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ABSTRACT BOOK

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Cancer and pregnancy, the burden of the problem

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The frequency of cancers, and in particular the epithelial ones, increases with age. Consequently the maximum incidence is observed after 50-60 years. However, some tumours show a significant frequency also in women in their childbearing age.
Table 1 shows the incidence of selected malignant tumours per 1000 deliveries.

	Incidence in pregnancy / 1000 deliveries	**Expected number of cases in Italy / year**
All cancer	0.8-1	450-500
Breast cancer	0.1-0.2	50-150
Tyroid cancer	0.1	50
Melanoma	0-05-0.085	20-40
Cervical cancer	0.1	50
Hodgkins disease	0.05	20-25

Pregnancy may be associated to diagnostic delay for tumor of the breast and melanoma or an "early" diagnosis for cervical cancer (Pereg et al., cancer treatment Reviews, 2008). More difficult is to assess the impact of pregnancy on the prognosis of the disease.The data in this regard are very limited and inconsistent.

In conclusion, a malignant tumor is rare in **pregnant women**. The impact of pregnancy on the diagnosis (late / early diagnosis) and the prognosis is still uncertain and requires further study.

European survey on cancer and pregnancy: the ESGO data

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The risk of developing cancer is getting higher with the advancing age. At the same time, a greater proportion women decide to postpone pregnancy desiring for financial security, completion of post-secondary education or wishing to establish a career. The age at first birth in Europe increased for in average 2 years during the last decade. This is why the association between the cancer and pregnancy may be expected more frequently.

Management of cancer during pregnancy is difficult. Both diagnostic and therapeutic interventions must be performed carefully, having in mind risk factors associated with both pregnant women and the fetus. Unfortunately, only a few single centers or alternatively multicenter studies provide sufficient data to serve as an evidence for oncological and obstetrical outcome of pregnant patients with cancer.

The clinical importance of the appropriate management of cancer in pregnancy has lead the ESGO Task Force on Pregnancy and Cancer to conduct a survey with the aim of exploring the current practice in management of pregnant patients diagnosed with cancer, in Europe.

A questionnaire has been designed to allow an insight into the numbers of pregnant patients diagnosed with cancer and physicians' practice behaviors in treatment of cancer in pregnancy. The data were collected retrospectively for the year 2010. The final sample consisted of 222 answers.

Among the participants of the survey, most were either general obstetricians/gynecologists (45.7%) or gynecologic oncologists (41.4%) and the remaining ones were medical oncologists or radiotherapists. The number of pregnant patients with cancer treated in their centers during 2010 was none or less than 10 in 72.1% of cases.

Malignancies usually treated in pregnancy were gynecological and breast cancers (84.5%).

Exploring who decides about the management of pregnant patient with cancer, in almost half of the cases it was the multidisciplinary team discussing the problem together with the patient and the husband (49.6%). Although the decision about the management is usually the responsibility of a multidisciplinary team, in one of ten cases the management relied on individual decision of obstetrician (5.0%) or even patient herself (4.1%).

In most of the cases (96.6%) the possibility to treat cancer during pregnancy (with surgery, chemotherapy, radiotherapy) is discussed. However, in very small number of patients treatment during pregnancy was actually provided. Very few centers performed surgery (19.4%), chemotherapy (13.4%) or radiotherapy (4.1%) during pregnancy in more than 5 cases.

The survey also explored the physician own practice behaviors in pregnancy and cancer. Answering the question about continuation of pregnancy in patients with cancer almost half of responders (48.3%) preferred the termination of pregnancy. Of those who would continue pregnancy, almost half participants answered that all potential harm for the fetus should be avoided (42.1%), meaning that no chemotherapy nor radiotherapy during pregnancy should not be given. Preterm delivery in order to start cancer treatment in the postpartum period is preferred by more then half responders (63.8%).

Optimal management of cancer in pregnancy should include adequate counseling about the future oncological and obstetrical risks, a clear decision-making process and the appropriate management and a careful follow-up within a multi-disciplinary setting with close cooperation between oncologist, perinatologist and neonatologist. There is a clear need to provide physicians with recommendations and education on the latest cancer and pregnancy treatment options. Findings from this study should provide a foundation for additional research and possible targeted interventions that hope to improve physician knowledge

The newborn of the pregnant mother with cancer: a neonatologist view

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Cancer treatment in a pregnant woman is still a matter of debate as life-saving therapies for the mother arise concerns about the potential detrimental effects for the developing fetus.
Recent data support the administration of chemotherapy from 14 weeks gestational age onwards as safe in terms of long-term cognitive and cardiac outcomes in children while impaired neurodevelopmental outcome appear to be related to prematurity.
Prematurity, and in particular "late preterm birth" (defined as gestational age at birth between 34+0 and 36+6 weeks) is indeed the commonest neonatal outcome for babies born from pregnant cancer mothers. Most of these babies are iatrogenically delivered prematurely, the decision being based mostly on non-obstetric reasons as the need to start cancer treatment or deterioration of the maternal health.
Late preterm births have enormously increased in the last decade and there is mounting evidence showing that infants born late preterm are less healthy than infants born at term. Late preterm infants experience greater morbidity compared to term infants consisting in an increased risk of temperature instability, respiratory distress syndrome, excessive weight loss and dehydration requiring intravenous infusion, sepsis, hypoglycemia and jaundice requiring phototherapy. These morbidities seem to be independently associated to late preterm birth and may contribute to the recently reported long-term neurodevelopmental impairment in this population. This observation, supported by small but growing literature, may be explained by the well-known vulnerability of the brain at this gestational age.
The late preterm brain has an intrinsic vulnerability related to the immaturity of the developing brain and an indirect vulnerability due to the detrimental neurological effects of perinatal morbidities. Late

preterm infants therefore present a risk to develop brain lesions which is lower than more premature babies but higher than term newborns and they can be affected by brain lesions common to both preterm and term infants.
In our population of neonates exposed to chemotherapy during pregnancy 18% (4/22) were born between 25 and 33 weeks of gestational age and 73% (16/22) between 34 and 36 weeks (9% at term, 2/22). Neonatal complications were respiratory distress syndrome (32%, 7/22), hypoglycemia (23%, 5/22) and jaundice (23%, 5/22). Two very preterm babies (<27 weeks gestation) developed brain lesions (intraventricular haemorrhage) detected by cranial ultrasound. No cardiac complications were observed in the neonatal period.
Long follow-up studies are needed to confirm the safety of cancer treatment during pregnancy in terms of long-term cognitive and neurobehavioural outcomes in order to define treatment strategies aimed to reduce iatrogenic preterm birth.

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Long term outcome of children after pregnancy and cancer

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Background While oncologic treatment of maternal cancer during pregnancy has become more acceptable in the last decade, the effect of prenatal exposure to chemotherapy on cardiac and neurodevelopmental outcomes of the offspring is still uncertain. We aimed to document general health, cardiac function and neurodevelopmental outcome in children who were prenatally exposed to chemotherapy.
Methods This is an interim analysis of a prospective multicentre study examining children who were prenatally exposed to maternal cancer staging and treatment, including chemotherapy. Children were examined at birth, at the age of 18 months, 5-6, 8-9, 11-12, 15-16, or 18 years. The tests comprised a clinical neurologic examination, testing of the general level of cognitive functioning (Bayley/IQ-test), an electro- and echocardiography and questionnaire on general health and development. From the age of five years, also an audiometry, Auditory Verbal Learning Test and subtasks of the Children's Memory Scale and Test of Everyday Attention for Children were performed and the Child Behavior Checklist was completed. This study is registered, clinicaltrials.gov number NCT00330447.
Findings In total, 236 cycles of chemotherapy were administered in 68 pregnancies. Seventy children, born at a median gestational age of 35·7 weeks (range, 28·3 – 41·0; 47/70 <37weeks), were included with a median follow-up period of 22·3 months (range, 16·8 –211·6). Although neurocognitive outcomes were within normal ranges, the high incidence of preterm birth had a negative influence on cognitive development. Children's behaviour, general health, hearing and growth were reported as in a general population. A severe neurodevelopmental delay was seen in both members of a twin (3%). Cardiac dimensions and functions were within normal ranges.
Interpretation Fetal exposure to chemotherapy was not associated with increased morbidity at the level of the central nervous system,

cardiac, and auditory functions, as well as general health and growth. More subtle changes in cardiac and neurocognitive measurements emphasize the need for longer follow up. Prematurity was frequently encountered, and was associated with impairment in cognitive development. Therefore, iatrogenic preterm delivery should be avoided as much as possible.

Pharmacokinetics and transplacental passage of antineoplastic drugs

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Pregnancy is associated with important changes in hemodynamics, renal and hepatic function, and protein binding. Related to these adaptations, pharmacokinetic profiles were shown to be altered in pregnancy for different types of drugs, among which also some chemotherapeutical agents.[1-4] In comparison to nonpregnant state, a decreased maximum plasma concentration (C_{max}), a reduced plasma drug exposure (Area Under the Curve, AUC) and an increase in distribution volume and drug clearance was described in several patients for paclitaxel, carboplatin, doxorubicin and epirubicin.[3,4]
The pharmacodynamic (antitumour activity and toxicity in relation to the dose administered) consequences of the reduced plasma drug exposure are difficult to predict and require further research. Yet there are no arguments that pregnant cancer patients have a worse prognosis than nonpregnant patients when the same dosage regimens of chemotherapy are used. Therefore, currently it is recommended to maintain the standard dosage regimens.[4,5]
Because teratogenic effects have been observed in the first trimester and since neonatal myelosuppression has been noticed after third trimester use of chemotherapeutic drugs, one assumes that at least a fraction of these drugs crosses the placenta.[6] However, existing data on transplacental drug transfer are not conclusive since only a few reports on anectodal foetal sample collections after abortion or delivery in patients receiving chemotherapy during pregnancy are available.[7,8]
Transplacental transfer mainly occurs by passive diffusion and is therefore determined by the concentration gradient, the physicochemical drug characteristics of the agents where unbound, uncharged, lipid soluble molecules with a low molecular weight (< 300 Da) will easily pass the placenta.[1] Furthermore, there is also active transport by placental protein pumps as P-glycoprotein,

Multidrug Resistance Proteins and Breast Cancer Resistance Protein. These pumps work as protecting mechanisms for the foetus against potential toxic agents and were shown earlier to have a regulating role in the transfer of certain chemotherapeutic agents like vinblastine, doxorubicin, epirubicin and paclitaxel.[1] Preclinical research in a mouse model and baboon model showed a wide variation in transplacental transfer of different chemotherapeutic agents. While for carboplatin and cytarabine important drug amounts were detected in foetal plasma samples (57-100% and ± 40%, respectively), foetal plasma levels of anthracyclines, taxanes, vinblastine, cytarabine and 4-OH cyclophosphamide were substantially lower compared to maternal drug concentrations (0-25%).[9-11] The placenta seems to fulfil its barrier-role for most of the chemotherapeutic drugs and reduces foetal exposure to chemotherapy.

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Supportive care during pregnancy, including antiemetics and opiates

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Multiple drug administration is an important aspect of clinical practice particularly in specific physiological situation such as in neonates, elderly or pregnancy, since in all such situations, possibility of unwanted effects increases due to altered body physiology.
Regarding the use of antiemetic drugs to prevent nausea and vomiting arising from chemotherapy, there are good safety data to support the use of antihistamines, phenothiazines, and metoclopromide during the pregnancy. After the administration of chemotherapy, free radicals are generated, leading to localized exocytotic release of 5-hydroxytryptamine (5-HT) from the enterochromaffin cells; 5-HT then interacts with 5-hydroxytryptamine (5-HT) receptors on vagal afferent terminals in the wall of the bowel. Vagal afferent fibers project to the dorsal brain stem, primarily to the nucleus tractus solitarius (NTS), and, to a lesser extent, the area postrema (AP), the two parts of the brain referred to collectively here as the dorsal vagal complex. Receptors for a number of neurotransmitters with potentially important roles in the emetic response are present in the dorsal vagal complex. These include the neurokinin-1, 5-HT3, and dopamine-2 receptors, which bind to substance P, 5-HT, and dopamine, respectively. Efferent fibers project from the dorsal vagal complex to the final effecter of the emetic reflex, the central pattern generator, which is an anatomically indistinct area occupying a more ventral location in the brain stem. Receptors for other locally released mediators, such as substance P, cholecystokinin, and prostaglandins, are also present on the vagal afferent terminals. However, the extent to which these mediators are involved at this peripheral site is unknown. Antineoplastic agents may also induce emesis through an interaction with the area postrema within the dorsal vagal complex. The area postrema is a circumventricular organ located at the caudal end of the floor of the fourth ventricle, which is accessible to blood and

cerebrospinal fluid–borne emetic stimuli. Other potential sources of efferent input that result in emesis after chemotherapy include a number of structures in the temporal lobe, such as the amygdala. Evidence for this pathway is less well established than for other proposed sites of chemotherapeutic action. The 5HT3 antagonist ondansetron also has a central chemoreceptor inhibition as well as a peripheral action on the small bowel and vagus nerve which inhibits vomiting. There is no reported increase in birth defects in humans with its use. Granisetron has been studied prospectively to prevent nausea and vomiting during cesarean section and has been shown to be safe and effective in this setting. There is not enough data to support the use of other 5-HT-serotonin antagonists or aprepitant.

Regarding the Granulocyte colony-stimulating factor use in pregnancy, it has been reported in a registry series of 20 patients with severe chronic neutropenia with a median dose of 2.7 mcg/kg/day administered daily or every other day during all three trimesters with an average duration of three trimesters. These data, although limited, did not reveal an increase in adverse congenital abnormalities or fetal death compared to pregnant patients that did not receive the drug.

Although the use of bisphosphonates during pregnancy has not been evaluated prospectively, a recent literature search including 51 patients exposed to bisphosphonates shortly prior to conception or during pregnancy did not find evidence of skeletal abnormalities or malformations in the products of the exposed mothers.

Finally, only selected patients may be treated with opiates during the pregnancy.

This house says: neoadjuvant chemotherapy is standard during pregnancy - in favor

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Cervical cancer is the most common gynecological cancer found during pregnancy with an incidence of 1,2-12/100.000 pregnancies. Most cases in developed countries are diagnosed at an early stage due to the frequent examinations during pregnancy. Based on the stage of the disease, week of pregnancy and patient´s preference several options with regard to the management can be considered. For IB1 and IB2 stage in non-pregnant women the standard treatment is radical hysterectomy C2 or chemoradiotherapy. Recently additional data on the use of neoadjuvant chemotherapy in early stage cervical cancer has been presented [Rydzewska et al., 2010]. Moreover a large set of patients undergoing neoadjuvant chemotherapy has been published in dose dense regimes [Robova et al., 2010]. Current knowledge on the use of chemotherapy shows encouradging data in terms of fetal outcome [Amant et al., 2012]. As radical surgery such as vaginal and especially abdominal radical trachelectomy poses high risks for the pregnancy outcome, the addition of neoadjuvant chemotherapy for the treatment of pregnant women gives the option of postponing the delivery to later stage (ideally over 36th week of pregnancy) as well as performing less radical surgery such as simple trachelectomy combined with lymphadenectomy.

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Cervical cancer during pregnancy: part of neoadjuvant chemotherapy

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The incidence of abnormal cervical cytology is estimated at 1-5% of all pregnancies and the reported rate of cervical cancers ranges between 1 to 12/10.000 pregnancies. The pregnancy does not have a deleterious impact on the prognosis of cervical cancer as pregnant patients have a similar outcome to non-pregnant women. Seventy percent of cervical cancers during pregnancy are diagnosed at stage I.

The management of cervical cancer is mainly dependent on four different criteria: the extent of local spread (reflected by the tumour stage and tumour size), the nodal status, the term of the pregnancy, and the histological subtype (patients with "conventional" subtypes versus those with rare subtypes [e.g. small cell carcinoma]) and worse outcomes, who need to be treated immediately and require pregnancy termination to deliver optimal therapy.

In most countries, the therapeutic recommendation for tumours exceeding 4cm (stage IB2 or greater) or for disease with nodal involvement is concomitant chemoradiation therapy (CRT). This treatment approach means pregnancy interruption. Several publications report cases of CRT for locally advanced stage disease or patients with nodal involvement diagnosed during the 1st trimester after a laparoscopic lymphadenectomy.

An alternative to CRT is neoadjuvant chemotherapy with preservation of the pregnancy. Completion surgery is then done after delivery. Twenty-five cases have been reported. Nine of these 25 patients were diagnosed with stage IB1 disease (which is not a conventional indication for neoadjuvant chemotherapy in non-pregnant patients). Most patients achieved a partial response with residual disease in the cervix and 6 had persistent nodal involvement after radical hysterectomy. Three patients had a poor response or progression and were switched to chemoradiation therapy. All the new-born children were normal with a follow-up ranging from birth

time to 80 months. Six patients died of disease including one who refused further treatment and two who had recurrent disease at the time of publication. One patient was still under treatment at the time of publication. Among the 16 patients with no evidence of disease, it is important to note that 9 had a short follow-up of less than 12 months.

There are only two published series of guidelines with specific management recommendations by stage and they differ in particular for the treatment of locally advanced stage disease (stage IB2-II). The French guidelines propose an interruption of the pregnancy before 18 WG followed by CRT. The European Consensus Meeting guidelines propose neoadjuvant chemotherapy as the first option because it allows preservation of the pregnancy. These differences between guidelines reflect a different philosophy of standard of care for the management of cervical cancer in non-pregnant patients between different countries.

Breast imaging during pregnancy

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During pregnancy and lactation, the breast parenchyma is influenced by a variety of hormones, resulting in glandular proliferation, ductal distention, and stromal involution.
These structural changes can make breast imaging examination difficult and the diagnosis of breast cancer challenging due to the hormone-induced changes that occur in breast tissue.
The ideal protocol for imaging the breast in a symptomatic pregnant or lactating woman is controversial.
Although most disorders related to pregnancy and lactation are benign, pregnancy associated breast carcinoma (PABC) represents the commonest malignancy in pregnant women. As an increasing number of women are delaying childbearing into, and beyond, the fourth decade of life, the incidence of pregnancy-associated breast cancer appears to be increasing.
A delay in diagnosis secondary to the breast tissue changes or to a lack of awareness of the possibility of breast cancer in this setting, has been postulated as the major factor responsible for the advanced stage and poor prognosis that are associated with PABC.
In contrast to the controversy that surrounds the utility of mammography, there is a consensus that ultrasound constitutes the most appropriate radiologic method for evaluating breast disorders in women during pregnancy and lactation. Breast magnetic resonance imaging (MRI) requires the use of gadolinium and should be reserved in selected cases, until after delivery.

Biology and prognosis of breast cancer during pregnancy

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Despite that several studies were conducted to address the prognosis of breast cancer diagnosed during pregnancy, it is not very clear whether diagnosis during pregnancy is independently associated with poor outcome. The relative rarity of the disease has hindered the conduction of large powered studies to address this question. Hence, evidence in this field relies mostly on small, retrospective, hospital-based studies. It is clear that patients diagnosed during pregnancy are often diagnosed with an advanced stage, which is probably secondary to diagnostic delay. To study the impact of pregnancy on prognosis in this population, we recently conducted a case-control study on patients diagnosed with breast cancer during pregnancy at the European Institute of Oncology in Milan during the past 10 years. To control for potential differences in stage, we selected controls that had the same pathological tumor size and nodal status along with other factors like age, year of diagnosis and the use of neoadjuvant chemotherapy. This study included 65 pregnant women and 130 matched controls. We found that patients diagnosed during pregnancy have significantly poorer disease free and a tendency of worse survival as well. This was observed even after adjusting for possible confounding covariates. More recently, we presented the results of a meta-analysis of around 30 published studies, which ran in line with these results suggesting that patients diagnosed during pregnancy have poorer prognosis independent of stage. We hypothesize that pregnancy impact the biology of breast cancer; however one should consider that in a large fraction of these studies, adequate systemic treatment was not offered during pregnancy which could certainly confound these results.

On the other hand, breast cancer diagnosed at a young age has unique biology but whether diagnosis during pregnancy adds a further layer to that, this remains an open question. Some studies have shown that more ER- tumors are diagnosed during pregnancy, while other studies failed to reproduce the same information. In a recent study by our

group, we found no differences in breast cancer subtypes using immunohistochemistry between patients diagnosed during pregnancy and matched controls of the same age and stage. No data is yet available on whether pregnancy induces changes on breast cancer biology at the molecular level. Preclinical evidence points out to a possible role of mammary stem cells in this regard; however this remains to be confirmed. To our knowledge, several experiments are currently on going in this regard and the results will be possibly available by the end of 2012.

Surgical treatment of breast cancer during pregnancy

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Mastectomy versus breast-conserving therapy

The occurrence of BCdP poses an acute and dramatic dilemma for the patient, her family, and her physician. The management of BCdP requires a collaborative team effort to provide the best medical options and most effective psychosocial support. Women with BCdP are often influenced by various opinions, which are often radical and difficult to argue against. However, probably more than any other medical condition, BCdP requires a thorough discussion. Obviously, the patient is looking for the physician's recommendation, but it is the physican's role to ensure that the patient is fully aware that she has a variety of treatment options to consider.

Historically, mastectomy was considered to be the standard surgical procedure in pregnant patients with breast cancer. There are two possible reasons for this: firstly, patients frequently presented with large tumors as a result of diagnostic delay, and secondly, there was a concern about the delay before administration of radiotherapy, which is contraindicated during pregnancy.

In our opinion, it is important to inform the patient that mastectomy is not mandatory for the treatment of BCdP and that outcome of patients treated with breast conserving surgery was similar to non-pregnant women, even though it should be acknowledged that data on this topic are limited.

In women diagnosed during the third or the late-second trimester radiotherapy might be safely postponed until after delivery. Unfortunately, there is limited and retrospective experience published on the delayed radiotheraphy after breast conservation and its effect on outcome. The concurrent diagnosis of breast cancer and an unexpected early pregnancy represents the most challenging treatment scenario. It is considered that abortion is not a therapeutic procedure in these cases but termination of pregnancy can be considered in order to facilitate completion of treatment. For patients at the first trimester

who desire to continue the pregnancy, treatment is possible but there is a limited number of options during the first weeks of gestation. In fact, chemotherapy is prohibited during the first trimester. Surgery is safe at any time but breast conservation performed during the first trimester is probably associated with an excessively long delay in post-operative radiotherapy. Therefore, in a patient at the first trimester who wants to continue the pregnancy and also wishes to conserve the breast all these issues have to be carefully discussed, and the patient has to be informed that a possible increased risk of local recurrence should be considered, even though this is difficult to quantify because of the lack of data.

Sentinel node biopsy

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When breast cancer is diagnosed during pregnancy, axillary lymph nodes are frequently positive, but when the tumor is diagnosed at an early stage, a considerable proportion of patients have node-negative disease and might therefore benefit from SLNB. The decision-making process regarding adjuvant treatment in pregnancy provides limited options. Tamoxifen and other endocrine agents are generally not recommended and other drugs, such as methotrexate are strongly contraindicated during pregnancy; in contrast, anthracyclines can be administered during the second and third. From this standpoint, axillary staging gives important prognostic information and allows better local control, but should not influence the type of systemic treatment administered during pregnancy. Sentinel lymph node biopsy (SLNB) has been evalauted in simulation studies and lymphoscintigraphy and SLNB can be safely performed during pregnancy, without any significant risks to the fetus at any phase of a potential pregnancy.
Recently our group published the clinical experience with twelve pregnant patients with breast cancer who received a low dose (10 MBq on average) lymphoscintigraphy using technetium-99^{m} (99^{m}Tc) human serum albumin nanocolloids. The sentinel lymph node (SLN) was identified in all patients. Ten of twelve had pathologically negative SLN. One patient had micrometastasis in 1 of 4 SLN. One patient had metastasis in the SLN and underwent axillary clearance. Eleven healthy babies were born with no malformations and normal weight. One baby, whose mother underwent lymphatic mapping at the 26^{th} week of gestation, was operated on at the age of 3 months for a ventricular septal defect and at 43 months is in good health. This malformation was suspected at the morphologic ultra-sound examination on week 21, well before lymphoscintigraphy, and was confirmed a posteriori by a different observer based on videotaped material. No overt axillary recurrence appeared in the patients with

negative sentinel lymph nodes after a median follow-up of 32 months. These initial encouraging data support the safety of SLNB in pregnant patients with breast cancer, when performed with a low dose lymphoscintigraphic technique.

However, there are some practical recommendations that can be followed to further minimize the exposure of the fetus, such as avoiding contact with other patients who might be potential sources of radioactivity (e.g. by scheduling pregnant patients as the first procedure of the day and keeping the patient in a single-bedded room), and reducing the time interval between lymphoscintigraphy and surgery, with a subsequent possible reduction in the administered radioactivity. Thus, in pregnant patients, SLNB can be performed within 2–3 h following injection of 3–5 MBq of 99mTc-radiocolloids.

Is breast radiation during pregnancy an issue?

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Although breast cancer is rarely diagnosed in pregnancy (about 1 per 1000), the event has devastating impact on the patient and her family [1]. Usually mastectomy with complete axillary node dissection is a first choice. Such choice is based on the advanced cancer stage in the majority of pregnant patients due to the physiological breat changes and restrictions on the use of diagnostic procedures that make early diagnosis difficult. Complete axillary dissection is chosen due to the perceived risk to the fetus associated with radiotracer use. However, a recently published dosimetry study of sentinel node biopsy with radioactive tracer showed that doses to different areas of the abdomen, indicative of the absorbed dose to the fetus at each trimester, were extremaly low, suggesting that sentinel node biopsy should have the same indications in pregnant as in nonpregnant women [cited in 2].
The conservative breast treatment including conservative breast surgery and postoperative (adiuvant) radiotherapy is usually not offered to the pregnant breast cancer patients because the postoperative radiotherapy would have to be delayed until post-partum. Embryo and fetus are extremaly sensitive to irradiation. Radiosensitivity changes with pregnancy period and is highest during the early organogenesis. The effects of radiation on embryo/fetus are divided in two categories: stochastic events (carcinogenesis with a very low thereshold dose of about 10 mGy) and deterministic events (mental retardation, growth retardation etc. with a threshold dose of about 100-200 mGy). A number of studies have assessed fetal dose in women undergoing radiotherapy for various malignancies including brain cancers, head and neck cancers, and Hodgkin's disease [cited in 2]. The fetal dose from high-energy photon beams in early pregnancy (up to 24 weeks) from the conventional breast cancer radiotherapy to the dose of 50 Gy in 25 daily fractions to the whole breast, has been estimated in the range of **20–240** mGy, increasing to 2,000 mGy in late pregnancy [cited in 2]. These doses are over the levels considered

safe by the International Commission on Radiological Protection (ICRP). ICRP considers a fetal dose of less than 1 mGy to be insignificant, and the doses of a few mGy acceptable as they are associated with no measurable increased risk of fetal damage [3]. Based on these data, ADIUVANT external photon beam radiotherapy should NOT be given during pregnancy [2]. The availabity of intraoperative radiotherapy with an extremaly collimated electron beam has launched the first dosimetry studies on the in-utero dose in the nonpregnant women in order to assess the safety of this procedure in pregnant women [2].

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Systemic Treatment of breast cancer during pregnancy

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Breast cancer during pregnancy accounts for approximately 2% of primary breast cancer patients. The median age of these women is below 35 years and the biology of breast cancer in very young women has a more aggressive phenotype. Having said that, breast cancer in the very young women is mostly treated with cytoxic agents as part of the systemic therapy. The type of adjuvant or neoadjuvant chemotherapy however, does not differ by age. It seems that young women benefit from neoadjuvant therapy also in terms of improved disease free and overall survival. Standard (neo) adjuvant chemotherapy regimen today comprise an anthracycline-taxane based therapy, either as combination or as sequential therapy. Dose-dense therapy seems to be superior, especially in hormone-receptor negative disease.

Today´s credo is to treat pregnant women with breast cancer as closely as possible to standards for young, non-pregnant women with breast cancer. Data are increasing to support this statement. Early preterm deliveries with a high risk of fetal morbidity and mortality are in general not indicated and the general recommendation is to treat the woman during pregnancy and deliver as closely as possible at term. Chemotherapy should be stopped around the 35^{th} week to allow for a 2-3 weeks chemofree interval prior to delivery.

As anthracyclines are accepted as chemotherapy for young women during pregnancy, taxanes are not and are in addition often not even recommended during pregnancy. However, the data for the taxanes are increasing and the smaller cohorts treated by taxanes during pregnancy do not indicate a worse outcome for the children exposed to a taxane in utero than for anthracyclines. Standard regimen to be used in pregnancy are e.g. FECx6; FEC-Doc; E(A)C-Doc; E(A)C-Paclitaxel weekly. “Chemo-light” with reduced cycles and agents e.g. epirubicin mono, or 4x TC if not completed after delivery is not indicated. No experimental regimen and agents should be used, e.g.

nab-Paclitaxel because it is also not indicated for non-pregnant primary breast cancer patients.
The percentage of breast cancer patients with a HER2-positive tumour is higher in young women. Our data have shown that around 1/3 of the patients with breast cancer during pregnancy had a HER2-positive disease. The use of trastuzumab during pregnancy is not indicated as the majority of cases treated accidentally with trastuzumab during pregnancy showed an oligo-anhydramnios. Recent data from the HERA study showed that in the 16 pregnancies that occurred while treated with trastuzumab or up to three months after end of trastuzumab treatment no oligohydramnios in the 5 women who continued pregnancy. But the spontaneous abortion rate was high with 25%. None of these patients was exposed longer than 2 months and all during the first trimenon. It seems comparing these data with the data from the case reports that the duration of trastuzumab is important but probably also the timing. Nevertheless, the data do not support to recommend trastuzumab during pregnancy. Today, most patients receive trastuzumab in addition to the chemotherapy or at least in addition to the taxane if a sequential regimen is been chosen. But so far, it has not been shown that the early start of trastuzumab is significantly superior to the start after completing chemotherapy as in HERA.
Other anti-HER2 agents such as laptinib or pertuzumab, which are currently investigated within in clinical trials for early breast cancer, are not indicated during pregnancy.
None of the experimental agents currently under investigation in the metastatic breast cancer are indicated to be used in early breast cancer patients with or without pregnancy.
Endocrine therapy, tamoxifen should not be given during pregnancy. The risk to induce fetal malformations such as urogenital syndromes as reported in the literature is high and should be omitted.
Conclusion:
Breast cancer during pregnancy can be treated closely to the standards for non-pregnant women. However, the treatment of such women is a challenge and the decision for the right systemic therapy within the whole breast cancer therapy concept (neoadjuvant vs. adjuvant, chemotherapy yes vs. no; taxane yes vs. no; early delivery yes vs. no,

trastuzmab if yes when to start, mastectomy vs. breast conservation) needs to be taken within an enlarged multidisciplinary team of breast cancer specialists implementing the praenatologist, obstetrician and neonatologist to take the best decision. At the end of the day it remains an individual decision

Immune tolerance and pregnancy, a possible role in cancer

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During pregnancy the immune system is set to tolerate the fetus. Trophoblasts that surround the embryo and that invade the decidua release immune modulators that recruit immune cells and regulate their activity. They also express on the cell surface non-classical MHC molecules like HLA-G that inhibit the cytotoxic activity of Natural killer and cytotoxic T cells. Together, these measures allow the maternal immune system to tolerate the fetus. Many similarities have been found between embryo development and tumor development. Trophoblast cells share many characteristics with tumor cells: they can proliferate, invade the tissue and induce neoangiogenesis. In addition, they release and express immunomodulating molecules. Hence, during pregnancy arising tumor cells find the perfect conditions to proliferate and metastasize as they are undisturbed by a 'tolerant' immune system. In this presentation we will discuss recent evidence supporting this view.

Imaging workup and the evolving role of whole body MRI during pregnancy

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Imaging modalities can provide essential information affecting the treatment options of pregnancy-associated cancers, but the types of imaging techniques that can be used for pregnant patients are limited. Magnetic resonance imaging (MRI) seems to be the most suitable technique for maternal health problems during pregnancy, since it does not expose the fetus to ionizing radiation and can provide multiplanar images with high tissue contrast in the absence of intravenous contrast agents. With these advantages, MRI has emerged as an important adjunct to ultrasound (US) for imaging the chest, abdomen, and pelvis of individuals during pregnancy.
In addition, the latest development in MR technology made available fast MR sequences with good spatial resolution allowing whole –body imaging by MR in one sitting. Whole body MRI is therefore increasingly used for the imaging workup of pregnant women with cancer.

Rare cancers during pregnancy

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Colorectal Cancer

Is rare during pregnancy (~ 0.008 %). Around 350 cases have been reported. Mean age is 31 year old. The clinical picture includes symptoms that overlap with pregnancy symptoms, leading to the diagnosis of advanced stage disease with more complications such as obstruction, perforation, etc. Rectal cancer is more common than colon cancer. Chemotherapy can be provided after the 2nd trimester.

Gastric Cancer

Is very rare cancer. Most cases published are coming from Japan (incidence 0.026%). Less than 200 cases have been reported. Mean age is 31.4 year old. Clinical picture overlaps with symptoms of pregnancy. Surgery is recommended in early disease. No adequate data from chemotherapy are available. In general, prognosis is poor. Almost 88% of these women are dead during the first year after diagnosis.

Pancreatic and Liver Cancers

Pancreatic adenocarcinomas are very rare (around 10 cases published), as well as neuroendocrine carcinomas (around 20 cases). Hepatomas are also very rare with less than 50 cases reported. Both pancreatic and liver carcinomas are carrying poor prognosis, while neuroendocrine tumors have a better outcome.

Lung Cancer

Still a rare coexistence with less than 50 cases reported so far. Non-small cell lung cancer is more common accounting for the 75% of all lung cancer cases. Most women received chemotherapy in the post-partum period with poor results. Gestational lung cancer is one of the tumors that can quite commonly involves fetal and placental products.

Thyroid Cancer

About 10% of thyroid cancers that occur during the reproductive years are diagnosed during pregnancy or in the first year of birth. The incidence is 14 cases per 100.000 deliveries. It is most commonly seen between the age of 25-35 years old. About 60% of the cases are localized and 30% regional disease. Tumor size ranges between 1-4 cm in approximately 60-65% of the patients. Papillary carcinoma are more common (66%) following by follicular histology (30%). Total thyroidectomy is the treatment of choice and prognosis is excellent.

Renal Cancer

Less than 100 cases have been reported. Renal cancer accounts for the 50% of renal masses diagnosed during pregnancy with angiomyolipoma to be the second (23%). Clinically, the classic triad of abdominal mass, pain and hematuria is present in only 26% of the cases. Diagnosis is usually incidental through regular physical examination and /or ultrasound. Ultrasound's sensitivity is 85% for masses > 3 cm. Another diagnostic tool is urine cytology. The therapeutic management of renal tumors in pregnancy is exclusively surgical. Patients diagnosed with a renal mass during the 1st trimester should go for radical surgery. Patients on the 2nd trimester should continue to week 28th and then proceed to nephrectomy at delivery, while patients on 3rd trimester could offered surgery after delivery.

Ovarian Cancer

Incidence is 4-5 cases per 100.000 pregnancies. Ovarian malignancies are usually diagnosed at early stages. Ultrasound is the most sensitive method. Histologically, epithelial tumors are the most common accounting for 50-60%, followed by germ cell tumors 25-40% and sex cord tumors 5-10%. IA, G1 tumors should be managed by adnexectomy, omentectomy, and peritoneal washings. IA, G2, G3, IB, IC and IIA tumors by lymphadenectomy (till 20th week) or postpone surgery after delivery. II_B or more advanced tumors should be treated with pregnancy termination and radical surgery, or cytoreductive surgery, chemotherapy and surgery during pregnancy. Paclitaxel with platinum are still the drugs of choice.

Management of lymphomas during pregnancy

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Although rare, Hodgkin and non-Hodgkin Lymphomas during pregnancy require special consideration. It is a difficult situation in which the physicians need to provide the best approach to optimize the outcome for both mother and baby. Multidisciplinary care should always involve the mother, the fetus, and the family during the pregnancy, and long-term strict follow-up is advisable.

There is no standardized approach for the management of cancer in pregnancy. The risks on the developing fetus associated with the use of classical chemotherapy are better known than those with monoclonal humanized IgG1 antibodies. In general, if possible, chemotherapy and Rituximab should be avoided during the first trimester, and whenever possible the pregnancy should be carried to term.
Not only treatment but also the staging procedures are affected and the fetal radiation exposure should be strictly limited. The intensity of fetal tissue 18F-FDG uptake in PET scans accidentally performed during pregnancy is poorly known, but it is very likely higher than current dosimetric standards.

Therapeutic abortion represents a complex issue with religious, ethical, psychological, social and cultural implications, which have to be taken into account. It does not appear to change the evolution of the disease and should be strictly reserved only for women who need urgent intervention. In fact, most published case reports with both maternal and fetal outcome support a pregnancy-conserving approach. It is, however, likely that the issue of therapeutic abortion is under-reported.
When treatment is necessary, mainly in second and third trimester, full doses of a properly chosen chemotherapy regimen can be administered with curative intent. This rarely seems to carry consequences for the fetus. The same seems to be true for rituximab

with, however, still limited clinical experience. Apparently, rituximab administration during pregnancy does not necessarily threat pregnancy and neonatal life, however it may increase the rates of first trimester miscarriages and those of premature births. Moreover, it may reversibly suppress the newborn B-cell component after birth without evidence of increased infections.

Pregnancy may not be an absolute contraindication for radiotherapy, but fetal exposure should be carefully estimated and appropriate shielding should be used. With the current management approach, most pregnant women with lymphoma can successfully carry the fetus to term and be successfully cured, often without fertility impairment.

Advances in fertility preservation for cancer patients

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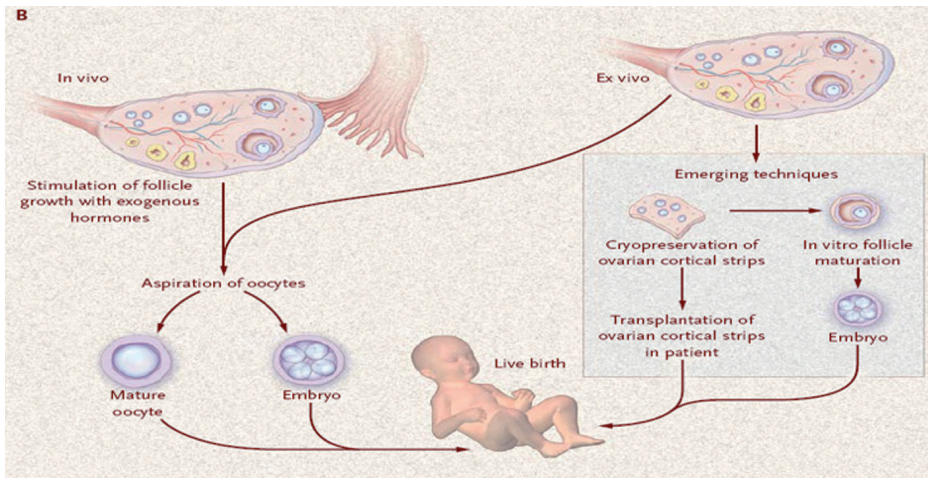
In United States around 60.000 individuals from 15 to 40 years of age are diagnosed annually with cancer, and approximately 60% of them are women. Infertility may occur after oncological treatments which concur to gamete loss both in males and females. Gamete loss is directly related to the quality of treatment delivered, being chemotherapy with alkylating agents the most gonadotoxic systemic treatment and pelvic surgery or radiotherapy the most gonadotoxic local treatment.
For male patients, sperm banking is an effective and convenient mean to preserve fertility at any age, and should be offered to all interested patients. The improvements of intracytoplasmatic sperm injection technology (ICSI) has given the opportunity of successful fatherhood also for men who froze a limited number of gametes before treatment. Moreover, a rapid referral for fertility counseling and sperm banking has overcome treatment delays, which were particularly relevant for young patients with aggressive tumors.
For female patients, more issues may interfere with effective fertility preservation. Age is directly related to oocyte quality and quantity. Assessment of ovarian reserve is complex, but measurement of serum follicle stimulating hormone (FSH), estradiol levels (E2)and anti mullerian hormone (AMH) may be helpful to select patients with realistic chances of effective preservation.
At diagnosis, plans for fertility preservation must take into consideration patients' priorities and treatment priorities. Available options should be offered within a thorough oncofertility counseling and rapid referral to the assisted reproductive technology (ART) centers should be implemented. Special care should be reserved for patients with endocrine responsive tumors and the use of LHRH analogues during chemotherapy might be offered in conjunction with other fertility-sparing modalities.

ART options for female patients are illustrated in the following figure (modified from Jeruss JS and Woodruff TK. NEJM 2009; 360:902-11)



Pregnancy and breastfeeding in cancer survivors

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Owing to the improvements in early detection programs and adjuvant systemic therapies, we are witnessing continuous decline in death rates secondary to cancer. This has resulted in more attention given to quality of life issues including fertility. Patients diagnosed with cancer at a young age coupled with the rising trend of delaying pregnancy to later in life have resulted in more women diagnosed with cancer before completing their families. Hence, more inquiries into chances of future conception are now encountered in the oncology clinics.
Data on the safety of pregnancy following childhood cancers are rather reassuring. There is no evidence that subsequent pregnancy in these patients could result in tumor recurrence. In adult cancers, the vast majority of evidence is in breast cancer. Being a hormonally driven tumor, concerns exist on whether subsequent pregnancy could stimulate breast cancer recurrence, particularly in women with history of endocrine-sensitive breast cancer (i.e. ER+). This concern has resulted that around 30% of women who become pregnant after breast cancer are advised to perform an abortion. Recently, we presented the results of a large international trial involving around 1,200 patients showing that patients with history of an ER+ breast cancer who became subsequently pregnant are not at an increased risk of relapse. Furthermore, induction of abortion did not improve their prognosis. Little information was available to address the safety of breastfeeding, so solid conclusions cannot be made in this regard. However, it is important to note that there are no evidence suggesting a possible detrimental effect, and hence we believe that breast cancer survivors should not be denied subsequent pregnancy or breastfeeding.
Apart from the concerns on the possible impact of pregnancy on cancer outcome, there are also concerns on the impact of cancer therapies received earlier on fetal outcome. In this regard, several studies have been conducted and showed that neither chemotherapy nor hormonal therapies have subsequent impact on fetal outcome. This is true for survivors of childhood and adulthood cancers. Available

evidence on targeted therapies is reassuring, yet remains very limited at the time being. Of concern, survivors of childhood cancers were who were subjected during childhood to uterine and ovarian irradiation, in which an increased risk of stillbirth and neonatal death was observed. As for breastfeeding, it should not pose a problem for newborns of cancer survivors as well, although evidence remains scarce. In breast cancer survivors, it is clear that milk production from the ipsilateral breast is diminished in up to 50% of patients, and hence lactation counseling could be helpful in these cases. However, it is important to note that there are no concerns on the fetus to be breastfed from a breast previously treated for breast cancer.

Psychological support to cancer survivors: fertility and sexuality issues

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Sexuality is an important component of the quality of life of every individual; it follows that the evaluation of quality of life in oncology must necessarily include sexuality among the parameters to be considered. Also the possibility (or impossibility) to become a mother is vital for the vast majority of women. So fertility issues should be addressed regularly in oncology.
One year after diagnosis, a large percentage of oncology patients complain of a marked deterioration in their sex lives. Such matters have lain largely unexplored for a long time, due to the difficulty in identifying and evaluating the variables involved; despite several very recent studies, a certain discomfort prevails among health personnel across the majority of cultures when talking with patients about this aspect of their lives.
Breast cancer carries with it not only physical but also – and arguably mainly - psychological implications, since it affects not only the breast as a physical organ but probably more importantly it affects what the breast represents for a woman: femininity, maternity, desire, attraction and gender identity. Gynaecological cancer directly involves the organs from which, together with other parts of one's body and mind, mainly orgasm is originated and maternity take place. Uterus is not only the somatic place of conceiving but is also the mental representation of woman's progressive capacity to hold her child and step forward in the internal construction of her self as a mother.
The increased awareness of women regarding the importance of a periodic breast and gynaecologic examination, together with the improved accuracy in image diagnosis technology, have considerably increased the number of young women of reproductive age who are diagnosed with a neoplasm. The impact of the disease and its treatment on sexuality and maternity could therefore be more relevant regarding this younger population.

Medical treatment includes the administration of endocrine modulators, and most of the time these lead to a disruption of ovarian functioning, causing patients to face a situation whereby their menopause is brought forward, thus making pregnancy impossible.
But sexuality and fertility problems are not addressed to breast and gynaecology patients only, and sexuality and maternity are not possible (or neglected) only because of their physical assets, but psychological and ethical aspects play a relevant role, together with the quality of the relationship as a couple.
Some feedbacks of the assessment carried out on breast cancer patients at the European Institute of Oncology will be given regarding sexuality and fertility issues.
Lecture will focus on the importance to understand the main reasons for, and domains of, dissatisfaction, with a view to setting up customized interventions and psychological support for women and their partners.

N O T E S