Overview dei tumori in gravidanza

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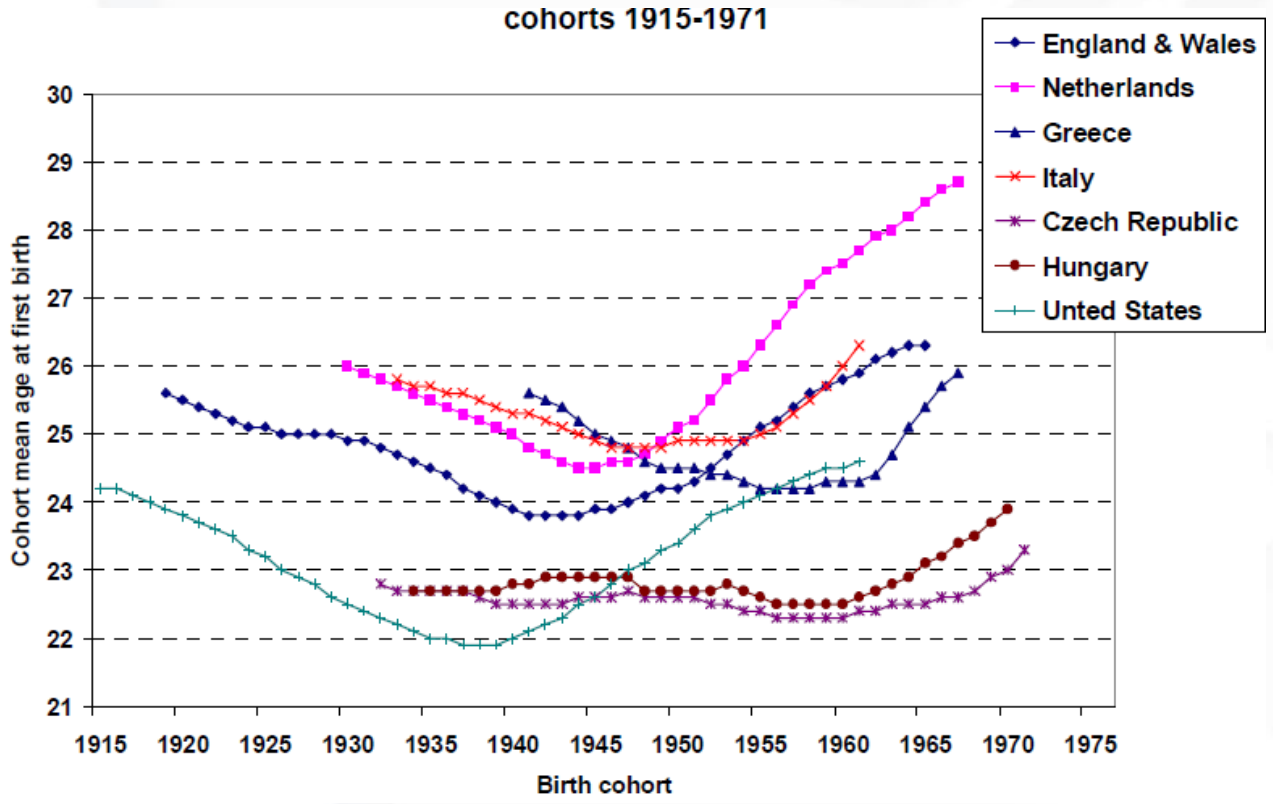
Epidemiology

Incidence 1/1000-1500 pregnancies in Europe 3000-5000 cases/year



Epidemiology

Figure 2. Percentage of first births, by age of mother: United States, 1970–2006

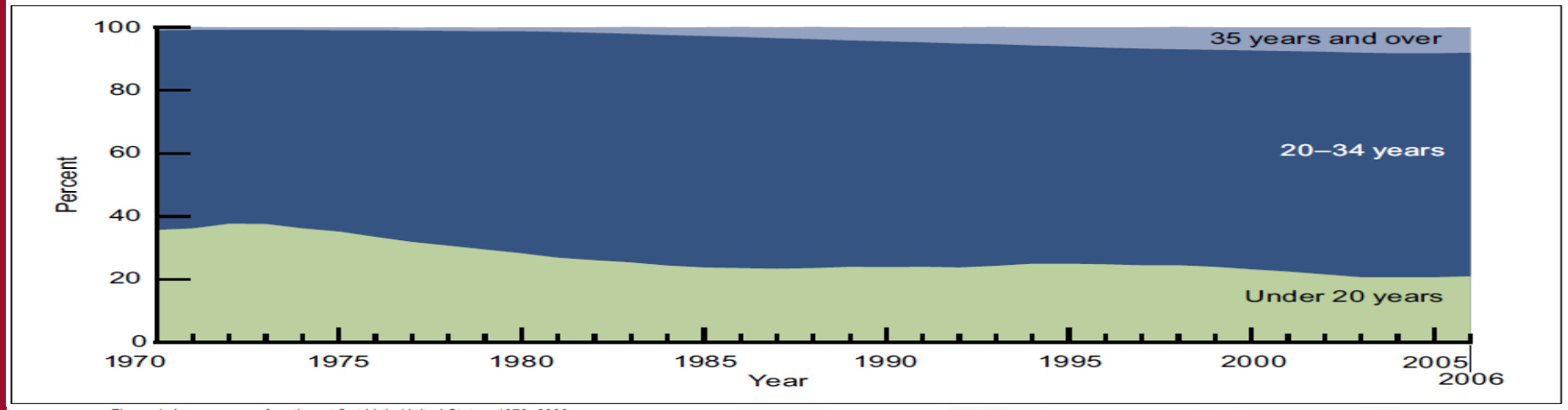


Figure 1. Average age of mother at first birth: United States, 1970–2006

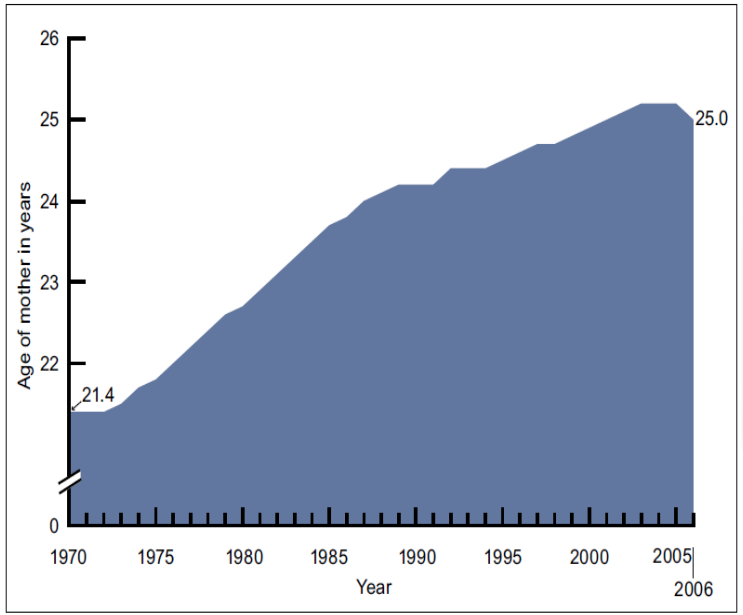
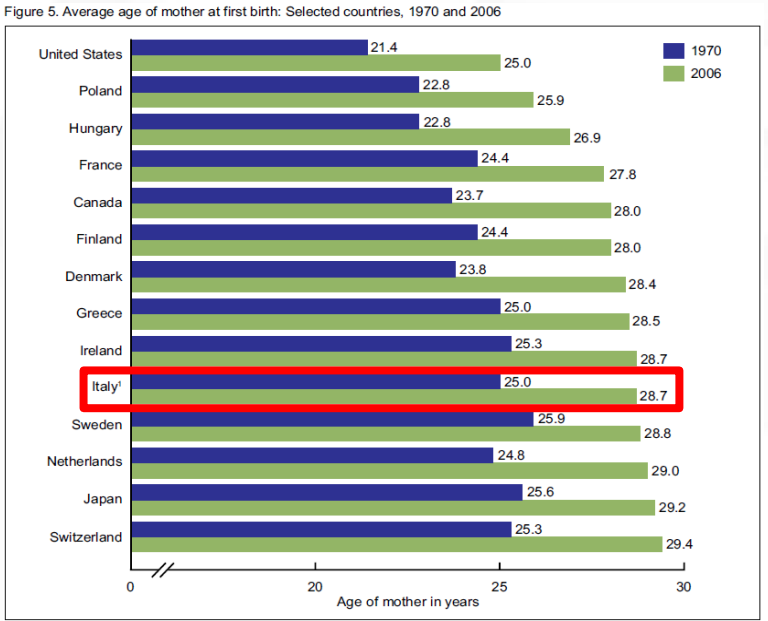
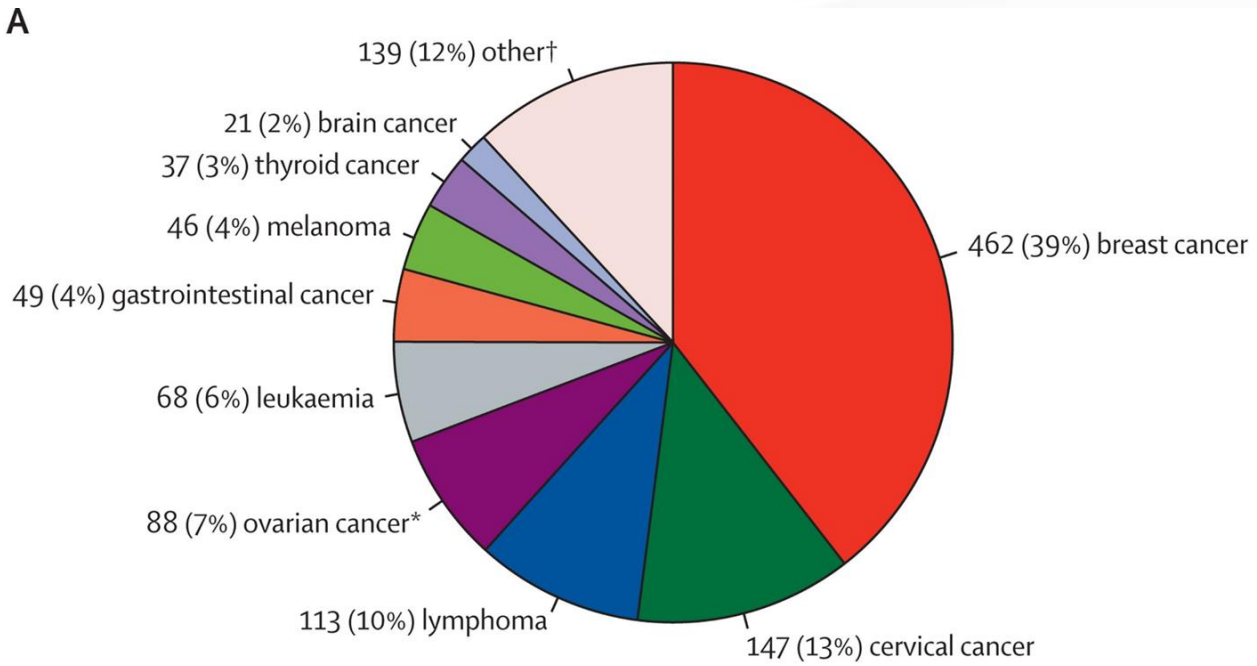


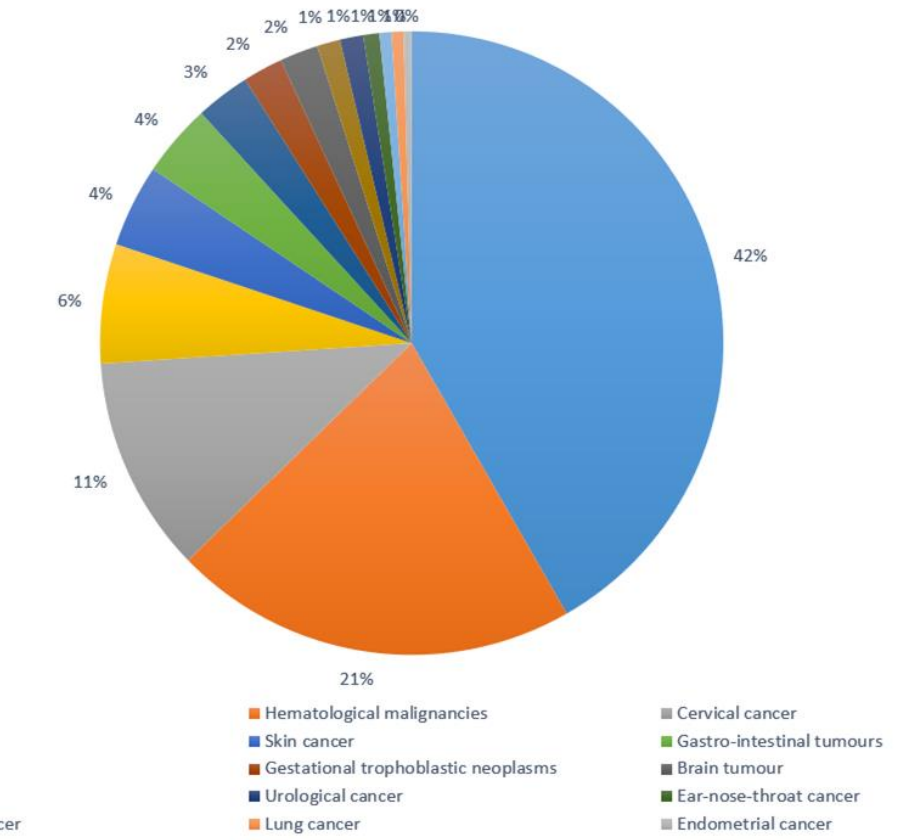
Figure 5. Average age of mother at first birth: Selected countries, 1970 and 2006



Epidemiology



De Haan J et al. Oncological management and obstetric and neonatal outcomes for women diagnosed with cancer during pregnancy: a 20-year international cohort study of 1170 patients. Lancet Oncol. 2018 Mar;19(3):337-346.



The physicians' attitude

- **94%** of respondents agreed that management of pregnant patients with cancer should be decided by a **multidisciplinary team**
- In the first or early second trimester **44%** of respondents prefer **termination of pregnancy**
- If the patient wishes to preserve the pregnancy, **77%** consider **deliberate delay and treatment later in pregnancy**

Han SN et al. Cancer in pregnancy: a survey of current clinical practice. Eur J Obstet Gynecol Reprod Biol. 2013 Mar;167(1):18-23

The physicians' attitude

- When cancer is diagnosed in the late second or third trimester of pregnancy, **58%** prefer **preterm delivery** in order to start cancer treatment in the postpartum period
- **37%** would **not give chemotherapy** or radiotherapy during pregnancy.
- Treatment during pregnancy with the aim of a term delivery is preferred by **41%** of respondents

Han SN et al. Cancer in pregnancy: a survey of current clinical practice. Eur J Obstet Gynecol Reprod Biol. 2013 Mar;167(1):18-23

The point of view of the mother

- Will I be able to reach the term of pregnancy?
- Will the treatments have a bad influence on the pregnancy?
- Will my baby be healthy?
- Will my baby have a normal life?

- Will the pregnancy have a negative impact on my prognosis?

The point of view of the mother

- Will I be able to reach the term of pregnancy?
- Will the treatments have a bad influence on the pregnancy?
- Will my baby be healthy?
- Will my baby have a normal life?
- Will the pregnancy have a negative impact on my prognosis?

Chemotherapy: long term neonatal outcome

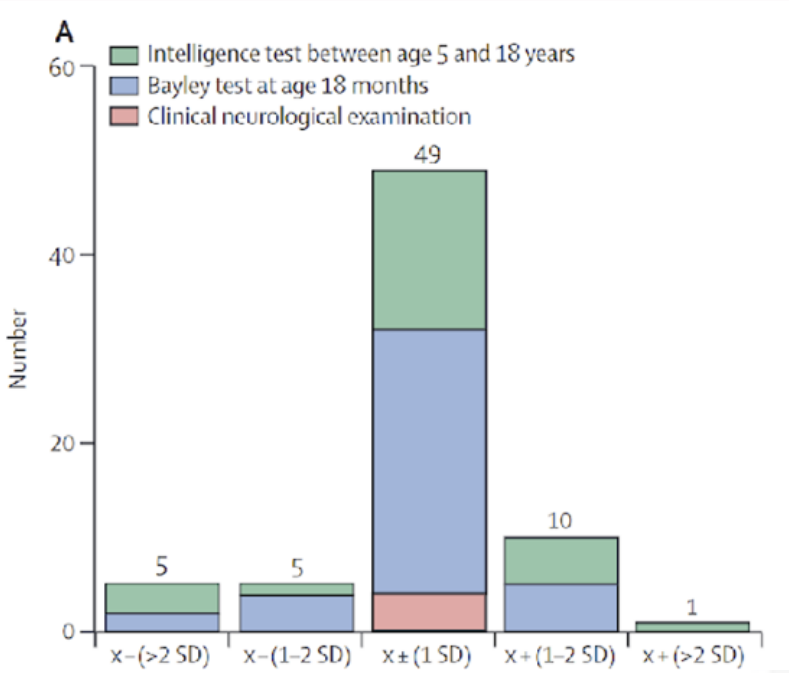
Avilés and Neri. Clinical Lymphoma 2001	N= 84 + 12 2nd generation children FU 18.7 year (range 6-29 year) (AraC-anthracycline, MOPP/ABVD, CHOP)	Normal biometry, neurological maturation, school results, IQ
Aviles et al, Ann Oncol 2006	N=81 (anthracyclines) FU 18.7 year (range 6-29 year)	Normal physical examination and echocardiography every 5 y Normal echocardiography and fraction shortening
Mathelin et al. Eur J Obstet Gynecol 2005	N=4 (FEC) FU: 1y, 3.5y, 11y, 17y	Normal physical, neurolopsychological , haematological function. IQ-scores
Zemlickis **Teratog Carcinog Mutagen 1993**	N=1, twin ALL Cyclophosphamide	- ♂, congenital malformations at 11 year thyroid cancer, at 14 year neuroblastoma - Twin sister is healthy

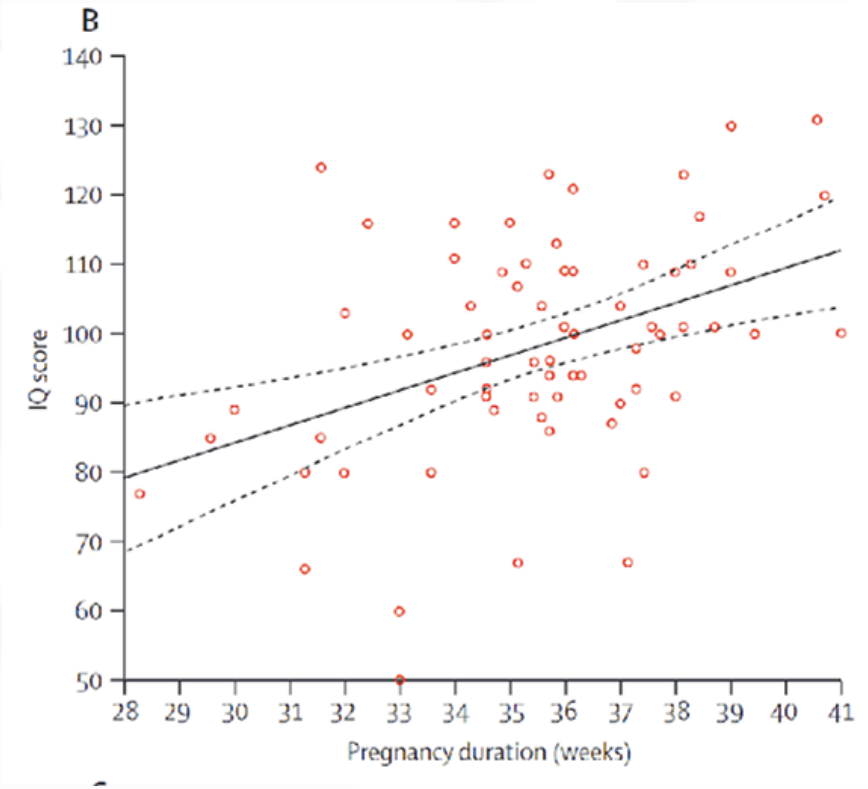
MILAN ULTRASOUND GYNECOLOGIC ONCOLOGY

Chemotherapy: long term neonatal outcome

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





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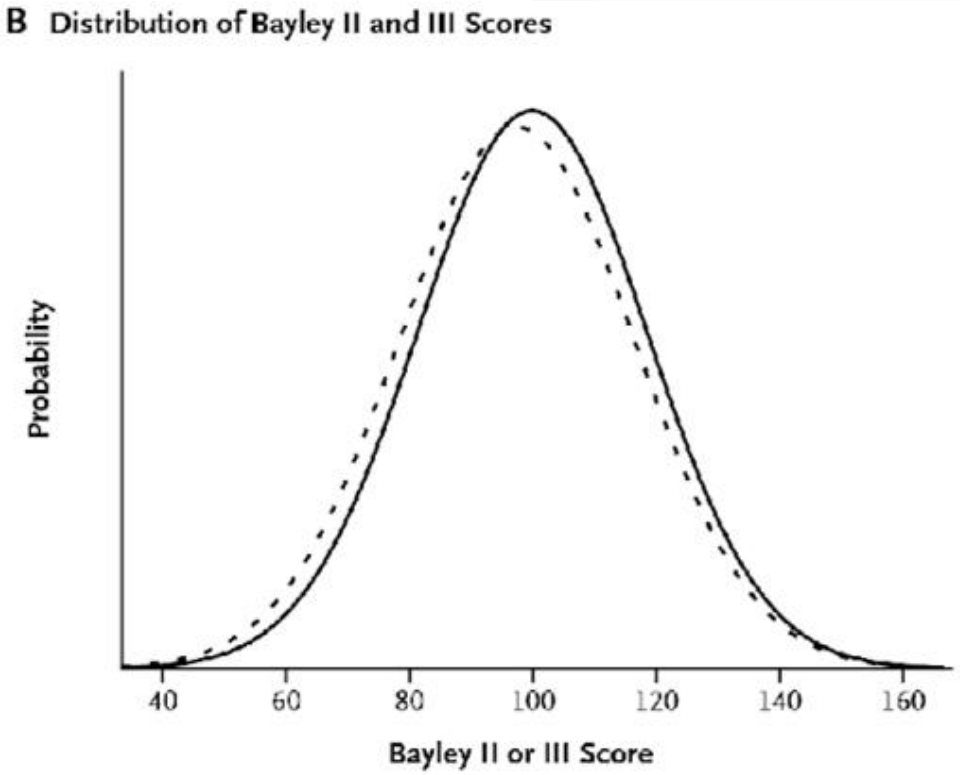
Chemotherapy: long term neonatal outcome

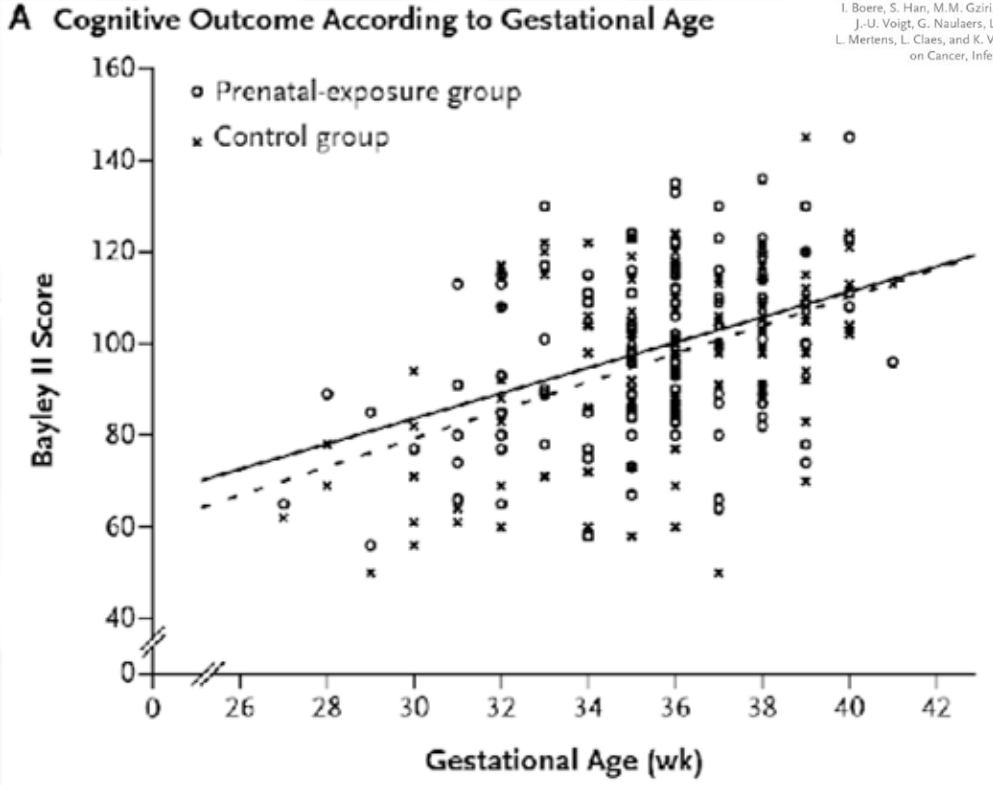
The NEW ENGLAND JOURNAL of MEDICINE

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. Vallaeys, F. Van den Heuvel, L. Lagae, L. Mertens, L. Claes, and K. Van Calsteren, for the International Network on Cancer, Infertility, and Pregnancy (INCIP)



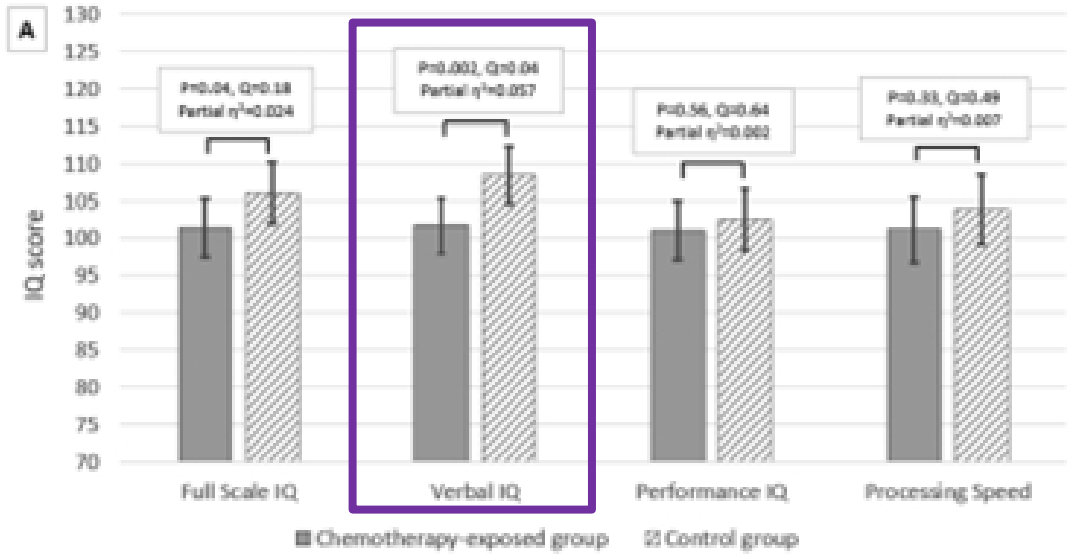


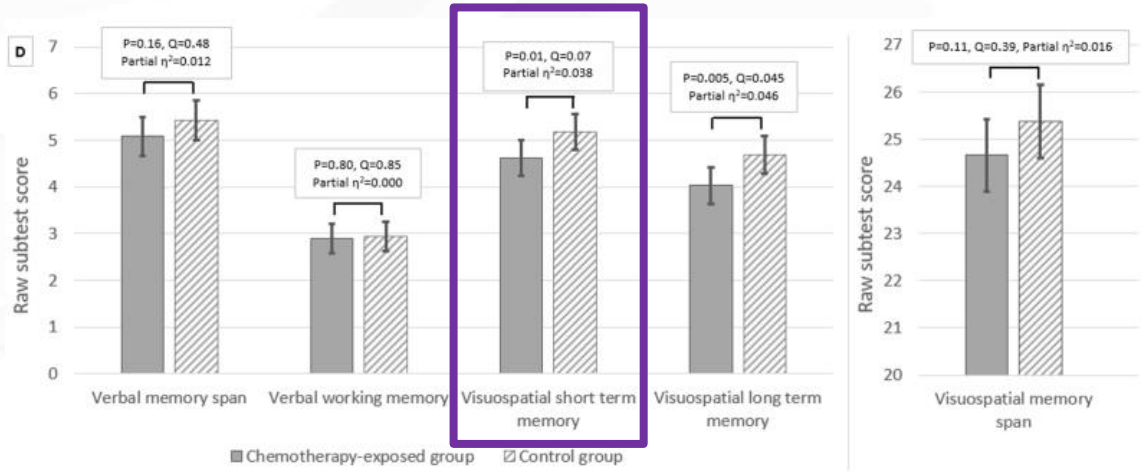
Chemotherapy: neonatal outcome

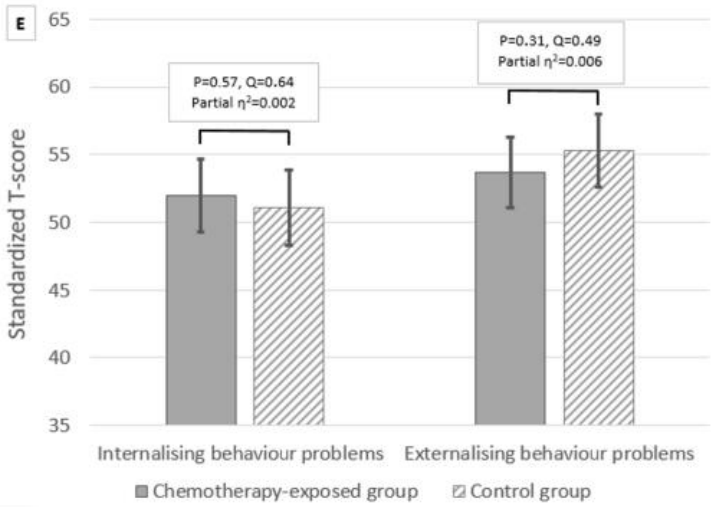
Original Research

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

Tineke Vandenbroucke [a,b,1], Magali Verheecke [a,b,1], Mathilde van Gerwen [c,d,1], Kristel Van Calsteren [a,e], Michael J. Halaska [f,g], Monica Fumagalli [h,i], Robert Fruscio [j], Amarendra Gandhi [k,l], Margreet Veening [d], Lieveen Lagae [m], Petronella B. Ottevanger [n], Jens-Uwe Voigt [o], Jorine de Haan [p], Mina M. Grziri [q], Charlotte Maggen [a,b], Luc Mertens [r], Gunnar Naulaers [s], Laurence Claes [t], Frédéric Amant [b,e,u,v] on behalf of The International Network on Cancer, Infertility and Pregnancy (INCIP)[1]







The point of view of the mother

- Will I be able to reach the term of pregnancy?
- Will the treatments have a bad influence on the pregnancy?
- Will my baby be healthy?
- Will my baby have a normal life?
- Will the pregnancy have a negative impact on my prognosis?

Will irradiation hurt my baby?

Technical examinations

- Irradiation in pregnancy: energy that comes from a source and travels through some material or through space
  - Non-ionizing radiation
  - Ionizing radiation
    - Deterministic effects
    - Stochastic effects
- Consider background radiation exposure

Diagnostic tools during pregnancy

Technical examinations

Irradiation in pregnancy

- Damage by ionizing radiation caused by deposition of energy in tissue: deterministic effects

	2 weeks	2-8 weeks	8-15 weeks	15-25 weeks	Term
Prenatal Mortality	100-200 mGy	250-500 mGy		5 Gy	20 Gy
Malformations		100-200 mGy			
Mental retardation			100 mGy	250 mGy	

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TABLE 2
Estimated fetal radiation absorption per procedure or event[11-17]

Clinical suspicion	Procedure	Estimated fetal absorption (mGy) per procedure	Estimated fetal absorption (rad) per procedure
Pneumonia	X-ray chest	<0.01	<0.001
Pulmonary embolism	CT scan	0.06-0.96	0.006-0.096
	VP scan	0.1-0.37	0.01-0.037
Appendicitis	Ultrasound	Nonionizing radiation	Nonionizing radiation
	CT scan abdomen	8-49	0.8-0.49
	MRI	Nonionizing radiation	Nonionizing radiation
Nephrolithiasis	Ultrasound	Nonionizing radiation	Nonionizing radiation
	X-ray abdomen	1-4.2	0.1-0.42
	Pyelogram	1.7-10	0.17-1
	CT scan abdomen	8-49	0.8-4.9
	MRI	Nonionizing radiation	Nonionizing radiation
Breast nodule	Ultrasound	Nonionizing radiation	Nonionizing radiation
	Mammogram	0.07-0.2	0.007-0.02
Colon pathology	X-ray abdomen	1-4.2	0.1-0.42
	Barium enema	7	0.7
Trauma			
Spine injury	X-ray lumbar spine	6	0.6
	X-ray thoracic/cervical spine	<0.01	<0.001
	X-ray skull	<0.01	<0.001
Pelvic injury	X-ray pelvis	1.1-4	0.11-0.4
	CT scan pelvis	20-79	2.0-7.9
Abdominal injury	Ultrasound (FAST)	Nonionizing radiation	Nonionizing radiation
	CT scan abdomen	8-49	0.8-4.9
	MRI	Nonionizing radiation	Nonionizing radiation
Background radiation	None	1 mSv	0.1 rem[a]
Commercial flight	Round trip Toronto-Frankfurt	0.1 mSv	0.01 rem[a]
	100 h of commercial flying	1 mSv	0.1 rem[a]

Table 2 Fetal radiation dose for the different ionizing radiation techniques (modified after[7,9])

Imaging technique	Fetal radiation dose (mGy)
Chest X-ray	<0.01
Mammography (two planes, bilateral)	<0.01
CT of the head	<0.005–0.5
CT of the chest	0.001–0.66
CT of the abdomen/pelvis	8–25
^{99m}Tc bone scintigraphy	3.3
^{18}F-FDG PET/CT	10–50

Vandecaveye V. et al Imaging modalities in pregnant cancer patients. Int J Gynecol Cancer. 2021 Mar;31(3):423-431

Groen RS et al. Fear of the unknown: ionizing radiation exposure during pregnancy. Am J Obstet Gynecol. 2012 Jun;206(6):456-62

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Surgery: general considerations

- Timing of surgery
- Laparoscopy or laparotomy
- Position of the patient
- Maintenance of maternal pressure
- Assessment of fetal health
- Tocolysis
- Thromboprophylaxis

Radiotherapy

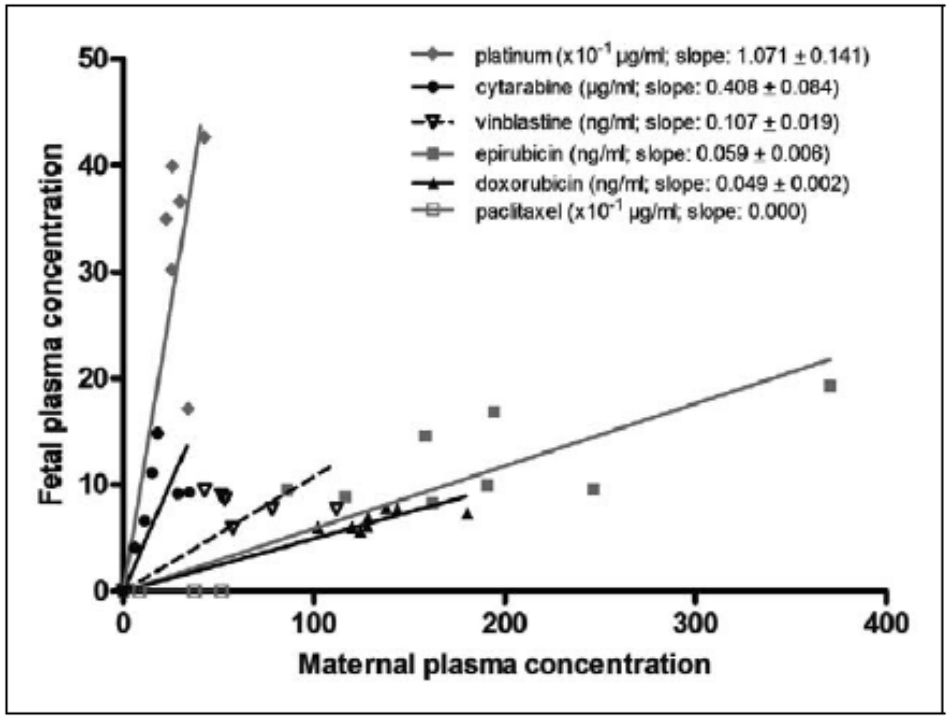
Field size (cm^2)	Conceptus dose (cGy)		
	First trimester	Second trimester	Third trimester
4.5 × 11.0	2.1–2.9	2.2–7.5	2.2–16.8
6.0 × 12.5	2.8–3.9	2.9–10.4	3.3–23.8
8.0 × 14.0	3.5–5.1	3.7–13.9	4.0–34.7
10.0 × 16.0	4.4–6.2	4.7–18.2	5.0–45.2
11.5 × 18.0	5.2–7.6	5.9–24.6	6.5–58.6

- Safe during 1° and 2° trimester
- Contrindicated during 3° trimester

Mazonakis M et al. Radiation dose to conceptus resulting from tangential breast irradiation. Int J Radiat Oncol Biol Phys. 2003 Feb 1;55(2):386-91

Chemotherapy

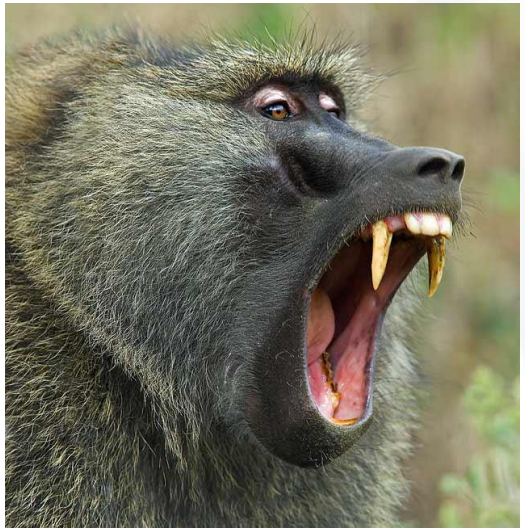
- Transplacental transfer in a mouse model
  - Wide variation among tested drugs
  - High transfer for platinum and cytarabine

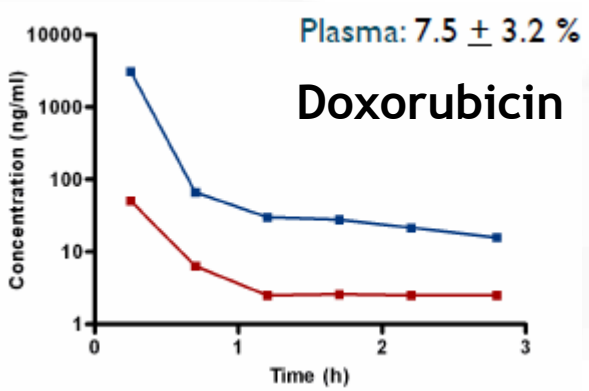


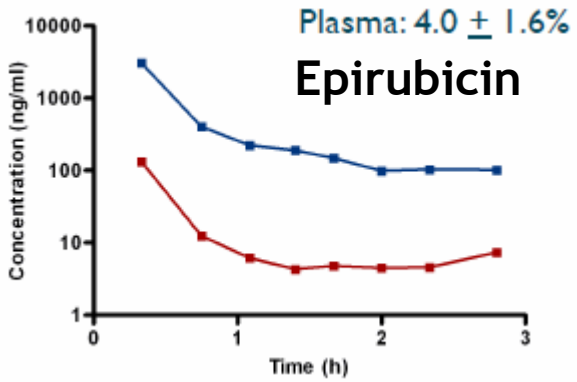
Van Calsteren K et al. Substantial Variation in Transplacental Transfer of Chemotherapeutic Agents in a Mouse Model. Reproductive Sciences 18(1) 57-63

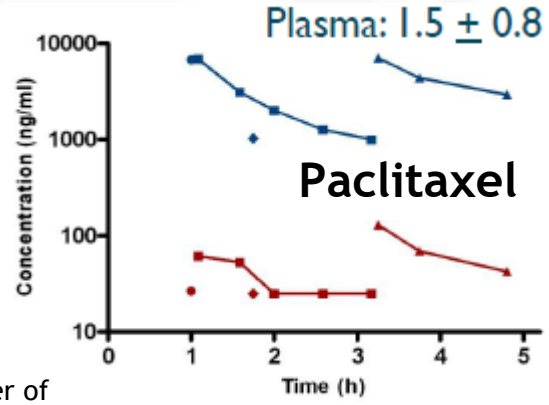
Chemotherapy

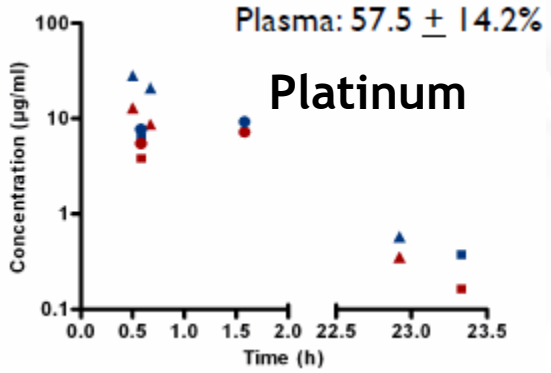
- Transplacental transfer in a baboon model











Van Calsteren K et al. Transplacental transfer of paclitaxel, docetaxel, carboplatin, and trastuzumab in a baboon model. Int J Gynecol Cancer. 2010 Dec;20(9):1456-64

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Chemotherapy

Physiological changes during pregnancy	Pharmacokinetic consequence
Delayed gastrointestinal (GI) motility	Delayed but more complete absorption
Altered hepatic function	↑ or ↓ metabolism
Changes in plasma protein levels and altered protein binding	Changes in free drug concentrations
↑ fat stores	↑ distribution volume
↑ plasma and extracellular fluid volume (by almost 50%)	↑ distribution volume
Amniotic fluid may behave as a third space for drugs	Prolonged exposure and delayed elimination
↑ renal blood flow and glomerular filtration rate	↑ renal elimination

Parameter	Mean Pregnant / Mean nonpregnant			
	Paclitaxel N=Pr 5 / NPr 2	Carboplatin N=Pr 2 / NPr 2	Doxorubicin N=Pr 7 / NPr 5	Epirubicin N=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 ↑

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MILAN ULTRASOUND GYNECOLOGIC ONCOLOGY

Chemotherapy: neonatal outcome

- Short term outcome: reassuring

Ebert et al Pharmacol Ther 1997	N= 217 Review 1983-1995	8.3% congenital anomalies, 0.9% chromosomal anomalies 1.8% MIU, 6.9% spontaneous miscarriage
Cardonick & Iacobucci Lancet Oncol 2004	N=376 Review 1966-2004	5% MIU, 1% neonatal † 9/11 malformations after 1st trim exposure 7% IUGR, 5% prematurity (without iatrogenic cases) 4% neonatal transient myelosuppression
Ring et al, J Clin Oncol 2005	N= 28 (FAC)	3.6% miscarriage, 3.6% hemangioma, transfer NICU: 17.9% 32% preterm delivey (4% spontaneous, 28% iatrogenic)
Hahn et al. Cancer 2006	N=57	Preeclampsia with IUGR (n=1), Down, (n=1), clubfoot (n=1), subarachnoidal hemorrhage with neutropenia and thrombocytopenia; (n=1)
Peccatori et al, Breast Cancer Res Treat 2009	N=20 (epirubicin weekly)	Polycystic kidney (n=1), early preterm delivery (n=1). At 24 months, all normal development, as reported by parents
Garcia-Manero et al., Eur J Surg Oncol 2009	N=17 (FEC, taxanes)	IUGR (n=1), cerebral palsy (n=1) probably due to intrapartum distress
Cardonick et al, Cancer 2010	N=104 ((F)AC, FEC, adria mono, navelbine, paclitaxel, docetaxel, taxotere)	8% IUGR, 1% placental abruption, 1% placenta praevia, 1% PVL, 3% congenital anomalies, 3% neonatal myelosuppression, 1 child died at 1 year due to severe autoimmune disorder

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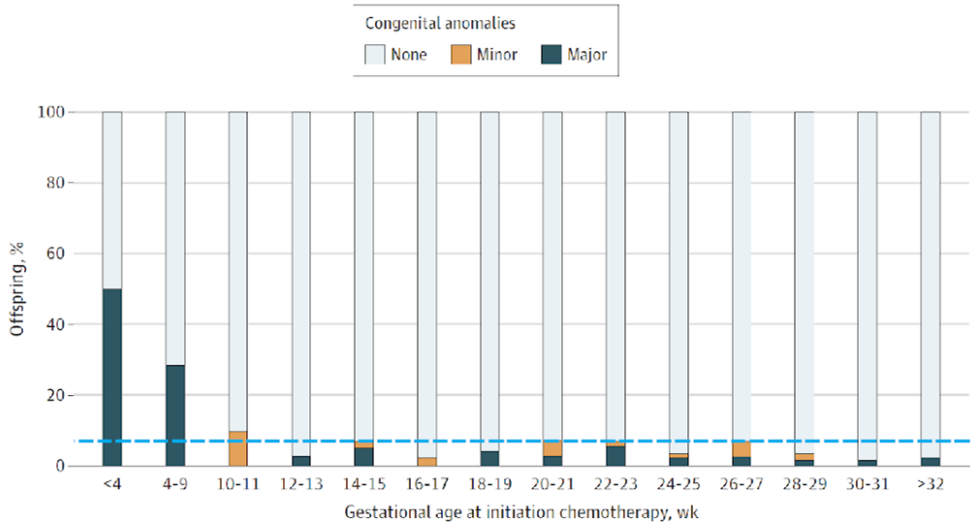
Chemotherapy: neonatal outcome

Figure. Frequency of Congenital Malformations According to Gestational Age at First Chemotherapy Exposure



Conclusions

These findings suggest that chemotherapy during the first 12 weeks of pregnancy was associated with increased risk for congenital malformations in the fetus. If an aggressive cancer diagnosis during early pregnancy does not allow treatment delay, parents should be counseled on fetal risks of malformations. If a patient incidentally becomes pregnant while receiving chemotherapy, prenatal counselling should include the risks of both short- and long-term adverse outcomes. Adequate anticonception and routine pregnancy tests should be offered to fertile women with cancer.

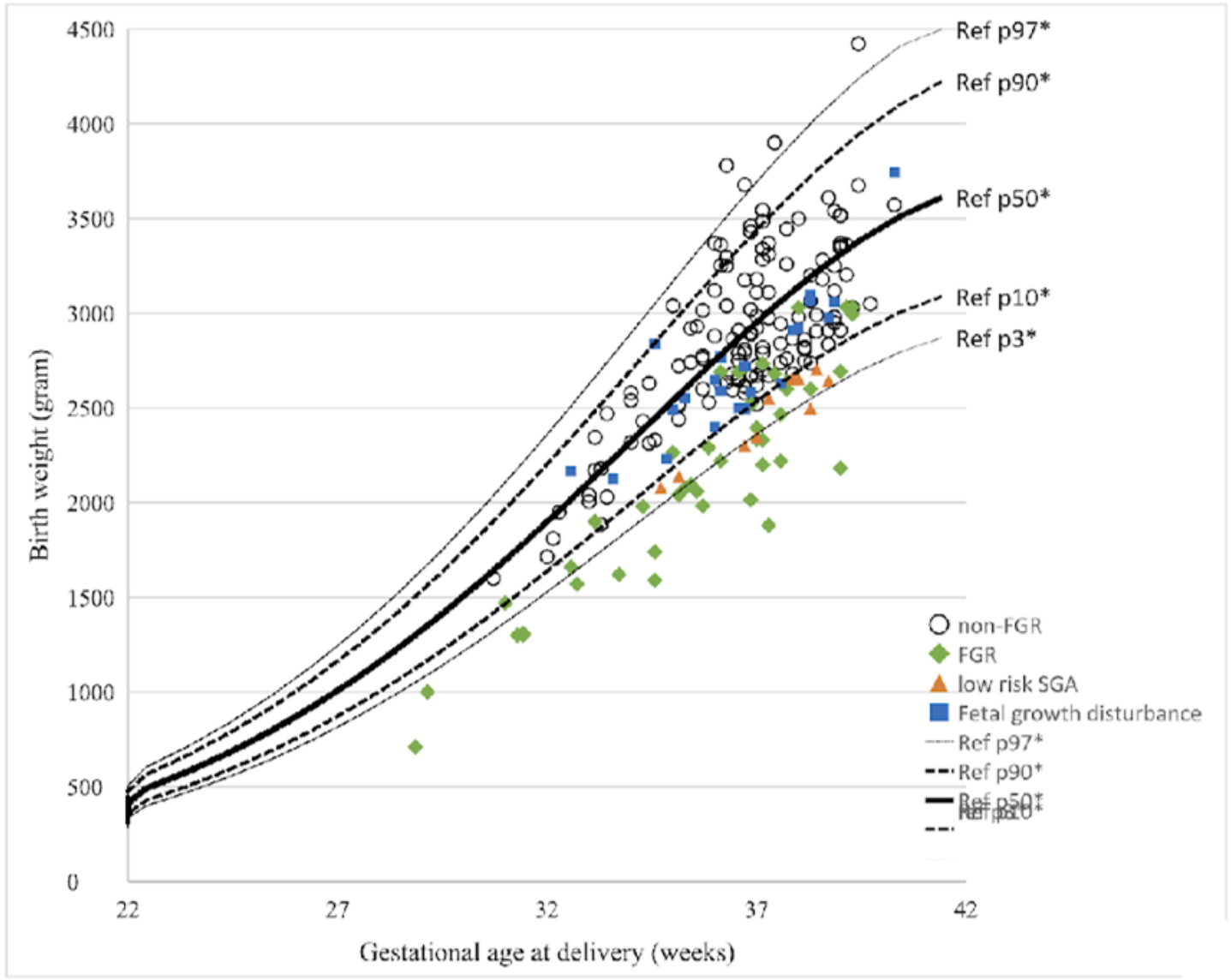
Van Gerwen M et al. Association of Chemotherapy Timing in Pregnancy With Congenital Malformation. JAMA Netw Open. 2021 Jun 1;4(6):e2113180

The point of view of the mother

- Will I be able to reach the term of pregnancy?
- Will the treatments have a bad influence on the pregnancy?
- Will my baby be healthy?
- Will my baby have a normal life?
- Will the pregnancy have a negative impact on my prognosis?

Figures

Figure 1: Scatter plot of birthweight according to gestational age at delivery, plotted on the reference chart by Nicolaides et al., 2018 (n=2

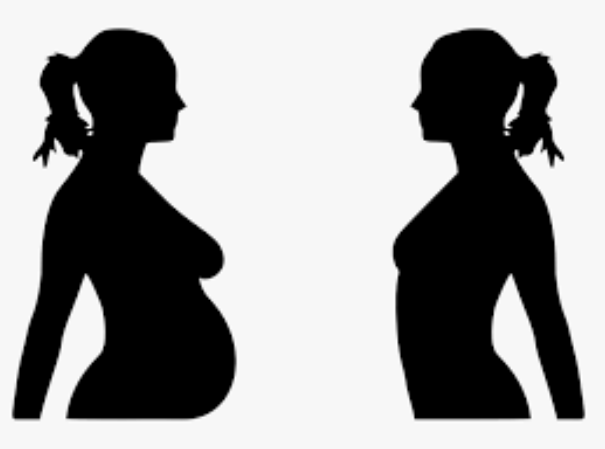


	PPROM or preterm contractions		Small for gestational age		Neonatal intensive care unit admission	
	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
Cancer type	..	0·16	..	0·86	..	<0·0001
Breast cancer*	Reference	..	Reference	..	Reference	..
Cervical cancer	0·74 (0·27–2·04)	..	0·75 (0·36–1·55)	..	2·22 (1·19–4·15)	..
Lymphoma	1·24 (0·49–3·12)	..	1·17 (0·52–2·60)	..	1·04 (0·53–2·04)	..
Ovarian cancer	0·60 (0·16–2·30)	..	0·39 (0·14–1·09)	..	0·60 (0·26–1·38)	..
Leukaemia	2·45 (0·80–7·48)	..	0·68 (0·23–2·03)	..	1·27 (0·53–3·03)	..
Gastrointestinal cancer	0·33 (0·06–1·96)	..	0·80 (0·29–2·22)	..	7·13 (2·86–17·7)	..
Melanoma	0·76 (0·19–3·12)	..	0·90 (0·29–2·76)	..	0·36 (0·13–1·04)	..
Thyroid cancer	0·52 (0·09–3·12)	..	0·73 (0·21–2·58)	..	0·14 (0·02–0·90)	..
Other malignant diseases	0·44 (0·15–1·31)	..	0·82 (0·36–1·83)	..	1·42 (0·73–2·75)	..
Period of diagnosis	..	0·69	..	0·32	..	0·019
1996–2004	Reference	..	Reference	..	Reference	..
2005–09	0·81 (0·44–1·48)	..	0·77 (0·45–1·31)	..	0·73 (0·48–1·11)	..
2010–16	0·77 (0·43–1·39)	..	1·04 (0·63–1·73)	..	0·55 (0·36–0·84)	..
Age at diagnosis (per 5 years)	1·08 (0·86–1·35)	0·53	1·36 (1·11–1·68)	0·0033	0·98 (0·82–1·17)	0·65
Diagnosis in third trimester vs before	0·64 (0·35–1·15)	0·14	0·78 (0·48–1·27)	0·33	1·13 (0·77–1·65)	0·52
Systemic vs non-systemic disease	1·43 (0·70–2·92)	0·34	1·86 (1·04–3·33)	0·039	1·14 (0·68–1·93)	0·52
Chemotherapeutic agents	..	0·056	..	<0·0001	..	0·0086
Non-platinum alkylating (yes vs no)	2·02 (0·81–5·02)	..	2·08 (0·88–4·91)	..	0·88 (0·46–1·70)	..
Anthracyclines (yes vs no)	1·11 (0·42–2·92)	..	0·50 (0·21–1·22)	..	1·21 (0·62–2·38)	..
Antimetabolites (yes vs no)	0·89 (0·46–1·71)	..	1·24 (0·70–2·22)	..	1·03 (0·60–1·74)	..
Taxanes (yes vs no)	1·11 (0·53–2·33)	..	2·07 (1·11–3·86)	..	2·37 (1·31–4·28)	..
Platinum (yes vs no)	2·29 (0·79–6·63)	..	3·12 (1·45–6·70)	..	1·66 (0·77–3·55)	..
Other (yes vs no)	1·48 (0·61–3·63)	..	2·34 (1·04–5·25)	..	1·63 (0·78–3·38)	..
Abdominal or cervical surgery (yes vs no)	0·42 (0·15–1·16)	0·083	1·31 (0·67–2·59)	0·45	0·30 (0·17–0·55)	<0·0001

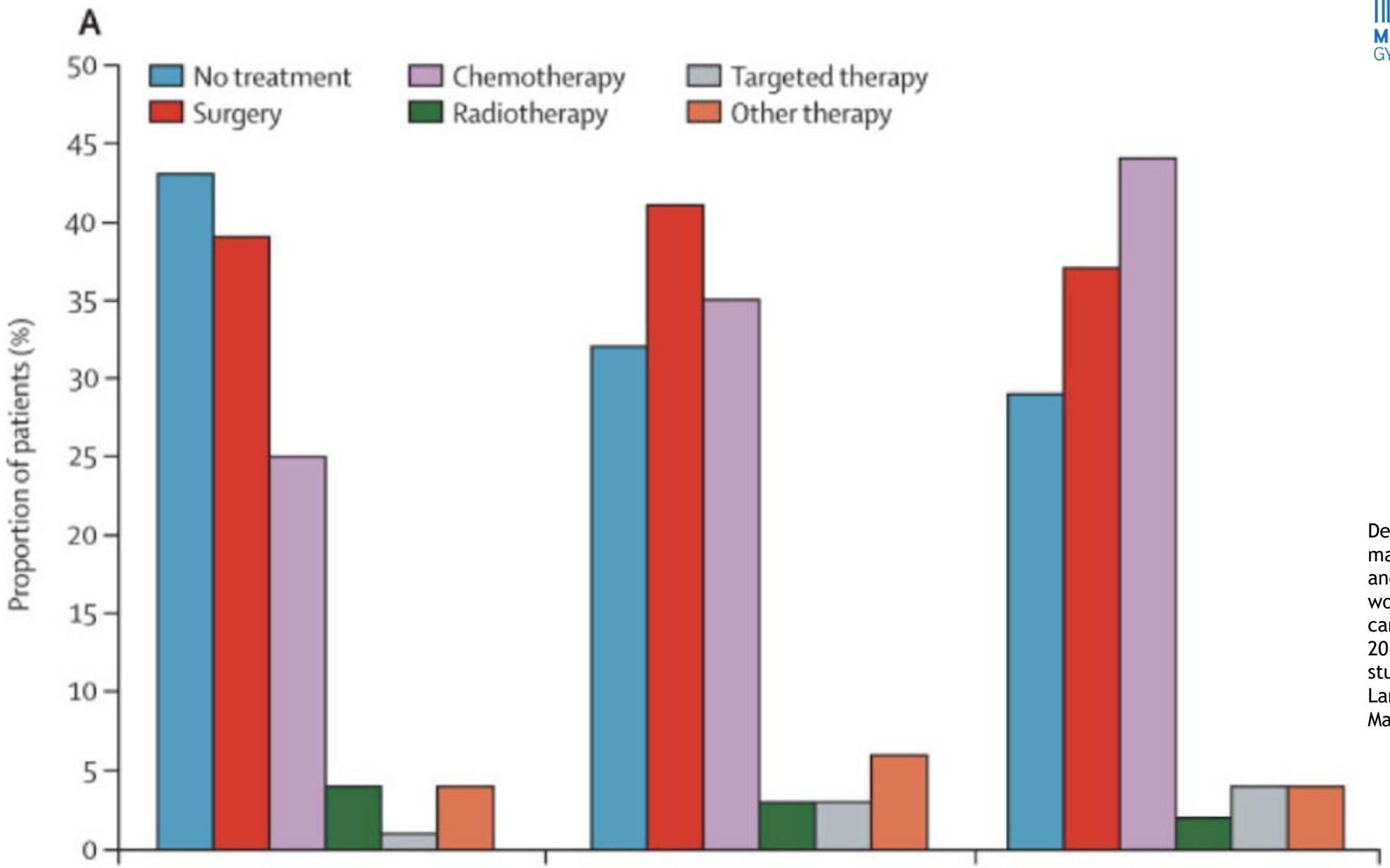
De Haan J et al. Oncological management and obstetric and neonatal outcomes for women diagnosed with cancer during pregnancy: a 20-year international cohort study of 1170 patients. Lancet Oncol. 2018 Mar;19(3):337-346.

The two aims that should be obtained

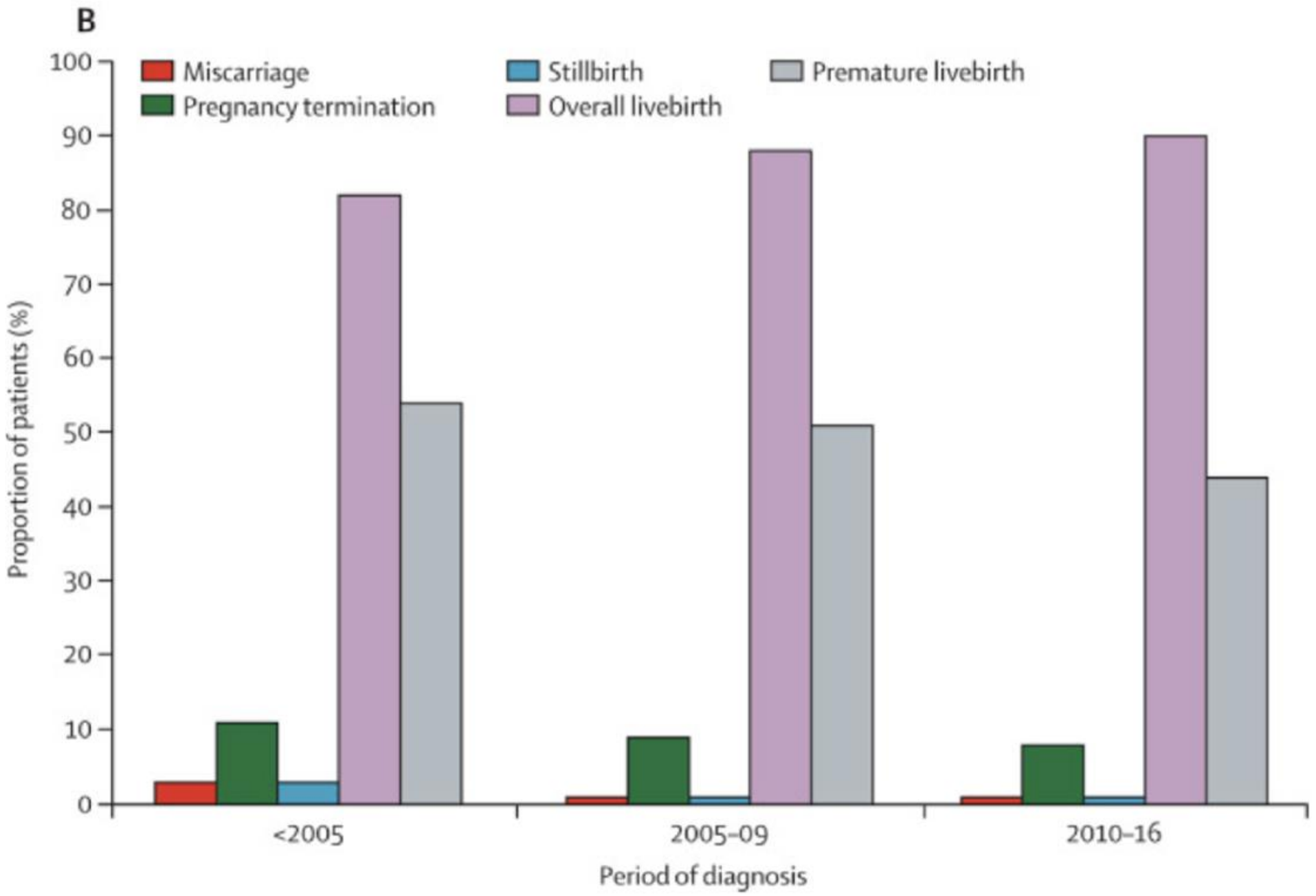
- Pregnant patients should as much as possible be treated as non-pregnant patients



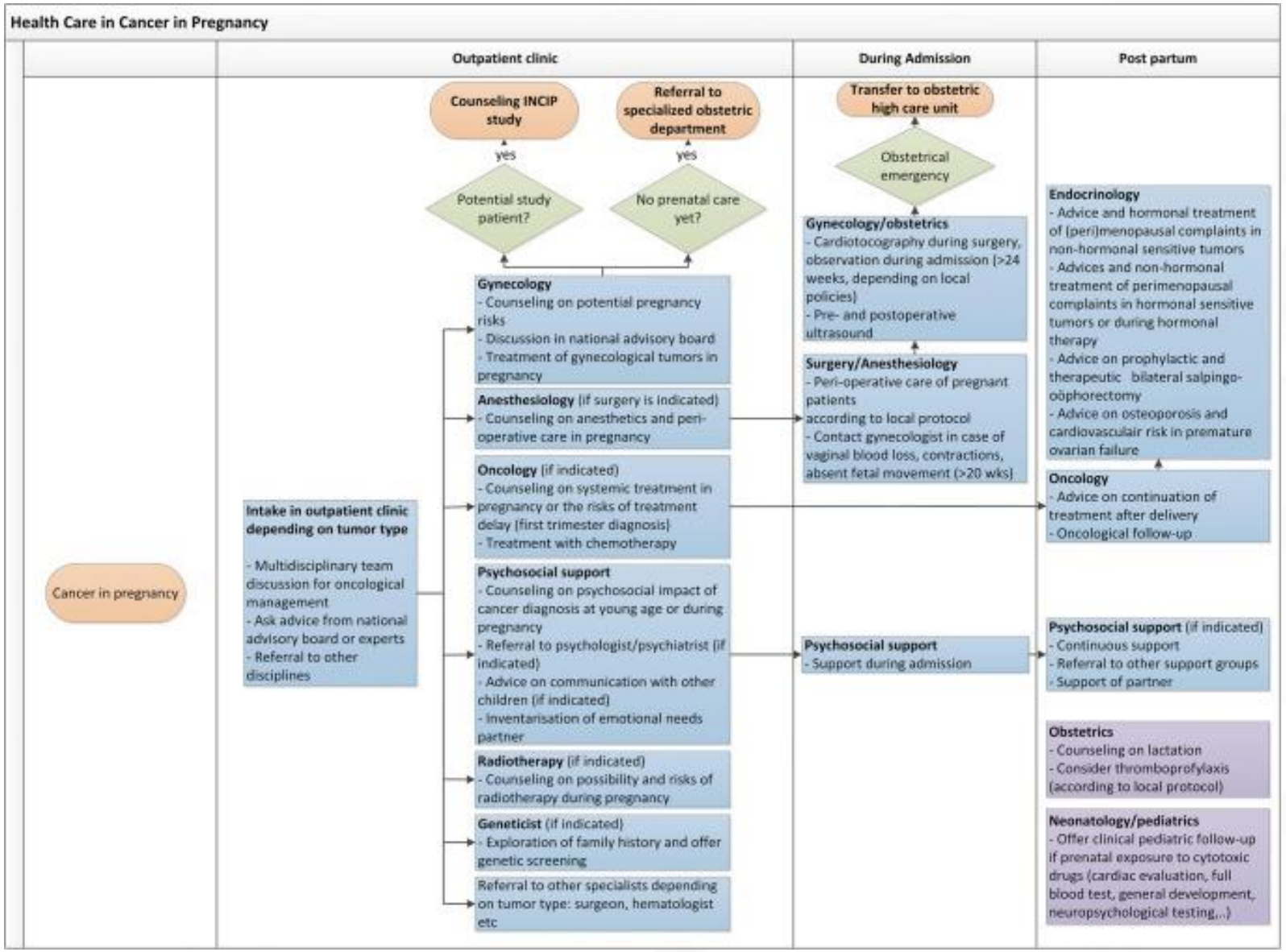
- Preterm delivery must be avoided



De Haan J et al. Oncological management and obstetric and neonatal outcomes for women diagnosed with cancer during pregnancy: a 20-year international cohort study of 1170 patients. Lancet Oncol. 2018 Mar;19(3):337-346.

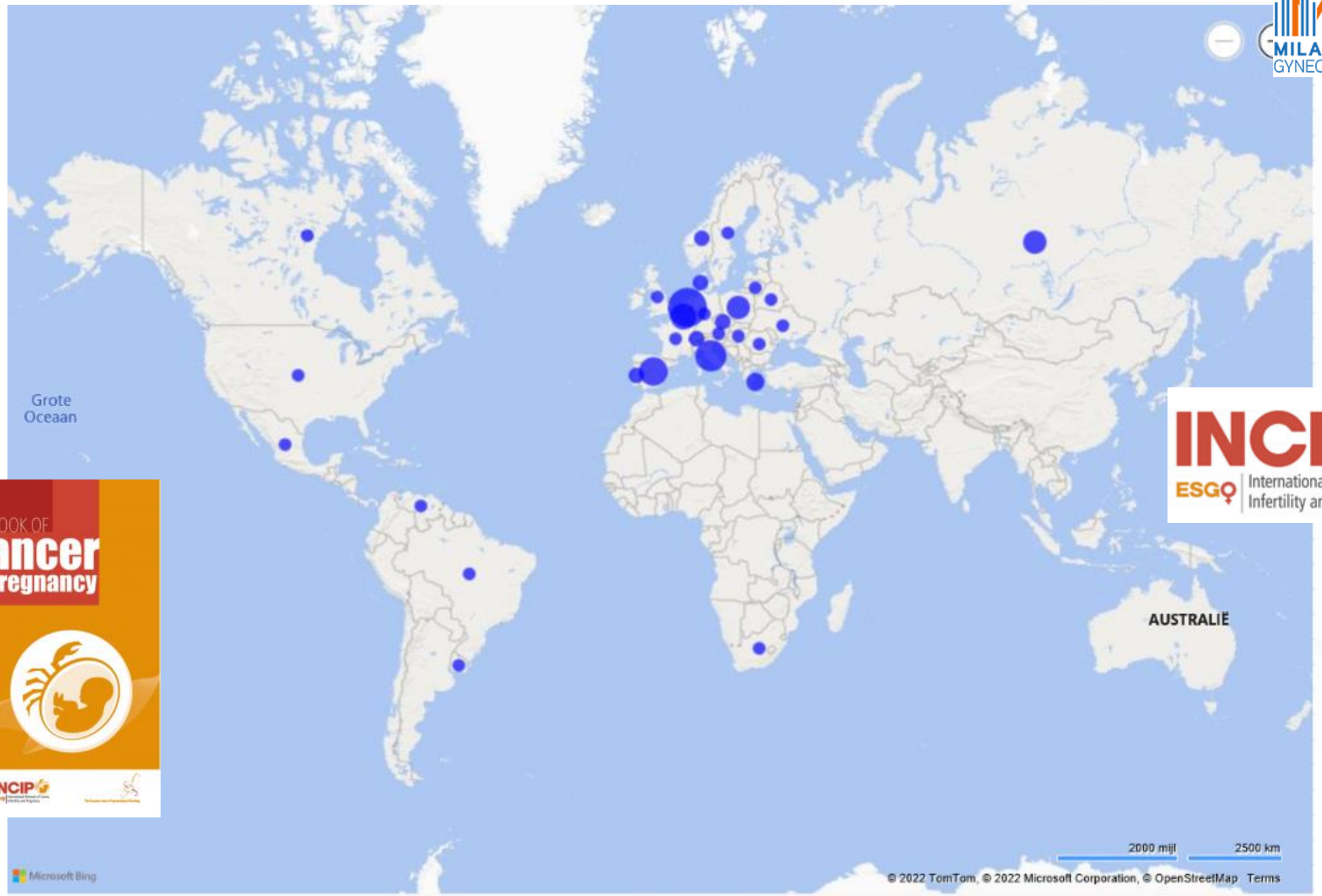


De Haan J et al. Oncological management and obstetric and neonatal outcomes for women diagnosed with cancer during pregnancy: a 20-year international cohort study of 1170 patients. Lancet Oncol. 2018 Mar;19(3):337-346.



Maggen C et al. Pregnancy and Cancer: the INCIP Project. Curr Oncol Rep. 2020 Feb 5;22(2):17

MILAN ULTRASOUND GYNECOLOGIC ONCOLOGY



INCIP
ESGO International Network on Cancer, Infertility and Pregnancy

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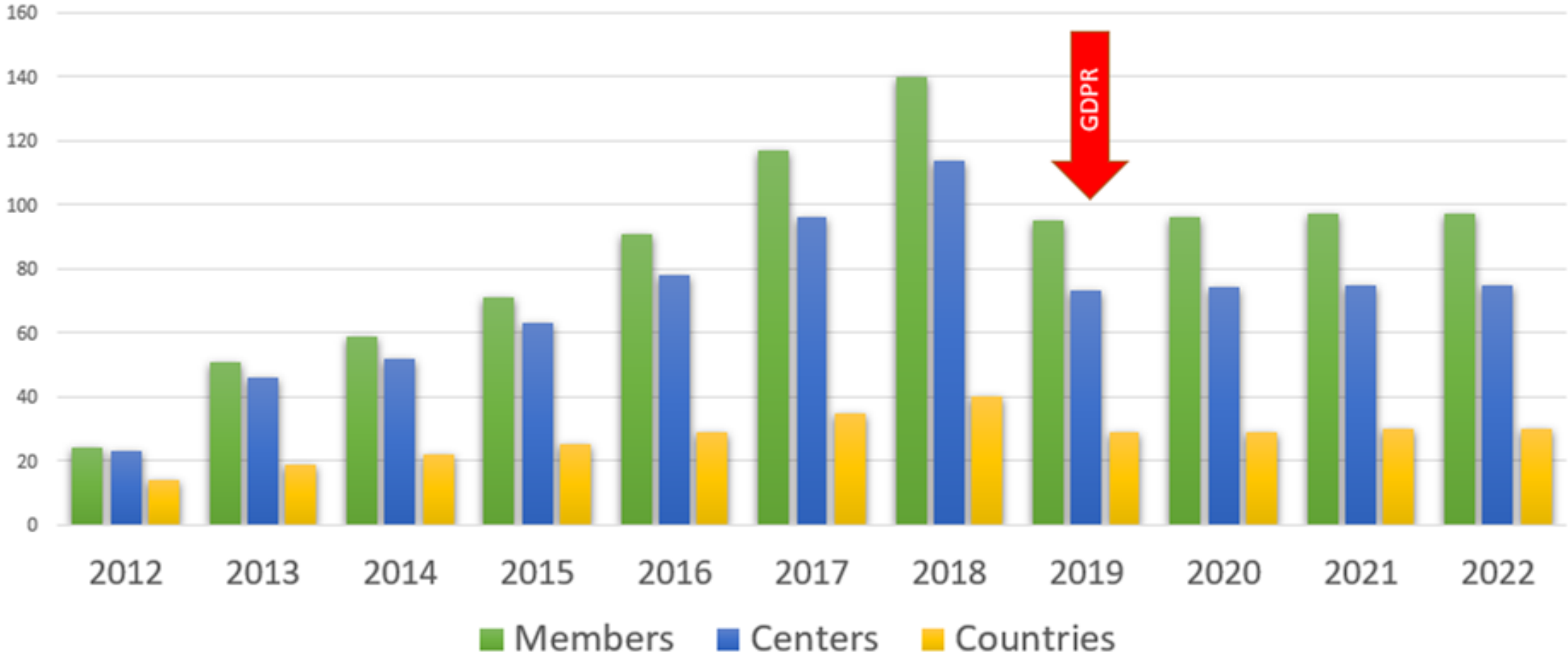
INCIP - membership (04/2022)



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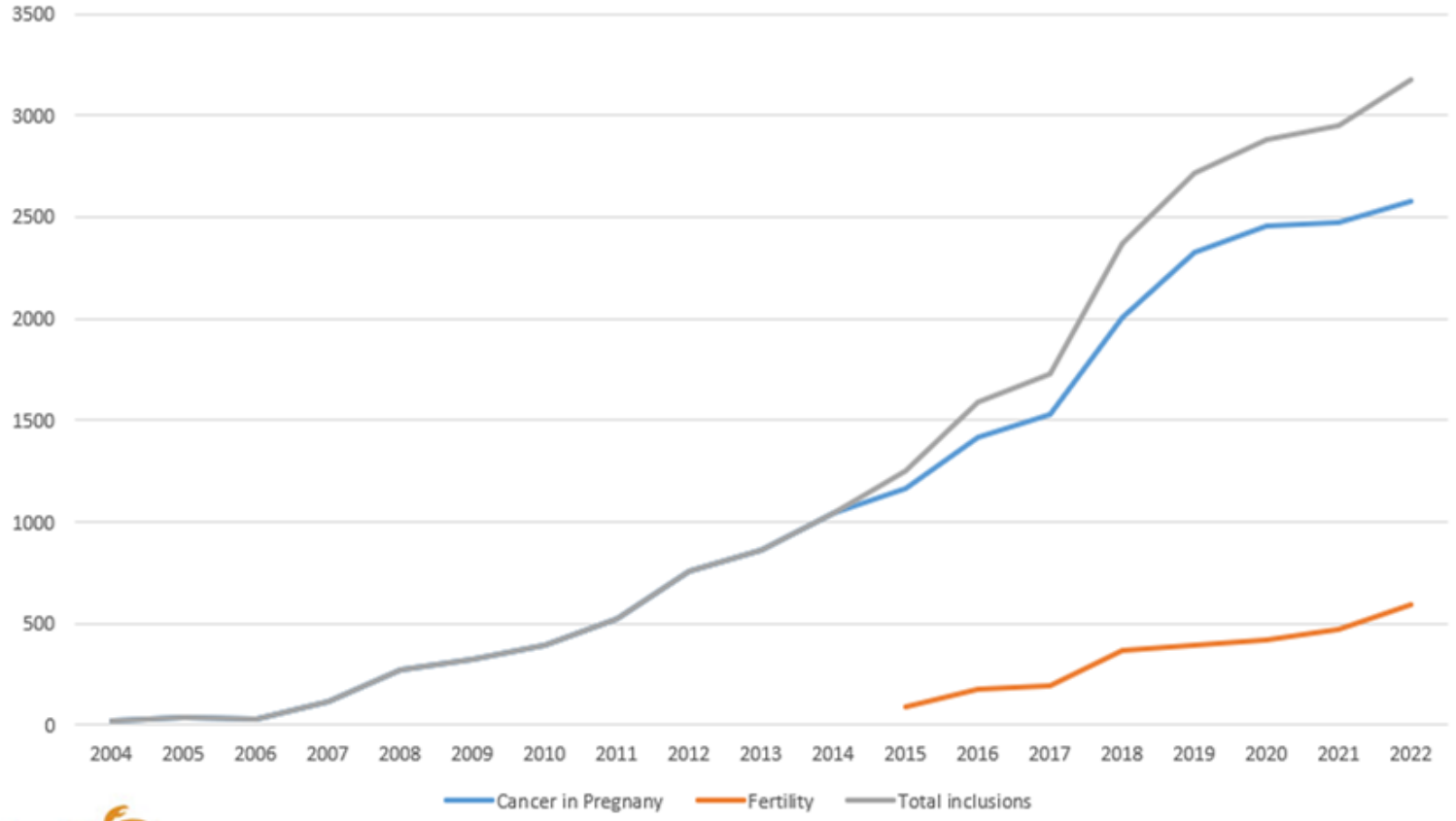
INCIP registration study: total patient inclusions (13/04/2022)



Total inclusions: 3173 patients

2577 CIP patients

546 Fertility preservation patients

From 75 centers

In 30 countries

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Thanks!!

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