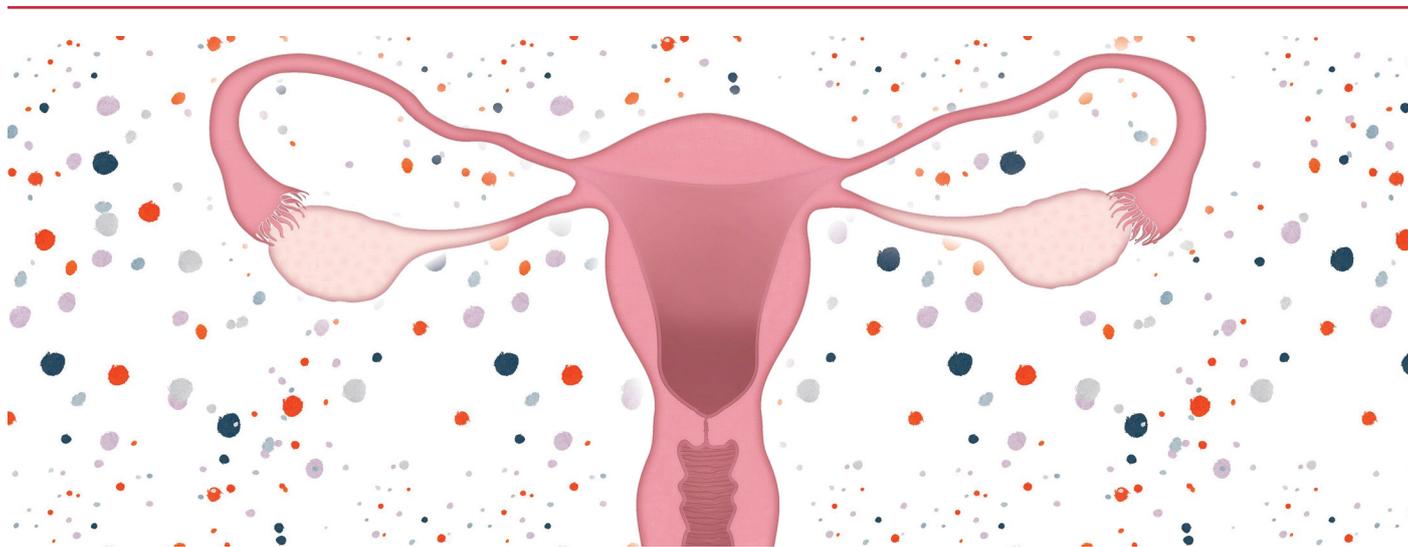


# Is it ethically justifiable for oncologists to deny female breast cancer patients of fertility preservation options prior to cancer treatment based on their pre-conceived concerns?

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Recent advances in cancer therapeutics has led to an exponential rise in the number of female cancer patients in reproductive ages surviving cancer, which raises the issue of post-treatment quality of life (QOL). Reports reveal that some oncologists have not been adhering to guidelines set out by the National Institute for Health and Care Excellence (NICE) in supporting routine fertility preservation consultation (FPC) prior to these patients undergoing gonadotrophic cancer treatments. From current research, some clinicians' presumptions and lack of knowledge of medical advances are hindering them from informing patients of the risks gonadotrophic therapeutics have on fertility and the various fertility preservation options available. This is impeding patients' right to autonomy, thus going against the principle of non-maleficence. The aim of this paper is to analyse the reasons why some clinicians do not provide crucial information about fertility to female cancer patients and whether the ethical implications it has on patient safety are justifiable.

## Introduction

Improvements in early diagnosis and therapeutic options in the last 40 years has led to an increase in survival rates, including those of female cancer patients of the reproductive age. Thus, adequate post-treatment quality of life (QOL) is increasingly significant.<sup>1</sup>

Cancer therapy, including chemotherapy, can cause off-target gonadotrophic effects leading to premature ovarian failure and, in some cases, permanent infertility.<sup>2</sup> Several international studies have recommended that an additional decision-making process, called fertility preservation consultation (FPC), is added in order to improve QOL.<sup>3</sup> As a result, the National Institute for Health and Care

Excellence (NICE) have published guidelines that ask for oncologists to discuss ways of improving long-term QOL for cancer patients, such as fertility preservation, before the commencement of gonadotrophic cancer treatment.<sup>4</sup> There are several fertility preservation options currently available, including embryo cryopreservation and oocyte cryopreservation.<sup>5</sup>

Despite the evidence and guidelines, many cancer patients of the reproductive age still do not receive adequate information about fertility preservation options or undergo FPC.<sup>6</sup> A UK survey on breast cancer patients found that up to 88% were not referred to fertility reproductive specialists and were uninformed of the adverse effects that chemotherapy would have on fertility.<sup>7</sup> In addition, a recent systematic review found that only 41–44% of adult breast cancer patients felt that their fertility concerns were adequately discussed.<sup>8</sup> Research indicates that these unmet needs have led to psychological distress in patients.<sup>9</sup>

The aim of this article is to highlight the reasons why some oncologists are not adhering to NICE guidelines on counselling female cancer patients on the side-effects of their treatment on fertility or referring them for fertility preservation treatments, and to discuss the ethical implications this has on patients.

## Methods

A comprehensive search was performed using PubMed, NICE evidence and google scholar to find articles and journals published between 2009 and 2019. The following search terms were used: "fertility preservation", "female breast cancer patient", "ethical

communication” and “oncologists”. Reference lists of chosen studies were screened for other potentially relevant publications.

Studies included were prospective, retrospective, randomised controlled trials (RCTs), population studies and meta-analyses. To minimise selection bias, studies that did not focus on breast cancer patients were excluded. In addition, generic google searches using the same inclusion criteria stated above were also carried out to find suitable websites and news articles to obtain information on patient perspectives.

## Results

### Concerns associated with fertility preservation

**Delay of cancer treatment** UK guidelines emphasised that at the time of diagnosis, clinicians should discuss the potential risk of infertility caused by cancer treatment.<sup>4</sup> However, this is not being consistently adhered to.<sup>6</sup>

In line with the principle of beneficence, which is to act in the best interest of the patient, several clinicians believe that it is justifiable to withhold information from women about fertility preservation options so that it would not cause delays in cancer treatment.<sup>10</sup> A recent survey carried out in doctors from across the world found that over one-third of clinicians have never consulted the guidelines on this topic.<sup>11</sup> One study found that the reason behind these types of actions by clinicians was owing to their beliefs that fertility preservation procedures would be time consuming and that initiation of treatment should be the priority instead.<sup>12</sup>

Recent literature has aimed to tackle this apparent time pressure to complete fertility preservation.<sup>13</sup> A novel treatment regime, called random-start ovarian stimulation, has been developed, which reduces the duration of ovarian stimulation, from 4 to 2 weeks, with the same success rates.<sup>14</sup> Similarly, a recent study by Kitano et al in 2019, with the largest sample of cases to date, found that undergoing fertility preservation was not associated with treatment delay in breast cancer patients.<sup>15</sup> Researchers have emphasised that early referral for fertility preservation is paramount for the procedure to occur in a timely manner. Therefore, this evidence should reduce concerns about perceived delays in cancer treatment, enabling more female cancer patients to undergo fertility preservation.<sup>16</sup>

**Breast cancer reoccurrence or proliferation** As breast cancer is the most prevalent cancer among reproductive women in the UK, many ethical concerns surround fertility preservation in this population of patients.<sup>17</sup> Previously, for fertility preservation, high levels of oestrogen were required for controlled ovarian hyperstimulation (COH) before oocyte and embryo cryopreservation can occur. Clinicians have speculated that these high levels of oestrogen may have negative consequences for ~60% of breast cancer patients who are ‘oestrogen-receptor (ER)-positive’. This means that their cancer cells grow in response to the hormone oestrogen, potentially leading to cancer reoccurrence.<sup>18</sup> Therefore, some doctors believe that allowing this to occur goes against the principle of non-maleficence as it may be deemed as unsafe practice.<sup>19</sup>

In a new study, novel protocols for fertility preservation that contain aromatase inhibitors, such as letrozole, in combination with gonadotrophins decreased the high levels of oestrogen previously observed during COH, whilst still allowing the collection of multiple oocytes. However, there were several limitations to this study, including small sample size, short time of monitoring and methodological issues, such as failure to report data on demographics.<sup>20</sup> Data from larger cohort studies showed promising results in that there was no difference in cancer reoccurrence in patients who did not undergo COH using aromatase inhibitors alongside gonadotrophins in comparison with those who did. Based on this evidence, the above method is now routinely used for ER-positive breast cancer patients undergoing oocyte

cryopreservation.<sup>21,22,23</sup> However, recent alternative methods, such as retrieval of immature oocytes after in vitro maturation, which requires no treatment to stimulate the ovaries, could pave the way for a preferable method for fertility preservation in breast cancer patients.<sup>24</sup> With implementation of these novel protocols being deemed safe based on recent evidence, doctors’ concerns over patient safety (non-maleficence) associated with COH should be reduced, promoting FPC to take place.

**Poor prognosis** Data from a survey revealed that oncologists found discussions related to the risk of infertility and fertility preservation options challenging and uncomfortable to have with female cancer patients who have poor prognosis for survival.<sup>25,26</sup>

In certain cases, a female cancer patient may die before the use of her stored gametes or ovarian tissue. With her consent, fertility preservation may be used to conceive a child following the death of the patient, otherwise known as posthumous assisted reproduction (PAR). Some doctors have raised concerns about whether it is ethically justifiable to allow a child to be conceived in these circumstances, knowing that the parent has a decreased life expectancy and may die prior to the birth of the child.<sup>27</sup>

PAR may be a legitimate procedure under the ethical principles of beneficence and autonomy. The European Society for Human Reproduction and Embryology (ESHRE) have stated that PAR is permitted within the conditions that: (1) written consent is collected; (2) the surviving partner is notified and thoroughly informed of possible future implications; and (3) treatment is initiated within a 5-year span after death of the parent. These outlines are useful; however, they do not mitigate how very challenging this topic is.<sup>28</sup> Therefore, each individual case must undergo considerable ethical analysis to weigh up the advantages and disadvantages of PAR, without any preconceptions from the doctor preventing key discussions with patients and their families.<sup>26</sup> More research is needed on the outcomes of PAR in children born as a result of PAR and their families, as limited data is available on this crucial topic.

## Conclusion

In conclusion, pre-conceived beliefs held by some oncologists, which hinder them from abiding to NICE guidelines, go against the ethical principle of autonomy. There is strong evidence that denying FPC to female cancer patients is correlated with a further decrease in QOL and psychological distress, which may affect their compliance to future treatment, leading to patient safety risks.<sup>9</sup> Data from several systematic reviews highlight the critical need for clinicians to provide timely, detailed and accurate information on the side effects of cancer treatments with regards to fertility, and the options for fertility preservation available to female cancer patients of reproductive age.<sup>8,9,20</sup>

Clinicians should be encouraged to continuously keep up to date with knowledge surrounding current protocols available for fertility preservation. This will aid them in supporting patients’ overall decision making and maximise opportunities for patients to have more cycles of COH prior to gonadotropic treatment plans.<sup>29</sup> Future research should aim to use larger sample sizes, novel methodology and longitudinal monitoring to analyse the concerns and experiences of female cancer patients with fertility preservation, which may lead to a deeper understanding of this crucial subject area.<sup>30</sup>

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