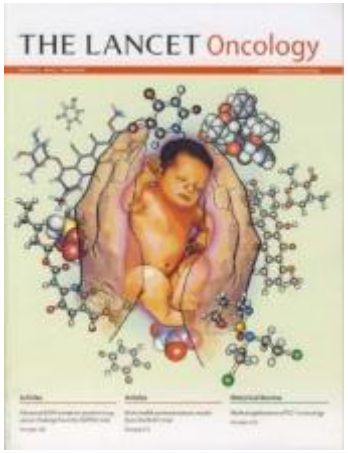


Breast cancer and pregnancy

3rd ICBDC Paris 7th february 2013

Frederic Amant MD PhD – Gynaecologische Oncologie - UZ Gasthuisberg, Leuven

UZ Leuven | Herestraat 49 B - 3000 Leuven | www.uzleuven.be tel. +32 16 33 22 11 | UNIVERSITY HOSPITALS LEUVEN

Great and sacred are the thoughtful deliberations required to preserve the lives and health of creatures

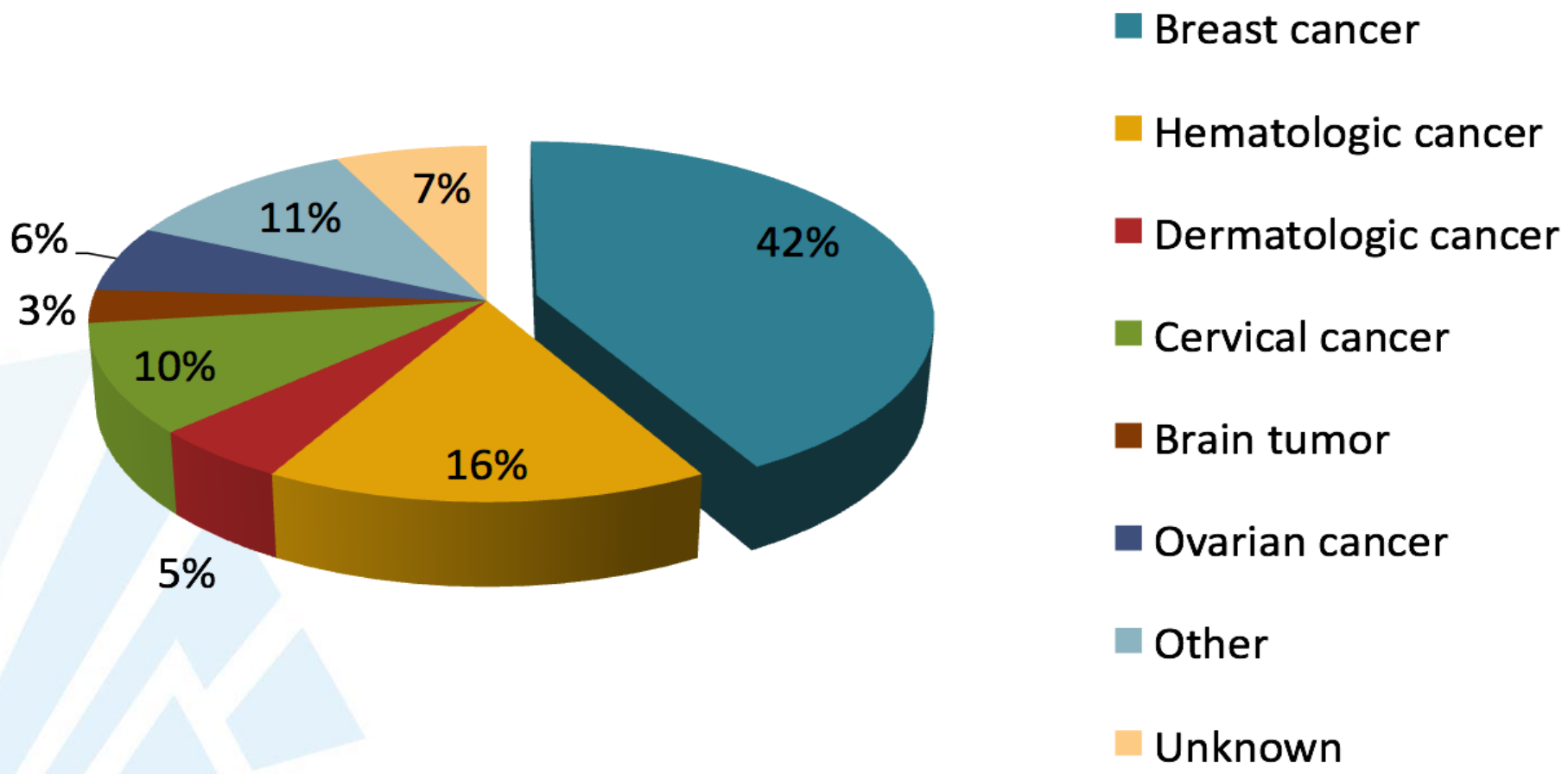
MAIMONIDES, 12TH-CENTURY PHYSICIAN

Breast cancer in pregnancy

- Introduction
- Surgery
- Radiotherapy
- Chemo and pregnancy outcome
- Chemo and follow up children ‘fetal safety’
- Take home message

European registry

www.cancerinpregnancy.org



Cancer is diagnosed during 1/1000-2000 pregnancies

→ annually 2500-5000 new cases in Europe

Diagnosis of BCP

- **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

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Radiotherapy of upper parts of the body during pregnancy

Safe during 1st and 2nd trimester of pregnancy, prohibited during the 3rd trimester (Mazonakis *et al.*, 2003)

with ↑ gestational age: ↑ proximity of the foetus to the primary irradiation field, ↑ conceptus dose (threshold dose 10 – 20 cGy)

FIELD SIZE (cm^2)	CONCEPTUS DOSE (cGy)		
	First trimester	Second trimester	Third trimester
4.5 x 11.0	2.1–2.9	2.2–7.5	2.2–16.8
6.0 x 12.5	2.8–3.9	2.9–10.4	3.3–23.8
8.0 x 14.0	3.5–5.1	3.7–13.9	4.0–34.7
10.0 x 16.0	4.4–6.2	4.7–18.2	5.0–45.2
11.5 x 18.0	5.2–7.6	5.9–24.6	6.5–58.6

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Cancer During Pregnancy: An Analysis of 215 Patients Emphasizing the Obstetrical and the Neonatal Outcomes

Kristel Van Calsteren, Liesbeth Heyns, Frank De Smet, Liesbet Van Eycken, Mina Mhallem Gziri, Willemijn Van Gemert, Michael Halaska, Ignace Vergote, Nelleke Ouwenger, and Frédéric Amant

From the Department of Obstetrics & Gynecology, University Hospital Gasthuisberg, Katholieke Universiteit, Leuven; National Alliance of Christian Sickness Funds; Belgian Cancer Registry, Brussels; Obstetrics and Gynecol-

ABSTRACT

Purpose

The aim of this study was to assess the management and the obstetrical and neonatal outcomes of pregnancies complicated by cancer.

Pregnancy outcome

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	. Prader-Willi . Congenital laryngomalacie . Hemangioma	3/58	(5.2)
Surgery	. Cardial hamartomas in tuberous sclerosis . Multiple congenital anomalies (ao hypospadia, left pink missing, abnl position left foot) . Hemangioma	3/46	(6.5)
Chemotherapy	. Hip subluxation . Pectus excavatum . Hemangioma	3/33	(9.1)
Chemo + RT	. Bilateral partial syndactily digiti II-III	1/1	(100)
Surgery +Chemo	. Bilateral small protuberance on phalanx-5 . Rectal atresia	2/25	(8.0)
Surgery + Chemo + RT	. 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)

Treatment of breast cancer during pregnancy: an observational study

Sibylle Loibl, Sileny N Han, Gunter von Minckwitz, Marijke Bontenbal, Alistair Ring, Jerzy Giermek, Tanja Fehm, Kristel Van Calsteren, Sabine C Linn, Bettina Schlehe, Mina Mhallem Gziri, Pieter J Westenend, Volkmar Müller, Liesbeth Heyns, Brigitte Rack, Ben Van Calster, Nadia Harbeck, Miriam Lenhard, Michael J Halaska, Manfred Kaufmann, Valentina Nekljudova, Frederic Amant

Summary

Background Little is known about the treatment of breast cancer during pregnancy. We aimed to determine whether treatment for breast cancer during pregnancy is safe for both mother and child.

Published Online
August 16, 2012
http://dx.doi.org/10.1016/

Obstetrical complications in women with early breast cancer with and without chemotherapy (n=343) (Loibl et al., Lancet Oncol 2012)

	No chemotherapy during pregnancy (N=164)	Chemotherapy during pregnancy (N=179)	p value
Any obstetrical complication			
No	149 (91%)	148 (83%)	0·027
Yes	15 (9%)	31 (17%)	
Gestational diabetes			
No	163 (99%)	177 (99%)	1·00
Yes	1 (1%)	2 (1%)	
Pre-eclampsia			
No	163 (99%)	177 (99%)	1·00
Yes	1 (1%)	2 (1%)	
Hypertension			
No	164 (100%)	178 (99%)	1·00
Yes	0 (-)	1 (1%)	
Oligohydramnios			
No	164 (100%)	176 (98%)	0·249
Yes	0 (-)	3 (2%)	
Cervical insufficiency			
No	164 (100%)	176 (98%)	0·249
Yes	0 (-)	3 (2%)	
Placenta insufficiency			
No	164 (100%)	177 (99%)	0·499
Yes	0 (-)	2 (1%)	
Placenta haematoma			
No	164 (100%)	178 (99%)	1·00
Yes	0 (-)	1 (1%)	
Solution placentae			
No	164 (100%)	178 (99%)	1·00
Yes	0 (-)	1 (1%)	
Bleeding			
No	163 (99%)	175 (98%)	0·374
Yes	1 (1%)	4 (2%)	
Vasa praevia			
No	164 (100%)	179 (100%)	NA
Congenital abnormality (pregnancy termination)			
No	164 (100%)	179 (100%)	NA
Intrauterine growth restriction			
No	163 (99%)	172 (96%)	0·069
Yes	1 (1%)	7 (4%)	

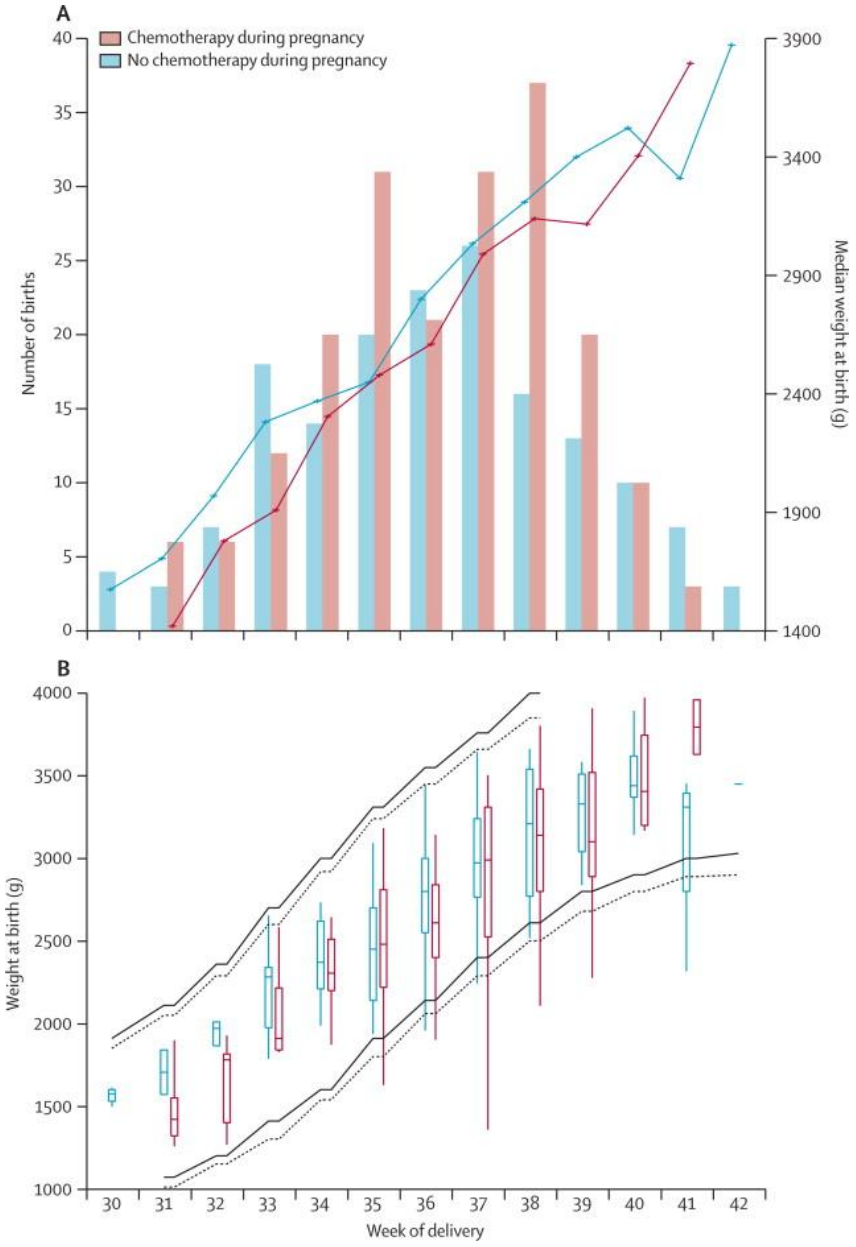
	No chemotherapy during pregnancy (N=164)	Chemotherapy during pregnancy (N=179)	p value
(Continued from previous column)			
Chorioamnionitis			
No	163 (99%)	179 (100%)	0·478
Yes	1 (1%)	0 (-)	
Spontaneous abortion (included in pregnancy interruptions)			
No	160 (98%)	179 (100%)	0·051
Yes	4 (2%)	0 (-)	
Spontaneous abortion of one twin			
No	164 (100%)	178 (99%)	1·00
Yes	0 (-)	1 (1%)	
Premature labour			
No	161 (98%)	169 (94%)	0·090
Yes	3 (2%)	10 (6%)	
Premature rupture of the membrane			
No	164 (100%)	174 (97%)	0·062
Yes	0 (-)	5 (3%)	
Fetal distress			
No	163 (99%)	177 (99%)	1·00
Yes	1 (1%)	2 (1%)	
Stillbirth			
No	162 (99%)	178 (99%)	0·608
Yes	2 (1%)	1 (1%)	
Pyelonephritis			
No	164 (100%)	179 (100%)	NA
Cholestasis			
No	163 (99%)	179 (100%)	0·478
Yes	1 (1%)	0 (-)	
Pruritus			
No	163 (99%)	179 (100%)	0·478
Yes	1 (1%)	0 (-)	

Data are number of women (%). NA=not applicable. [a] Data was not available for 35 women who did not have chemotherapy during pregnancy and for 18 women who had chemotherapy during pregnancy.

Table 4: Obstetrical complications in women with early breast cancer with and without chemotherapy during pregnancy (n=343)[a]

Median birthweight, by exposure to chemotherapy in utero and week of delivery, N=373 (203 with chemotherapy exposure in utero, 170 without)

Loibl et al., Lancet Oncol 2012



Breast cancer in pregnancy

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- Take home message

Long-term cognitive and cardiac outcomes after prenatal exposure to chemotherapy in children aged 18 months or older: an observational study

Frédéric Amant, Kristel Van Calsteren, Michael J Halaska, Mina Mhallem Gziri, Wei Hui, Lieven Lagae, Michèl A Willemsen, Livia Kapusta, Ben Van Calster, Heidi Wouters, Liesbeth Heyns, Sileny N Han, Viktor Tomek, Luc Mertens, Petronella B Ottevanger

Summary

Background Chemotherapy for the treatment of maternal cancers during pregnancy has become more acceptable in the past decade; however, the effect of prenatal exposure to chemotherapy on cardiac and neurodevelopmental outcomes of the offspring is still uncertain. We aimed to record the general health, cardiac function, and neurodevelopmental outcomes of children who were prenatally exposed to chemotherapy.

Methods We did an interim analysis of a multicentre observational cohort study assessing children who were prenatally exposed to maternal cancer staging and treatment, including chemotherapy. We assessed children at birth, at age 18 months, and at age 5–6, 8–9, 11–12, 14–15, or 18 years. We did clinical neurological examinations, tests of the general level of cognitive functioning (Bayley or intelligence quotient [IQ] test), electrocardiography and echocardiography, and administered a questionnaire on general health and development. From age 5 years, we also did audiometry, the Auditory Verbal Learning Test, and subtasks of the Children's Memory Scale, and the Test of Everyday Attention for Children, and we also completed the Child Behavior Checklist. This study is registered with ClinicalTrials.gov, number NCT00330447.

Findings 236 cycles of chemotherapy were administered in 68 pregnancies. We assessed 70 children, born at a median gestational age of 35·7 weeks (range 28·3–41·0; IQR 3·3; 47 women at <37 weeks), with a median follow-up period

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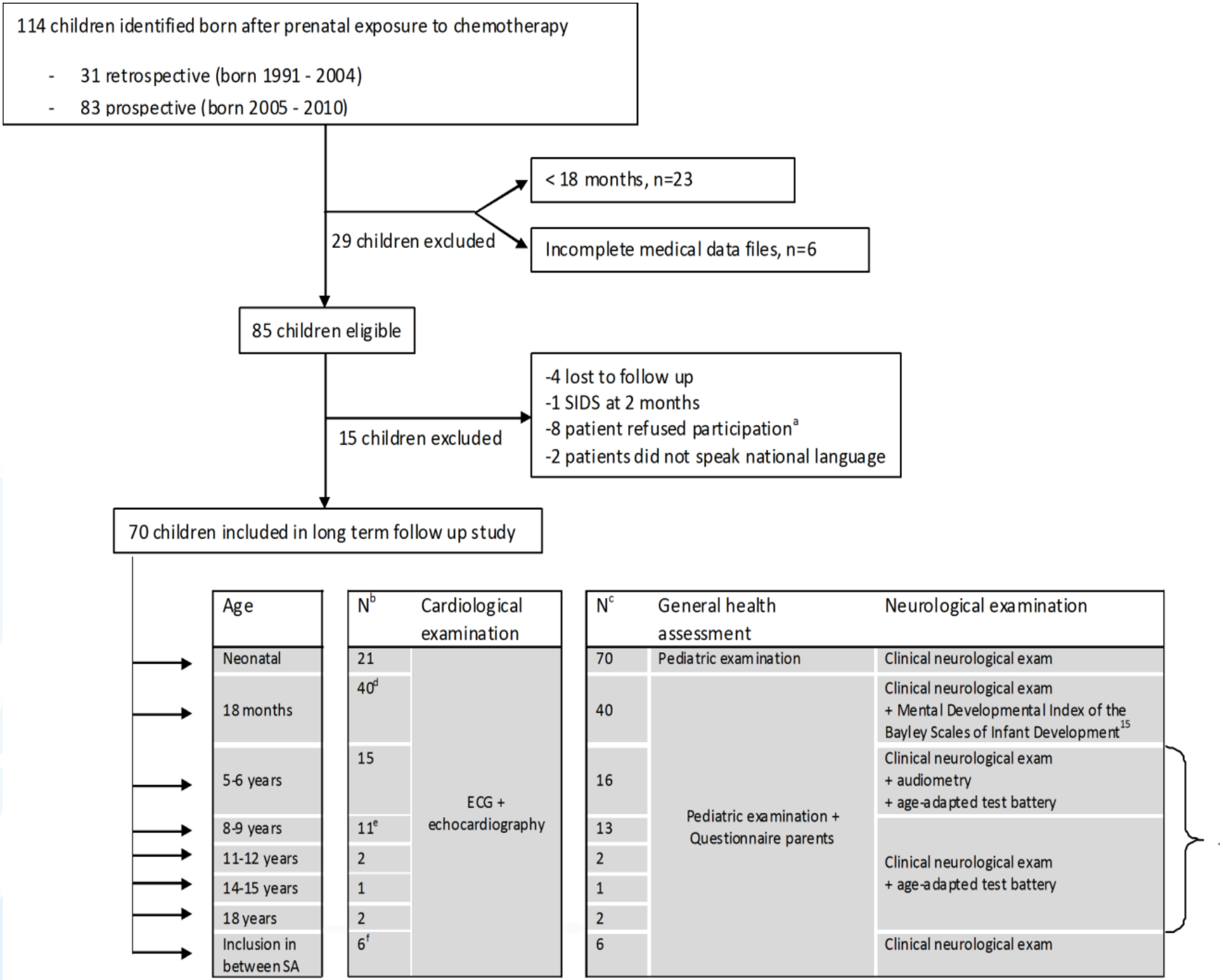
DOI:10.1016/S1470-2045(11)70363-1

See Online/Comment
DOI:10.1016/S1470-2045(11)70408-9

See Series *Lancet* 2012; **379**: 558, 570, and 580

Leuven Cancer Institute, Gynaecologic Oncology (F Amant PhD, B Van Calster PhD, L Heyns MSc, S N Han MD), **Department of Obstetrics and Gynaecology** (K Van Calsteren PhD, M Mhallem Gziri MD, B Van Calster), **and Department of Paediatrics** (L Lagae PhD,


114 children identified born after prenatal exposure to chemotherapy
- 31 retrospective (born 1991 - 2004)
- 83 prospective (born 2005 - 2010)
29 children excluded
< 18 months, n=23
Incomplete medical data files, n=6
85 children eligible
15 children excluded
-4 lost to follow up
-1 SIDS at 2 months
-8 patient refused participation[a]
-2 patients did not speak national language
70 children included in long term follow up study
Age
N[b]
Cardiological examination
N[c]
General health assessment
Neurological examination
Neonatal
21
ECG + echocardiography
70
Pediatric examination
Clinical neurological exam
18 months
40[d]
40
Clinical neurological exam + Mental Developmental Index of the Bayley Scales of Infant Development[15]
5-6 years
15
16
Clinical neurological exam + audiometry + age-adapted test battery
8-9 years
11[e]
13
Pediatric examination + Questionnaire parents
11-12 years
2
2
Clinical neurological exam + age-adapted test battery
14-15 years
1
1
18 years
2
2
Inclusion in between SA
6[f]
6
Clinical neurological exam

Age adapted neuropsychological test battery

	5-6 years	8-9, 11-12, 14-15 years	18 years
Intelligence	WPPSI-R	WISC-III	WAIS-III
Attention		Tea-Ch	
Memory **A. Verbal**	Subtask from CMS: Numbers	Subtask from CMS: Numbers AVLT	AVLT
B. Non-verbal	Subtasks from CMS: Dots Locations, Faces, Pictures	Subtasks from CMS: Dots Locations, Faces, Pictures	
Behavior	CBCL	CBCL	CBCL

TEACH, Test of Everyday Attention for Children;
CMS, Children's Memory Scale;
AVLT, Auditory Verbal Learning Test;
CBCL, Child Behavior Checklist was completed.

Results: maternal disease and treatment

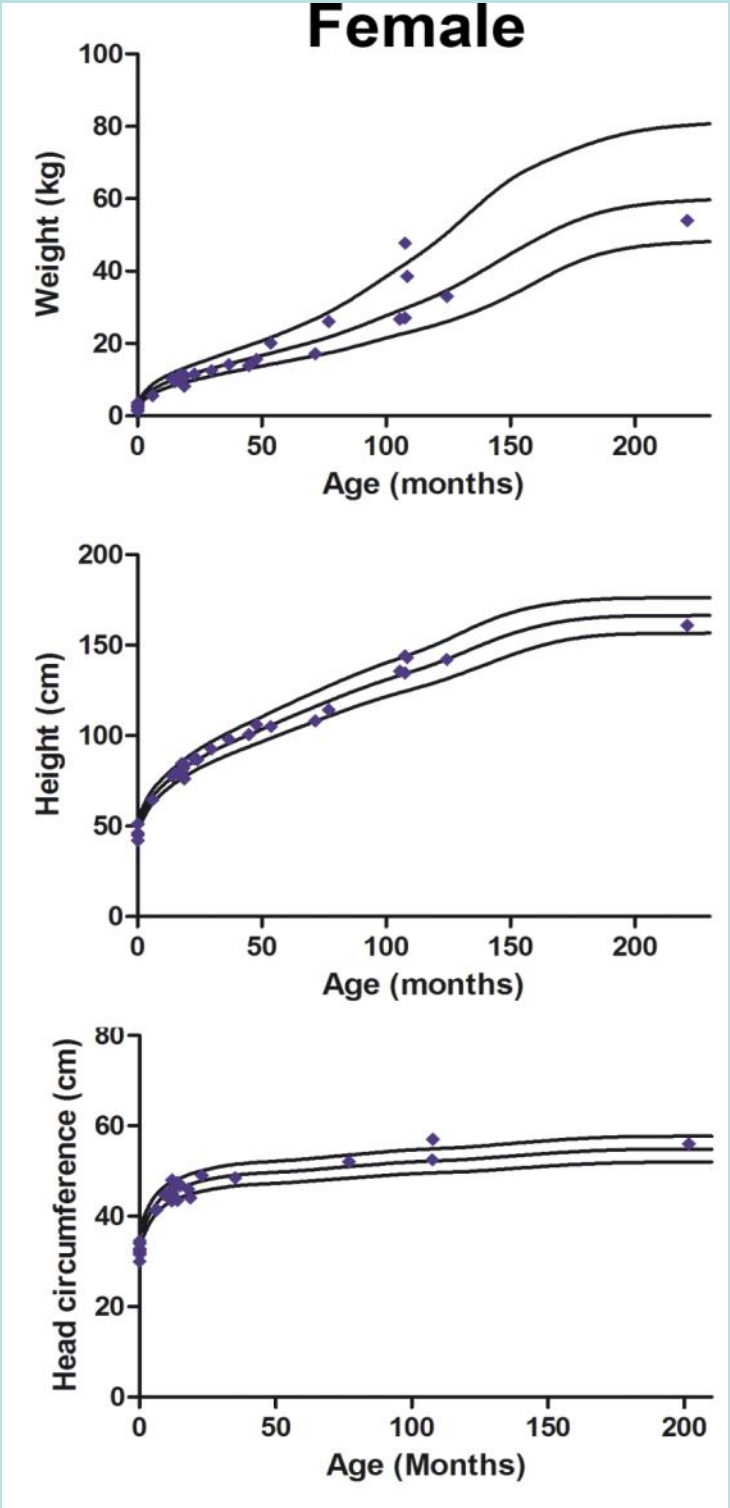
Maternal malignancy	Number	
Breast cancer	35	(51.5%)
Hematological malignancy - ALL - AML - Hodgkin - Non-hodgkin	18 5 2 7 4	(26.5%)
Ovarian cancer	6	(8.8%)
Cervical cancer	4	(5.9%)
Basal cell carcinoma	1	(1.5%)
Brain tumor	1	(1.5%)
Ewing sarcoma	1	(1.5%)
Colorectal carcinoma	1	(1.5%)
Nasopharyngeal cancer	1	(1.5%)

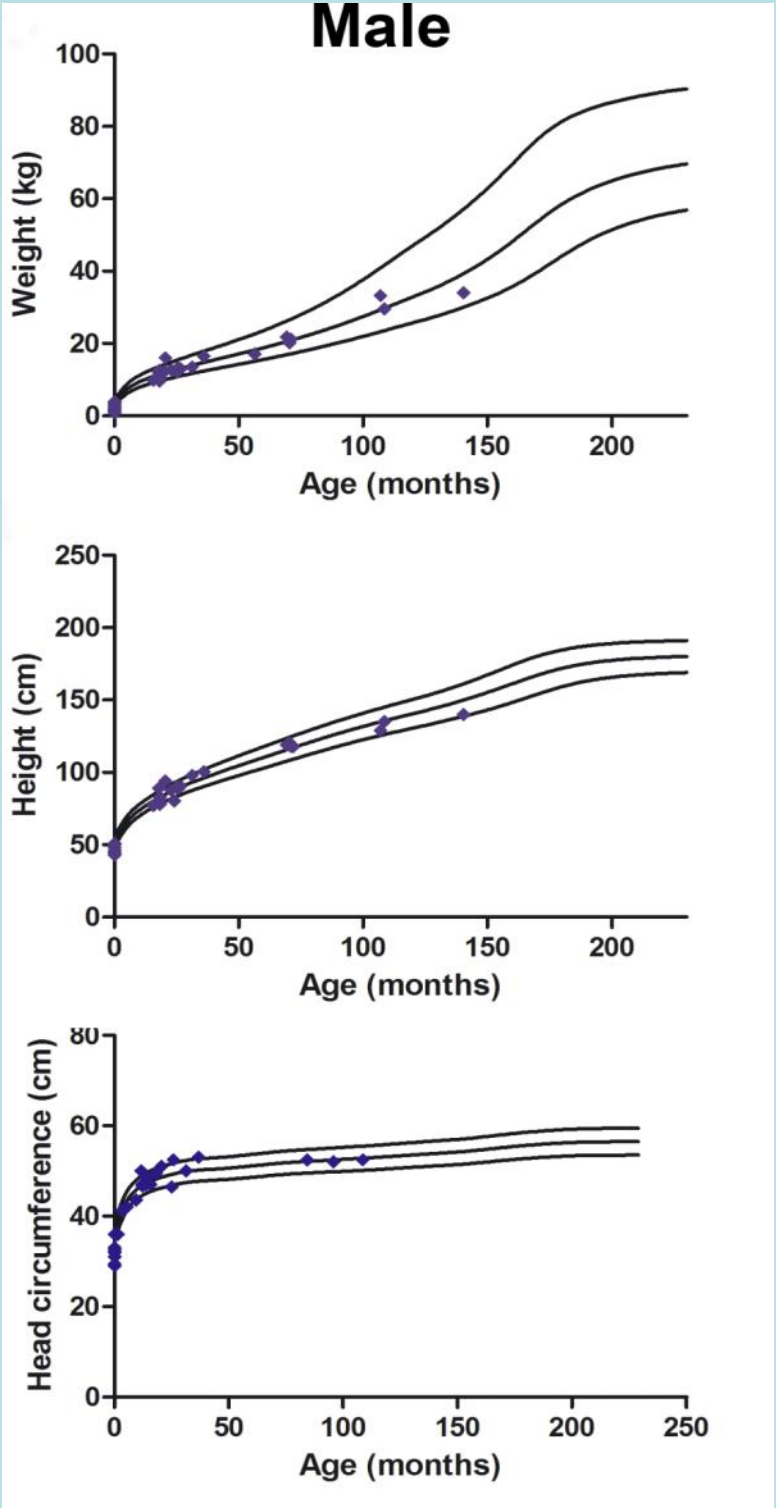
Treatment during pregnancy	Number	
Chemotherapy	34	(50.0%)
Chemotherapy + RT	1	(1.5%)
Surgery + chemotherapy	27	(39.7%)
Surgery + chemotherapy + RT	6	(8.8%)

Results: neonatal neurological examination (n=70)

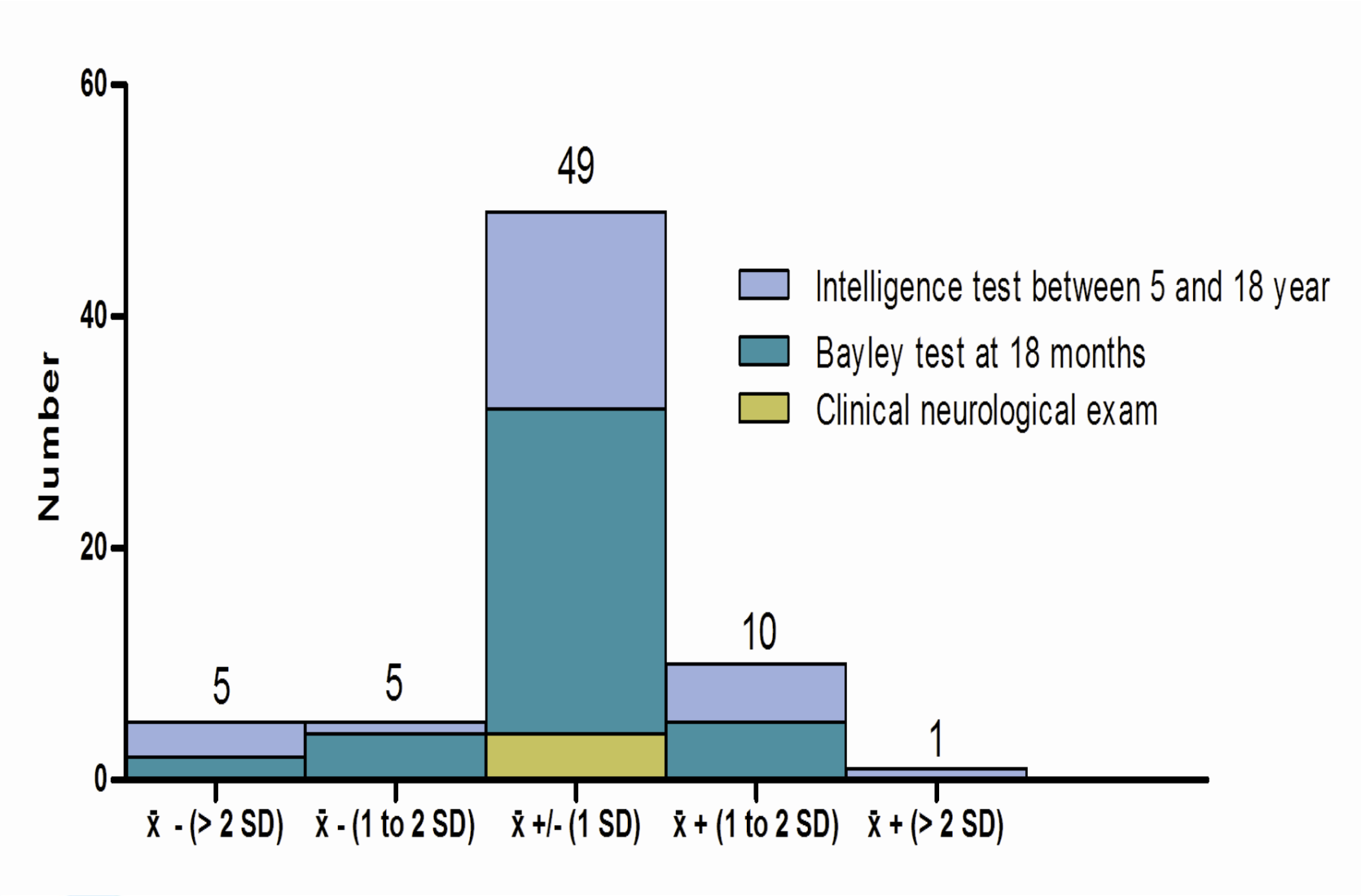
Findings	Number
Normal findings	64 (91.4%)
Transient hypotonia	5 (7.1%)
Benign sleep myoclonus	1 (1.4%)
Contracture of right elbow	1 (1.4%) (born 28 weeks)

Results: biometry

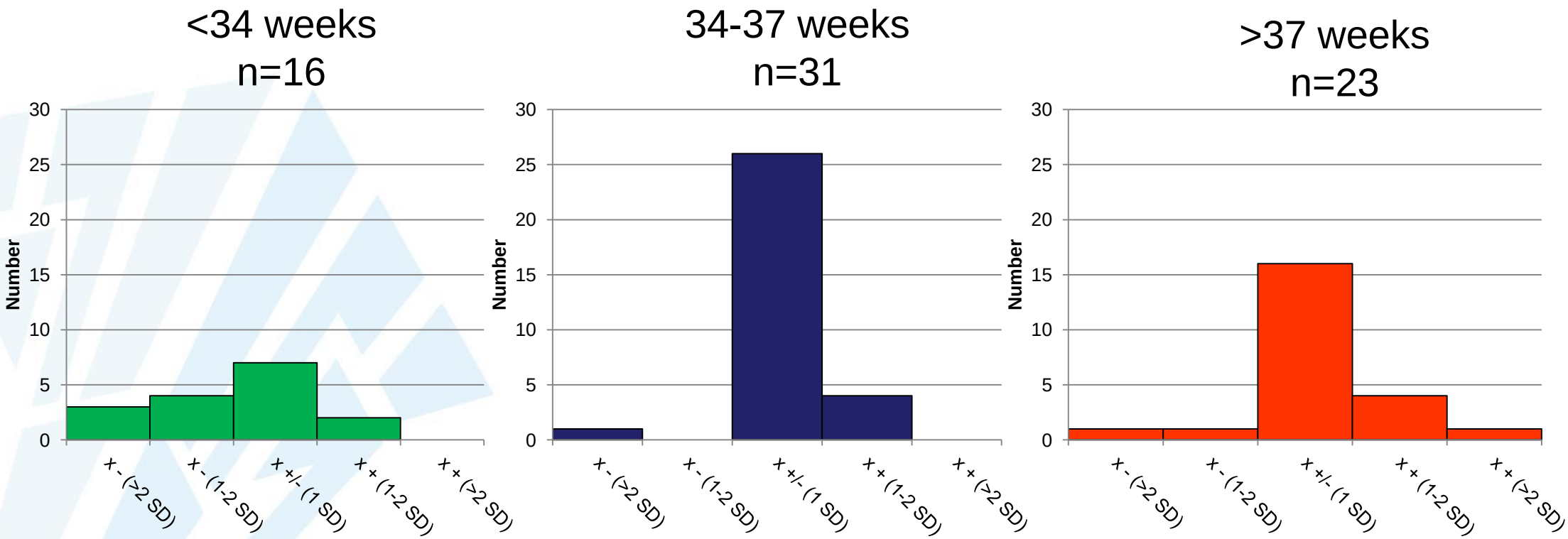




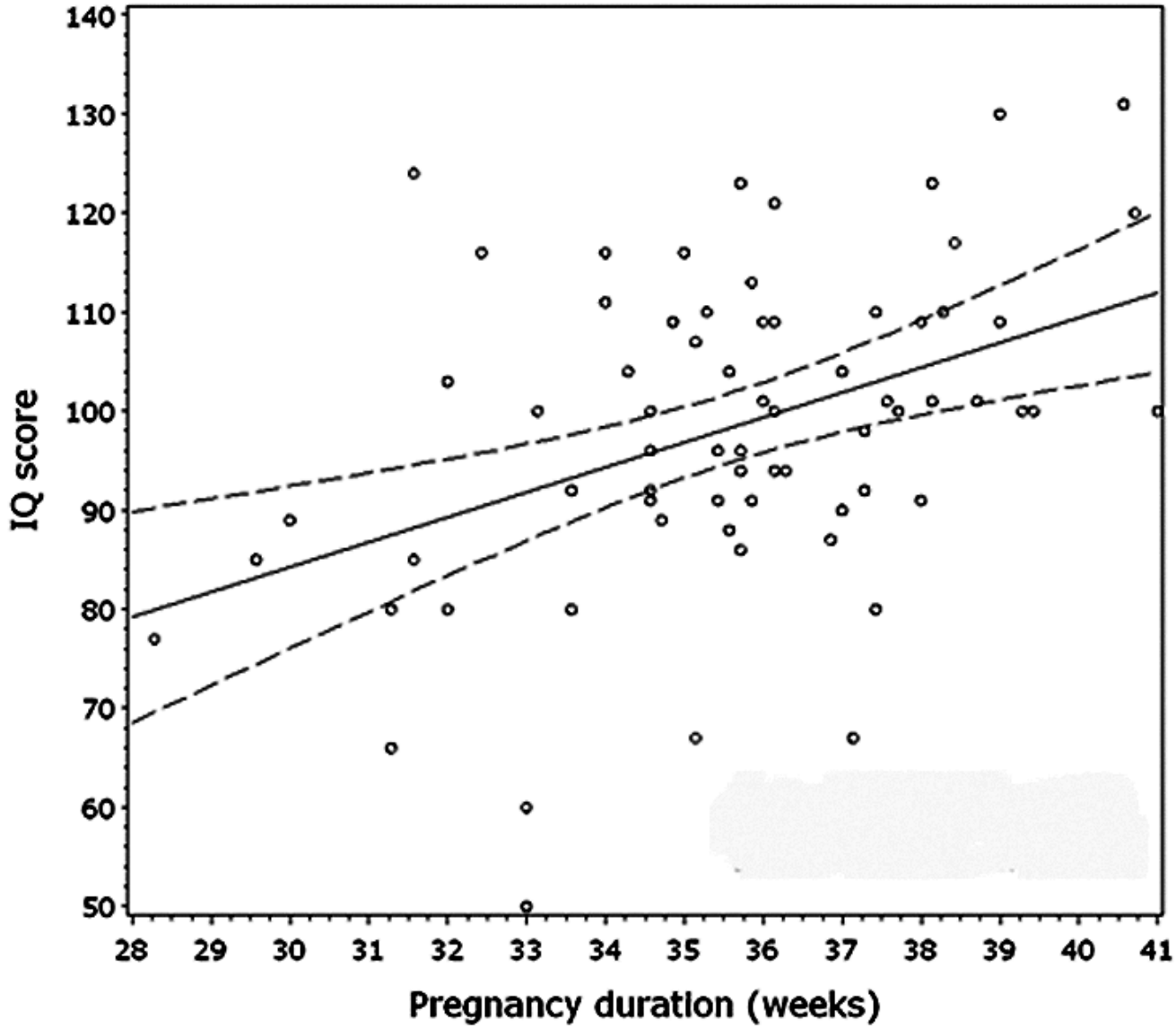
Results: cognitive functioning



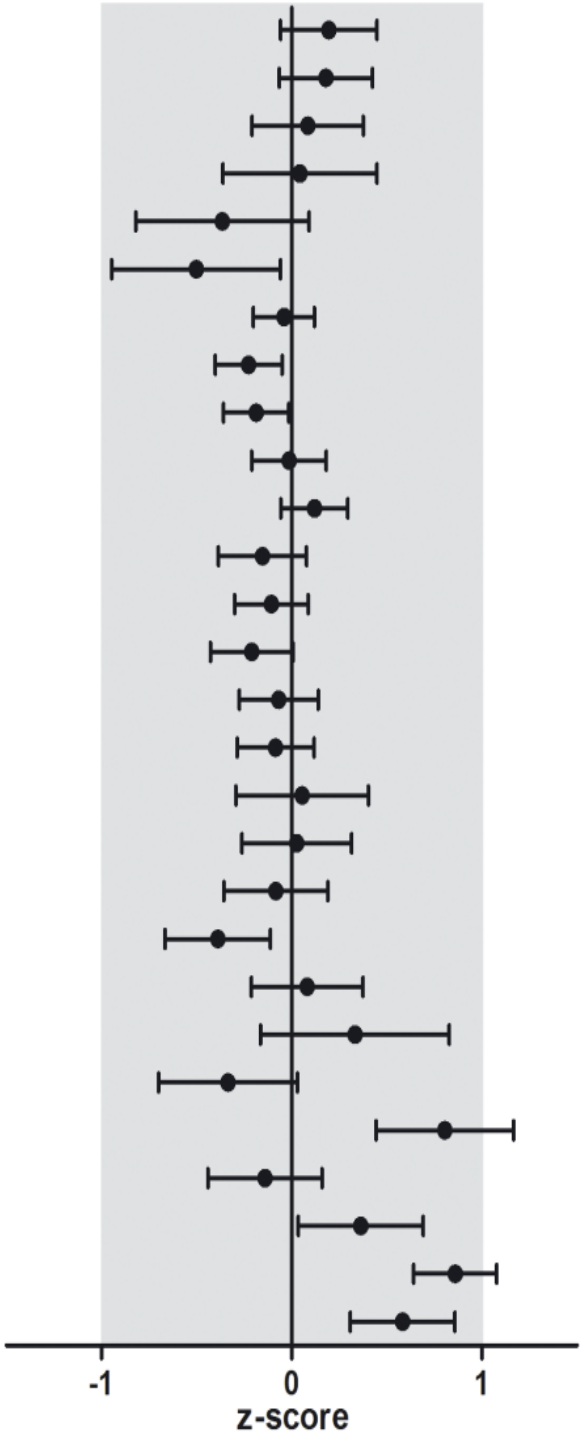
Results, cognitive functioning: prematurity vs IQ score



IQ score increases with 2.5 (95% CI:1.2-3.9) for each week increase in pregnancy duration (p= 0.0003).



Tested function	(Sub)task	Tested parameter	N	Median age (range) in years
Behavior	CBCL	Internalizing	21	8.7 (5.0-15.9)
		Externalizing	21	8.7 (5.0-15.9)
		Total problems	21	8.7 (5.0-15.9)
Verbal memory	AVLT	Learning	12	9.0 (8.5-15.9)
		Immediate recall	12	9.0 (8.5-15.9)
		Delayed recall	12	9.0 (8.5-15.9)
Verbal memory span	CMS Numbers	Forward	25	8.5 (5.0-17.6)
		Backward	25	8.5 (5.0-17.6)
		Total numbers	25	8.5 (5.0-17.6)
Non-verbal memory	CMS Dots	Learning	25	8.5 (5.0-17.6)
		Immediate recall	25	8.5 (5.0-17.6)
		Delayed recall	24	8.2 (5.0-17.6)
	CMS Faces	Immediate recall	25	8.5 (5.0-17.6)
		Delayed recall	24	8.2 (5.0-17.6)
Non-verbal memory span	CMS Pictures		25	8.5 (5.0-17.6)
Selective attention	Tea-Ch Sky Search	Correct score	12	9.0 (8.5-15.9)
		Time score	12	9.0 (8.5-15.9)
		Attention score	12	9.0 (8.5-15.9)
	Tea-Ch Map Mission		12	9.0 (8.5-15.9)
Sustained attention	Tea-Ch Score		12	9.0 (8.5-15.9)
	Tea-Ch Code Transmission		12	9.0 (8.5-15.9)
	Tea-Ch Sky Search DT*		12	9.0 (8.5-15.9)
	Tea-Ch Score DT*		12	9.0 (8.5-15.9)
	Tea-Ch Walk/Don't Walk**		12	9.0 (8.5-15.9)
Attentional flexibility	Tea-Ch Creature Counting	Correct score	12	9.0 (8.5-15.9)
		Time score	11	9.0 (8.5-15.9)
	Tea-Ch Opposite World	Same world	12	9.0 (8.5-15.9)
		Opposite world	12	9.0 (8.5-15.9)



Results: cardiac data

- No congenital heart malformations
- Normal ECG
- Normal heart diameters
- Normal systolic and diastolic heart functions

Conclusion

- ✓ Child's behavior, general health, hearing and growth was reported as in a general population;
- ✓ Most of the children have an age-adequate neurological development (intelligence, attention, memory) and cardiac function;
- ✓ Prematurity was frequently encountered, and was associated with impairment in cognitive development.

Clinical implications

- Less terminations of pregnancy
- Less delay of maternal treatment
- Less iatrogenic premature delivery

Results of transplacental transfer of chemotherapeutic agents in a pregnant baboon model, based on simultaneously collected maternal and foetal plasma samples.

Van Calsteren et al., IJGC 2010, Van Calsteren et al., Gynecol Oncol 2010

Drug	Baboon (%)	(Samples)
Doxorubicin	7.5 ± 3.2	(n = 6) (in 9 other fetuses <LLQ)
Epirubicin	4.0 ± 1.6	(n=8) (in 3 other fetuses <LLQ)
Carboplatin	57.5 ± 14.2	(n = 7)
Paclitaxel	1.4 ± 0.8	(n = 7) (in 4 other fetuses <LLQ)
Docetaxel	ND	(n=9 < LLQ in foetus)
4-OH-cylophosphamide	25.1 ± 6.3	(n=3) (<LLQ in 1 foetus and mother)
Vinblastine	18.5 ± 15.5	(n=9) (in 1 other fetus <LLQ).

LLQ, lower limit of quantification; ND, not detectable

Chemotherapy during pregnancy

- Until more data are available: current dosage ~ actual height and weight
- Possible adjuvant regimens include: FEC, EC, FAC, AC, Taxanes, Platin

Targeted treatment during pregnancy

- **Herceptin**: **not recommended** due to an increased risk of **oligo/anhydramnios**
  - effect on renal epithelium in which HER2/neu is strongly expressed (Press *et al.*, 1990)
  - inhibion of the VEGF, which regulates production and reabsorption of the amniotic fluid (Pant *et al.*, 2008)

- **Tamoxifen**: **not recommended** due to **birth defects**
  - Goldenhar syndrome (Cullins *et al.*, 1994)
  - Ambiguous genitalia (Tewari *et al.*, 1997)
  - Pierre Robin sequence (Berger and Clericuzio, 2008)

Series

Malignancies in Pregnancy 2

Breast cancer in pregnancy

Frédéric Amant, Sibylle Loibl, Patrick Neven, Kristel Van Calsteren

Lancet 2012; 379: 570–79

See Comment page 495

See Perspectives page 511

See *Lancet Oncol* Online/Articles

DOI:10.1016/S1470-2045(11)70363-1

This is the second in a Series of three papers about malignancies in pregnancy

Multidisciplinary Breast Cancer Center, Leuven Cancer Institute, Katholieke

Breast cancer staging and treatment are possible during pregnancy, and should be defined in a multidisciplinary setting. Tumour biology, tumour stage, and gestational stage at diagnosis determine the appropriate approach. Surgery for breast cancer is possible during all trimesters of pregnancy. Radiotherapy is possible during pregnancy but, dependent on the fetal dose received, can result in poor fetal outcomes. The decision to give radiotherapy should be made on an individual basis. Evidence increasingly supports administration of chemotherapy from 14 weeks' gestation onwards. New breast cancer treatments might be applicable to pregnant patients, but tamoxifen and trastuzumab are contraindicated during pregnancy. Cancer treatment during pregnancy will decrease the need for early delivery and thus prematurity, which is a major concern in management of breast cancer in pregnancy.

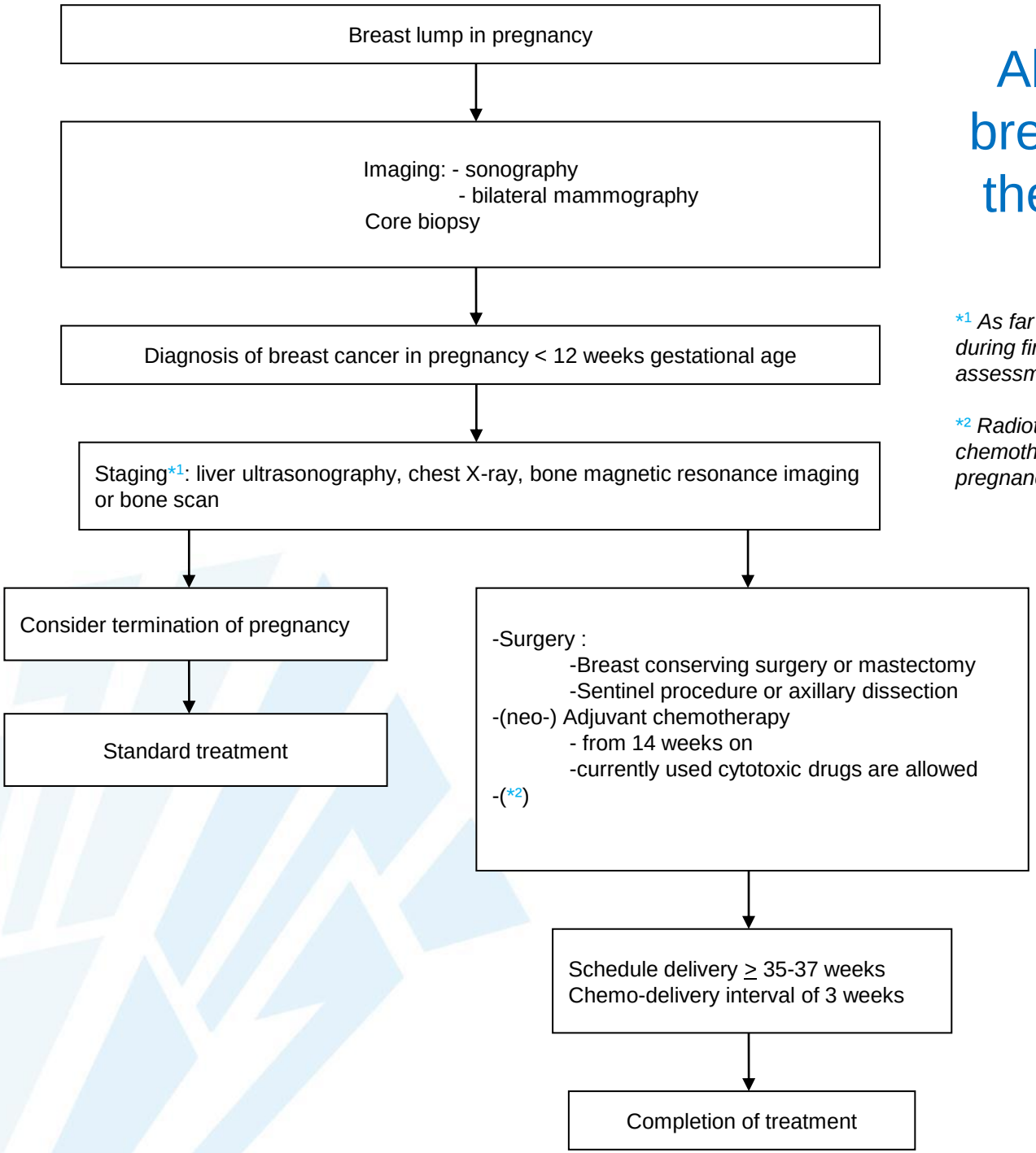
Introduction

Although breast cancer was known in ancient times, it

which cancer complicates pregnancy is expected to become more common. We discuss the diagnosis,

Algorithm for the treatment of breast cancer diagnosed during the first trimester of pregnancy

(Lancet, 2012)



*1 *As far as this will change clinical practice, especially important during first trimester. Staging examinations and tumor biology assessment will parallel the decision to continue pregnancy.*

*2 *Radiotherapy is not considered after surgery and before chemotherapy in order to reduce treatment modalities during pregnancy*

Physiologic adaptations in pregnancy:ADME

- **A**bsorption
- **D**istribution
- **M**etabolism
- **E**xcretion

In the absence of valid data, standard height-weight based dosages of chemotherapy are administered in pregnant women

Pharmacokinetics in pregnant women

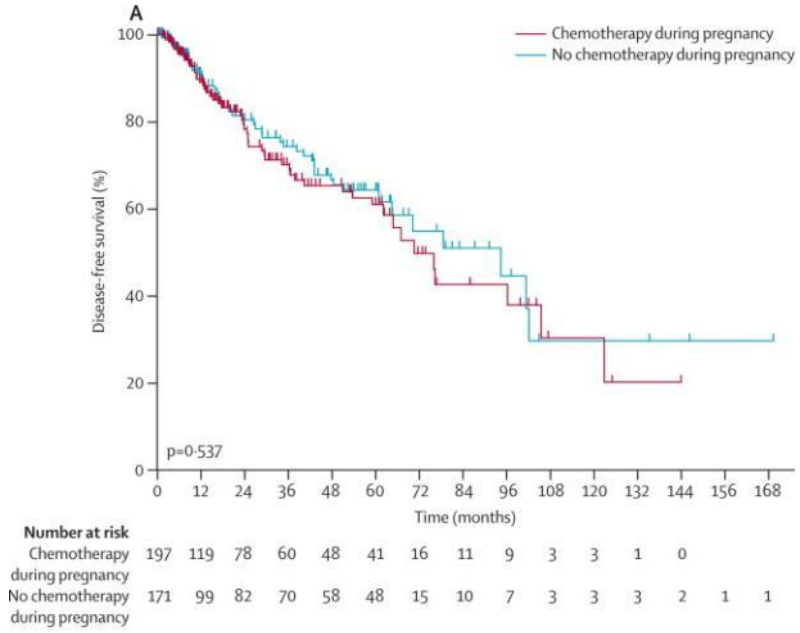
Van Calsteren K (Acta Scand Gynecol Obstet 2010)

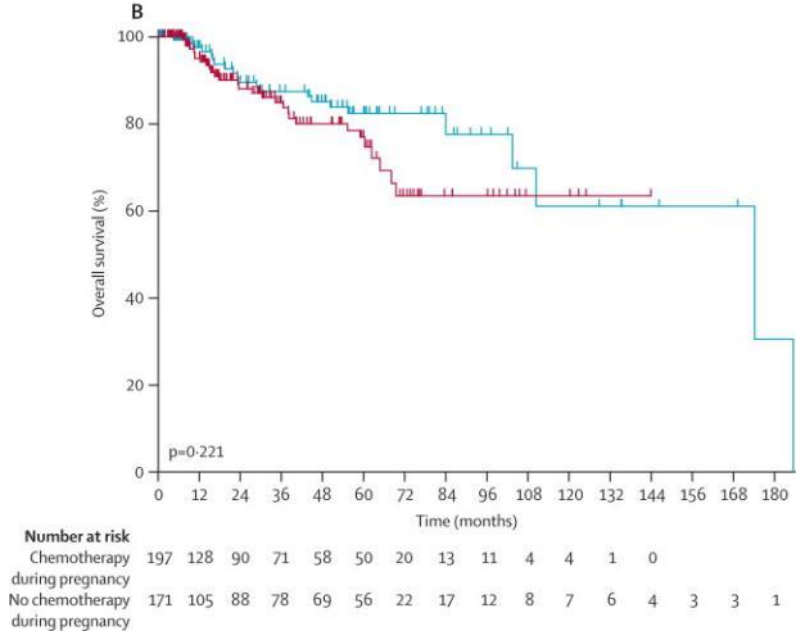
Results human pooled analysis

Parameter	Mean Pregnant / Mean nonpregnant			
	Paclitaxel Pr 5 / NPr 2	Carboplatin Pr 2 / NPr 2	Doxorubicin Pr 7 / NPr 5	Epirubicin Pr 4 / NPr 4
Age (year)	1.0	1.0	1.0	1.0
BSA (m^2)	1.0	1.1	1.1	1.3
Cmax-D*IT (ng/ml/mg*h)	0.5 ↓	0.6 ↓	0.7 ↓	0.6 ↓
AUC-D (h*ng/ml/mg)	0.8 ↓	0.6 ↓	0.8 ↓	0.7 ↓
$t_{1/2}$ (h)	1.3	0.8	1.0	0.9
Clearance (l/h)	1.2 ↑	1.7 ↑	1.3 ↑	1.4 ↑
Vd (l)	1.7 ↑	1.4 ↑	1.3 ↑	1.2 ↑

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

Loibl et al., Lancet Oncol 2012





Check list when prenatal care in breast cancer patients is designed

Amant et al., Lancet 2012

At diagnosis	- Confirm evolutionary pregnancy and determine gestational age - Exclude preexisting fetal anomalies by ultrasonography before examinations or interventions are performed
Obstetrical follow up during oncological treatment	- Consider intraoperative foetal monitoring from 24-26 weeks onwards according to local policy - Chemotherapy is possible during 2nd or 3rd trimester *check for fetal wellbeing and general development *check for preterm contractions *check for intrauterine growth restriction *no chemotherapy after 35 weeks of gestation - Radiotherapy is possible during 1st or 2nd trimester *check for preterm contractions *check for intrauterine growth restriction *after every cycle, check foetal wellbeing, growth and morphology
Delivery	- Mode of delivery is determined by obstetrical indications - Timing of delivery: * preferable after 35-37 weeks * at least 3 weeks after chemotherapy * in case preterm delivery is inevitable fetal lung maturation is mandatory
Postpartum	- Examine placenta for metastatic disease - Breast feeding * if physiologically possible e.g. after radiotherapy * contraindicated in case of recent chemotherapy - Oncological treatment can be continued immediately after vaginal delivery, and one week after uncomplicated c-section

Breast cancer in pregnancy

- Introduction
- Surgery
- Radiotherapy
- Chemo and pregnancy outcome
- Chemo and follow up children ‘fetal safety’
- Take home message

Key messages

- **Termination Of Pregnancy** is unlikely to improve prognosis
- **Maternal prognosis** similar to non-pregnant state
- **Oncological surgery** appears to be safe
- **Chemotherapy** safe after 1st trimester
- **Radiotherapy** upper body during 1st & 2nd trimester
- **Standard treatment** should be aimed for
- Prevention of **prematurity**
- No emergency, **take time** (for second opinion)

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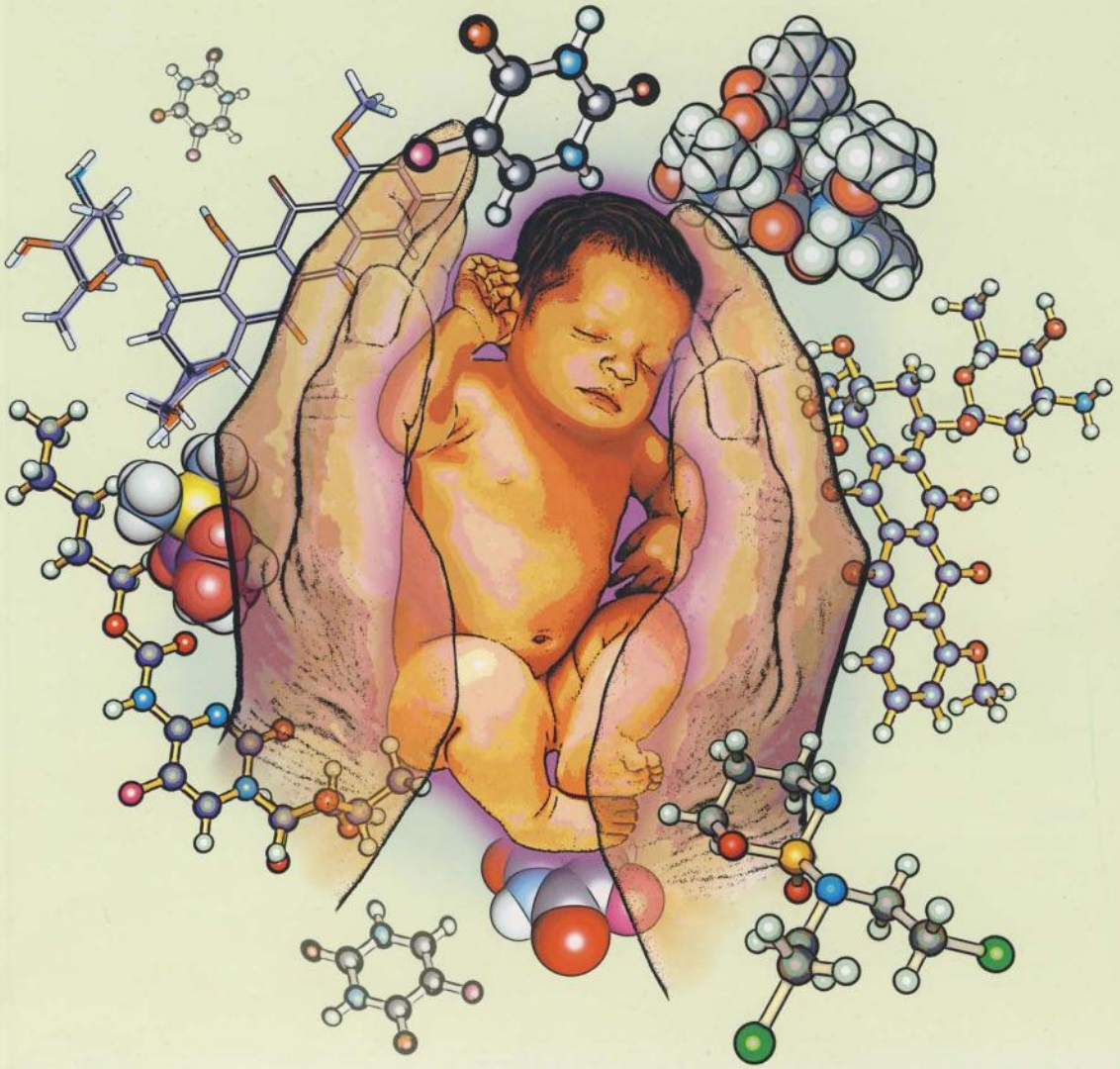

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Bone health and exemestane: results from the MAP.3 trial

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Historical Review

Medical applications of PET in oncology

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