

# Cancer et Grossesse

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# Conflits d'intérêt

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**Aucun**

# Objectifs d'Apprentissage

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- Reconnaître l'épidémiologie des néoplasies les plus fréquentes en grossesse;
- Discuter des principes généraux quant à l'investigation et aux traitements des néoplasies pendant la grossesse;
- Évaluer les impacts foetaux de la néoplasie et de son traitement pouvant nécessiter un suivi en grossesse et en postpartum.

# Cas Clinique Numéro 1

32 ans, origine chinoise, G2 P1 A0

- Douleur abdominale et augmentation de l'abdomen depuis le début de la grossesse
- Echographie à 25 semaines de grossesse révèle de l'ascite
- Ponction d'ascite avec cellules malignes compatibles avec une origine digestive haute
- Gastroskopie: linite plastique, pas d'examen radiologique

# Cas Clinique Numéro 1

32 ans, origine chinoise, G2 P1 A0

- Grossesse de 24 semaines
- Ascite avec cellules malignes compatibles avec une origine digestive haute, linite plastique confirmée à la gastroscopie

**Quelle conduite serait la plus appropriée?**

- 1. Avortement et traitement de chimiothérapie**
- 2. Chimiothérapie et continuer la grossesse**
- 3. Attendre 35 semaines de grossesse pour accoucher la patiente et la traiter ensuite en chimiothérapie**
- 4. Aucune idée**

CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

Founded by Richard C. Cabot  
Eric S. Rosenberg, M.D., *Editor*  
Virginia M. Pierce, M.D., David M. Dudzinski, M.D., Meridale V. Baggett, M.D.,  
Dennis C. Sgroi, M.D., Jo-Anne O. Shepard, M.D., *Associate Editors*  
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Emily K. McDonald, Sally H. Ebeling, *Production Editors*



## Case 32-2018: A 36-Year-Old Pregnant Woman with Newly Diagnosed Adenocarcinoma

Janet E. Murphy, M.D., M.P.H., Kimberly Shampain, M.D., Laura E. Riley, M.D.,  
Jeffrey W. Clark, M.D., and Kristen M. Basnet, M.D.

# Cas Clinique Numéro 2

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- Case 32-2018: A 36-Year-Old Pregnant Woman with Newly Diagnosed Adenocarcinoma
- Diagnostic: Cancer du colon métastatique
- Grossesse de 32 semaines et 4 jours

## Cas du NEJM octobre 2018

- Because the gestational age was now almost 34 weeks, the results of fetal testing had been reassuring, and betamethasone had been administered to assist in the progression of fetal lung maturity, the neonatal outcome was likely to be excellent.
- BB delivered at 35 weeks and mother died one week afterwards without having received chemotherapy



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- Gastroskopie: linite plastique, pas d'examen radiologique
- **Chimiothérapie Folfox à 26 semaines**
- **Accouchement à 35 semaines, petite fille normale**
- **Patiente vivante et montrant les photos de sa fille 12 mois après le diagnostic**

## Epidémiologie du cancer en grossesse

- Prevalence: 1-2 cas/1,000 naissances vivantes
- Site enregistreur tous les cas de cancer en grossesse ([www.cancerinpregnancy.org](http://www.cancerinpregnancy.org))

The International Network on Cancer, Infertility and Pregnancy registers all cancers occurring during gestation ([www.cancerinpregnancy.org](http://www.cancerinpregnancy.org)). Patient accrual is ongoing and essential, because registration of new cases and long-term follow-up will improve clinical knowledge and increase the level of evidence.  
J. Clin Oncology 2016; 34: 501-508

# Incidence du Cancer en Grossesse

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- Incidence est la même que la population en général pour le même groupe d'âge

**Table 2. Distribution of cancer in pregnant women**

<b>Site</b>	<b>n of cases</b>	<b>%</b>
Breast	298	26
Cervix	294	26
Leukemia	174	15
Lymphoma	119	10
Melanoma	93	8
Thyroid	45	4
Miscellaneous	111	11
<b>Total</b>	<b>1,134</b>	<b>100</b>

**Table 1**

Epidemiology of cancer in pregnancy.

Type of Malignancy	Incidence in Pregnancy (per 100,000 pregnancies)	References
<u>Gynecologic Malignancies</u>		
Breast	10–35	[1,5–9]
Cervix	10–12	[1,2]
Ovarian	0.6–5.2	[1,10,11]
<u>Other Malignancies</u>		
Hematologic (Lymphoma and Leukemia)	13–16	[1,12]
Thyroid	2–14	[1,13]
Melanoma	2.8–8.7	[1,14]
Colon	2.8–7.7	[1,15–17]

# Incidence du Cancer en Grossesse

- Incidence est la même que la population en général pour le même groupe d'âge
- Donc rare par définition compte tenu du jeune âge des femmes enceintes
- La grossesse ne semble pas augmenter ou diminuer l'incidence du cancer
- Peut survenir à tous les stades de la grossesse

# Comment soupçonner le cancer en grossesse

## *Ne pas ignorer les signes ou symptômes*

TABLE 2

### Overview of cancer types, symptoms, and evaluation in pregnancy

Cancer type	Incidence	Symptoms	Initial evaluation
Breast cancer <sup>4,15</sup>	1:3000-10,000	Palpable, painless mass Bloody nipple discharge Skin changes (retraction/ redness)	Ultrasound Core needle biopsy
Cervical cancer <sup>4,13</sup>	1-2:2000-10,000	Abnormal cervical cytology Friable, exophytic mass	Colposcopy/biopsy conization
Melanoma <sup>21</sup>	1-2.6:1000	New or growing pigmented skin lesion	Tumor excision/biopsy
Ovarian cancer <sup>13</sup>	1:10,000	Mass found incidentally on ultrasound Abdominal pain or bloating	Ultrasound Surgery
Lymphoma <sup>4</sup>	1:1000-6000	Painless lymphadenopathy Systemic symptoms such as fever or chills	Chest radiograph Bone marrow biopsy Abdominal ultrasound
Thyroid cancer <sup>4,22</sup>	0.2-1.4:10,000	Palpable thyroid nodule	Fine-needle aspiration
Colorectal cancer <sup>4,23</sup>	1:13,000	Bloody stool Abdominal pain Diarrhea	Colonoscopy

Salani. *Cancer in pregnancy. Am J Obstet Gynecol* 2014.

# Comment Investiguer selon le type de Cancer suspecté

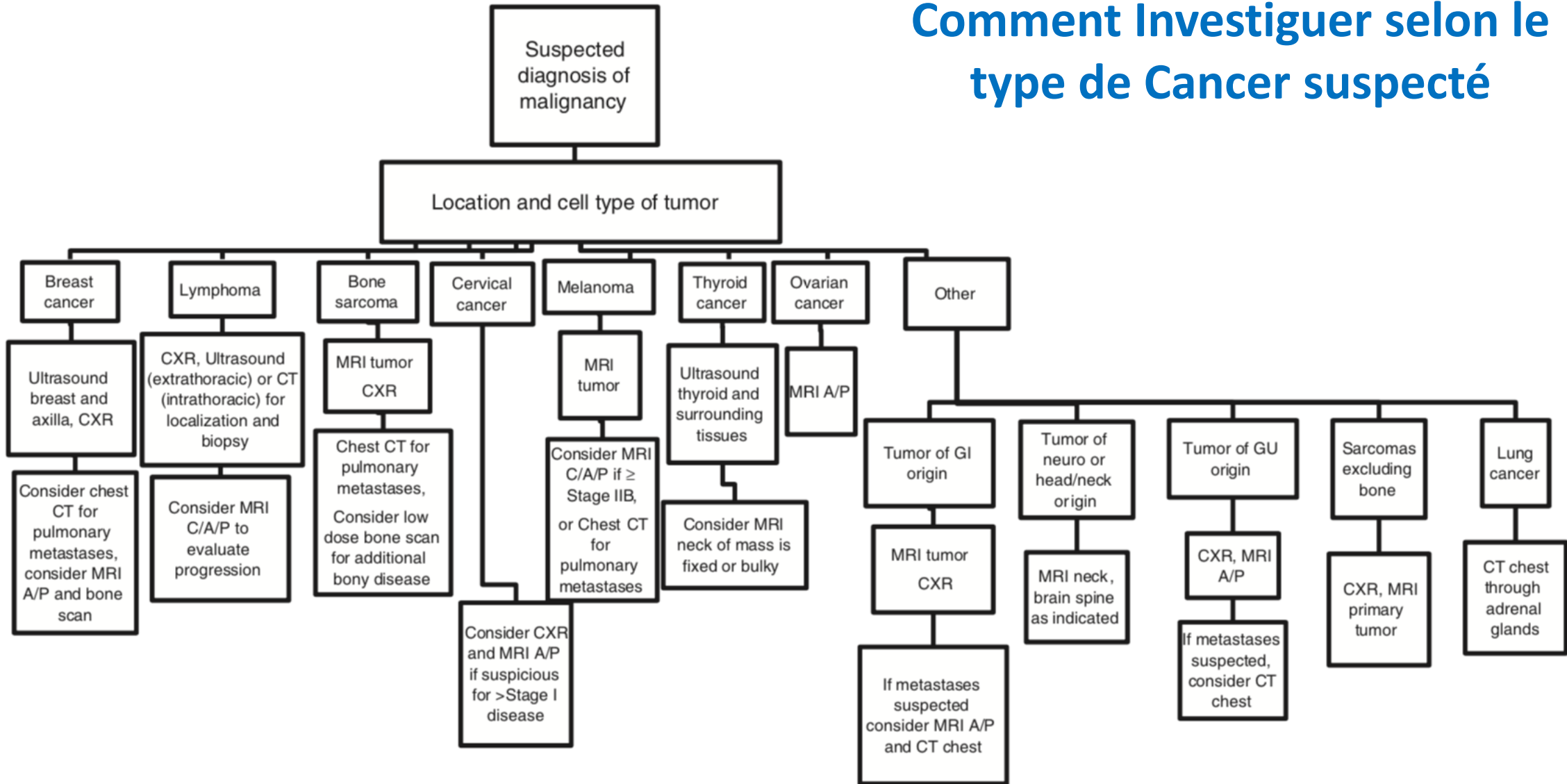


Fig. 2. Imaging algorithm.



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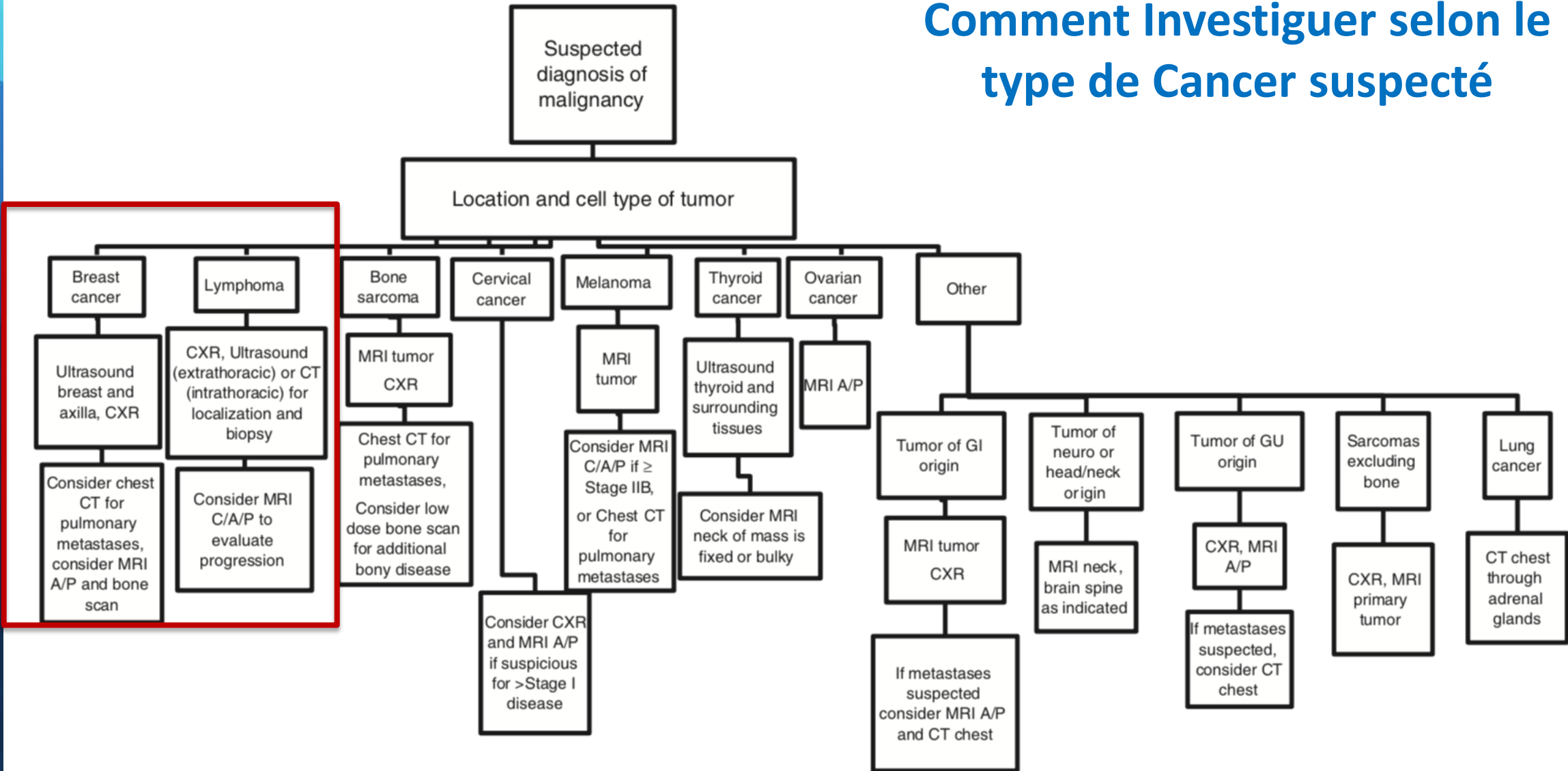


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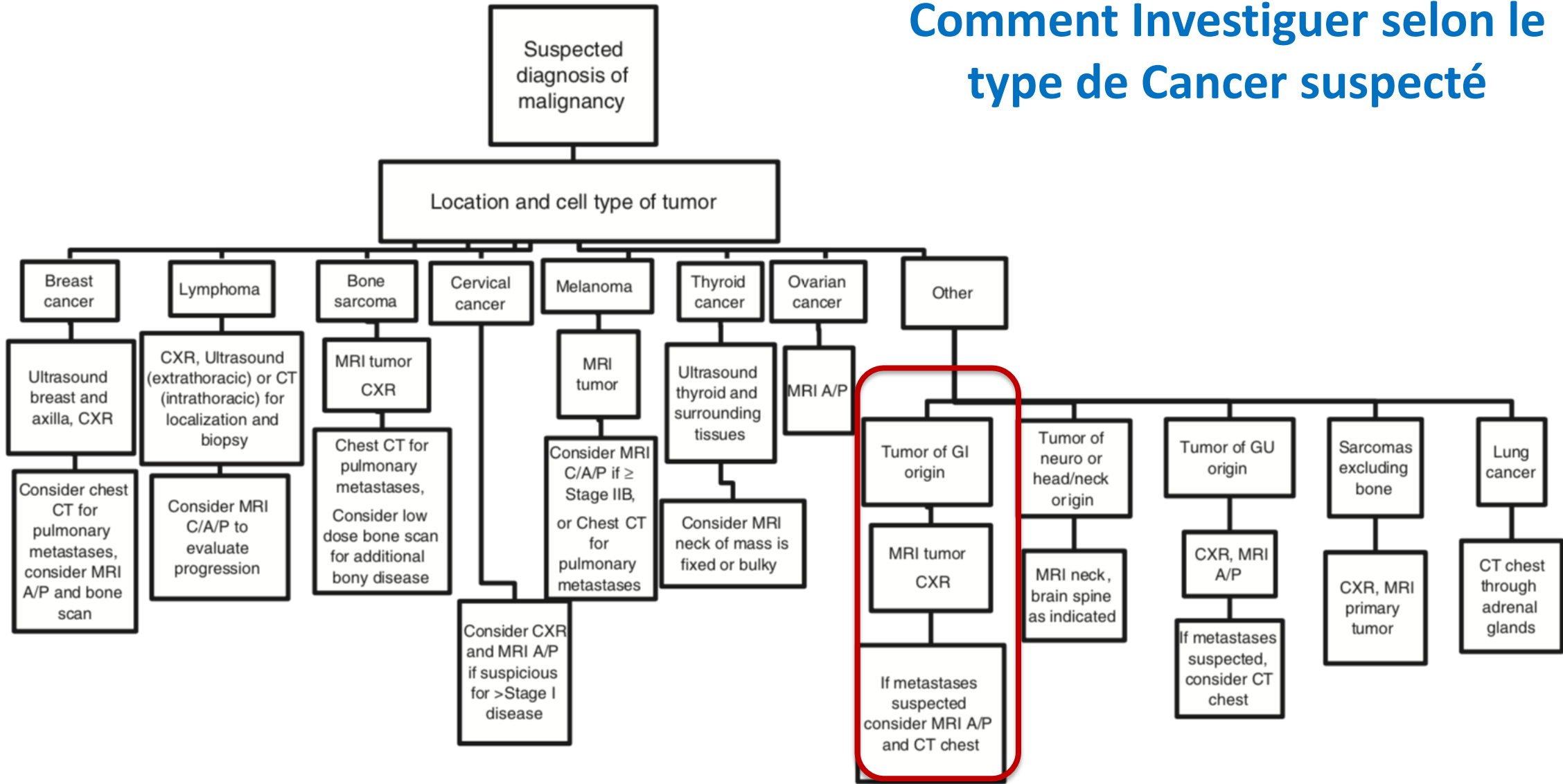


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### Table 3. Radiation dose effect on fetal life

Dose	Effect on fetus
<0.1 Gy (<10 rad)	No major effect
0.1-0.15 Gy (10-15 rad)	Increased risk
2.5 Gy (250 rad)	Malformations in most
>30 Gy (300 rad)	Abortion

# Risque de l'irradiation foetale selon les imageries

TABLE 1

**Fetal radiation dose exposure of common imaging methods**

<b>Imaging</b>	<b>Estimated fetal dose (rads)</b>
Plain radiograph	
Chest	<0.01
Abdominal (2 views)	0.02
Extremities	0.001
Mammogram	
	0.020
Computed tomography	
Head	<0.05
Chest	<0.10
Abdomen/pelvis	2.60
Background radiation (control)	0.10

Salani. *Cancer in pregnancy. Am J Obstet Gynecol* 2014.

# Risque de radiothérapie pour le fœtus

*F. Amant et al. / Best Practice & Research Clinical Obstetrics and Gynaecology 29 (2015) 741–753*

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**Table 2**

Risks of radiotherapy to fetus during pregnancy (reproduced from AAPM) [4].

Gestational age (weeks)	Risk
Preimplantation (1)	Lethality <sup>a</sup>
Organogenesis (2–7)	Lethality, gross malformations <sup>a</sup> , growth retardation <sup>a</sup> , sterility, cataracts, other neuropathology, malignant disease
Early fetal (8–15)	Lethality, gross malformations, growth retardation, mental retardation <sup>a</sup> , sterility, cataracts, malignant disease
Midfetal (16–25)	Gross malformations, growth retardation, mental retardation, sterility, cataracts, malignant disease
Late fetal (>25)	Growth retardation, sterility, cataracts, malignant disease

<sup>a</sup> high incidence.

## Box 1

### Recommendations for imaging studies during pregnancy.

- Non-abdominal or pelvic X-ray examination with abdominal shielding might be used during all trimesters of pregnancy.
- There are no limitations for ultrasound examination.
- MRI without gadolinium administration might be used in the second and third trimesters.
- CT scan should be avoided.
- Iodine-based contrast agent is contraindicated during all stages of pregnancy.
- Gadolinium should not be used during all stages of pregnancy.

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# Comment Traiter le Cancer en Grossesse

- **Premier principe:** le cancer doit se traiter de la même manière que chez une femme non enceinte
- La survie avec traitement efficace est comparable stade pour stade

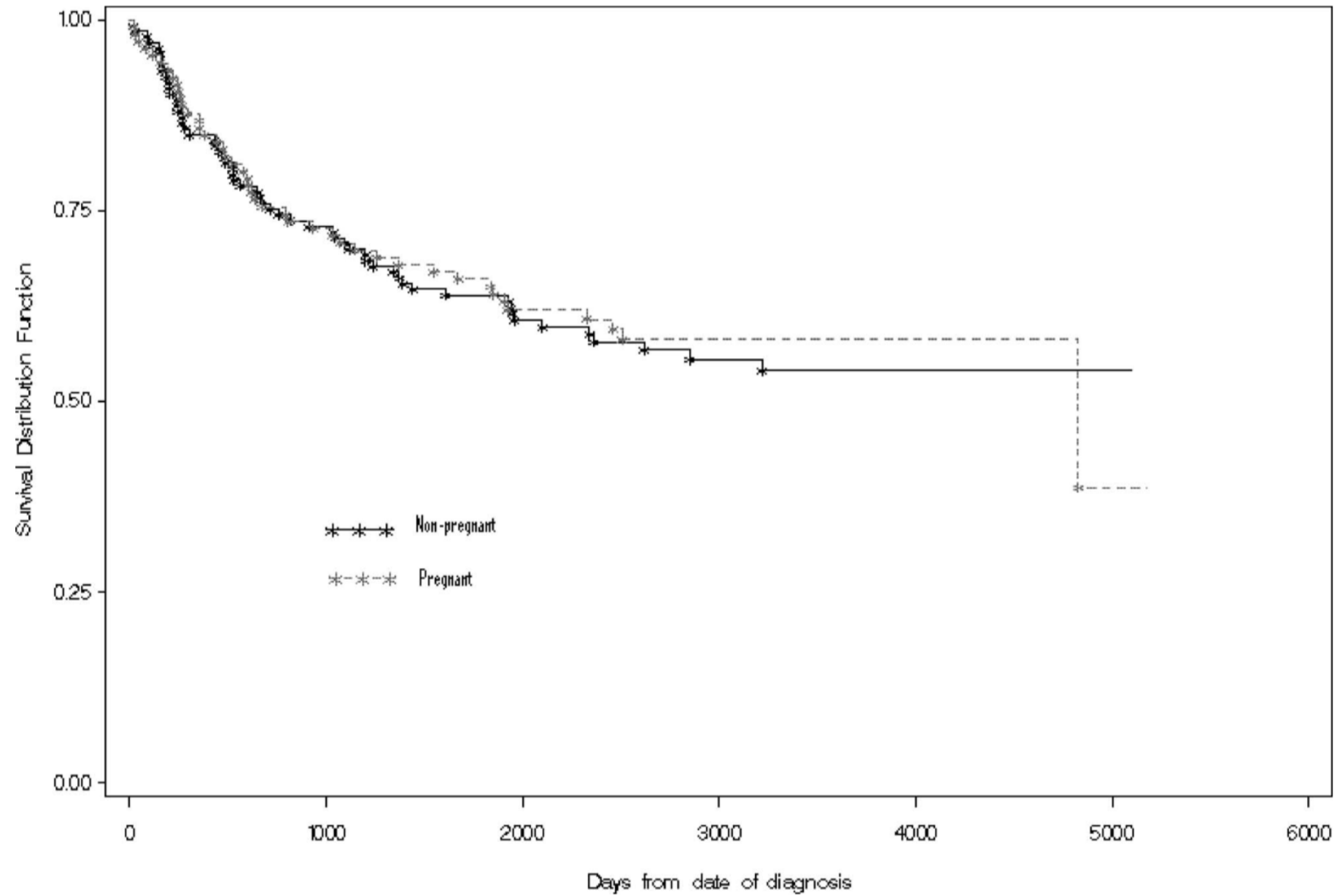


Figure 1. Kaplan-Meier survival distribution for women diagnosed with colon cancer in CA, 1991-1999.

# Comment Traiter le Cancer en Grossesse

- **Premier principe:** le cancer doit se traiter de la même manière que chez une femme non enceinte
- La survie avec traitement efficace est comparable stade pour stade
- **Second principe:** la santé de la mère entraîne le bien-être du BB
- **Bémols:**
  - paucité des études (12,000 citations revues de 1960 à 2018)
  - Toxicité pour le BB selon le stade de la grossesse

# Considérations générales pour le traitement

- Equipe multidisciplinaire essentielle
- Monitoring sérié de la croissance et malformations du BB
- Monitoring foetal étroit durant la chimiothérapie
- Accouchement selon les indications obstétricales et le plus à terme possible
- Chimiothérapie à éviter 2 à 3 semaines pré-accouchement
- Placenta à examiner pour éliminer métastases (surtout pour les mélanomes et les leucémies)

Aucun cancer rapporté chez les enfants avec métastases placentaires

## Practice points

- The treatment of cancer during pregnancy is complex and infrequent. Therefore, a multi-disciplinary approach is mandatory.
- Termination of pregnancy does not improve the maternal prognosis for breast cancer.
- Surgery during pregnancy is possible in all trimesters of pregnancy.
- Chemotherapy can safely be administered from 12 to 14 weeks of gestational age onwards.
- Radiotherapy of the upper body parts is safe during the first and second trimester of pregnancy when the distance to a small uterus is large.
- Cancer treatment during pregnancy adds in the prevention of prematurity.

## Impact de la chimiothérapie du premier trimestre à terme: données en évolution

- Plusieurs case reports de chimiothérapie avant de connaître la grossesse sans conséquences pour le foetus
- Plusieurs cas de chimiothérapie donnée dès la 13<sup>ème</sup> semaine de grossesse sans conséquences pour le foetus (lymphomes, sein, digestif)

# Risque de la chimiothérapie maternelle pour le Fœtus

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*I. Avivi et al. / Blood Reviews 28 (2014) 213–220*

**Table 2**

Major pregnancy-related side effects of commonly used chemotherapeutic drugs for NHL

Drug	Side effects in the 1st trimester	Side effects in the 2nd & 3rd trimesters	References
Cyclophosphamide	Central nervous system Skeletal anomalies	Growth restriction Pre-term delivery Low birth weight	Kirshon B et al. [104] Mirkes PE [105]
Adriamycin	Eye and limb deformities	Growth restriction Pre-term delivery Low birth weight	Reynoso EE et al. [39]
Vincristine	Central nervous system Eyes anomalies Skeletal deformities <sup>a</sup>	No precise data available	Joneja M et al. [106]
Methotrexate	Aminopterin syndrome	Aminopterin syndrome (up to the middle of the 2nd trimester)	Sherer DM et al. [76]
Cytarabine	Limb deformities	Growth restriction Intrauterine death	Wagner VM et al. [70] Artlich A et al. [71] Ebert U et al. [72] Schafer AI [73]
Rituximab	Not teratogenic	Pre-term delivery, transient hematological abnormalities, e.g., lymphopenia and neutropenia	Chakravarty EF [58]

<sup>a</sup> Data from animal studies only.

# Risque de Malformations Foetales Chimiothérapie au Premier Trimestre

**Table 7.** Treatment given during first trimester and estimated risk of malformation

<b>Drug</b>	<b>Risk</b>
Chlorambucil	1:2
Nitrogen mustard	1:3
Aminopterin	1:3
5-fluorouracil	1:3
Methotrexate	1:4
Cyclophosphamide	1:6
Cytosine arabinoside	1:8
Busulfan	1:9



**Table 3.** Cases of CRC in pregnancy treated with chemotherapy

Case [reference]	Chemotherapy regimen	Infant at birth	Infant follow-up	Mother follow-up
mCRC, age 33 yr [15] Chemotherapy initiated: 22 weeks' gestation	FOLFOX; total cycles: 6	Vaginal delivery at 38 weeks' gestation • Reported healthy • No immediate complications	Infant follow-up (2 yr): • Met developmental milestones • No recognizable complications	Receiving palliative chemotherapy
mCRC, age 40 yr [16] Chemotherapy initiated: 23–24 weeks' gestation	FOLFOX; total cycles: 4	Cesarean delivery at 31.5 weeks' gestation • Admitted to neonatal unit • Small for gestational age • Hypothyroidism	Infant follow-up (approximately 11 mo) • Weight (50th percentile corrected for prematurity) • Length (90th percentile) • Head circumference (90th percentile) • Result of Denver developmental screening test was normal for adjusted age	Deceased 5 mo after mCRC diagnosis (declined more CRC treatment)
mCRC, age 26 yr [17] Chemotherapy initiated: 13 weeks' gestation	FOLFOX; total cycles: 10	Cesarean delivery at 33 weeks' gestation • No malformations reported	Twins' follow-up (2 yr) • Developing normally	Deceased 1 yr after mCRC diagnosis
mCRC, age 25 yr [18] Chemotherapy initiated: 20 weeks' gestation	FOLFOX; total cycles: 6	Vaginal delivery at 33.6 weeks' gestation • No malformations reported	Infant follow-up (3.5 yr) • Height: 60th percentile • Weight: 45th percentile • No deficits reported	1 yr, no evidence of disease after metastatic liver resection
mCRC, age 38 yr [19] Chemotherapy initiated: 19 weeks' gestation	FOLFOX; total cycles: 3	Cesarean delivery at 36 weeks' gestation • Small for gestational age • Normal neurological examination • No malformations reported	Infant follow-up (10 mo) • Weight: 10th–25th percentile • Head circumference: 10th–25th percentile • No deficits reported	Receiving treatment at 13 mo since diagnosis
mCRC, age 33 yr [20] Chemotherapy initiated: 23 weeks' gestation	FOLFIRI; total cycles: 3 cycles	Cesarean delivery at 30 weeks' gestation • Admitted to neonatal unit because of prematurity and intrauterine growth restriction • No malformations reported	Infant follow-up (13 mo) • Healthy • Achieved appropriate growth and development milestones	FOLFOX with progression after 4 cycles followed by best supportive care
Krukenberg tumor primary, determined to be CRC, age 34 yr [21] Chemotherapy initiated: 18 weeks' gestation	FOLFIRI; total cycles: 10	Vaginal delivery at approximately 37 weeks' gestation • No malformations reported	Infant follow-up (4 mo) • Normal development	Adjuvant chemotherapy
CRC, age 31 yr [22] Chemotherapy initiated: 29 weeks' gestation	5-FU; total cycles: NR	Delivery: 39 weeks' gestation with uneventful delivery • Reported healthy • No malformations reported	NR	NR

Abbreviations: CRC, colorectal cancer; FOLFIRI, 5-fluorouracil, irinotecan, folinic acid; FOLFOX, 5-fluorouracil, oxaliplatin, and leucovorin; mCRC, metastatic colorectal cancer; NR, not reported.

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mCRC, age 40 yr [16] Chemotherapy initiated: 23–24 weeks' gestation	FOLFOX; total cycles: 4	Cesarean delivery at 31.5 weeks' gestation • Admitted to neonatal unit • Small for gestational age • Hypothyroidism	Infant follow-up (approximately 11 mo) • Weight (50th percentile corrected for prematurity) • Length (90th percentile) • Head circumference (90th percentile) • Result of Denver developmental screening test was normal for adjusted age	Deceased 5 mo after mCRC diagnosis (declined more CRC treatment)
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CRC, age 31 yr [22] Chemotherapy initiated: 29 weeks' gestation	5-FU; total cycles: NR	Delivery: 39 weeks' gestation with uneventful delivery • Reported healthy • No malformations reported	NR	NR

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# Chimiothérapie du Cancer Colo-rectal

**Table 1** Cases of Colorectal Cancer Treated With Chemotherapy During Pregnancy

Case	Agents	Trimester Agents Given	Fetal Outcome
1	5-FU, leucovorin, oxaliplatin	2, 3	Twins healthy at birth and at follow-up at 2 years of age
2 <sup>6</sup>	5-FU, leucovorin, oxaliplatin	2, 3	Healthy at birth and at follow-up at 3 years of age
3 <sup>5</sup>	5-FU, leucovorin, oxaliplatin	2, 3	Growth restricted at birth. Healthy at follow-up at 1 year of age. Hypothyroid
4 <sup>20</sup>	5-FU, leucovorin	2, 3	Healthy at birth
5 <sup>20</sup>	5-FU, leucovorin	2, 3	Healthy at birth
6 <sup>20</sup>	5-FU, leucovorin	2, 3	Healthy at birth and at follow-up at 3 years of age
7 <sup>20</sup>	5-FU, leucovorin	2, 3	Hemi-hypertrophy of lower extremity
8 <sup>20</sup>	Capecitabine, oxaliplatin	1	Healthy at birth and at follow-up at 2 years of age

# Chimiothérapie dans 147 lymphomes

**Table 1** Summary of case series of lymphoma diagnosed during pregnancy since 2013

Article	Sample	Treatment	Survival outcomes	Fetal outcomes
Pinnix et al. (JAMA Oncol. 2016) [14]	<i>N</i> = 39 pregnant patients (31 HL; 8 NHL); <i>n</i> = 32 (82%) had stage I–II disease	24 patients received antenatal therapy (chemotherapy and/or RT); 12 deferred therapy until after delivery; 3 electively terminated pregnancy to receive systemic therapy	5-year PFS: 74.7%; 5-year OS: 82.4% (no difference in outcome based on timing of therapy)	4 miscarriages in patients receiving antenatal therapy (2/4 in 1st trimester) No difference in time to delivery between patients receiving antenatal vs post-natal treatment ( <i>p</i> = 0.21) No fetal abnormalities were observed.
Bachanova et al. (Curr Hematol Malig Rep. 2013) [16]	<i>N</i> = 18 pregnant patients with HL	11 patients received post-natal treatment; 6 patients required vinblastine to control disease	2/4 deaths were due to HL	No apparent abnormalities of children post delivery
Evens et al. (J Clin Oncol 2013) [13]	<i>N</i> = 90 pregnant patients (40 HL; 50 NHL); <i>n</i> = 54 (60%) had stage I–II disease	56 received antenatal treatment (Chemotherapy and/or RT), with therapy initiated in the 2nd trimester in 37/56 patients (66%); 6 patients had termination of pregnancy. No patients treated during 1st trimester	3-year PFS and OS were 53 and 82% in NHL cases, and 85 and 97% in HL cases 8 deaths related to NHL	Full term gestation in 56% of patients; 1 case of fetal demise No differences in complications detected among patients who received antenatal vs deferred therapy. One case of microcephaly and one case of pelviactasis were detected in infants whose mother received antenatal treatment.

*NHL* non-Hodgkin lymphoma, *HL* Hodgkin lymphoma, *PFS* progression-free survival, *OS* overall survival, *RT* radiation therapy

Lishner. M et al, *J Clin Oncol* 2016 ; 34:501-508

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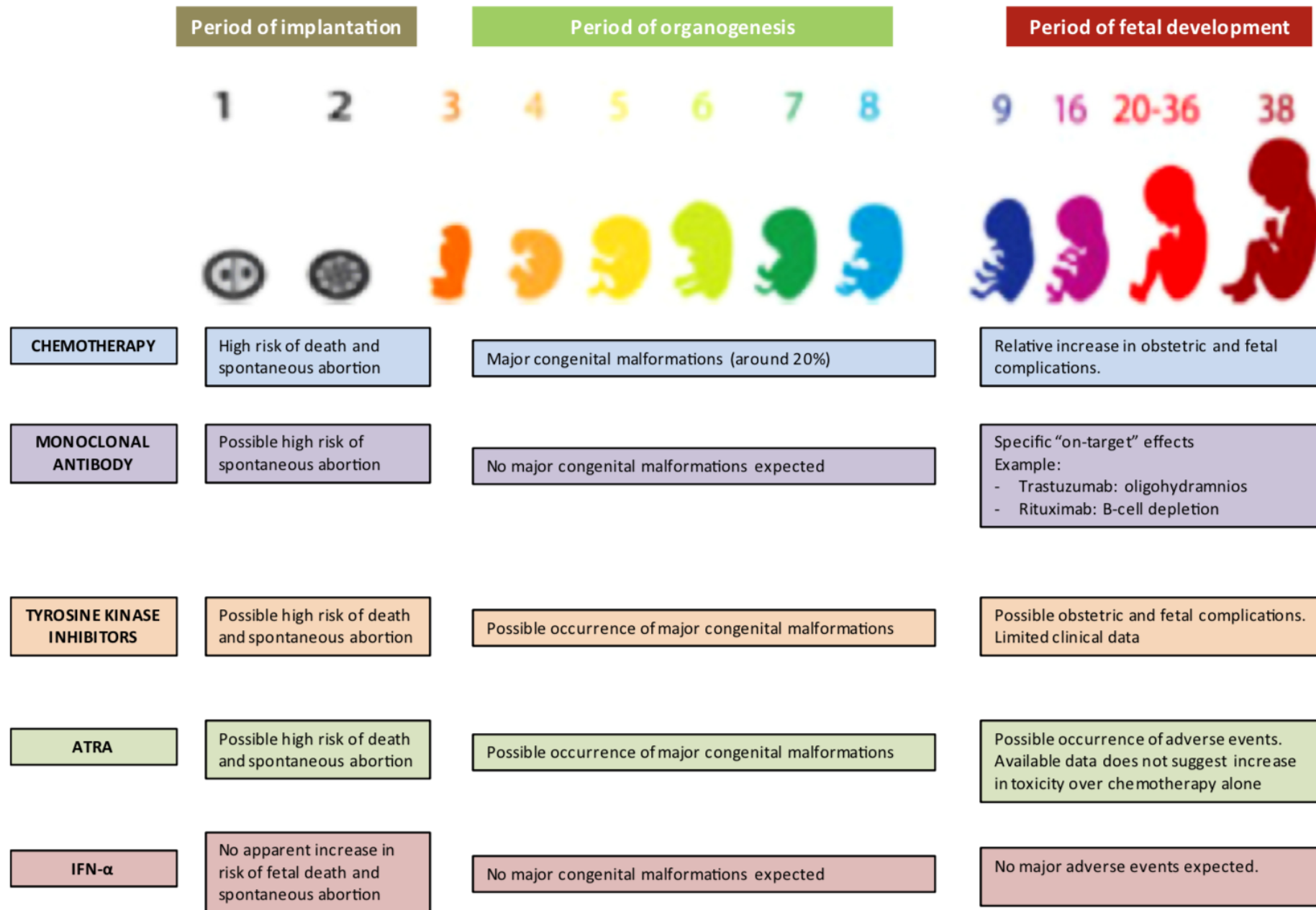
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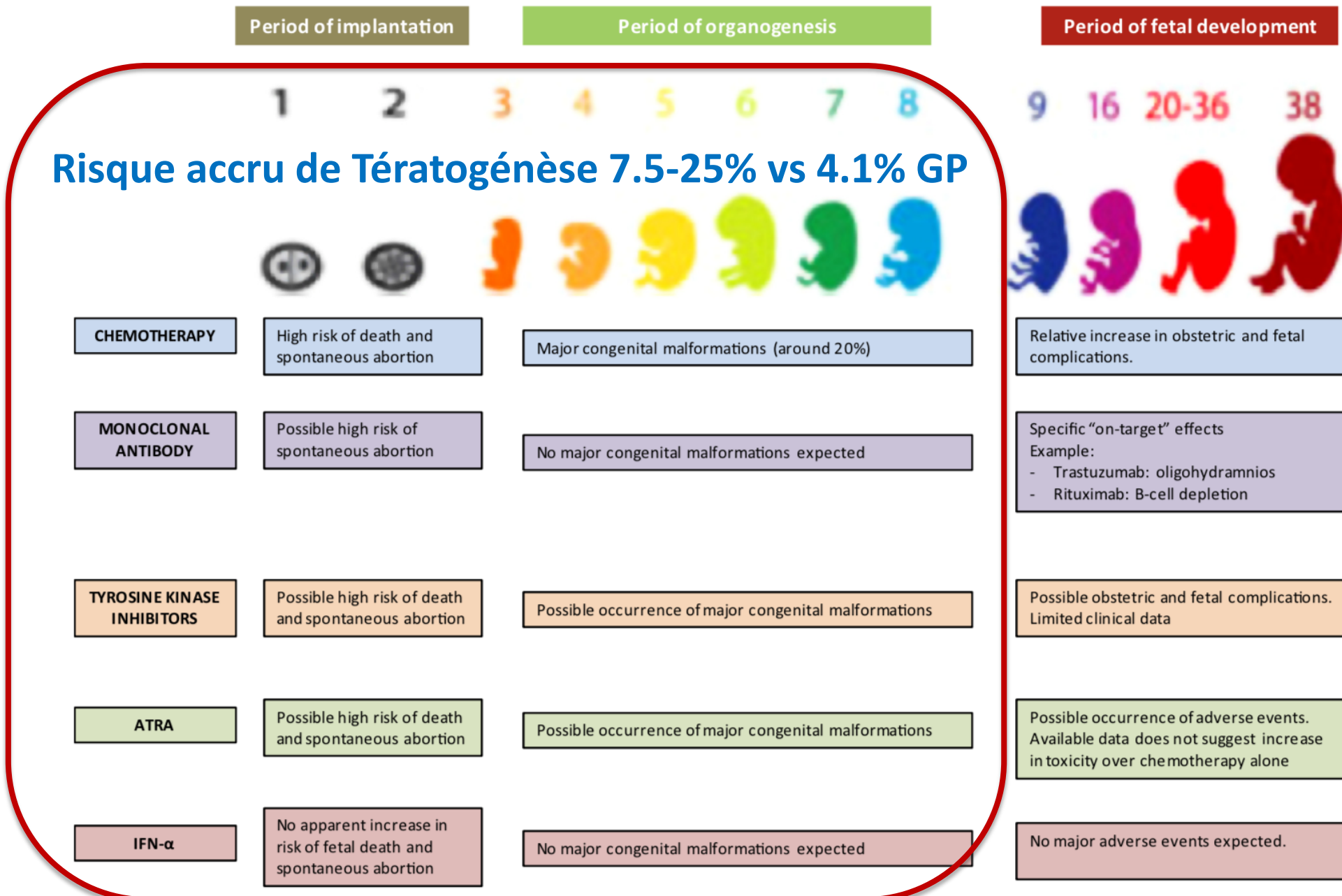
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Lishner. M et al, *J Clin Oncol* 2016 ; 34:501-508

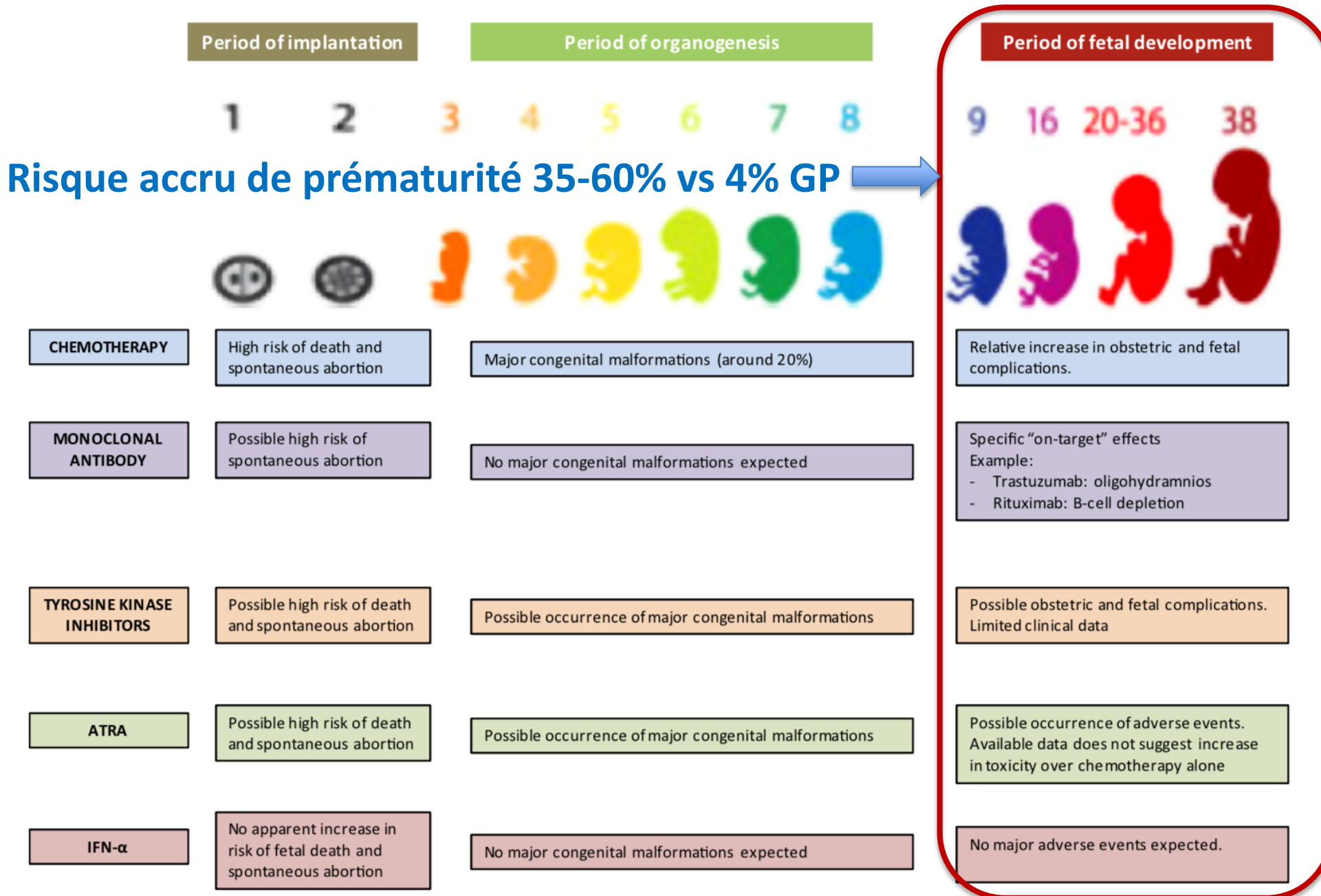


**Fig. 1.** Key differences between chemotherapy and different classes of targeted agents in terms of their expected toxicity during pregnancy.

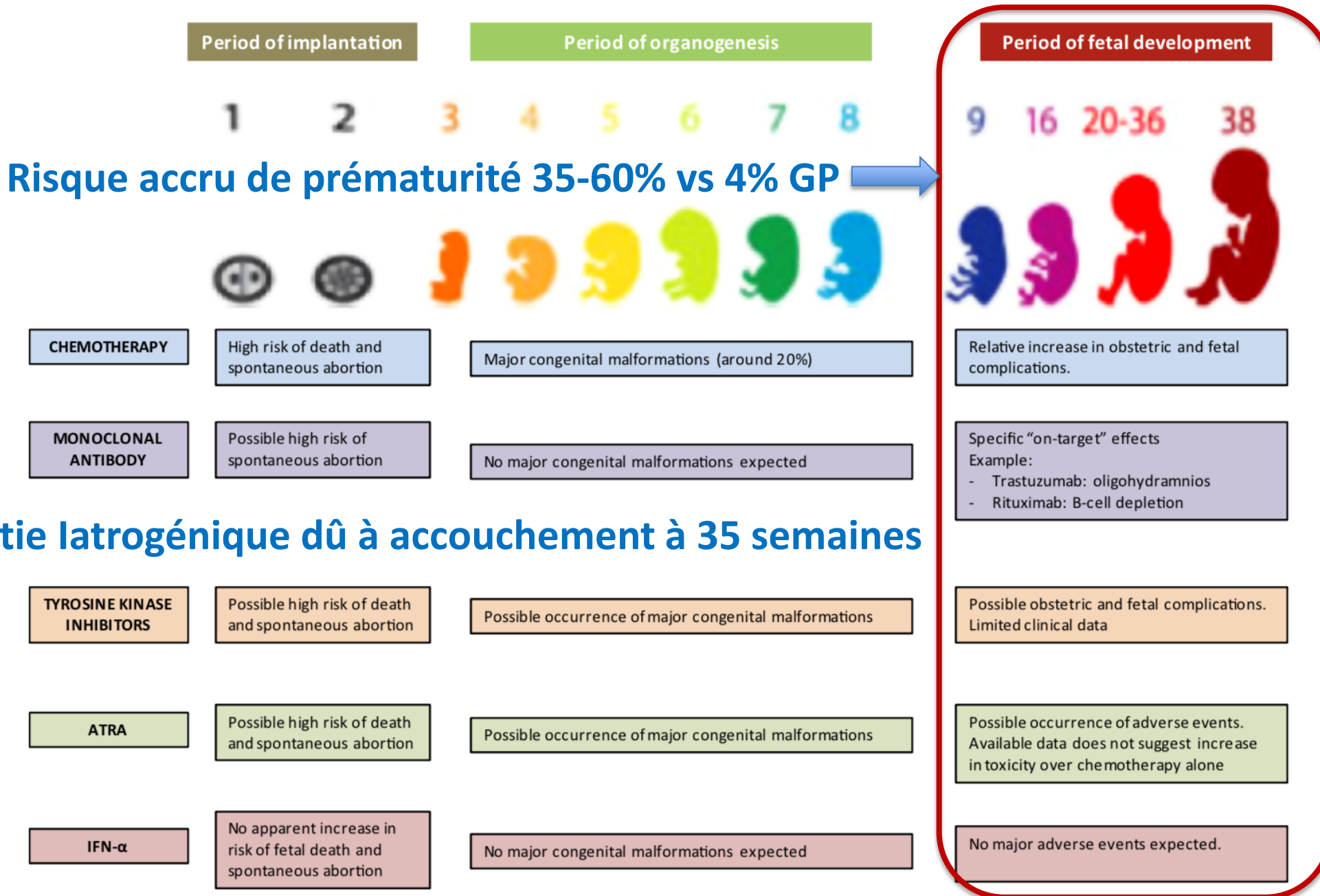


**Fig. 1.** Key differences between chemotherapy and different classes of targeted agents in terms of their expected toxicity during pregnancy.





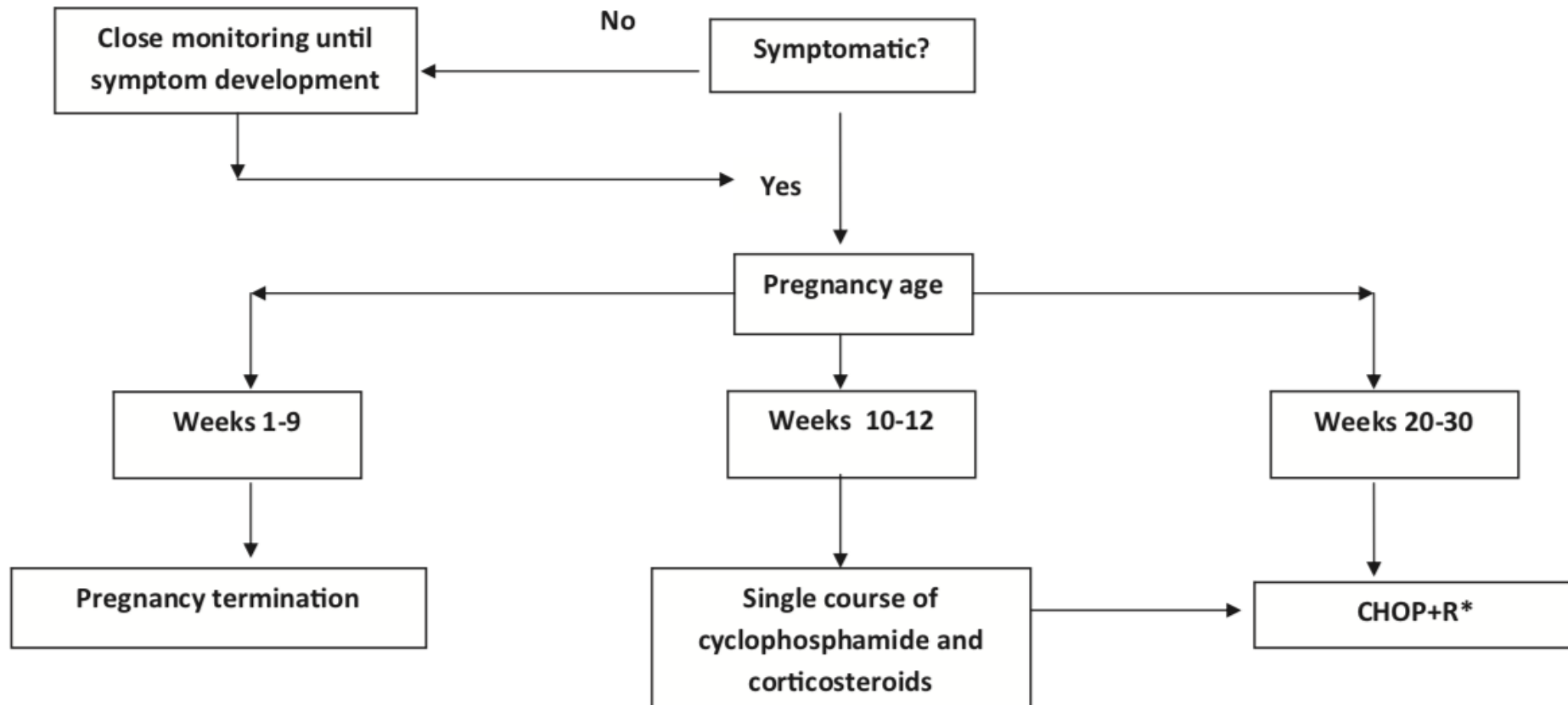
**Fig. 1.** Key differences between chemotherapy and different classes of targeted agents in terms of their expected toxicity during pregnancy.



**Fig. 1.** Key differences between chemotherapy and different classes of targeted agents in terms of their expected toxicity during pregnancy.

# DLBCL

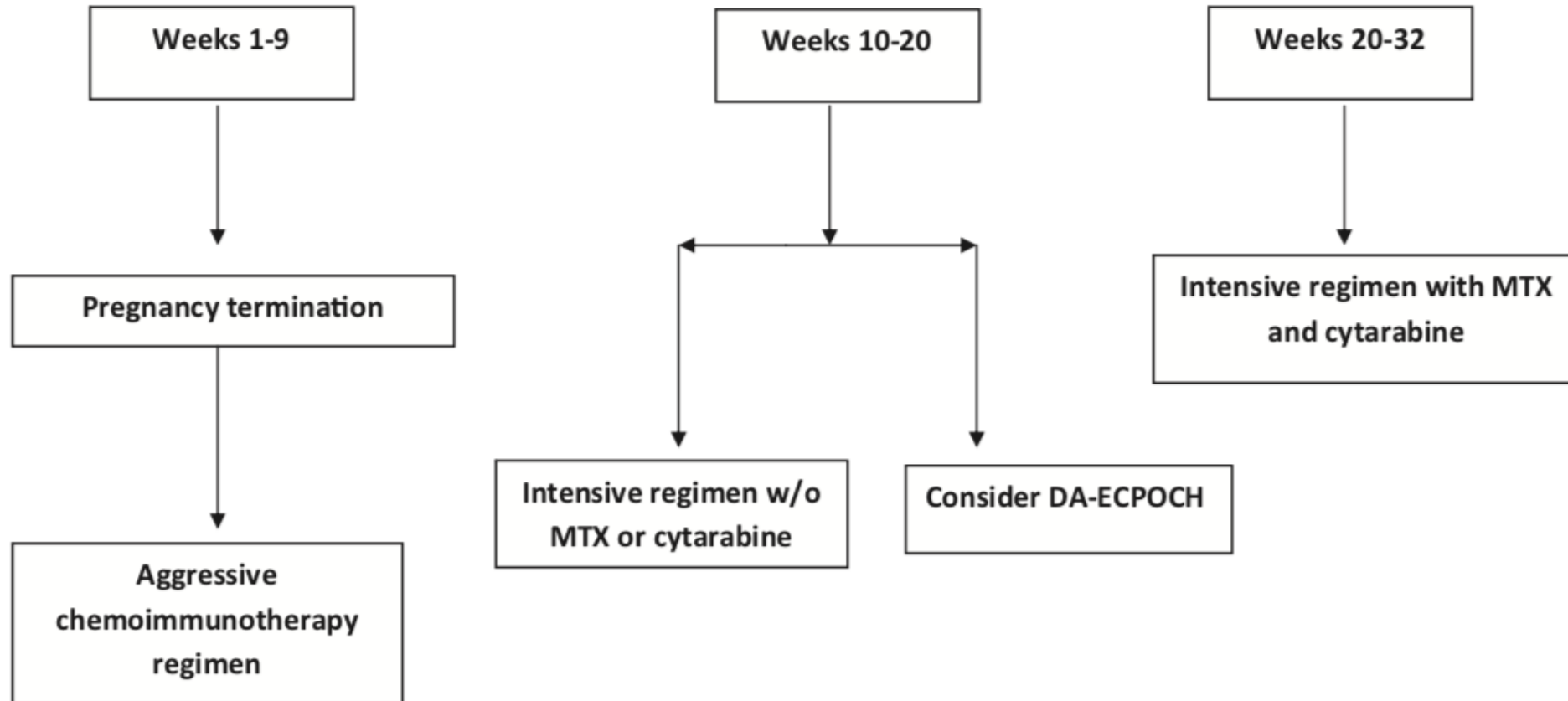
Lishner. M et al, *J Clin Oncol* 2016 ; 34:501-508



- High-dose MTX, if indicated for CNS prophylaxis, should be postponed until after delivery

**Fig. 1.** Algorithm for treatment of DLBCL diagnosed during pregnancy. High-dose MTX, if indicated for CNS prophylaxis, should be postponed until after delivery.

# Lymphomes de Burkitt

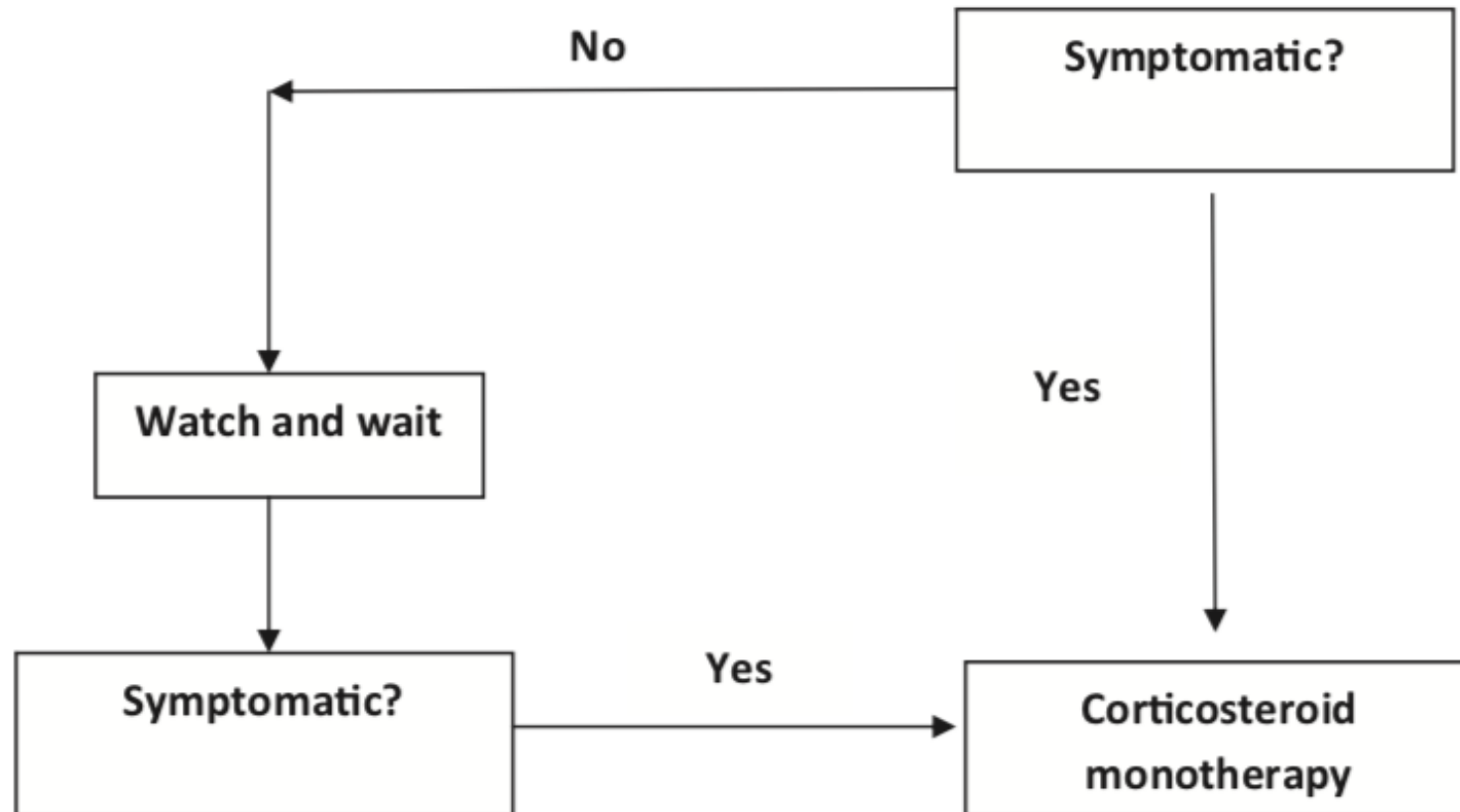


**Fig. 2.** Algorithm for treatment of Burkitt lymphoma diagnosed during pregnancy.

# Lymphome Folliculaire

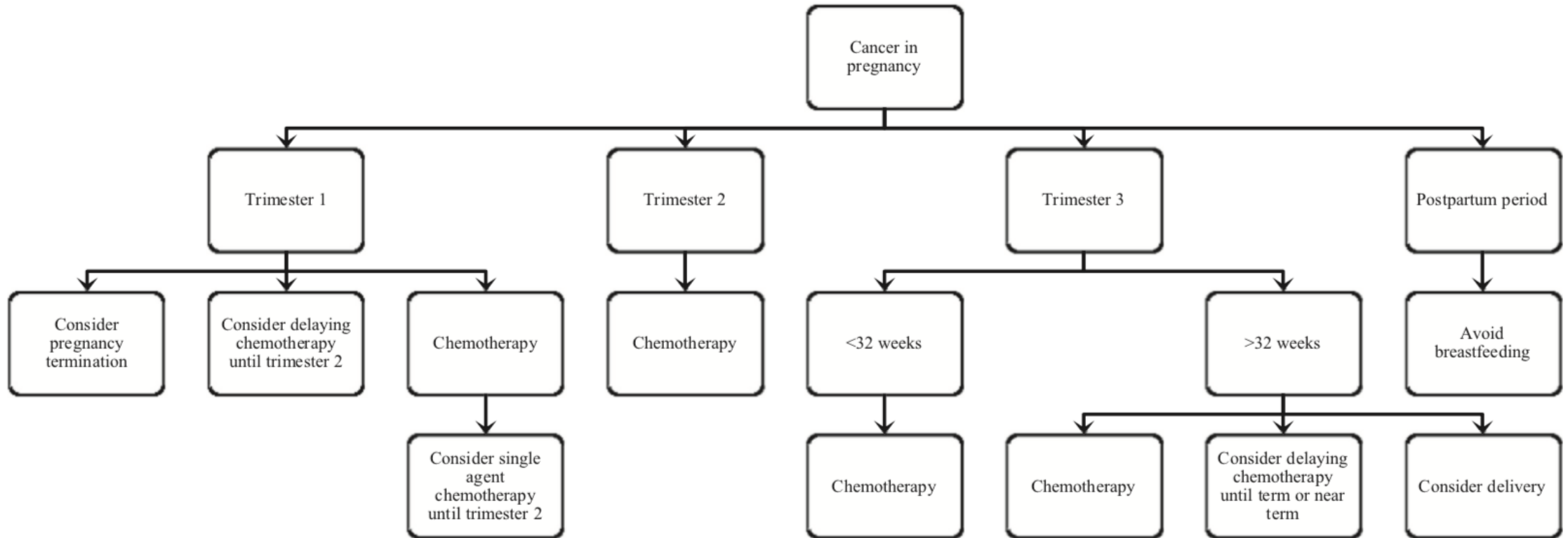
218

*I. Avivi et al. / Blood R*



**Fig. 3.** Algorithm for treatment of follicular lymphoma diagnosed during pregnancy.

# Prise en charge suggérée en 2016



**Fig. 1.** Suggested management plan for women requiring chemotherapy during pregnancy.

# Impact à long terme sur les enfants

- 84 enfants suivis sur 18.7 années en moyenne
  - Fertilité et habilités cognitives normales
  - Etude récente prospective a démontré une diminution de 2.5 points de IQ pour chaque semaine de prématurité chez les enfants exposés à la chimiothérapie
  - La prématurité iatrogénique (accouchement prématuré) devrait être évitée

Aviles A. et al *Annals of Oncology* 2006, 17: 286

Original Article

# Pediatric Outcome after Maternal Cancer Diagnosed during Pregnancy

Frédéric Amant, M.D., Ph.D., Tineke Vandenbroucke, M.Sc., Magali Verheecke, M.D., Monica Fumagalli, M.D., Michael J. Halaska, M.D., Ph.D., Ingrid Boere, M.D., Ph.D., Sileny Han, M.D., Ph.D., Mina Mhallem Gziri, M.D., Ph.D., Fedro Peccatori, M.D., Ph.D., Lukas Rob, M.D., Ph.D., Christianne Lok, M.D., Ph.D., Petronella Witteveen, M.D., Ph.D., Jens-Uwe Voigt, M.D., Ph.D., Gunnar Naulaers, M.D., Ph.D., Lore Vallaeys, M.D., Frank Van den Heuvel, Ph.D., Lieven Lagae, M.D., Ph.D., Luc Mertens, M.D., Ph.D., Laurence Claes, Ph.D., Kristel Van Calsteren, M.D., Ph.D., for the International Network on Cancer, Infertility, and Pregnancy (INCIP)

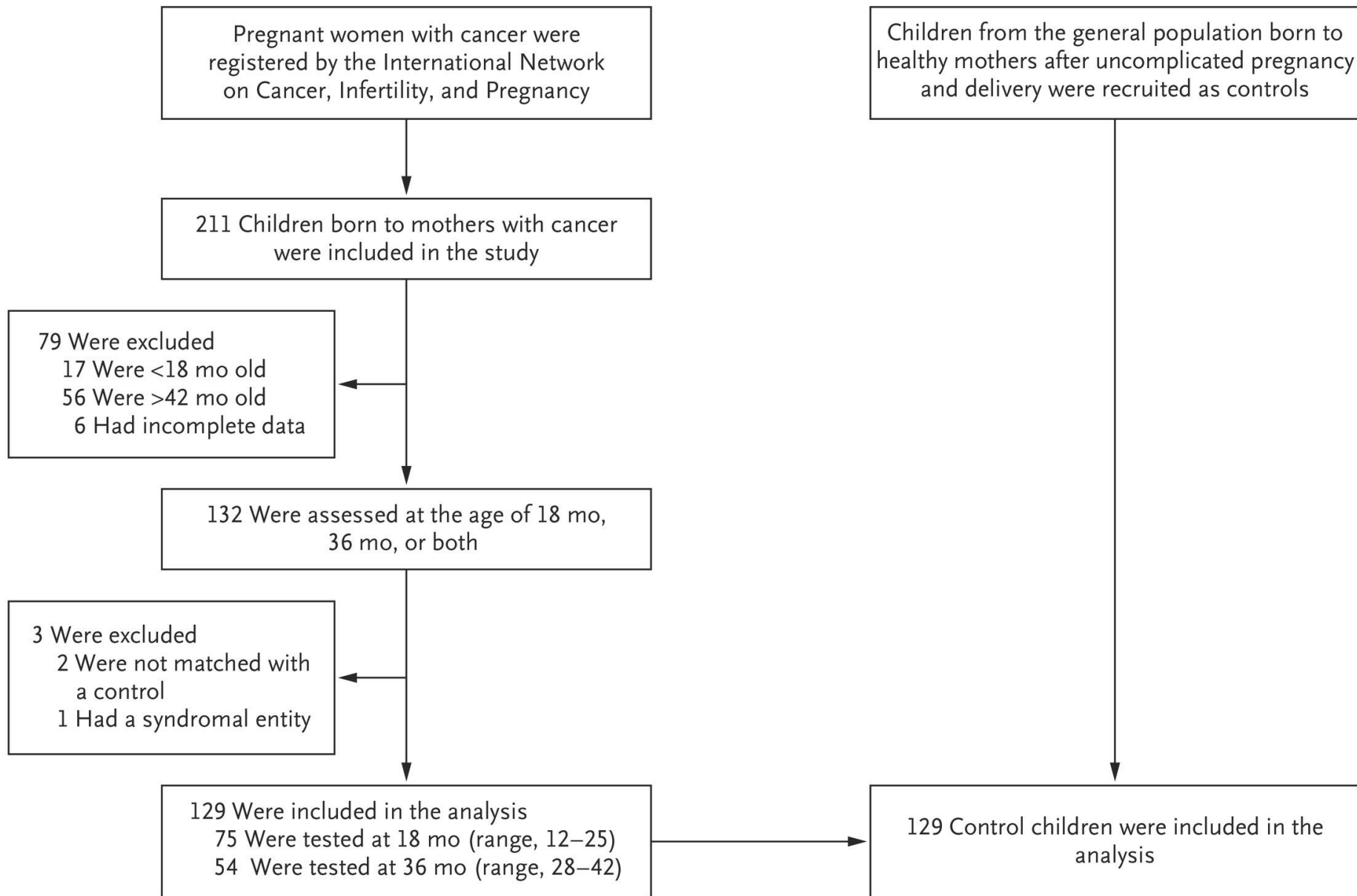
N Engl J Med  
Volume 373(19):1824-1834  
November 5, 2015



The NEW ENGLAND  
JOURNAL of MEDICINE



## Study Design and Recruitment.



# Conclusions

- Prenatal exposure to maternal cancer with or without treatment did not impair the cognitive, cardiac, or general development of children in early childhood.
- Prematurity was correlated with a worse cognitive outcome, but this effect was independent of cancer treatment.



# Options de traitement selon le trimestre

**Table 3**

Cancer treatment options according to trimester of pregnancy.

	Surgery	Chemotherapy	Radiotherapy <sup>a</sup>
First trimester	Possible	Contraindicated	Possible with adequate shielding
Second trimester	Possible, consider intraoperative fetal heart rate monitoring $\geq 24$ –26 weeks	Possible $\geq 12$ –14 weeks	Possible with adequate shielding
Third trimester	Possible, consider intraoperative fetal heart rate monitoring	Possible, aim for 3-week interval between 3-weekly chemotherapy and delivery	Contraindicated <sup>b</sup>

<sup>a</sup> of upper parts of the body; fetal exposure needs to be calculated.

<sup>b</sup> individualization is important and may be possible in selected cases if distance is large enough.

# Impact de différents traitements anti-cancer

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## KEY POINTS

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- Evidence is growing that chemotherapy during pregnancy is possible, depending on type and timing of treatment.
  - The effect of new targeted therapies is often still unclear and should therefore not be advised in pregnancy.
  - Hormonal therapy during pregnancy is contraindicated.
  - Available data concerning fetal outcome are reassuring with a modest increase in complications such as growth restriction and preterm birth.
-