Evidence tables female fertility preservation

Who should be informed about potential infertility risk?			
Gupta et al. Assessing information and service needs of young adults with cancer at a single institution: the importance of information on cancer diagnosis, fertility preservation,diet and exercise**.** Supportive Care in Cancer 2013; 21:2477-2484			
Study design & Main study objective	**Participants and relevant characteristics**	**Relevant results (per outcome)**	**Additional remarks**
1. Study design Single center cross-sectional (survey) study 2. Main study objective To identify the information and service needs of young adults with cancer to inform a program development 3. Additional study characteristics, if relevant Survey conducted November 2010 Adapted existing survey to use Likert Scale of importance (1-10) Study participants were asked how important it was to them to get information on a certain resource as part of a program for young adult cancer survivors, or have it	1. Type and number of participants 243 cancer patients receiving treatment, or within 5 years of completion of treatment 61.3% male 40.1% currently receiving cancer treatment 2. Age (at diagnosis) of participants NR Age at study: median 28 years (17-35 years) 3. Number of participants per diagnosis 23(9.5%) brain tumour 19(7.8%) breast, ovarian, cervical cancers 46(18.9%) leukaemia 69(28.4%) lymphoma 21(8.6%) sarcoma 40(16.5%) testicular cancers 25(10.5%) colon, other cancers 4. Additional participants characteristics, if relevant 162 (66.7%) Single/never married 68 (28%) Married/common-law	1. Outcome(s) definition Outcome 1: Importance of information on fertility effects from treatment and fertility preservation Outcome 2: Importance of information on treatments for infertility and other options for having children 2. Results outcome 1 and outcome 2 *Desire for information in fertility preservation discussion* Survey question: *Information about effects of cancer treatment on your ability to have children in the future and how to preserve your fertility before starting treatment* Median 10 (range 1-10); mean (SD) 8.77 (2.23) males: mean 8.45 (2.34) females: mean 9.28 (1.94) Survey question: *Information on treatment for infertility and other options for having children (i.e. artificial insemination, in vitro fertilization, surrogacy, adoption etc)* Median: 9 (range 1-10); mean (SD) 7.81 (2.85) males: mean (SD) 7.50 (2.90) females: mean (SD) 8.30 (2.72) 3. If applicable, results per additional outcomes - Females rated information on FP methods (p=0.004) and risk of infertility (p=0.033) as more important than did males - Presence of existing children did not significantly impact on	1. Strengths - The questionnaire used was an existing published item, adapted to reflect the study site, and piloted - Participants were representative of a wide range of diagnoses relevant in this age group, and of both on and off treatment groups 2. Limitations - Single center study (results have low external validity) - Risk of selection bias: no information on how the 243 patients were selected - Convenience sample (survey administered to those attending ambulatory care centre of Canadian adult tertiary cancer centre) - No report of ethnicity of participants - Actual questions of survey not included in report

included in the program Fertility items were 2 out of 18 questions Item responses averaged for entire sample	49 (20.3%) Have existing children	importance of information regarding risk to fertility from cancer treatment (p=0.65) - Those who had completed active therapy showed a trend towards rating receiving information about fertility as more important than those on active treatment p=0.052	- Risk of reporting bias (as use of survey)

NR: not reported; SD: standard deviation; FP: fertility preservation; SD: standard deviation

Who should be informed about potential infertility risk?			
Yeomanson et al. Discussing fertility preservation at the time of cancer diagnoses: dissatisfaction of young females. Ped Blood Cancer 2013;60:196-2000			
Study design & Main study objective	**Participants and relevant characteristics**	**Relevant results (per outcome)**	**Additional remarks**
1. Study design Structured and standardized survey 2. Main study objective To ascertain if the increased level of academic and clinical interest in fertility preservation has led to a change in self-reported experiences of discussions about FP or any improvement in level of satisfaction of those	1. Type and number of participants 290 current and former cancer patients attending a cancer trust conference: 150 delegates in 2004 140 delegates in 2011 *Participation rate:* In 2004: 150/179 = 84% (69 males; 81 females) In 2011: 140/152= 92% (71 males; 69 females) Inclusion criteria: current or former patient < 13 years at start of treatment/diagnosis in 2011 sample: not participated in 2004	1. Outcome(s) definition Outcome 1. Recall of FP discussion taking place Outcome 2. Timing of FP discussion Outcome 3. Satisfaction with FP discussion 2. Results outcome 1 Boys 60, 87% (2004) ; 57, 80.3% (2011) Girls 50, 61.7% (2004); 45, 65.2% (2011) 3. Results outcome 2 • Before treatment Boys 2004 N=38 (63.3%); Boys 2011 N=44()77.2%; Girls 2004 N=19(38%), Girls 2011 N=31(68.9%)** • During treatment Boys 2004 N=16(26.7%); Boys 2011 N=12(21.1%); Girls 2004 N=26(52.0%); Girls 2011 N=8(17.8%) • After treatment: Boys 2004 N=6(10.0%); Boys 2011 N=1(1.8%); Girls 2004 N=5(10.0%); Girls 2011 N=6(13.3%)	1. Strengths - Large cohorts with same data collection method allowing comparisons between 2004 and 2011 - Data collection technique by pressing buttons of handset (non-embarrassing, non-threatening) 2. Limitations - Risk of selection bias as study sample recruited from participants on a conference for former cancer patients and their

discussions <u>3. Additional study characteristics, if relevant</u> - Two cohorts of delegates of a teenage cancer trust conference for young current and former cancer patients (in 2004 and 2011)	<u>2. Age (at diagnosis) of participants</u> Median age start treatment: 2004: Boys 16 years (13-22); girls 15 years (13-21) 2011: Boys 16years (13-22); girls 17 years (13-22) Median age at study: 2004: Boys 18years (14-23); girls 17years (14-23) 2011: Boys 18 years (14-23); girls 19 years (14-23) <u>3. Number of participants per diagnosis</u> 2004 - 2011 Leukemia N=42, N=30 Lymphoma N=30, N=39 Bone N=26, N=17 Brain N=19, N=21 Testicular/ovarian N=6, N=8 Sarcoma N=19, N=11 Other N=2, N=16 Unknown N=6, N=2 <u>4. Additional participants characteristics, if relevant</u> - Delegates were invited to respond to each question by pressing the buttons on a remote handset that transmitted their response to a central microcomputer and captured the data in an Excel spreadsheet - Both conferences took place in Nottingham, United Kingdom	**Differences between 2004 and 2011 were significant for girls who reported discussion before treatment Chi square 12.27 p=0.002 No differences in timing found for boys between 2004/2011 <u>3. Results outcome 3</u> *Satisfaction with content of fertility preservation discussion* 35.8% of male patients and 50% of female patients were unsatisfied with the content of fertility preservation discussion There was no significant difference in satisfaction between 2004 and 2011 Boys satisfaction with content of FP discussion: 36(64.3%) in 2004; 34(64.2%) in 2011 Girls satisfaction with content of FP discussion: 19(40.4%) in 2004; 22(50%) in 2011 <u>4. If applicable, results per additional outcomes</u> -	relatives (may impact generalizability of results) - Risk of reporting bias as use of self-reported data, collected retrospectively (no check with medical records)

Who should be informed about potential infertility risk?			
Benedict et al. Young Adult Female Cancer Survivors' Unmet Information Needs and Reproductive Concerns Contribute to Decisional Conflict Regarding Posttreatment Fertility Preservation. Cancer 2016;122(13):2101-9			
Study design & Main study objective	**Participants and relevant characteristics**	**Relevant results (per outcome)**	**Additional remarks**
1. Study design Cross-sectional (survey) 2. Main study objective: To characterized the posttreatment fertility information needs, reproductive concerns, and decisional conflict regarding future options for posttreatment FP among YAFC 3. Additional study characteristics, if relevant: - Internet survey completed between February and March 2015 - The survey was designed by an interdisciplinary team with	1. Type and number of participants: 346 YAFC *Response rate*: 96% (out of 359 who met eligibility criteria) 714 respondents accessed the survey, 359 (50%) met eligibility criteria 2. Age (at diagnosis) of participants: Age at diagnosis of whole cohort: 23.6 years (birth-35) Age at diagnosis of subgroup: 23.4 (birth-34) 3. Number of participants per diagnosis: 79(23%) Lymphoma 68(20%) Breast cancer 50(14%) Gynecologic cancer 45(13%) Leukemia	1. Outcome(s) definition: Outcome 1. Reasons for not pursuing FP pretreatment Outcome 2. Unmet information needs* Outcome 3. Reproductive concerns* Outcome 4. Decisional conflict regarding future FP* *Analysis done in subgroup of patients (N=179): women with uncertain fertility status who had not previously undergone/attempted FP and either wanted future children or were unsure. 2. Results outcome 1 *Barriers to fertility preservation* 30% of patients did not know about fertility preservation; 29% of patients were feeling too distressed or overwhelmed; and 27% of patients reported cost as barrier 3. Results outcome 2 *Information needs regarding fertility preservation discussion (from subgroup analysis)* Female cancer patients reported unmet information needs regarding fertility risks (58-60%), options to assess and preserve fertility (51-62%), and options for alternative family building (43%) 4. Results outcome 3 • 64% of respondents were concerned they may not be able to have (more) children • 41% reported it was stressful to think about getting	1. Strengths: - First study to examine the decisional conflict of young female survivors when prompted to consider posttreatment FP - Large sample size 2. Limitations: - Internet survey with responses not validated externally - Risk of reporting bias as use of survey - Risk of selection bias as those who participated might be different than those who did not

input from YAFC survivors	27(8%) Colorectal 23(7%)Sarcoma 13(4%) Brain 54(16%)Other <u>4. Additional participants characteristics, if relevant:</u> Gonadotoxic treatment: 59(17%) Pelvic radiation 285(82%)Chemotherapy 36(10%)Surgery 35(10%) Bone marrow transplant	pregnant • 59% were worried about passing on a genetic risk for cancer • 53% of women were concerned their partner or a future partner would be disappointed if they were unable to have children <u>5. Results outcome 4</u> High levels of decisional conflict: • 13% believed they were informed regarding their FP options • 74% were unclear about their personal values related to the decision • 70% believed they did not have enough advice • 35% believed they did not have enough support to make a decision <u>6. Additional outcomes (if applicable)</u> In bivariate analysis: • Greater decisional conflict was associated with having greater unmet information needs ($p<.001$) and reproductive concerns ($p<.001$) • Across all information topics, women who indicated that they had unmet information needs reported higher levels of decisional conflict ($p's<0.01$) In multiple regression analysis controlling for current age, age at treatment completion, income, relationship status, nulliparity, and prior fertility evaluation: • The relation between greater unmet information needs and higher levels of decisional conflict about future FP remained significant $p <0.001$ • Greater reproductive concerns were associated with greater conflict at the trend level • Having undergone a fertility evaluation after treatment was found to be related to lower decisional conflict • Unmet information needs and reproductive concerns accounted for 22% of the variance in decisional conflict	

FP: fertility preservation; YAMC: young adult female cancer survivors; NA: not applicable;

Who should be informed about potential infertility risk?			
Quinn et al. Fertility Preservation and Adolescent/Young Adult Cancer Patients: Physician Communication Challenges. J Adolesc Health 2009;44(4):394-400			
Study design & Main study objective	**Participants and relevant characteristics**	**Relevant results (per outcome)**	**Additional remarks**
1. Study design Cross sectional study with qualitative semistructured in-depth interviews 2. Main study objective To examine barriers experienced by physicians in discussing cancer-related fertility issues with patients aged 12-18yrears 3. Additional study characteristics, if relevant - Study used a subset of data from a larger study examining knowledge, attitudes, and behaviors of pediatric oncologists - All interviews were tape recorded and transcribed. The transcripts were read through and the content	1. Type and number of participants 24 Pediatric oncologists working in 15 clinics in Florida (US) *Response rate*: 41% participated (59 asked to participate) 2. Age (at diagnosis) of participants NA 3. Number of participants per diagnosis NA 4. Additional participants characteristics, if relevant NA	1. Outcome(s) definition Outcome 1: Healthcare system barriers Outcome 2: Perception of parent/patient desire for FP information Outcome 3: Awareness of FP resources Outcome 4: Patient characteristics that may impact FP discussions Outcome 5: Issues unique to adolescent patients 2. Results outcome 1: - Perceptions that the financial costs of FP were too high for most families (FP not covered by insurance) - Combination of lack of resources and lack of training or guidelines for having discussions 3. Results outcome 2: - About half of physicians said the cancer diagnosis is such a shock that an issue like fertility is often put on the ”back burner” - Other half thought that parents and teens do want this information but are either to embarrassed to discuss it or have no background on the topic and do not know how to begin a discussion 4. Results outcome 3: - One third of physicians were aware of sperm banking facilities - Remainder said their facility had no FP resources or they	1. Strengths Provides information on barriers to discussing FP in pediatric oncology, implying that new methods of communication between all parties must be examined and utilized 2. Limitations - Results cannot be generalized to other pediatric hematology/oncology physicians or other populations - Authors state that interview may have limited the amount of in-depth discussion on any one topic - Risk of selection bias: responders more interested in the topic and more likely to engage in discussions about and/or encourage FP might have been participants - Risk of interviewer induced bias

analyzed through intuitive analysis. Key themes were identified - Author used theoretical saturation, in which each new participant we recruited refined new theoretical constructs. Midway in the data analysis we ascertained no new information was emerging; thus, we perceived we had reached theoretical saturation and made no further attempts to recruit additional physicians		were unaware of resources for females (except oophoroypexy) - Physicians typically had low levels of knowledge about resources to refer patients to for FP procedures or consultations - Few pediatric oncologsist reported that the nationally distributed educational brochure they used was not always relevant to the local level and needed improvement <u>5. Results outcome 4:</u> - Most were comfortable in a general sense - However, many experienced barriers related to patient specific diagnosis or socioeconomic situation (ranged from perceived cultural or religious differences to knowing a family could not afford FP) <u>6. Results outcome 5:</u> - All found that it is an important issue to address for teens who have reached puberty - Most agreed that these conversations were awkward because resources were usually limited and there was a fine line between establishing a sense of trust with the patient, while not excluding parents - Conversations about fertility were related to issues of sexuality, and this was a source of embarrassment for both the patient and parents <u>4. If applicable, results per additional outcomes</u>	

NA: not applicable; FP: fertility preservation

Who should be counselled about fertility preservation?				
Byrne et al. Early menopause in long-term survivors of cancer during adolescence. Am J Obstet Gynecol 1992;166:788-793				
Study design Treatment era Years of follow-up	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**

1. Study design Multi-center cohort study (nested case control) 2. Treatment era 1945-1974 3. Follow-up >19 yr after cancer diagnosis	1. Type and number of participants From 5 cancer registries 1048 female CCS ≥21 years of age at study entry; 954 were menstruating before study entry and 94 became menopausal before they were eligible for the cohort 2. Diagnoses Female genital cancer (n=90), Hodgkin's disease (n=206), non-Hodgkin's lymphoma (n=31), soft tissue sarcoma (n=115), leukaemia (n=15), brain or CNS tumour (n=133), bone cancer (n=65), other (n=393) 3. Age at diagnosis Mean (on average) 13.6 yr 4. Age at follow-up Mean (on average)32.3 yr 5. Controls: 1596 menstruating siblings at age 21 yr; Mean age at follow-up 33.0 yr	1. Chemotherapy only 68 (6.5%) 2. Alkylating agents and radiotherapy above diaphragm 38 (3.6%) 3. Alkylating agents and radiotherapy below diaphragm 79 (7.5%) 4. Radiotherapy only 261 (24.9%) 5. Surgery only 493 (47.0%) 6. Sterilizing surgery and chemotherapy and radiotherapy 25 (2.4%) 7. Other treatments 84 (8.0%)	1. Outcome definitions Amenorrhea: woman's report of whether she was still having menstrual periods 2. Results Amenorrhea: - 123/954 (12.9%) menopausal after study entry - 831/954 (87.1%) still menstruating Age-specific relative risks for amenorrhea survivors vs. controls: - All survivors aged 21-25: RR 4.32, 95% CI 2.28-8.17 - All survivors aged 26-30: RR 1.61, p>0.05 - All survivors aged 31-40: RR 0.78, p>0.05 - All survivors aged 41+: RR 0.98, p>0.05 - Alkylating agents alone aged 21-25: RR 9.17, 95% CI 2.67-31.49 - Radiotherapy below diaphragm and alkylating agents aged 21-25: RR 27.39, 95% CI 12.42-60.35 - Radiotherapy below diaphragm and alkylating agents aged 26-30: RR 4.64, p<0.01 - Radiotherapy alone aged 21-25: RR 3.66, 95% CI 1.34-9.99 - Radiotherapy alone aged 26-30: RR 2.41, p<0.05 - Radiotherapy alone aged 31-40: RR 0.90, p>0.05 - Radiotherapy alone aged 41+: RR 1.22, p>0.05 - Aged 0-12 at diagnosis aged 21-30 at follow-up: RR 0.62, p>0.05 - Aged 13-19 at diagnosis aged 21-30 at follow-up: RR 2.32, 95% CI 1.63-3.291	1. Strengths - Study sample 2. Limitations - Self-reported outcome - Control group not representative for general population 3. Risk of bias A. Selection bias: Unclear Reason: unclear how many patients were included in the original cohort of survivors B. Attrition bias: Low risk Reason: 90% of eligible survivors completed follow-up assessment. At follow-up, 10% of the survivors and 1% of the controls had died C. Detection bias: Unclear Reason: unclear if the outcome assessors were blinded for important determinants related to the outcome D. Confounding: High risk Reason: Controls not matched to cases

Abbreviations: yr, years; CCS, childhood cancer survivors; CNS, central nervous system.

Who should be counselled about fertility preservation?				
Chiarelli et al. Early menopause and Infertility in Females after Treatment for Childhood Cancer diagnosed in 1964-1988 in Ontario, Canada. Am J Epidemiol 1999;150(3):245-54.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
1. Study design Retrospective cohort study 2. Treatment era 1964-1988 3. Follow-up Follow-up >5 yr after diagnosis: 5-10 yr: 25.2% 11-15 yr: 24.9% 16-20 yr: 26.3% 21-30 yr: 23.6%	1. Type and Number of Participants 719 from total cohort of 1,581 female CCS Excluded: sterilising surgery 2. Diagnoses Lymphoma (28.8%), epithelial neoplasm (17.9%), CNS tumour (12.8%), soft-tissue sarcoma (7.4%), bone tumour (6.5%), renal tumour (6.4%), gonadal and germ cell (4.0%), other (5.0%) 3. Age at diagnosis Range 0-19 yr 4. Age at follow-up Median 28 yr (range 18-49) 5. Controls Non-sterilizing surgery group: n=162	1. Chemotherapy Alkylating agents: 150 (20.1%) Alkylating agent score: 1-13 low, 14-21 medium, >22 high risk. 2. Radiotherapy to ovaries Abdominal pelvic radiation: 154 (21.4%) Dose: <20 Gy, 20-35 Gy, > 35 Gy 3. Alkylating agents + radiotherapy to ovaries 71 (9.9%) 4. Non-sterilizing surgery 162 (22.5%) 5. Other treatments 182 (25.3%)	1. Outcome definitions Menopausal status based on Telephone questionnaire: “Have you stopped having periods?”, “Have you ever used hormonal supplement pills?” 2. Results 63 (8.8%) menopausal after treatment at median age of 24 yr of whom 29 (46%) surgical menopause Age-adjusted risk ratios for menopause: -Alkylating agents and abdominal-pelvic RT vs. non-sterilizing surgery: RR 2.58 (95% CI 1.14-5.80) -Alkylating agents vs. non-sterilizing surgery: RR 0.77 (95% CI 0.30-1.97) -Abdominal-pelvic RT vs. non-sterilizing surgery: RR 1.62 (95% CI 0.80-3.28) -Other treatments vs. non-sterilizing surgery: RR 0.75 (95% CI 0.34-1.65) -Abdominal-pelvic RT vs. non-sterilizing surgery: <2000 cGy: RR 1.02 (95% CI 0.29- 3.59) 2000-3499 cGy: RR 1.36 (95% CI 0.57-3.25) ≥3500 cGy: RR 3.27 (95% CI 1.57-6.81) -Alkylating agent score vs. non-sterilizing surgery:	1. Strengths -Equal amount of patients in each of the 4 follow up 5 year periods. -Diagnoses represent common pediatric cancer diagnosis. 2. Limitations -Subset not representative for cohort. -Based on telephone questionnaire. -Unclear if patients treated with BMT included. -The study has self-selected specific treatments which may cause infertility but has assumed that radiotherapy to brain and abdomen and pelvis gives the same effect and analysed this together. -TBI included with abdominal pelvic radiation even though most would have a sterilizing dose. -No information on ovarian transposition. -No details of non-sterilizing surgical procedures and how similar this patient group was. 3. Risk of bias

			1-13: RR 1.13 (95% CI 0.41-3.09) 14-21: RR 1.90 (95% CI 0.52-6.92) ≥21: RR 3.08 (95% CI 1.15-8.21)	A. Selection bias High risk Reason: the study group consisted of 719/1581 (45%) of the original cohort of survivors B. Attrition bias Low risk Reason: the outcome was assessed for the whole study group (n=719) C. Detection bias Unclear Reason: Unclear if the outcome assessors were blinded for important determinants related to the outcome. D. Confounding Low risk Reason: Analyses were adjusted for age

Abbreviations: Yrs, years; CT, chemotherapy; AA, alkylating agents; RT, radiotherapy; BMT, bone marrow transplantation; TBI, total body irradiation.

Who should be counselled about fertility preservation?				
Laverdiere et al. Long-Term Complications in Survivors of Advanced Stage Neuroblastoma. Pediatric Blood Cancer 2005;45:324-332				
Study design Treatment era Years of follow-up	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
1. Study design Retrospective single center cohort study 2. Treatment era	1. Type and Number of Participants n=63 survivors of advanced stage neuroblastoma n=32 (51%) female	1. Chemotherapy 63 (100%) - cyclophosphamide mean 9.5g (1.5-30.8) n=63 - doxorubicin mean 258 mg/m2 (75-554) n=61	1. Outcome definitions Ovarian failure, not further specified Graded based on CTCAEv3; does not talk about transient vs permanent 2. Results	1. Strengths Relatively large group of advanced NB patients 2. Limitations -Retrospective

1991-2001 3. Follow-up Median 7.06 yr (range 1.9-25.5) since diagnosis	2. Diagnoses advanced stage NB stage 2 and 4 and 1 visit to LTFU 3. Age at diagnosis Median age 3.0 years (range 0.07 – 23.5) Mean age 6.85 years for patients with ovarian dysfunction 4. Age at follow-up Median follow-up 2.13 years (range 0-11.4) Median age last clinical visit 11.62 years (range 4-30) 5. Controls (if applicable) None	- cisplatin mean 514 mg/m2 (123-1324) n=56 - etoposide mean 1162 mg (153-3450) n=54 - carboplatin mean 948 mg (540-1496) n=17 2. Radiotherapy 56 (88.9%) - abdominal, mean 2174 cGy n=46 - chest, mean 1976 cGy n=15 - cranial, mean 2381 cGy n=15 - spinal, mean 2093 cGy n=6 - TBI, mean 1075 cGy n=6 3. Surgery 100% various sites no gonadal surgery reported 4. BMT 35 (55.6%) 5. Other treatments - Immunotherapy 39 (61.9%) - Radioimmunotherapy 19 (30.2%)	- 13/32 (41%) developed ovarian failure - Grade 1-2 moderate, dysfunction was transient: n=6 - Grade 3-4 severe, dysfunction was persistent: n=7 - mean age at diagnosis: 6.85 years - 13/13 (100%) received cyclophosphamide - 10/13 (76.9%) received abdominal/pelvic irradiation Risk factors for acute ovarian failure adjusted for age ≤1 and ≥1 year, stage at diagnosis, MYCN status, sites of primary tumours and survival status: Cyclophosphamide ≥7.4g vs. <7.4g: OR 9.62 (95% CI 1.4-67.2)	-End point is not infertility but ovarian dysfunction. -Not clear the diagnostic criteria used for ovarian dysfunction. -Some ovarian dysfunction was transient which is unusual at > 2 years after the completion of Cancer Rx. -Not clear if permanent ovarian failure or any ovarian dysfx asso with cyclo > 7.4 gm compared to whom - Relative short follow up of patients may underestimate rate of POI - “tailored testing” would seem to predispose to bias in ascertainment of late effects. 3. Risk of bias A. Selection bias Unclear Reason: the number patients originally included in the study is not mentioned. B. Attrition bias Low risk Reason: All the included patients were assessed. C. Detection bias Unclear Reason: Unclear if the outcome assessors were blinded for important determinants related to the outcome

				D. Confounding Low risk Reason: analysis adjusted for age, stage at diagnosis, MYCN status, sites of primary tumours and survival status

Who should be counselled about fertility preservation?				
Chemaitilly et al. Acute Ovarian Failure in the Childhood Cancer Survivor Study. J Clin Endocrinol Metab. 2006; 91:1723–1728.				
Study design Treatment era Years of follow-up	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
1. Study design Multi-center retrospective cohort study 2. Treatment era 1970-1986 3. Follow-up >5 years after cancer diagnosis	1. Type and Number of Participants 3,390 patients were eligible from 6,079 female CCS ≥18 years of age at study entry; diagnoses associated with ovarian dysfunction (e.g. Turner syndrome), cranial irradiation above 3000 cGy (known to cause hypogonadotropic hypogonadism), tumour located in the hypothalamic pituitary region, history of bilateral oophorectomy, and incomplete radiation records were excluded. 2. Diagnoses ALL (n=1032), AML	1. Chemotherapy Alkylating agents: 1,684/3,390 (49.7%) 2. Radiotherapy Abdominal/pelvic radiotherapy: 832/3,390 (24.5%) Alkylating agents + abdominal/pelvic radiotherapy : 393/3,390 (11.6%) 3. Treatment groups *Patients with vs without AOF* Chemotherapy±surgery only: 5.6% *vs* 30% RT±surgery only: 6.5% *vs* 8.9% Chemotherapy+ RT±surgery: 87.9% *vs* 51.1% Alkylating agents:	1. Outcome definitions Acute ovarian failure (AOF): patients who reported never menstruating or who had ceased having menses within 5 years after their cancer diagnosis (primary or secondary amenorrhoea). 2. Results Prevalence AOF: 215/3390 (6.3%) Risk factors associated with AOF in multivariable logistic regression analyses: Age at diagnosis 0-12 yr: - Procarbazine yes vs. no: OR 3.2 (95% CI 1.3-7.3) - Cyclophosphamide yes vs. no: OR 1.2 (95% CI 0.7-2.1) - RT to ovaries 1-99 vs. 0 cGy: OR 3.7 (95% CI 1.6-10.2) - RT to ovaries 100-999 vs. 0 cGy: OR 9.0 (95% CI 3.4-26.5) - RT to ovaries 1000-1999 vs. 0 cGy: OR	1. Strengths Large study sample 2. Limitations Self-reported amenorrhea 3. Risk of bias A. Selection bias High risk Reason: the study group consisted of 3390/6079 (56%) of the original cohort of survivors. B. Attrition bias Low risk Reason: Outcome assessed for all patients. C. Detection bias Unclear Reason: unclear if the outcome assessors were blinded for important determinants related

	(n=99), Hodgkin's disease (n=553), non-Hodgkin's lymphoma (n=187), soft tissue sarcoma (n=317), Wilms' tumour (n=364), Neuroblastoma (n=248), other (n=590) 3. Age at diagnosis Mean 9.8/ 8.3 yr (with/ without AOF) (Range 0-20 yr) 4. Age at follow-up Mean 32.9/ 29.6 yr (with /without AOF) 5. Controls (if applicable) No controls.	67% *vs* 48.6% Cyclophosphamide 55.3% *vs* 42.1% Procarbazine: 24.7% *vs* 8.7% Abdominal/pelvic RT: 75.3% *vs* 21.1% Abdominal/pelvic RT+AA: 52.6% *vs* 8.8 % RT to ovaries 1–99 cGy: 18.6% *vs* 36.6% RT to ovaries 100–999 cGy: 17.7% *vs* 8.2 % RT to ovaries 1000–1999 cGy: 15.8% *vs* 1.9% RT to ovaries >2000 cGy: 38.1% *vs* 0.6% BMT: 8.8 *vs* 1.3 %	55.3 (95% CI 22.3-157.8) - RT to ovaries ≥2000 vs. 0 cGy: OR 950.1 (95% CI 352.9-3043.2) Age at diagnosis 13-20 yr: - Procarbazine yes vs. no: OR 2.6 (95% CI 1.4-4.7) - Cyclophosphamide yes vs. no: OR 4.9 (95% CI 2.8-9.2) - RT to ovaries 1-99 vs. 0 Gy: OR 2.9 (95% CI 1.2-8.3) - RT to ovaries 100-999 vs. 0 cGy: OR 17.2 (95% CI 6.8-49.5) - RT to ovaries 1000-1999 vs. 0 cGy: OR 90.9 (95% CI 29.1-323.5) - RT to ovaries ≥2000 vs. 0 cGy: OR 171.2 (95% CI 55.8-609.8) Significant interactions between age at diagnosis and high doses of radiotherapy to the ovary (p=0.03 for dose ≥2000cGy) and between age at diagnosis and treatment with cyclophosphamide (p=0.0006), with this drug being a significant risk factor only for the older age group. Univariate analysis association age at diagnosis and AOF: ≥12 yr vs. <12 yr: OR 1.8 (95% CI 1.4-2.4)	to the outcome D. Confounding Low risk Reason: multivariable analyses performed including alkylating agents and radiotherapy, stratified by age.

Who should be counselled about fertility preservation?				
Sklar et al. Premature Menopause in Survivors of Childhood Cancer: A Report from the Childhood Cancer Survivor Study. J Natl Cancer Inst 2006;98(13):890-6.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
1. Study design Retrospective, multicentre survey: self-report 2. Treatment era 1970 – 1989 3. Follow-up >5 years after cancer diagnosis	1. Type and Number of Participants 2,819 CCS were eligible from 6,079 female CCS ≥18 years of age at study entry 2. Diagnoses Leukaemia 1,025(36%); HL 404 (14%); tumours of bone 324(11%); kidney 297(11%); brain 137(5%); sarcomas 271(10%); NBl 154(5%) 3. Age at diagnosis Median 7 yr (range 0-20 yr) 4. Age at follow-up Median 29 yr (range 18-50 yr) 5. Controls N=1,065 siblings Sibling subset of CCS cohort with spontaneous menstruation Median age: not reported	1. Chemotherapy Alkylating agents: 1359 (48.2%) Alkylating agent score 1: 539 (19.1%) 2: 373 (13.2%) 3: 293 (10.4%) 2. Radiotherapy Radiation to ovaries: 1472 (52.2%) 1-99 cGy: 1140 (40.4%) 100-999 cGy: 258 (9.2%) ≥999 cGy: 74 (2.6%) 3. Surgery Any: 2040 (72.4%) 4. BMT 32 (1%)	1. Outcome definitions Self-reported: if subjects had not experienced a spontaneous menses for >6 months and other causes, e.g. pregnancy, use of agents such as injectable progesterone and GnRH-a have been excluded 2. Results Premature menopause (<40yrs): - N: 126 CCS, 33 control siblings - Cumulative incidence CCS: 15% - Rate ratio 1.05 (95% CI 1.04-1.07) (p<0.001) compared to siblings - Surgical premature menopause not significantly different in CCS and siblings (RR 0.8, 95% CI 0.52-1.23) - Non-surgical premature menopause: 8% in CCS, 0.8% in siblings (RR 13.21, 95% CI 3.26-53.51, p<0.001) Risk-factors non-surgical premature menopause in multivariable Poisson regression analysis: - Attained age: RR 1.15, 95% CI 1.09-1.21, p< 0.001 - RT dose to ovary vs. no RT: RT 1-99 cGy: RR 4.30, 95% CI 1.20-15.47, p=0.04) RT 100-999 cGy: RR 5.70, 95% CI 1.12-28.99, p=0.04	1. Strengths Well-performed large study 2. Limitations - Self-reported outcomes - Among non-menopausal women 20% of survivors and 24% siblings were taking OC (however after exclusion of these subjects results were almost identical to entire cohort) 3. Risk of bias A. Selection bias High risk Reason: the study group consisted of 2819/4620 (61%) of the original cohort of survivors B. Attrition bias Low risk Reason: the outcome was assessed for the whole study group C. Detection bias Unclear Reason: Unclear if study participants were blinded for important determinants related to the outcome

			RT ≥1000 cGy: RR 109.59, 95% CI 28.15-426.70, p<0.001 - AA score vs. no alkylating agents: AA score 1-2: RR 2.3, 95% CI1.08-4.90, p=0.03 AA score 3: RR 5.78, 95% CI 2.9-11.55, p<0.001 - HL (minimum ovarian RT): No ovarian RT: RR 9.18, 95% CI 1.52-55.24, p=0.02 1-99 cGy: RR 12.26, 95% CI 3.41-44.14, p<0.001 100-999 cGy: RR 11.41, 95% CI 2.75-47.26, p<0.001 ≥1000 cGy: RR 6.74, 95% CI 0.63-71.74, p=0.11 (Age at diagnosis not associated, data not shown) <u>Cumulative incidence of non-surgical premature menopause by age 40 years (see figure below):</u> - AA only: ± 15% - Abdominopelvic RT only: ± 5% - AA + abdominopelvic RT: ± 30% Among CCS without RT to ovaries, HL 9.18-fold higher risk of premature menopause than other types of cancer (95% CI 1.52-55.24, p=0.02).	<u>D. Confounding</u> Low risk Reason: Analyses were adjusted for age and treatment

Abbreviations: FU, follow-up; yrs, years; CCS, childhood cancer survivors; n, number; HL, Hodgkin lymphoma; Nbl, neuroblastoma; AOF, acute ovarian failure; CT, chemotherapy; RT, radiotherapy; SCT, stem cell transplantation; PM, premature menopause; AA, Alkylating agents; GnRH-a, gonadotrophin-releasing hormone analogue.

Who should be counselled about fertility preservation?				
Laverdiere et al. Long-term outcomes in survivors of neuroblastoma: a report from the Childhood Cancer Survivor Study. J Natl Cancer Inst. 2009;101(16):1131-40.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
1. Study design CCSS multicenter retrospectively ascertained cohort study of CCS compared with siblings. 2. Treatment era Diagnosed between 1970-1986 3. Follow-up >5 yr post-diagnosis	1. Type and Number of Participants N=954/1358 5-yr survivors of neuroblastoma 2. Diagnoses Neuroblastoma 3. Age at diagnosis Median 0.9 (range 0-20.7) yr 4. Age at follow-up Median age at baseline survey: 17.2 (range 5.7-44.2) yr; Median age at completion of latest questionnaire: 23.3 (range 5.7-45.2) yr 5. Controls (if applicable) N=3,899 siblings	1. Chemotherapy Only: n=4 (0.4%) + surgery: N=216 (26%) 2. Radiotherapy Only: n=3 (0.3%) + surgery: N=132 (16%) 3. Surgery Only: N=200 (24%) 4. Other treatments Chemotherapy + radiotherapy + surgery: N=268 (32%) Chemotherapy + radiotherapy: n=6 (0.6%) No treatment : n=3 (0.3%)	1. Outcome definitions Ovarian failure: patients who reported never menstruating or who had ceased having menses within 5 years after their cancer diagnosis 2. Results Ovarian failure: 13/204 (6.4%) evaluable women Risk factors for ovarian failure in univariate analysis: - Radiotherapy to ovaries: OR 8.4 (95% CI 1.1-67.7) - Alkylating agent score >3: OR 12 (95% CI 2.0-71.0) - Alkylating agent score 2: OR 2.0 (95% CI 1.0-33.2) - Cumulative cyclophosphamide dose >5g: OR = 7.1 (95% CI 1.5-34.0) Risk factors for ovarian failure in multivariable analysis: - Radiotherapy to ovaries: p<0.05 (no effect measure reported) - Age at diagnosis, cyclophosphamide exposure, surgery and alkylating agent score were not significant	1. Strengths Large cohort, well-described cohort, well-described design. 2. Limitations -Self-reported ovarian failure. -No further medical information (lab results, diagnosis) on this diagnosis. -Unclear definition of 'ovarian failure'. -No further information on RT doses. -Ovarian failure is just stated briefly. 3. Risk of bias A. Selection bias High risk Reason: the study group consisted of 954/1375=69% of the original cohort of survivors B. Attrition bias Low risk Reason: 832/954 (87%) available treatment information from medical records C. Detection bias

				Unclear Reason: Unclear if the outcome assessors were blinded for important determinants related to the outcome <u>D. Confounding</u> Low risk Reason: multivariable analyses performed

Abbreviations: CCSS=childhood cancer survivor study, yr(s)=year(s), CCS=childhood cancer survivor, N=number, OR=odds ratio, CI=confidence interval.

Who should be counselled about fertility preservation?				
Gracia et al. Impact of cancer therapies on ovarian reserve. Fertil Steril 2012;97:134-140.				
Study design Treatment era Years of follow-up	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
<u>1. Study design</u> Single-center cohort study <u>2. Treatment era</u> Not mentioned <u>3. Follow-up</u> >1 yr after cancer treatment	<u>1. Type and Number of Participants</u> 71 postmenarchal female cancer survivors 15-39 years of age <u>2. Diagnoses</u> Hodgkin lymphoma (n=15), non-Hodgkin lymphoma (n=9), leukaemia (n=23), sarcoma (n=10), Wilms' tumour (n=4), breast cancer (n=3), other (n=7) <u>3. Age at diagnosis</u> Median 11 (0.3-29) yr <u>4. Age at follow-up</u> Mean 25.7 (24.2-27.2) yr	<u>1. Chemotherapy</u> Alkylating agents: 63 (88.7%) <u>2. Radiotherapy</u> Pelvic radiation (including TBI): 13 (18.3%) <u>3. Surgery</u> Not reported <u>4. BMT</u> 16 (22.5%) of which 10 (14.1%) TBI	<u>1. Outcome definitions</u> Amenorrhea: woman's report of whether she was still having menstrual periods <u>2. Results</u> <u>Menstrual characteristics:</u> - Age at menarche: 12.5 yr survivors vs. 12.4 yr controls (p=0.67) - Regular cycles: 49 (69.0%) survivors vs. 65 (91.5%) controls <u>Geometric mean (95% CI) reproductive hormone measures survivors vs. controls adjusted for age, race and BMI:</u> - FSH (mIU/mL): 11.12 (9.47-13.6) vs. 7.25 (6.0-8.8), p=0.001 - E_2 (pg/mL): 24.2 (20.9-28.1) vs. 29.4 (24.7-34.9), p=0.084 - AMH (ng/mL): 0.8 (0.6-1.1) vs. 2.9 (2.1-3.9), p<0.001	<u>1. Strengths</u> - Prospective enrolment and valid comparisons were made with an unexposed control population of similar age - Early follicular phase measures - Cancer diagnoses and treatments were validated with medical records <u>2. Limitations</u> - Unclear what proportion of eligible patients were included in the study - Differences in baseline characteristics of unexposed and exposed groups (adjusted in analysis) - The cohort is not representative of the general population of survivors <u>3. Risk of bias</u> <u>A. Selection bias</u> Unclear

	5. Controls 67 postmenarchal controls; Mean age 27.3 (26.1-28.4) yr		- AFC: 14.6 (10.8-18.3) vs. 27.2 (23.1-31.4), p<0.001 Geometric mean (95% CI) reproductive hormone measures survivors treated with alkylating agent score ≥3 or pelvic radiation or TBI vs. other treatment vs. controls adjusted for race and BMI: - FSH (mIU/mL): 10.6 (8.7-12.9) vs. 7.9 (6.6-9.5) vs. 6.9 (6.1-7.9), p<0.001 - E_2 (pg/mL): 10.6 (18.1-29.1) vs. 24.5 (19.9-30.3) vs. 31.8 (27.3-37.1), p<0.05 - AMH (ng/mL): 0.5 (0.3-0.9) vs. 1.9 (1.2-3.2) vs. 3.1 (2.2-4.4) Geometric mean reproductive hormone measures survivors treated with pelvic radiation vs. controls adjusted for age, race and BMI: - FSH (mIU/mL): 28.4 vs. 9.4, p<0.001 - AMH (ng/mL): 0.15 vs. 1.24, p<0.001 - AFC: 2.9 vs. 17.5, p=0.001 Effect alkylating agent score in survivors treated without pelvic radiation corrected for age, race and BMI: - Each unit increase in alkylator score, geometric mean FSH values increased by 0.91 mIU/mL (p=0.016) and geometric mean AMH levels decreased by 0.55 ng/mL (p=0.003) - Differences in E_2 and AFC were not significant	Reason**:** Unclear how many patients were included in the original cohort of survivors. B. Attrition bias Low risk Reason: The outcome was assessed for the whole study group. C. Detection bias Unclear Reason: Unclear if the outcome assessors were blinded for important determinants related to the outcome. D. Confounding Low risk Reason: Analysis adjusted for age, race and BMI. Confounding has been reduced by restricting the study to nonpregnant nonlactating females not using hormones and without other causes of ovarian dysfunction. Evaluation of ovarian reserve was performed and hormone variability was minimized by obtaining early follicular phase measures.

Abbreviations: yr, years; TBI, total body irradiation; BMT, bone marrow transplantation; FSH, follicle-stimulating hormone; E2, oestradiol; AMH, anti-Müllerian hormone; AFC, antral follicle count; BMI, body mass index.

Who should be counselled about fertility preservation?

Borgmann-Staudt et al. Fertility after allogeneic haematopoietic stem cell transplantation in childhood and adolescence. Bone Marrow Transplantation 2012;47:271-276.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
1. Study design Multi centre cohort study 2. Treatment era 2000-2005 3. Follow-up Median 6 yr from HSCT (range 3-12 yr)	1. Type and Number of Participants 138 paediatric female patients treated with allogeneic HSCT, aged ≥12 yr at time of study 2. Diagnoses ALL (25%), AML (11%), CML (14%), MDS (12%), SAA (11%), FA (3%), ES (3%), thalassaemia major (3%), NHL (1%), other (18%) 3. Age at HSCT Median 13 (range 4-27) yr 4. Age at follow-up Median 19 (range 12-34) yr 5. Controls (if applicable) N/A	1. Chemotherapy - Busulfan and cyclophosphamide: 25 (18%) - Busulfan, cyclophosphamide and melphalan: 15 (11%) - Cyclophosphamide only: 26 (19%) - Etoposide: 31 (23%) - Others: 42 (30%) 2. Radiotherapy 54 (39%) TBI Median 12.0 (range 2.0-14.4) Gy 3. Surgery N/A 4. BMT 133 (100%)	1. Outcome definitions Impaired fertility: amenorrhoea, hormone substitution, elevated FSH/LH >15 U/L or low estradiol (<30 pgl/mL) 2. Results Impaired fertility: 111/133 (83%); 9/38 women with information on their menstrual cycle had amenorrhoea, 68 were receiving hormone substitution and 42 of the women not taking hormone replacement therapy had abnormal values on hormone analysis Risk factors for impaired fertility in multivariable logistic regression analyses: - Pubertal patients vs pre-pubertal patients: OR 4.7 (95% CI 1.5-14.9) - TBI vs. no TBI: OR 4.9 (95% CI 1.2-19.9) - Busulfan yes vs. no: OR 47.4 (95% CI 5.4-418.1) - Cyclophosphamide and etoposide not significantly associated (no effect measures reported)	1. Strengths … 2. Limitations In 10 of the 111 patients classified as infertile, hormone substitution was the only criterion for suspected infertility. It is possible that some of these 10 women only used hormone substitution for contraceptive reasons meaning that the infertility rate may be lower than 83%. 3. Risk of bias A. Selection bias Unclear Reason: total number of patients in the original cohort not mentioned. B. Attrition bias Low risk Reason: for 133 out of 138 (96.4%) patients hormone analysis was performed. However, only for 38 patients details on menstrual cycle were available. C. Detection bias Unclear

				Reason: Unclear if the outcome assessors were blinded for important determinants related to the outcome. D. Confounding Low risk Reason: Analyses were adjusted for treatment and pubertal stage at HSCT.

Abbreviations:; ALD = adrenoleukodystrophy; ES = Ewing sarcoma; FA = Fanconi anaemia; FSH = follicle-stimulating hormone; HSCT = haematopoeitic stem cell transplantation; LH = luteinizing hormone; MDS = myelodysplastic syndrome; NHL = non-Hodgkin's lymphoma; SAA = severe aplastic anaemia

Who should be counselled about fertility preservation?				
Thomas-Teinturier et al. Age at menopause and its influencing factors in a cohort of survivors of childhood cancer: earlier but rarely premature. Human Reproduction 2013;28:488-495				
Study design Treatment era Years of follow-up	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
1. Study design Multi-center (n=5) prospective cross-sectional study 2. Treatment era 1945-1985 3. Follow-up >5 yr since cancer diagnosis	1. Type and Number of Participants 706 female CCS 2. Diagnoses Nephroblastoma 213 (30%), neuroblastoma 144 (20.5%), Hodgkin's disease 48 (7%), non-Hodgkin's lymphoma 58 (8%), brain tumours 26 (3.5%), soft tissue	1. Chemotherapy - Any alkylating agent: 337 (47.7%) - Cyclophosphamide: 284 (40.2%), median dose 6700 (range 4480-10490) mg/m^2 - Procarbazine: 51 (7.2%), median dose 4890 (range 2590-7800) mg/m^2 - Lomustine: 15 (2.1%), median dose 415 (range 345-535) mg/m^2 - Mechlorethamine: 40 (5.7%), median dose 36 (range 24-61)	1. Outcome definitions Menopause: 12 months of amenorrhea and reporting menopause 2. Results Menopause: - 97 (13.7%) at median age of 44 yr - 62 (8.9%) nonsurgical menopause - 35 (5.0%) surgical menopause Premature menopause before age 40: - 29 (4.1%)	1. Strengths - Detailed therapy data on agents and dose 2. Limitations - Self-reported outcome data 3. Risk of bias A. Selection bias: High Risk Reason: 706/1522 (46.4%) were included in the study.

	sarcoma 76 (11%), leukaemia (ALL, n=5; 5%), bone sarcoma 52 (7.5%), gonadal and germ cell tumours 39 (5.5%), retinoblastoma 18 (2.5%), others 32 (4.5%) 3. Age at diagnosis Median 4.0 (range 0-17) yr 4. Age at follow-up Median 36 (range 21-66) yr 5. Controls None	mg/m^2 - Ifosfamide: 22 (3.1%), median dose 35610 (range 18100-59590) mg/m^2 - Dacarbazine: 18 (2.5%), median dose 2260 (range 1470-2910) mg/m^2 - Carmustine: 14 (2.0%), median dose 60 (range 52-580) mg/m^2 - Melphalan: 9 (1.3%), median dose 350 (range 180-360) mg/m^2 - Thiotepa: 1 (0.1%), median dose 75 mg/m^2 2. Radiotherapy Radiation to the ovaries: <0.01 Gy: 306 (43.5%) 0.01-<1 Gy: 203 (28.5%) 1-<10 Gy: 155 (22.0%) ≥10 Gy: 42 (6.0%) 3. Stem cell transplantation Not reported 4. Surgery - Unilateral oophorectomy: 40 (5.7%) - Oophorectomy for cancer treatment: 28 (4.0%)	- 15 (2.1%) nonsurgical premature menopause - 14 (2.0%) surgical premature menopause Risk factors for nonsurgical menopause in multivariable analyses adjusted for age at diagnosis and pubertal period: *Model 1:* - Minimal radiation dose to ovaries per Gy: RR 1.1 (95% CI 1.0-1.6) - Procarbazine dose per g/m^2: RR 2.5 (95% CI 1.4-5.8) - Cyclophosphamide dose per g/m^2: RR 1.3 (95% CI 1.0-2.1) - Melphalan yes vs. no: RR 15.2 (95% CI 3.2-52.7) - Oophorectomy yes vs. no: RR 3.7 (95% CI 1.1-11.2) *Model 2:* - Minimal radiation dose to ovaries 0.01-<1 vs. <0.01 Gy: RR 1.3 (95% CI 0.6-2.9) - Minimal radiation dose to ovaries 1-<10 vs. <0.01 Gy: RR 2.3 (95% CI 1.0-5.1) - Minimal radiation dose to ovaries ≥10 Gy vs. <0.01 Gy: RR 3.8 (95% CI 1.2-11.6) - Alkylating agents before pubertal period vs. none: RR 2.8 (95% CI 1.2-6.5) - Alkylating agents during pubertal period vs. none: RR 14.8 (95% CI 4.2-52.8) - Alkylating agents after menses vs. none: RR 7.6 (95% CI 3.0-19.1) Risk factors for nonsurgical premature menopause <age 40 yr in multivariable analysis: - Age at diagnosis per yr: RR 1.3 (95% CI 1.04-1.6) - Melphalan yes vs. no:	B. Attrition bias: Low risk Reason: the outcome was assessed for the whole study group. C. Detection bias Unclear Reason: unclear if the outcome assessors were blinded for important determinants related to the outcome D. Confounding Low risk Reason: Important prognostic factors (i.e. age, co-treatment, ultrasound procedure) were taken into account

			RR 32.0 (95% CI 2.0-530.0) - Cumulative cyclophosphamide dose per g/m^2: RR 1.1 (95% CI 1.02-1.3) - Radiation dose to ovaries per Gy: RR 1.1 (95% CI 1.0-1.2)	

Who should be counselled about fertility preservation?				
Bresters et al. Ovarian insufficiency and pubertal development after hematopoietic stem cell transplantation in childhood. Pediatr Blood Cancer 2014; 61:2048-2053.				
Study design Treatment era Years of follow-up	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
1. Study design Single center cohort study 2. Treatment era 1975-2008 3. Follow-up Median 7.2 years from BMT (at least >2 years)	1. Type and Number of Participants 109 consecutive female patients <19 years of age at HSCT, surviving >2 yr form HSCT, aged ≥10 yr at time of study 2. Diagnoses i: malignant hematological disease: AML, ALL, myelodysplastic syndrome n=69 (64%) ii: immune deficiency/inborn errors of metabolism (IEM): SCID, hemophagocytic lymphohistiocytosis, metachromatic leukodystrophy, and	1. Chemotherapy - Alkylating agents: 109 (100%) - Alkylating agents only: 51 (46.8%) - Cyclophosphamide: 99 (90.8%) 20-200mg/kg - Busulfan: 34 (31.2%) oral 8-20mg/kg, IV 16 mg/kg - Melphalan: 22 (20.2%) 140 mg/m2 - Ifosfamide: 2 (1.8%) 2-6 g/m2 - Treosulfan: 8 (7.3%) 42 mg/m2 - Tiothepa: 3 (2.8%) 8 mg/kg - Etoposide: 5 (4.6%) 2. Radiotherapy 58 (53.2%) TBI/TAI 4-12 Gy 3. Surgery	1. Outcome definitions Ovarian Insufficiency: elevated FSH/LH >10 U/L and low estradiol levels (<40 pmol/L). In pre-pubertal females the absence of spontaneous pubertal development after the age of 12 years or in pubertal or post-pubertal females the absence of menses. 2. Results Ovarian insufficiency: 61 (56%) at median age 14.4 yr (range 11.0-25.5) Cumulative incidence ovarian insufficiency: - Pubertal status at time of BMT: post-pubertal 79% (n=22), pubertal 67% (n=8), pre-pubertal 45% (n=31); p = 0.01 - Cancer diagnosis: malignant hematological disease 68% (n=47), immune deficiency/IEM 33% (n=3), benign hematological disease: 39%	1. Strengths Well-performed study 2. Limitations - 64% malignant disease - Small number of patients in subgroups - Short follow up/young age of cohort - No analysis of other chemotherapy agents used in conditioning regimens - Therapy prior to BMT conditioning unknown/not described 3. Risk of bias A. Selection bias Low risk Reason: the study group consisted of 109/141 (77%) of the original cohort of survivors.

	osteopetrosis n=9 (8%) iii: benign hematological disease: bone marrow failure/aplastic anemia, beta-thalassemia, fanconi anemia, and blackfan diamond anemia n=31 (28%) <u>3. Age at diagnosis</u> Median 9.3 (range 0.3-18.9) yr <u>4. Age at follow-up</u> Median 21.4 (range 10.9-45.2) yr <u>5. Controls (if applicable)</u> N/A	N/A <u>4. BMT</u> 109 (100%)	(n=12); *p*=0.008 - Treatment: Radiotherapy 57% (n=33/58), TBI 68% (n=30/44), TAI 21% (n=3/14), chemo with busulfan 68% (n=23/34), chemo without busulfan 29% (n=5/17), any chemo only 55% (n=28/51) - Age at HSCT: <5 yr 35% (n=11/31), 5-10 yr 77% (n=27/35), 15-20 yr 79% (n=11/14); *p*=0.001 <u>Risk factors for ovarian insufficiency in multivariable Cox regression analyses:</u> - Pubertal patients vs pre-pubertal patients: RR 4.42 (95% CI 1.90-10.27) - Post-pubertal vs pre-pubertal patients: RR 22.08 (95% CI 9.46-51.54) - Malignant hematological disease vs benign hematological disease: RR 1.69 (95% CI 0.87-3.26) - Immune deficiency/IEM vs benign hematological disease RR 0.80 (95% CI 0.22-2.88) - TBI/TAI vs chemotherapy only: RR 0.77 (95% CI 0.44-1.35) - Chemotherapy with busulfan vs. without busulfan: RR 2.98 (95% CI 0.99-9.03), p=0.05	<u>B. Attrition bias</u> Low risk Reason: the outcome was assessed for the whole study group. <u>C. Detection bias</u> Unclear Reason: Unclear if the outcome assessors were blinded for important determinants related to the outcome. <u>D. Confounding</u> Low risk Reason: Analyses were adjusted for diagnosis, treatment and pubertal stage at HSCT.

Who should be counselled about fertility preservation?				
Thomas-Teinturier et al. Ovarian reserve after treatment with alkylating agents during childhood. Human Reproduction 2015; 30:1437-1446				
Study design Treatment era Years of follow-up	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
1. Study design Multi-center (n=5) prospective cross-sectional study 2. Treatment era Not reported 3. Follow-up >3 yr after end of therapy	1. Type and Number of Participants 108 female CCS without an ovarian tumour, treated with alkylating agents and without brain, pelvic or total body radiation or busulfan/thiotepa 2. Diagnoses Neuroblastoma (n=23;22%), Hodgkin's disease (HL, n=21; 20%), non-Hodgkin's lymphoma (NHL, n=15; 14%), soft tissue sarcoma (n=16; 15%), leukaemia (ALL, n=5; 5%), bone sarcoma (n=16; 15%), other (n=3 Wilm's tumour and n=1 malignant germ cell tumour; 4%). 3. Age at diagnosis Median 9.3 yr (range 0.04-17.7) 4. Pubertal status at treatment	1. Chemotherapy Alkylating agents: 108 (100%) - Cyclophosphamide: 71 (67.6%), median dose 4.6 g/m^2 [n=12 (11.4%) ≥ 10 g/m^2] - Ifosfamide: 33 (31.4 %), median dose 48 g/m2 [n=20 (19%) 40 g/m2] - Procarbazine: 23 (21.9%) [20/23 treated for HL] 2. Radiotherapy Subdiaphragmaic radiotherapy: 19 (17.6%), median dose 20 Gy; 12/19 treated for HL 3. Autologous stem cell transplantation 14 (13.3%) 4. Surgery 0 oophorectomy	1. Outcome definitions Altered ovarian function/POF was defined by FSH>15 UI/l at least twice, AMH <3.6 pmol/l and amenorrhoea after stopping oral contraceptives 2. Results POF: 8 (7.6%) Ovarian markers in CCS *vs* controls *(*median): - FSH: 6.2 (2.1-52.6) *vs* 5.8 (3.5-11) IU/l, p=0.1 - AMH: 10.7 (0-98) *vs* 22 (3.3-47) pmol/l p=0.003 - Ovarian surface per ovary: 3.5 (1.1-7.1) *vs* 4.4 (2.1-10.3) cm2, p=0.0004 FSH levels by cancer treatment and diagnosis *vs* controls: - Significant higher FSH levels in CCS treated with alkylating agents + subdiaphragmatic radiotherapy *vs* alkylating agents alone: p=0.009 - Significant higher FSH levels in CCS treated with alkylating agents + subdiaphragmatic radiotherapy *vs* controls: p=0.0009 - Significant higher FSH levels in CCS diagnosed with Hodgkin lymphoma *vs* other cancer diagnoses, p<0.02 - Significant higher FSH levels in CCS	1. Strengths Detailed analyses of ovarian reserve markers in a cohort of CCS not treated with brain or pelvic or total body radiation therapy or busulfan/thiotepa 2. Limitations The small percentage of participating CCS (26% of the original cohort, 105/408) does not allow conclusions on fertility issues. The impact of risk factors on ovarian reserve surrogates were analyzed, but not the impact on POF. The control group was small and younger. 3. Risk of bias A. Selection bias: High Risk Reason: 105 CCS out of 408 were enrolled (26% of the original cohort fulfilling inclusion criteria). B. Attrition bias: Low risk Reason: the outcome was assessed for the whole study group. 105 were analyzed (n=3 excluded: n=1 polycistic

	62% before puberty 13% during puberty 25% after menarche 5. Age at follow-up Median 25 yr (range 17-40.7) 6. Controls n=20 healthy menstruating females before OCP (n=7 still on OCP), median age 21.5 yr (range 15-34)		diagnosed with Hodgkin lymphoma *vs* controls, p=0.0001 Risk factors for elevated FSH levels in multivariable analysis: - Age at evaluation (beta 0.018, p=0.01) - Oral contraceptive use (beta 0.140, p=0.09) - Procarbazine dose (beta 0.012, p<0.001) - High-dose alkylating agents (BMT patients) (beta 0.197, p=0.09)	syndrome, n=2 wrong time of assessement) C. Detection bias Unclear Reason: unclear if the outcome assessors were blinded for important determinants related to the outcome D. Confounding Low risk Reason: Important prognostic factors (i.e. age, co-treatment, ultrasound procedure) were taken into account

Who should be counselled about fertility preservation?				
Chemaitilly et al. Premature ovarian insufficiency in childhood cancer survivors: A report from the St Jude Lifetime Cohort. J Clin Endocrinol Metab 2017;102:2242-2250.				
Study design Treatment era Years of follow-up	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
1. Study design Retrospective cohort study 2. Treatment era 1962-2001 3. Follow-up Median 24.0 (range 10.2-48.1) yr after cancer diagnosis	1. Type and number of participants 921 from total cohort of 1,644 female CCS ≥10 yr postdiagnosis aged ≥18 yr at follow-up 2. Diagnoses Leukaemia 398 (43.2%), lymphoma 165 (17.9%), CNS tumour 52 (5.7%), embryonal tumours 178 (19.3%), bone and soft	1. Chemotherapy Alkylating agents: 542 (58.8%) Cyclophosphamide equivalence dose (CED): <4000 mg/m^2: 85 (9.2%) ≥4000- <8000 mg/m^2: 166 (18.0%) ≥8000- <12000 mg/m^2: 164 (17.8%) ≥12000- <20000 mg/m^2: 86 (9.3%) ≥20000 mg/m^2: 41 (4.5%)	1. Outcome definitions Premature ovarian insufficiency (POI): persistent amenorrhea with evidence of a primary ovarian origin before age 40 yr; In amenorrheic women <40 yr old not on sex hormone replacement therapy or oral contraceptive pills, estradiol <17 pg/mL with FSH >30 IU/L was considered indicative of POI; In individuals receiving sex hormone replacement therapy or oral contraceptives, the diagnosis of POI was based solely on historical medical information	1. Strengths Large well-performed study 2. Limitations Difficulties in assessing with certainty ovarian function in a subset of patients on sex hormone replacement therapy or oral contraceptives 3. Risk of bias A. Selection bias: High risk

	tissue sarcoma 105 (11.4%), carcinomas 12 (1.3%), other 11 (1.2%) 3. Age at diagnosis 0-18 yr 4. Age at follow-up Median 31.7 (range 19.0-60.6) yr 5. Controls None	2. Radiotherapy Pelvic radiation: 153 (13.3%) Ovarian radiation: 165 (17.9%) <100 cGy: 53 (5.8%) 100-999 cGy: 53 (5.8%) 1000-1999 cGy: 32 (3.5%) ≥2000 cGy: 27 (2.9%) Hypothalamic/pituitary radiation: 291 (31.6%) <1000 cGy: 0 (0%) 1000-1499 cGy: 16 (1.7%) 1500-2999 cGy: 219 (23.8%) ≥3000 cGy: 56 (6.1%) 3. Surgery Oophoropexy: 58 (6.3%) 4. BMT Not reported	2. Results POI: 100 (10.9%) of whom 31 (31%) received sex hormone replacement therapy Risk factors for POI in multivariable Cox regression analyses: - Age at cancer diagnosis: HR 0.97 (95% CI 0.92-1.02) - Oophoropexy yes vs. no: HR 1.33 (95% CI 0.70-2.53) - Ovarian radiation dose >999 vs. 0 cGy: HR 13.85 (95% CI 6.50-29.51) - Ovarian radiation dose ≥1000 vs. 0 cGy: HR 132.34 (95% CI 62.88-278.53) - CED <8000 vs. 0 mg/m^2: HR 1.55 (95% CI 0.77-3.11) - CED 8000-11999 vs. 0 mg/m^2: HR 2.77 (95% CI 1.18-6.51) - CED 12000-19999 vs. 0 mg/m^2: HR 3.90 (95% CI 1.80-8.43) - CED ≥20000 vs. 0 mg/m^2: HR 4.13 (95% CI 1.63-1050) - BMI <18.5 vs. ≥18.5-24.9 kg/m^2: HR 1.52 (95% CI 0.71-3.23) - BMI 25-29.9 vs. ≥18.5-24.9 kg/m^2: HR 0.93 (95% CI 0.54-1.61) - BMI ≥30 vs. ≥18.5-24.9 kg/m^2: HR 0.43 (95% CI 0.22-0.86) Risk factors for POI after combining treatment modalities in multivariable Cox regression analyses: - Age at cancer diagnosis: HR 1.02 (95% CI 0.98-1.06) - Oophoropexy yes vs. no: HR 0.72 (95% CI 0.42-1.23) - Alkylating agents only vs. no alkylating agents nor ovarian radiotherapy: HR 2.98 (0.63-14.06) - Ovarian radiation only vs. no alkylating	Reason: 921/1644 (65.0%) patients form the original cohort were included in the study. B. Attrition bias: Low risk Reason: Outcome was assessed for the whole study group. C. Detection bias: Unclear Reason: Unclear if the outcome assessors were blinded for important determinants related to the outcome D. Confounding: Low risk Reason: Analyses were adjusted for age, BMI and cancer treatment.

			agents nor ovarian radiotherapy: HR 71.7 (16.50-311.58) - Alkylating agents and ovarian radiation vs. no alkylating agents nor ovarian radiotherapy: HR 95.56 (23.30-391.93) - BMI <18.5 vs. ≥18.5-24.9 kg/m^2: HR 1.87 (95% CI 0.97-3.59) - BMI 25-29.9 vs. ≥18.5-24.9 kg/m^2: HR 0.92 (95% CI 0.56-1.52) - BMI ≥30 vs. ≥18.5-24.9 kg/m^2: HR 0.36 (95% CI 0.20-0.65)	

Abbreviations: BMI, body mass index; BMT, bone marrow transplantation; CCS, childhood cancer survivors; CED, cyclophosphamide equivalence dose; HR, hazard ratio; POI, premature ovarian insufficiency; yr, year.

Who should be counselled about fertility preservation?
Levine et al. Nonsurgical premature menopause and reproductive implications in survivors of childhood cancer: A report from the Childhood Cancer Survivor Study. Cancer 2018;124:1044-1052.

Study design Treatment era Years of follow-up	Participants	Treatment	Main outcomes	Additional remarks
1. Study design Retrospective cohort study 2. Treatment era 1970-1986 3. Follow-up >5 yr from cancer diagnosis	1. Type and number of participants 2,930 female CCS ≥5 yr postdiagnosis aged ≥18 yr at follow-up without surgical premature menopause; patients with Turner syndrome, menstruating ended within 5 yr after cancer diagnosis and CRT >30 Gy were excluded 2. Diagnoses Leukaemia 1149 (39.2%), Hodgkin lymphoma 348 (11.9%), kidney tumours 344 (11.7%), bone tumours 311 (10.6%), neuroblastoma 254 (8.7%), soft tissue sarcomas 224 (7.6%), CNS tumours 157 (5.4%), non-Hodgkin lymphoma 143 (4.9%) 3. Age at diagnosis Median 6 (range 0-20) yr 4. Age at follow-up Median 35 (range 18-58) yr 5. Controls 1399 siblings	1. Chemotherapy - Alkylating agents: 1361 (46.5%) - Procarbazine: 201 (7.2%) 0-4000 mg/m^2: 29 (1.0%) ≥4000 mg/m^2: 128 (4.4%) - Alkylating agents only: 552 (18.8%) 2. Radiotherapy - Ovarian radiation: 1624 (55.4%) >0-500 cGy: 1496 (51.1%) >500 cGy: 115 (3.9.%) - Ovarian radiation only: 792 (27.0%) - Alkylating agents and ovarian radiation: 804 (27.4%) - Procarbazine and ovarian radiation: 172 (5.9%) 3. Surgery Unilateral oophorectomy: 62 (2.1%) 4. BMT 17 (0.6%)	1. Outcome definitions Nonsurgical premature menopause: sustained menses cessation occurring for ≥6 months beginning 5 years after the cancer diagnosis but before age 40 years that was not due to pregnancy, surgery, or medications 2. Results Nonsurgical premature menopause - 110 (3.8%) at median age 32 (range 16-40) yr - Prevalence at age 40 yr survivors vs. controls: 9.1% vs. 0.9%; OR 10.5 (95% CI 4.2-26.3) Risk factors for nonsurgical premature menopause in multivariable logistic regression analysis: - Minimum ovarian radiation dose >0-500 cGy vs. 0: OR 2.73 (95% CI 1.33-5.61) - Minimum ovarian radiation dose >500 cGy vs. 0: OR 8.02 (95% CI 2.81-22.85) - Procarbazine dose <4000 mg/m^2 vs. 0: OR 3.07 (95% CI 0.76-12.43) - Procarbazine dose ≥4000 mg/m^2 vs. 0: OR 8.96 (95% CI 5.02-16.00) - Stem cell transplant yes vs. no: OR 6.35 (95% CI 1.19-33.93) Other risk factors for nonsurgical premature menopause in univariate logistic regression analysis (non-significant factors and therefore not included in the multivariable model): - Cyclophosphamide equivalence dose <6000 mg/m^2 vs. 0: OR 0.80 (95% CI 0.32-2.01)	1. Strengths Large well-performed study. 2. Limitations - NSPM is selfreported and therefore may be subject to both overreporting and underreporting. - Cases of NSPM may be masked by women who are taking oral contraceptives. 3. Risk of bias A. Selection bias: High risk Reason: 2930/6919 (42.3%) patients form the original cohort were included in the study. B. Attrition bias: Low risk Reason: Outcome was assessed for the whole study group. C. Detection bias: Unclear Reason: Unclear if the outcome assessors were blinded for important determinants related to the outcome D. Confounding: Low risk Reason: Analyses were adjusted for cancer treatment and age. Other factors considered in the

			- Cyclophosphamide equivalence dose ≥6000 mg/m^2 vs. 0: OR 3.47 (95% CI 2.08-5.78) - Cyclophosphamide equivalence dose without procarbazine <6000 mg/m^2 vs. 0: OR 0.71 (95% CI 0.28-1.83) - Cyclophosphamide equivalence dose without procarbazine ≥6000 mg/m^2 vs. 0: OR 1.07 (95% CI 0.50-2.28) - Unilateral oophorectomy yes vs. no: OR 1.52 (95% CI 0.56-4.07) - Age at diagnosis 10-14 yr vs. 0-9 yr: OR 1.14 (95% CI 0.63-2.06) - Age at diagnosis 15-20 yr vs. 0-9 yr: OR 1.98 (95% CI 1.16-3.38)	model were smoking status and BMI.

Abbreviations: BMI, body mass index; BMT, bone marrow transplantation; CCS, childhood cancer survivors; OR, odds ratio; yr, year.

Who should be counselled about fertility preservation?				
Fernandez-Pineda et al. Impact of ovarian transposition before pelvic irradiation on ovarian function among long-term survivors of childhood Hodgkin lymphoma: A report from the St. Jude Lifetime Cohort Study. Pediatr Blood Cancer 2018;11:e27232.				
Study design Treatment era Years of follow-up	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**

1. Study design Single-center cohort study 2. Treatment era Not mentioned 3. Follow-up: >10 yr from diagnosis	1. Type and Number of Participants 90 female pediatric Hodgkin lymphoma survivors treated with pelvic radiation who survived >10 yr from diagnosis with an attained age of ≥18 yr 2. Diagnoses Hodgkin lymphoma (100%) 3. Age at diagnosis Median 16 (range 4-22) yr 4. Age at follow-up Median 39 (range 25-60) yr 5. Controls (if applicable) N/A	1. Chemotherapy Cyclophosphamide equivalence dose: - 0 to ≤8,000 mg/m^2: 45 (52%) - 8,000 to ≤12,000 mg/m^2: 18 (21%) - 12,000 to ≤20,000 mg/m^2: 20 (23%) - >20,000 mg/m^2: 4 (4.6%) - Median 8818.2 (range 1800.0-28980.0) mg/m^2 Nitrogen mustard: 3 (3.3%) - Median 18.4 (range18.1-36.7) mg/m^2 Procarbazine: 37 (41%) - Median 4433.3 (range 857.1-15633.3) mg/m^2 2. Radiotherapy Pelvic radiation dose: - ≤1,500 cGy: 32 (37%) - >1,500 cGy: 55 (63%) 3. Surgery Oophoropexy: 49 (54%) 4. BMT 0 (0%)	1. Outcome definitions Premature ovarian insufficiency: absence of menses 5 years post cancer diagnosis or loss of spontaneous menses prior to 40 years of age with laboratory or historic evidence of primary (ovarian) origin; In the absence of treatment with oral contraceptive pills or sex-hormone replacement therapy at the time of study participation, individuals <40 years old experiencing amenorrhea for a period > 6 months and having plasma estradiol levels < 17 pg/ml coinciding with follicle stimulating hormone levels ≥ 30 IU/l were considered to have POI 2. Results Premature ovarian insufficiency: Number of events not reported Risk factors for premature ovarian insufficiency in multivariable Cox proportional hazard regression analysis: - Cyclophosphamide equivalence dose 8,001-12,000 vs. ≤8,000 mg/m^2: HR 3.3 (95% CI 0.7-16.0) - Cyclophosphamide equivalence dose 12,001-20,000 vs. ≤8,000 mg/m^2: HR 11.2 (95% CI 3.4-36.8) - Cyclophosphamide equivalence dose >20,000 vs. ≤8,000 mg/m^2: HR 36.9 (95% CI 5.2-260.5) - Pelvic radiation dose ≤1,500 vs. >1,500 cGy: HR 25.2 (95% CI 3.1-207.3) - Ovarian transposition yes vs. no: HR 06 (95% CI 0.2-1.9)	1. Strengths Large well-performed study. 2. Limitations ... 3. Risk of bias A. Selection bias: Low risk Reason: 90/127 (70.9%) patients form the original cohort were included in the study. However, the patient and treatment characteristics of the participants and non-participants are not significantly different. B. Attrition bias: Low risk Reason: Outcome was assessed for the whole study group. C. Detection bias: Unclear Reason: Unclear if the outcome assessors were blinded for important determinants related to the outcome D. Confounding: Low risk Reason: Analyses were adjusted for cancer treatment and age at diagnosis.

Who should be counselled about fertility preservation?				
Wallace et al. The radiosensitivity of the human oocyte. Hum Reprod 2003;18(1):117-121.				
Study design Treatment era Years of follow-up	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
1. Study design Retrospective cohort study 2. Treatment era Cohort 1: Treatment era not reported, Scotland Cohort 2: treatment 1966-1975, UK 3. Follow-up Years of follow-up not reported	1. Type and Number of Participants 27 post-pubertal women treated with radiotherapy for childhood cancer Two cohorts (n=27): 2. Diagnoses Cohort 1: leukaemia (n=8) Cohort 2: intra-abdominal tumour (n=19) 3. Age at diagnosis Cohort 1: Median 11.5 yr (4.9-15.1) Cohort 2: Median 4 yr (1.3-13.1) 4. Age at follow-up Cohort 1: Median 17.1 (15.4-21.5) Cohort 2: not mentioned 5. Controls N/A	1. Chemotherapy: Cohort 1: 8 (100%) Cohort 2: 11 (57.9%) vincristine, adriamycin, actinomycin D 2. Radiotherapy: Cohort 1: 8 (100%) TBI 14.4 Gy in 8 fractions over 2 days Cohort 2: 19 (100%) whole abdominal RT (ovaries in RT field, no shielding) 30 Gy, 16-26 fractions 3. Surgery Cohort 1: 0 (0%) Cohort 2: 19 (100%) 4. BMT 0 (0%)	1. Outcome definitions Ovarian failure: failure to undergo or complete pubertal development, or the onset of a premature menopause before age 40 years, in association with persistently elevated gonadotrophin levels (FSH and LH >32 IU/L) and low estradiol concentration (<40 pmol/L) 2. Results Ovarian failure cohort 1: 6/8 (75%) Median age 13.2 yr (range 12.5-16.0) Ovarian failure cohort 2: 18/19 (94,7%) Median age 12.7 yr (range 9.7-15.9) Based on Faddy-Gosden mathematical model: Dose of radiation required to destroy 50% of the oocytes (LD50) = 1.99 Gy	1. Strengths 2. Limitations - Not based on exact radiation dose received by each ovary. - Small sample n=27. - Estimations based on mathematical model - Model created from small cohorts and has not validated in a broader population. - Cohort 1 TBI, cohort 2 abdominal irradiation, comparable? **Risk of bias** A. Selection bias Unclear Reason: It is not reported how the selection of patients took place i.e. from what original group of patients. B. Attrition bias Low risk Reason: the outcome was assessed for the whole study group. C. Detection bias Unclear Reason: Unclear if the outcome

				assessors were blinded for important determinants related to the outcome. D. Confounding High risk Reason: no adjustment for important confounding factors.

Abbreviations: UK, United Kingdom; yr(s), year(s); CT, chemotherapy; TBI, total body irradiation; RT, radiotherapy; POI, premature ovarian insufficiency.

Who should be counselled about fertility preservation?				
Wallace et al. Predicting age of ovarian failure after radiation to the field that includes the ovaries. Int J Radiation Oncology Biol Phys 2005;62(3):738-744.				
Study design Treatment era Years of follow-up	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
1. Study design Retrospective cohort study 2. Treatment era Cohort 1: Treatment era not reported, Scotland Cohort 2: treatment 1966-1975, UK 3. Follow-up Years of follow-up not reported.	1. Type and Number of Participants 27 post-pubertal women treated with radiotherapy for childhood cancer Two cohorts (n=27): 2. Diagnoses Cohort 1: leukaemia (n=8) Cohort 2: intra-abdominal tumour (n=19)	1. Chemotherapy: Cohort 1: 8 (100%) Cohort 2: 11 (57.9%) vincristine, adriamycin, actinomycin D 2. Radiotherapy: Cohort 1: 8 (100%) TBI 14.4 Gy in 8 fractions over 2 days Cohort 2: 19 (100%) whole abdominal RT (ovaries in RT field, no shielding) 30 Gy, 16-26 fractions 3. Surgery Cohort 1: 0 (0%)	1. Outcome definitions Ovarian failure: failure to undergo or complete pubertal development, or the onset of a premature menopause before age 40 years, in association with persistently elevated gonadotrophin levels (FSH and LH >32 IU/L) and low estradiol concentration (<40 pmol/L) 2. Results Ovarian failure cohort 1: 6/8 (75%) Median age 13.2 yr (range 12.5-16.0) Ovarian failure cohort 2: 18/19 (94,7%) Median age 12.7 yr (range 9.7-15.9)	1. Strengths 2. Limitations - Not based on exact radiation dose received by each ovary. - Small sample n=27. - Estimations based on mathematical model - Model created from small cohorts and has not validated in a broader population. - Cohort 1 TBI, cohort 2 abdominal irradiation, comparable?

	3. Age at diagnosis Cohort 1: Median 11.5 yr (4.9-15.1) Cohort 2: Median 4 yr (1.3-13.1) 4. Age at follow-up Cohort 1: Median 17.1 (15.4-21.5) Cohort 2: not mentioned 5. Controls N/A	Cohort 2: 19 (100%) 4. BMT 0 (0%)	Based on Faddy-Gosden mathematical model (estimation): Effective sterilizing dose (POI occurs immediately after treatment in 97.5% of patients): At birth: 20.3 Gy At 10 yr: 18.4 Gy; At 20 yr: 16.5 Gy; At 30 yr: 14.3 Gy	**Risk of bias** A. Selection bias Unclear Reason: It is not reported how the selection of patients took place i.e. from what original group of patients. B. Attrition bias Low risk Reason: the outcome was assessed for the whole study group. C. Detection bias Unclear Reason: Unclear if the outcome assessors were blinded for important determinants related to the outcome. D. Confounding High risk Reason: no adjustment for important confounding factors.

Abbreviations: UK, United Kingdom; yr(s), year(s); CT, chemotherapy; TBI, total body irradiation; RT, radiotherapy; POI, premature ovarian insufficiency.

Who should be counselled about fertility preservation?				
Jadoul et al. Clinical and biologic evaluation of ovarian function in women treated by bone marrow transplantation for various indications during childhood or adolescence. Fertil Steril 2011;96(1):126-133.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**

1. Study design Cross-sectional, single-centre study 2. Treatment era Treatment era not reported 3. Follow-up Mean 15.5 (range 3.3-33.7) yr from BMT	1. Type and Number of Participants 35 (of 59 eligible) females >16 yr who underwent BMT at age <19 yr, in complete remission for ≥3 yr 2. Diagnoses 23 (66%) diagnosed with a malignancy (AML, ALL, NHL, neuroblastoma, rhabdomyosarcoma, Hodgkin's lymphoma); 12 (34%) diagnosed with a benign disease 3. Age at BMT 66% pre-menarcheal at BMT Mean age at BMT (range): 9.8 +/-5.2y (1.2-19.0) 4. Age at follow-up Mean age at study: 25.3+/-7.2y (16.6-46.4) Mean years of follow up from BMT: 15.5+/-5.5y (3.3-33.7)	1. Chemotherapy Alkylating agents: 35 (100%) Busulfan + cyclophosphamide + melphalan: 1 (2.9%) Busulfan + cyclophosphamide: 9 (25.7%) Busulfan + melphalan: 3 (8.6%) Cyclophosphamide only: 7 (20.0%) Melphalan only: 13 (37.1%) Unknown: 2 (5.7%) 2. Radiotherapy 18 (51.4%) TBI (4-12Gy) 3. Surgery 0 (0%) 4. BMT 19 (54%) allogeneic; 16 (46%) autologous All patients with malignancy had appropriate previous CT for their disease	1. Outcome definition Absence of pubertal development or progression and secondary amenorrhea, confirmed by menopausal FSH levels 2. Results Persistent ovarian function: - 16/35 (45.7%) persistent ovarian function (but 36% when 10 yr after BMT) - 85% low AMH levels (<1.2 ug/L) - Any time after BMT 8/23 (35%) for malignancy vs. 8/12 (67%) for benign disease (p=0.07) - 10 yr after BMT 5/21 (24%) for malignancy vs. 7/12 (58.3%) for benign disease (p=0.047) Clinically proven ovarian failure and hormone measurement: *Prevalence POI post-BMT*: - 21/35 (60.0%) ovarian failure 10 yr after BMT (immediate 19, subsequently 2) - 35 (100%) low oestradiol and high FSH 10 yr after BMT *No POI before evaluation (n=14):* - AMH 0.25-2.83 microg/L (median 0.90) - 5/14 (36%) normal AMH values - No significant difference in AMH levels between patients treated for a malignant disease and benign pathology Ovarian function by treatment (not analysed for malignant disease separately) - Persistent ovarian function after TBI + alkylating agents: 4/18 (22%) vs. alkylating agents only: 12/17 (71%) (p<0.005); this remained significant at 10 yr post-BMT (p=0.01) - Independent negative effect of TBI on	1. Strengths Small numbers but hormonal assessment (AMH) Long term follow-up 2. Limitations Missing information: Fractionation of TBI not stated. Single fraction TBI generally has greater adverse effect on ovarian function Previous cranial or other radiation not stated Fertility preservation procedure not stated 27/35 patients with HRT or OC at the time of evaluation. Time of FU at Last FSH values without treatment (retrospective data) is not reported. Was the ovarian function really assessed at the time of evaluation? No separate analyses for group with BMT for malignant disease Multivariate analyses: only p-values shown Additional comments: 3 patients with less than 10y of FU were considered in the 10y post BMT analysis. 3. Risk of bias A. Selection bias High risk Reason: the study group

			ovarian failure (p=0.014) in logistic regression analysis (no effect measure reported and unclear what factors were included in the regression model) - Persistent ovarian function after allotransplant: 9/19 (47%) vs. autotransplant: 7/16 (44%); this remained non-significant at 10 yr post-BMT <u>Ovarian function by age and menarcheal status</u> - Ovarian function 10-yr post-BMT in girls aged ≤10 yr at BMT: 10/17 (59%) vs. aged >10 yr 2/16 (13%) (p=0.007) - 100% girls aged >10 yr at BMT with TBI had irreversible premature ovarian failure vs. 40% girls aged <10 yr at BMT spontaneous puberty - Independent protective effect of young age at BMT (p=0.004) in logistic regression analysis (no effect measure reported and unclear what factors were included in the regression model) <u>Ovarian function by age at evaluation and time since BMT:</u> Not significant (no effect measure reported)	consisted of 35/59 (59%) of the original cohort of survivors <u>B. Attrition bias</u> Low risk Reason: the outcome was assessed for the whole study group <u>C. Detection bias</u> Unclear Reason: Unclear if the outcome assessors were blinded for important determinants related to the outcome <u>D. Confounding</u> Unclear Reason: multivariable analysis performed but not mentioned which determinants were included in the models

Who should be counselled about fertility preservation?				
Vatanen et al. Ovarian function after allogeneic hematopoietic stem cell transplantation in childhood and adolescence. Euro Journal of Endocrinology, 2014: 170(2): 211-218				
Study design Treatment era Years of follow-up	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**

1. Study design Multi-center (2) cohort study 2. Treatment era 1978-2000 3. Follow-up >5 years after HSCT Mean follow-up time 13 (range 6-27) yr	1. Type and Number of Participants 92 female survivors of allogeneic HSCT, <20 years of age at HSCT, survived >5 years from HSCT and reached puberty/sexual maturity or showed ovarian failure by latest follow up visit at time of study entry 2. Diagnoses ALL n=33 (36%) AML n=24 (26%) SAA n=13 (14%) Others n=22 (24%) =nonmalignant disorders or malignant diseases without cytotoxic therapy given before HSCT 3. Age at HSCT Mean 9 ± 4.3 yr (range 1-19) 4. Age at follow-up Mean 22 ± 6.3 yr (range 9-41) 5. Controls (if applicable) N/A 6. Other Remission status for leukaemia: CR1 n=28 CR2-4 n=29	1. Chemotherapy - Alkylating agents: 92 (100%) - Cyclophosphamide: 71 (77.2%) - Busulfan: 10 (10.9%) - Melphalan: 3 (3.3%) - Etoposide: 1 (1.1%) - Melphalan: 3 (3.3%) - Cytarabine: 16 (17.4%) 2. Radiotherapy TBI: 71 (77.2%) TNI: 1 (1.1%) CRT: 12 (13.0%) 3. Surgery N/A 4. BMT 92 (100%) 5. BMT conditioning regimen: - sTBI (10-12Gy) + cyclophosphamide (120mg/kg): 29 (32%) - fTBI (10-12Gy) + cyclophosphamide (120mg/kg): 22 (24%) - fTBI (10-12Gy) + cyclophosphamide (120mg/kg) + etoposide (9 mg/m2): 1 (1%) - fTBI (10-12Gy) +cytarabine (36g/m2): 16 (17%) - fTBI (10-12Gy) +melphalan (210mg/m2): 3 (3%) - Busulfan (16mg/kg): 2 (2%)	1. Outcome definitions - Absence spontaneous puberty: increased FSH >25 IU/L and absence of breast development - Premature menopause: increased FSH >25 IU/L and failure to accomplish pubertal maturation or cessation of menstruation among girls who showed some ovarian activity after HSCT - Ovarian failure: increased FSH >25, no ovarian activity after HSCT 2. Results - 54/92 (58.7%) no ovarian function - Pre-pubertal at HSCT (n=70): 40 (57%) spontaneous onset of puberty, 30 (43%) spontaneous menses, 14 (20%) subsequently premature menopause at a mean of 11 ± 4.4 yr after HSCT at mean age of 17 ± 3.1 yr - Mid-pubertal at HSCT (n=12): 3 (25%) spontaneous menses; 2 entered premature menopause at 5 and 13 years post BMT at ages 18 and 22, respectively - Post-pubertal at HSCT (n=8): 6 (75%) resumed spontaneous menses - All patients who received only cyclophosphamide as conditioning had spontaneous menses - No difference in rates of spontaneous puberty/menses among patients who received TBI regimen vs. busulfan regimen - FSH levels significantly higher in patients treated with TBI or busulfan compared to cyclophosphamide: 39±35.5 (TBI) vs. 57±48.3 (busulfan) vs. 7±8.0 (cyclophosphamide), p<0.01 Risk factors for no spontaneous puberty	1. Strengths - Extended follow up - Well documented treatment exposure 2. Limitations - Young mean age at follow up - No details of chemo prior to BMT – unable to assess insult prior to conditioning regimen 3. Risk of bias A. Selection bias Low risk Reason: the study group consisted of 92/102 (90%) of the original cohort of survivors. B. Attrition bias Low risk Reason: 76/92 (82%) available information about serum levels of FSH. C. Detection bias Unclear Reason: Unclear if the outcome assessors were blinded for important determinants related to the outcome . D. Confounding Low risk Reason: Multivariable analyses having no spontaneous menses adjusted for diagnosis and age at HSCT.

		- Busulfan (16mg/kg) + cyclophosphamide (120mg/kg): 8 (9%) - Cyclophosphamide only (200mg/kg): 10 (11%) - Cyclophosphamide (200mg/kg) + TNI: 1 (1%)	<u>or menses in bivariate logistic regression analysis:</u> *No spontaneous puberty* - Age at HSCT: OR 1.2 (95% CI 1.0-1.4) *No spontaneous menses* - SAA diagnosis no vs. yes: OR 6.1 (95% 1.3-31.0) - TBI yes vs. no: OR 5.2 (95% CI 1.6-16.5) - Leukaemia diagnosis yes vs. no: OR 3.6 (95% CI 1.3-9.7) - Age at HSCT: OR 1.1 (95% CI 0.99-1.30) - FSH: OR 1.03 (95% CI 1.01-1.06) - LH: OR 1.09 (95% CI 1.03-1.14) *Estrogen substitution at the latest follow-up visit* - sTBI: OR 4.3 (95% CI 1.3-14.1) - SAA diagnosis: OR 0.2 (95% CI 0.1-0.9) <u>Risk factors for no spontaneous menses in multivariate stepwise logistic regression analysis:</u> - TBI yes vs. no: OR 5.2, 95% CI 1.6-16.5 - Other factors (see bivariate analyses) not significantly associated	

Abbreviations: FU, follow-up; HSCT, hematopoietic stem cell transplantation; AML, acute myeloid leukaemia; ALL, acute lymphoblastic leukaemia; sTBI, single-fraction total body irradiaton; Cy, cyclophosphamide; fTBI, fractioned total body irradiation; TNI, total lymph node irradiation.

What female reproductive preservation methods are appropriate to offer in counselling?

Babayev et al. Evaluation of ovarian and testicular tissue cryopreservation in children undergoing gonadotoxic therapies. J Assist Reprod Genet 2013; 30:3-9				
Study design Treatment era Years of follow-up	**Participants**	**Intervention**	**Main outcomes**	**Additional remarks**
1. Study design Prospective observational cohort/case series, single centre 2. Treatment era NR 3. Follow-up: Mean length of tissue cryo-preservation was 5.2±0.8 years, but no outcomes assessed at follow-up	1. Type and Number of Participants 28 female patients 2. Diagnoses 21/28 (75%) females with malignant disease (various) 3. Age at diagnosis Females: mean 13.9±1.5 years (2.3-20.9) 4. Age at follow-up NA 5. Controls (if applicable) NA 6. Additional study characteristics, if relevant 9 males 9/28 (32%) females were prepubertal 7. Chemotherapy 12/24 (50%) had chemotherapy before ovarian tissue harvest 8. Radiotherapy NR	1. Fertility Preservation method 28 patients underwent laparoscopic ovarian tissue cryopreservation *Transplantation* 0/28 ovarian tissue transplantations	1. Outcome definitions Complications Times: Operation time, anesthesia time, discharge time 2. Results *Complications* 0/21 Complications (minimal or none blood loss) *Operation time* In females: - Mean operative time 2.3±0.4h - Mean anesthesia time 4.9±1.2h - Mean discharge time 23.2±8.9h Comparing bundled and unbundled cases (including females as well as males): - Mean operative time 2.5±0.5h (bundled) and 1.1±0.2h (unbundled) - Anesthesia time 4.8±1.2 (bundled) and 1.7±0.3 (unbundled) - Discharge time 23.2±8.9h (females) and 4.6±0.6h (males) *Harvested ovarian tissue* No malignant cells	1. Strengths - 2. Limitations - No clear inclusion and exclusion criteria - Description of operative outcomes and complications only, no efficacy outcomes assessed at follow-up - Different numbers reported throughout the paper for same outcome 3. Risk of bias *1. Selection bias* Unclear Reason: no information on original cohort or inclusion/exclusion criteria. Unclear if consecutive. *2. Attrition bias* Low risk Reason: outcomes assessed for all patients *3. Detection bias* Reason: unclear if outcome assessors were blinded for important determinants related

	9. Surgery See intervention. In 13/28 (46%) of females, the intervention was bundled with a Port-a-Cath insertion for chemotherapy 10. Other treatments NR			to the outcome *4. Confounding bias* Not applicable

Abbreviations: NA: not applicable; NR: not reported; pts: patients

What female reproductive preservation methods are appropriate to offer in counselling?				
Biasin et al. Ovarian tissue cryopreservation in girls undergoing haematopoietic stem cell transplant: experience of a single centre. Bone Marrow Transplant 2015;50:1206-1211				
Study design Treatment era Years of follow-up	**Participants**	**Intervention**	**Main outcomes**	**Additional remarks**
1. Study design Single-centre cohort study 2. Treatment era August 2000 - September 2013 3. Follow-up: Median follow-up time: 6.5 (0.3-13.7) years	1. Type and Number of Participants 38 female cancer patients planned to receive HSCT *Original cohort:* 47 females planned to receive HSCT 2. Diagnoses 38/47(80.8%) females with malignant disease 1(2.1%) Diamond-Blackfan anemia 3(6.4%) Ewing sarcoma 2(4.3%) Immunodeficiency 11(23.4%) Acute myeloblastic leukaemia 14(29.8%) Acute lymphoblastic leukaemia 5(10.6%) Chronic myeloblastic leukaemia 2(4.3%) Non-Hodgkin Lymphoma 2(4.3%) Myelodisplastic syndrome 7(14.9%) Thalassemia 3. Age at diagnosis Median 11.1 (0-17.5) years	1. Fertility Preservation method 47 patients underwent laparoscopic ovarian tissue cryopreservation *Transplantation* 1/47 autologous orthotopic ovarian tissue transplantation	1. Outcome definitions Hypogonadism: at least 2 of 3 identifying features: - primary or secondary amenorrhea - high levels of FSH (>20 UI/mL) with low levels of estradiol (<30 pg/mL) or low levels of anti-Mullerian hormone (<0.1 ng/mL) Live births Complications of intervention 2. Results *Live births* 1/1 (100%) transplanted thalassemia patient had a healthy live birth *Pregnancies* 1/1 (100%) spontaneous pregnancy *Hypogonadism* 26/28 (93%) evaluable pts developed hypergonadotropic hypogonadism at median of 23.3(1.1-123.4) months after HSCT *Complications* 0/38 Acute or chronic complications after OTC *Harvested ovarian tissue* Histological examination revealed no	1. Strengths Outcome definitions well reported 2. Limitations Limited follow-up time for transplantation outcomes but also hypogonadism (evaluable in 60%), especially since patients are very young at diagnosis 3. Risk of bias *1. Selection bias* Unclear Reason: 47/228 patients underwent OTC. Number of patients and reasons for exclusion unclear *2. Attrition bias* Low risk Reason: 28/47 (60%) evaluable for hypogonadism, owing to: - death (7 pts) - early age (9 pts) - loss to follow-up (2 pts) - continuous treatment with estroprogestinics after transplant (1 patient) Not assessing hypogonadism in 9 patients of early age and 1

	4. Age at follow-up Median age at last follow-up 18.6 (5.5-29.4) years 5. Controls (if applicable) - 6. Additional study characteristics, if relevant Median age at time of OTC: 13 (2.7-20.3) years 24(51%) prepubertal patients at intervention 7. Chemotherapy 36(76.6%) had received chemotherapy before intervention 21(44.7%) busulfan based chemotherapy (condition regimen post intervention) 8. Radiotherapy 23(48.9%): total body irradiation (12 Gy) (condition regimen post intervention) Additional RT after HSCT: 1(2.1%) pelvic radiotherapy (54 Gy) 1(2.1%) lower limb radiotherapy (54 Gy) 9. Surgery See intervention OTC before HSCT		tumour contamination	patient with continuous hormonal treatment is 'fair' and does not give risk of bias. So not including them: 28/37 -> 76% *3. Detection bias* NA Reason: unclear if outcome assessors were blinded for important determinants related to the outcome *4. Confounding bias* Not applicable

	<u>10. Other treatments</u> 47 pts (100%) HSCT 1(2.1%) imatinib 1(2.1%) second HSCT All post-intervention			

Abbreviations: NA: not applicable; NR: not reported; pts: patients; HSCT: haemopoietic stem cell transplant

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Chambon et al. Cryopreservation of ovarian tissue in pediatric patients undergoing sterilizing chemotherapy. Hum Fert (Camb) 2016;19:23-31				
Study design Treatment era Years of follow-up	**Participants**	**Intervention**	**Main outcomes**	**Additional remarks**
1. Study design Retrospective single center study 2. Treatment era Sept 2000 - Sept 2013 3. Follow-up: Median post-harvest follow-up time 36 months (1-112) Median post sterilizing treatment follow-up time 30 months	1. Type and Number of Participants 28 females with malignant disease *Total cohort:* 36 females 2. Diagnoses 8 (22%) had non-malignant disease (various) 28 (78%) had malignant disease (various) 3. Age at diagnosis <20 years old at diagnosis Median age at ovarian tissue harvest: 13 (2-19)years 4. Age at follow-up Mean age FU 17 (5-26) years 5. Controls (if applicable) NA 6. Additional study characteristics, if relevant - 7. Chemotherapy Post-intervention: - 32/36 (89%) high-dose chemo-/radiotherapy followed by auto-HSCT or	1. Fertility Preservation method 36 females underwent laparoscopic ovarian tissue cryopreservation *Transplantation* 0/36 ovarian tissue transplantations	1. Outcome definitions Ovarian tissue harvest: unclear outcome definition Post-treatment hormonal status: clinical evaluation and plasma levels of LH, FSH, AMH and inhibin-B Complications of intervention 2. Results *Harvested ovarian tissue* - Ovarian tissue harvest: median duration of surgery 40 min (20 – 60 min) - No malignant cells in harvested ovarian tissue *Complications* 1/36 Post OTC bleeding and delay of CT (in patient with sickle cell disease and protein S deficiency) Post-treatment hormonal status available for 27 patients: 22/27 (59%) POI 19/27 (70%) POI in malignant disease patients *Pregnancies* No pregnancies	1. Strengths Hormonal assays were performed at a range of times after treatment 2. Limitations Unclear description of patient selection 3. Risk of bias *1. Selection bias* Unclear Reason: unclear what the original cohort was and if patients were excluded and for what reasons *2. Attrition bias* Low risk Reason: hormonal status outcome was assessed for 27/36 (75%) Very variable duration of follow-up time *3. Detection bias* unclear Reason: unclear if outcome assessors were blinded for important determinants related to the outcome *4. Confounding bias* Not applicable

	allo-HSCT - 4/36 (11%) standard chemotherapy including alkylating drugs 28/36 patients received chemotherapy <u>before</u> ovarian tissue harvest <u>8. Radiotherapy</u> See 7 <u>9. Surgery</u> See intervention OTC at the latest before sterilizing chemotherapy <u>10. Other treatments</u> HSCT in 32 pts post-intervention			

Abbreviations: NR: not reported; HSCT: LH: luteinizing hormone; FSH: follicle-stimulating hormone; AMH: Anti-Mullerian Hormonel POI: premature ovarian insufficency

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Dolmans et al. A review of 15 years of ovarian tissue bank activities**.** J Assist Reprod Genet 2013; 30:305-314				
Study design Treatment era Years of follow-up	**Participants**	**Intervention**	**Main outcomes**	**Additional remarks**
1. Study design Retrospective longitudinal analysis of data from an ovarian tissue bank 2. Treatment era April 1997 - January 2012 3. Follow-up: NR	1. Type and Number of Participants 391 female patients with malignant disease *Total cohort*: 476 female patients 2. Diagnoses 85/476 (18%) benign disease 391/476 (82%) malignant disease: Hodgkins N=85; NHL N=26; acute leukaemia N= 39; chronic leukaemia N=6; ovarian cancer N= 56; sarcoma N= 41; CNS N= 19; breast cancer N=85 3. Age at diagnosis NR Mean age at OTC 23.0 ± 8.5 years (9 months - 39 years) 96.2% were ≤ 35 years old 35.3% aged 15 - 24 years 17.2% aged 9 months - 14 years 4. Age at follow-up NR 5. Controls (if applicable)	1. Fertility Preservation method 476 female patients underwent laparoscopic ovarian tissue cryopreservation *Transplantation* 11/476 ovarian tissue transplantations (7/11 in malignant disease patients)	1. Outcome definitions Histological evaluation Postcryopreservation clinical outcomes Complications of intervention 2. Results *Harvested ovarian tissue* 5/11 Malignant cells after histological ovarian tissue evaluation (in 3 leukaemia pts; 2 NHL pts) 7/12 positive ovarian tissue at PCR analysis in acute leukaemia patients with clear tissue at histology; 4 xenografted mice developed leukemic masses after 6 months *Live births* 5/11(45%) transplanted patients had healthy live births 1/11(9%) transplanted patients had ongoing pregnancy (Unclear if the live births are from malignant disease patients)* *Pregnancies* 4/6 (66%) spontaneous pregnancies 2/6 (33%) pregnancies after in vitro fertilization *Complications*	1. Strengths Description of the design and outcomes of one of the largest and most comprehensive existing ovarian tissue cryobank databases 2. Limitations - The study is retrospective. Data before 2007 had to be obtained from multiple sources - No data on ovarian reserve status post treatment - Unclear if the live births are from malignant disease patients, authors refer to other of their publications 3. Risk of bias *1. Selection bias* Unclear Reason: patient selection not clearly described *2. Attrition bias* Low risk Reason: outcomes assessed for all patients *3. Detection bias* unclear Reason: unclear if outcome assessors were blinded for

	None 6. Additional study characteristics, if relevant - 7. Chemotherapy 93% (N=442) had no exposure to gonadotoxic therapy prior to OTC 7% had undergone chemotherapy prior to OTC 8. Radiotherapy 93% (N=442) had no exposure to gonadotoxic therapy prior to OTC 9. Surgery See intervention 10. Other treatments Cryopreserved embryos were also obtained from 28 patients after OTC		0/476 Serious complications post-surgery such as bowel, nerve or vascular injury, thromboembolism or cardiorespiratory distress 13/476 hospitalized for more than 72 h because they underwent OTC at the same time as another surgical procedure (breast surgery in particular)	important determinants related to the outcome *4. Confounding bias* Not applicable

Abbreviations: NA: not applicable; NR: not reported; pts: patients; OTC: ovarian tissue cryopreservation

* Authors refer to the following studies for more information*: Donnez et al*. Restoration of ovarian function in orthotopically transplanted cryopreserved ovarian tissue: a pilot experience. Reprod Biomed Online 2008;16:694-704; *Donnez et al*. Children born after autotransplantation of cryopreserved ovarian tissue. A review of 13 live births. Ann Med 2011;43:437-50; *Donnez et al*. Live birth after transplantation of frozen-thawed ovarian tissue after bilateral oophorectomy for benign disease. Fertil Steril 2012;98:720-5

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Lima et al. Ovarian tissue collection for cryopreservation in pediatric age: laparoscopic technical tips. J Pediatr Adolesc Gynecol 2014;27:95-7				
Study design Treatment era Years of follow-up	**Participants**	**Intervention**	**Main outcomes**	**Additional remarks**
1. Study design Single center cohort study 2. Treatment era January 2002 - January 2013 3. Follow-up: Patients discharged after 48 hours (48 hrs)	1. Type and Number of Participants 48 female patients *Total cohort*: 54 female patients 2. Diagnoses 48/54 (89%) malignant diseases (various) 6/54 (11%) non-malignant diseases (various) 3. Age at diagnosis NR Mean age at ovarian harvest 160.9 ± 6.9 months 4. Age at follow-up Same 5. Controls (if applicable) NA 6. Additional study characteristics, if relevant 48/54 (89%) Pubertal 7. Chemotherapy 22/54 (41%) patients had started chemotherapy before ovarian tissue harvest	1. Fertility Preservation method 54 patients underwent laparoscopic ovarian tissue cryopreservation *Transplantation* *0/54 ovarian tissue transplantations*	1. Outcome definitions Ovarian tissue collection Surgical complications 2. Results *Ovarian tissue collection* Mean operative time 40±15 min All patients discharged after 48 hours *Surgical complications* 1/54 Intraoperative bleeding requiring red blood cell transfusion 0/54 Postoperative or long-term complications; no delay of the oncological treatment	1. Strengths 11-year treatment era 2. Limitations -Describes the surgical technique only -No information on the quality of the collected tissue -No long-term data on efficacy or effect on ovarian reserve (particularly notable as the procedure described involves removing 2/3 of each ovary) 3. Risk of bias *1. Selection bias* Low risk Reason: 54/54 selected, looks like a consecutive series *2. Attrition bias* Low risk Reason: follow-up time 48 hours, 100% *3. Detection bias* unclear Reason: unclear if outcome assessors were blinded for important determinants related to the outcome

	Chemotherapy type: NR <u>8. Radiotherapy</u> NR <u>9. Surgery</u> 4/54 (7%) had undergone laparotomy before intervention <u>10. Other treatments</u> -			*4. Confounding bias* Not applicable .

Abbreviations: NR: not reported; NA: not applicable

What female reproductive preservation methods are appropriate to offer in counselling?

Poirot et al. Feasibility of ovarian tissue cryopreservation for prepubertal females with cancer. Pediatr Blood Cancer 2007;49:74-78				
Study design Treatment era Years of follow-up	**Participants**	**Intervention**	**Main outcomes**	**Additional remarks**
1. Study design Single centre cohort study 2. Treatment era September 2000 – February 2005 3. Follow-up: Median follow-up time 30 months (range 10-60)	1. Type and Number of Participants 47 prepubertal female patients 2. Diagnoses All malignant disease: 20(43%) Metastatic neuroblastoma 6 (13%) Leukaemia 6 (13%) Rhabdomyosarcoma 4 (9%) Ewing sarcoma 3 (6%) Medulloblastoma 2 (4%) Osteosarcoma 2 (4%) Nephroblastoma 2 (4%) Lymphoma 1 (2%) Neuroectodermal tumour 1 (2%) Hodgkin's disease 3. Age at diagnosis NR Median age at ovarian tissue harvest: 5 years (10 months - 15 years) 4. Age at follow-up NR 5. Controls (if applicable) - 6. Additional study characteristics, if relevant	1. Fertility Preservation method 47 patients underwent ovarian tissue cryopreservation: 40 laparoscopic and 7 minilaparotomy *Transplantation* 0/47 ovarian tissue transplantations	1. Outcome definitions Feasibility of ovarian tissue cryopreservation (unclear outcome definitions) Complications of intervention 2. Results Mean 17.6±6.5 ovarian tissue fragments cryopreserved per patient (range 7 - 41) *Complications* 0/47 Postoperative complications; No delay of the oncological treatment *Harvested ovarian tissue* None of the patients had visible ovarian tumour components *Follicle count* Follicle concentration was evaluated histologically for 46 patients and a strong inverse correlation was found between age and follicular density (P=0.0011)	1. Strengths - Seems to be a consecutive series - Homogeneous patient group (all prepubertal, all had malignant disease, all received CT pre-harvest) - Relatively large sample size for this type of study 2. Limitations Outcome definitions not clearly reported 3. Risk of bias *1. Selection bias* Low risk Reason: 47/49 (96%) of original group. In one case, the patient herself refused and in the other, parents refused OTC for their daughter. Reasons for refusal were new technique and uncertainty. *2. Attrition bias* Low risk Reason: 37/47 (79%) follow-up. However, reported outcomes assessed for all patients (100%) *3. Detection bias*

	Entire ovary collected by: 24 (51%) laparoscopy 23 (49%) laparotomy <u>7. Chemotherapy</u> All patients received (non-sterilizing) chemotherapy before ovarian tissue harvest Post-harvest sterilizing CT: 33 (70%) High-dose busulfan 2 (4%) High-dose thiotepa <u>8. Radiotherapy</u> Post-harvest sterilizing RT: 7 (15%) Total body irradiation 5 (11%) Abdominopelvic irradiation including both ovaries <u>9. Surgery</u> See intervention <u>10. Other treatments</u> NR			unclear Reason: unclear if outcome assessors were blinded for important determinants related to the outcome *4. Confounding bias* Not applicable

Abbreviations: NR: not reported; NA: not applicable

What female reproductive preservation methods are appropriate to offer in counselling?

Rosendahl et al. Evidence of residual disease in cryopreserved ovarian cortex from female patients with leukaemia**.** Fertil Steril 2010;94:2186-2190				
Study design Treatment era Years of follow-up	**Participants**	**Intervention**	**Main outcomes**	**Additional remarks**
1. Study design Retrospective analysis of data in a clinical project 2. Treatment era 10-year period, years not reported 3. Follow-up: Cryopreserved ovarian tissue fragments were thawed and examined. No follow-up time reported.	1. Type and Number of Participants 26 patients with leukaemia *Original cohort:* 37 patients diagnosed with leukaemia 2. Diagnoses 13/26 (50%) ALL 7/26 (27%) AML 5/26 (19%) CML 1/26 (4%) JMML 3. Age at diagnosis NR Median age at time of ovarian tissue harvest: 16 (2-31) years 4. Age at follow-up NR 5. Controls (if applicable) Positive and negative controls used for PCR 6. Additional study characteristics, if relevant Disease status at time of cryopreservation: 18/26 (69%) complete remission	1. Fertility Preservation method 37 laparoscopic or minilaparotomy OTC *Transplantation* 0/37 ovarian tissue transplantations	1. Outcome definitions Presence of leukemic cells in frozen/thawed ovarian tissue by histology, immunohistochemistry or PCR Complications of intervention 2. Results *Complications* NM *Harvested ovarian tissue* 0/37 No malignant cells detected by histology or immunohistochemistry 8/37 (22%) patients with PCR technique applied (these patients had a specific chromosomal abnormality that could be used as a genetic marker for detection of malignant cells by PCR) 6/8 (75%) evidence of leukemic cells 3/6 (50%) in complete remission at time of ovarian tissue removal	1. Strengths Study covers PCR technique for detecting malignant cells in harvested ovarian tissue: in situations where genetic markers are demonstrable, PCR increases detection of leukemic cells, even for patients in complete remission, where histology and IHC does not 2. Limitations -The presence of malignant cells does not equate to viability, malignant potential and risk of reintroduction of disease if transplanted, hence the practical significance is not clear - Not known what number of malignant cells is required to cause relapse - Only in 8/26 patients possible to perform PCR because of the presence of genetic markers - Limitations of PCR technique: possible that some leukemic cells were undetected. Also depends on the quality of techniques preceding the PCR itself 3. Risk of bias *1. Selection bias*

	4/26 (15%) chronic phase 2/26 (7%) active phase 2/26 (7%) unknown 8/26 (31%) specific chromosomal abnormality detected by PCR: 6/8 BCR-ABL 1/8 TEL-AML 1/8 CBFB-MYH11 <u>7. Chemotherapy</u> Sterilizing chemotherapy and conditioning <u>after</u> ovarian tissue harvest <u>8. Radiotherapy</u> Not clearly reported, possibly as part of conditioning regimen (<u>after</u> ovarian tissue harvest) <u>9. Surgery</u> See intervention <u>10. Other treatments</u> NR			High risk Reason: 26/37 (70%) original cohort. 2 did not respond, 2 declined, 7 were deceased *2. Attrition bias* Low risk Reason: outcomes were assessed for all 26 patients. However, PCR possible in only 8 patients. *3. Detection bias* unclear Reason: unclear if outcome assessors were blinded for important determinants related to the outcome *4. Confounding bias* Not applicable

Abbreviations: NR: not reported; NA: not applicable; PCR: polymerase chain reaction

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Seshadri et al. Lack of evidence of disease contamination in ovarian tissue harvested for cryopreservation from patients with Hodgkin lymphoma and analysis of factors predictive of oocyte yield. Br J Cancer 2006;94:1007-1010				
Study design Treatment era Years of follow-up	**Participants**	**Intervention**	**Main outcomes**	**Additional remarks**
1. Study design Retrospective single centre study 2. Treatment era December 1995 - August 2005 3. Follow-up: NR/NA	1. Type and Number of Participants 26 female patients with Hodgkin lymphoma 24/26 Data regarding patient's disease status 2. Diagnoses Hodgkin lymphoma 3. Age at diagnosis Median age 22 years (13-29) 4. Age at follow-up NR/NA 5. Controls (if applicable) None 6. Additional study characteristics, if relevant At diagnosis of HL 9 (37%) Stage III or Stage IV disease At the time of harvest: 7/26 (29%) disease below the diaphragm 5/7 (71%) intra-abdominal disease 1/7 (14%) bony disease in the femur 1/7 (14%) exact site(s) of	1. Fertility Preservation method 26 laparoscopic ovarian tissue cryopreservation *Transplantation* 0/26 ovarian tissue transplantation	1. Outcome definitions - Subclinical involvement by HL by morphology/immunohistochemistry - Patient and treatment factors predictive of oocyte yield (follicle density was examined) - Complications of intervention 2. Results *Complications* NR *Harvested ovarian tissue* 0/26 No evidence of HL involvement by morphology or immunohistochemistry (95% CI for ' true' rate of involvement 0-11%) *Patient and treatment factors predictive of oocyte yield* range of follicle densities was 45-4512 follicles mm^{-3} 7/26 pts receiving ABVD showed no difference in follicle density compared to patients not receiving treatment (14/26) (median=1555 *vs* 1620 mm^3 *p*=0.97) *However, it is possible that more cycles of chemotherapy could be associated with reduced follicle density on harvest Follicle density measurement showed no correlation with patient age (R^2=0.0001, *P*=0.99)	1. Strengths Well-reported study 2. Limitations - Data regarding premature ovarian failure in the cohort following HL treatment was not collated - The point in treatment when this tissue was obtained was left to the discretion of the treating physician and the patient - Single biopsy of an ovary: adequate to exclude HL involvement of the entire ovary? - Also, distribution of follicle density varies throughout the ovary - Immunohistochemistry as detection method, sensitive but no PCR 3. Risk of bias *1. Selection bias* Unclear Reason: unclear how the 26 patients were selected. Majority of patients had low risk features (not intra-abdominal disease or B-symptoms)

	infradiaphragmatic disease at the time of harvest were not recorded B symptoms at diagnosis: 9 (37%) Yes 15 (63%) No 7. Chemotherapy 9/24 (38%) received chemotherapy prior to ovarian harvest: - 7/9 ABVD - 1/9 ChlVPP (chlorambucil, vinblastine, procarbazine, prednisolone), and - NR		*However, young patient group with a maximum age of 29 years	*2. Attrition bias* Low risk Reason: outcomes assessed for >75% of patient group, no follow-up needed for study aim *3. Detection bias* unclear Reason: unclear if outcome assessors were blinded for important determinants related to the outcome Not applicable
What female reproductive preservation methods are appropriate to offer in counselling?				
Wallace et al. Fertility preservation for girls and young women with cancer: population-based validation of criteria for ovarian tissue cryopreservation. Lancet Oncol 2014;15:1129-36				
Study design Treatment era Years of follow-up	**Participants**	**Intervention**	**Main outcomes**	**Additional remarks**
1. Study design Retrospective analysis 2. Treatment era January 1996 - June 2012 3. Follow-up: Median FU for the following groups: • Offered and underwent OTC with tissue successfully cryopreserved and for ovarian function	1. Type and Number of Participants 20 female cancer patients *Original cohort:* 410 female cancer patients 34/410 were offered OTC (based on the Edinburgh selection criteria): • 20/34 underwent OTC: 4 <12years age at FU, 1 died, 1 on hormonal contraception -> 14 with successful ovarian tissue stored and for ovarian function assessment	1. Fertility Preservation method 20 ovarian tissue cryopreservation: 18 laparoscopic, 2 oophorectomies (21 consented to OTC but in 1/21 procedure failed due to technical problems with surgical equipment, no adverse effect on the patient) *Transplantation* NR	1. Outcome definitions POI defined with least 2 of 3 features: - Amenorrhea for at least 4 months - Serum FSH > 25 IU/L at least 2 occasions - Low (<150 pmol/L) serum oestradiol concomitant with raised (>25 IU/L) FSH Absence of POI confirmed by 1 or more of 3 features: - Premenarcheal, but progressing normally through puberty - Regular menses while not taking hormonal contraception - Normal concentrations of gonadotropins and oestradiol Complications of intervention	1. Strengths - Well-defined outcomes - Clearly reported study 2. Limitations Large part of patients not available for follow-up 3. Risk of bias *1. Selection bias* High risk Reason: Only 34/410 (8%) patients of original cohort matched the selection criteria and were offered OTC. The criteria are fair and are supposed to only include those at high risk

Abbreviations: NR: not reported; NA: not applicable

assessment, N=14: 6.0 years (IQR 3.5–14.9) • Offered OTC but declined, N=6: 10.9 years (IQR 7.4-13.7) • Not-offered OTC, N=141 : 10.7 years (IQR 6.1-13.8)	• 13/34 declined OTC -> 6 for ovarian function assessment 376/410 were *not* offered OTC ->141 for ovarian function assessment 2. Diagnoses Only reported for pts who consented to OTC (N=21): 6 Hodgkin Lymphoma 6 Sarcoma (various) 5 Rhabdomyosarcoma 1 Wilms tumour 1 Leukaemia 1 Medulloblastoma 1 Ependymoma 3. Age at diagnosis <18 years at diagnosis 4. Median age at follow-up Offered group (N=20): 16.9 years (IQR 15.5-21.8) at data cut-off Not-offered group (N=141): 17.9 years (IQR 15.6-22.0) 5. Controls (if applicable) • Offered but declined group • Not offered group 6. Additional study characteristics, if relevant Edinburgh selection criteria: • Age younger than 35 years		2. Results *Live births* 1 live birth in a non-transplanted patient (patient with Ewing sarcoma diagnosis and POI)* *Pregnancies* 1 spontaneous pregnancy *Ovarian function* • Offered and underwent OTC with tissue successfully cryopreserved: 6/14 (43%) POI • Offered OTC but declined: 1/6(17%) POI • Not-offered OTC: 1/141(1%) POI Cumulative probability of developing POI after treatment: significantly higher for patients offered OTC vs. those who were not offered OTC (15-year probability 35% (95% CI 10-53) vs 1% (0-2); p<0·0001; HR 56.8 (95% CI 6.2-521.6) at 10 years) *Complications* 0/21 Complications of OTC	of POI, but authors give little information on the differences between the offered and the not-offered group, such as diagnoses, age, treatment *Attrition bias* High risk Reason: Offered and underwent OTC: 70% follow-up Offered but declined OTC: 46% follow-up Not-offered: 38% follow-up Reasons for no follow-up: death, on oral contraceptives, medical records missing. Also, in patients <12 years POI could not be assessed, which is important as less risk at POI if treatment at young age *3. Detection bias* Unclear Reason: unclear if outcome assessors were blinded for important determinants related to the outcome *4. Confounding bias* High risk Reason: no multivariate analyses done

	• No previous CT or RT if aged 15 years or older at diagnosis, but mild, non-gonadotoxic chemotherapy acceptable if younger than 15 years • A realistic chance of surviving for 5 years • A high risk of POI (>50%) • Informed consent • Negative serology results for HIV, syphilis, and hepatitis B • Not pregnant and no existing children <u>7. Chemotherapy</u> 19/21 CT (with or without RT) after OTC 2/21 RT before OTC <u>8. Radiotherapy</u> See Chemotherapy <u>9. Surgery</u> See Intervention <u>10. Other treatments</u> -			

Abbreviations: POI: premature ovarian insufficiency; pts: patients; OTC: Ovarian tissue cryopreservation; FU: follow-up; CT: chemotherapy; RT: radiotherapy

*Authors refer to another publication for more information: *Bath LE et al*. Spontaneous conception in a young woman who had ovarian cortical tissue cryopreserved before chemotherapy and radiotherapy for a Ewing's sarcoma of the pelvis: case report. Hum Reprod 2004; 19: 2569–72

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Tanbo et al. Autotransplantation of cryopreserved ovarian tissue after treatment for malignant disease – the first Norwegian results. Acta Obstet Gynecol Scand. 2015;94:937-41				
Study design Treatment era Years of follow-up	**Participants**	**Intervention**	**Main outcomes**	**Additional remarks**
1. Study design Case series in institution (Oslo University Hospital) 2. Treatment era January 2004 – December 2014 3. Follow-up: 11 years 15 patients died during observation period	1. Type and Number of Participants 164 patients underwent ovarian cryopreservation 6 patients requested autotransplantation, 2 underwent autotransplantation 2. Diagnoses Breast cancer 40% Lymphoma 25% Sarcoma 15% Other malignant or benign conditions 20% 3. Age at diagnosis NR - Patients with systematic disease: upper age limit 25 years Patients with localized tumour or non-malignant disease: upper age limit of 35 years 4. Age at follow-up NR 5. Controls (if applicable) NA 6. Additional study	1. Fertility Preservation method 164 patients OTC (mostly unilateral oophorectomy; in few women laparoscopy) *Transplantation* 2 patients with autotransplantation	1. Outcome definitions 1. Complications of intervention (tissue harvesting and transplantation) 2. Live births 1. Complications of tissue harvesting 1/6 patients with contamination of leukemic cells in cryopreserved tissue (diagnosed with acute lymphatic leukaemia at 22 years) 2. Live births 1 spontaneous pregnancy in a non-transplanted patient (breast cancer, unknown age at diagnosis) 1/2 spontaneous pregnancy with 1 healthy live birth (induction 1 week before for intrauterine growth restriction) in a transplanted patient (T-cell lymphoma diagnosis at 24 years) 1/2 transplanted patient delivered 1 healthy live birth (HL diagnosis at 22 years)	1. Strengths - Experience in Oslo with OTC and autotransplantation - Follow-up of 11 years 2. Limitations - Small sample size 3. Risk of bias *1. Selection bias* Low risk Reason: all girls who had OTC in the treatment era were included *2. Attrition bias* Reason: low risk 149(164-15, 90%) patients available for follow-up *3. Detection bias* unclear Reason: unclear if outcome assessors were blinded for important determinants related to the outcome *4. Confounding bias* Not applicable

	characteristics, if relevant - 7. Chemotherapy - Patient with T-cell lymphoma: Cyclophosphamide, doxorubicin, vincristine, etoposide Relapse: high-dose chemotherapy with stem cell support (HMAS) - Patient with HL: HMAS and irradiation of supradiaphragmatic lymph nodes 8. Radiotherapy See above 9. Surgery - 10. Other treatments -			

NR: no reported; NA: not applicable; HL: Hodgkin Lymphoma

What female reproductive preservation methods are appropriate to offer in counselling?				
Dolmans et al. Evaluation of minimal disseminated disease in cryopreserved ovarian tissue from bone and soft tissue sarcoma patients. Hum Reprod 2016;31:2292-302				
Study design Treatment era Years of follow-up	**Participants**	**Intervention**	**Main outcomes**	**Additional remarks**
1. Study design Observational study, case series? 2. Treatment era NR 3. Follow-up: No follow-up (36 still alive, 12 died)	1. Type and Number of Participants 48 sarcoma patients 2. Diagnoses All sarcoma: 28/48 (58%) bone sarcoma 20/48 (42%) soft tissue sarcoma Diagnoses of pts whose ovarian tissue could be analyzed (n=26) - Ewing sarcoma family of tumours (n=14) - Soft tissue sarcoma (n=12) 3. Age at diagnosis NR Mean age at OTC: 16.3 years ±SD 7.27 4. Age at follow-up NA, no follow-up 5. Controls (if applicable) NA 6. Additional study characteristics, if relevant Testing:	1. Fertility Preservation method 48 Ovarian tissue cryopreservation *Transplantation* NM	1. Outcome definitions Presence of specific markers in primary tumoural tissue) Presence of minimal disseminated disease in frozen-thawed ovarian tissue Complications of intervention 2. Results *Complications* NM *Harvested ovarian tissue* 26/48 (54%) patients with ovarian tissue analyzed with disease-specific markers (26 IHC, 19 qPCR) 0/26 minimal disseminated disease detected 22/48(46%) patients could not have ovarian tissue analyzed: 20/22 absence of specific markers in their primary tumoural tissue 1/22 1 Li-Fraumeni syndrome 1/22 both reasons above	1. Strengths Various sensitive detection methods applied 2. Limitations - Study is not clearly reported, difficult to read - Only the tissue samples that had molecular markers could be analyzed (54%) 3. Risk of bias *1. Selection bias* Low risk Reason: 48 sarcoma patients had tissue stored and of all patients (100%) tissue could be thawed and examined *2. Attrition bias* High risk Reason: ovarian tissue of only 26/48 (54%) pts could be analyzed for presence of malignant cells *3. Detection bias* unclear Reason: unclear if outcome assessors were blinded for important determinants related

	- FISH or immunohistochemistry (IHC) to detect specific markers in primary tumoural tissue - IHC and/or quantitative PCR (qPCR) to detect MDD in frozen-thawed ovarian issue <u>7. Chemotherapy</u> 2/26 patients had undergone chemotherapy prior to intervention <u>8. Radiotherapy</u> NR <u>9. Surgery</u> See intervention <u>10. Other treatments</u> NR			to the outcome *4. Confounding bias* Not applicable

Abbreviations: NR: not reported; MDD: Minimal disseminated disease; PCR: polymerase chain reaction; IHC: immunohistochemistry; qPCR: real-time quantitative RT-PCR

What female reproductive preservation methods are appropriate to offer in counselling?				
Jensen et al. Cryopreservation of ovarian tissue for fertility preservation in a large cohort of young girls: focus on pubertal development. Hum Reprod 2017;32:154-164				
Study design Treatment era Years of follow-up	**Participants**	**Intervention**	**Main outcomes**	**Additional remarks**
<u>1. Study design</u> Retrospective cohort study (multi-centre)	<u>1. Type and Number of Participants</u> 140 females with childhood cancer diagnosis	<u>1. Fertility Preservation method</u>	<u>1. Outcome definitions</u> - Subgroup 1: incidence of POI was evaluated POI definition: FSH >20 IU/L at age of <u>≥</u> 12	<u>1. Strengths</u> Relatively large patient sample for this type of study

2. Treatment era NR OTC between March 2000 - August 2015 3. Follow-up: NR	*Original cohort*: 176 females who underwent OTC 2. Diagnoses 140/176(79%) childhood cancer diagnosis: 67(38%) Malignant tumours 42 (24%) Malignant haematological diseases 31 (18%) Lymphomas Other: 26 (15%) Benign diseases 8(5%) Sex chromosome anomalies 2 (1%) Kidney diseases 3. Age at diagnosis NR Age <18 years at OTC Total cohort: mean age at OTC 11.3 years (0.6–17.11) 4. Age at follow-up Subgroup 1: mean age 21.1 years Subgroup 2: mean age 17.6 years 5. Controls (if applicable) NA 6. Additional study characteristics, if relevant - 7. Chemotherapy and 8. Radiotherapy Subgroup 2 (n=32) - Group 1) 12/32 received high dose CT and either TBI prior to SCT or irradiation to the pelvis, abdomen or spinal axis	140 laparoscopic oophorectomy OTC *Transplantation* Unclear Two subgroups: - Subgroup 1: 60/176 had OTC after 12 years old, alive at study - Subgroup 2: 32/176 had OTC before 12 years old (premenarcheal), above 14 years old at study	yrs, no signs of puberty development or menarche - Subgroup 2: association between treatment and requirement for medical puberty induction was examined 2. Results *Live births* 2 healthy live births (from AML and HL patients) 1 induced abortion (from HL patient) *POI incidence in subgroup 1* 27/60 (45%) regular natural menstrual cycles 26/60 (43%) hormone replacement therapy (17/26 (65%) patients with malignant diseases) 7/60 (17%) unknown (6 could not be assessed as oral contraception continuously since CT; 1 no information obtained) *Risk of reintroducing malignant cells** All the women who had ovarian tissue transplanted did not show an increased risk of relapse compared to the women who did not have OTC *Treatment and requirement for puberty induction in subgroup 2* 23/32 (72%) medical puberty induction 9/32 (28%) developed a spontaneous puberty (4 received high dose alkylating agents, 5 conventional CT)	2. Limitations - Longer follow-up of this cohort is needed to obtain a more accurate estimation of who will develop POI later on in life - Some information is missing because of retrospective design E.g. no information on cancer treatment in subgroup 1, only subgroup 2. Therefore not possible to evaluate whether the girls from subgroup 1 who developed POI had higher doses of treatment compared to the other girls who did not develop POI 3. Risk of bias *1. Selection bias* Low risk Reason: all girls who had OTC in the treatment era were included *2. Attrition bias* High risk Reason: POI could be assessed in 85/176 patients (48%) Reasons for no assessment: - 38 girls died - 46 girls still <12 years old - 6 girls oral contraception - 1 girl no information Even without taking into account the 46 young girls plus 6 girls with oral contraception, the attrition is 85/124 (69%) *3. Detection bias*

	- Group 2) 11/32 received high dose alkylating agents, 2/32 received lower doses. All prior to SCT, no irradiation - Group 3) 6/32 received alkylating agents as part of conventional CT - Group 4) 1/32 no gonadotoxic treatment Timing of gonadotoxic therapy (before or after OTC): NR <u>9. Surgery</u> NR <u>10. Other treatments</u> NR		Treatment groups within subgroup 2: Group 1: 10/12 puberty induction Group 2: 11/13 puberty induction Group 3: 1/6 puberty induction Group 4: 1/1 puberty induction	unclear Reason: unclear if outcome assessors were blinded for important determinants related to the outcome *4. Confounding bias* Not applicable

Abbreviations: NR: not reported; NA; not applicable; OTC: ovarian tissue transplantation

*Authors refer to another study for further information: Jensen et al. Outcomes of transplantations of cryopreserved ovarian tissue to 41 women in Denmark. Hum Reprod 2015;30:2838-2845

What female reproductive preservation methods are appropriate to offer in counselling?				
Jadoul et al. Efficacy of ovarian tissue cryopreservation for fertility preservation: lessons learned from 545 cases. Hum Reprod. 2017;32:1046-1054				
Study design Treatment era Years of follow-up	**Participants**	**Intervention**	**Main outcomes**	**Additional remarks**
1. Study design Case series in single institution and prospective questionnaire 2. Treatment era NR OTC between April 1997-December 2013 3. Follow-up: NR Mean follow-up time in surviving patients: 7.6 ± 3.5 years (at time of questionnaires sent)	1. Type and Number of Participants 397 (73%) females with malignant disease 157 (29%) females with malignant disease below 18 years *Total cohort:* 545 females who underwent OTC *Responders from questionnaire:* 143/451(31.7%) (deceased patients (n = 54) and those with no further postal address (n = 40) were excluded from questionnaire) 2. Diagnoses In total cohort: 127(23%) Lymphomas 50(9%) Leukaemia 94(17%) Breast cancer 51(9%) Sarcoma 33(6%) Gynecology malignancies 26(5%) Neurological malignancies	1. Fertility Preservation method 545 patients OTC (majority laparoscopic OTC) *Transplantation* 21/545(3.9%) patients had autotransplantation of their ovarian cortex* *Unknown age at diagnosis or OTC for these patients 19/21 (90.4%) Malignant indications for OTC: 14(58%) hematological diseases 2 (8%) gynecological malignancies 1 (4%) breast cancer 1 (4%) rectal cancer 1 (4%) neurological cancer 5(21%) Non-malignant indications: 3 (12%) benign ovarian pathologies 2 (8%) systemic conditions	1. Outcome definitions 1. Ovarian function after OTC 2. Complications after OTC 3. Live births 4. Pregnancies 2. Results 1. *Ovarian function after OTC* 92/143 (64%) patients with evaluable clinical ovarian function: 31.5% (n=29) were menopausal 68.5% (n=63) had functional ovaries 2. *Complications of OTC* 5/140 patients with minor complications (raised temperature, labial hematoma, urinary infection, bowel irritation and psychological distress) 1/140 patient with major complication (patient had second laparoscopy for intra-abdominal hemorrhage due to ovarian biopsy) Questionnaire reported 3. *Live births* 7 transplanted patients had 10 healthy live births (1 patient delivered two live births; 1 patient delivered three live births)	1. Strengths Relatively large patient sample for this type of study 2. Limitations Questionnaire was used to assess ovarian function, complications of OTC, pregnancies and outcome of pregnancy 3. Risk of bias *1. Selection bias* *Low risk* Reason: all identified patients had OTC *2. Attrition bias* *Low risk* Reason: POI could be assessed in 92(64%) of the 143 questionnaire responders and live births was assessed by medical records and questionnaire *3. Detection bias*

	16(3%) Gastrointestinal malignancies Other: 11(2%) Systemic diseases requiring CT 14(3%) Benign hematologic pathologies diseases requiring BM transplantation 95(17%) Benign and borderline ovarian pathologies 19(3%) Other (Turner Syndrome family history of early menopause, Galactosemia) 9(2%) Other <u>3. Age at diagnosis</u> NR Mean age at OTC (total cohort): 22.3 ± 8.8 years (6 months -39 years) 157(29%) below 18 years at OTC 15% prepubertal at OTC <u>4. Age at follow-up</u> NR Age at questionnaire (responders from questionnaire, n=451): 29.5 ± 9.5 years <u>5. Controls (if applicable)</u> NA <u>6. Additional study</u>	(In 3 patients that came back for reimplantation, transplantation was not performed because of possible risk of grafting leukemic cells)	(Unclear age at diagnosis of the transplanted patients) 4*. Pregnancies* From questionnaire (140 patients): 25 pregnancies (natural conception) in patients with malignant disease 4 pregnancies obtained non-naturally: 1 pregnancy with oocyte donation 2 pregnancies with transfer of embryos frozen before gonadotoxic therapy 1 pregnancy after ovarian cortex autotransplantation	Unclear Reason: unclear if outcome assessors were blinded for important determinants related to the outcome *4. Confounding bias* Not applicable

	characteristics, if relevant Between January 2003 and December 2015, 24/545 patients (4.4%) had autotransplantation of ovarian cortex 7. Chemotherapy and 8. Radiotherapy NR 9. Surgery NR 10. Other treatments NR			

Abbreviations: NR: not reported; NA; not applicable; OTC: ovarian tissue transplantation; BM: bone marrow

What female reproductive preservation methods are appropriate to offer in counselling?				
Silber et al. Cryopreservation and transplantation of ovarian tissue: results from one center in the USA. J Assist Reprod Genet. 2018;35:2205-2213				
Study design Treatment era Years of follow-up	**Participants**	**Intervention**	**Main outcomes**	**Additional remarks**
1. Study design Retrospective cohort study 2. Treatment era OTC between 1997-2017 3. Follow-up: NR	1. Type and Number of Participants 108 females who underwent OTC; 66 females had a malignant diagnosis 2. Diagnoses Hodgkin disease (18.5%), breast cancer (12.0%), leukaemia (6.5%), non-Hodgkin lymphoma (4.6%), other tumours (19.4%), non-malignant disease (39.0%) 3. Age at diagnosis NR Median age at OTC: 24 years (range 6-35) 4. Age at follow-up Range 25-36 years 5. Controls (if applicable) NA 6. Additional study characteristics, if relevant NR	1. Fertility Preservation method 108 patients OTC by using minilaparotomy; 19 of cancer patients underwent slow freeze prior to September 2007, and 47 subsequent cases underwent vitrification of their ovarian tissue *Transplantation* 13/108 (12.0%) patients had ovarian cortex transplantation; 10 (76.9%) were younger than age 25 years at time of freezing; 8 (61.5%) had a malignant diagnosis	1. Outcome definitions 1. Ovarian function after OTC determined by return of FSH to normal levels and regular menstrual cycling 2. Live births 3. Complications 1. *Ovarian function after OTC* - 13/13 (100%) had return of ovarian function from 4-5 months after transplantation - 8/13 (61.5%) grafts were still functioning from 28-62 months after surgery - 5/13 (38.5%) grafts ceased functioning from 22-51 months 2. *Live births* Among females with a malignant diagnosis before age 25 years: 5/8 (62.5%) women had 9 live births from spontaneous pregnancies 3. *Complications* - 3/13 (23.1%) of transplants were in leukaemia survivors without evidence of cancer recurrence - No evidence for cancer recurrence in other patients	1. Strengths - 2. Limitations - 3. Risk of bias *1. Selection bias* *Low risk* Reason: all identified patients had OTC *2. Attrition bias* *Low risk* Reason: Outcome was assessed for all patients that underwent transplantation of cryopreserved ovarian tissue *3. Detection bias* Unclear Reason: unclear if outcome assessors were blinded for important determinants related to the outcome *4. Confounding bias* Not applicable

	7. Chemotherapy and 8. Radiotherapy NR 9. Surgery NR 10. Other treatments NR			

Abbreviations: NR: not reported; NA; not applicable; OTC: ovarian tissue transplantation

What female reproductive preservation methods are appropriate to offer in counselling?				
Poirot et al. Ovarian tissue cryopreservation for fertility preservation in 418 girls and adolescents up to 15 years of age facing highly gonadotoxic treatment. Twenty years of experience at a single center. Acta Obstet Gynecol Scand. 2019:98;630-637				
Study design Treatment era Years of follow-up	**Participants**	**Intervention**	**Main outcomes**	**Additional remarks**
1. Study design Retrospective cohort study 2. Treatment era OTC between April 1998-December 2018 3. Follow-up: NR	1. Type and Number of Participants 418 females who underwent OTC below 15 years of age 2. Diagnoses hematological disease (23.2%), solid tumours (51.7%), non-malignant disease (25.1%) 3. Age at diagnosis NR Median age at OTC: 6.9 years (range 0.3-15) 66.5% below 10 years at OTC	1. Fertility Preservation method 418 patients OTC (majority laparoscopic OTC) In majority an entire ovary was removed *Transplantation* 3/418 (0.7%) patients had ovarian cortex transplantation	1. Outcome definitions 1. Ovarian function after OTC 1. *Ovarian function after OTC* Case 1: Non-cancer patient 10 years old at the time of OTC. The grafting of three fragments of ovarian cortex subcutaneously allowed a spontaneous induction of puberty Case 2: Neuroblastoma patient 12 years old at time of OTC. Currently there has been no recovery of ovarian function. A second transplant is scheduled. Case 3:	1. Strengths Large patient sample 2. Limitations - 3. Risk of bias *1. Selection bias* *Low risk* Reason: all identified patients had OTC *2. Attrition bias* *Low risk* Reason: Outcome was assessed for all 3 patients that underwent

	35.9% below 5 years at OTC 4. Age at follow-up NR 5. Controls (if applicable) NA 6. Additional study characteristics, if relevant NR 7. Chemotherapy and 8. Radiotherapy NR 9. Surgery NR 10. Other treatments NR		Sickle cell disease patient 11.2 years old at time of OTC with a child wish. Ovarian cortex transplant performed in February 2019.	transplantation of cryopreserved ovarian tissue *3. Detection bias* Unclear Reason: unclear if outcome assessors were blinded for important determinants related to the outcome *4. Confounding bias* Not applicable

Abbreviations: NR: not reported; NA; not applicable; OTC: ovarian tissue transplantation

What female reproductive preservation methods are appropriate to offer in counselling?				
Rowell et al. Laparoscopic unilateral oophorectomy for ovarian tissue cryopreservation in children. J Pediatr Surg. 2019;54:543-549				
Study design Treatment era Years of follow-up	**Participants**	**Intervention**	**Main outcomes**	**Additional remarks**
1. Study design Retrospective cohort study 2. Treatment era OTC between January 2011-December 2017 3. Follow-up: NR 41 (64.1%) patients are ≥1 yr from time of OTC	1. Type and Number of Participants 64 females who underwent OTC below 23 years of age 2. Diagnoses Malignant disease (82.8%), benign hematological disorder requiring stem cell transplant (9.4%), disorder of sex development (7.8%) 3. Age at diagnosis NR Median age at OTC: 12 years (range 0.4-23) 48% premenarchal 4. Age at follow-up Median 12 years (inter quartile range 7-15) 5. Controls (if applicable) NA 6. Additional study characteristics, if relevant Eight patients underwent OTC at the time of disease relapse rather than at the time of initial diagnosis. They did not qualify for OTC initially	1. Fertility Preservation method 64 patients OTC (majority laparasopic unilateral oophorectomy) *Transplantation* None	1. Outcome definitions Complications 2. Results *Complications* - No intraoperative complications related to the laparoscopic oophorectomy occurred - Median estimated blood loss of patients undergoing OTC, without primary mass excision: 3 ml - For patients who underwent laparoscopy, 39 (66%) had their OTC performed as same-day surgery, while 18 (30%) were observational admissions (< 24 h) - No reported 30-day postoperative complications - Median time from operation to initiation of medical therapy: 6 days with no unanticipated delays in treatment initiation - 57/59 patients with a cancer or hematologic diagnosis had normal ovarian tissue with identifiable follicles on pathologic evaluation, regardless of their treatment history; 1 neuroblastoma patient had infiltrated B-lymphoblastic lymphoma/leukaemia; 1 acute lymphoblastic leukaemia patient who received multiple rounds of non-gonadotoxic chemotherapy prior to OTC was noted to have rare follicles on histologic examination	1. Strengths - 2. Limitations - 3. Risk of bias *1. Selection bias* Low risk Reason: all identified patients had OTC *2. Attrition bias* Low risk Reason: outcome was assessed for all patients that underwent OTC *3. Detection bias* Unclear Reason: unclear if outcome assessors were blinded for important determinants related to the outcome *4. Confounding bias* Not applicable

	but became candidates for FP at the time of relapse owing to their cumulative gonadotoxic therapy or need for SCT. <u>7. Chemotherapy and 8. Radiotherapy</u> NR <u>9. Surgery</u> NR <u>10. Other treatments</u> NR			

Abbreviations: NR: not reported; NA; not applicable; OTC: ovarian tissue transplantation

What female reproductive preservation methods are appropriate to offer in counselling?				
Longhi et al. Effect of oral contraceptive on ovarian function in young females undergoing neoadjuvant chemotherapy treatment for osteosarcoma. Oncol Rep 2003; 10:151-155				
Study design Treatment era Years of follow-up	**Participants**	**Intervention**	**Main outcomes**	**Additional remarks**
1. Study design Single centre retrospective cohort study with historical control group 2. Treatment era Group 1: 1997 – 2000 Group 2: 1974 – 1995 3. Follow-up: Group 1: Mean follow-up time post-chemotherapy 29.4 months (9-43) Group 2: no information, these patients were treated within a time span of 22 years	1. Type and Number of Participants Study group: 31 female patients Control group: 90 female patients 2. Diagnoses Osteosarcoma 3. Age at diagnosis Study group: mean age 19.4 years (4-40). 4 patients aged >35 years. Control group: mean age 16.8 years (7-43). 3 patients aged >35 years. 4. Age at follow-up Study group: mean age at time of interview in 2001 23.6 years (8-42) Control group: mean age at time of interview in 2001 27.8 years (15-52) 5. Controls (if applicable) See above 6. Additional study characteristics, if relevant Study group: 24/31	1. Fertility Preservation method *Study group*: Oral contraceptives (desogestrel 0.150 mg + etinilestradiol 0.020 mg) given continuously during neo-adjuvant chemotherapy (duration about 36 weeks) 5/24 postpubertal pts had no oral contraceptives: 3 pts refused and 2 pts stopped it early due to thrombophlebitis 3 patients from the study group who refused OC were considered in the control group *Control group*: no oral contraceptives	1. Outcome definitions Age of menarche Amenorrhea during or post-CT Early menopause Desire for pregnancy Pregnancies 2. Results *Menarche:* Study group: 2/7 prepubertals menarche at 13.5 yrs and 14 yrs; of these, 1 irregular menstruation Control group: 22/22 prepubertals menarche at mean age 13 yrs (11-16); 8/22 irregular cycles *Permanent amenorrhea post CT* Study group: 3/24 (13%) Control group: 3/71 (4%) *Pregnancy:* Study group: 0/24 desired pregnancies 2/24 (8%) voluntary abortions Control group: 24/31 (77%) pregnant females delivered 24 healthy live births 4/31 (13%) voluntary abortions 3/31 (9.7%) spontaneous abortions	1. Strengths 2. Limitations - Historical control group, were re-interviewed in 2001 - Limited follow-up time study group - Different CT protocols in study and control group, which differ significantly in the alkylant dosage 3. Risk of bias *1. Selection bias* High risk Reason: No statistical evaluation of similarity/difference between study and control groups in terms of age, length of follow-up, ifosfamide dose etc. Also, how patient inclusion had taken place is not described *2. Attrition bias* Low risk Reason: outcomes assessed for almost all patients. (However, mean follow up only 29.4 months (range 9-43) in study group so seems inadequate for results) *3. Detection bias*

	postpubertal, 7/31 prepubertal Control group: 68/90 postpubertal, 22/90 prepubertal <u>7. Chemotherapy</u> Study group: IOR 6 protocol. High-dose ifosfamide, methotrexate, adriamycin, cisplatinum Control group: IOR 1-IOR 5 protocol. IOR 1 and IO 2 did not employ alkylants so 31/90 pts who were on these protocols did not receive alkylants <u>8. Radiotherapy</u> - <u>9. Surgery</u> NR <u>10. Other treatments</u> NR		2/90 (2%) failed pregnancies (1/90 gynaecological problem unrelated to CT, 1/90 failed to become pregnant)	Unclear Reason: unclear if outcome assessors were blinded for important determinants related to the outcome *4. Confounding bias* High risk Reason: CT protocols differ significantly in study and control groups, no multivariate analysis .

Abbreviations: NR: not reported; NA: not applicable; OC: oral contraceptive; pts: patients

What female reproductive preservation methods are appropriate to offer in counselling?

Pereyra et al. Use of GnRH analogs for functional protection of the ovary and preservation of fertility during cancer treatment in adolescents: a preliminary report. Gynecol Oncol 2001;81:391-397				
Study design Treatment era Years of follow-up	**Participants**	**Intervention**	**Main outcomes**	**Additional remarks**
1. Study design Prospective single centre study, with retrospective controls. Addition of a retrospective premenarchal "control group" 2. Treatment era NR 3. Follow-up: Study group followed up to 5 years (mean or range NR) Control groups were historical controls. Control group 1 was followed for 18 years Control group 2 was followed for 6 years	1. Type and Number of Participants *Study group* 12 postmenarchal patients: *Original cohort*: 21 patients *Control groups* Control group 1: premenarchal patients (n=5) previously treated with CT Control group 2: postmenarchal patients (n=4) previously treated CT and BMT 2. Diagnoses *Study group* Subgroup 1: 4 Hodgkin Lymphoma; 1 Non-Hodgkin lymphoma Subgroup 2: 7 Hodgkin *Control group 1* 2 Lymphoma, 1 Thymoma, 2 ALL *Control group 2* 3 Hodgkin; 1 AML 3. Age at diagnosis *Study group*	1. Fertility Preservation method GnRH analog during chemotherapy in Group B only (3.75 mg im depot monthly until 30 days after chemotherapy)	1. Outcome definitions Menarche, menstrual regularity, and pregnancy: lab tests, gynaecological echography and bone densitometry 30 days after the last GnRH injection 2. Results *Menstrual disorders* - *Study group:* 0/12 (0%) amenorrhea - *Control group 1:* 1/5 (20%) oligomenorrhea - *Control group 2:* 4/4 (100%) hypergonadotrophic hypoestrogenic amenorrhea 4/4 hormone replacement therapy *Live births* *-Study group - Subgroup 1:* 2/2 (100%) pregnant females delivered 3 healthy live births *-Control group 1:* 3/3 (100%) pregnant females delivered 5 healthy live births *-Control group 2:* No pregnancies *Pregnancies* *Study group – subgroup 1:* 3/3 (100%) spontaneous pregnancies (1	1. Strengths - 2. Limitations - 22 patients were studied in study group but only 12 included, reasons for exclusion of the 9 patients unclear - Small sample sizes - Use of historic controls - Heterogenous diagnoses and treatments - Only descriptive results - Unclearly reported - Can control group 1 be considered control group as this is a premenarchal group and the study group is postmenarchal? 3. Risk of bias *1. Selection bias* High risk Reason: only 12/22 of studied patients were included in intervention group, unclear how *2. Attrition bias* High risk Reason: follow-up data unclear or not available

	14.7 – 20 years old Subgroup 1: 14.7-18 years old Subgroup 2: 15-20 years old *Control group 1* 3 – 7.5 years old *Control group 2* 15.9 – 20 years old <u>4. Age at follow-up</u> NR <u>5. Controls (if applicable)</u> Control group 2 were historical controls <u>6. Additional study characteristics, if relevant</u> - <u>7. Chemotherapy</u> Heterogeneous treatment protocols, not all patients received BMT - Subgroup 1 (n=5) treated with CT before BMT - Subgroup 2 (n=7) treated with CT and supradiaphragmatic irradiation but no BMT <u>8. Radiotherapy</u> Supradiaphragmatic irradiation in Group B2 with gonad protection (during chemotherapy?) - Subgroup 1 (n=5) treated with CT before BMT		patient had 2 pregnancies) Control group 1: 4/5 spontaneous pregnancies 1/5 ovulation induction (2 patients had 2 pregnancies each)	*3. Detection bias* Unclear Reason: unclear if outcome assessors were blinded for important determinants related to the outcome *4. Confounding bias* High risk Reason: Only descriptive results

	- Subgroup 2 (n=7) treated with CT and supradiaphragmatic irradiation but no BMT <u>9. Surgery</u> NR <u>10. Other treatments</u> NR			

Abbreviations: NR: not reported; NA: not applicable; CT: chemotherapy; GnRH: gonadotropin releasing hormone; im: intramuscular; BMT: bone marrow transplantation

What female reproductive preservation methods are appropriate to offer in counselling?				
Meli et al. Triptorelin for Fertility Preservation in Adolescents Treated With Chemotherapy for Cancer. J Pediatr Hematol Oncol. 2018 May;40(4):269-276				
Study design Treatment era Years of follow-up	**Participants**	**Intervention**	**Main outcomes**	**Additional remarks**
1. Study design Retrospective cohort study 2. Treatment era 2000-2015 3. Follow-up: Median 5 years (range 1-17) since end of treatment	1. Type and Number of Participants 36 2. Diagnoses Leukaemia (33.3%), Hodgkin lymphoma (47.2%), non-Hodgkin lymphoma (8.3%), other tumour (11.1%) 3. Age at diagnosis Median 14 years (range 10-18) 4. Age at follow-up Median 20 years (range 14-32) 5. Controls (if applicable) NA 6. Additional study characteristics, if relevant Before the diagnosis of cancer, 89 had a normal menstrual cycle, whereas 11% had oligomenorrhea 7. Chemotherapy 100% treated with alkylating	1. Fertility Preservation method Monthly depot intramuscular injection of 3.75 mg GnRH-a (Decapeptyl) or a triple dose of GnRH-a (11.25 mg) every 3 months Decapeptyl administered for 3 to 12 months (median 8 mo) according to duration of chemotherapy	1. Outcome definitions - Premature ovarian failure: persistent hypergonadotropic amenorrhea (FSH >40 U/L on at least 2 determinations) and low estradiol (E2) levels; - Cyclic ovarian function: regular spontaneous menstrual cycles, normal gonadotropin and E2 levels, ovulatory progesterone, and visualization of ovarian follicles or corpora lutea and/or spontaneous conception - Live births - Complications 2. Results *Menstrual cycles in 1st year after therapy:* - 24 (66%) had regular menstrual cycles - 7 (19%) had oligomenorrhea - 5 (14%) had amenorrhea - Median time of 3 months elapsed between end of treatment with Decapeptyl and restart of the menstrual cycle *Menstrual cycles/sexual hormone levels at last follow-up:* - 29 (81%) had regular menstrual cycles - 3 (8%) had oligomenorrhea - 4 (11%) had amenorrhea	1. Strengths - Long follow-up - Young population including peripubertal patients 2. Limitations - Heterogeneous small patient population - No control group included 3. Risk of bias *1. Selection bias* Unclear Reason: unclear how many patients were included in the original cohort *2. Attrition bias* Low risk Reason: follow-up available for all included patients. *3. Detection bias* Unclear Reason: unclear if outcome assessors were blinded for important determinants related to the outcome

	agents 8. Radiotherapy 2.8% TBI 0% ovarian irradiation 9. Surgery NR 10. Other treatments 25.0% HSCT and high-dose alkylating agents		- In 4/9 (44%) treated with HSCT and high-doses of alkylating agents ovarian function was not preserved *Live births* - Five patients (2 with ALL, 1 with HL, 1 with Ewing sarcoma, and 1 with rhabdomyosarcoma) reported a total of 8 pregnancies resulting in 8 healthy live births - No miscarriages were reported *Complications:* No late effects occurred	*4. Confounding bias* High risk Reason: Only descriptive results

Abbreviations: NR: not reported; NA: not applicable; GnRH: gonadotropin releasing hormone

What female reproductive preservation methods are appropriate to offer in counselling?				
Morice et al. Fertility results after ovarian transposition for pelvic malignancies treated by external radiation or brachytherapy. Hum Reprod 1998; 13:660-663				
Study design Treatment era Years of follow-up	**Participants**	**Intervention**	**Main outcomes**	**Additional remarks**
1. Study design retrospective analysis of a consecutive case series 2. Treatment era Dec 1974 - Aug 1994 3. Follow-up: Minimum of 2 years after	1. Type and Number of Participants 37 female patients with pelvic malignancies 2. Diagnoses Group 1 (n=27): clear cell adenocarcinoma of the vagina and/or cervix Group 2 (n=10): ovarian pure dysgerminoma (9),	1. Fertility Preservation method Ovarian transposition (either by laparotomy (n=24), or by laparoscopy (n=13, since 1993) When the ovaries were macroscopically normal both ovaries were transposed. For patients with an ovarian	1. Outcome definitions Ovarian function considered normal when FSH concentration was <10 mIU/ml, oestradiol >50 pg/ml and when follicles were present on the ultrasound scan Fertility: number of pregnancies, their evolution and the outcome of newborns 2. Results *Menstrual disorders* Group 1: 9/27 (33.3%) - 5 (18.5%) amenorrhea	1. Strengths Reproductive outcome assessed using both ovarian function (ultrasound + hormonal) and number of pregnancies/live births. 2. Limitations - Little information on follow-up - Menstrual disorders and pregnancies reported, but not results of hormones or ultrasound

complete remission	para-uterine soft tissue sarcoma (1) 3. Age at diagnosis Mean age at time of treatment 20.7 years (SEM 2.8) (7-32) 4. Age at follow-up NR 5. Controls (if applicable) NA 6. Additional study characteristics, if relevant Patients in group 1 were treated for clear cell adenocarcinoma, following exposure to diethylstilboestrol (DES) in 60% 7. Chemotherapy NA 8. Radiotherapy + 9. Surgery Group 1: combined radio-surgical therapy: Complete exploration, transposition of both ovaries, pelvic lymphadenectomy. - 20/27 brachytherapy alone (60 Gy) - 7/27 external irradiation (45 Gy) and brachytherapy (15 Gy)	dysgerminoma, transposition of the non-affected ovary was performed	- 4 (14.8%) oligomenorrhea (unusual long interval between menstrual periods >50days) Group 2: 1/10 (10%) - 1 oligomenorrhea with normal biological tests (gonadotrophin and oestradiol levels); menstrual cycles normalized a few months after end of irradiation *Pregnancies* 18 pregnancies: 16 (88%) spontaneous 2 (11%) after IVF 12 (67%) with abdominal ovary 4 (22%) with repositioned ovary 5/18 (28%) pregnant females had miscarriages Median time between end of tumour treatment and first pregnancy was 4.3 years (SEM 0.8) (2-7 years) *Pregnancy rate* 12/37(32%) pregnant patients: - 4/27 (15%) group 1 - 8/10(80%) group 2 - No significant difference between laparoscopy or laparotomy (25% (3/13) versus 37% (9/24), respectively) *Live births* 13/18 (72%) pregnant females delivered 15 live births (no fetal malformations related to maternal history)	3. Risk of bias *1. Selection bias* High risk Reason: consecutive series. However, 37/79 (47%) included, with limited information on those excluded (7 lost to FU, 14 died, 11 hysterectomy at later stage, 10 follow-up < 2 years) *2. Attrition bias* low risk Reason: the results that are reported (menstrual disorders + pregnancies) seem to be assessed in all included patients. However, results of hormonal assays and ultrasound are missing. FU after a minimum of 2 years of CR, which seems good, but no further info on FU. *3. Detection bias* unclear Reason: unclear if outcome assessors were blinded for important determinants related to the outcome *4. Confounding bias* Not applicable

	Group 2: combined radio-surgical therapy: - Pure ovarian dysgerminoma: unilateral adnexectomy, transposition of contralateral ovary, peritoneal biopsies. Only external irradiation (25 or 35 Gy) Mean ovarian dose in group 1: 2.2 Gy (0.54-10) Mean ovarian dose in group 2: 1.9 Gy (0.5-3.4) <u>10. Other treatments</u> NR			

Abbreviations: NM, not mentioned; SEM: standard error of mean; FU: follow-up; CR: complete remission

What female reproductive preservation methods are appropriate to offer in counselling?				
Fernandez-Pineda et al. Impact of ovarian transposition before pelvic irradiation on ovarian function among long-term survivors of childhood Hodgkin lymphoma: A report from the St. Jude Lifetime Cohort Study. Pediatr Blood Cancer. 2018 11:e27232				
Study design Treatment era Years of follow-up	**Participants**	**Intervention**	**Main outcomes**	**Additional remarks**
1. Study design Cohort study (St Jude Lifetime Cohort Study, SJLIFE) 2. Treatment era NR Questionnaire pertaining to reproductive health before June 2015 3. Follow-up: NR	1. Type and Number of Participants 90 Hodgkin's Lymphoma female cancer survivors *Total cohort:* 127 eligible females with Hodgkin's Lymphoma, 90 (71%) participated in SJLIFE 2. Diagnoses Hodgkin's Lymphoma 3. Age at diagnosis Patients with OT: Median 15(4-19) years 4. Age at follow-up Patients with OT: Age at questionnaire: 38(25-51) years 5. Controls (if applicable) Age at diagnosis Median 16(6-22) years Age at questionnaire: 39(26-60) years 6. Additional study characteristics, if relevant Defined as:	1. Fertility Preservation method 49 patients with OT before pelvic radiotherapy: 48(98%) Open surgical technique; 1(2%) Laparoscopic *Controls:* 41 patients without OT	1. Outcome definitions 1. POI after OT 2. POI after pelvic radiation 3. POI after alkylating agent 4. Pregnancy and live births 1. POI after OT *Hazard ratio (95% CI) for POI* OT yes vs. no: HR 0.6 (0.2-1.9) (in model adjusting for age at diagnosis); HR 1.1 (0.5-2.7) (subanalysis in survivors who received lower CED <12,000 mg/m^2 and in model adjusting for age at diagnosis) 2. POI after pelvic radiation *Hazard ratio (95% CI) for POI* Pelvic radiotherapy dose, >1,500 vs ≤1,500: HR 25.2 (3.1-207.3) (in model adjusting for age at diagnosis); HR 17.8 (2.3-136.5) (subanalysis in survivors who received lower CED <12,000 mg/m^2 and in model adjusting for age at diagnosis) 3. POI after alkylating agent *Hazard ratio (95% CI) for POI* Alkylating agent CED, mg/m^2, >20,000 vs. ≤8000: HR 36.9 (5.2-260.5) (in model adjusting for age at diagnosis); Alkylating agent CED, mg/m^2, 12,001-20,000 vs. ≤8000:	1. Strengths - Long follow-up - Assessment of effect of OT as fertility preservation method in relation to gonadotoxic treatment with information on doses 2. Limitations - Questionnaire data for pregnancy and live births outcome 3. Risk of bias *1. Selection bias* Low risk Reason: 90/127 (70.9%) patients from the original cohort were included in the study. However, the patient and treatment characteristics of the participants and non-participants are not significantly different. *2. Attrition bias*

	POI defined as absence of menses 5 years post cancer diagnosis or loss of spontaneous menses prior to 40 years of age with laboratory or historic evidence of primary (ovarian) origin In the absence of treatment with oral contraceptive pills or sex-hormone replacement therapy (HRT) at the time of SJLIFE participation, individuals <40 years old experiencing amenorrhea for a period > 6 months and having plasma estradiol levels < 17 pg/ml coinciding with follicle stimulating hormone levels ≥ 30 IU/l were considered to have POI <u>7. Chemotherapy</u> Patients with OT Alkylating agents CED: 0 to ≤8,000: 19 (40%) 8,000 to ≤12,000: 12 (25%) 12,000 to ≤20,000: 13 (27%) >20,000: 4(8.3%) Median (range) 10151.7 (1806.2–28980.0) Controls: Alkylating agents CED: 0 to ≤8,000: 26 (67%) 8,000 to ≤12,000: 6 (15%) 12,000 to ≤20,000: 7 (18%) >20,000: 0		HR 11.2 (3.4-36.8) (in model adjusting for age at diagnosis); Alkylating agent CED, mg/m^2, 8,001-12,000 vs. ≤8000: HR 3.3 (0.7-16.0) (in model adjusting for age at diagnosis); <u>4. Pregnancy and live births</u> 30/49(61%) survivors with at least one pregnancy 27/30(90%) pregnant females delivered a live birth at least once No difference between probability of a first pregnancy or live birth before age 40 between OT group vs. non-OT group	Low risk Reason: follow-up data available for all patients *3. Detection bias* Unclear Reason: unclear if outcome assessors were blinded for important determinants related to the outcome *4. Confounding bias* Low (for POI, pelvis radiation and alkylating agents outcome) High (for probability of first pregnancy and live births) Reason: no multivariate analysis for probability of first pregnancy and live births; multivariable analysis done adjusting for age at diagnosis for rest of outcomes

	Median (range) 7434.6 (1800.0–16486.8) <u>8. Radiotherapy</u> Pelvic radiation dose for patients with OT: ≤1,500: 9(18%) >1,500: 40(82%) Controls: ≤1,500: 23(61%) >1,500: 15(40%) <u>9. Surgery</u> - <u>10. Other treatments</u> -			

POI: premature ovarian insufficiency; OT: ovarian transposition; CED: cyclophosphamide equivalent dose

What female reproductive preservation methods are appropriate to offer in counselling?				
Vernaeve et al. Endometrial receptivity after oocyte donation in recipients with a history of chemotherapy and/or radiotherapy. Hum Reprod 2007;22:2863-7				
Study design Treatment era Years of follow-up	**Participants**	**Intervention**	**Main outcomes**	**Additional remarks**
1. Study design Retrospective matched controlled analysis 2. Treatment era January 2000 - November 2005 3. Follow-up: NR	1. Type and Number of Participants 33 female cancer survivors (various diagnoses) Controls: 33 females without history of cancer therapy 2. Diagnoses Hodgkin's lymphoma (n = 12, 36.4%) Non-Hodgkin's lymphoma (n = 3, 9.1%) Leukaemia (n = 7, 21.2%) Ovarian cancer (n = 6, 18.2%) Ewing's sarcoma (n = 2, 6.1%) Breast cancer (n = 1, 3.0%) Sympathoblastoma (n = 1, 3.0%) Histiocytosis X (n = 1, 3.0%) 3. Age at diagnosis Mean age at diagnosis 21.0 years (95% CI 17.3–24.7) 4. Age at follow-up Mean age 33.1 yrs (95% CI 30.9-35.3) 5. Controls (if applicable) Matching was performed to the	1. Fertility Preservation method OD cycle with fresh embryo transfer (after ICSI); in total: 50 OD cycles (some patients repeated the OD procedure) OD according to the Spanish Act on Reproduction Donation Anonymous and altruistic, donors aged 18- 35 years. Clinical and psychological workup performed, including karyotype	1. Outcome definitions • Pregnancy: each pregnancy with at least one intrauterine sac revealed by ultrasonography 5 weeks after transfer • Implantation rate: ratio of gestational sacs to the number of embryos transferred • Ongoing pregnancy: a viable pregnancy confirmed on an ultrasound scan performed at the 12th week • Pregnancy rates were defined per embryo transfer 2. Results *Pregnancy outcomes cancer survivors vs. controls* Pregnancies after OD: 19/33 (57.6%) vs. 13/33 (39.4%); p=0.1 Ongoing pregnancies after OD: 15/33 (45.4%) vs. 9/33 (27.3%); p=0.1 Delivery rate: 15/33 (45.4%) cancer survivors delivered 18 babies vs. 9/33 (27.3%) controls delivered 10 babies, p=0.1	1. Strengths Comparison was made with the general population of oocyte recipients matched for the main confounding factors 2. Limitations Small number of patients studied 3. Risk of bias *1. Selection bias* Unclear Reason: no information on original cohort or on how the 33 patients were included *2. Attrition bias* Low risk Reason: outcomes assessed for >75% of patient group *3. Detection bias* unclear Reason: unclear if outcome assessors were blinded for important determinants related to the outcome *4. Confounding bias* Low risk

	chronologically closest patient without a history of cancer therapy (control group) according to: - number of days of hormonal stimulation before embryo replacement (+5 days); -number of replaced embryos; -day of embryo replacement (day 2 or day 3); -origin of sperm (ejaculated or testicular) Repeated OD cycles were not used for matching No matching was performed on the basis of age, as in the study centre they have found no correlation between recipient's age and OD outcome <u>6. Additional study characteristics, if relevant</u> 29/33 (88%) POF Mean age of onset of the menopause was 23.9 years (95% CI 19.7 – 28.0) <u>7. Chemotherapy and</u> <u>8. Radiotherapy</u> 23/33 pts (70%) CT and RT 9/33 pts (27%) CT only 1/33 pts (3%) RT only Concerning the 24 pts (31 cycles) who received RT, the localization was:		Complications in study group: 3/15 (20%) premature delivery (<37 weeks) 1/15 (7%) placental hemorrhage with stillborn child 1/15 (7%) Pre-eclampsia Complications in control group: 1/9 (11%) premature delivery (<37 weeks)	Reason: patients were compared with other recipients matched for the main confounding factors. General characteristics of the study and control group were similar, except that the patients were significantly younger and had fewer previous deliveries than the controls. .

	- pelvic in 8 pts (11 cycles) - TBR in 7 pts (10 cycles) - supradiaphragmatic in 9 pts (10 cycles) 9. Surgery - 10. Other treatments -			

Abbreviations: NM: not mentioned; OD: Oocyte donation; ICSI: Intracytoplasmic sperm injection

What female reproductive preservation methods are appropriate to offer in counselling?				
Marklund et al. Pregnancy achieved using donor eggs in cancer survivors with treatment-Induced ovarian failure: obstetric and perinatal outcome. Journal of Women's Health 2018;27:939-945.				
Study design Treatment era Years of follow-up	**Participants**	**Intervention**	**Main outcomes**	**Additional remarks**
1. Study design Prospective cohort study 2. Treatment era 2003-2015 3. Follow-up: Mean 14.9 (range 2-34) year	1. Type and Number of Participants 31 female cancer survivors (various diagnoses) with iatrogenic infertility 2. Diagnoses Leukaemia (n=13) Hodgkin/non-Hodgkin lymphoma (n=5) Ovarian tumour (n=6) Wilms tumour (n=3) Other (n=4)	1. Fertility Preservation method Donor eggs to achieve pregnancy Cancer survivors underwent 102 egg donor treatment cycles (52 with fresh embryos and 50 with cryopreserved embryos)	1. Outcome definitions • Pregnancy • Obstetric and perinatal complications 2. Results *Pregnancy outcomes cancer survivors vs. controls* • Cancer survivors: 25 pregnancies in 20 females • Controls: 244 pregnancies in 212 females *Odds ratios (95% CI) for obstetric and*	1. Strengths Comparison was made with females without a cancer diagnosis 2. Limitations Small number of patients studied 3. Risk of bias *1. Selection bias* Low risk Reason: All cases of iatrogenic

	3. Age at diagnosis Mean 20.2 (range 3-38) year 4. Age at follow-up Mean 35.1 (range 24-45) yr at egg donor treatment 5. Controls 212 females without history of cancer therapy who underwent treatment with donor eggs 6. Additional study characteristics, if relevant - 7. Chemotherapy Not reported 8. Radiotherapy to ovaries 15 (48.4%) 9. Surgery - 10. Other treatments -		*perinatal outcomes in cancer survivors vs. controls adjusted for BMI and maternal age at first antenatal visit* • Preeclampsia: 2.79 (1.07-7.34) • Hypertensive disorders of pregnancy: 1.80 (0.69-4.69) • Preterm premature rupture of membranes: 3.85 (0.96-15.42) • Hemorrhage (>1000 mL): 1.22 (0.34-4.38) • Small for gestational age: 2.12 (0.24-18.68) • Neonatal intensive care unit: 1.14 (0.36-3.61) • Very preterm birth: 17.39 (3.99-75.79) • Moderate preterm birth: 2.92 (0.88-9.66) • APGAR <7: 2.40 (0.24-24.46)	infertility due to antineoplastic treatment, regardless of the type and stage of cancer at the moment of diagnosis and the interval between the cancer diagnosis and the donor egg treatment, were included. *2. Attrition bias* Low risk Reason: outcomes assessed for >75% of patient group *3. Detection bias* unclear Reason: unclear if outcome assessors were blinded for important determinants related to the outcome *4. Confounding bias* Low risk Reason: analyses were adjusted for BMI and age.