Treatment of breast cancer diagnosed during pregnancy (BCP)

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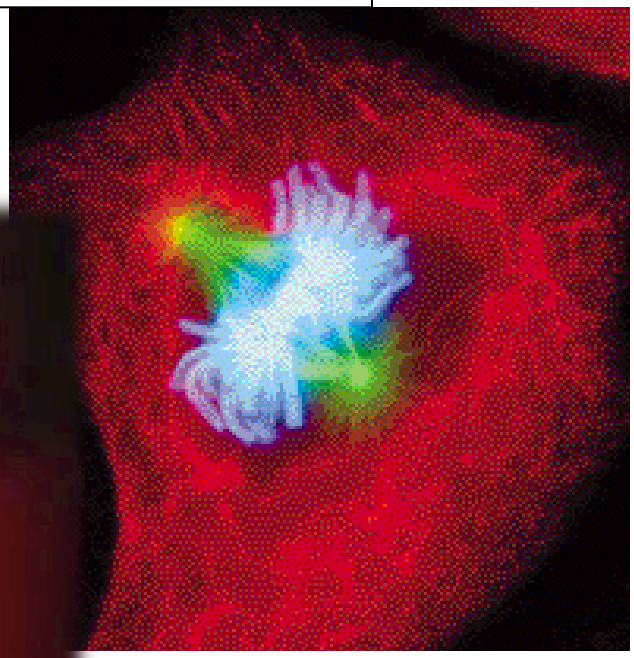
Århus 18/5 -2016

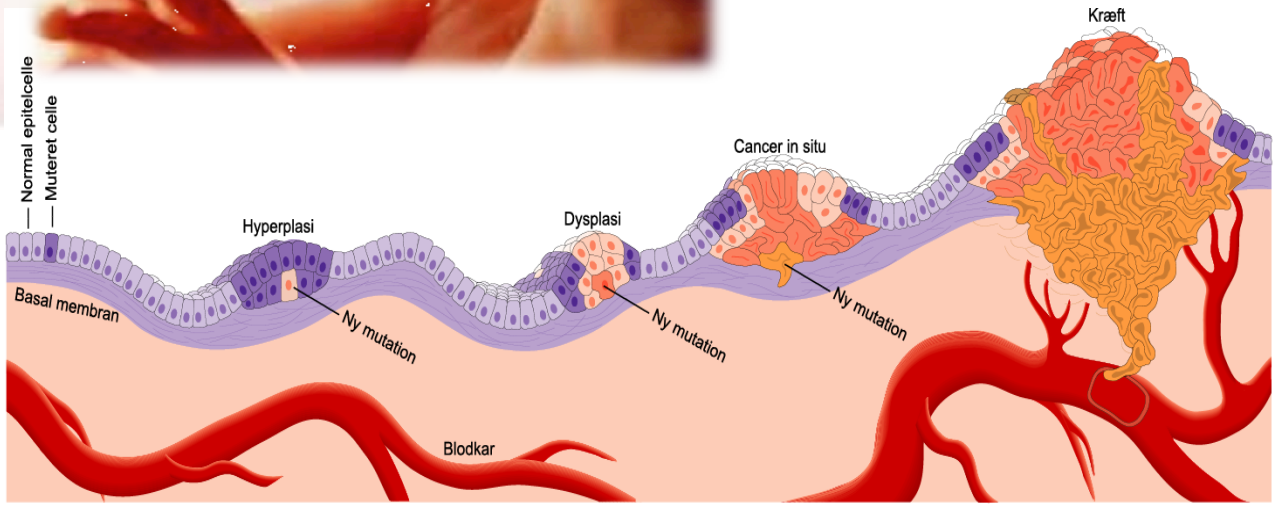
Breast cancer during pregnancy(BCP)

DBCG



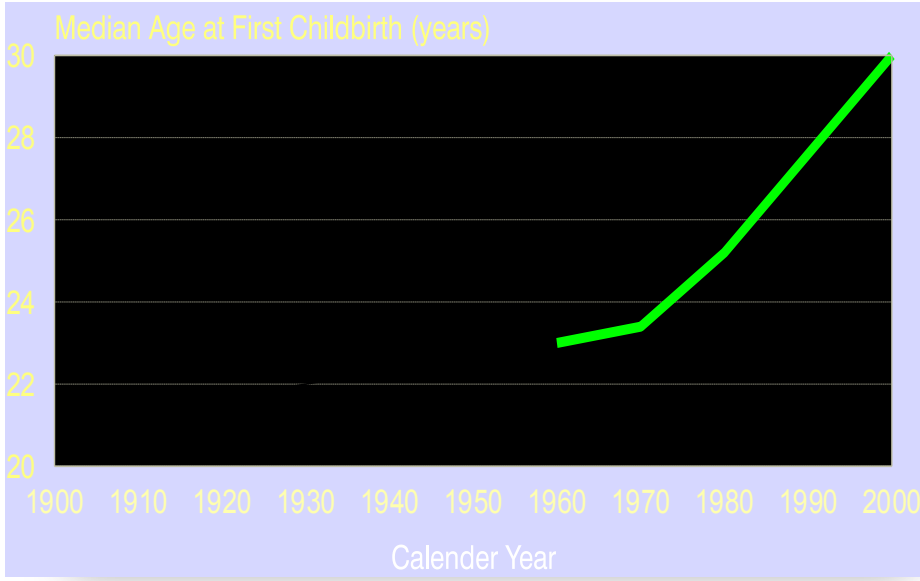
INCIP

ESGO International Network on Cancer, Infertility and Pregnancy



Incidence of cancer during pregnancy

- Cancer during pregnancy 1 : 2000
- About 40% is ass. with breast-cancer
- BC in Age 25-29 , 20% are ass.to pregn.
- 19% diagn. in 1.trim.
- 10-15 pat./year in DK.
- 2-5 pat./ year in Vejle.
- 31 pat.2002-2016.(DB)
- 5 patients 2015.
- Currently 3 in treatment



What to do with breast cancer during pregnancy?

Past:

Termination of pregnancy or preterm delivery

→ oncologic treatment afterwards

NICU admission
Respiratory distress
Metabolic: hypoglycemia
Hyperbilirubinaemia
Feeding problems, GI complications
Apnea
Susceptibility to infections
Neuropsychological outcome

What to do with breast cancer during pregnancy?

Present:

Treatment during pregnancy as similar as possible to that for nonpregnant women with breastcancer

Avoid preterm birth

Maternal prognosis

VOLUME 31 · NUMBER 20 · JULY 10 2013

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Prognosis of Women With Primary Breast Cancer Diagnosed During Pregnancy: Results From an International Collaborative Study

Frédéric Amant, Gunter von Minckwitz, Sileny N. Han, Marijke Bontenbal, Alistair E. Ring, Jerzy Giermek, Hans Wildiers, Tanja Fehm, Sabine C. Linn, Bettina Schlehe, Patrick Neven, Pieter J. Westenend, Volkmar Müller, Kristel Van Calsteren, Brigitte Rack, Valentina Nekljudova, Nadia Harbeck, Michael Untch, Petronella O. Witteveen, Kathrin Schwedler, Christoph Thomssen, Ben Van Calster, and Sibylle Loibl

Multicentric European cohort study

Period 2000-2011

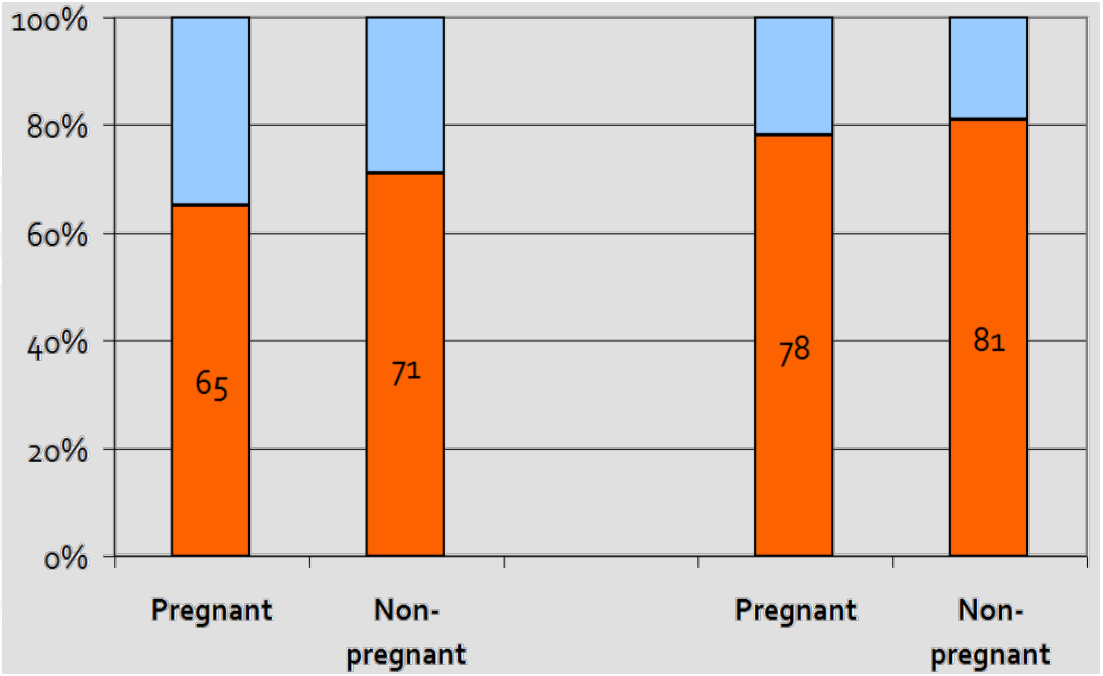
Median follow-up 61 months

311 pregnant patients vs 865 controles (1:3)

Cox proportional hazards regression
Effect of pregnancy

Outcome, analysis	Coefficient	SE	HR (95% CI)	P
DFS				
Main analysis: IPW on age	0.289	0.197	1.34 (0.93 – 1.91)	0.14
OS				
Main analysis: IPW on age	0.173	0.261	1.19 (0.73 – 1.93)	0.51

DFS



OS

Adjusting for age, stage, grade, hormone receptor status, HER2 status, histology, type of treatment

Comparison with outcome in literature

Table 4. Outcome Rates of Breast Cancer During Pregnancy As Reported in Literature Since 1985*

Study	Year	Total Patients: Pregnant No.	Pregnant %	Postpartum No.	Postpartum %	Nonpregnant No.	Follow-Up Period	DFS (%): Pregnant	DFS (%): Nonpregnant	OS (%): Pregnant	OS (%): Nonpregnant	Authors' Conclusion
Nugent and O'Connell[17]	1985	19				155	5 years			57	56	No difference in OS
Greene[18]	1988	8				36	90 months			87.5	81.7	No difference in OS
Trotti et al[13]	1988	20	57	15	43	40	4 years			15	60	Worse survival for BCP
Guinee et al[12]	1994	26				139	5 years			40	74	Worse survival for BCP
Ezrat et al[19]	1996	28				84	7 years	37	33	57	61	No difference in DFS or OS
Ibrahim et al[20]	2000	72				216	47.5 months			67	58	No difference in DFS or OS
Bladström et al[11]	2003	94				7,779	10 years			43.9	68.6	Worse DFS and OS for BCP
Middleton et al[25]	2003	39					43 months	56		80		—
Ring et al[26]	2005	28					40.5 months	63		67		—
Hahn et al[27]	2006	57					38.5 months	70.2		77		—
Matthiln et al[15]	2008	18	45	22	55	61	10 years			72	97	Worse DFS and OS for BCP
Stensheim et al[22]	2008	59	56	46	44	13,106	4.9 years			56	69	No difference in OS
Beadle et al[21]	2009	51	49	53	51	668	91 months			62.6	64.6	No difference in OS
Halaska et al[22]	2009	16	50	16	50	32	142 months	81.3	62.5	87.5	71.8	No difference in DFS or OS
Cardonick et al[28]	2010	130					3.14 years			Stage I, 100; stage II, 86; stage III, 86; stage IV, 0		Survival for stages I to III seems similar to nonpregnant survival rates according to American Cancer Society Surveillance Research
Johansson et al[16]	2011	107	10	1,003	90	14,611						Worse survival for BCP
Azim et al[14]	2012	65				130	5 years	52.1	74.3	79.6	88.4	Significantly poorer DFS for BCP; no difference in OS observed
Current study		311				865	5 years	65	71	78	81	No difference in DFS or OS

NOTE. Table shows 17 studies with survival outcome of patients with BCP published since 1985; for studies making subdifferentiation between breast cancer during and after pregnancy (percentages specified), results of DFS and OS for postpartum and lactating patients with breast cancer are not shown, because this was not the aim of our study.[12,15,16,21-23]

Abbreviations: BCP, breast cancer during pregnancy; DFS, disease-free survival; OS, overall survival.

*Postpartum breast cancer excluded.

Conclusion on prognosis

- Similar survival for patients diagnosed with breast cancer during pregnancy compared to non-pregnant patients

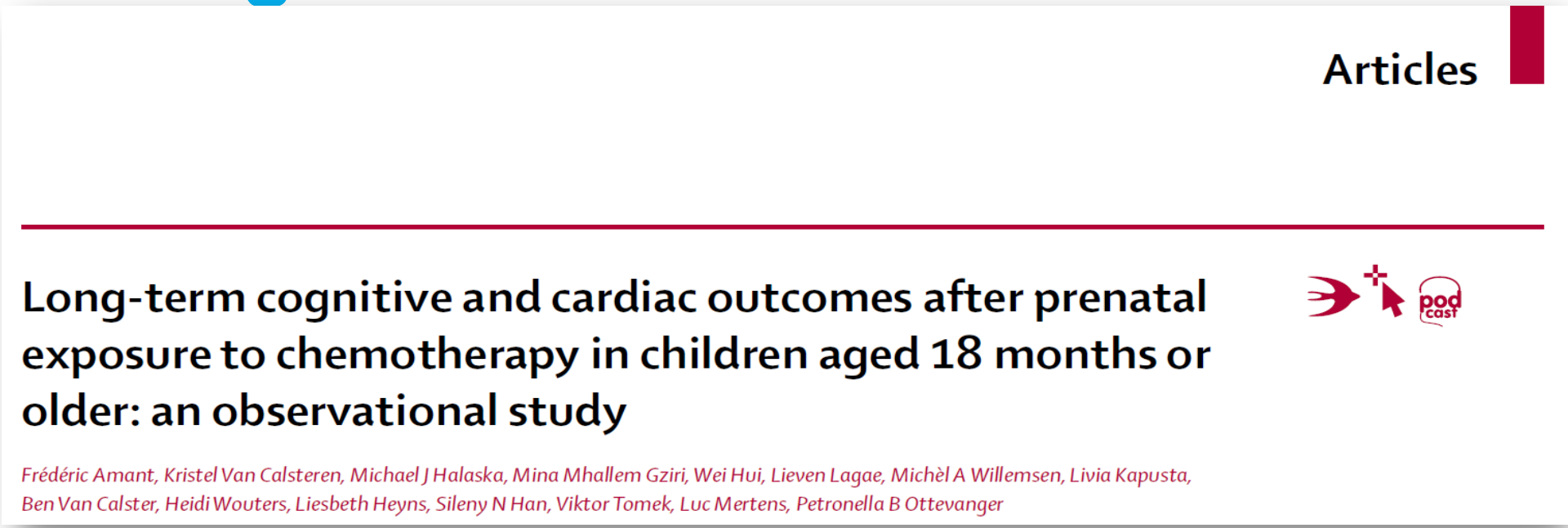
- no difference for patients who received chemoterapy during vs after delivery

- Termination of the pregnancy does not change the maternal prognosis.

- This supports the option to start treatment with continuation of pregnancy provided that standard treatmen is administered.

Is in accordance with the DBCG-guideline

Prognosis for the child



70 children

Belgium, The Netherlands, Czech Republic

Follow-up: median 22,3 months (range 16,8-211months)

Amant et al. *Lancet Oncol* 2012

Methods:

Test moments: 18m, 3y, 6y, 9y, 12y, 15y, 18y

General

Clinical exam by pediatrician, biometric data, questionnaire on general health status, school performance, recreation and social situation.

Cardiac

Blood pressure, ECG, echocardiography for structural and functional assessment

Neurodevelopmental

age-adapted test battery for the assessment of intelligence, verbal and non-verbal memory, attention, working memory, and executive functions

Conclusion

<u>After prenatal exposure to chemotherapy</u>:

- Child's growth and development was comparable to the general population.

- There was normal cardiac outcom

- Prematurity was frequently encountered, and associated with impairment in cognitive development.

- Subtle changes in cardiac and neurocognitive measurements emphasize the need for longer follow up.

Malformations

Chemoterapy is contraindicated during first trimester.

-Prevalence 14-16% when given in 1 trimester.

-Prevalence 2-3 % when given in 2. and 3. trimester

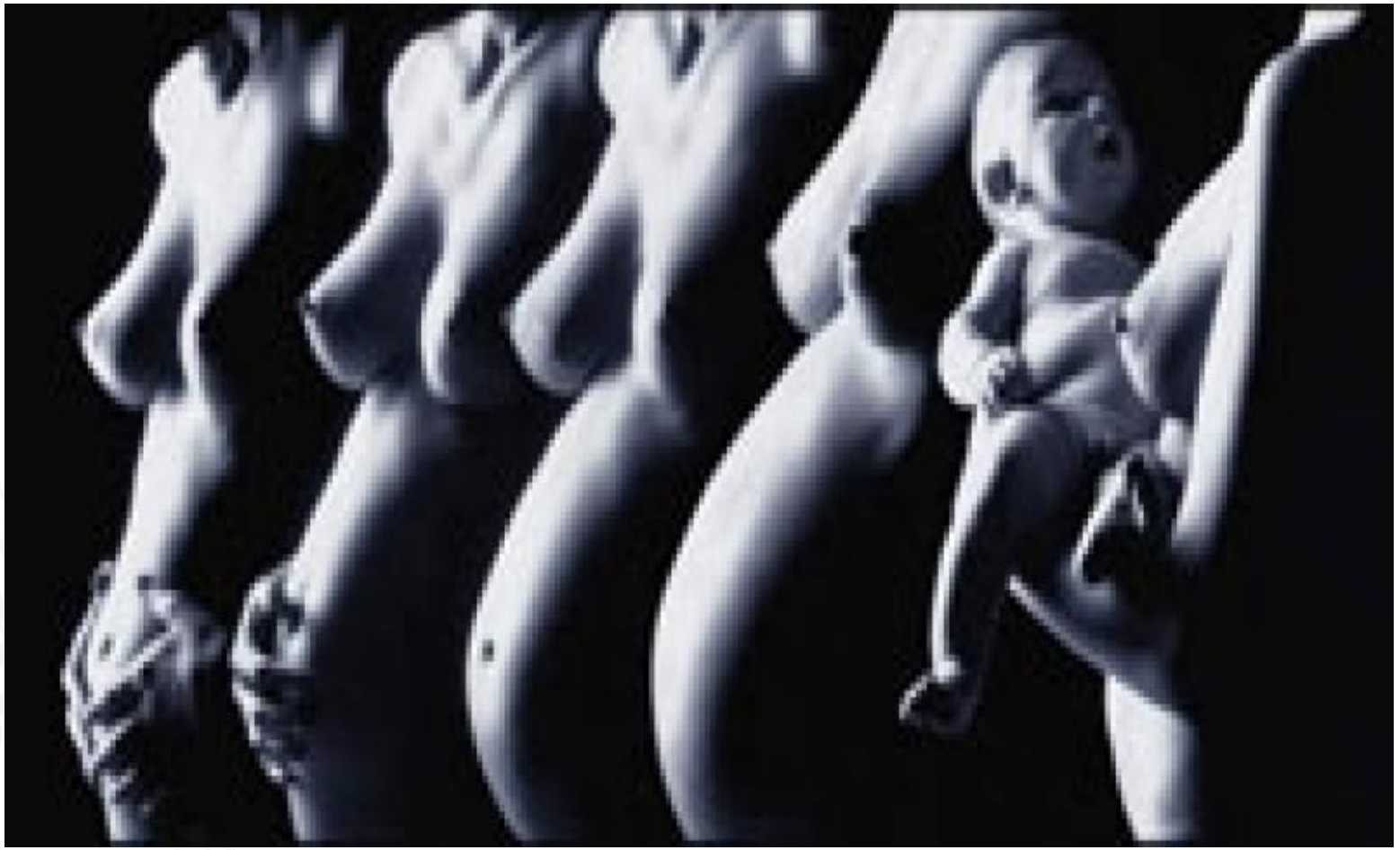
-Prevalence in general population 2-3%

Amant F Lancet 2012

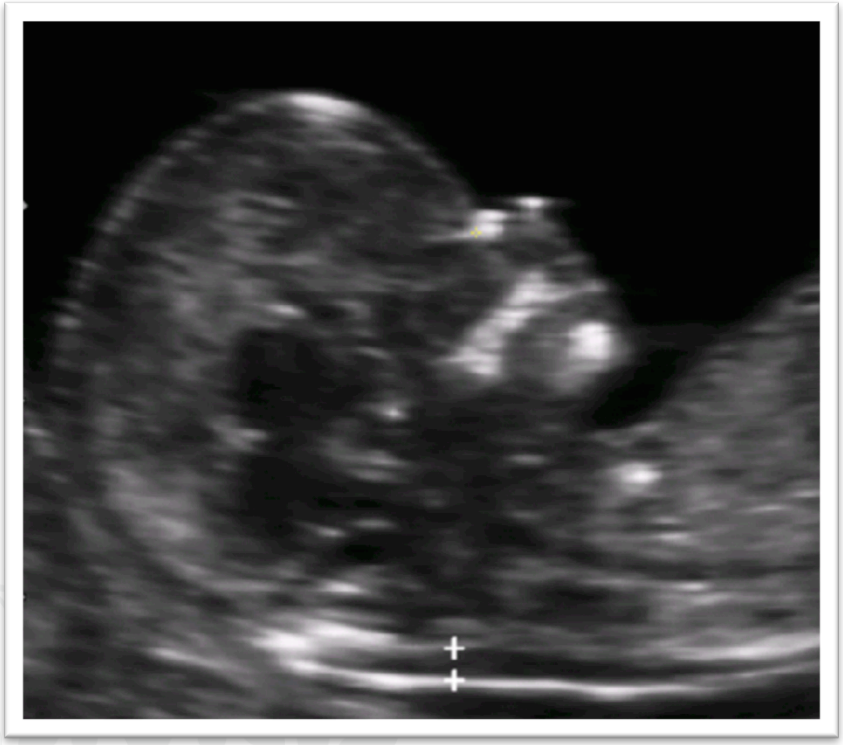
Murthy RK BCR 2014

Chardonick AJOG 2015

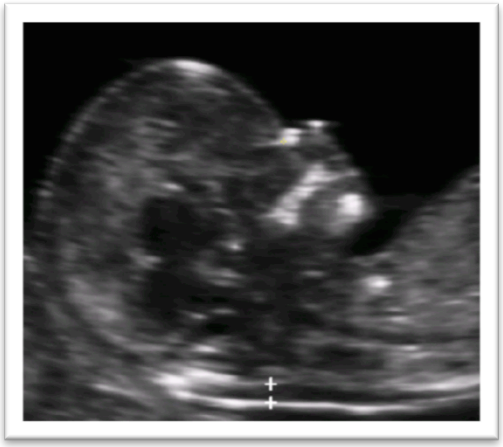
Treatment during pregnancy???!



Cancer during pregnancy
-2 patients-



Multidisciplinary team: gynecologist, oncologist, surgeon, general physician, pediatrician, radiologist, radiotherapist, pathologist, nurse, midwife, physiotherapist, pychologist, etc…



Fetal malformations

Intrauterine growth restriction

Neuropsykologic - dysfunktion

Cardiac toxicity

Second cancers

Fertility problems

Delay in diagnosis and treatment

Suboptimal staging and treatment

More aggressive tumor biology?

Change in:

- -Immune system
- -Pharmacokinetics
- -Hormonal milieu

→ Worse prognosis

DIAGNOSIS

Local:

- Ultrasound(Sen. 93%)
- Mammography(Sens.falls to 68%)

Biopsi:

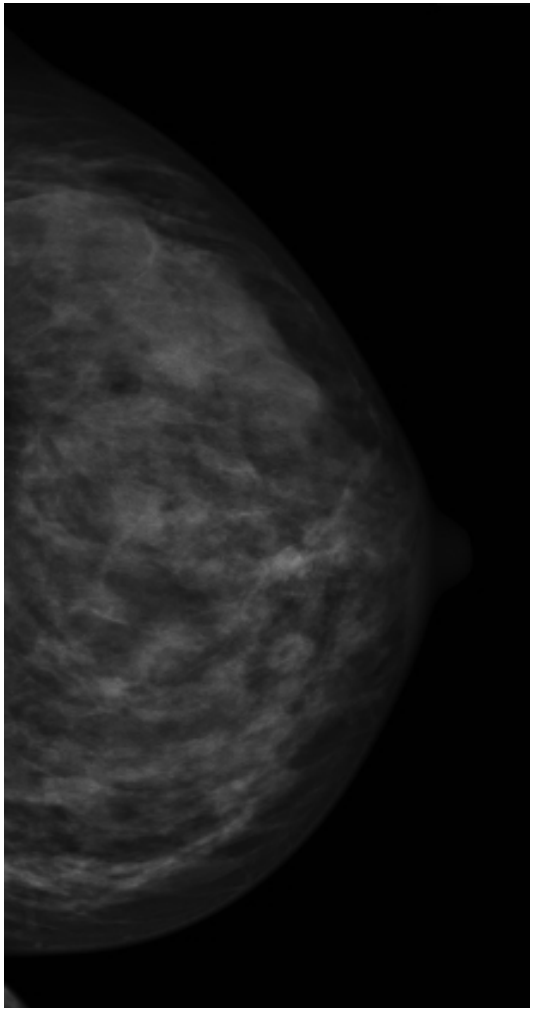
- Core biopsi

Distant:

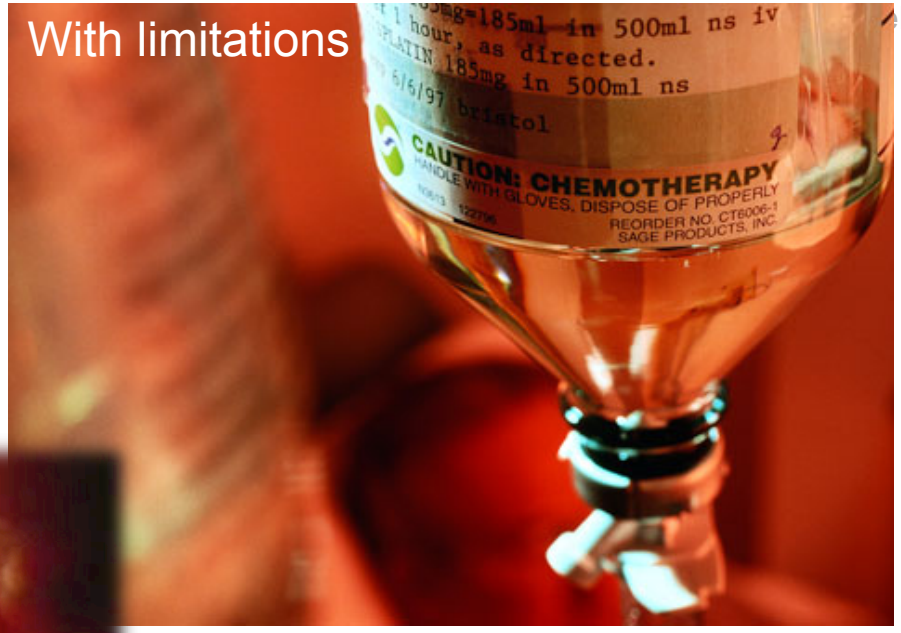
- Chest X-ray
- Liver ultrasound
- (Whole body MRI)
- Whole body diffusion weighted MRI

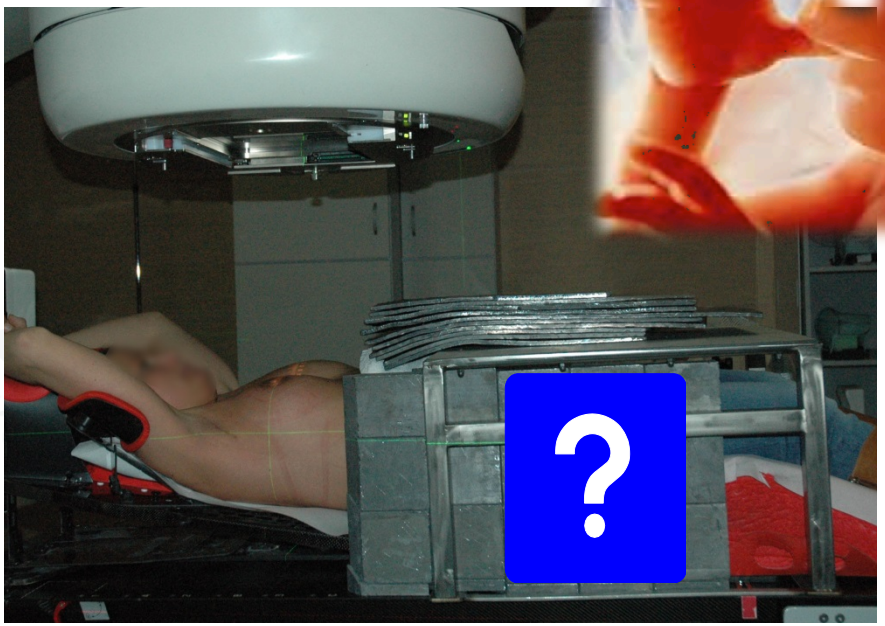
BRCA:

- Allways test (20% pos.)



Treatment modalaties

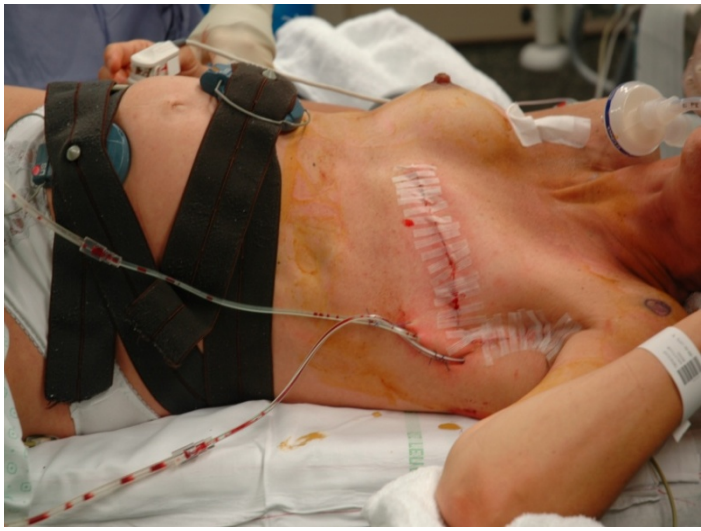




Surgery during pregnancy

- Surgical approach as for nonpregnant

- Mastectomy or breast conserving surgery



- Axillary lymph node dissection (ALND) or sentinel lymph node biopsi(SLNB)

- Obs No radiotherapy

- Immediate breast rekonstruction is not recommended

- Tissue expander can be used

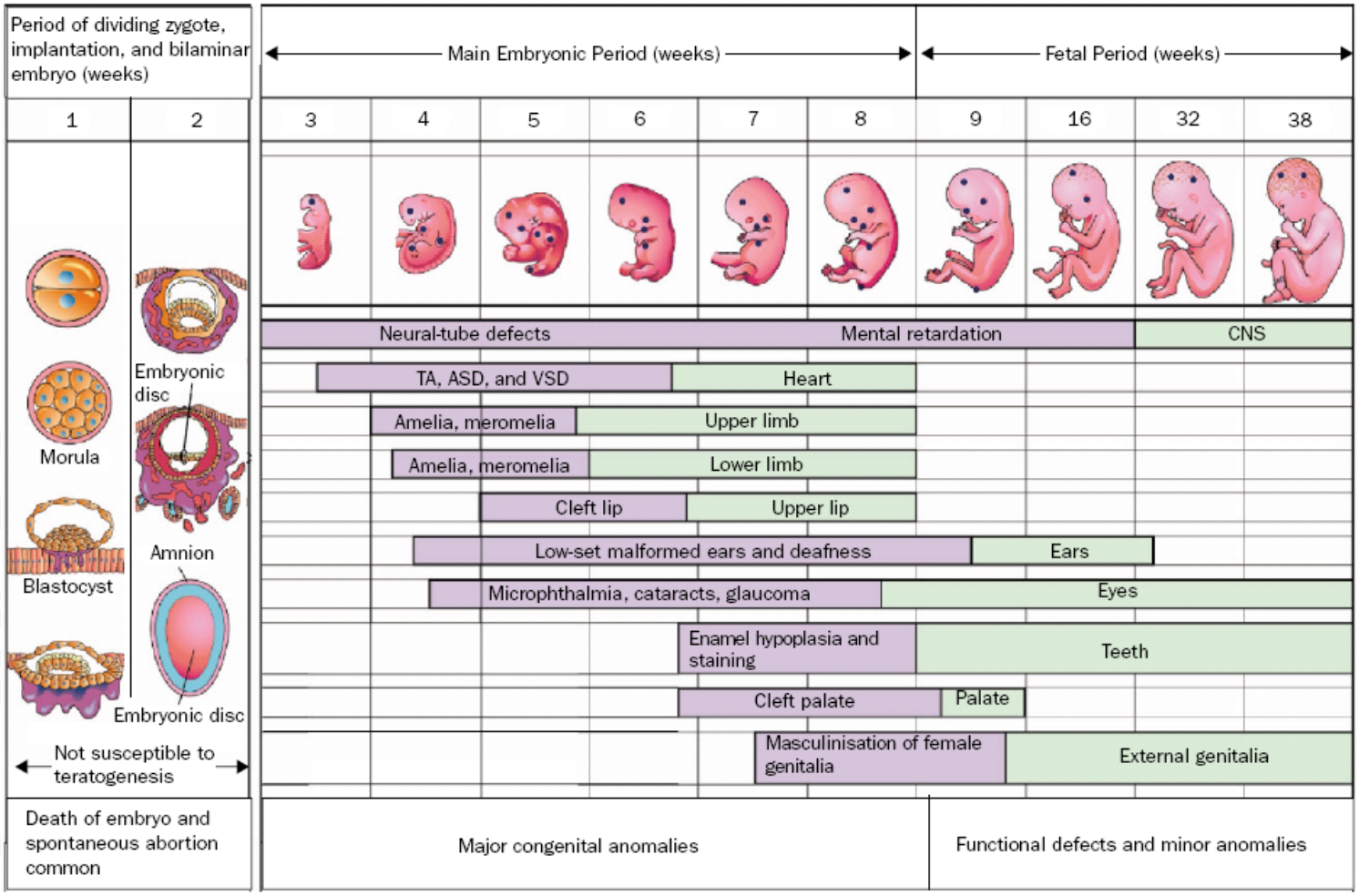
Chemotherapy during pregnancy

Recommended regimes :

EC, Taxanes

Timing is everything

Potential effects of cytotoxic treatment on the fetus



Chemoterapy and timing

- Chemotherapy is contraindicated in first trimester(15-20%)

- Start in week 14-16.(organogenesis w 13 ,Throphob. W 15)

- 1 course of chemotherapy is planned so last course of chemo. can be given in week 35.

- Start with EC but if there is significant emesis - start with a taxane(paclitaxel)

-The remaining chemoterapy or remaining treatment will start 1 week after delivery

- Vaginal delivery is most optimal

Chemoterapy and dosing

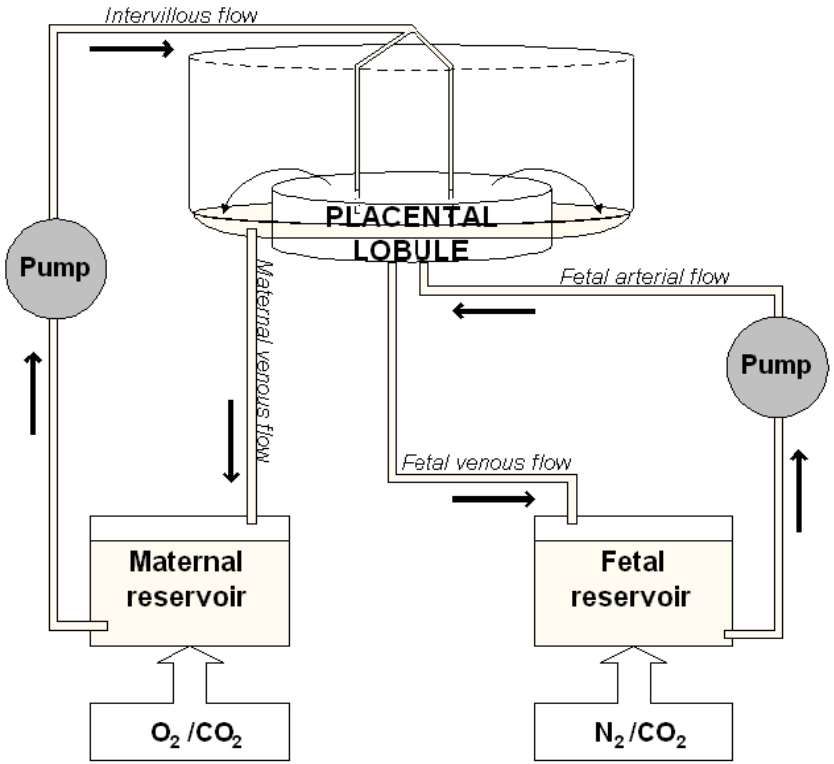
- Use conventional dosis

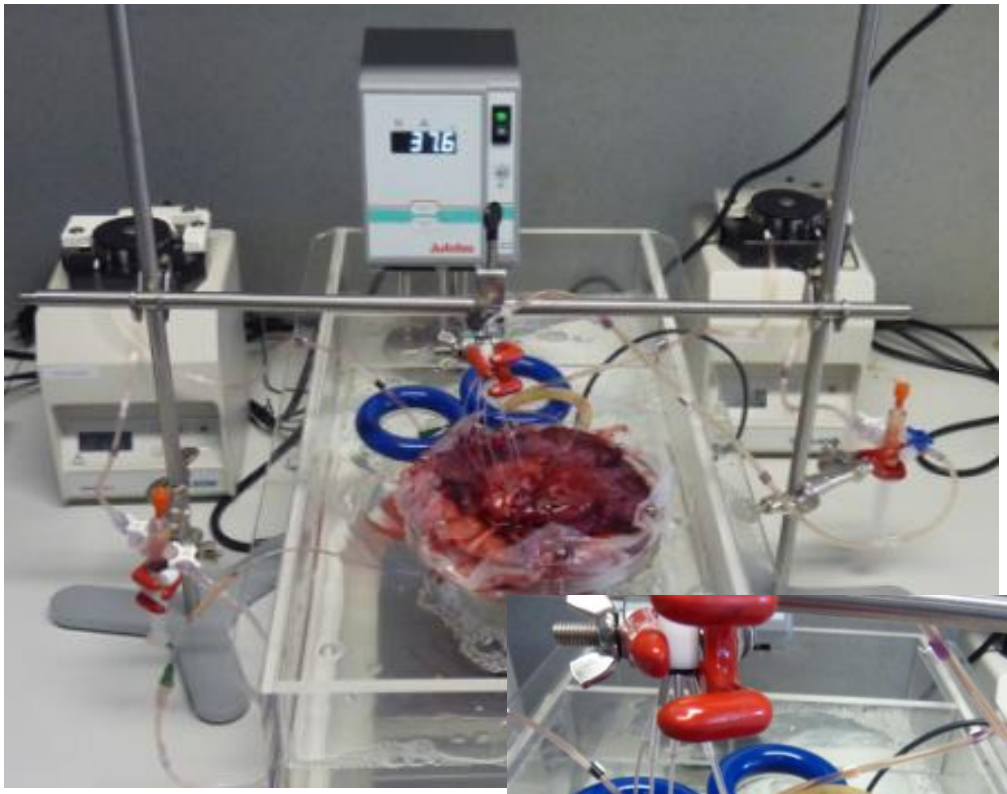
- Dose according to aktual body weight

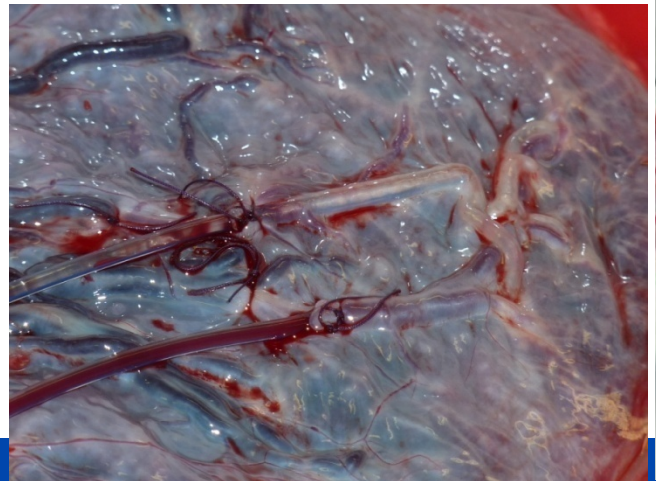
- Weekly placlitaxel is choice of taxan(interpatient variability by Docetaxel)

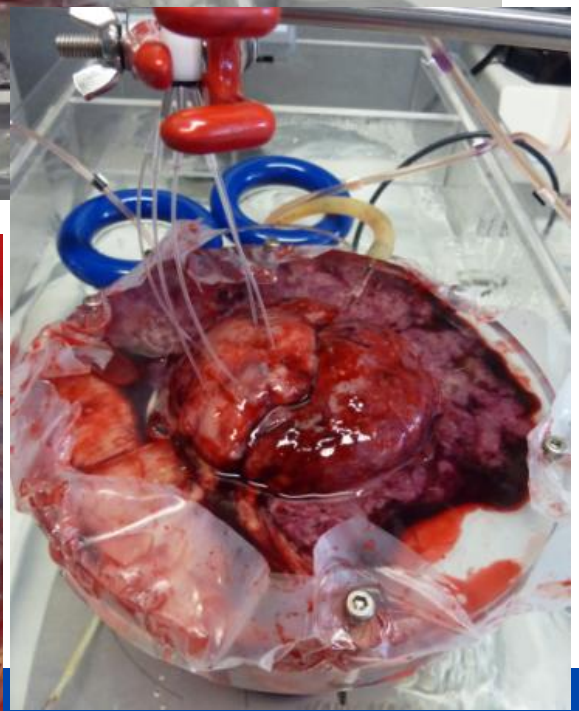
- Carboplatin and methtrexat is not recommended

Placenta perfusion model









Epirubicin	4-6 %
Cyklophosphamide	22-28%
Paclitaxel	1-2%
Doctaxel	2-15%
Carboplatin	50-60%

Supportive care

- 5-HT3 antagonists can be used(granisitron)
- no data for palanosetron(aloxi).
- NK 1 inhibitores can not be recommended (no data)

- H1-antagonist can be used
- H2 antagonist can be used

- Metoclopramide can be used
- Motilium can not be recommended (no data)

- Methylprednisolon is the preferred corticostroid (metabolised in placenta)

- Avoid Picc-line and PAC if possible (DVT-risk)

Anti-HER2 Treatment

- trastuzumab
- Petuzumab
- Lapatinib

-Are contrindicated in BCP

-mainly due to reports of oligohydramnios and anhydramnios (33%)

Endocrin therapy

Tamoxifen is contraindicated in BCP

-Due to reports of malformations

-must be used after delivery.

Zoladex is contraindicated in BCP

-No data.

Bisfonates are contraindicated in BCP

- No data

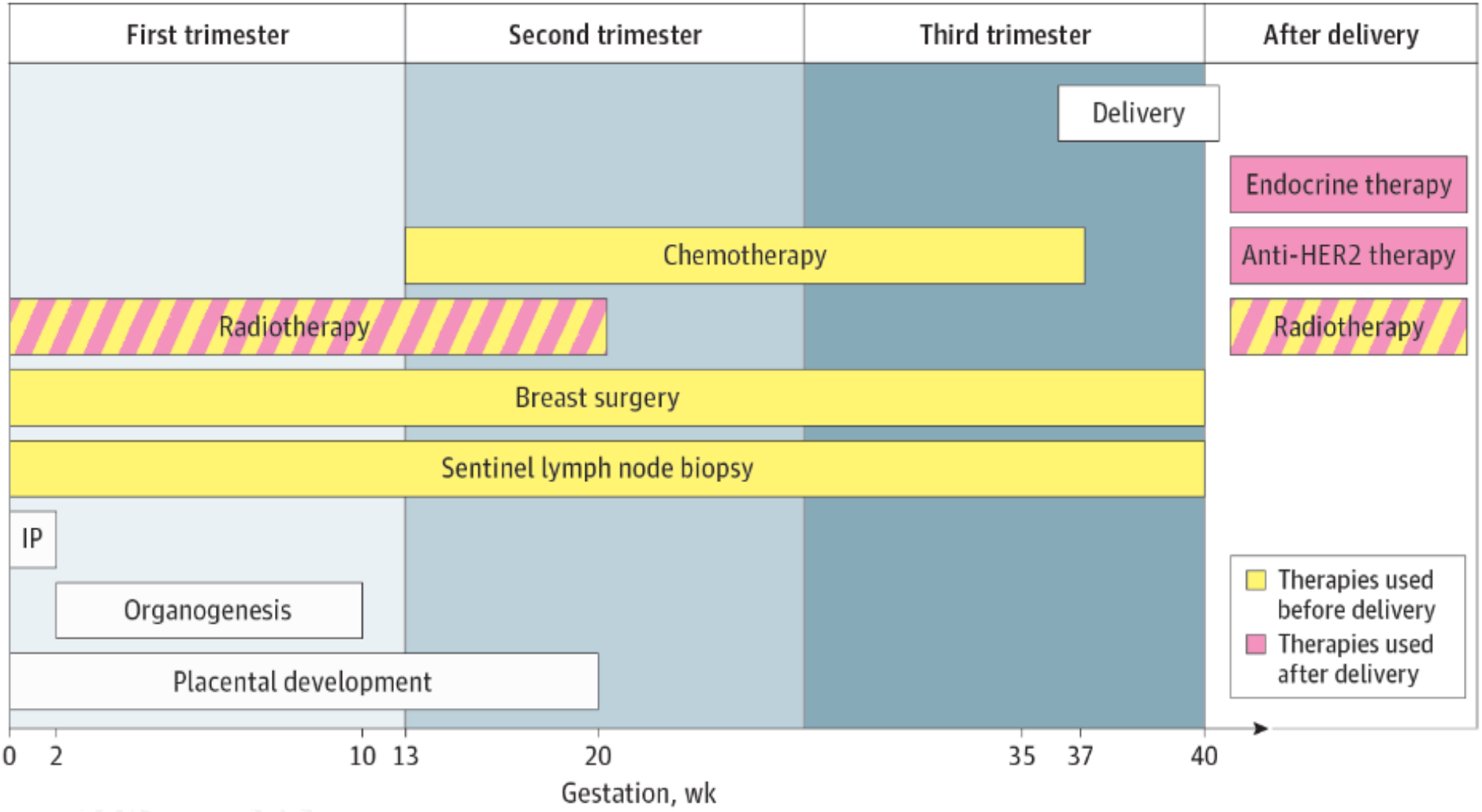
Radiotherapy

-Is contrainicated during 2.-and 3.trimester.

- is relatively contraindicated during 1.trimester.

- due to risk of long term risk of cancer and fertility for the child.

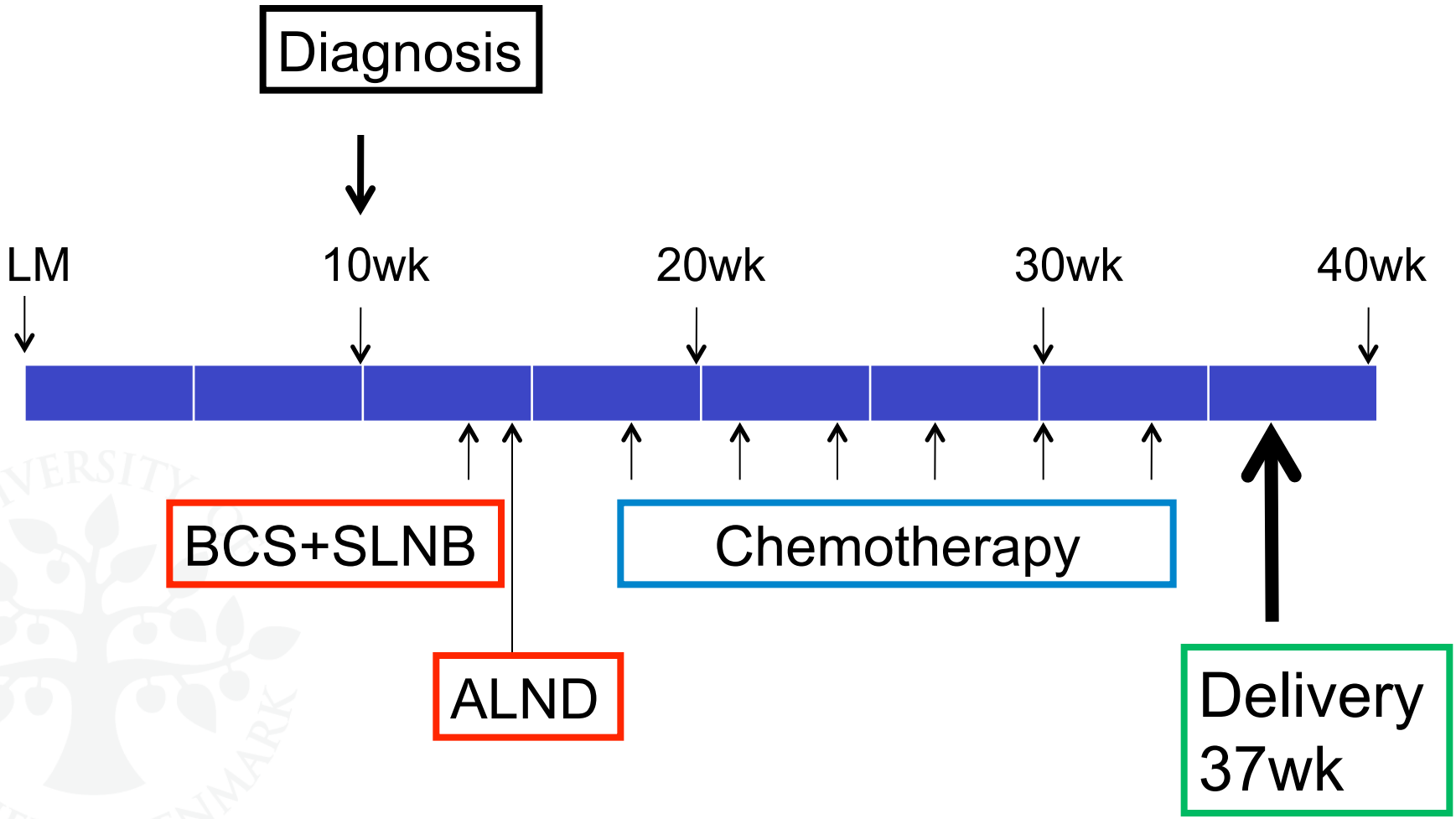
Treatment-guidline



SHARED DECISION MAKING

Nothing about me without me!

Mrs A, 33y, T2N1M0, IDC III, ER+HER2+ positive



RT, trastuzumab and tamoxifen postpartum

END

PAS PÅ HVAD DU SIGER

UNIVERSITY OF
SOUTHERN DENMARK

Forløb

- Vi vil gerne have patienten henvist ved diagnosestart
  Obs der skal foreligge grovnålsbiopsi

- Alternativt efter operation efter forudgående konf.
  præoperativt.(mast/lump/Gentest/amning?)

- Hvis præop.- Diskuteres på MDT.

- alle får lavet klin mammografi,rt-thorax/ul hepar + evt helkrops MR(begrundet mistanke)

- Behandlingforløb/plan fastlægges.

Forløb

- Patienten indformeres om plan.
- Patienten tilknyttes 2 specialesgp.
- Patienten henvises til obstetrisk afd.-primært Århus med plan for kemoforløb og forventet/ønsket fødselstidspunkt.
- Patienten ses hver 3. uge med læge vurdering og journalkopi til obstetrisk afd.
- Ved komplikationer kontaktes onkolgisk afd primært.Der konf med team1 bagvagt.
- Ønsket fødselstidpunkt - til termin - ved postop behandling helst 37-38 uge mhp start på samt/behandling 1 uge efter fødsel.
- - Om muligt foretrækkes vaginal fødsel.
- Ved plan om postop. behandling stoppes mælkeproduktion v fødsel.

Opfølgning

- Alle patienter følges til de bliver 50
- Alle børn følges samme tid (problemregistrering)
- Data indgår i database.

Timing

-Vi starter helst kemoterapi efter 16. uge - og aldrig før 14.uge.(organudvikling(13.uge) samt throphoblast udvikling(18.-19.uge).

-Start på 1.kemoterapi planlægges så sidste forventede serie kemoterapi gives i 35-36.uge.afh. af regime.

-Der startes sædvanligvis med EC men ved svær emesis startes med ugentlig paclitaxel.

-Resterende planlagt kemoterapi gives umiddelbart 1uge efter forløsning-Afh. Af fødselsforløb og kemoregime.

Dosering

Doseres efter overflade på starttidspunkt.

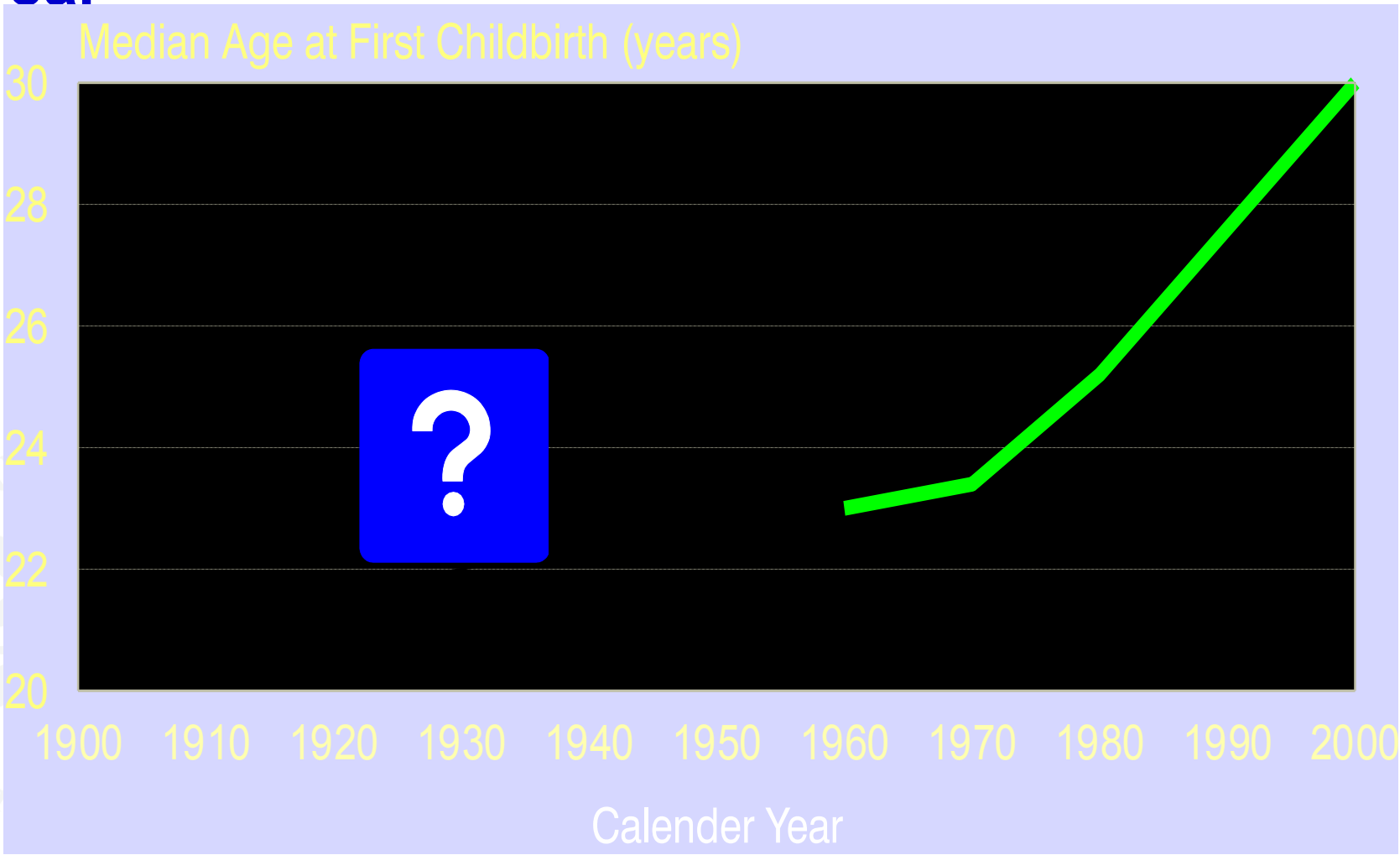
Der tages ikke hensyn til farmakokinetiske ændringer under graviditet(enzymaktivering,albuminændringer) – heller ikke ved taxaner.

Vi anvender ugentlig paclitaxel da studier af placenta viser stor variabilitet i konc af docetaxel i placenta og maternel serum.

GCSF anvendes efter vanlige retningslinier.

Breast Cancer Etiology

Age at First Childbirth According to Calender Year



Potential effects of cytotoxic treatment on the fetus

1/timing

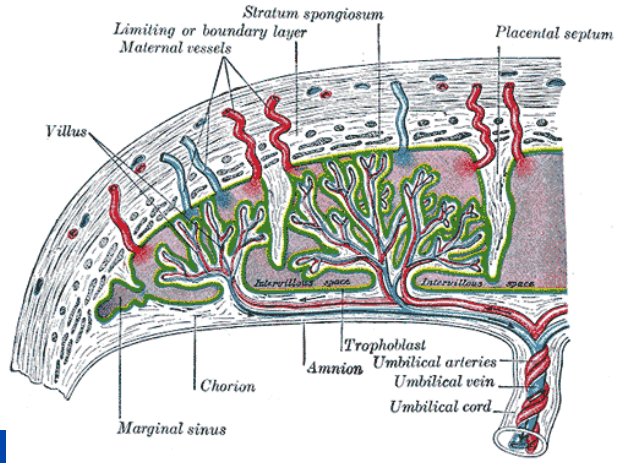
2/transplacental transfer

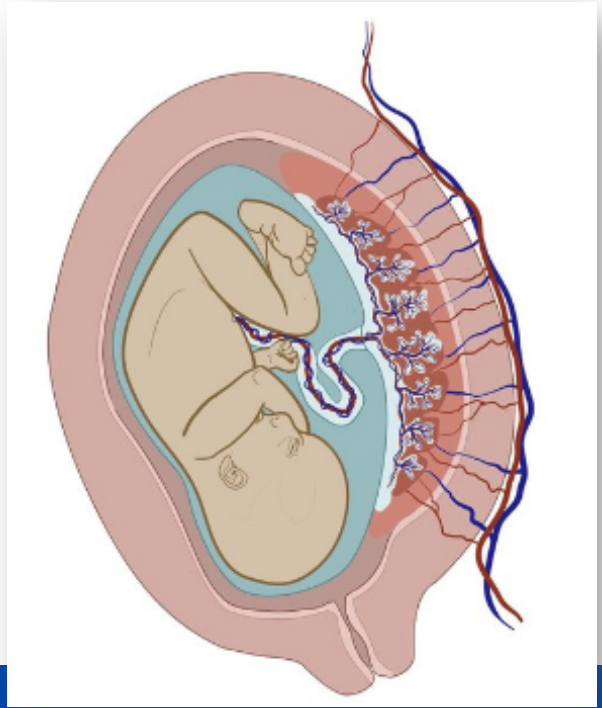
Fysico-chemical properties: molecular weight, fat solubility, polarity

Concentration gradient and blood flow

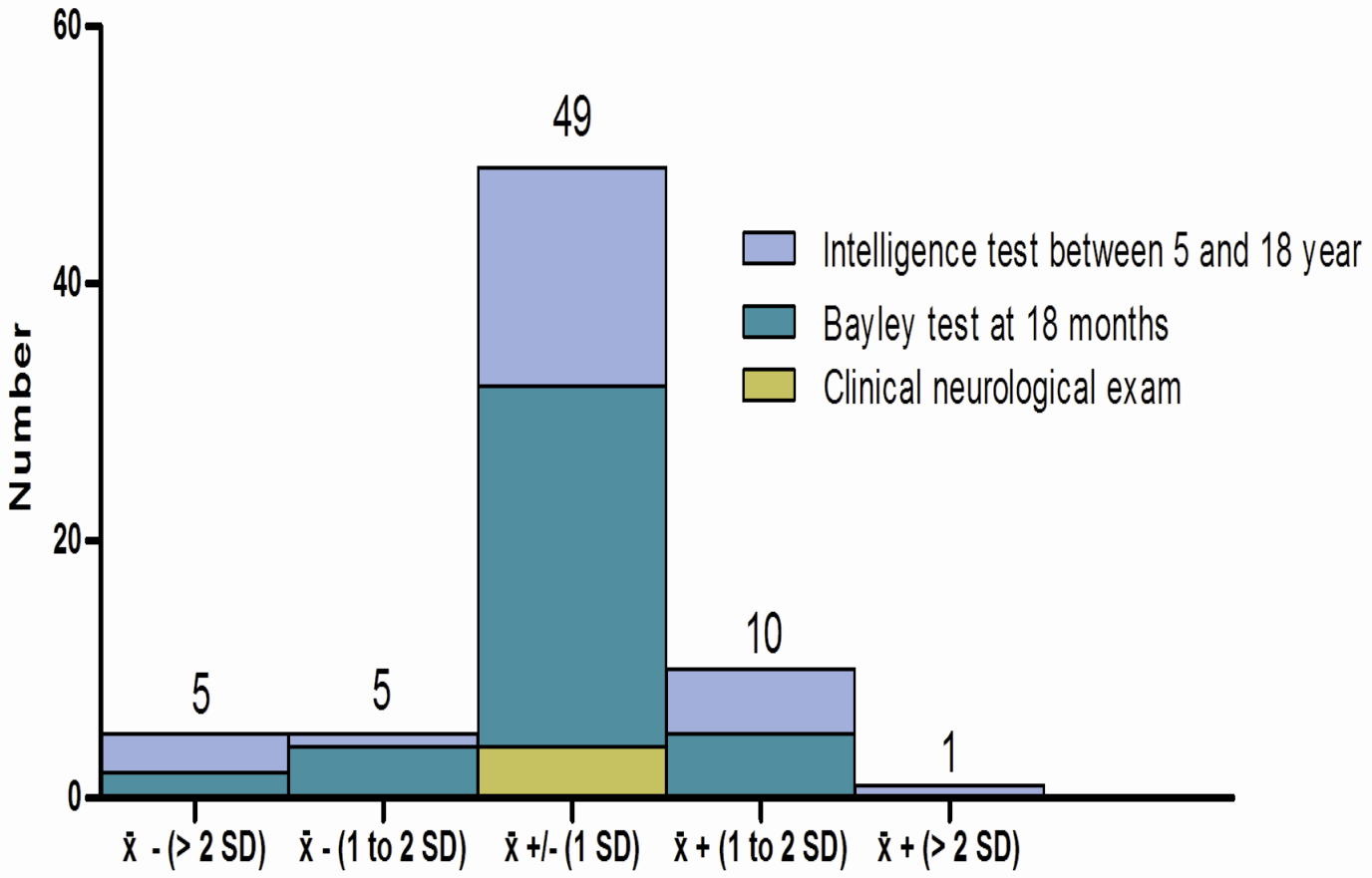
Protein binding

Active efflux transporters





Results: Cognitive function

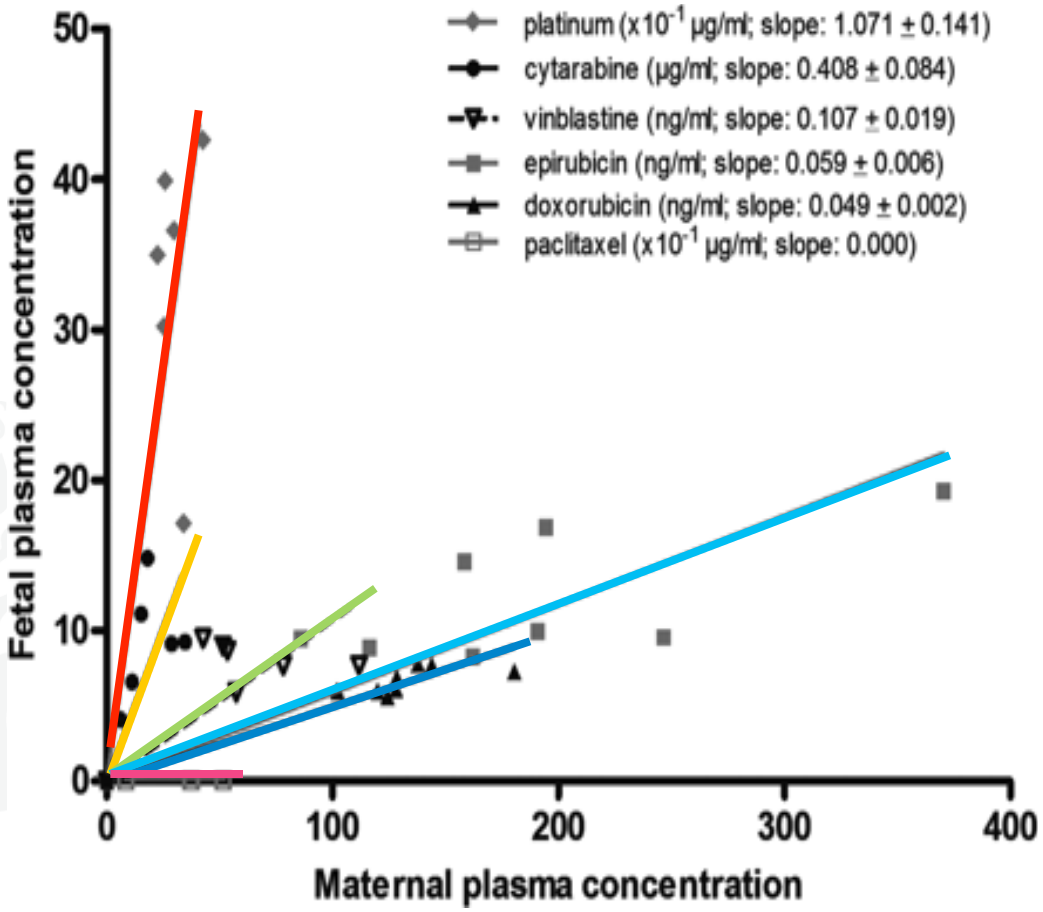


BREAST CANCER DURING PREGNACY (BCP)

- Epidemiologi
- Prognoses
- Diagnosis
- Surgigal treatment
- Systemic Therapy
  - Chemotherapy
  - Endocrine Therapy
  - HER2 –targeteret treatment
- Radiation Therapy
- Supportive Treatment
- Treatment overview
- Follow up

Transplacental transfer mouse model

C57Bl6J mice, i.v. chemotherapy on day 18.5
+90' fetal + maternal blood sample
HPLC / AAS measurement

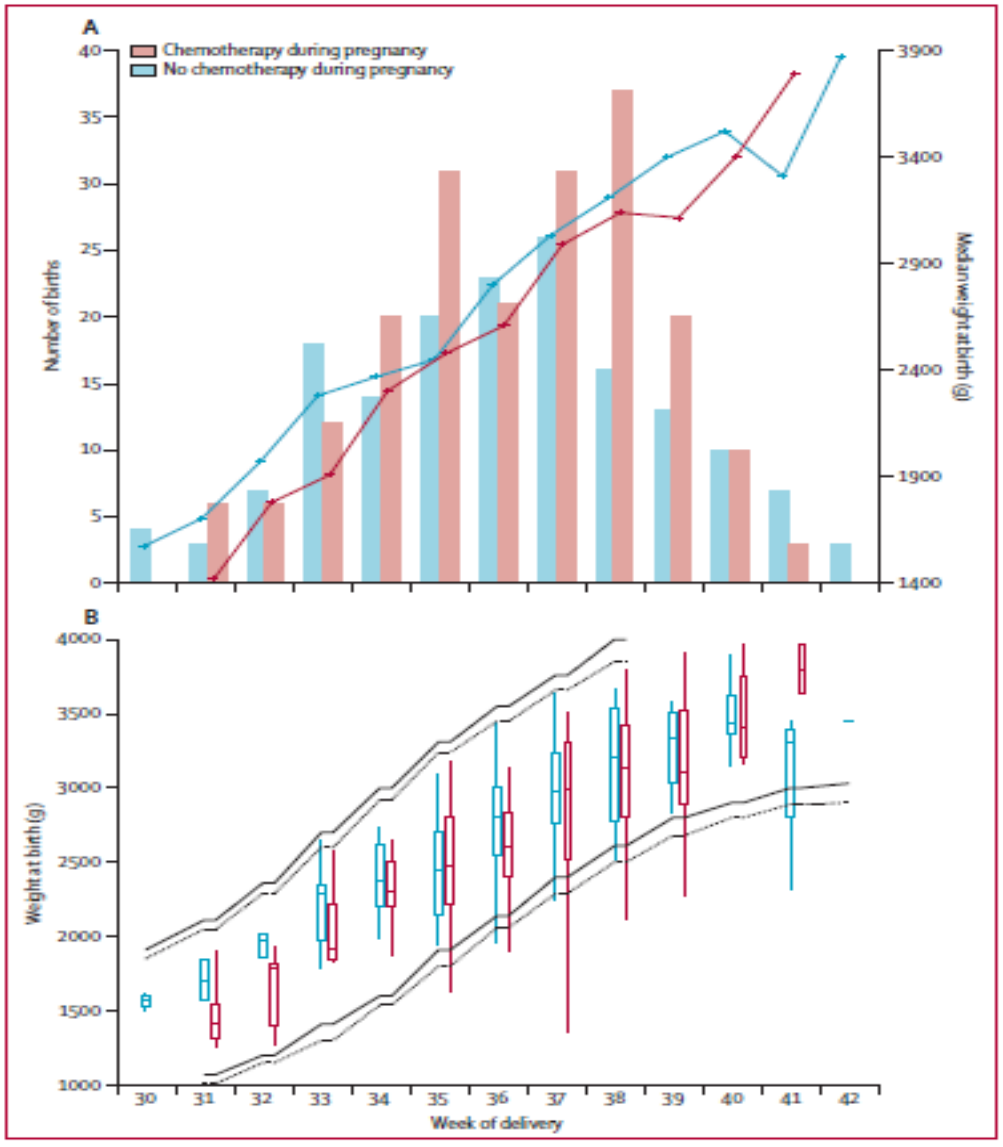


Van Calsteren et al.
Reprod. Sci ,2011.

Type of treatment

Treatment	Pregnant patients N=311	%	Non-pregnant patients N=865	%
Surgery				
- None	2	0,6	10	1,2
- Breast conserving	140	45,0	433	50,1
- Mastectomy	147	47,3	422	48,8
Chemotherapy setting				
- None	4	1,3	219	25,3
- Adjuvant	208	66,9	544	62,9
- Neoadjuvant	99	31,8	102	11,8
- During pregnancy	200	64,3	-	-
Taxanes	169	54,3	247	28,6
Trastuzumab	76	24,8	140	17,0
Radiotherapy	205	73,3	768	88,8
Endocrine therapy	117	41,5	580	67,1

Intrauterine growth

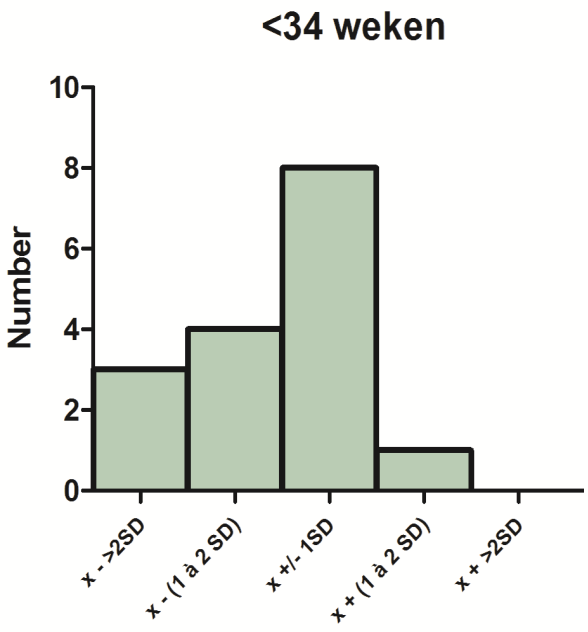


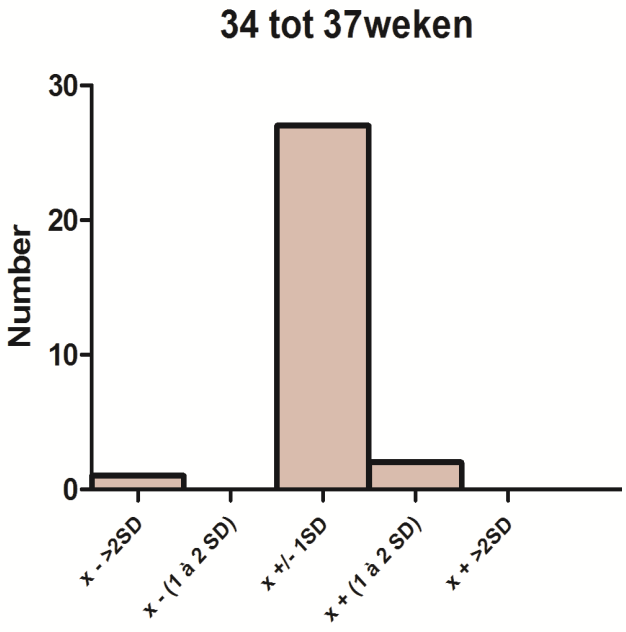
Birth weight:

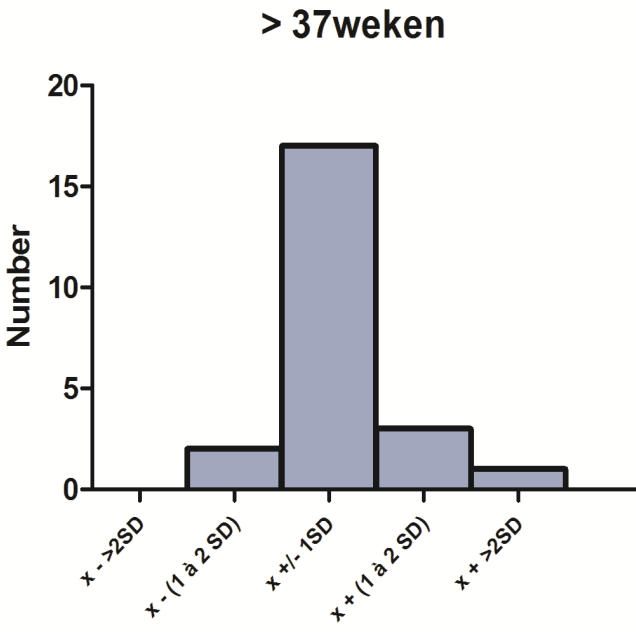
No significant difference in the frequency of intrauterine growth restriction between fetuses exposed to chemotherapy and those without exposure (p=0,069).

Cognitive function:

- Prematurity vs IQ score



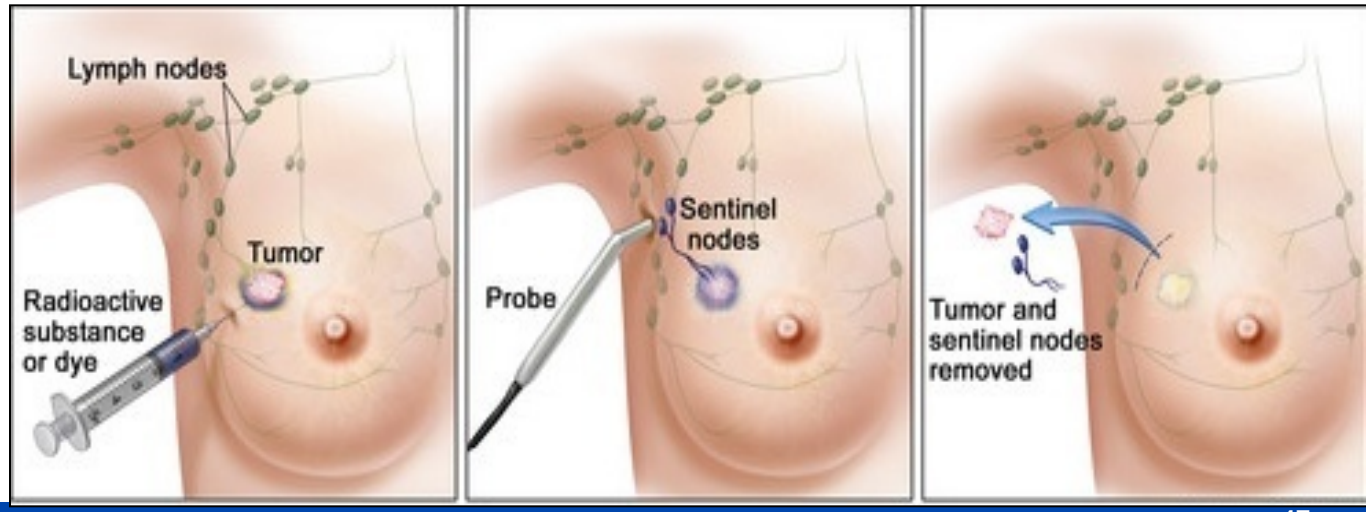




SLN biopsy during pregnancy: to do or not to do?

Pro: Lower morbidity rate

Contra: Are lymphatic pathways altered during pregnancy? Effect on survival, regional control, morbidity, and accuracy?



Conclusion

- SLN biopsy during pregnancy has a low axillary recurrence rate

- This staging method should be used during pregnancy instead of standard ALND for early stage, clinically node negative breast cancer

- It is recommended to do tracer injection on the op.-day

- Blue dye is not recommended in BCP

Han SN, Amant F, Loibl S, et al.

- This is in accordance with up-coming DBCG-guidline.

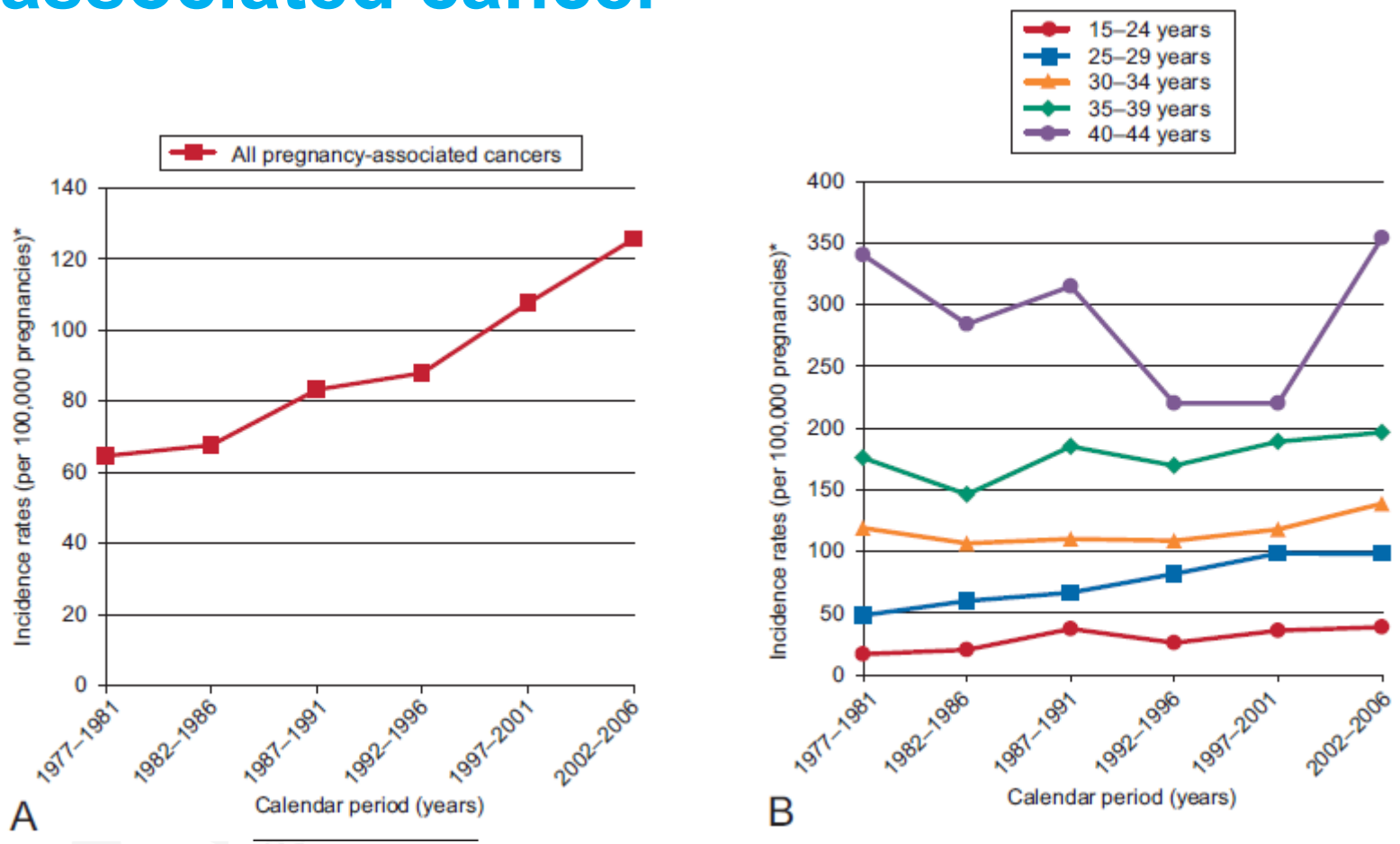
Conclusions on survey of current clinical practice

Termination of pregnancy, delay of treatment and iatrogenic preterm delivery are frequently applied strategies in the management of pregnant breast cancer patients

This is not in line with current evidence and recommended treatment strategies

Centralization of treatment is needed

Rising incidence of pregnancy associated cancer



Incidence rates of pregnancy-associated cancer among Danish patients aged 15-44 years during 1977-2006.

Eibye et al. *Obstet Gynecol* 2013