSCT en fonction du mode de conception

Table 5

OBST LEA population study: pregnancy, obstetric and perinatal outcomes after HSCT for childhood acute leukemia according to conception mode: oocyte donation Vs pregnancies with autologous oocytes. n=86 pregnancies

Characteristics	Oocyte donation n =25 TBI, n = 23 Alkylating-agent regimen, n = 2	Autologous oocytes n=61 TBI, n= 32 Alkylating-agent regimen n= 29	P value
Live birth rate	13 (52)	25 (41)	0.350
Live birth rate without induced abortion	13 (52)	25 (46)	0.065
Hemorrhage events	8 (32)	12 (20)	0.219
Early miscarriage	6 (24)	16 (26)	0.854
Late miscarriage	4 (16)	10 (16)	1.0
Total pregnancy loss	10 (40)	26 (43)	0.823
Live Births n=38	n=13	n=25	
Fetal growth restriction	2 (15)	3 (12)	1.0
Hospitalization	9 (69)	8 (32)	0.029*
Post-partum hemorrhage	4 (31)	4 (16)	0.407
Caesarian section	8 (62)	3 (12)	0.003*
Singleton Live births n=27	n=12	n=25	
Prematurity	4 (33)	6 (24)	0.686
Low birth weight	3 (25)	3 (12)	0.367
Small for gestational age	2 (17)	4 (16)	1.0
Birth weight (g) mean (±SD)	2823 (±246)	2968 (±174)	0.636
Neonatal complications composite criteria	5 (42)	9 (36)	1.0

Note: Values are presented as number (percentage), unless indicated otherwise.
SD = standard derivation, TBI : total body irradiation. * Statistically significant,

Pas de différence de LBR et d'issues de grossesses entre DO et grossesse intraconjugale

Taux de césarienne 62% et 69% d'hospitalisation mais 90% de grossesses après TBI parmi les DO

Pas de différence sur les issues néonatales

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## Do cancer therapies damage the uterus and compromise fertility?

Meaghan J. Griffiths, Amy L. Winship[†], and Karla J. Hutt [iD] *,†
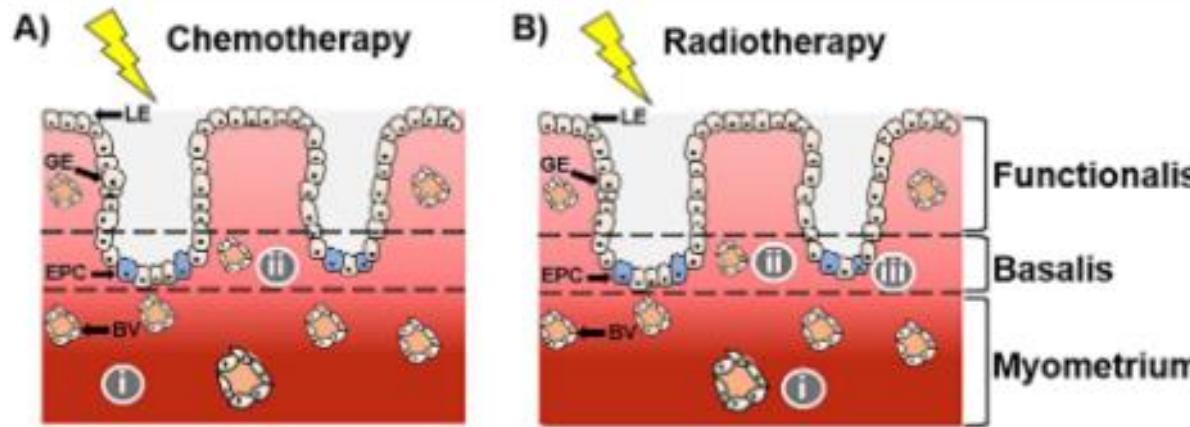
Augmentation du volume utérin après chimio et HSCT sous THS (mais toujours diminué par rapport au groupe contrôle)
Pas d'impact positif du THS sur le volume utérin après irradiation corps entier

Courbiere et al. 2023

Merci à tou.te.s