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Cancer Before the Third Trimester of Pregnancy: How to Handle the Bioethical Dilemmas?

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ABSTRACT

Background: ethical issues that arise during the care of a pregnant woman with cancer are challenging to physicians, policymakers, lawyers, and the bioethics community. This article is restricted to a discussion of ethical dilemmas and controversial case reports, mainly focused before the third trimester of pregnancy, when a conflict could exist between cancer and pregnancy outcomes.

Methods: published literature was retrieved through searches in PubMed or Medline, CINAHL, the Cochrane and Google Academic in April 2020, using appropriate controlled keywords (cancer, neoplasm, pregnancy, ethics). Results were restricted to review articles, ethical perspectives, clinical practice guidelines and case-based teaching guides.

Discussion: when a conflict arises in the maternal-foetus dyad, like the one related with cancer treatment and the risk of foetal demise, a range of ethical frameworks might be useful to consider in the decision-making process. Pragmatic theoretical approaches include case-based analysis, ethics of care, feminist theory, and traditional ethical principlism using the framework of autonomy, beneficence, non-maleficence, and justice. Also, societal and practitioner values could add value and an ethics consultation may be helpful to mediate conflict resolution. The physician must balance autonomy and beneficence-based obligations to the pregnant woman with cancer, along with beneficence-based obligations to the foetus.

Conclusions: ethical challenges have received less attention in the literature, particularly before the third trimester of pregnancy. Best, unbiased and balanced information must be granted both to the patient and to the family, regarding the benefits and harms for the woman herself as well as for the foetal outcome.

Keywords: cancer, neoplasm, pregnancy, ethics.

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Background

Cancer is the second most common cause of death during reproductive years and complicates between 0.02 and 0.1% of all pregnancies.[1,2] The incidence is expected to boost with the increase in childbearing age and unplanned pregnancies. In Europe, 3,000 to 5,000 patients are diagnosed yearly with cancer during pregnancy, whereas 3,500 cases are reported in the USA.[3] The most common neoplasms associated with pregnancy are breast and cervical carcinomas, thyroid cancer, malignant melanoma, lymphomas and acute leukaemias and ovarian cancer.[4,5]

The problematics of how to handle cancer during pregnancy has been a long-termed matter of debate in the medical community. The many ethical issues arisen in the care of pregnant women involve many stakeholders – such as family, physicians, legislators, jurisdiction and the bioethics community - and its boundaries are imperfect since many contexts intersect.

This article restricts the discussion to the clinical/pharmacological background and ethical issues that emerge from the medical management before the third trimester of a pregnant woman with cancer that occurs whenever the therapy toxicity creates a conflict of interest unbalancing cancer and pregnancy outcomes.

Methods

Published literature was retrieved through research in PubMed or Medline, CINAHL, the Cochrane and Google Academic search engine in April 2020, using appropriate controlled keywords (cancer, neoplasm, pregnancy, ethics).

Results were restricted to review articles, ethical perspectives, clinical practice guidelines and case-based teaching guides (only available English and Portuguese abstracts or text). A total of 33 publications were manually reviewed according to the authors´ criteria of relevance of the subject and availability of the full article.

Discussion

1. Medical background. About cancer during pregnancy

In 1880, Samuel Gross stated that breast cancer in pregnancy would clinically present with accelerated growth, including an “excessively malignant” clinical course.[6] In 1943, after treating 20 patients with breast cancer, a group at Columbia University Presbyterian Hospital concluded that pregnancy “made the disease inoperable”.[7] Ten years later, it was consensual that abortion was linked to improved patient survival.[6] This attitude has slackened, considering that the outcome in patients with both breast cancer and pregnancy is the same as their non-

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pregnant counterparts when matched for age and disease stage.[8,9]

The main challenge while managing cancer in pregnancy is balancing therapeutic regimen and foetus welfare. In addition, as an estimated 50% of pregnancies are unplanned, many women are exposed to teratogens before realizing they are pregnant.[10] This condition demands attention and careful protocols.

All over Europe, there are differences between countries regarding availability, conditions and gestational limit. In Portugal, since 2007, and after a National Referendum, the voluntary termination of pregnancy until 10 weeks of gestation was legalised (law nº16/2007). In that same legal document, it is stated that in case of danger of death or physical and/or psychic injury, the possibility of interrupting the pregnancy until 12 weeks of gestation is allowed.

2. Complementary diagnostic exams and trimester considerations

During the last decades, imaging of the pregnant patient has been performed with radiography, computed tomography, magnetic resonance imaging, scintigraphy, positron emission tomography scan, and ultrasonography (US). US imaging has emerged as the primary imaging modality, because it provides real-time images without the use of ionising radiation.

A clear link between the severity of foetus impairment, gestational stage, and cumulative radiation dose received has already been established.[11] For instance, during the organogenesis, there is a higher likelihood of induction major malformations and the threshold dose is above 100 mGy. There are also other issues besides ionising radiation. The radioactive iodine (I-131) crosses the placenta and has the ability to affect foetal thyroid and gadolinium teratogenic in animal studies. More invasive imaging tests should only be performed if the diagnosis and/or staging is expected to contribute decisively to the prognosis of the mother or foetus and that the risks and benefits are perfectly clarified and understood by the mother.[11]

Although the foetus is unscathed by laboratory tests, our main concern will be the influence that pregnancy will have on diagnosis, staging and follow-up, due to the fact that the serum biomarkers lack sensitivity and specificity during this period. There are tumour biomarkers that may be increased, such as CA 15-3, SCC, CA 125 and AFP, and others that are not so much, such as the example of CEA, CA 19-9, LDH, AMH and HE-4. Inhibited B and LDH increased in the last trimester may be a laboratory sign of hypertensive abnormalities linked to pregnancy.[11]

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3. Treatment options and trimester considerations

Approximately 0.5% of all births occur before the third trimester of pregnancy and the majority of these very early deliveries result in neonatal deaths and more than 40% in infant deaths. The delivery before 23 weeks of gestation, usually leads to neonatal death (5-6% survival), and among rare survivors remains significant morbidity (98-100%). When delivery is anticipated near the limit of viability, families and healthcare teams are faced with complex and ethically challenging decisions.[12] For most cytotoxic and targeted therapies, there is a lack of data regarding the risk of teratogenesis, based on case reports and retrospective series. The potential mutagenic, teratogenic and carcinogenic effects of ionising radiation and cytotoxic agents in the embryo are well known and depend on the dose, nature of the compound, treatment field and gestational stage.

a) Surgery

This represents a safe method of treatment, because it has robust evidence demonstrating the safety of surgical procedures and use of anaesthetics, during pregnancy. However, the risk of miscarriage is slightly incremented (1-2%), especially regarding the first trimester. In addition, there is a higher risk of low birth weight and premature delivery (1.5–2 times relative risk), an increased rate of complications and higher morbidity in major abdominal and pelvic procedures. Relatively to anaesthetic drugs, there is a record of good safety and none of them stands in the drug list of proven teratogens. Given the fact that there is a minimal risk to the foetus and potential benefits of the treatment, there should not be any delay on the surgery, if indicated.[11]

b) Radiotherapy

Regarding radiation, foetal exposure to doses higher than 50–100 mGy should be avoided. Below these doses, there is a low risk of stochastic biological effects (mutations), and non-stochastic effects (malformations, developmental disorders) are as frequent as in general population (3–5%).[4] In certain cases, it is necessary to use radiotherapy in the tumour, so the clinician must use it, in the period that it is least harmful to the foetus. From 2 to 12 weeks, the use of radiation has the risk of teratogenesis and growth retardation. Until 20 weeks, the foetus can present mental and growth retardation, microcephaly, eye, palate and genital deformities and beyond that, there is an increased risk of sterility, malignancies and genetic defects.[3]

c) Chemotherapy

The most sensitive and critical period of drug exposure is organogenesis, which occurs roughly 2 to 8 weeks post-conception[10], especially during the gastrulation period when tissues are differentiating rapidly, and damage becomes vast and irreparable.[13] Therefore, during the first trimester, the risk of spontaneous abortions, foetal death and major congenital malformations

are increased, reaching 10 to 20% and decline to about 6% when folate antagonists like methotrexate are excluded. The effects of antineoplastic agents during the second trimester are related to intrauterine growth restriction, low birth weight, miscarriage and premature birth (20-40%).[3] During the perinatal period, the effects are related to maternal/foetal myelosuppression, infections, and haemorrhage. Long-term outcomes of children exposed to chemotherapeutic agents in utero are not well examined. It is known that it is safe to give some drugs during the third trimester without causing long-term damage to the baby, for example for Hodgkin's disease or breast cancer.[14]

d) **Endocrine treatment**

Most of pregnancy-associated breast cancer have a higher likelihood of being hormone-receptors positive (positivity of oestrogen and progesterone receptors). However, in order to maintain a healthy pregnancy and foetal development, the physiological changes on the mother are mainly hormone driven. Consequently, the blockade of oestrogen (e.g., with tamoxifen), which is frequently used in hormone-positive breast cancer, might interfere with these physiological modifications and can be teratogenic and associated with birth defects. Therefore, hormonal treatment is contraindicated during pregnancy.[11]

e) **Targeted agents**

Most of these targeted agents commonly used in breast cancer, such as trastuzumab, bevacizumab, among others, should not be used because they present some undesirable adverse effects, but also due to the fact that there is missing much information yet. In general, human epidermal growth factor receptor 2 (HER2) agents are safe during the first trimester, although that through the second and third trimesters oligohydramnios, preterm delivery and neonatal deaths may be present. Rituximab, an anti-CD20, imatinib, an anti-Bcr-Abl tyrosine kinase, and ATRA, a trans retinoic acid, can be used with caution although they cross the placenta. Rituximab is safe in the first trimester, nevertheless, in the next trimesters, it causes cytopoenia and B cell depletion, reversible at birth, while imatinib is safe in second and third trimesters, with the risk of causing major malformations in the first trimester. ATRA is mainly dangerous in the first trimester due to the risk of abortion. The only targeted agent safe throughout pregnancy is interferon-α (IFN-α) (Table 1).[15]

f) **Immunotherapy**

A plethora of immunotherapy options are being used in the investigation and active treatment of several malignancies. Since it is so recent, there is not much information regarding the security of these drugs during human pregnancy. However, as we all know, mother and foetus are not genetically identical. Therefore, an immunological tolerance from the mother towards the foetus is necessary in order for the pregnancy to develop successfully.[11]

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Immune checkpoints, such as programmed cell death protein-1 (PD-1), PD-1 ligand (PD-L1), and cytotoxic T-lymphocyte–associated protein 4 (CTLA-4), play a crucial role in the process aforenamed. Consequently, the foetus can be harmed by an aggressive immune response after the inhibition of these immune checkpoints. Furthermore, the drugs that can inhibit the checkpoints are IgG4 antibodies that have the ability to cross the placenta and cause toxicity directly to the foetus. In animal models, these drugs demonstrated that their use could increase abortion rates, stillbirths, premature delivery and higher incidence of infant mortality, namely in the third trimester. However, there was not an increase on foetus malformations. In summary, since these drugs are so recent and have so little information regarding their security among pregnant women, immune checkpoint inhibitors are not recommended.[11]

g) **Supportive medication**

Our concern about pregnancy in women with cancer should not only focus on antineoplastic agents, but even on non-antineoplastic agents used in clinical cancer practice, such as bisphosphonates and granulocyte colony-stimulation factor (GCS-F).[11]

Because bisphosphonates inhibit bone resorption, they are used in the treatment of hypercalcemia, osteoporosis, metastatic bone disease, and Paget disease. The bisphosphonates inhibit osteoclastic bone resorption via a mechanism that differs from that of other antiresorptive agents. In addition to their inhibitory effect on osteoclasts, bisphosphonates appear to have a beneficial effect on osteoblasts. These biological effects can lead to reduce serum calcium in the maternal blood and its availability to the foetus, which might induce skeletal malformations, reduced bone growth and low birth weight. It can, inclusively, affect adversely parturition by reducing uterine contractions. Therefore, it is contraindicated during pregnancy.[11]

Regarding GCS-F, this agent is recommended in cases of severe neutropoenia or as primary/secondary prophylaxis during treatment with some chemotherapy regimens. Its safety during the pregnancy period is still unknown. However, in animal studies, it seems to cross the placenta and increase the rate of spontaneous abortion and low birth weight.[11]

4. The ethical issue: balancing interests

Pregnancy appears as an exceptional circumstance in medical ethics as the primary medical principle *Primum non nocere* can be questioned, as the access to the foetus occurs exclusively through intervention on the pregnant mother and treating the mother may imply harming the foetus. This is a unique situation since the welfare of both mother and foetus must be considered on any treatment planning.

When a conflict arises in the maternal-foetus dyad, caregivers must understand the pregnant woman´s mindset, broad social network, values, cultural and religious beliefs, as this may impact their decisions.[16] Consequently, it is imperative to promote the autonomy and physical integrity of the pregnant woman, ensuring that all available information on pregnancy and cancer outcomes is provided in order to allow for a fully informed consent consistent with her values[17] since the woman's decision is absolute and unlimited. Therefore, in cases when the woman's decision may harm her foetus (e.g., treatment of cancer during the first trimester) coercion to force treatment is never justified.

In the child-to-be perspective, there are extra layers of ethical complexity to address, because the antineoplastic treatment typically affects not only the pregnant woman but also the foetus. The developing foetus clearly has no capacity for autonomous choice, and there is no formula for balancing the interests and moral claims of the foetus with those of the mother. Furthermore, the welfare of the foetus is typically not independent of the interests of its mother.[18]

When a conflict arises in the maternal-foetus dyad, such as cancer treatment and the risk of foetal demise, a range of ethical frameworks may be useful in the decision-making process. It is clear that the physician has beneficence-based and autonomy-based obligation to the pregnant cancer patient.[19] Because of an immature central nervous system, the foetus cannot meaningfully be said to possess values and beliefs, although this is tremendously arguable.

Hence, scientifically there cannot be autonomy-based obligations to any foetus, although women's beliefs may hasten her to judge differently.[19] However, the physician can have beneficence-based obligations to the foetus, if the foetus is considered as a patient.[20] The pregnant woman is free to withhold patient status, confer patient status, or, after conferring it, withdraw it from her pre-viable foetus.[19] The foetus has no claim to patient status independently of the pregnant woman's autonomy. When the woman is uncertain about or is not able to confer the status, the foetus can be provisionally regarded as a patient.[19,20] However, these approaches have been criticised for their tendency to emphasize the divergent rather than shared interests of the pregnant woman and the foetus. In fact, in most cases, the interests of the pregnant woman and foetus actually converge.[17]

Whenever a pregnant woman is presented with a cancer diagnosis, several ethical concerns addressing technicalities must be approached, while keeping in mind the surrounding emotional issues.

There is no established *modus operandi* for the physician, which raises pertinent questions: (i) should the patient be included in the decision-making to the best of her abilities in a limited way, or should paternalistic decision-making take over? (ii) Should a proxy decision-maker decide based on the perceived patient's best interest?[21]

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To allow for an informed decision, the patient must be well aware of multiple medical facts, such as cancer prognosis, the possibilities of antineoplastic therapy, its main toxicities and its aim, namely: whether curative or palliative, if it will improve quality of life, or overall and progression-free-survival, if there is risk of preterm delivery or if peripartum complications are expected.

The timing of treatment must also be considered - is the mother symptomatic and needs to initiate treatment quickly or is it possible to delay it until the third trimester, when there is no significant risk for foetal defects in a short and long-term? Besides technical issues, before starting the treatment, the physician must consider emotional issues, such as the possibility of the child-to-be meeting its mother.

There are several established ethical frameworks for conflict resolution and decision-making. Pragmatic theoretical approaches include case-based analysis, the ethics of care, feminist theory, and traditional ethical principlism that scrutinises the framework of autonomy, justice, beneficence, and nonmaleficence. In addition, society and practitioner values could benefit this complex process.

5. Two case reports, illustrating the complexity of the bioethical dilemmas

For instance, the 1987 case of Angela Carder was paradigmatic: a 27-year-old woman, who had cancer relapse during her pregnancy, brought these issues to ahead. Although fully committed to saving her life, at the end of the second trimester, it became clear that the patient was dying. The Medical Centre tried to insist upon an early caesarean section delivery in order to save her foetus. She refused the intervention with the support of her family, knowing it would almost certainly kill her, but the hospital forced the delivery through a court order. Both the patient and her extremely premature baby survived for only a short while after the surgery. In 1990, the Court of Appeals posthumously vacated the court-ordered caesarean section, holding that the patient is totally autonomous to make healthcare decisions for herself and her foetus and that only in the most exceptional circumstances should a pregnant woman's right to refuse interventions be called into question.[22]

Despite the media exposure of this case, others with similar ethical issues were far from being elucidated.[23,24] Some authors advocate that, if pregnancy occurs while the patient is under endocrine treatment (e.g., tamoxifen) or chemotherapy, a pregnancy termination should be recommended if it is done in the first trimester.

In 2016, on February 20, 17-week-pregnant Sandra Pedro, 37 years-old, collapsed after an intracerebral haemorrhage, probably related to a kidney tumour she had been diagnosed with ten years prior and that had now relapsed.[25] Soon after physicians declared her brain dead.[26] The hospital ethics committee and the family were enquired. It was explained to both parties -

mother's family and the foetus's father - that, to allow for the foetus survival, the woman should be kept on life-sustaining treatment to reach at least its 32 weeks, the earliest date doctors felt that a successful caesarean delivery would be possible.[27] This emphasizes the role of the "mother's body as a cadaveric incubator", "mother as the organ donor and foetus as the recipient" and the concern for "possible damages to the foetus".[28,29] Some professionals believe that it is not ethically acceptable to maintain the mother's body after brain death to use it as a "foetal container." Such a decision should not be assumed, but it must be debated. If the mother is to be considered a "cadaveric incubator" with no autonomous rights, the rights of the foetus should legally prevail. Another argument claims that the continued somatic support itself is actually organ donation with the foetus as the recipient.[27] The family strongly expressed that the mother would have wanted her life preserved in order to give the foetus a chance for survival. The ethics committee equated the foetus life to a child at risk and allowed the support to the brain-dead mother.[25] The decision was taken in a meeting of the neurosurgical, critical care, obstetrics, neonatal, transplant and ethical staff, along with the patient's family. One hundred seven days later, the baby was born healthy, and the life-sustaining machines were turned off.[27]

Since the number of cases describing the management of extended maternal somatic support after brain death is limited, every case should be continuously reassessed and adapted along with the increasing experience and knowledge.[26]

In these difficult cases, mainly before the third trimester, the sovereign decision should be taken after thorough discussion between mother, father and the treating physician. While respecting the principle of autonomy, another final ethical issue is the right of the physicians to conscientiously object to certain treatment options.[30]

As stated before, physicians should not bias with their recommendations and should present to consider three scenarios: (i) treatment during pregnancy, with close monitoring for side effects and reconsideration of termination before viability; (ii) treatment with termination of the pregnancy and (iii) treatment delay until foetal lung maturity, when it's reasonably safe to deliver the baby avoiding the risk of treatment delay until full-term delivery.[20,31]

The available international guidelines recommend that maternal foetal medicine consultation should include counselling on maintaining or terminating a pregnancy, including a review of the treatment options. These guidelines support a framework of shared decision-making in the context of maternal-foetal conflict to provide guidance for compassionate conflict resolution. An ethics consultation may be helpful to mediate conflict resolution. Intervention by the courts is rarely appropriate or indicated and should be avoided.[17]

Based on a validated method for analysing and working up clinical ethical problems, we suggest an adaptation of an algorithm for biomedical decision making in cancer before the third trimester of pregnancy (Figure 1).[32]

The first task in this ethical decision-making process is to establish the medical and pregnancy facts of the case. The second step is to determine pertinent nonmedical issues, which is more challenging. These steps are followed by an assessment of the goods relevant in the case. The immediate concern is clearly what is suitable for the woman medically, but that is followed closely by an attempt to understand the patient's overall good -- e.g., psychological good, good in terms of family and relations, spiritual good, and good in terms of the patient's preceding life history and values. While ensuring the good of the woman is the primary aim, this is insufficient in itself, as the goods of foetus and others must also be considered.[32]

The principles that apply in the case at hand are then evaluated, specifying what a given principle means in this case and balancing it against the moral claims of each of the others. In themselves, principles can become mere abstractions, perhaps even sterile nostrums for dealing with these complex ethical dilemmas. Therefore, virtue ethics, another bioethical approach that has received increased attention in recent years, addresses the nature of the relationship between patient and healer, with particular attention to the character of the physician.[32] Pellegrino and Thomasma have presented a detailed analysis of how they interpret the virtues that are essential to medical practice. These virtues include phronesis, compassion, fidelity, trust, integrity, self-effacement, justice, fortitude, and temperance.[33]

In any case, a consideration of the virtues and principles on the one hand, and guidelines recommendations and prior similar cases analysis on the other, provide more guidance for a right answer to bioethical dilemmas.

Conclusions

Scientific and clinical data addressing the risks and the efficacy of treating a pregnant woman with cancer have already been explored in the literature. However, the surrounding ethical challenges have received less attention, particularly before the third trimester of pregnancy.

A pregnant woman with cancer faces the choice between best antineoplastic treatment versus maximal foetal welfare. Best, unbiased and balanced information about the benefits and harms for the woman herself as well as for foetal outcome must be granted both to the patient and to the family.

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Abbreviations

AFP – Alpha-fetoprotein;
AMH – Anti-Müllerian hormone;
ATRA – All-trans retinoic acid;
Bcr-Abl – Breakpoint cluster region protein-Abelson murine leukaemia viral oncogene homolog 1;
CA –Carbohydrate antigen;
CTLA-4 – Cytotoxic T-lymphocyte–associated protein-4;
GCS-F – Granulocyte colony-stimulation factor;
HE-4 – Human epididymis protein – 4;
HER2 – Human epidermal growth factor receptor 2;
IFN-α – Interferon alpha;
I-131 – Radioactive iodine;
IgG4 – Immunoglobulin G4;
LDH – Lactate dehydrogenase;
mGy – mili Gray units;
PD-1 – Programmed cell death protein-1;
PD-L1 – Programmed cell death protein-ligand 1;
PDGFR-α – Platelet-derived growth factor receptor alpha;
RAR – Retinoic acid receptor;
SCC – Squamous cell carcinoma;
TK – Tyrosine kinase;
US – Ultrasonography;
USA – United States of America.

Ethics approval and consent to participate

Not applicable.

Consent for publication

All co-authors have given their permission for publishing the manuscript, have read the submission and agree to be listed as co-authors.

Availability of data and material

Published literature was retrieved through searches in PubMed or Medline, CINAHL, the Cochrane and Google Academic. Results were restricted to review articles, ethical perspectives, clinical practice guidelines and case-based teaching guides.

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Author´s contributions

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Figure Legends

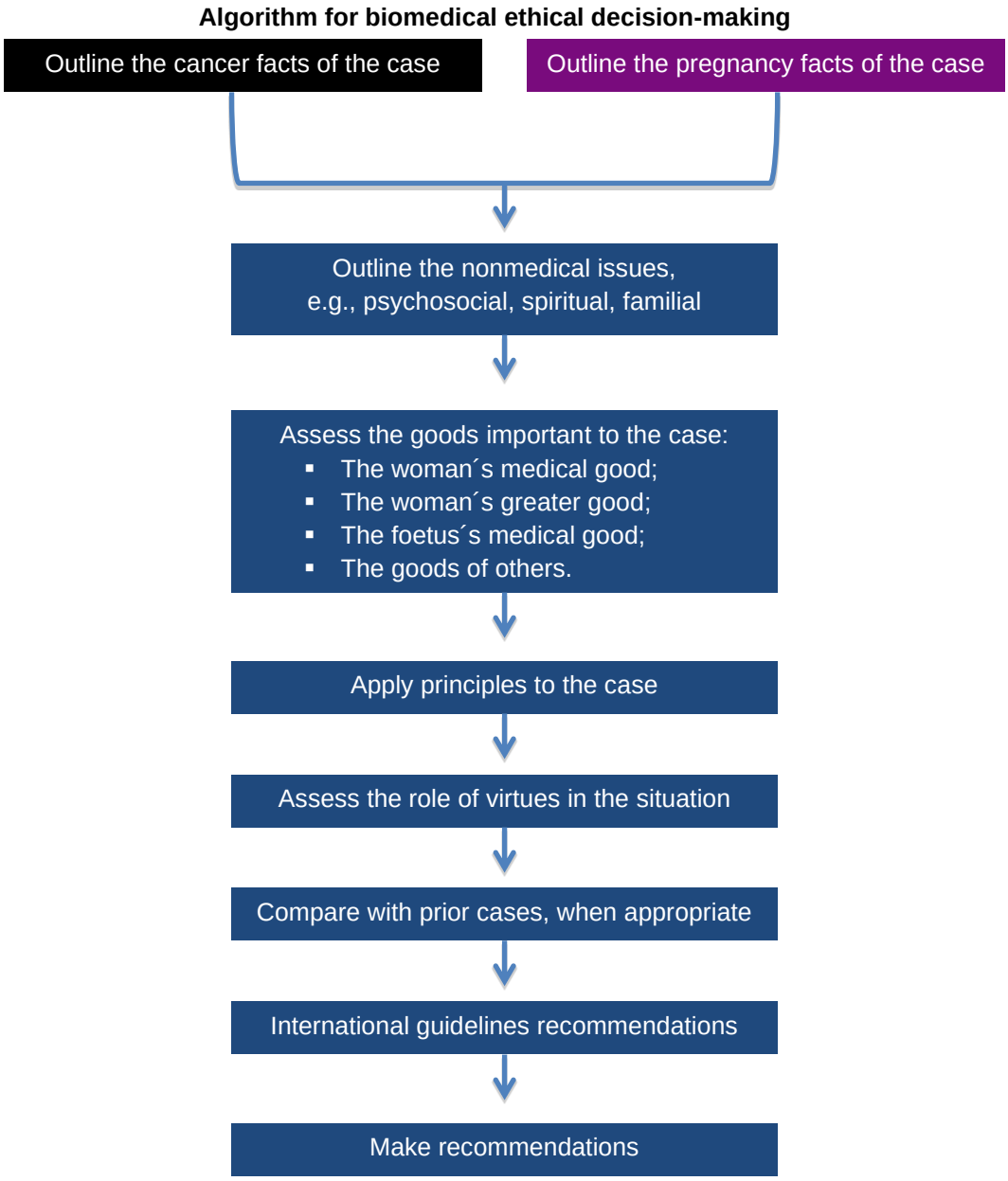

Figure 1. Algorithm for biomedical ethical decision-making.
Adapted from Cancer Control 2002 H. Lee Moffitt Cancer Center and Research Institute, Inc.

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Targeted agents and their effect on pregnancy

Agent	Potential effect on pregnancy	1st trimester	2nd / 3rd trimesters	Use during pregnancy
Trastuzumab	HER2 involved in cardiac and neural development, early conception and implantation phases	No congenital malformation	Oligohydramnios, preterm delivery and neonatal death	Not to use
Rituximab	CD20 important in the function of human lymphocytes	No congenital malformations	Cytopoenia and B-cell depletion at birth with recovery within days-few months	To use with caution
Imatinib	Bcr-Abl tyrosine kinase (TK), PDGFR-α and other TKs play a key role during organogenesis	Major malformations (skeletal defects with or without urogenital malformations)	No adverse effects	To use with caution
ATRA	RAR plays a key role in foetal development	Induced and spontaneous abortions but no congenital malformations	No major complications	To use with caution
IFN-α	Pleiotropic cytokine involved in embryonic development and implantation phase	No adverse effects	No adverse effects	To use throughout pregnancy

Table 1. Targeted agents and their effect on pregnancy (adapted from Lambertini M, et al.[15]).
Abbreviations:
ATRA, all-trans retinoic acid; Bcr-Abl, breakpoint cluster region protein-Abelson murine leukaemia viral oncogene homolog 1; HER2, human epidermal growth factor receptor 2; IFN-α, interferon alpha; PDGFR-α, platelet-derived growth factor receptor alpha; RAR, retinoic acid receptor; TK, tyrosine kinase.