Discussing motherhood when the oncological prognosis is dire: ethical considerations for physicians

Alma Linkeviciute, Barbara Buonomo, Nicola Fazio, Francesca Spada, Fedro A Peccatori

Abstract
Physicians are increasingly open to discussing and supporting pregnancy after cancer treatment. However, counselling patients who are seeking pregnancy despite advanced oncological disease and/or uncertain prognosis is still challenging. Two paradigmatic cases are presented and analysed to illustrate the ethical uneasiness faced by treating physicians when seriously ill patients seek fertility preservation and/or pregnancy. Review of ethical issues is built around the four principles of biomedical ethics. Respect for patients autonomy in relation to managing realistic expectations and avoiding giving patients false hopes opens the analysis. It is followed by considering fair allocation of resources and meaningful distinction between protecting patients from harm and contributing to their welfare. Responsibilities towards the unborn child are discussed in a light of maternal and fetal interdependency. Respecting personal autonomy requires abstaining from controlling inferences to the individual patient’s choices, but it does not mean that patients should be left on their own to pick and choose their disease management approaches without advice and guidance from healthcare professionals. Physicians should reason evaluating the potential harms and checking if benefits will outweigh the risks and if costs will produce the best overall results. Responsibilities towards the unborn child can be managed by balancing the respect for maternal autonomy and beneficence for pregnant woman and her fetus. The oncologist cannot determine how patients should view their disease but with empathy and compassion can help them understand the logical rationale behind clinical advice.

Introduction
Great advances have been made in the field of oncology during the last decades, with consistent improvement of disease-free survival or overall survival for the most frequent cancers in women of the reproductive age. Thus, discussions about quality of life need to address also pregnancy issues that are highly valued by young women with cancer. Most guidelines recommend an oncofertility counselling to all young patients with cancer, but while physicians seem to be increasingly open to discussing and supporting pregnancy after cancer treatment, unsolved questions remain. Available evidence, including large cohort studies, show that pregnancy after cancer does not impair the oncological prognosis, but this mainly refers to patients who have undergone a curative treatment. Guidelines for patients with high risk or metastatic tumours are not available. Thus, patient counselling can become troublesome when physicians are talking to patients with a dire prognosis where these patients are seeking fertility preservation (FP) or pregnancy despite uncertain future.

The aim of this paper is to provide a review and offer a perspective about ethical issues faced by oncologists and experts in reproductive medicine when patients seek to exercise their reproductive autonomy against the odds of uncertain prognosis.

Case Presentation
To illustrate the ethical uneasiness that physicians face in such situations, we would like to present two cases from our practice.

Case 1
A 24-year-old single woman was diagnosed with a typical pulmonary carcinoid with hepatic metastases. The patient underwent fertility counselling and expressed interest in oocyte cryopreservation. She was treated with the somatostatin analogue (SSA) octreotide long-acting release (LAR). Her disease was stable at the time of oncofertility counselling, and she was waiting for the first cycle of peptide receptor radionuclide therapy (PRRT) with 177Lu-DOTATATE ([177Lu-DOTA-Tyr3]-octreotate). Several fertility issues in the context of her disease were discussed, particularly the unknown gonadotoxic effects of PRRT and the risks of tumour growth potentially induced by controlled ovarian stimulation (COS). In April 2019, she underwent COS using a gonadotropin-releasing hormone antagonist short protocol. On the day of oocyte retrieval, 15 mature oocytes

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1 Department of Gynaecologic Oncology, European Institute of Oncology IRCCS, Milano, Italy
2 Division of Gastrointestinal Medical Oncology and Neuroendocrine Tumors, European Institute of Oncology IRCCS, Milano, Italy

Correspondence to
Dr Fedro A Peccatori; fedro.peccatori@ieo.it
were harvested. The procedure was well tolerated. Then, in May 2019, she started PRRT. At present, her disease is stable, and she remains asymptomatic. She is still not interested in thawing her frozen oocytes.

Case 2
A 28-year-old married woman was diagnosed with pancreatic neuroendocrine tumour and carcinoid syndrome. In March 2008, she underwent duodenal cephalopancreatico-cestomy. Then, she started medical therapy with octreotide LAR until 2009. In September 2010, the patient presented with flushing and diarrhoea. A CT scan revealed a hepatic focal lesion, confirmed by OctreoScan. She resumed octreotide LAR and underwent four cycles of PRRT. Her disease was stable, and she was asymptomatic until September 2017 when she decided to stop therapy to attempt a pregnancy. The patient was informed within a multidisciplinary consultation about the possible maternal risks of pursuing a pregnancy and withdrawing SSA. She was also informed about the paucity of clinical data on the effects of octreotide LAR on fetal integrity and growth. After onset of pregnancy, she did not experience a significant worsening of symptoms, and the disease remained stable until today. In June 2019, a healthy male infant was delivered at term by caesarean section without complications.

REVIEW OF ETHICAL ISSUES
Managing conversation about reproductive issues when the prognosis is dire could be very hard. These two cases are paradigmatic. In the first case, we have a patient who expressed interest in FP: for her, preserving fertility meant the possibility of becoming a mother in the future, even if her prognosis remained quite uncertain at the time of the procedure. The patient considered FP as a source of comfort and reassurance that her life might return to normal, even if she understood that the opportunity to conceive in the future was quite dim. Conversely, oncologists and reproductive endocrinologists felt that the enthusiasm for FP could also be seen as a source of false hope and unfair allocation of resource, with the only objective of boosting short-term emotional well-being of a seriously ill patient.

Respect for autonomy is one of the core principles in biomedical ethics, which emphasises personal liberty and agency as core values allowing self-rule, self-management and self-creation. The concept evolved from the principle of ‘respect for persons’ found in the Belmont Report, which to this day remains one of the main documents regulating biomedical and behavioural research. Ethical principles for research, however, cannot be considered equivalent to ethical principles for everyday clinical practice because patients do not volunteer for medical care potentially without benefit for themselves as they would do if taking part in research studies. They need medical care and evidence-based treatment to get better because their well-being is compromised by illness.

Therefore, critics observed that over the time, ‘respect for autonomy’ has lost its scope and purpose and sometimes is perceived inadequately in public debates. Just as if it has been displaced leaving aside the person whose autonomy is expected to be respected and singling out the autonomy itself. Respecting personal autonomy indeed requires abstaining from controlling inferences to the choices an individual wishes to make. Building on Beauchamp and Childress’s work that has been developed, updated and upgraded over a few decades, it is increasingly being recognised that patient’s autonomy, especially where reproductive choices are concerned, does not exist just as an abstract principle. Patient’s wishes to follow certain treatments can be influenced by her social interactions, perceived societal expectations and desire to create a self-narrative allowing to become a certain kind of person in the future.

Research has shown that preserving ability to have children in the future is important for cancer patients, and it is widely agreed that FP options should be discussed with all cancer patients no matter what their individual circumstances are. However, little has been written about conversations with patients where FP might not be the first choice from a clinical point of view, or where the physician does not agree with the procedure. Respect for autonomy appears to have become an attempt to make all possible choices available to the patient even if these are not cost-effective and might even result in difficult choices in the future.

This opens the door to another ethical issue when counselling cancer patients with uncertain prognosis: nurturing a hope to get better vs facilitating a false hope. Even though there are large cohort studies available that show that pregnancy after cancer does not compromise maternal and fetal outcomes, it is important to stress that most cancer patients who proceed to carry a pregnancy achieved a curative outcome following their cancer treatment and have been in generally good health. There are some studies reporting a 20%–44% higher abortion rates among cancer survivors as compared with general population, which suggests that some patients with cancer might reconsider their reproductive choices even in a light of good prognosis.

Generally speaking, the option of having children in the future indicates that patient’s life might return to normality, and this could help in maintaining a positive attitude during the cancer treatment. However, this premise only holds if we disregard all other ways to have a meaningful life, including looking after children other than one’s own, adoption, foster care, supporting friends and relatives with childcare needs and working or volunteering in formal and informal education settings. These options are rarely mentioned or discussed in the FP counselling, rather the difficulties cancer survivors might encounter when trying to adopt are used as arguments to support FP. Nevertheless, FP should not be used as a form of therapy to provide patients with ‘options’ for a wider range of choices in the future because such
practice is ethically problematic. First, it nurtures false expectations and even has a potential to impair patient’s autonomy because she will be planning her future on false presumptions. Second, it creates a problem of fair allocation of resources in healthcare systems where PF is universally funded for all patients with cancer or results in a futile financial burden where PF is self-funded. Patients will be expecting the highly unlikely outcomes, which if not impossible, would be risky to their own health and also the health of their offspring. In addition, it would prevent other patients of getting the services they need due to limited resources in a universally funded healthcare system or would require significant financial commitment from very ill patients with cancer to self-fund PF, which is unlikely to result in motherhood.

The latter leads to a broad non-maleficence and beneficence debate where healthcare team has to balance their obligations to the patient not to harm her and to contribute to her welfare. This is a difficult balancing act for any healthcare professional and more so in oncofertility care where some questions do not have the robust evidence-based answers. The biomedical ethics principle of non-maleficence is usually placed before the principle of beneficence meaning that obligation not to harm prevails the obligation to contribute to one’s welfare. However, Beauchamp and Childress also agree that attending to patient’s welfare and not merely avoiding harm is the goal and rationale of medicine. Further elaboration on what beneficence entails helps to make a meaningful distinction between protecting patients from harm and contributing to their welfare. Patients have a right to act in ways that would inflict harm to them, for example, refuse treatment, seek alternative care or disregard healthy behaviours. Healthcare team might not always be able to intervene and prevent such harms. For example, if a cancer patient with uncertain prognosis decides to stop her cancer treatment in order to conceive and subsequently does, she can autonomously choose to carry the pregnancy against her doctor’s advice. However, if medical intervention is needed to help such patient to conceive, the doctor can reason evaluating the potential harms and checking if benefits will outweigh the risks and if costs will produce the best overall results.15

The second patient was very much determined to become a mother. For her, uncertainty about the potential risks related to the interruption of therapy was not a barrier to motherhood. Her physicians, however, were concerned about the need of interrupting SSA, about the impact her pregnancy will have on the growth of the liver metastases and about the possible pregnancy complications (including premature birth or intrauterine growth restriction), which could affect neonatal outcomes. Moreover, some of her healthcare providers raised the issue of leaving a minor child bereft of one parent, if the tumour was going to overgrow because of the pregnancy.

Many physicians feel uneasy about their responsibilities towards the unborn child, who indeed can be seen as vulnerable and in need of protection. However, distinguishing a pregnant woman and her fetus as two different entities could be inappropriate, because until the child is born, mother and fetus are interdependent. Therefore, careful balancing of respect for maternal autonomy and beneficence for pregnant woman and her fetus are considered two key principles in cancer care of pregnant women.26 27 One could argue that it might be unethical to enable people to reproduce in situations in which the parent faces a greatly lowered life span or ability to care for a child.28 However, also the American Society for Reproductive Medicine concludes that the argument citing child’s welfare as a reason against reproduction is not persuasive. First, the risk of recurrence is difficult to estimate in a given patient; second, the child will likely have a meaningful life even if he or she loses a parent; and third, children experience stress and sorrow from a variety of circumstances in their lives that might be comparable with a parental death.28

**DISCUSSION**

Conversations with patients with cancer who have high-risk oncological diseases or metastatic cancer can turn troublesome when FP and pregnancy are brought to the discussion by the patients. Even though currently available treatments might allow a prolonged life without symptoms, the best approach to counsel such patients is still under discussion. The main obstacles faced by healthcare professionals are lack of robust evidence-based data, clinical uncertainty and ethical issues surrounding patient consultations. Even though respecting personal autonomy requires abstaining from controlling inferences to the individual patient’s choices, it does not mean that patients should be left on their own to pick and choose their disease management approaches without advice and guidance from healthcare professionals. FP should not be used as a form of therapy to provide patients with ‘options’ for a wider range of choices in the future because it creates false expectations and may require futile financial investment. Physicians should reason evaluating the potential harms and checking if benefits will outweigh the risks and if costs will produce the best overall results. Responsibilities towards the unborn child can be managed by balancing the respect for maternal autonomy and beneficence for pregnant woman and her fetus. The oncologist cannot determine how patients should view their disease but can help them understand the logical rationale behind clinical advice. Compassion to patient’s fears and suffering, recognition of the patient as another human being, physical and emotional presence in the conversation with the patient can help to have a meaningful fertility counselling session with patients in advanced stages of their disease, who are looking to make risky reproductive choices.

Twitter Fedro A Peccatori @phaedro

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ORCID iDs
Alma Linkeviciute http://orcid.org/0000-0001-8988-7581
Fedro A Peccatori http://orcid.org/0000-0001-8227-8740

REFERENCES
1 Globocan. Breast [Internet]. 2019. Available: https://gco.iarc.fr/today/data/factsheets/cancers/20-Breast-fact-sheet.pdf [Accessed 28 Jul 2020].

2 Peccatori FA, Azim HA, Orecchia R, et al. Cancer, pregnancy and fertility. ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2013;24:v160–70.

3 Oktay K, Harvey BE, Partridge AH, et al. Fertility preservation in patients with cancer: ASCO clinical practice guideline update. JCO 2018;36:1994–2001.

4 Tang M, Webber K. Fertility and pregnancy in cancer survivors. Obstet Med 2018;11:110–5.

5 Paluch-Shimon S, Cardoso F, Partridge AH, et al. ESO-ESMO 4th International consensus guidelines for breast cancer in young women (BCY4). Annals of Oncology 2020;31:674–96.

6 Rosenberg SM, Gelber R, Gelber RD, et al. Oncology physicians’ perspectives on practices and barriers to fertility preservation and the feasibility of a prospective study of pregnancy after breast cancer. J Adolesc Young Adult Oncol 2017;6:429–34.

7 Lambertini M, Fontana V, Massarotti C, et al. Prospective study to optimize care and improve knowledge on ovarian function and/or fertility preservation in young breast cancer patients: results of the pilot phase of the pregnancy and fertility (prefer) study. Breast 2018;41:51–6.

8 Mascioli MC, Bartholomew AJ, Haslinger M, et al. Physician perspectives on fertility preservation discussions with premenopausal breast cancer patients: results from a multisite health care system. Ann Surg Oncol 2019;26:3210–5.

9 Choi M, Han J, Yang BR, et al. Prognostic impact of pregnancy in Korean patients with breast cancer. Oncologist 2019;24:1268–76.

10 Lambertini M, Ameye L, Hamy A-S, et al. Pregnancy after breast cancer in patients with germline BRCA mutations. J Clin Oncol 2020;38:3013–22.

11 Linkeviciute A, Boniolo G, Chiavari L, et al. Fertility preservation in cancer patients: the global framework. Cancer Treat Rev 2014;40:1019–27.

12 Linkeviciute A, Notarangelo M, Buonomo B, et al. Breastfeeding after breast cancer: feasibility, safety, and ethical perspectives. J Hum Lact 2020;36:40–3.

13 Catania C, Del Signore E, Spitaleri G. The desire for life and motherhood despite metastatic lung cancer. JAMA Oncol 2019;5:1537.

14 Fuchs AB, Brannigan RE. Disparities in Adolescent Patient–Provider Communication Regarding Fertility Preservation Care. In: Woodruff TK, Clayman ML, Wainscoat JE, eds. Oncofertility communication: sharing information and building relationships across disciplines. New York, NY: Springer New York, 2014: 111–20. http://link.springer.com/10.1007/978-1-4614-8235-2

15 Beauchamp TL, Childress JF. Principles of biomedical ethics. 7 edn. Oxford: Oxford University Press, 2013.

16 Department of Health, Education, and Welfare. National commission for the protection of human subjects of biomedical and behavioral research. The BELMONT report office of the Secretary ethical principles and guidelines for the protection of human subjects of research., 1979. Available: https://www.hhs.gov/ohrp/sites/default/files/the-belmont-report-508c_FINAL.pdf [Accessed 28 Jun 2020].

17 Lysaught MT. Respect: or, how respect for persons became respect for autonomy. J Med Philos 2004;29:665–80.

18 DeGrazia D. Human identity and bioethics. Cambridge: Cambridge University Press, 2005.

19 Snyder KA, Thazin MK, Pearse WB, et al. The Fertility-Related Treatment Choices of Cancer Patients: Cancer-Related Infertility and Family Dynamics. In: Woodruff TK, Zoloth L, Campo-Engelstein L, et al, eds. Oncofertility: ethical, legal, social, and medical perspectives. Boston, MA: Springer US, 2010: 413–28. http://link.springer.com/10.1007/978-1-4419-6518-9

20 Goncalves V, Sehovic I, Quinn G. Childbearing attitudes and decisions of young breast cancer survivors: a systematic review. Hum Reprod Update 2015;21:112–27.

21 Linkeviciute A, Oncofertility PFA. Oncofertility. In: Ethical counselling and medical decision-making in the era of personalised medicine: a practice-oriented guide. Springer: Springer Nature, 2016: 97–104.

22 Lambertini M, Anserini P, Levaggi A, et al, eds. Fertility counseling of young breast cancer patients. J Thorac Dis 2013;5:S68–80.

23 Backhus LE, Zoloth L. Today’s Research, Tomorrows Cures: The Ethical Implications of Oncofertility. In: Woodruff TK, Snyder KA, eds, eds. Oncofertility: fertility preservation for cancer survivors. Boston, MA: Springer US, 2007: 163–79. http://link.springer.com/10.1007/978-0-387-72293-1

24 Quinn GP, Stearsman DK, Campo-Engelstein L, et al. Preserving the right to future children: an ethical case analysis. Am J Bioeth 2012;12:38–43.

25 Gardino SL, Russell AE, Woodruff TK. Adoption After Cancer: Adoption Agency Attitudes and Perspectives on the Potential to Parent Post-Cancer.. In: Woodruff TK, Zoloth L, Campo-Engelstein L, et al, eds. Oncofertility: ethical, legal, social, and medical perspectives. Boston, MA: Springer US, 2010: 153–70. http://link.springer.com/10.1007/978-1-4419-6518-9

26 Chervenak FA, McCullough LB, Knapp RC, et al. A clinically comprehensive ethical framework for offering and recommending cancer treatment before and during pregnancy. Cancer 2004;100:215–22.

27 Linkeviciute A. Caring for pregnant cancer patients. In: Schmitz D, Clarke A, Dondorp W, eds. The fetus as a patient: a contested concept and its normative implications. Routledge, 2010: 153–70. https://www.routledge.com/The-Fetus-as-a-Patient-A-Contested-Concept-and-its-Normative-Implications/Schmitz-Clarke-Dondorp/p/book/9780367591373

28 Ethics Committee of the American Society for Reproductive Medicine. Fertility preservation and reproduction in cancer patients. Fertil Steril 2005;83:1622–8.