Drugs used to treat cancer during pregnancy

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Aims of this talk

- Review scale of problem on cancer during pregnancy
- Theoretical concerns regarding using of systemic anti-cancer treatment
- Available data
- Breast and haematological malignancies as exemplars
- What do we know about mAb and TKI
- Childhood outcomes
- Next steps

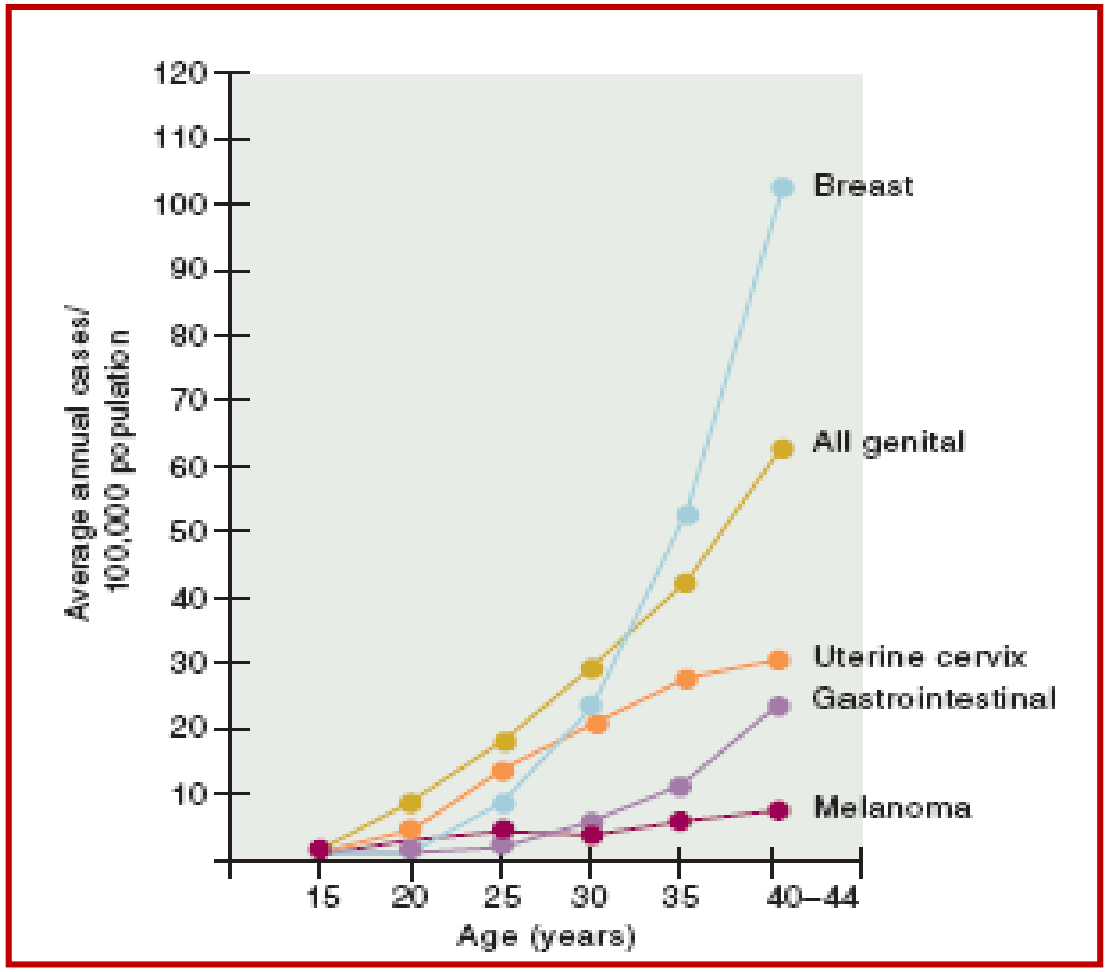
Incidence of Cancer During Pregnancy

- 1/1000 – 1/1500 term pregnancies
- Incidence increasing: delayed childbearing

Frequency by Cancer Type	Frequency in Reproductive Age Group
Breast Cancer	**30%**
Lymphoma	**10%**
Leukemia	**23%**
Melanoma	**30%**
Cervix	**35%**
Ovary	**15%**
Bone/soft tissue tumors	**25%**
Thyroid	**50%**

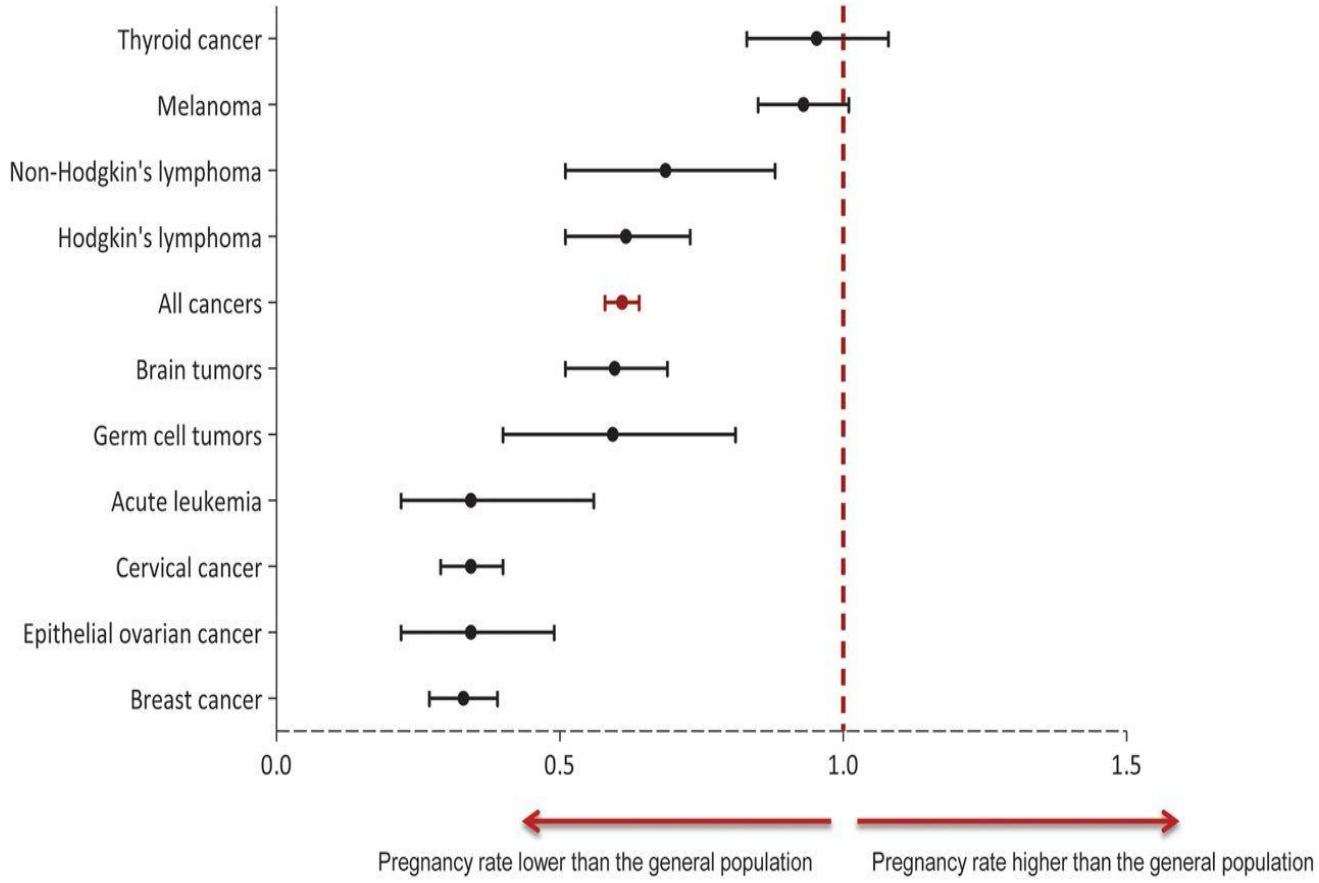
Increasing incidence lung and colorectal cancer in younger women

Incidence by Age of the More Common Malignancies Seen in Pregnancy



American Cancer Society, Facts and Figures, 1995

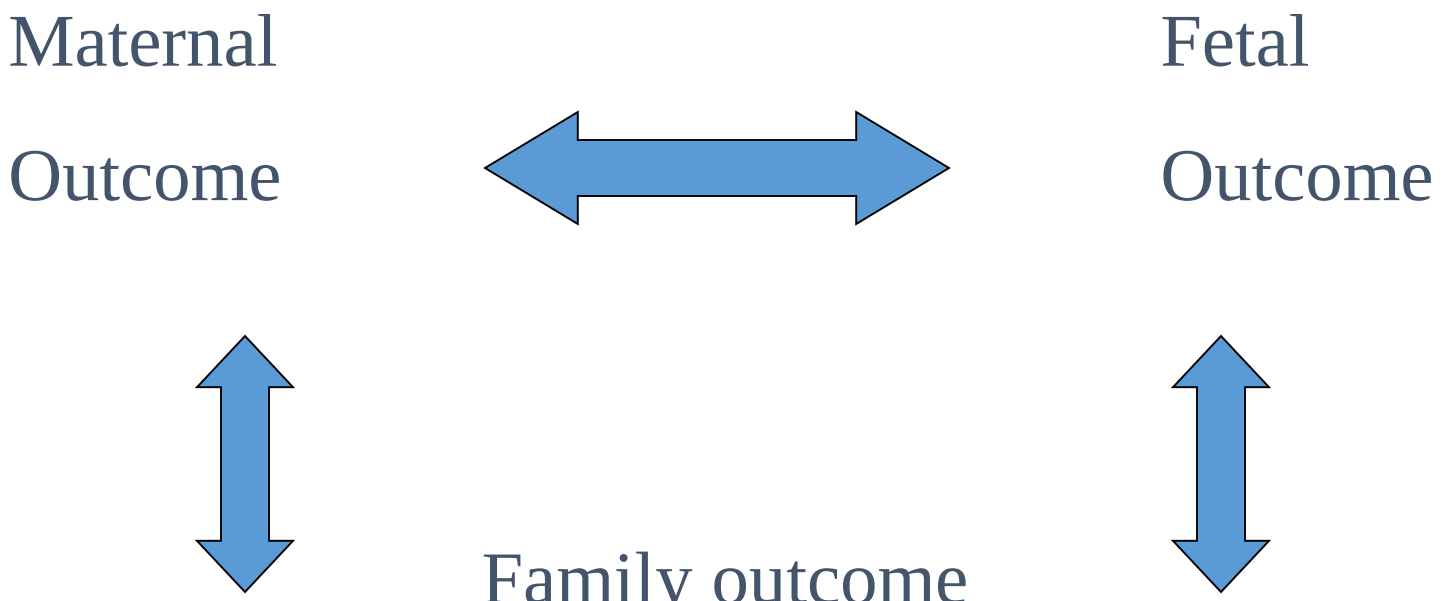
Female cancer survivors have 40% less chance of becoming pregnant compared with the general population



Annals of Oncology, Volume 24, Issue suppl_6, October 20

13, Pages vi160–vi170, https://doi.org/10.1093/annonc/mdt199

CANCER DURING PREGNANCY



Drug Safety Categories in Pregnancy

- A Safety established using human studies
- B Presumed safety based on animal studies
- C Uncertain safety; no human studies; animal do not show adverse effect
- D Unsafe; evidence of risk that may in certain clinical circumstances be justifiable
- X Highly unsafe

Potential Adverse Effects (1)

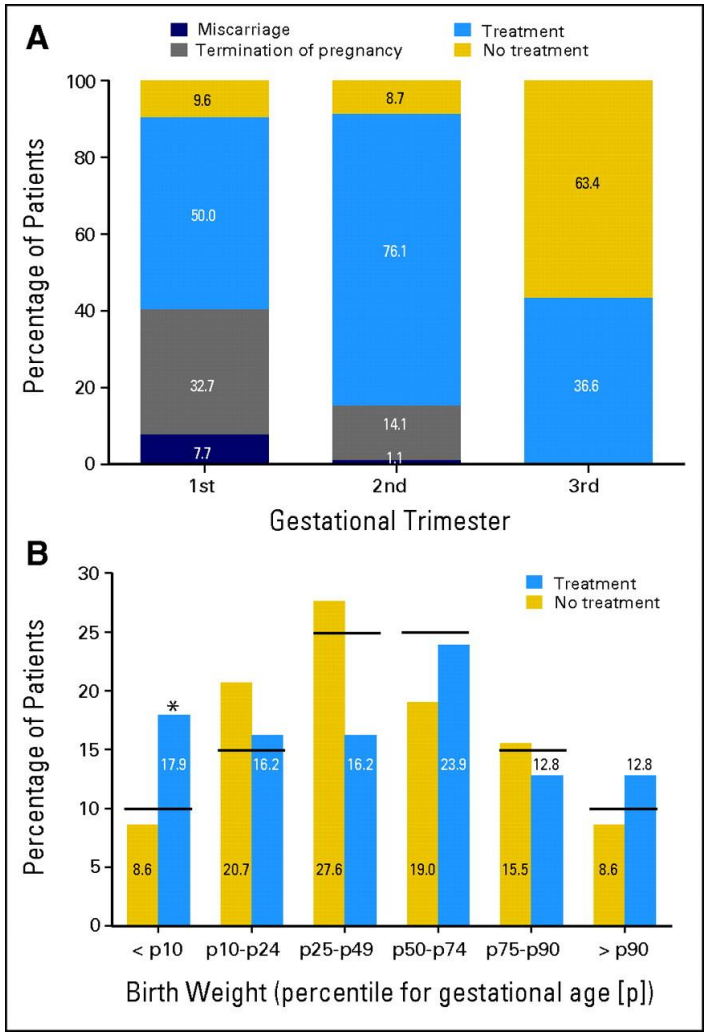
- Spontaneous miscarriages
  - First trimester (congenital malformation)
  - Second trimester (malformation or maternal illness on chemotherapy e.g. neutropenia)
- Foetal problems
  - Intra-uterine growth retardation
  - End-organ damage (e.g. heart, kidneys)
  - Developmental abnormality (malformation)
- Obstetric complications
  - Infection (depending on timing of chemotherapy and delivery)
  - Prematurity (foetal lung development and subsequent infant development)
  - Caesarean section
  - Stillbirths
  - Breast feeding
  - Maternal baby bonding
- Neonatal side effects
  - Withdrawal reactions
  - Drug side effects in neonate

Potential adverse effects (2)

- Childhood and later
  - Prematurity
  - Lack of breast feeding
  - Congenital abnormality
  - Organ dysfunction
  - Developmental (physical and emotional)
  - Malignancy
  - Fertility
  - Prematurity

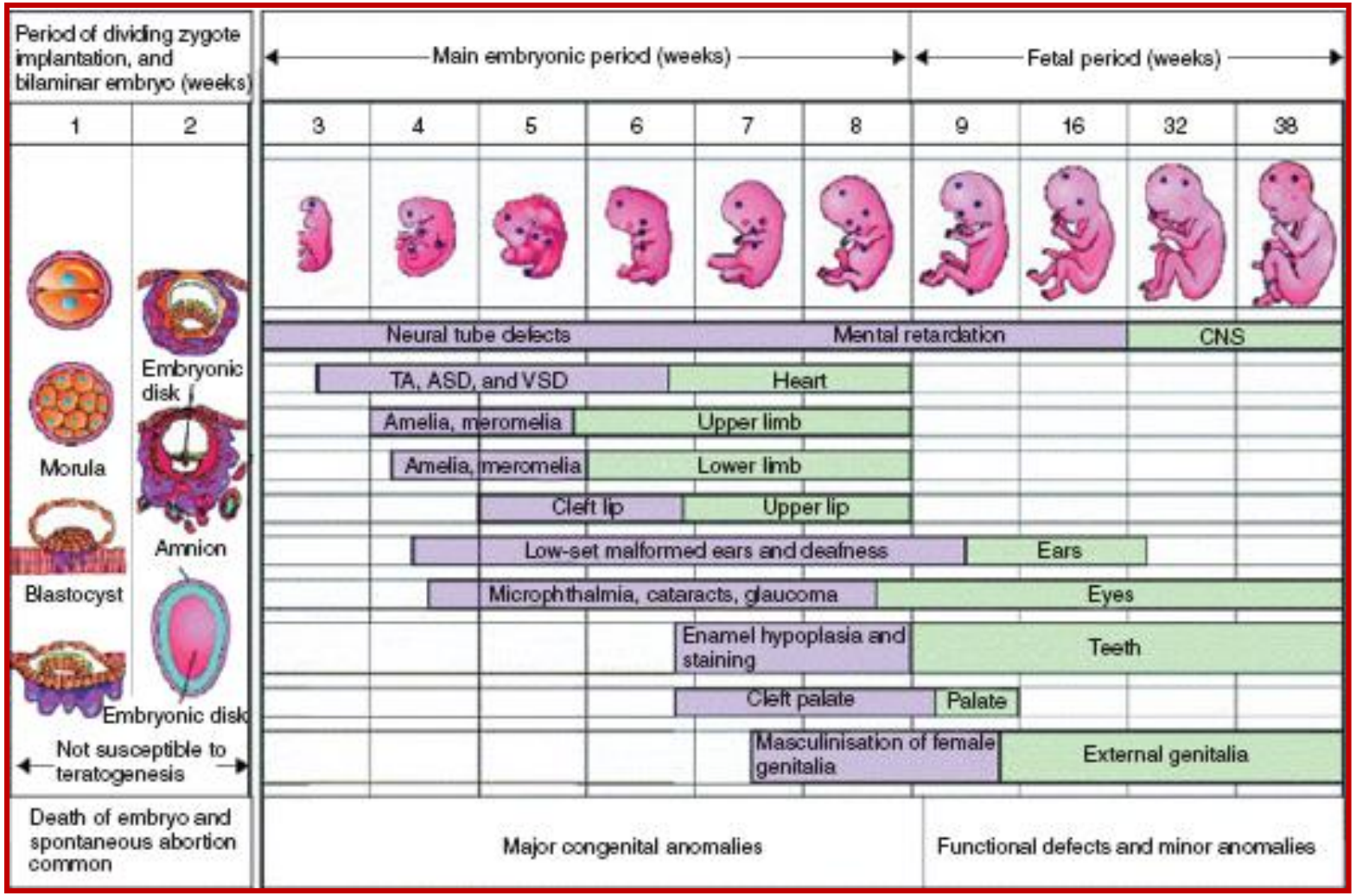
These children are individuals in their own right which can make longitudinal studies difficult

Management of cancer during pregnancy per trimester (n = 215).



Van Calsteren K et al. JCO 2010;28:683-689

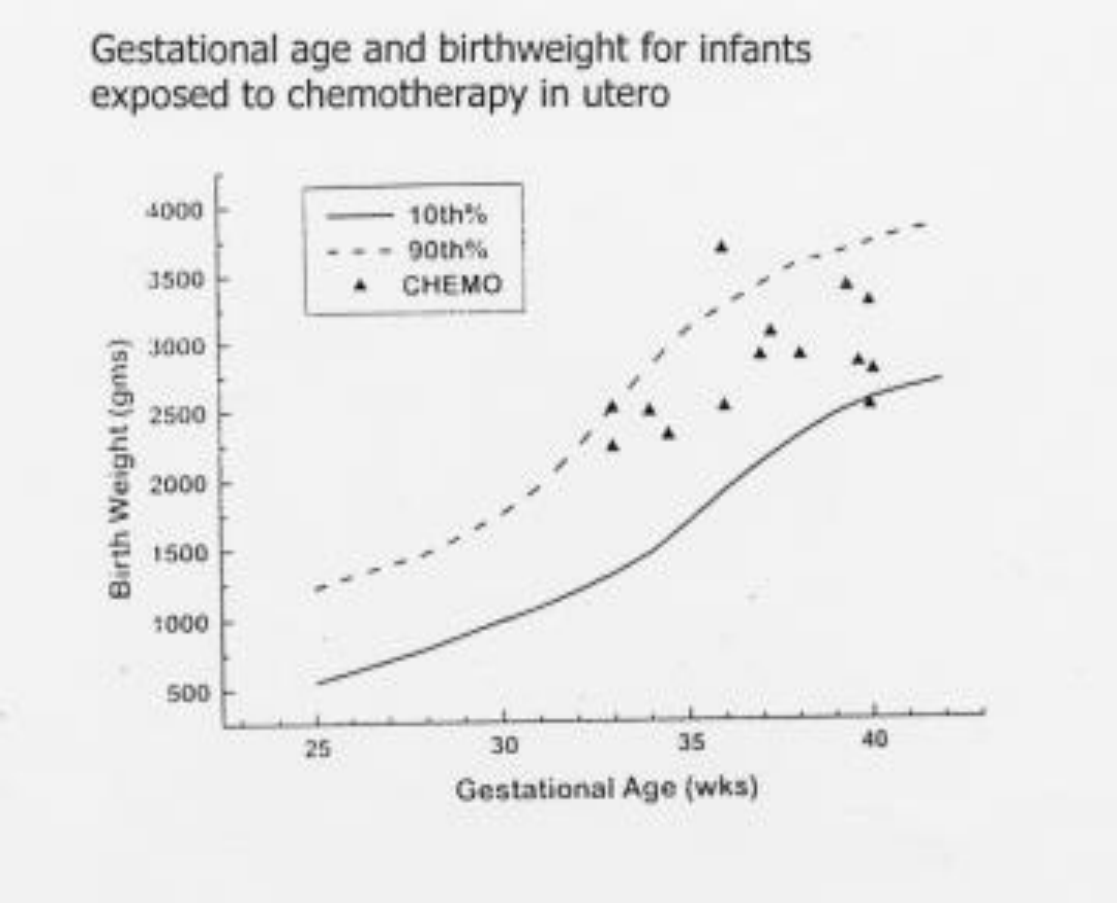
Crucial Periods in Prenatal Development



Moore P (ed). The Developing Human, 6th Ed, 1998

Effects of Maternal Chemotherapy by Gestational Stage

Stage	**Effect**
1st Trimester	Miscarriage 20-30% Malformations 10-25%
2nd and 3rd Trimester	IUGR, Low birth weight Prematurity, End oragan damage
Perinatal Period	Transfer to breast milk



Lubchenko et al 1966

Chemotherapy & Pregnancy

- Can be administered in second and third trimester
- Most experience is with anthracycline and taxane based regimens in breast cancer and hematological malignancy (Category A)
- Experience with platinum in gynecological and lung malignancy (category A)
- Experience with monoclonal antibodies and TKIs ia more limited (category B/C)
- The drugs will cross the placenta and will enter breast milk
- Fetal neutropenia and thrombocytopenia may occur if chemotherapy is given within 2 weeks of a planned delivery
- Anti-emetics are safe in second and third trimester
- Growth factors (e.g. G-CSF) have been used in both PABC and leukaemia/lymphoma associated with pregnancy (it is safest to avoid neutropenia in the mother)

Anthracyclines and PABC

Number	Regimen	Gestational Age	Congenital Abnormality
130 [1]	AC/FAC/FEC	20 +/- 5.4	Pyloric Stenosis (4; 3.8%) Pulm Art Fistula (1) Holoprosencephalopathy (1) Talipes (1)
57 [2]	FAC	23 (11-24)	Downs (3; 5.3%) Ureteral reflux(1) Club Foot (1)
20 [3]	Weekly E	19 (16-30)	Polycystic kidney (1)
26 [4]	E/A	Second Trimester	Polycystic kidney (1)
28 [5]	AC/EC/CMF	20 (15-33)	Nil

1 Cardonick 2010;2 Hahn 2006; 3Pecatori 2009; Azim 2008; Ring 2005

Taxanes and PABC

	Paclitaxel (21)	Docetaxel (16)
Maternal age	36 (30-42)	34 (26-44)
Gestational age (T1/2/3)	0/17/4	2/10/4
Cumulative dose mg/m^2	550 (300-1620)	300 (175-570)
Toxicity	Bilirubin (1) IUGR (1) Preeclampsia (1) Anhydramnios(1)*	Anhydramnios(1)* PPE (1) Preeclampsia (1)
Neonatal abnormality	Anaemia (1)	Ventriculomegaly (2)^ Haloprosencephaly (1)

- *Concurrent trastuzumab
- ^ Diagnosed before docetaxel

Mir et al Ann Oncol 2010

Supportive Medications

- Anti-emetics
  - Ondansetron and metoclopramide safe
  - Corticosteroids associated with cleft palate in first trimester
- GCSF; no evidence of problems (Category A) and safest to avoid neutropenia during pregnancy
- Anticoagulation; discuss with obstetrician as potential for LMWH because;
  - pregnant
  - Venous access (e.g Portacath)
  - malignancy

Endocrine treatment

- Tamoxifen is teratogenic in rats (wavy ribs) and should not be used during pregnancy
- Anecdotal reports of malformation of female genital organs in women receiving tamoxifen during pregnancy

Targeted Treatment (trastuzumab) in PABC

- Her2 expression is high in embryonic tissue(possible role in neural and cardiac development) [1]
- Trastuzumab crosses placenta in animal studies
- Case reports of reversible oligohydramnios or anhydramnios (? Effect on foetal renal epithelium)
- 3 reports transient neonatal respiratory/renal failure

CAUTION; if essential monitor amniotic fluid and limit exposure

[1] Lee et al 1995

Bisphosphonates during pregnancy associated cancer

- Bisphosphonates are not teratogenic in animal models (although long term effects on bone growth and development are not known)
- Transient hypocalcaemia has been reported in neonates. This may be related to foetal parathyroid suppression because of maternal hypercalcaemia rather than a direct drug effect
- A review of 51 patients exposed to bisphosphonates for various indications has not shown any foetal adverse effects [1] A review of 21 patients treated in first trimester showed no adverse impact [2]

[1] Djokanovic et al 2008
[2] Levy et al 2009

ESMO Clinical Practice Guidelines

	First Trimester	
Soft tissue sarcoma	Observe to second trimester versus termination	Single agent doxorubicin
Epithelial Ovarian cancer	Observe to second trimester versus termination	Carboplatin (AUC 5 or 6) + weekly paclitaxel (80mg/m2)
Germ cell ovarian tumours	Observe to second trimester versus termination	Cisplatin (75mg/m2) + weekly paclitaxel (avoid etoposide because high rate IUGR and foetal neutropenia Avoid bleomycin because potential lung problems
Non small cell lung cancer	Observe to second trimester versus termination	Carboplatin (AUC 5 or) + weekly paclitaxel Avoid antimetabolites Limited data TKI

If diagnosed later in third trimester consider preterm delivery and initiation of systemic treatment thereafter

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ESMO Clinical Practice Guidelines

	First Trimester	Second Trimester	Third Trimester
Acute leukaemia (ALL or AML)	Discuss termination	Induction therapy with doxorubicin and cytarabine	Induction delivery then therapy
Acute promyelocytic leukaemia	Discuss termination	Doxorubicin and ALL Trans Retinoic Acid (ATRA) (NB Coagulation problems)	Induction delivery then therapy
Chronic myeloid leukaemia (19% patients diagnosed < 40 years)	Discuss termination	Interferon alpha or imatinib	Interferon alpha or imatinib
NHL	Discuss termination	CHOP (avoid rituximab; increased B cell depletion in newborn)	CHOP (avoid rituximab; increased B cell depletion in newborn) Or delivery then chemotherapy
Hodgkins	Discuss termination	A(B)VD	A(B)VD

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Outcome in 265 described pregnancies in CML Imatinib-treated patients.

Table 1

Pregnancy outcome	Total number N=265	(%) with known outcome N=210	Real % (excluding elective termination with no known problems)
	Outcome in 265 described pregnancies in CML Imatinib-treated patients.		
Normal Live Infant	128	60% **(210 pregnancies)**	77% **(167 pregnancies)**
Elective Termination	43	20%	excluded
Fetal Abnormality	15	7%	9%
Spontaneous Abortion	24	11%	14%
Unknown	55	0	0

Lung Cancer in Pregnancy (N=66)

- Median age 26 years
- Gestational age 27.3 weeks (8- 38)
- Histopathology
  - NSCLC 82%
  - SCLC 18%
- Smoking
  - Yes 23 (35%)
  - No 18 (27%)
  - Unknown 25 (38%)
- Stage
  - Early (stage1 or2) 1 (1.5%)
  - Advanced (stage 3 and 4) 64 (97%)

Mitrou et all 2016 J Adv Res

Lung Cancer in Pregnancy (N=66)

- Treatment
  - During gestation 16 (24%)
  - Post partum 34 (51.5%)
  - No treatment 9 (13.5%
- Treatment type
  - Chemotherapy (platinum based) 40 (60.5)
  - Erlotinib/Gefitinib 3 (4.5%)
  - Crizotinib 2 (3%) 12 months or more 12 (18%)
  - Radiotherapy 3 (4.5%)
- Maternal Outcome
  - Death 1 month post partum 8
  - Alive 3 to 5 months 26 (39.5%
  - Alive 6 to 11 months 20 (30.5%)
  - Alive 12 months or more 12 (18%)

Foetal metastases 3 (4.5%); Placental Metastases 11 (17%)

Mitrou et all 2016 J Adv Res

Pregnancy Risk Classification of Some of the Most Used Targeted Therapies and Immunotherapies in Medical Oncology

Drug	**Pregnancy/neonatal complication**	**Teratogenic**
Imatinib	Not associated	Yes
Rituximab	Neonatal B-cell depletion	Not associated
Trastuzumab	Oligohidramnios	Not associated
Lapatinib	Possibly oligohydramnios	Yes (animal studies)
Bevacizumab	Possibly pre-eclampsia	No data
Ipilimumab	Abortion, stillbirths, premature delivery and higher incidence of infant mortality	Not associated
PD-1/PD-L1 inhibitors	Abortion, stillbirths, premature delivery and higher incidence of infant mortality	Not associated

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Breast Feeding

- Cytotoxic drugs are detected in breast milk
- Given long half life of monoclonal antibodies these would also be detected in breast milk
- Breast feeding is not recommended during chemotherapy
- At least 2 weeks should elapse from last chemotherapy to breast feeding

German Registry Study PABC (313 patients) Selected Newborn Events

Events	Chemotherapy during pregnancy (n = 142)	Chemotherapy after delivery (n = 118)	*p*-value
Total*	17 (12%)	8 (6.7%)	0.16
Congenital malformations†	3	1	—
Trisomy-18	1	0	—
Persistent foramen ovale	2	0	—
Infections	4	0	—
Neutropenia	2	1	—
Anemia	2	0	—
Necrotic enterocolitis	1	0	—

*Eight and five newborns that were prematurely delivered experienced an event in the chemotherapy during versus chemotherapy after delivery groups, respectively;†Polydactylia (n = 2), rectal atresia (n = 1), hypospadia (n = 1)

Loibl S et al. *Proc SABCS* 2010;Abstract S6-2.

Obstetric complications, foetal weight and complications at birth secondary to chemotherapy in second/third trimester

	Cancer type	Obstetric complications		Fetal weight below 10th percentile		Fetal complications at birth	
		Chemo[a]	**No chemo**	**Chemo**	**No chemo**	**Chemo**	**No chemo**
Van Calsteren et al. [9]	**All**	**17/62 (27%)**	**11/118 (9%)**	**14/62 (22%)**	**12/113 (11%)**	**7/62 (11%)**	**6/113 (5%)**
Cardonick et al. [10]	**Breast Cancer**	**22/104 (22%)**	**NR**	**8/104 (7.5%)**	**0/12 (0%)**	**12/104 (11%)**	**2/12 (16%)**
Loibl et al. [11]	**Breast Cancer**	**31/179 (17%)**	**15/149 (9%)**	**15/175 (9%)**	**5/139 (4%)**	**31/203 (15%)**	**7/170 (4%)**

3 large cohort studies; 85 % treatment was anthracycline based

Studies of Long-Term Follow-Up of Individuals Exposed to Intrauterine Chemotherapy

	N	Years of follow-up	Findings
Sokal et al (1960) [34]	17	2 - 9.5	All individuals reported to have no abnormalities.
Reynoso et al (1987) [35]	6	1- 16	One individual with two cancers(thyroid and neuroblastoma) and low IQ. All other individuals have no abnormalities.
Nulman et al (2001) [36]	111	1m - 22	Neurocognitive evaluation normal in all individuals.
Aviles et al (2001) [37]	84	6 - 29	All individuals had normal growth, development, educational performance and behavior. Twelve individuals had normal offspring.
Amant et al (2012) [38]	70	1.4 - 17.5	Individuals exposed to chemotherapy during the second and third trimester. No difference in comparing to general population in regard to general health, development, cognition, behavior, cardiologic or neurologic diseases.

What about patients who conceive on SACT

- Chemotherapy; high risk of miscarriage and congenital abnormality therefore recommend termination
- Tamoxifen
- Tamoxifen Increased risk fetal malformation therefore discuss termination (NB however tamoxifen is used as fertility treatment in IVF)
- Monoclonal antibodies do not cross placenta in first trimester (safety data from HERA(N=160 and case reports (n=5) no increased malformation therefore stop antibody and continue pregnancy
- TKI cross placenta in first trimester (data on imatinib high risk fetal malformation and miscarriage

Advise active contraception on SACT and for 3 to 6 months following last dose

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Conclusions

- Some chemotherapy can be safely administered during pregnancy
- Limited data on TKIs and mAb
- End organ damage and placental problems also important (i.e not only congenital abnormality risk)
- Share information and learn from other tumour types and talk to colleagues
- Always involve obstetrician at an early stage (? Level2/3 unit)
- Local champions
- Contribute to data bases