ESMO Open Cancer Horizons

Cancer in pregnancy: disentangling treatment modalities

Flora Zagouri,[1] Constantine Dimitrakakis,[2] Spyridon Marinopoulos,[2] Alexandra Tsigginou,[2] Meletios-Athanassios Dimopoulos[1]

To cite: Zagouri F, Dimitrakakis C, Marinopoulos S, *et al*. Cancer in pregnancy: disentangling treatment modalities. *ESMO Open* 2016;**1**:e000016. doi:10.1136/esmoopen-2015-000016

► Prepublication history for this paper is available online. To view these files please visit the journal online (http://dx.doi.org/10.1136/esmoopen-2015-000016).

Received 29 February 2016
Revised 29 March 2016
Accepted 30 March 2016

[1]Department of Clinical Therapeutics, Alexandra Hospital, National and Kapodistrian University of Athens, School of Medicine, Athens, Greece
[2]Department of Obstetrics and Gynecology, Alexandra Hospital, National and Kapodistrian University of Athens, School of Medicine, Athens, Greece

Correspondence to
Dr Flora Zagouri;
florazagouri@yahoo.co.uk

ABSTRACT

Pregnancy-associated cancer constitutes an uncommon and difficult to manage clinical situation. It is defined as the cancer diagnosed from the first day of childbearing to 1 year post partum. Coexistence of cancer with pregnancy adds complexity to treatment recommendations, as both the mother and the fetus may be affected. The optimal therapeutic management of pregnant women with cancer diagnosis should take into account, apart from medical factors, a host of other parameters (ethical, psychological, religious, legal, etc). Unfortunately, this situation becomes more complex as more women delay childbearing, and consequently the incidence of cancer during pregnancy is constantly increasing. This manuscript summarises the general principles in managing pregnant patients with cancer and gives detailed instructions in the management of pregnant patients with breast cancer, ovarian cancer, melanoma, lymphoma, lung cancer, soft-tissue sarcoma and cervical cancer. Of note, management of pregnant women with cancer diagnosis should be performed in specialised centres with experience and all cases should be discussed in multidisciplinary meetings composed of multiple specialists (medical oncologists, obstetricians, surgeons, radiologists and paediatricians).

INTRODUCTION

Pregnancy-associated cancer constitutes an uncommon and difficult to manage clinical situation. It is defined as the cancer diagnosed from the first day of childbearing to 1 year post partum.[1] Unfortunately, coexistence of cancer with pregnancy adds complexity to treatment recommendations, as both the mother and the fetus may be affected. Of note, at this point it should be clearly stated that there are insufficient data for the proper management of pregnant women with cancer; guidelines are mainly based on data coming from small retrospective studies or case series with limited follow-up.[1 2] Moreover, the optimal therapeutic management of pregnant women with cancer diagnosis should take into account, apart from medical factors, a host of other parameters, that is, ethical, psychological, religious and even legal considerations. Hence, management of pregnant women with cancer diagnosis should be performed in specialised centres with experience and all cases should be discussed in multidisciplinary meetings composed of multiple specialists (medical oncologists, obstetricians, surgeons and paediatricians).

Unfortunately, this situation becomes more complex as more women delay childbearing, and consequently the incidence of cancer during pregnancy is constantly increasing.[3]

STATISTICS

It is estimated that 1 in every 1000 pregnant women is diagnosed with cancer.[4 5] Breast cancer, melanoma, cervical cancer, lymphoma and acute leukaemia are the most common diagnosed malignancies during pregnancy.[4 5] The incidence of breast cancer is about one case of 3000–10 000 deliveries.[6] Most of these cases are diagnosed post partum; of note, <5% of breast cancer is pregnancy associated.[4 6] On the other hand, melanoma is probably the most aggressive malignancy during pregnancy and accounts for 0.14–2.8 cases per 1000 pregnancies (8% of all malignancies during pregnancy).[5–7] Cervical cancer appears in 0.8–1.5 per 10 000 births, with worse survival outcomes when diagnosed post partum.[5 8] Of note, up to 5% of cervical intraepithelial neoplasia I-II may progress to invasive cancer during gestation.[8] Finally, acute leukaemia and lymphomas are present in 1:75 000–1:100 000 and 1:1000–1:6000 pregnancies, respectively.[5 9] Hodgkin's lymphoma is the more frequent hematological malignancy occurring during pregnancy; approximately 3% of Hodgkin's lymphomas are pregnancy associated.[5 9]

GENERAL PRINCIPLES IN MANAGING PREGNANT PATIENTS WITH CANCER

Obstetric care and fetal monitoring

Management of pregnant patients with cancer is a particularly delicate affair as both

the mother and the fetus may be affected. The general golden rule in the management of pregnant women with cancer diagnosis is that treatment should not differ between pregnant and not pregnant women, if this is feasible. The main concerns in the treatment of pregnant patients with cancer are first the prognosis from the malignancy, the proper treatment and the overall survival from the disease. In the meantime, it is of great importance to take into consideration the consequences from the chemotherapeutic drugs on the developing fetus as well as the long-term complications after *in utero* exposure to anticancer therapy. Pregnancy in coexistence with cancer diagnosis should always be considered as high risk and regular fetal monitoring with morphometric ultrasound and umbilical artery Doppler during gestation is mandatory.[1 2]

Full-term pregnancy (ie, ≥37 weeks) should be always the goal, according to all current treatment guidelines, since prematurity influences the emotional and cognitive development of babies.[10 11] The last chemotherapy dose should be administered 3 weeks before the planned date of delivery, in order to avoid haematological toxicity in both the mother and the baby and in order to prevent fetal drug elimination.[1 11] The mode of delivery should be based exclusively on the obstetrician's recommendations, except for cases of gynaecological cancer.[1 11] However, sometimes a caesarean section is the preferred method of delivery by physicians, since it is possible to determine the exact date of delivery.[11] Of note, the placenta should always be carefully evaluated for micrometastases, especially in patients with melanoma, which is the most common neoplasm involving the fetus and the placenta.[7 12]

Staging of malignancy during pregnancy

Staging of malignancy during pregnancy should always follow the same system, as this is the case for non-pregnant patients with cancer diagnosis (ie, TNM system for breast or lung cancer, International Federation of Gynecology and Obstetrics (FIGO) staging for cervical or ovarian cancer, etc).[1 11] Clinical examination, ultrasound, chest X-ray and mammogram with abdominal shielding may be used for the staging preoperatively in pregnant women in an effort to limit the exposure to ionising radiation.[13] MRI of the abdomen without gadolinium may be used in selected cases with a high suspicion of metastases from previous examinations.[13 14] Gadolinium has been found to cross the placenta and to stimulate malformations in animal models; hence, use of gadolinium during pregnancy is contraindicated, especially in the first trimester of pregnancy.[13 14] Moreover, bone scanning, CT scans and positron emission tomography (PET) scan are contraindicated during pregnancy.[13] Finally, tumour markers are not reliable; they have no diagnostic value and consequently they should not be performed during pregnancy.[15]

Surgery during pregnancy

Surgery can relatively safely be performed during pregnancy; of note, there is a slightly elevated risk of miscarriage during the first trimester, whereas very close monitoring, especially after the 25th week of gestation, should be performed.[1 11] Of note, increased morbidity and higher rates of complications may happen in major pelvic and abdominal surgery; in these cases, a multidisciplinary team approach and detailed discussion with the patient are mandatory.[1 11] Nonetheless, surgery should never be delayed during pregnancy.

Chemotherapy during pregnancy

Systemic chemotherapy should not be administrated in the first trimester, due to the higher risk of miscarriage and congenital malformations, as the first trimester is the period of organogenesis of the fetus.[16 17] Of note, the risk of malformations varies from 10% to 20% in the first trimester of pregnancy and it drops to 1.3% in the third trimester.[18] Hence, pregnancy termination should be considered in pregnant patients with cancer who need chemotherapy administration in the first trimester.[1 11] On the basis of multiple studies, it seems that it is relatively safe to give chemotherapy after the first trimester; however, there is a relatively higher risk of premature rupture of membranes, intrauterine growth restriction and premature labour.[16–18] Moreover, according to available data, it seems that there are not significant long-term complications in fetuses exposed to chemotherapy during the second and third trimesters of pregnancy.[16–18]

Obviously, chemotherapy agents that cross the placenta at increased levels should be postponed after delivery. Weekly chemotherapeutic schedules are generally preferred, as close monitoring of adverse events is more feasible.[1 11] As far as the dosage of chemotherapeutic drugs is concerned, there are few pharmacokinetic and pharmacodynamic data available during pregnancy; hence, despite the fact that pregnancy may alter the pharmacokinetics of these agents, doses should not vary from those used outside pregnancy.[19]

Radiotherapy during pregnancy

Radiotherapy should be avoided during pregnancy due to its teratogenic effects on the fetuses; hence, it is strongly suggested to delay irradiation post partum, apart from the cases with an urgent clinical need and provided that the radiation field is adequately far from the uterus.[1 2 11] In all cases, adequate shielding should be used. Radiotherapy may cause detrimental effects to the fetus, that is, intrauterine growth restriction, congenital malformations, mental retardation, carcinogenesis, etc.[20 21] Of note, there is an increased risk of congenital malformations and mental retardation with radiation doses >100–200 mGy; however, lower doses may cause the development of cancer or leukaemia in childhood and sterility.[20 21] Table 1 summarises the

Table 1 Radiation dosages along with the effect on the fetus and in relation to the gestational age

Radiation dosages	Effect on the fetus
<0.1 Gy	No major effect
0.1–0.15 Gy	Increased risk for malformations
2.5 Gy	Malformations in most cases
>30 Gy	Abortion
From conception to 10 days	Lethal
Weeks 2–12	Malformations in almost all cases, growth retardation
Weeks 13–16	Mental and growth retardation
Weeks 17–26	Malignancies, sterility, genetic defects

radiation dosages along with the effect on the fetus and in relation to the gestational age.

Supportive care during pregnancy

Vomiting and nausea are often symptoms during pregnancy; metoclopramide is the first choice for these symptoms, whereas ondansetron can safely be given.[22 23]

The granulocyte colony-stimulating factor (G-CSF) can cross the human placenta at least in the second and third trimesters.[24] According to the limited available data, the use of G-CSF during pregnancy does not seem to cause any significant *sequelae* on either the mother or the newborn.[25] However, G-CSF is considered as agent belonging in category C for use during pregnancy and its use should be based on clinical necessity.[24 25] There are no published safety data regarding the use of human erythropoietin in pregnant patients with cancer; however, according to published data on pregnant women with renal failure, it seems that recombinant human erythropoietin does not cross the placental barrier and consequently may be used relatively safely.[26 27]

Regarding antibiotics, penicillins, carbapenems, cephalosporins and the majority of macrolides (erythromycin azithromycin and spiramycin) are considered as agents belonging in category C for use during pregnancy and may be used during pregnancy.[28]

Concerning bisphosphonates, their use during pregnancy should be avoided, as they remain in mineralised bone for several years.[29] However, in a review on 78 pregnant women exposed to bisphosphonates, no increased maternal or fetal morbidity was recorded.[30]

SPECIAL CONSIDERATIONS BY SPECIFIC SITE CANCER

Breast cancer

Modified radical mastectomy is considered the standard of care in the first trimester of pregnancy due to the potential consequences of postponing radiotherapy after delivery, whereas breast-conserving surgery can safely be performed in the second and third trimesters.[1 31] There are insufficient data on the safety of the sentinel lymph node biopsy (SLNB); however, in a case series on 12 pregnant women who underwent SLNB with Technetium-99, no fetal defects were recorded and no evidence of local relapse was documented with a median follow-up of 32 months.[32] Of note, blue dye is contradicted due to its potential allergic reactions (2%).[33] Moreover, adjuvant radiotherapy should always be given after the delivery, given the potential *sequelae* on the fetus.[22 23]

Regarding the indications of adjuvant chemotherapy in pregnant women with breast cancer diagnosis, they should be identical with those in non-pregnant patients with cancer; however, in the outline of the therapeutic plan, it is mandatory to take into account the gestational age at diagnosis and the estimated date of delivery.[1 31] Anthracycline-based regimens (ie, Adriamycin, Cyclophosphamide (AC); Epirubicin, Cyclophosphamide (EC); Fluorouracil, Adriamycin, Cyclophosphamide (FAC); or Fluorouracil, Epirubicin, Cyclophosphamide (FEC)) represent the first choice of treatment, as the majority of safety data are available with the use of anthacyclines;[1] of note, no increased risk of cardiotoxicity of the neonates due to *in utero* exposure of anthracyclines has been documented.[34] As far as taxanes are concerned, data from animal models have shown minimal transplacental transfer of both agents, probably due to the high expression of P-glycoprotein in the placenta.[35] In a systematic review on 50 pregnant patients with breast cancer, who had received taxanes during pregnancy, a completely healthy neonate was born in 76.7% of cases, whereas 90% of children were completely healthy with a median follow-up of 16 months.[36] Consistent with these results are the data from the American-based and European-based registries.[37 38] Hence, on the basis of these data and according to the European Society for Medical Oncology (ESMO) guidelines, taxanes may be used in selected cases during pregnancy (ie, selected cases of triple-negative or HER2-positive breast cancer) or in cases where anthracyclines are contraindicated.[1] Of note, more data are available with the use of paclitaxel than of docetaxel during pregnancy; consequently, weekly paclitaxel schedule is the preferred treatment option in selected cases of patients with breast cancer during pregnancy.[1 31]

According to current treatment guidelines, trastuzumab is contraindicated during pregnancy, due to its apparent risk of oligohydramnios and/or anhydramnios as well as to the unknown long-term effects on the fetus.[1 2] However, studies in cynomolgus monkeys have not found placental transfer of the antibody in monkeys and have failed to identify any harm to the fetus.[39] According to a recently published meta-analysis, trastuzumab administration seems to be relatively safe during the first trimester, whereas there is a high incidence of oligohydramnios and/or anhydramnios when the monoclonal antibody is used beyond the first trimester.[40] An interesting finding of this meta-analysis is that all children exposed to trastuzumab exclusively during the first trimester were completely healthy, without evidence of

malformations.[40] Of note, oligohydramnios/anhydramnios was recorded in pregnancies exposed to trastuzumab in the second and/or third trimester.[31 40] Interestingly enough, Pentsuk and van der Laan[41] found that the exposure of the fetus to trastuzumab is really limited in the first trimester, increases from the second trimester of pregnancy and reaches at birth a drug concentration comparable to that of the mother.

For women becoming accidentally pregnant while on trastuzumab administration, they can preserve their pregnancy, based on the data of HERA trial; in these cases, trastuzumab should be discontinued and the patient should be informed that this recommendation is based on data from a limited number of cases.[42]

Pertuzumab is contraindicated during pregnancy, as there are limited data for its toxicity. Despite one published case report with lapatinib exposure resulting in uncomplicated delivery of a healthy neonate, the agent should not be recommended during pregnancy; its pharmacological characteristics (ie, massive transplacental transfer), along with the insufficient data on its use during pregnancy, strongly suggest against its use.[43]

Endocrine treatment (ie, tamoxifen, luteinizing hormone-releasing hormone analogues) is contraindicated during pregnancy due to the high risk of birth defects, up to 20% of exposures.[44–46] Hence, tamoxifen use should be delayed after delivery. Moreover, for patients becoming accidentally pregnant while on tamoxifen use, termination of pregnancy should be advised due to the high risk of congenital malformations.[1 31 45]

Lymphomas

For patients diagnosed with advanced Hodgkin's lymphoma in the first trimester, pregnancy termination should be considered; on the other hand, for patients diagnosed with early-stage Hodgkin's lymphoma in the first trimester, close monitoring and initiation of chemotherapy in the second trimester can be advised.[1 9 47] The combination of adriamycin, bleomycin, vinblastine and dacarbazine (ABVD) is the recommended therapy after the first trimester of gestation, without significant fetal complications been reported.[1 9 47] Of note, no safety data exist for other chemotherapeutic combinations during gestation (ie, Stanford V or BEACOPP); hence their use cannot be recommended during pregnancy.

For patients with aggressive non-Hodgkin's lymphoma (NHL), immediate treatment is mandatory; hence, for patients diagnosed in the first trimester of gestation pregnancy, termination should be considered, whereas for patients diagnosed in the second and third trimester, Cytoxan, Hydroxyrubicin (Adriamycin), Oncovin (Vincristine), Prednisone (CHOP) is the standard chemotherapy regimen, without significant increased fetal morbidity.[1 9 47] Regarding rituximab, on the basis of the data of a retrospective analysis that evaluated the outcomes of 253 pregnancies with exposure to rituximab during pregnancy, it seems that rituximab administration in the second and third trimesters of pregnancy seems to be relatively safe, without significant increased risk of fetal adverse effects; however, a relatively increased risk of neonatal infection and transient B cell depletion without related infection in the neonates has been documented.[48] Moreover, rituximab does not cross the placenta early in gestation; consequently, patients becoming accidentally pregnant during rituximab administration can preserve their pregnancy, provided that treatment is stopped during pregnancy.[1]

Melanoma

Surgical resection in pregnant patients with melanoma is the mainstay of treatment; SLNB procedure using Technetium-99, rather vital blue is recommended, despite the limited published data.[1 49] For patients with metastatic disease, interferon-α may be used, due to the lack of safety data of ipilimumab, vemurafenib, dabrafenib, trametinib and cobimetinib during gestation.[1 9]

Cervical cancer

Management of pregnant patients with cervical cancer differs from the standard treatment of patients with cervical cancer outside the pregnancy setting, due to the fact that radical surgery and pelvic radiation, the mainstay of cervical cancer treatment, would cause fetal death and pregnancy termination. Of note, this difference may have an impact on the survival data of pregnant patients. For pregnant patients with early-stage cervical cancer who want to preserve the pregnancy, therapy may be delayed until after delivery; of note, close monitoring in these cases is of great importance.[1 8 50] For pregnant patients with stage IB1, IB2 or IIA, lymphadenectomy is the mainstay of treatment; lymphadenectomy can safely be performed during pregnancy, despite a slightly increased risk of bleeding and other complications.[1 50] Notably, radical surgery can be performed concurrently with the caesarean section.[50]

According to current guidelines, platinum-based chemotherapy (cisplatin 75 mg/m^2 q 3 weeks or carboplatin), with or without paclitaxel, may be used, especially in patients with locally advanced disease or with high-risk tumour.[1 51] Of note, local response rates reported in pregnant patients with cervical cancer are similar to those recorded outside the pregnancy setting.[51 52]

Epithelial ovarian cancer

For patients with epithelial ovarian cancer, the combination of carboplatin (5 or 6 AUC) with weekly paclitaxel (60–80 mg/m^2) is recommended after the first trimester and seems to be relatively safe.[1] According to a recently published systematic review, conducted on 11 pregnancies (12 newborns), a completely healthy child was born in 92.3% of cases with a median follow-up of 20 months.[53]

Germ cell ovarian tumours

According to ESMO guidelines, the combination of cisplatin (75 mg/m^2) and weekly paclitaxel (80 mg/m^2) is

highly recommended for patients with germ cell ovarian tumours, after the first trimester; this combination is based on the safety data during pregnancy and on the efficacy data coming from non-pregnant patients with relapsed germ cell tumours.[1] Of note, the etoposide-platinum based combination (BEP or EP), typically used for the treatment of germ cell tumours, is not proposed due to the relatively increased risk of fetal intrauterine growth restriction and neonatal complications that have been reported.[54–56]

Non-small cell lung cancer

For patients with non-small lung cancer, the combination of carboplatin (5 or 6 AUC) with weekly paclitaxel (60–80 mg/m^2) is recommended after the first trimester and seems to be relatively safe.[1 57–59] The use of gemcitabine and pemetrexed should be discouraged due to the lack of data. Moreover, epidermal growth factor receptor inhibitors are not favoured during pregnancy.

Soft tissue sarcomas

For pregnant patients with metastatic soft tissue sarcomas, single-agent doxorubicin is highly recommended, after the first trimester, extrapolating the safety data of the use of anthracyclines in pregnant patients with malignancy.[1] The combination of doxorubicin with ifosfamide has been evaluated in nine patients during pregnancy;[60] however, this combination is not recommended for pregnant patients with metastatic soft tissue sarcoma due to the limited safety profile of ifosfamide along with the increased toxicity and the lack of survival benefit of the combination versus monotherapy.[1 60]

Conclusion

Treatment of patients with malignancy during pregnancy is a particularly delicate issue as both the mother and the fetus may be affected; treatment should be personalised and performed in specialised centres with great experience. Unfortunately, the optimal therapeutic management of pregnant women with cancer coexistence is mainly based on small retrospective studies; hence, improved collaboration between cancer centres and registries is more than necessary in an effort to record survival data of patients and the long-term effects of the drugs on the developing children. This registration is more than mandatory taking into consideration that the coexistence of cancer and pregnancy would be encountered more and more often in the forthcoming years, as women to tend to postpone childbearing.

Contributors FZ wrote the manuscript. CD, SM and AT made the first draft and were involved in the literature search. M-AD critically revised the manuscript and gave the final approval for its publication.

Competing interests None declared.

Provenance and peer review Commissioned; externally peer reviewed.

REFERENCES

1. Peccatori FA, Azim HA Jr, Orecchia R, *et al*. Cancer, pregnancy and fertility: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2013;24(Suppl 6):vi160–70.
2. NCCN Clinical Practice Guidelines in Oncology. Breast cancer, version 1. 2016. https://www.nccn.org/professionals/physician_gls/f_guidelines.asp
3. Matthews TJ, Hamilton BE. First births to older women continue to rise. *NCHS Data Brief* 2014;152:1–8.
4. Stensheim H, Møller B, van Dijk T, *et al*. Cause-specific survival for women diagnosed with cancer during pregnancy or lactation: a registry-based cohort study. *J Clin Oncol* 2009;27:45–51.
5. Pentheroudakis G, Pavlidis N. Cancer and pregnancy: poena magna, not anymore. *Eur J Cancer* 2006;42:126–40.
6. Pentheroudakis G, Orecchia R, Hoekstra HJ, *et al*. Cancer, fertility and pregnancy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010;21(Suppl 5):v266–73.
7. Wielowieyska-Szybińska DK, Spałkowska M, Wojas-Pelc A. Melanoma in pregnancy: a case report and review of the literature. *Postepy Dermatol Alergol* 2015;32:483–7.
8. Hecking T, Abramian A, Domröse C, *et al*. Individual management of cervical cancer in pregnancy. *Arch Gynecol Obstet* 2016;293:931–9.
9. Lavi N. An update on the management of hematologic malignancies in pregnancy. *Womens Health (Lond Engl)* 2014;10:255–66.
10. Van Calsteren K, Heyns L, De Smet F, *et al*. Cancer during pregnancy: an analysis of 215 patients emphasizing the obstetrical and the neonatal outcomes. *J Clin Oncol* 2010;28:683–9.
11. Amant F, Deckers S, Van Calsteren K, *et al*. Breast cancer in pregnancy: recommendations of an international consensus meeting. *Eur J Cancer* 2010;46:3158–68.
12. Alexander A, Samlowski WE, Grossman D, *et al*. Metastatic melanoma in pregnancy: risk of transplacental metastases in the infant. *J Clin Oncol* 2003;21:2179–86.
13. de Haan J, Vandecaveye V, Han SN, *et al*. Difficulties with diagnosis of malignancies in pregnancy. *Best Pract Res Clin Obstet Gynaecol* 2015. Published Online First. 19 Oct 2015. doi:10.1016/j.bpobgyn.2015.10.005
14. Bulas D, Egloff A. Benefits and risks of MRI in pregnancy. *Semin Perinatol* 2013;37:301–4.
15. Han SN, Lotgerink A, Gziri MM, *et al*. Physiologic variations of serum tumor markers in gynecological malignancies during pregnancy: a systematic review. *BMC Med* 2012;10:86.
16. Azim HA Jr, Peccatori FA, Pavlidis N. Treatment of the pregnant mother with cancer: a systematic review on the use of cytotoxic, endocrine, targeted agents and immunotherapy during pregnancy. Part I: Solid tumors. *Cancer Treat Rev* 2010;36:101–9.
17. Azim HA Jr, Pavlidis N, Peccatori FA. Treatment of the pregnant mother with cancer: a systematic review on the use of cytotoxic, endocrine, targeted agents and immunotherapy during pregnancy. Part II: Hematological tumors. *Cancer Treat Rev* 2010;36:110–21.
18. Ring AE, Smith IE, Jones A, *et al*. Chemotherapy for breast cancer during pregnancy: an 18-year experience from five London teaching hospitals. *J Clin Oncol* 2005;23:4192–7.
19. Van Calsteren K, Verbesselt R, Ottevanger N, *et al*. Pharmacokinetics of chemotherapeutic agents in pregnancy: a preclinical and clinical study. *Acta Obstet Gynecol Scand* 2010;89:1338–45.
20. Kal HB, Struikmans H. Radiotherapy during pregnancy: fact and fiction. *Lancet Oncol* 2005;6:328–33.
21. Fenig E, Mishaeli M, Kalish Y, *et al*. Pregnancy and radiation. *Cancer Treat Rev* 2001;27:1–7.
22. Smith HS, Cox LR, Smith EJ. 5-HT3 receptor antagonists for the treatment of nausea/vomiting. *Ann Palliat Med* 2012;1:115–20.
23. Einarson A, Maltepe C, Navioz Y, *et al*. The safety of ondansetron for nausea and vomiting of pregnancy: a prospective comparative study. *BJOG* 2004;111:940–3.
24. Calhoun DA, Rosa C, Christensen RD. Transplacental passage of recombinant human granulocyte colony-stimulating factor in women with an imminent preterm delivery. *Am J Obstet Gynecol* 1996;174:1306–11.
25. Calhoun DA, Christensen RD. A randomized pilot trial of administration of granulocyte colony-stimulating factor to women before preterm delivery. *Am J Obstet Gynecol* 1998;179(Pt 1):766–71.

26. Scott LL, Ramin SM, Richey M, *et al*. Erythropoietin use in pregnancy: two cases and a review of the literature. *Am J Perinatol* 1995;12:22–4.
27. Schneider H, Malek A. Lack of permeability of the human placenta for erythropoietin. *J Perinat Med* 1995;23:71–6.
28. Broe A, Pottegård A, Lamont RF, *et al*. Increasing use of antibiotics in pregnancy during the period 2000–2010: prevalence, timing, category, and demographics. *BJOG* 2014;121:988–96.
29. Levy S, Fayez I, Taguchi N, *et al*. Pregnancy outcome following in utero exposure to bisphosphonates. *Bone* 2009;44:428–30.
30. Stathopoulos IP, Liakou CG, Katsalira A, *et al*. The use of bisphosphonates in women prior to or during pregnancy and lactation. *Hormones (Athens)* 2011;10:280–91.
31. Zagouri F, Psaltopoulou T, Dimitrakakis C, *et al*. Challenges in managing breast cancer during pregnancy. *J Thorac Dis* 2013;5 (Suppl 1):S62–7.
32. Gentilini O, Cremonesi M, Trifirò G, *et al*. Safety of sentinel node biopsy in pregnant patients with breast cancer. *Ann Oncol* 2004;15:1348–51.
33. Khera SY, Kiluk JV, Hasson DM, *et al*. Pregnancy-associated breast cancer patients can safely undergo lymphatic mapping. *Breast J* 2008;14:250–4.
34. Peccatori FA, Azim HA Jr, Scarfone G, *et al*. Weekly epirubicin in the treatment of gestational breast cancer (GBC). *Breast Cancer Res Treat* 2009;115:591–4.
35. Van Calsteren K, Verbesselt R, Van Bree R, *et al*. Substantial variation in transplacental transfer of chemotherapeutic agents in a mouse model. *Reprod Sci* 2011;18:57–63.
36. Zagouri F, Sergentanis TN, Chrysikos D, *et al*. Taxanes for breast cancer during pregnancy: a systematic review. *Clin Breast Cancer* 2013;13:16–23.
37. Loibl S, Han SN, von Minckwitz G, *et al*. Treatment of breast cancer during pregnancy: an observational study. *Lancet Oncol* 2012;13:887–96.
38. Cardonick E, Bhat A, Gilmandyar D, *et al*. Maternal and fetal outcomes of taxane chemotherapy in breast and ovarian cancer during pregnancy: case series and review of the literature. *Ann Oncol* 2012;23:3016–23.
39. Calsteren KV, Verbesselt R, Devlieger R, *et al*. Transplacental transfer of paclitaxel, docetaxel, carboplatin, and trastuzumab in a baboon model. *Int J Gynecol Cancer* 2010;20:1456–64.
40. Zagouri F, Sergentanis TN, Chrysikos D, *et al*. Trastuzumab administration during pregnancy: a systematic review and meta-analysis. *Breast Cancer Res Treat* 2013;137:349–57.
41. Pentsuk N, van der Laan JW. An interspecies comparison of placental antibody transfer: new insights into developmental toxicity testing of monoclonal antibodies. *Birth Defects Res B Dev Reprod Toxicol* 2009;86:328–44.
42. Azim HA Jr, Metzger-Filho O, de Azambuja E, *et al*. Pregnancy occurring during or following adjuvant trastuzumab in patients enrolled in the HERA trial (BIG 01-01). *Breast Cancer Res Treat* 2012;133:387–91.
43. Kelly H, Graham M, Humes E, *et al*. Delivery of a healthy baby after first-trimester maternal exposure to lapatinib. *Clin Breast Cancer* 2006;7:339–41.
44. Cullins SL, Pridjian G, Sutherland CM. Goldenhar's syndrome associated with tamoxifen given to the mother during gestation. *JAMA* 1994;271:1905–6.
45. Braems G, Denys H, De Wever O, *et al*. Use of tamoxifen before and during pregnancy. *Oncologist* 2011;16:1547–51.
46. Halakivi-Clarke L, Cho E, Onojafe I, *et al*. Maternal exposure to tamoxifen during pregnancy increases carcinogen-induced mammary tumorigenesis among female rat offspring. *Clin Cancer Res* 2000;6:305–8.
47. Lishner M, Avivi I, Apperley JF, *et al*. Hematologic malignancies in pregnancy: management guidelines from an international consensus meeting. *J Clin Oncol* 2016;34:501–8.
48. Friedrichs B, Tiemann M, Salwender H, *et al*. The effects of rituximab treatment during pregnancy on a neonate. *Haematologica* 2006;91:1426–7.
49. Andtbacka RH, Donaldson MR, Bowles TL, *et al*. Sentinel lymph node biopsy for melanoma in pregnant women. *Ann Surg Oncol* 2013;20:689–96.
50. Morice P, Uzan C, Gouy S, *et al*. Gynaecological cancers in pregnancy. *Lancet* 2012;379:558–69.
51. Zagouri F, Sergentanis TN, Chrysikos D, *et al*. Platinum derivatives during pregnancy in cervical cancer: a systematic review and meta-analysis. *Obstet Gynecol* 2013;121(Pt 1): 337–43.
52. Fruscio R, Villa A, Chiari S, *et al*. Delivery delay with neoadjuvant chemotherapy for cervical cancer patients during pregnancy: a series of nine cases and literature review. *Gynecol Oncol* 2012;126:192–7.
53. Zagouri F, Sergentanis TN, Chrysikos D, *et al*. Taxanes for ovarian cancer during pregnancy: a systematic review. *Oncology* 2012;83:234–8.
54. Han JY, Nava-Ocampo AA, Kim TJ, *et al*. Pregnancy outcome after prenatal exposure to bleomycin, etoposide and cisplatin for malignant ovarian germ cell tumors: report of 2 cases. *Reprod Toxicol* 2005;19:557–61.
55. Cardonick E, Usmani A, Ghaffar S. Perinatal outcomes of a pregnancy complicated by cancer, including neonatal follow-up after in utero exposure to chemotherapy: results of an international registry. *Am J Clin Oncol* 2010;33:221–8.
56. Ghaemmaghami F, Abbasi F, Abadi AG. A favorable maternal and neonatal outcome following chemotherapy with etoposide, bleomycin, and cisplatin for management of grade 3 immature teratoma of the ovary. *J Gynecol Oncol* 2009;20:257–9.
57. Sarıman N, Levent E, Yener NA, *et al*. Lung cancer and pregnancy. *Lung Cancer* 2013;79:321–3.
58. Azim HA Jr, Scarfone G, Peccatori FA. Carboplatin and weekly paclitaxel for the treatment of advanced non-small cell lung cancer (NSCLC) during pregnancy. *J Thorac Oncol* 2009;4:559–60.
59. García-González J, Cueva J, Lamas MJ, *et al*. Paclitaxel and cisplatin in the treatment of metastatic non-small-cell lung cancer during pregnancy. *Clin Transl Oncol* 2008;10:375–6.
60. Mir O, Berrada N, Domont J, *et al*. Doxorubicin and ifosfamide for high-grade sarcoma during pregnancy. *Cancer Chemother Pharmacol* 2012;69:357–67.