

Cancer treatment during pregnancy

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Take home message

- *Chemotherapy during pregnancy is possible*
- *Cervical cancer is most challenging*
- *Interdisciplinary approach in referral centers*

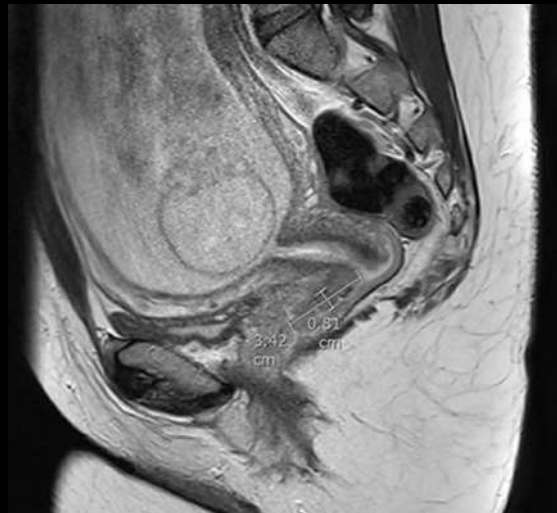
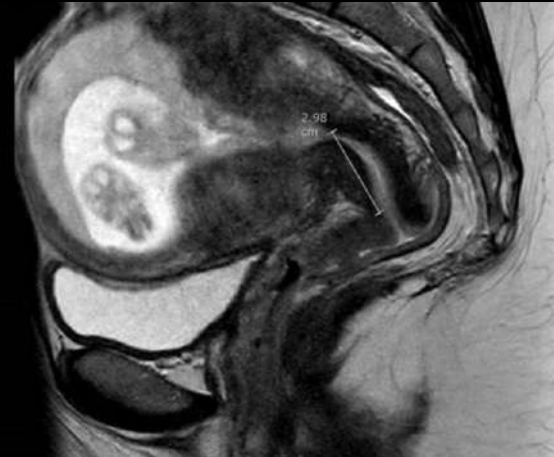
Gynaecological cancer during pregnancy, with an emphasis on chemotherapy: agenda

- ***Case study***
- ***Epidemiology, diagnosis and staging***
- ***Surgery***
- ***Radiotherapy***
- ***Chemotherapy***
- ***Long term pediatric outcomes***
- ***Multidisciplinary setting including obstetrical high care units***

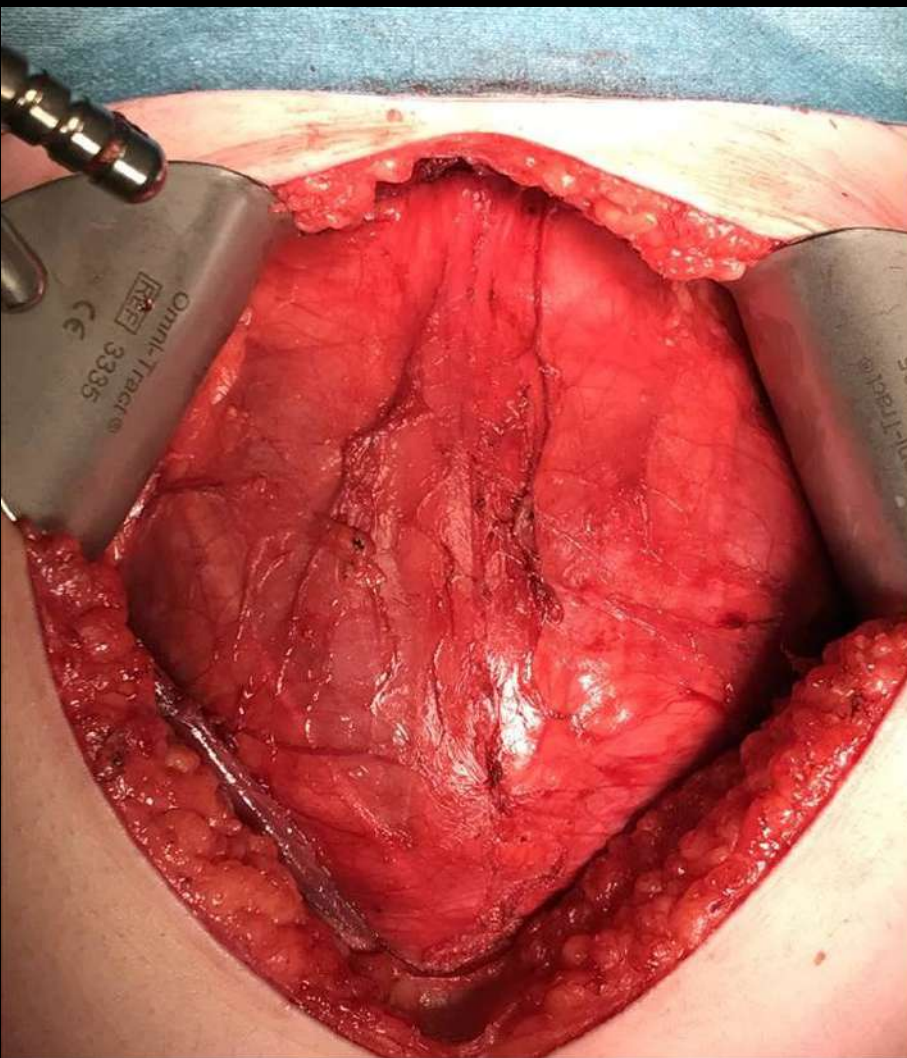
**Stage IB2 CxCa, squamous type,
monochorial twin, 14 w**

April 2019

History: preterm twin delivered at 26w



Extraperitoneal lymphadenectomy (0/24 nodes)



Clinical and radiological respons after 3 cycles paclitaxel-carboplatin



5 cycles paclitaxel-carboplatin
C/section at 34 5/7 w
Wertheim abandoned due to adhesions
radiochemotherapy

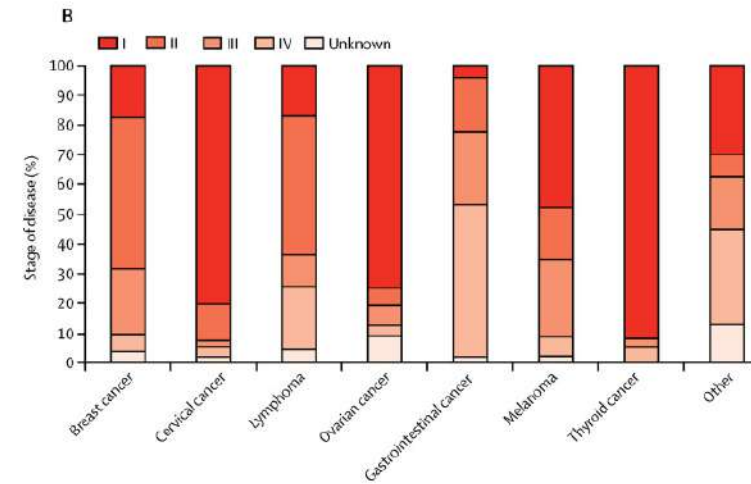
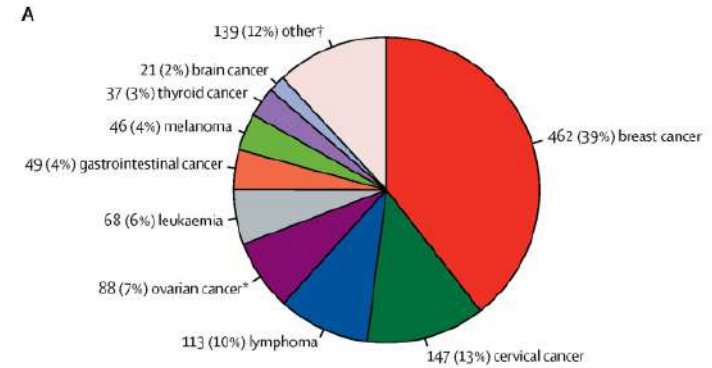
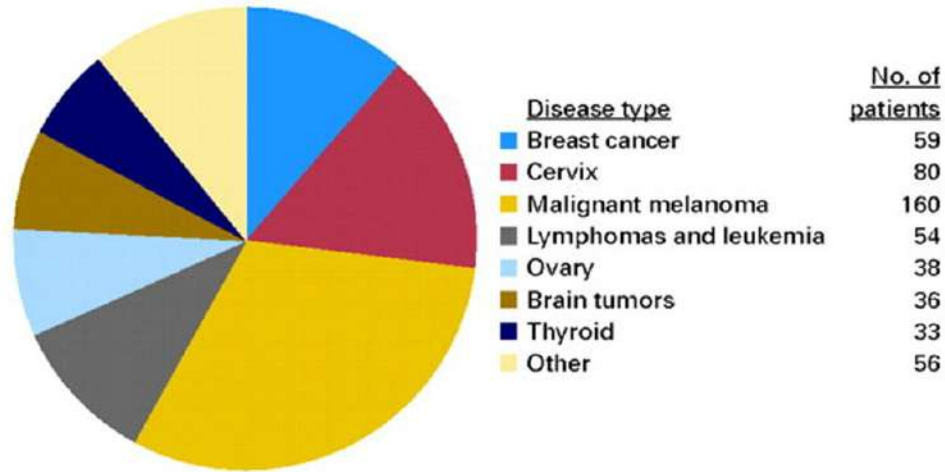
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Epidemiology

Stensheim H, et al, JCO, 2015; de Haan et al., Lancet Oncol 2018

Cancer Diagnosed During Pregnancy (n = 516)

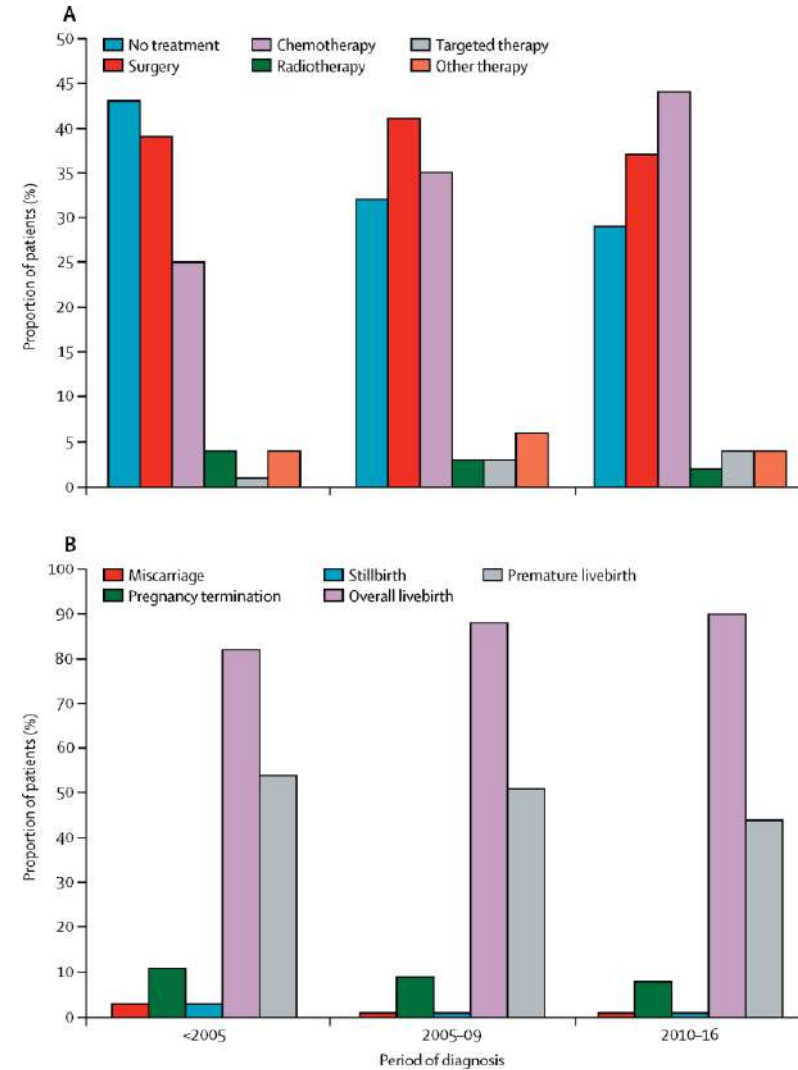


Changes in 20 years

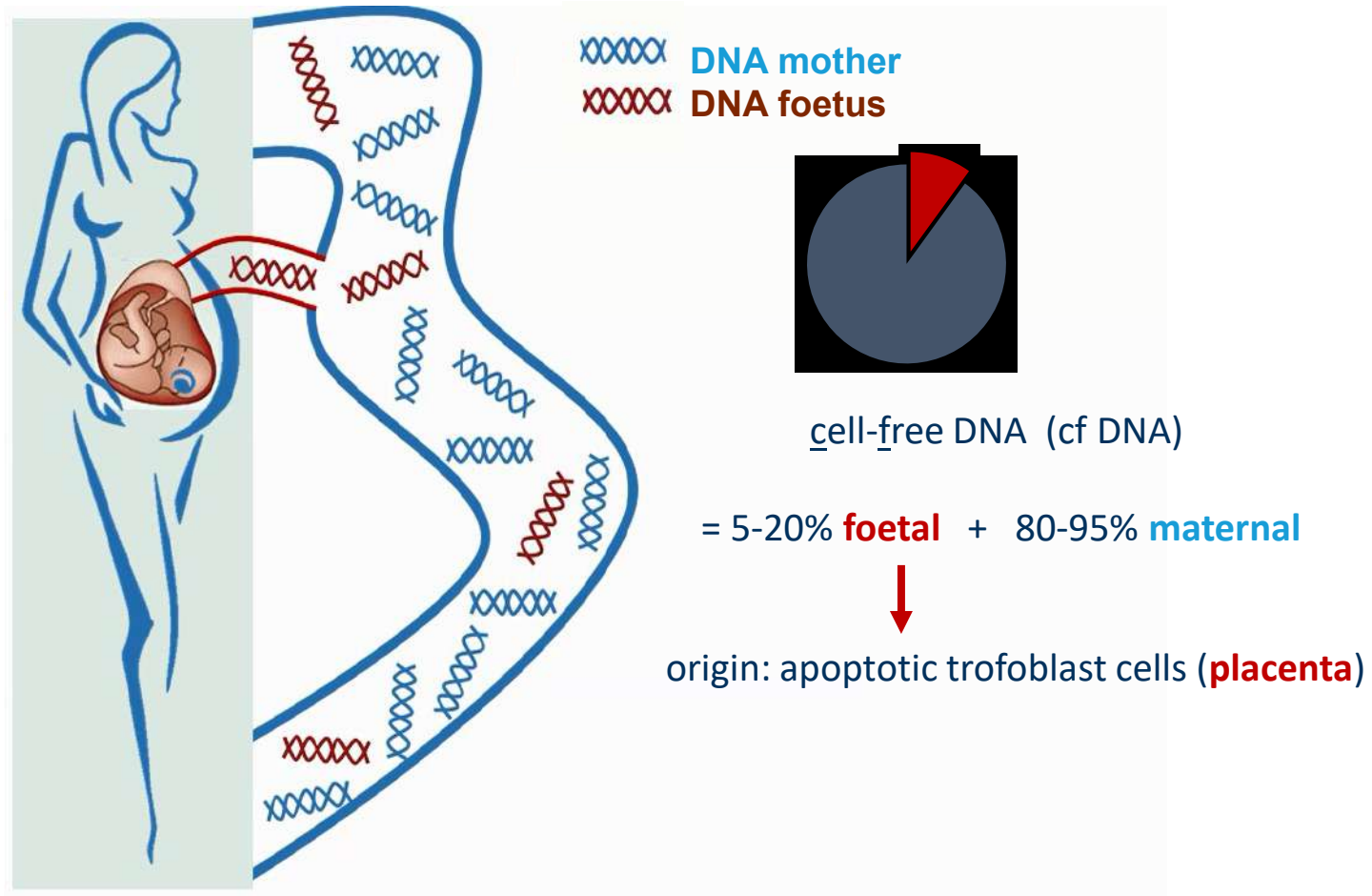
de Haan et al., Lancet Oncol 2018

Every five calendar years:

- 10% more patients treated during pregnancy
 - 31% more patients received chemotherapy during pregnancy
- 4% more live births
- 7% fewer preterm live births
- 9% fewer iatrogenic preterm live births
- 9% fewer NICU admissions
- 16% more SGA



Non-invasive prenatal testing (NIPT)



NIPT: incidental maternal cancer diagnosis

JAMA Oncology

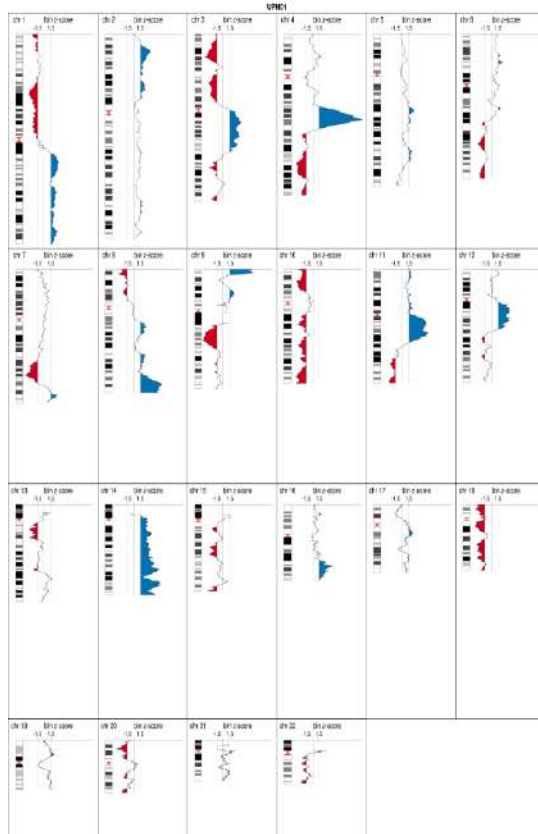
Brief Report

Presymptomatic Identification of Cancers in Pregnant Women During Noninvasive Prenatal Testing

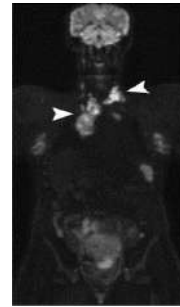
Fridéric Amant, MD, PhD; Magali Verheesche, MD; Iwona Wlodarska, PhD; Luc Dehaese, PhD; Paul Brady, PhD; Nathalie Brisson, PhD; Kris Van Den Bogert, PhD; Daan Dierckx, MD, PhD; Vincent Vandecasteele, MD, PhD; Thomas Tousseyn, MD, PhD; Philippe Moerman, MD, PhD; Adriaan Vanderschuerle, MD; Ignace Vergote, MD, PhD; Patrick Neven, MD, PhD; Patrick Berteloot, MD; Katrien Putseys, MD; Lode Danneels, MD; Peter Vandenbergh, MD, PhD; Eric Legius, MD, PhD; Joris Robert Vermeesch, PhD

♀, 27y, G2P1

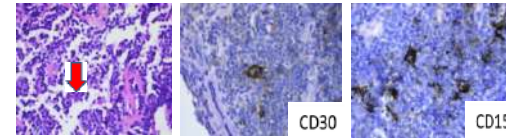
NIPT 12 weeks gestation



MRI Whole Body



Pathology

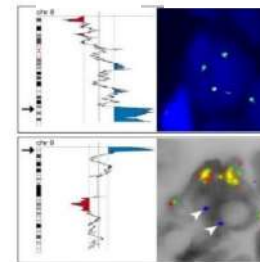


early-stage nodular sclerosing
Hodgkin lymphoma



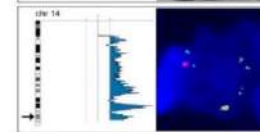
NIPT FISH

MYC
JAK2



3-6 MYC signals
JAK2 highly amplified

IGH



4-5 IGH signals

Pregnancy may mimic cancer symptoms

▪ History: risk assessment

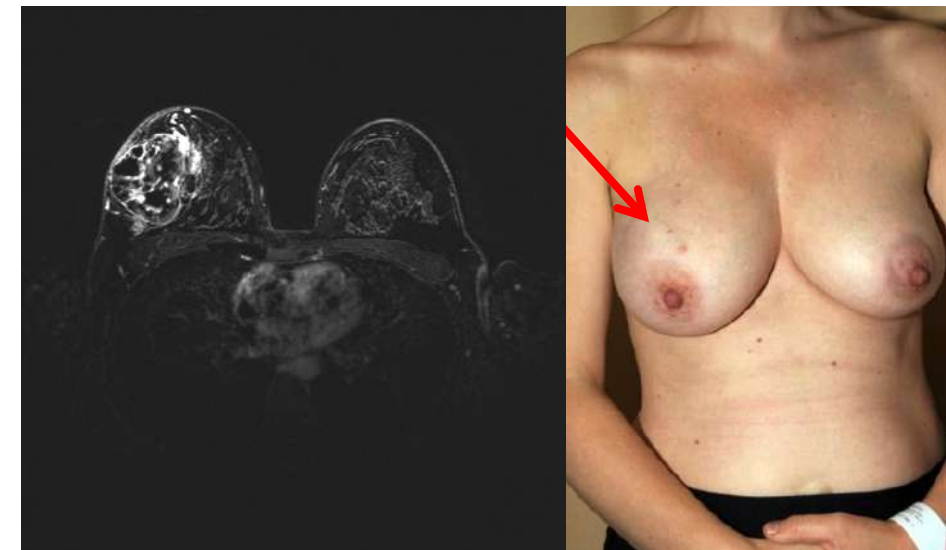
- **BRCA mutation** (2-29% in young women) (Samphao et al, 2009)
- Consider genetic counseling given a young age

▪ Clinical examination

- most often **symptomatic**, usually detected as a **painless, palpable mass**
- more difficult to interpret and diagnosis might be delayed
- **every suspect mass = investigation in detail: core biopsy**

▪ Histopathology

- Comparable to young nonpregnant women (Loibl et al., 2012)
- Mainly IDA, hormone receptor negative, poorly differentiated



Approximate fetal absorbed doses during imaging studies

(Toppenberg, 1999)

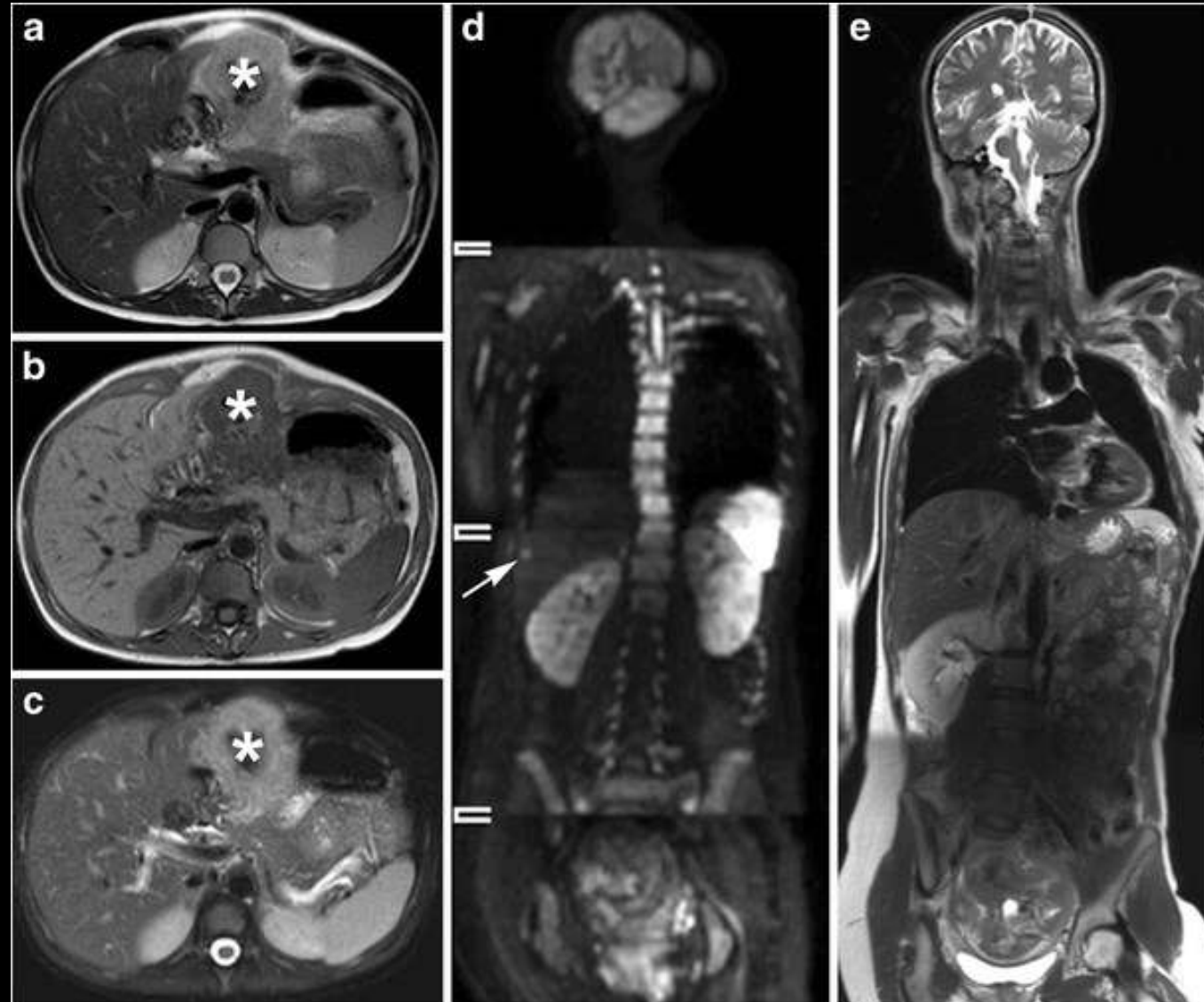
The threshold dose for fetal damage is estimated to vary between 10-20 cGy

Procedure	Fetal dose (cGy)	Procedure	Fetal dose (cGy)
Chest x-ray (PA & lateral)	0.00006	Lumbosacral spine	0.2 – 0.6
Abdominal x-ray	0.15 – 0.26	Mammography	0.01 – 0.04
Pelvic x-ray	0.2 – 0.35	CT thorax	0.01 – 1.3
Intravenous pyelography	0.4 – 0.9	CT abdomen	0.8 – 3
Barium enema	0.3 – 4	CT pelvis	2.5 – 8.9
Dorsal spine	< 0.001	Tc bone scan	0.15 – 0.20
Lumbar spine	0.4 – 0.6		

Sonography and magnetic resonance imaging are considered safe and preferred, especially for the abdomen or pelvis

Whole-body diffusion-weighted MRI (WB-DWI/MRI)

Han et al., Eur Radiol 2018



Sentinel node during pregnancy: fetal safety

➤ **18.5 MBq ^{99m}Tc safe in breast cancer patients**

- Fetal dose < 0.05 mGy (threshold is 100mGy)
- Low dosages
- Capture of ^{99m}Tc in lymph nodes
 - Keleher et al. Breast J 2004
 - Gentilini et al., Ann Oncol 2004

➤ **60-80 MBq safe in vulvar cancer**

- 80 % remains in injection site or lymph nodes
- Distance to fetus at least 10 cm
- Fetal exposure for 100MBq is around 0.1 mGy ie 1000 times lower than threshold of 100mGy
 - Personal communication Ate Van der Zee

➤ **Patent blue is not recommended**

- Anaphylactic reaction during pregnancy is hazardous

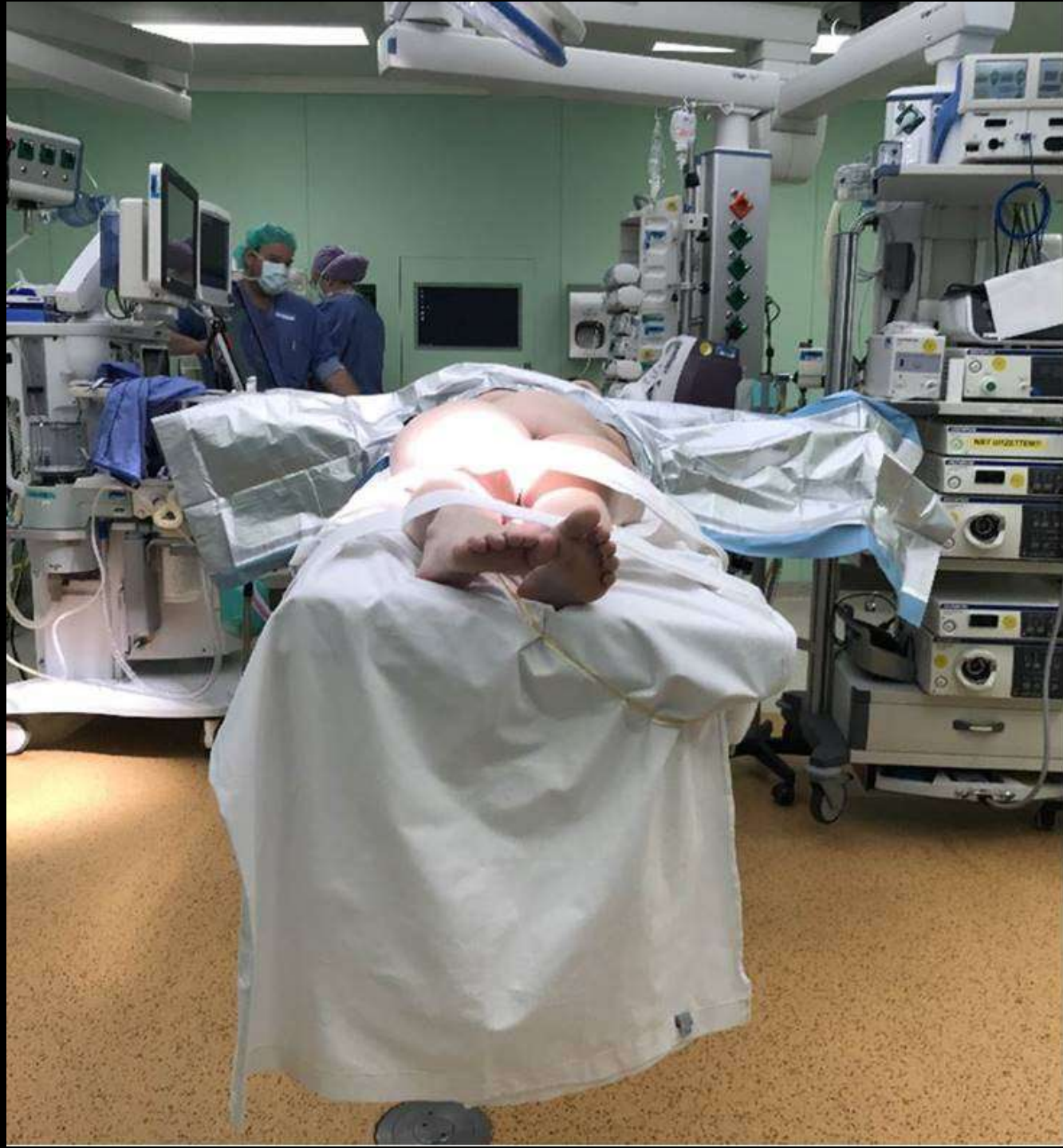
Indocyanine green sentinel node in CxCa

Courtesy Michael Halaska, Prague



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Recommendations for maternal and fetal surveillance when pregnant women are operated

Anaesthesia	Position pregnant patients in left lateral tilt Prevent hypoxia, hypotension and hypoglycemia Adequate postoperative analgesia
Fetal monitoring	Screening ultrasonography before surgery Assessment fetal well-being immediately pre and post-surgery
Uterine monitoring	Pre- and post-surgery
Lung maturation	Dexamethasone or betamethasone 24 hours before interventions between 24-34 weeks
Tocolytic drugs	Case-related: to be discussed with obstetrician Consider when uterine manipulation is expected Should be started in case of preterm labor
Thrombosis prophylaxis	Low molecular weight heparin recommended
Laparoscopy	Open technique Limit pressure (max 15mmHg) and time (< 90min) of pneumoperitoneum

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General Rules for Safe Application of Chemotherapy During Pregnancy

Loibl et al., JAMA Oncol 2015

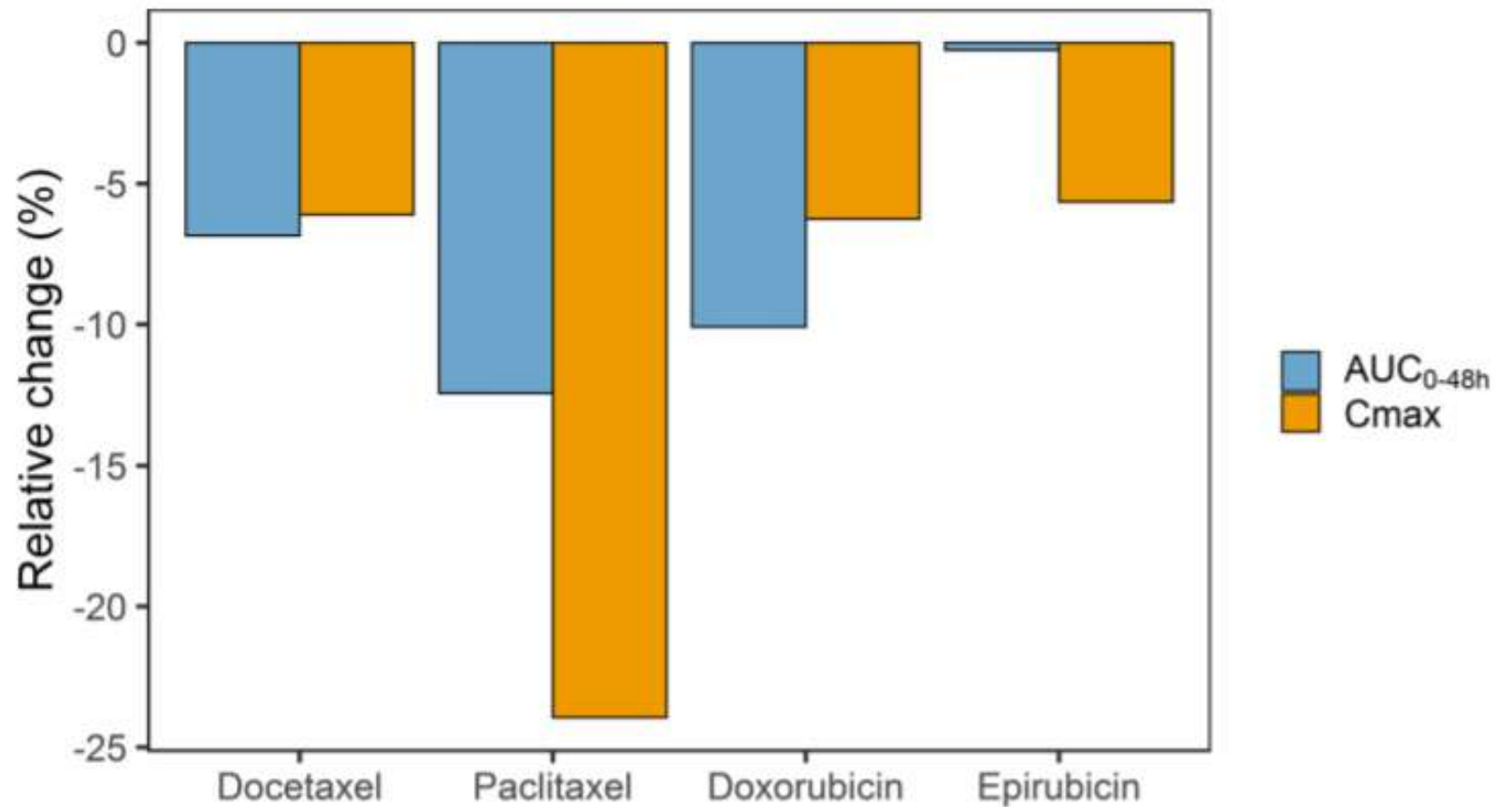
Table 2. General Rules for Safe Application of Chemotherapy During Pregnancy

Rule	Comment
Maintain dose intensity	Important to discuss timing of the chemotherapy start in relation to delivery
Use published standard protocols	Neither decrease nor increase the dose. Do not increase treatment intervals
Dose according to actual body weight	Important to avoid underdosing, which is a risk factor during pregnancy, due to physiologic variation in drug pharmacokinetics. We do not recommend dose adaptation in overweight nonpregnant women
Do not increase the dose	Some data show a lower area under the concentration-time curve and maximum serum concentration in women treated with taxanes during pregnancy vs nonpregnant women. On the basis of 11 cases without outcome data, dose increase cannot be recommended
Recommended to discontinue chemotherapy at approximately week 35 to 37 of gestation	To allow the bone marrow to recover and prevent hematologic toxicity to mother and child

Population Pharmacokinetics of Docetaxel, Paclitaxel, Doxorubicin and Epirubicin in Pregnant Women with Cancer: A Study from the International Network of Cancer, Infertility and Pregnancy (INCIP)

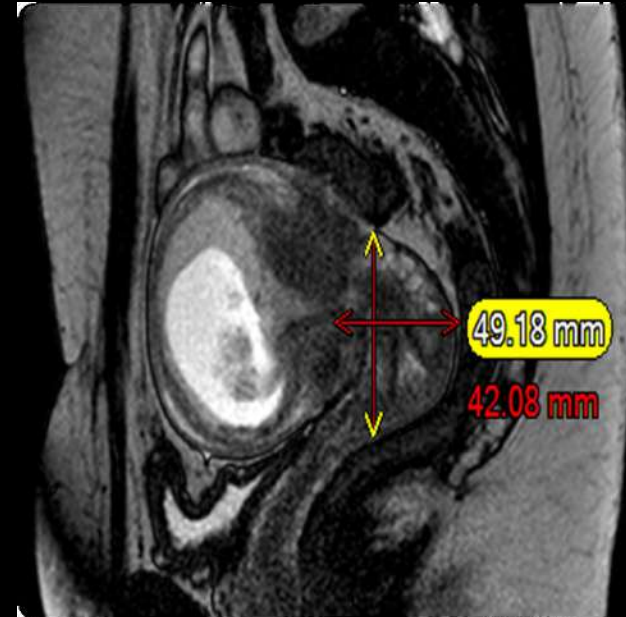
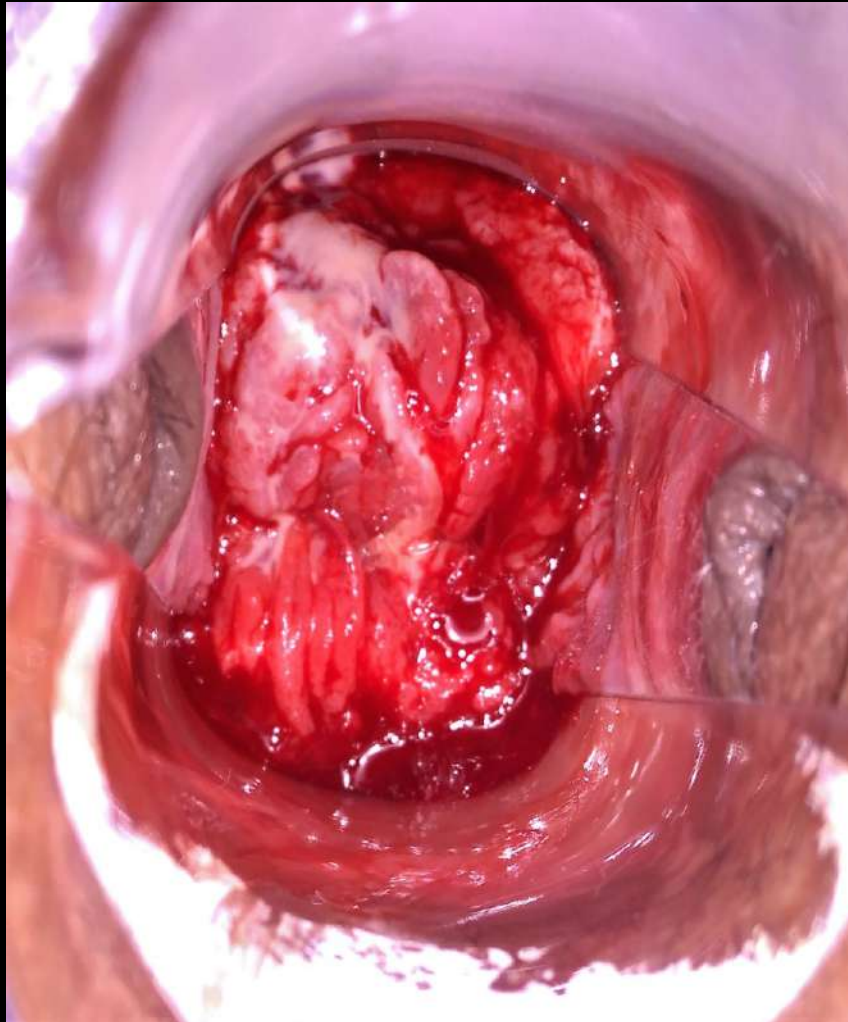
Janssen et al., Clin Pharmacokinetics 2021

Fig. 2 Relative change in AUC_{48} and C_{max} for docetaxel, paclitaxel, doxorubicin and epirubicin in pregnant patients compared with non-pregnant patients using the final pharmacokinetic models ($n = 1000$; relative change (%) = ((pregnant – non-pregnant)/non-pregnant) \times 100%). AUC_{48} area under the plasma concentration-time curve from time zero to 48 h, C_{max} maximum plasma concentration



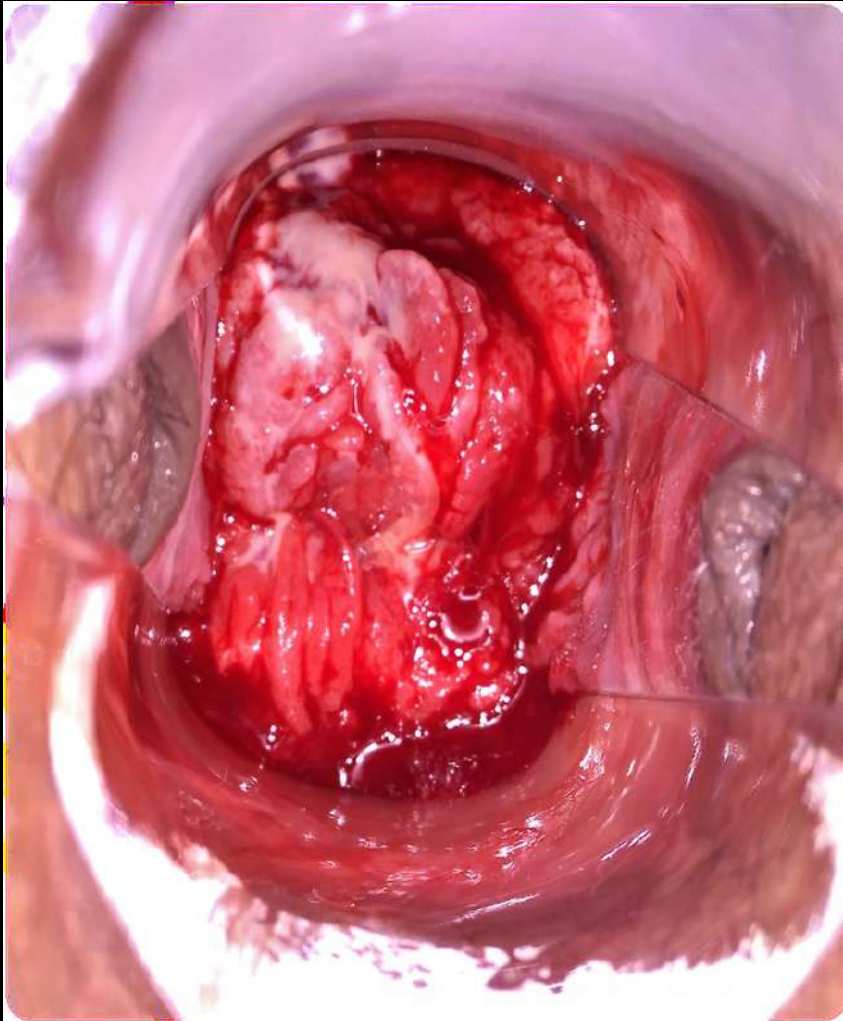
Squamous type stage IIB cervical cancer at 11 weeks GA

Courtesy dr Jorge Hoegl, Venezuela



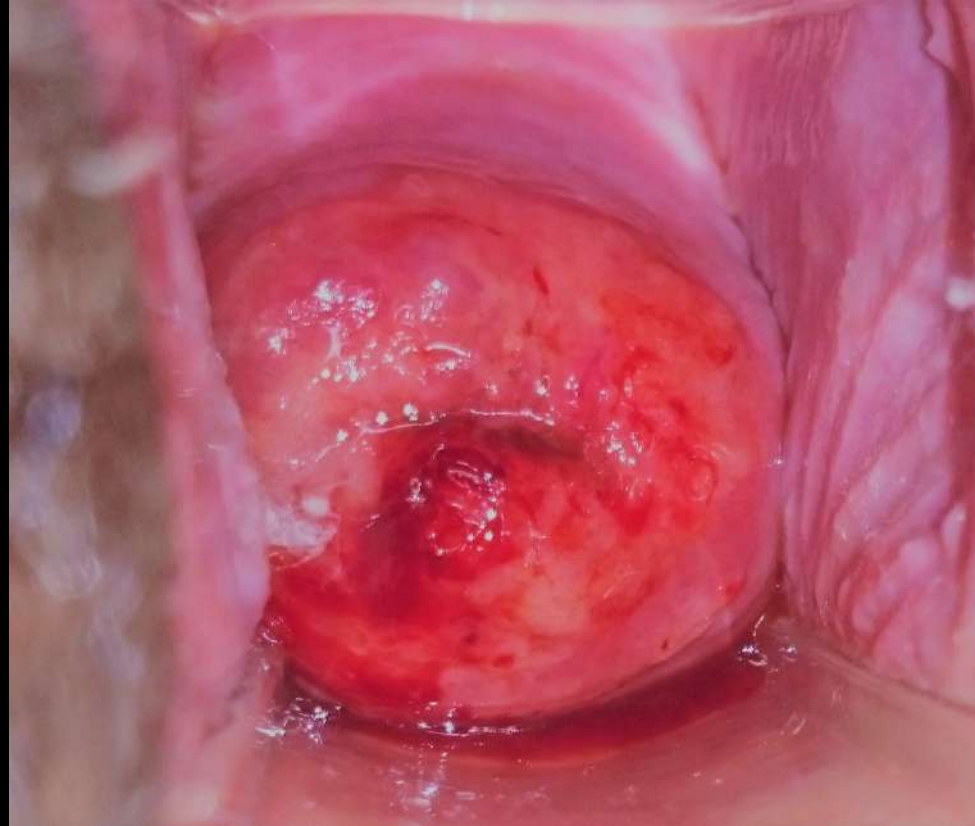
*In speculo comparison before and after 4th cycle (of 6)
paclitaxel-carboplatin*

Courtesy dr Jorge Hoegl, Venezuela



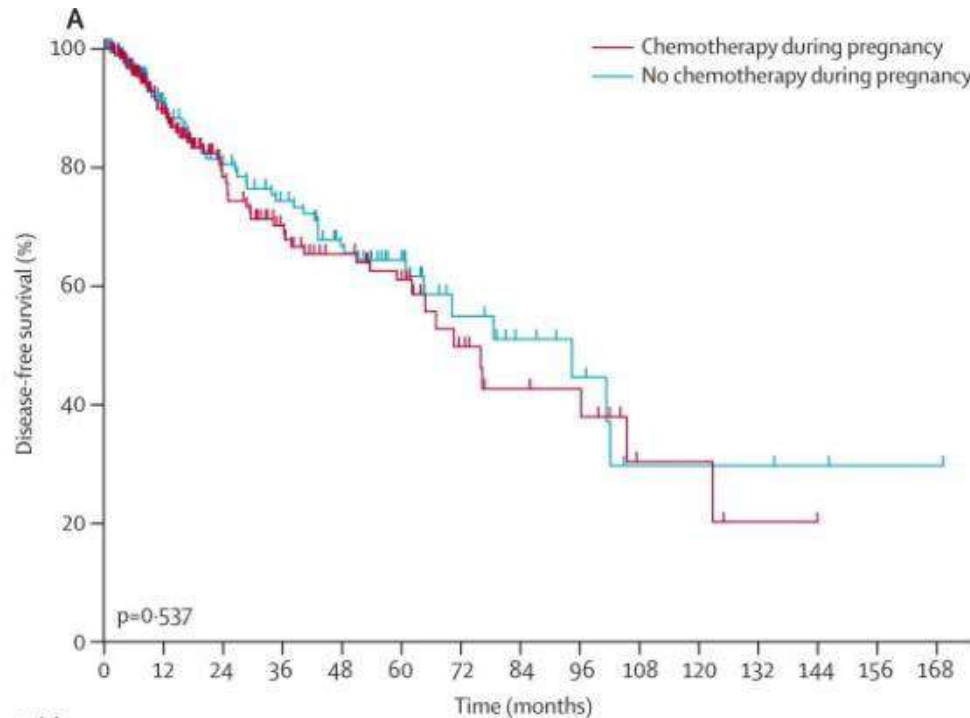
Postdelivery and post radiochemotherapy status

Courtesy dr Jorge Hoegl, Venezuela

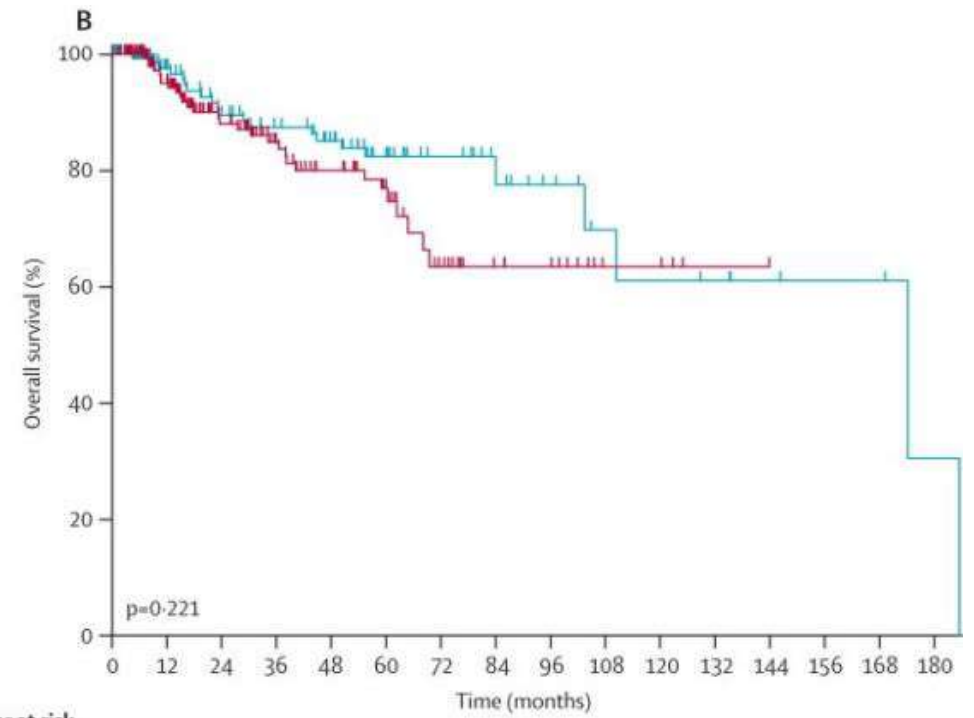


Disease free (A) and overall (B) survival curves for patients with early breast cancer.

Loibl et al., Lancet Oncol 2012



Number at risk	0	12	24	36	48	60	72	84	96	108	120	132	144	156	168
Chemotherapy during pregnancy	197	119	78	60	48	41	16	11	9	3	3	1	0		
No chemotherapy during pregnancy	171	99	82	70	58	48	15	10	7	3	3	3	2	1	1



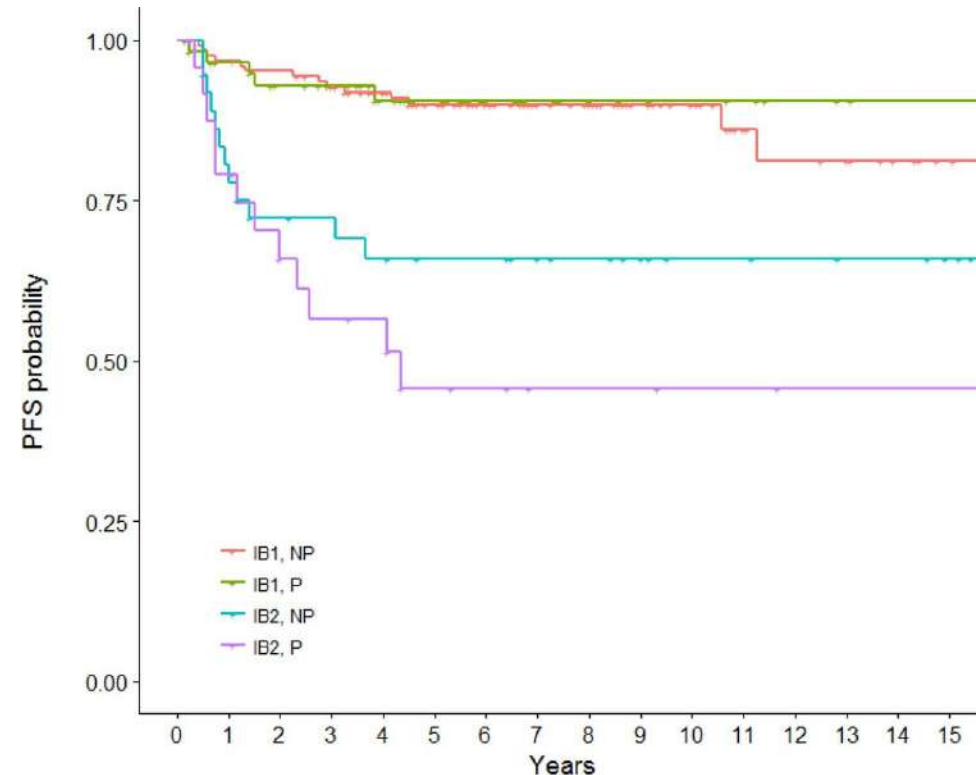
Number at risk	0	12	24	36	48	60	72	84	96	108	120	132	144	156	168	180
Chemotherapy during pregnancy	197	128	90	71	58	50	20	13	11	4	4	1	0			
No chemotherapy during pregnancy	171	105	88	78	69	56	22	17	12	8	7	6	4	3	3	1

Prognosis of cervical cancer in pregnancy

Table 3. Cause-Specific Survival for the Subgroups Not Pregnant, Pregnant, And Lactating When Diagnosed With Cancer (first analysis)

Cancer Site	Cause-Specific Death			
	Crude HR	95% CI	HR	95% CI
All sites				
Not pregnant	1.00 (ref)		1.00 (ref)	
Pregnant	0.79*	0.66 to 0.93	1.03	0.86 to 1.22
Lactating	0.76*	0.64 to 0.90	1.02	0.86 to 1.22
Malignant melanoma				
Not pregnant	1.00 (ref)		1.00 (ref)	
Pregnant	1.23	0.83 to 1.84	1.52*	1.01 to 2.31
Lactating	0.92	0.55 to 1.53	1.10	0.65 to 1.85
Cervical cancer				
Not pregnant	1.00 (ref)		1.00 (ref)	
Pregnant	0.86	0.51 to 1.46	0.89	0.52 to 1.53
Lactating	0.61	0.37 to 1.02	0.94	0.56 to 1.57
Breast cancer				
Not pregnant	1.00 (ref)		1.00 (ref)	
Pregnant	1.77*	1.20 to 2.60	1.23	0.83 to 1.81
Lactating	3.44*	2.40 to 4.92	1.95*	1.36 to 2.78
Lymphoma and leukemia				
Not pregnant	1.00 (ref)		1.00 (ref)	
Pregnant	1.09	0.74 to 1.61	1.15	0.77 to 1.70
Lactating	0.72	0.44 to 1.18	0.89	0.54 to 1.46
Thyroid cancer				
Not pregnant	1.00 (ref)		1.00 (ref)	
Pregnant	1.34	0.18 to 9.71	4.58	0.59 to 35.87
Lactating	0.00	0.00 to ∞	0.00	0.00 to ∞
Ovarian cancer				
Not pregnant	1.00 (ref)		1.00 (ref)	
Pregnant	0.17*	0.06 to 0.46	0.46	0.17 to 1.23
Lactating	0.93	0.44 to 1.95	2.23	1.05 to 4.73

NOTE. Univariate analyses are presented as crude HR. Multivariate analyses (right column) are adjusted for age, diagnostic period and initial extent of disease. Abbreviations: HR, hazard ratio; ref, reference. *Indicates significant HRs; $P < .05$.



Number at risk

	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
IB1, NP	126	121	118	111	103	86	75	61	53	40	31	20	16	15	11	6
IB1, P	60	54	49	45	37	31	22	18	16	14	11	10	8	7	6	6
IB2, NP	37	29	24	23	21	19	19	17	15	13	9	9	8	7	7	5
IB2, P	25	19	16	12	11	7	6	4	4	4	3	3	2	2	2	2

Michael J Halaska et al. Int J Gynecol Cancer 2019

Stensheim H et al., JCO 2015



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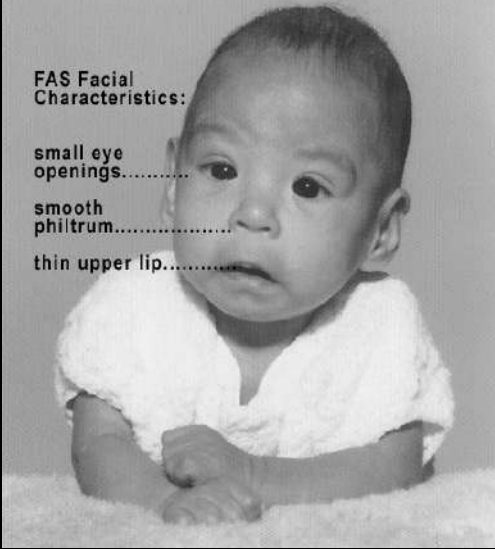
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Baby with Fetal Alcohol Syndrome

FAS Facial Characteristics:

- small eye openings.....
- smooth philtrum.....
- thin upper lip.....



W A R N I N G
FROM THE LIQUOR CONTROL BOARD



Avoid alcohol during pregnancy.

Alcohol use during pregnancy may cause birth defects such as Fetal Alcohol Syndrome.

For more information about FAS please visit March of Dimes at www.marchofdimes.com

To re-order this sign, please call your local Liquor Control Board Office.

Washington State Liquor Control Board #AP-4 509





After first trimester no more or other congenital malformations

Van Calsteren et al, J Clin Oncol 2010

Congenital malformations (n = 13/175: 7.4%; 2.9% major and 4.6% minor)




Treatment during pregnancy	Malformation	n	(%)
None	<ul style="list-style-type: none"> Prader-Willi Congenital laryngomalacie Hemangioma 	3/58	(5.2)
Surgery	<ul style="list-style-type: none"> Cardial hamartomas in tuberous sclerosis Multiple congenital anomalies (ao hypospadias, left pink missing, abnl position left foot) Hemangioma 	3/46	(6.5)
Chemotherapy	<ul style="list-style-type: none"> Hip subluxation Pectus excavatum Hemangioma 	3/33	(9.1)
Chemo + RT	<ul style="list-style-type: none"> Bilateral partial syndactily digiti II-III 	1/1	(100)
Surgery +Chemo	<ul style="list-style-type: none"> Bilateral small protuberance on phalanx-5 Rectal atresia 	2/25	(8.0)
Surgery + Chemo + RT	<ul style="list-style-type: none"> Doubled cartilage ring in both ears 	1/3	(33.3)
RT, Surgery + RT, Other (hormonal, IFN, antibody)		0/2, 0/2, 0/5	(0.0)

ORIGINAL ARTICLE

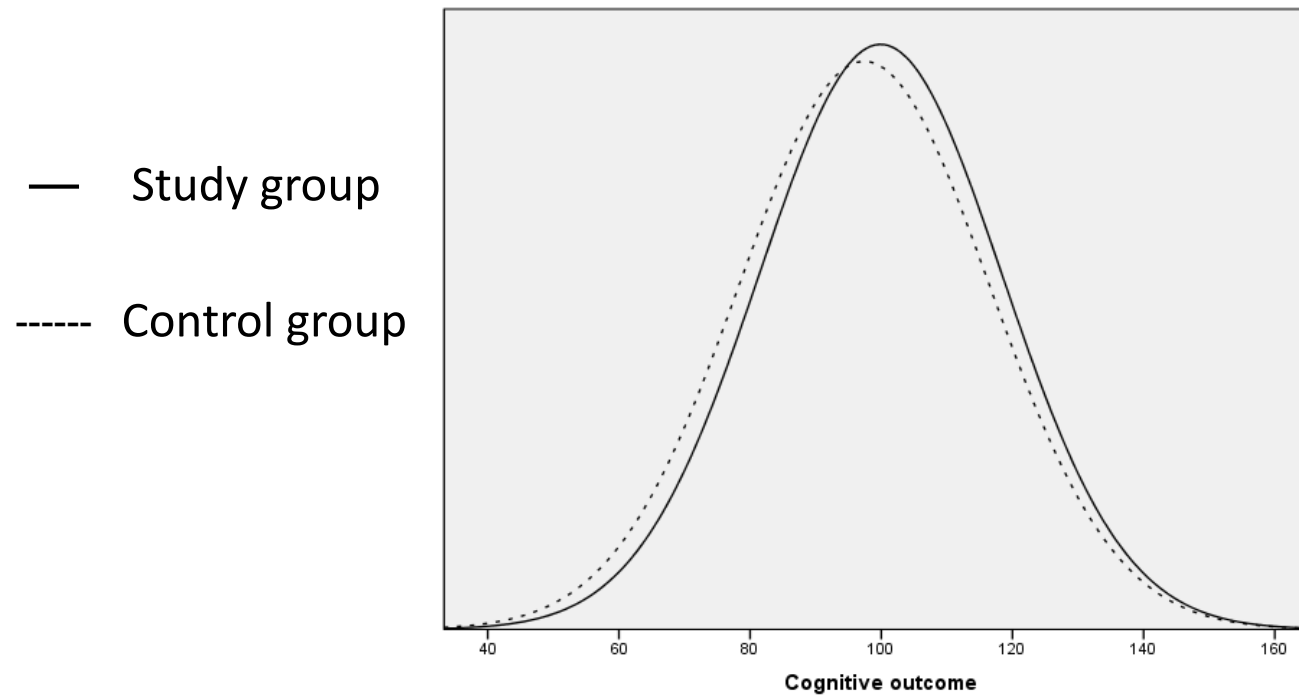
Pediatric Outcome after Maternal Cancer Diagnosed during Pregnancy

F. Amant, T. Vandenbroucke, M. Verheecke, M. Fumagalli, M.J. Halaska, I. Boere, S. Han, M.M. Gziri, F. Peccatori, L. Rob, C. Lok, P. Witteveen, J.-U. Voigt, G. Naulaers, L. Vallaey, F. Van den Heuvel, L. Lagae, L. Mertens, L. Claes, and K. Van Calsteren, for the International Network on Cancer, Infertility, and Pregnancy (INCIP)

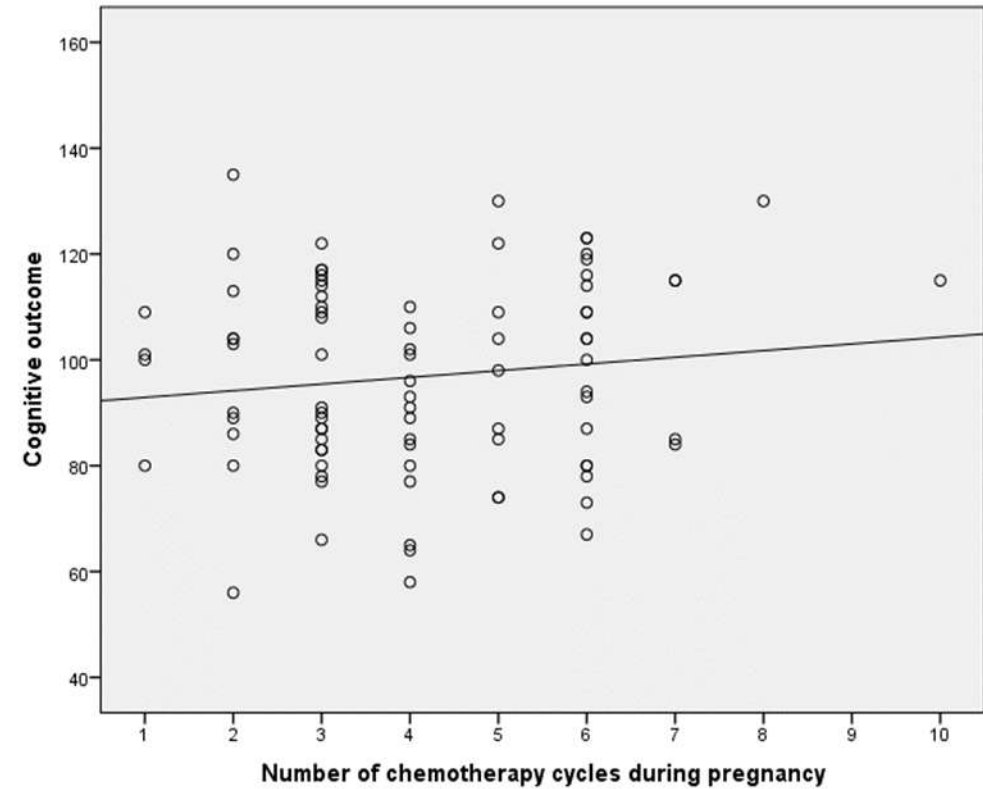
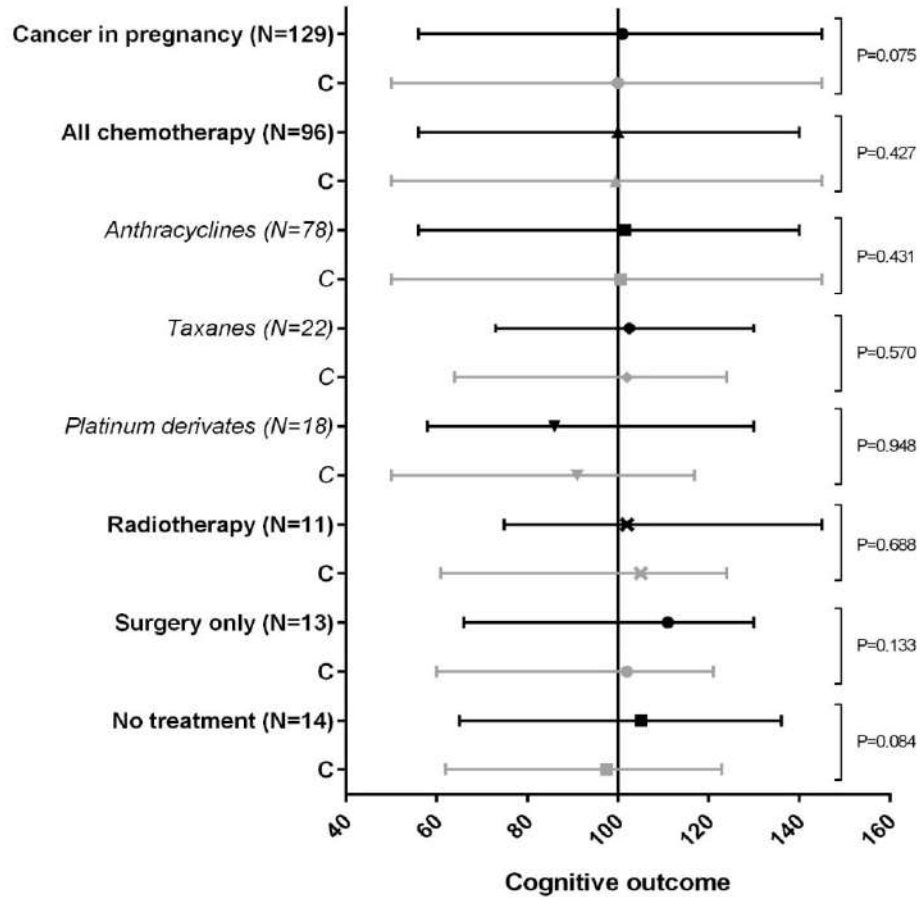
Methods

General Health	Cognitive outcome	Heart morphology and functions
General pediatric and clinical neurological examination	Bayley Scales of Infant Development – second / third edition	Echocardiography
General health questionnaire		Electrocardiography
		

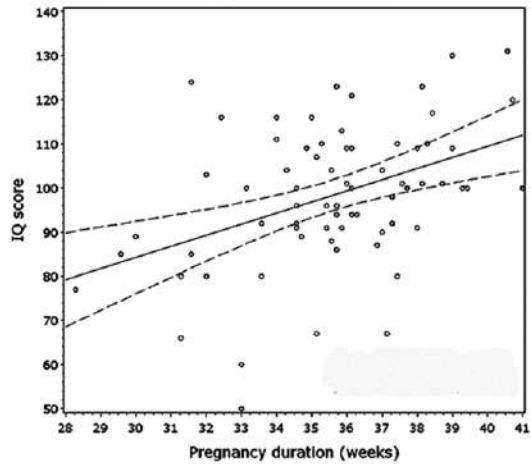
Cognitive outcome



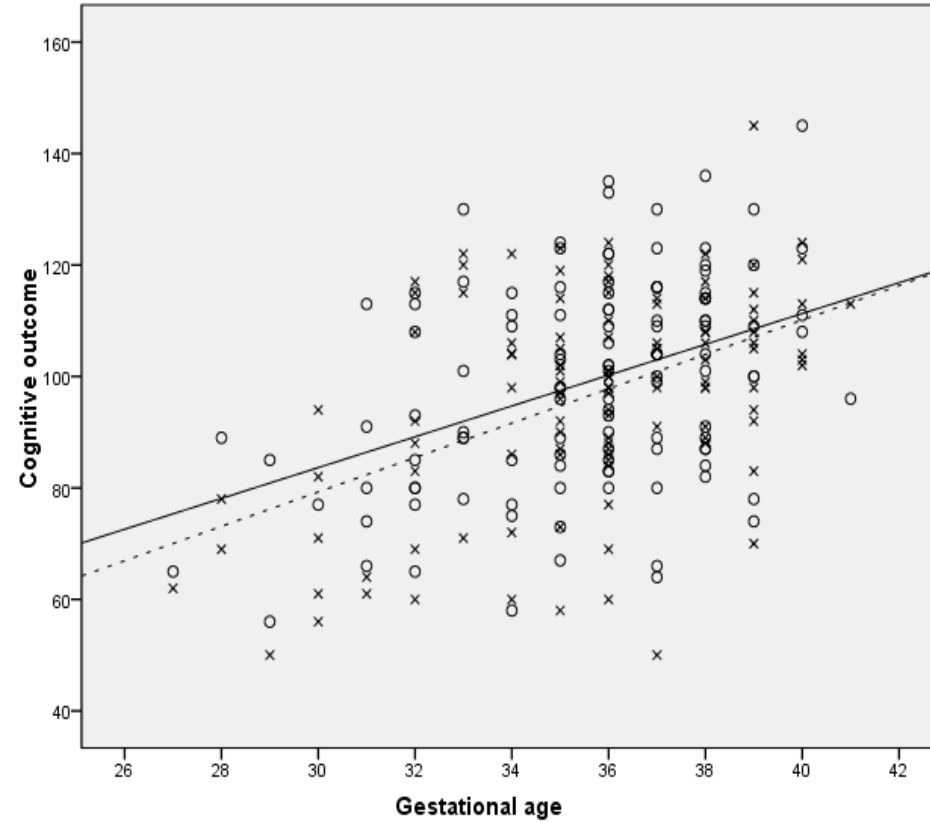
Cognitive outcome per treatment and number of chemo cycles



Cognitive outcome and prematurity



○ Study group
—
X Control group
- - -



Cisplatin-induced hearing loss

Geijteman E et al., Obstet Gynecol 2014

- Single case report
- Cervical cancer, diagnosed at 26w5d GA
- 5 cycles of 70mg/m² **cisplatin** during pregnancy
- Cesarean section at 34w4d GA
- Boy with severe bilateral perceptive hearing loss
 - After birth: hearing loss of 30dB on the right and 60dB on the left

Child development at 6 years after maternal cancer diagnosis and treatment during pregnancy

Vandenbroucke et al, Eur J Ca, 2020

- **132 study children matched with 132 controls**
- **97 children exposed to chemotherapy and stress, imaging studies, supportive drugs**

BARCELONA
2019 **ESMO** congress

Organised by:

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BETTER MEDICINE
BEST PRACTICE

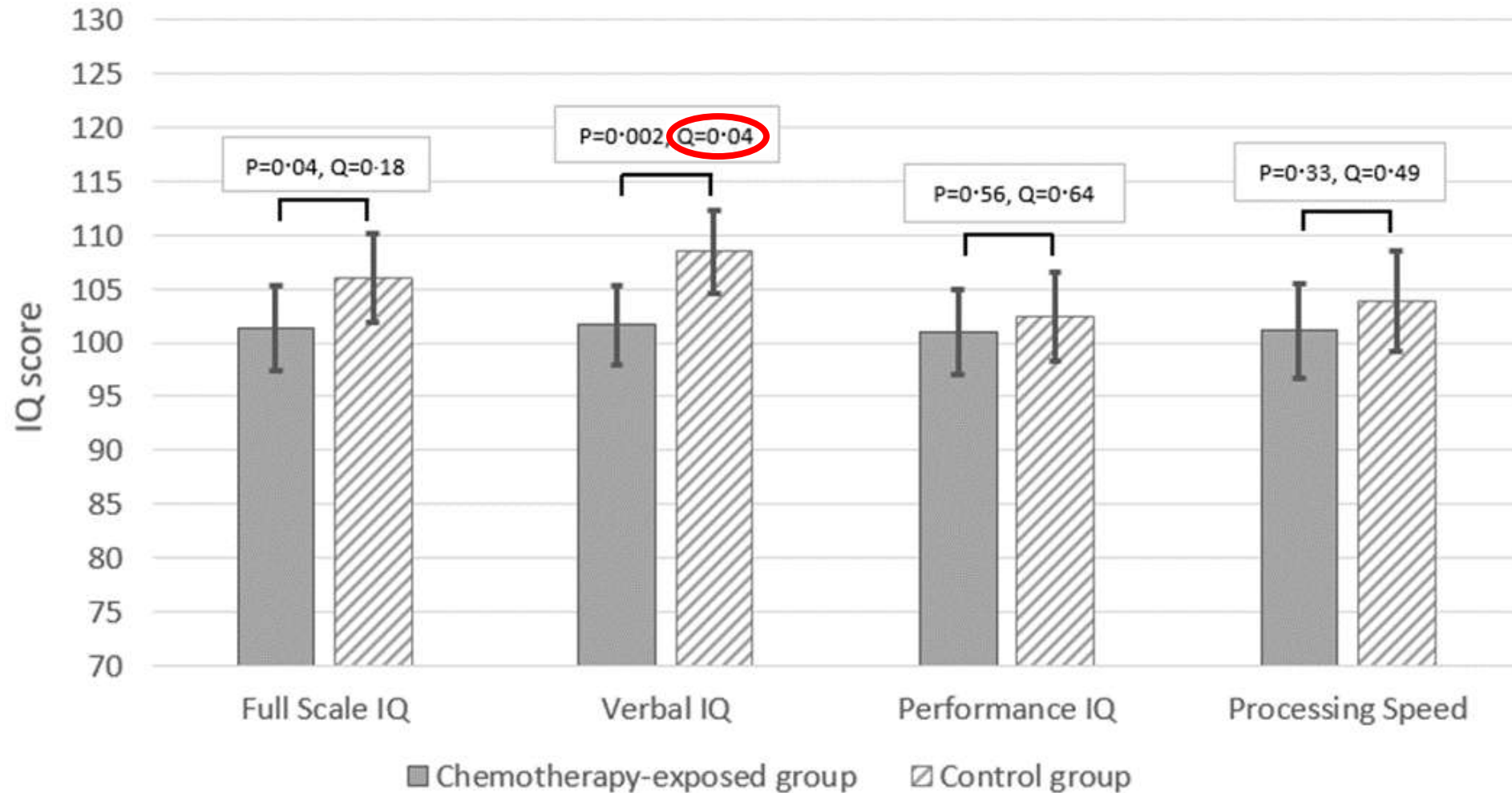
In partnership with:

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European Association
for Cancer Research

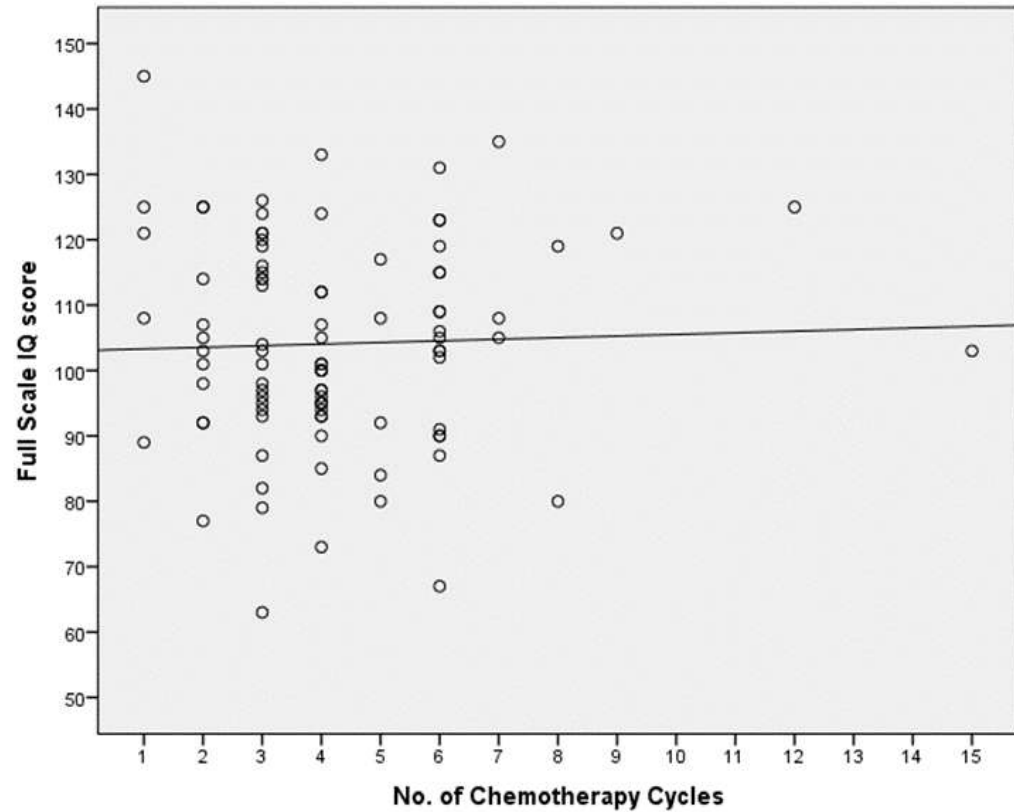
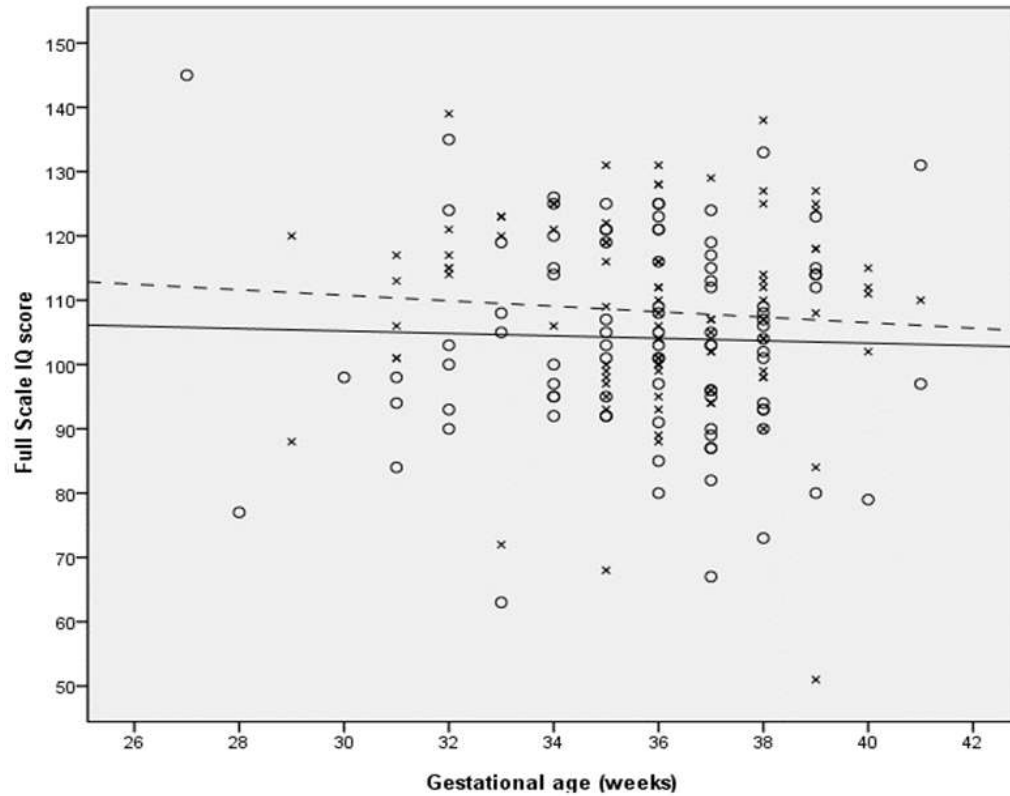
27 SEPT – 1 OCT 2019

Barcelona, Spain

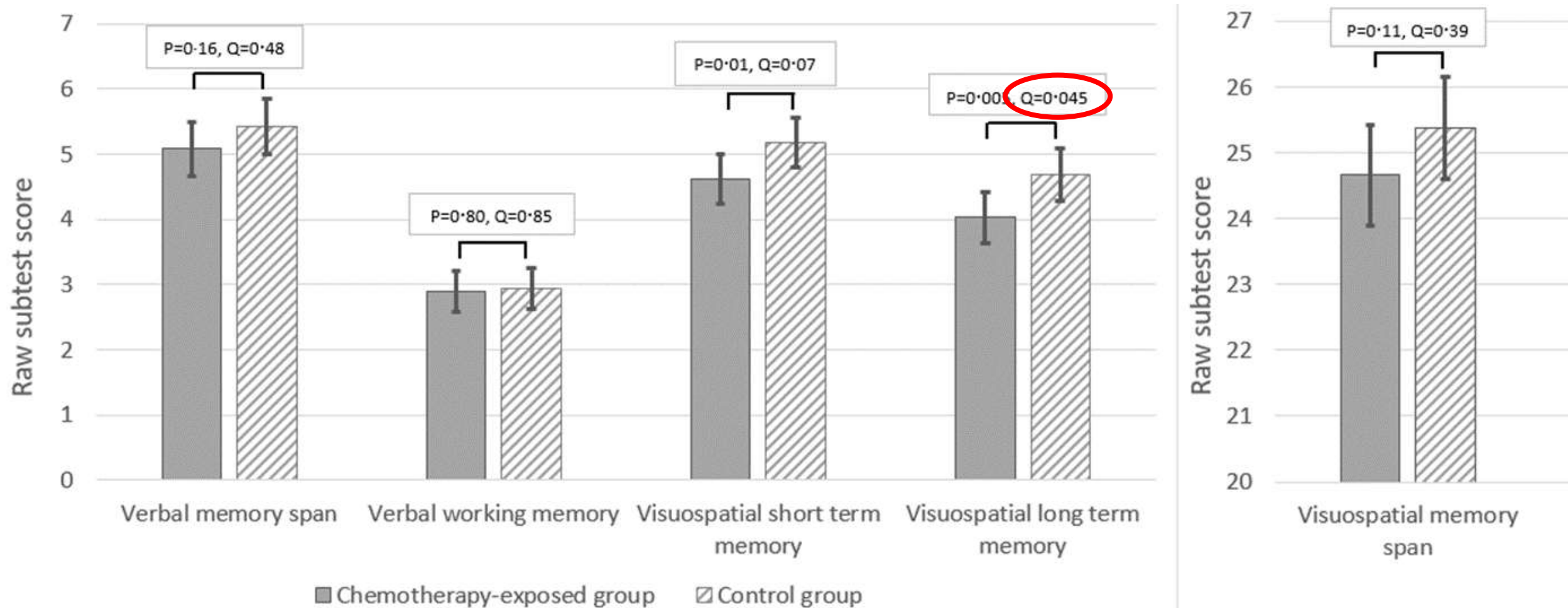
Cognitive outcome: Comparison of the mean Full Scale IQ, Verbal IQ, Performance IQ and Processing Speed



No relation between Full Scale IQ and gestational age at birth (in weeks) and number of chemo cycles



Comparison of the raw memory scores from the subtests of the Children's Memory Scale between the chemotherapy-exposed group and the control group



Child development at 6 years after maternal cancer diagnosis and treatment during pregnancy : summary

- Significant differences:
 - Although within normal ranges, the mean **Verbal IQ score** was lower(6 points)
 - 15 IQ points when mother died.....
 - Lower score for **visuospatial long-term memory**
- No significant differences:
 - Full Scale IQ
 - Performance IQ
 - Processing Speed
 - Memory span, short-term memory
 - Attention and behaviour problems
 - Cardiac dimensions and left ventricular function
- 3 times more likely to wear glasses

Recommendation

Special attention for the evaluation and additional **stimulation of early language development** in these children may be advised to prevent delay in language development and verbal intelligence.



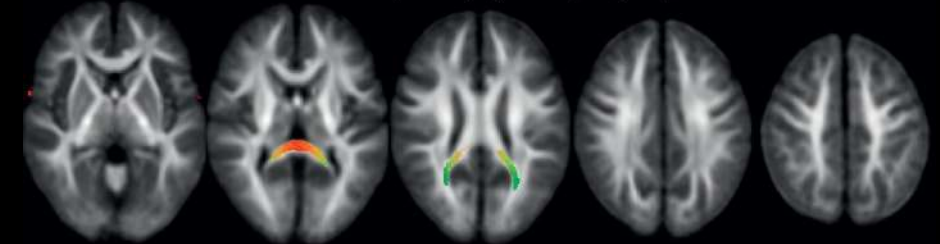
The impact of cancer and chemotherapy during pregnancy on child neurodevelopment: A multimodal neuroimaging analysis

J. Blommaert, A. Radwan, C. Sleurs, C. Maggen, M. van Gerwen, V. Wolters, D. Christiaens, R. Peeters, P. Dupont, S. Sunaert, K. Van Calsteren, S. Deprez, F. Amant

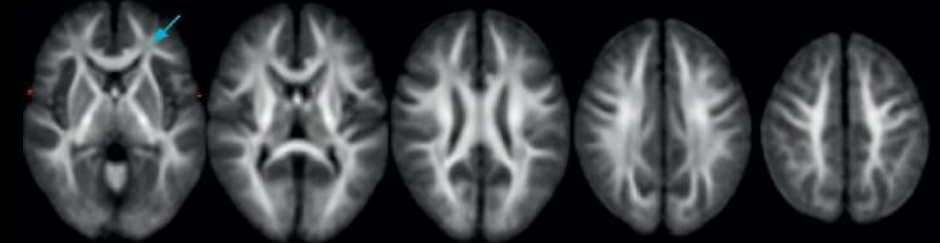
EClinicalMedicine
Volume 28 (November 2020)

Local structural white matter and grey matter differences, but no whole-brain or functional differences

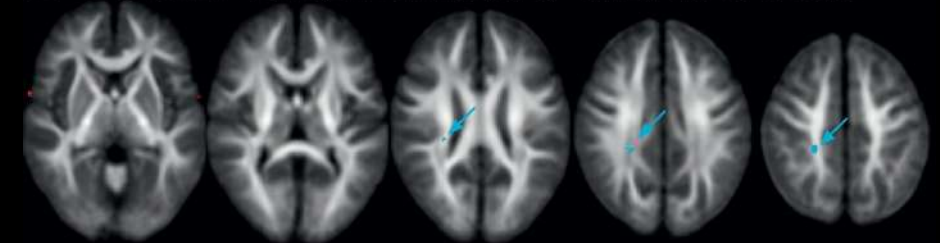
A: Lower FDC in children born to cancer-complicated pregnancies (n=42) compared to matched controls.



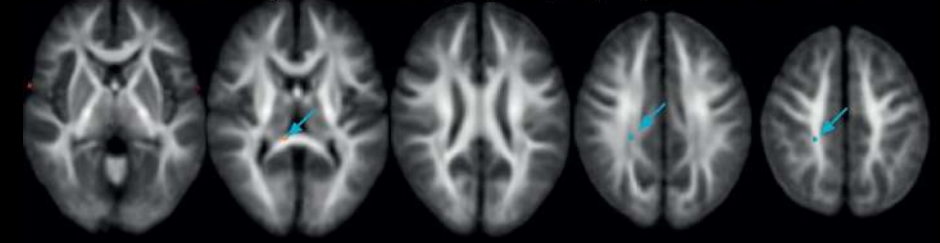
B: Higher FCS in children born to cancer-complicated pregnancies (n=42) compared to matched controls.



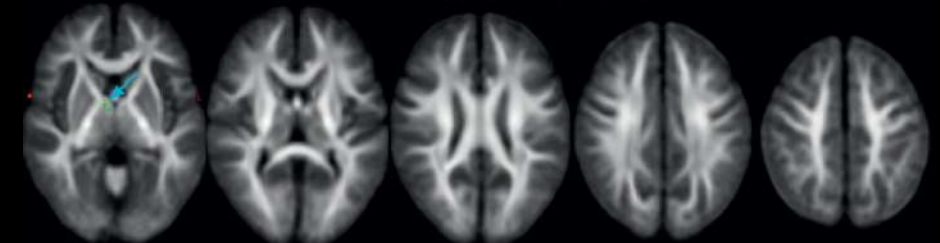
C: Lower FCS in children with prenatal chemotherapy exposure (n=30) compared to matched controls.



D: Lower FDC in children with prenatal chemotherapy exposure (n=30) compared to matched controls.



E: Higher FDC in children with prenatal chemotherapy exposure (n=30) compared to matched controls.





Gynaecological cancer during pregnancy, with an emphasis on chemotherapy: agenda

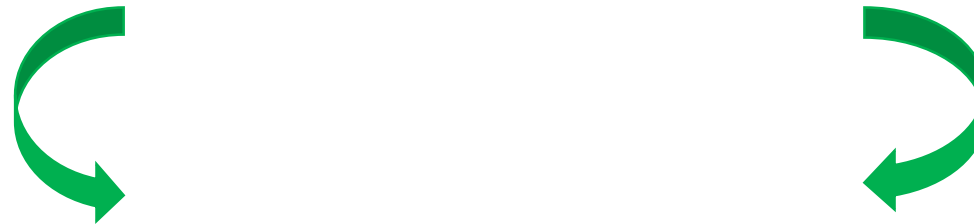
- ***Case study***
- ***Epidemiology, diagnosis and staging***
- ***Surgery***
- ***Radiotherapy***
- ***Chemotherapy***
- ***Long term pediatric outcomes***
- ***Multidisciplinary setting including obstetrical high care units***

Oncological management and obstetric and neonatal outcomes for women diagnosed with cancer during pregnancy: a 20-year international cohort study of 1170 patients



Jorine de Haan, Magali Verheecke*, Kristel Van Calsteren, Ben Van Calster, Roman G Shmakov, Mina Mhallem Gziri, Michael J Halaska, Robert Fruscio, Christianne A R Lok, Ingrid A Boere, Paolo Zola, Petronella B Ottevanger, Christianne J M de Groot, Fedro A Peccatori, Karina Dahl Steffensen, Elyce H Cardonick, Evgeniya Polushkina, Lukas Rob, Lorenzo Ceppi, Gennady T Sukhikh, Sileny N Han, Frédéric Amant, for the International Network on Cancer, Infertility and Pregnancy (INICIP)*

- 1. Less terminations**
- 2. More cancer treatment (especially chemotherapy)**
- 3. Less prematurity**



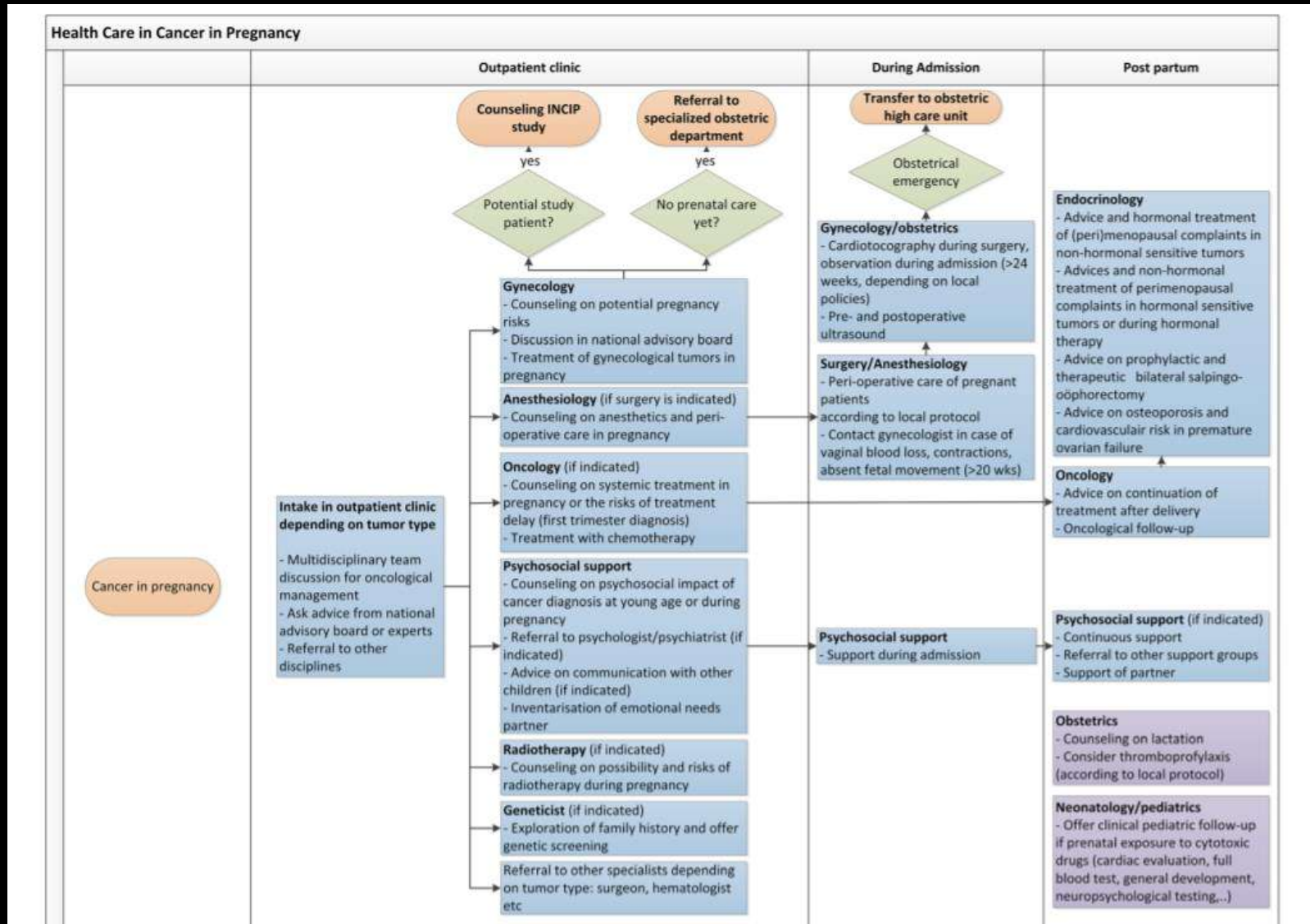
Small for Gestational Age (SGA) babies and Neonatal Intensive Care Unit (NICU) admission



Obstetrical high care units when antenatal chemotherapy

Pregnancy and Cancer: the INCIP Project

Maggen C et al., Curr Oncol Rep, 2020



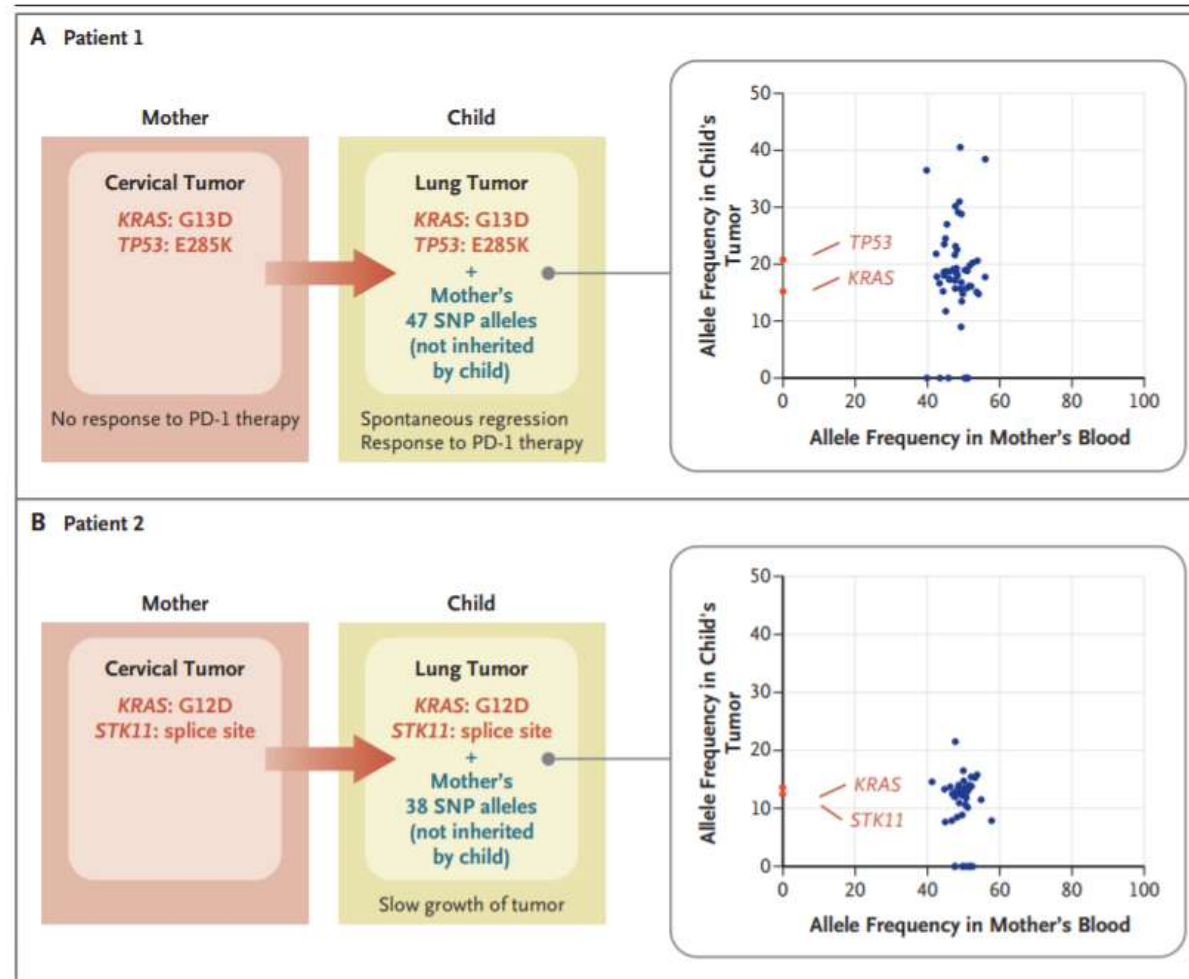
Episiotomy site recurrence after vaginal delivery (n=13)

Van Calsteren et al., Best Pract Res Clin Obstet Gynaecol 2005;19:611-30

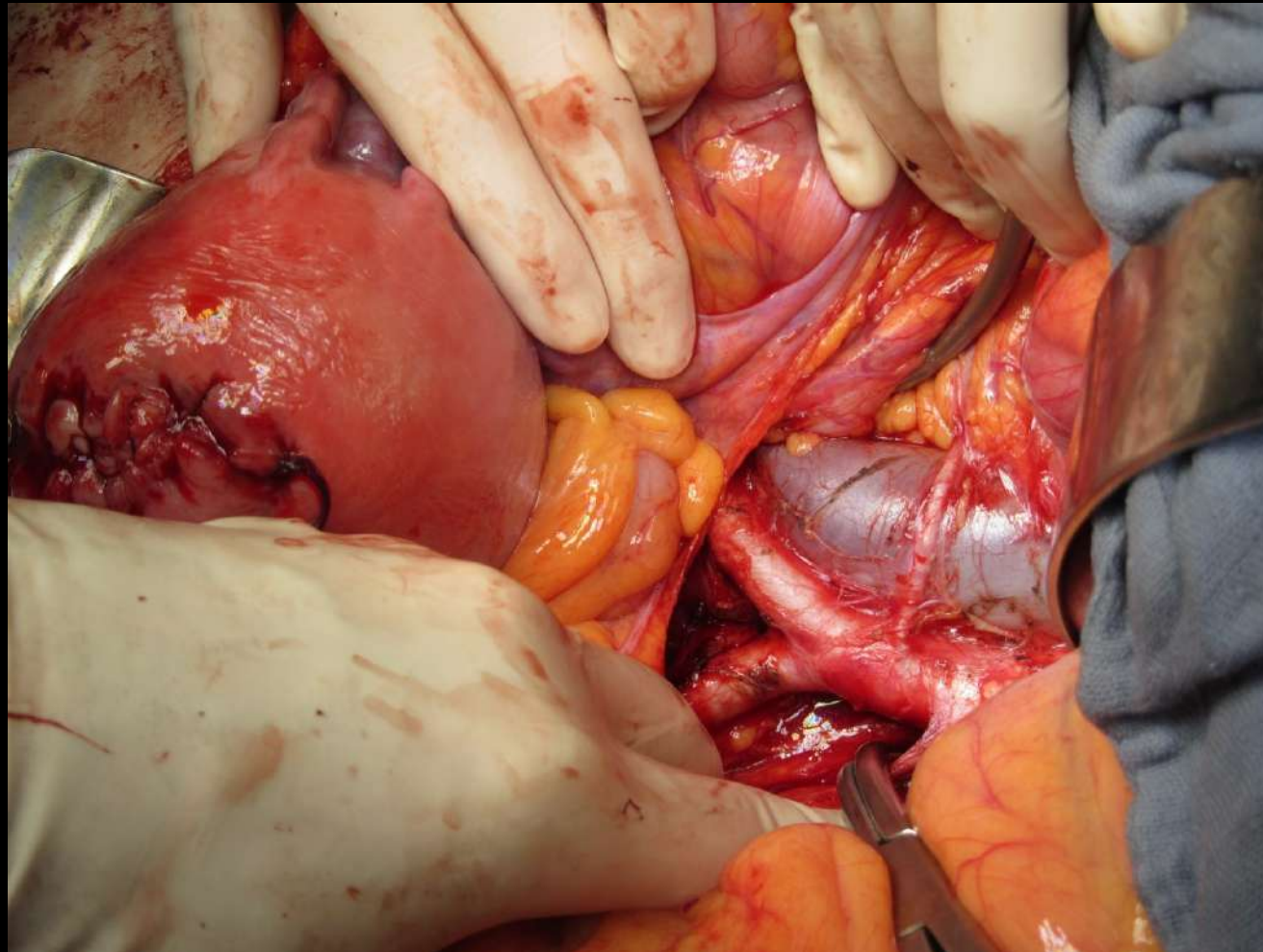
Author	Histology	Stage	DFS (mts)	R/ recurrence	FU (mts)	Survival
Burgess & Waymont, 1987	Sq	IB	17	Exenteration		
Copeland, 1987	Adeno	IB	3	Surg, RT	>60	NED
	Adeno	IB	5	Surg, RT	10	NED
Gordon, 1989	Sq	IB	1	Surg, RT	42	NED
Van Dam, 1992	Sq	IIIA		Chemo		
Khalil, 1993	Adeno	IB	3	Surg, RT	>120	NED
Cliby, 1994	Sq	IIIB	3	Chemo, RT	4	DOD
	Sq	IB	2	Chemo	6	DOD
	Sq	IB	24	Chemo, surg, RT	12	NED
	Sq	IB	3	RT, exent	42	DOD
	Sq	IB	1	Surg, RT	6	DOD
Vandenbroek, 1995	Adeno	IA1	1.5	Surg	12	DOD
Goldman & Goldberg, 2003	Sq	IB	66	Surg, RT	>54	NED

Vaginal Transmission of Cancer from Mothers with Cervical Cancer to Infants

Arakawa et al NEJM 2021



Surgical staging in node positive disease after chemotherapy and after C/section



INCIP members

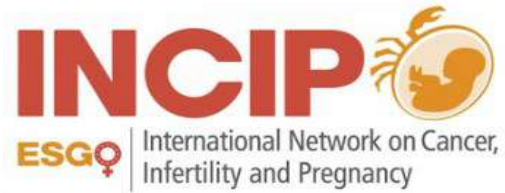
Our international network counts 125 members in 36 countries.



Europe					Other continents		
Austria: 5	Belgium: 8	Czech Republic: 2	Denmark: 3	Finland: 1	Australia: 1	Canada: 2	Chile: 1
France: 3	Germany: 10	Greece: 7	Hungary: 1	Ireland: 1	Israel: 4	Kazakhstan: 1	Mexico: 1
Italy: 10	Lithuania: 2	Norway: 3	Poland: 6	Portugal: 3	Qatar: 1	Russia: 4	China: 1
Romania: 1	Serbia: 2	Slovenia: 1	Spain: 5	Sweden: 2	Tunisia: 1	Turkey: 2	United States: 4

Take home message

- *Chemotherapy during pregnancy is possible*
- *Cervical cancer is most challenging*
- *Interdisciplinary approach in referral centers*



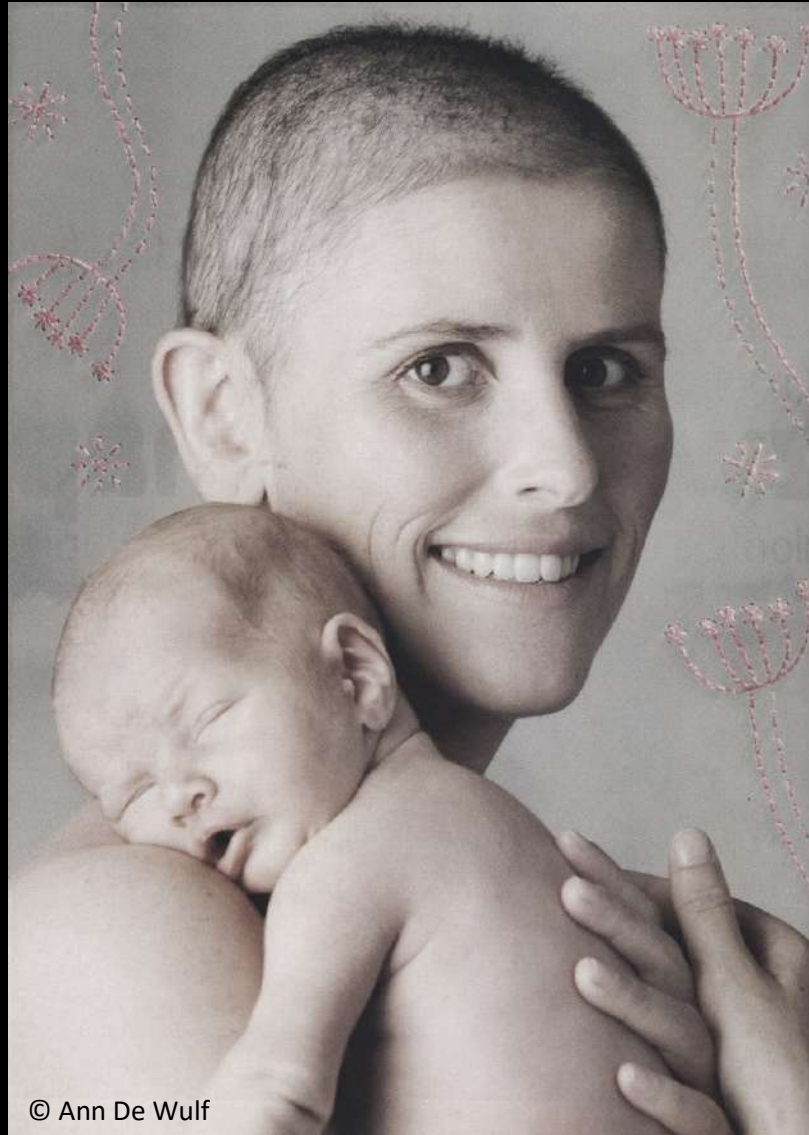
European Research Council



Onderzoek naar
Kanker en
Zwangerschap

KU LEUVEN





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