Original Article

Utilisation of Cryopreserved Gametes in Cancer Patients who Underwent Fertility Preservation

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Abstract

Background: Cancer treatments such as chemotherapy and radiotherapy often compromise fertility by damaging gonadal function, creating a critical need for fertility preservation options. Despite advancements in fertility preservation techniques, there is a significant lack of research focused on their application in Asian cancer patients and their utilisation remains underexplored in this population. **Aim:** This study aims to evaluate the utilisation rates and outcomes of cryopreserved gametes in cancer patients who underwent fertility preservation before their cancer treatment. **Settings and Design:** This retrospective study was conducted at our hospital from January 2003 to May 2023. It investigated the utilisation of cryopreserved gametes in 557 male patients aged 15–50 years and 39 female patients aged 15–40 years who opted for fertility preservation before chemotherapy or radiotherapy. **Materials and Methods:** Data were retrospectively collected, including patient demographics and fertility preservation outcomes. Various fertility preservation methods were employed based on patient suitability and availability. Participants were surveyed to identify reasons for non-utilisation of cryopreserved gametes. All data were collected and analysed following institutional ethical guidelines. **Statistical Analysis Used:** Descriptive statistics were used to calculate utilisation rates and report clinical pregnancy and live birth rates. Reasons for non-usage were categorised into mortality, spontaneous pregnancies, financial constraints and social factors. **Results:** Out of 596 participants, only 11 utilised their cryopreserved gametes, yielding a utilisation rate of 1.8%. Among those who used their gametes, clinical pregnancy rates were 66.66% for males and 50% for females, with live birth rates of 33.33% for males and 50% for females. Non-usage was primarily due to mortality, spontaneous pregnancies, financial constraints and social issues. **Conclusion:** The utilisation rate of cryopreserved gametes was low at 1.8%. Challenges such as mortality, financial constraints and social factors highlight the need for improved counselling and a refined approach to fertility preservation, ensuring services better align with patients' future needs.

Keywords: *Assisted reproductive technologies, cancer, cryopreserved gametes, fertility preservation, oncofertility*

Introduction

Cancer remains a significant global health challenge with millions of new cases and deaths each year. Although advances in medical sciences have led to easier and better detection of the disease and newer

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treatment strategies have evolved improving the survival rates, cancer still remains significant global burden.[1,2]

The World Health Organization and the International Agency for Research on Cancer reported a growing global cancer burden estimating 20 million new cases and 9.7 million deaths in 2022. Lung, breast and colorectal cancers were the most common, with stark inequities observed in cancer burden by the human development index. Predictions for 2050 indicate a 77% increase in cases emphasising the urgent need for equitable cancer care globally.[3]

In 2022, the projected incidence of cancer cases in India was approximately 1,461,427 (with a crude incidence rate of 100.4 per 100,000 population). The most prevalent types of cancer among men and women in India are lung and breast cancer, respectively. Forecasts suggest a 12.8% increase in cancer incidence in 2025 relative to 2020.[4]

In the reproductive age group in India, the primary reproductive cancers affecting females include cervix, ovary and corpus uteri cancers constituting around 25% of total cancer cases among females. For males, the significant contributors would be prostate, penile and testicular cancers making up about 9% of total cases. The choice of treatment varies by cancer type, with combinations of radiotherapy, chemotherapy, surgery and hormone therapy being common.[5]

Chemotherapy and radiotherapy can adversely affect gonadal function potentially causing temporary or permanent infertility by damaging the DNA of gametes and impairing hormone production essential for reproduction. The degree of gonadal damage varies with the treatment modality, dosage and the patient's age with a higher likelihood of gonadal function recovery in younger individuals. Pre-treatment fertility preservation is vital for those desiring future parenthood. Cancer treatments may lead to persistent harm to primordial sperm cells, manifesting as oligospermia or azoospermia. Chemotherapeutic agents, known to attack cells with a high mitotic activity, can traverse the blood-testis barrier and damage the germinal epithelium. While chemotherapy-induced Leydig cell failure and consequent androgen insufficiency are rare, most male cancer survivors experience normal puberty and maintain standard levels of circulating testosterone.[6-8] Chemotherapy has toxic effects on the ovaries and causes the loss of the primordial follicle reserve.

Fertility preservation represents a medical strategy designed to protect an individual's future reproductive potential, particularly beneficial for those facing treatments potentially detrimental to fertility. This approach aims to ensure the feasibility of biological parenthood post-treatment that poses risks to reproductive function.[9] In females, techniques for preserving fertility encompass embryo cryopreservation, oocyte cryopreservation, ovarian tissue cryopreservation (OTC) and *in vitro* maturation of immature oocytes.[10] Fertility preservation in males comprises techniques such as sperm banking, testicular shielding, testicular sperm extraction and testicular tissue freezing aimed at safeguarding future reproductive potential.[11] Over the past two decades, female fertility preservation methods have evolved, with vitrification replacing slow freezing in the 2010s, improving survival rates and outcomes. More recently, OTC has emerged as an option for immediate treatment for younger patients, further enhancing reproductive success in cancer care.[12]

The need for this research into the application of cryopreserved gametes for fertility preservation among Asian cancer patients is highlighted by two key considerations: First, a significant research void exists about this particular population with no existing studies directly targeting it. Second, the absence of systematic monitoring and follow-up protocols for cryopreserved gametes in these individuals is conspicuous. Resolving these challenges is essential for the creation of customised fertility preservation tactics and the enhancement of post-treatment quality of life for cancer survivors within the Asian context.

Materials and Methods

This retrospective cohort study was conducted in our hospital from 1 January 2003 to 31 May 2023.

This study was a secondary data analysis, and no major ethical issues were involved. The confidentiality and privacy of the information were maintained, and the registered Institutional Ethics Committee (IEC) approved the study (approval number: EC/OA/50/2023). A waiver of informed consent was granted by the ethics committee since the study involved retrospective data collection with minimal risk to participants and no direct interventions. The study adhered to the ethical principles outlined in the Declaration of Helsinki.

The present study selected data based on specific criteria to ensure a focused and relevant sample. The inclusion criteria targeted males aged 15–50 years and females aged 15–40 years who were diagnosed with cancer and had chosen to utilise fertility preservation services before the initiation of any chemotherapy or radiotherapy treatments. Conversely, the study excluded patients with advanced stages of cancer, severely debilitated cancer patients and those who had already undergone at least

one session of chemotherapy or radiotherapy. All eligible participants were purposively selected, facilitating a targeted analysis of fertility preservation outcomes among cancer patients at the onset of their treatment.

Study methods

Following the ethical approval from the IEC, data collection commenced using a meticulously designed case record form. The data involved male and female cancer patients who opted for fertility preservation services. These patients underwent detailed counselling about the gonadotoxic effects of chemotherapy and radiotherapy as well as the critical importance of considering fertility preservation before commencing such treatments. Comprehensive informed consent was obtained after patients were fully informed about the various fertility preservation techniques available, including their advantages and potential drawbacks.

Particular emphasis was placed on explaining the risks associated with cryopreservation, such as cryo injury to gametes or embryos during the freeze-thaw cycle, which could lead to decreased sperm concentration and motility, oocyte maturation defects, growth arrest, and in some cases, the absence of viable gametes or embryos after the procedure. Patients were also advised that pregnancy could not be guaranteed with the use of frozen samples.

For male patients, semen samples were collected and analysed for key parameters before cryopreservation. These data were then categorised according to the corresponding cancer types. Female patients, depending on their circumstances, were offered oocyte cryopreservation if they were single. Married women with a stable partner were offered embryo cryopreservation. Laparoscopic cortical tissue cryopreservation was an option for women with time constraints.

Five hundred and ninety-six patients underwent cryopreservation of their biological samples at our hospital. As a social initiative, all patients referred for fertility preservation with diagnosis of cancer were offered free consultation. Ovarian stimulation, oocyte retrieval, laparoscopic cortical tissue retrieval, freezing of gametes/embryos/cortical tissue all was done free of cost as a charitable programme till 2021. After which the services are continued to be offered at a nominal price. Over time, cryopreservation methods have evolved. Until 2012, oocytes and embryos were preserved using slow freezing with CL-863/Cryogenesis V3.2, followed by a transition to vitrification with Kitazato media. Ovarian tissue was preserved by slow freezing methods using Planer Kryo 360–1.7. Initially, semen was cryopreserved without seminal plasma using slow cooling until 2020, then rapid freezing of seminal plasma was instituted from 2021 and samples were stored in liquid nitrogen. Over 20 years, as of May 2023, the patients who did not return to use the cryopreserved gametes were surveyed telephonically to record the reasons for such non-usage. The patients were adequately informed of the reasons for the call and informed consent was obtained to include their responses in the study data. The reasons for such non-usage were tabulated accordingly for those who responded to the telephone survey.

Outcomes

The primary outcome of this study was to analyse the utilisation of cryopreserved gametes in cancer patients who elected for fertility preservation before undergoing cancer treatment. The secondary outcome was to evaluate the success rates of assisted reproductive technologies, specifically clinical pregnancy and live birth rates in cancer patients utilising cryopreserved gametes.

Definitions

Clinical pregnancy rate

Clinical pregnancy rate was defined as pregnancies with at least one gestational sac divided by the number of embryos transfers.[13]

Live birth rate

Live birth rate was defined as the ratio between the number of patients with live-born babies and the number of embryos transfers.[13]

Statistical analysis

Epi info CDC 7 version is developed and maintained by the Centers for Disease Control and Prevention (CDC), (Atlanta, Georgia, United States) was used to enter and analyse data. Mean and standard deviation were used to represent continuous variables. Proportions were used for categorical variables. Figure 1 depicts patient enrolment flowchart.

Results

Table 1 presents the demographic characteristics of 659 participants, divided into 619 males and 40 females. Males had a mean age of 26.3 years (±5.7) and females 28.03 years (±5.05). Most males were in the 20–35 years (82.55%), and 80% of females were concentrated in the 20–35 years range. Cancer types varied, with 37.64% of males having testicular cancers and 47.5% of females having breast cancer.

Table 2, illustrated in Figure 2, shows the utilisation rates of cryopreserved gametes, providing details on the number of gametes preserved and subsequently utilised by both male and female participants. Among 619 male and 40 female cancer patients who came to the hospital, 596 patients contributed to the cryopreservation of

gametes. Of these, seven gametes were utilised by male participants and four by female participants, resulting in utilisation rates of 1.25% for males, 10.2% for females, and an overall rate of 1.8%. A total of 1322 vials were frozen for males, with seven semen vials utilised post-preservation. Eight embryos were utilised for females, with no use of preserved oocytes or ovarian tissue.

In the cohort, seven male gametes (comprising two via Intrauterine Insemination and five through Intracytoplasmic Sperm Injection) and 4 female gametes were utilised, resulting in 11 treatment cycles. Of these, conception was achieved in 4 male patients and 2 female patients, leading to 6 successful outcomes. The success rates were calculated as 57.14% for male subjects, 50% for female subjects and an overall rate of 54.5%, as shown in Table 3.

Table 4 showcases the outcomes of assisted reproductive procedures for male and female patients. It emphasises essential factors such as embryo transfers, pregnancies with gestational sacs, clinical pregnancy rates, live births and live birth rates, thereby shedding light on the efficacy of assisted reproductive technologies within both male and female cohorts.

Table 5 outlines various outcomes post-treatment, including mortality (49 cases), disease progression (3 cases), financial constraints (7 cases), social issues such as separation from a partner or partner unaware of the condition (7 cases), disinterest in family planning (2 cases), psychiatric issues (3 cases), spontaneous pregnancies (42 cases) and decisions to continue freezing (52 cases). However, large number of

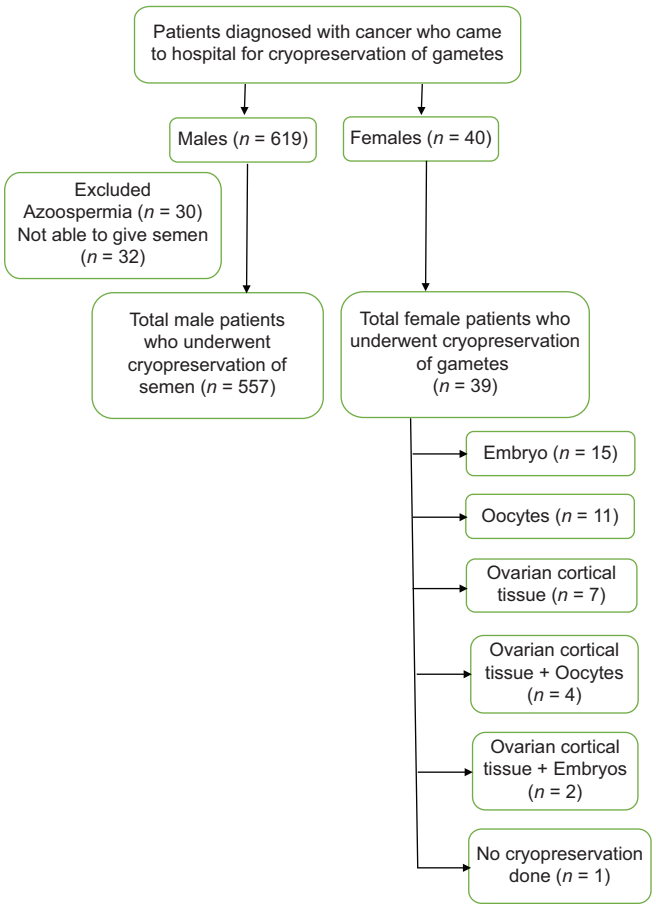

Figure 1: Participants enrolment flow chart

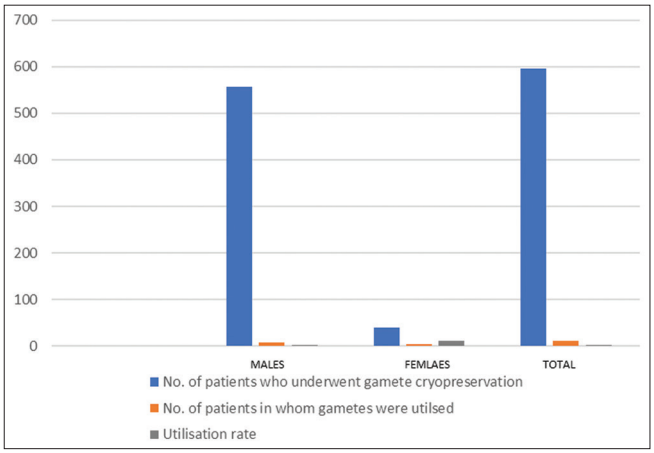

Figure 2: Utilisation rate of cryopreserved gametes

Table 1: Characteristics of the participants

Variables	Male (*n*=619), *n* (%)	Female (*n*=40), *n* (%)
Mean age (years)	26.3±5.7	28.03±5.05
Age group (years)		
<20	79 (12.8)	4 (10)
20–35	511 (82.55)	32 (80)
>35	29 (4.7)	4 (10)
Cancer types	Testicular cancer - 233 (37.64)	Breast cancer - 19 (47.5)
	Hodgkin's lymphoma - 143 (23.1)	Ovarian cancer - 9 (22.5)
	Non-Hodgkin's lymphoma - 22 (3.55)	Uterine cancer - 1 (2.5)
	Leukemia - 15 (2.42)	Hodgkin's lymphoma - 3 (7.5)
	B cell lymphoma - 29 (4.68)	Non-Hodgkin's lymphoma - 1 (2.5)
	Others - 134 (21.64)	Others - 7 (17.5)
	Data not available - 43 (6.94)	

Table 2: Utilisation rate of cryopreserved gametes

	Male (*n*=619)	Female (*n*=40)	Total (*n*=659)
Number of the patients who underwent gamete preservation	557	39	596
Number of patients in whom gametes were utilised	7	4	11
Utilisation rate (%)	1.25	10.2	1.8

Table 3: The success rate of cryopreserved fertility treatments

	Male	Female	Total
Number of patients in whom gametes were utilised	7 (2 - IUI and 5 - ICSI)	4	11
Number of patients who conceived	4	2	6
Success rate (%)	57.14	50	54.5

ICSI=Intracytoplasmic sperm injection, IUI=Intrauterine insemination

Table 4: Assisted reproductive technology outcomes

Parameter	Male	Female
Number of embryos transfers	6	4
Number of pregnancies with at least one gestational sac	4	2
Clinical pregnancy rate (%)	66.66	50
Number of live-born babies	2	2
Live birth rate (%)	33.33	50

Table 5: Post-cancer treatment outcomes for patients who opted for fertility preservation

Post-treatment outcomes	*n*=596
Mortality	49
Progression of disease	3
Financial constraints	7
Social issues - separation from a partner, partner unaware of condition	7
Disinterest in planning a family	2
Psychiatric issue	3
Spontaneous pregnancy	42
Decision to continue freezing	52
Unresponsive	420
Utilisation of gametes	11

patients were unresponsive to phone calls (420) as they might have changed their phone number and have not provided alternate number for communication. Same are depicted in Figure 3. We also came across hostile relatives who would not give out any information.

Discussion

The rising incidence of cancer among young adults alongside advancements in cancer therapies accentuates the significance of fertility preservation within oncological care. Oncological treatments–

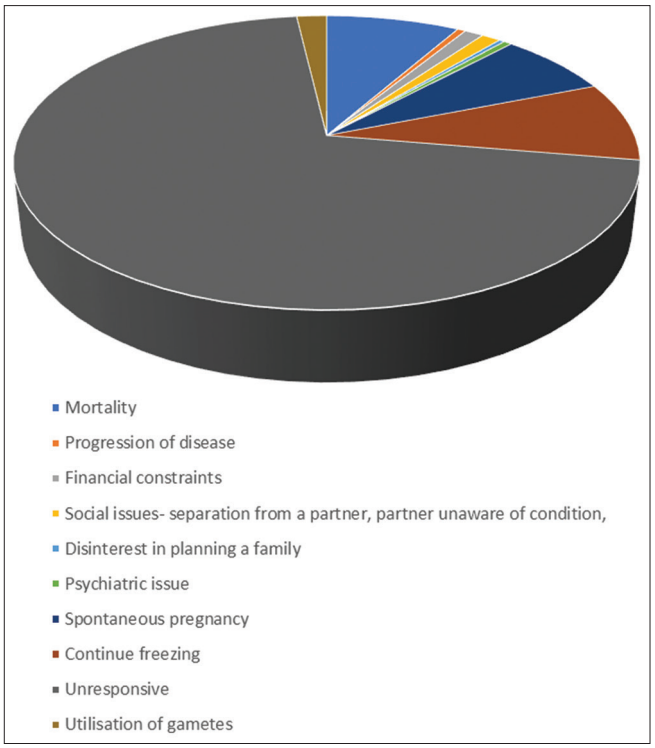

Figure 3: Post-treatment outcomes for cancer patients utilising fertility preservation services

namely surgery, chemotherapy and radiation–jeopardize reproductive capacities, catalysing a shift toward oncofertility, which melds oncology with fertility to protect patients' potential for future parenthood. Oncofertility care offers several fertility preservation techniques, such as oocyte and embryo cryopreservation, ovarian cortical tissue freezing and semen cryopreservation, aiming to minimise the impact of cancer treatments on fertility. Despite these advancements, the immediate priority of starting cancer treatment often overshadows the consideration of fertility preservation, leading to potential regrets over lost fertility opportunities. Thus, enhancing awareness and facilitating pre-treatment discussions on fertility options are pivotal in improving quality of life post-cancer care empowering young cancer survivors with informed reproductive choices.[14-16]

Furthermore, the domain of assisted reproduction has witnessed significant strides in fertility preservation methods, crucial for individuals facing gonadotoxic cancer therapies or natural fertility decline due to ageing. For females with cancer, oocyte cryopreservation has yielded promising results, enabling pregnancy with embryos derived from cryopreserved oocytes after treatment. For males affected with cancer, sperm cryopreservation is the most effective and non-invasive method for preserving fertility.[17,18]

In the current study, the distribution of cancer types shows significant variation between genders, with males predominantly affected by testicular cancers (37.64%) and Hodgkin's lymphoma (23.1%), while 47.5% of females had breast cancer. In Specchia *et al*.'s findings, breast cancer was also the most prevalent diagnosis, affecting 59.9% of their study cohort, and the study highlighted a diverse array of cancers among women, including significant incidences of Hodgkin's and non-Hodgkin's lymphoma (27.4%). Other cancers, such as those affecting soft tissues, the ovary, digestive system, leukaemia and the uterine cervix, were less common, collectively making up a smaller percentage of the diagnoses.[19]

van der Kaaij *et al*.[20] observed a 21% utilisation rate among men who cryopreserved semen before gonadotoxic treatments, whereas Fu *et al*.[21] reported that 9.7% of their cohort used their cryopreserved sperm for assisted reproductive technology (ART). Machen *et al*.[22] noted a utilisation rate of 1.5% in cancer patients. Systematic reviews and additional studies further support these findings; Ferrari *et al*.[23] reported an aggregated utilisation rate of 8%, and Ko *et al*.[24] also reported a rate of 9.8% for returning to use cryopreserved sperm. These comparisons highlight a significant variance, with the current study showing a much lower utilisation rate of 1.25%.

In the present study, 39 female patients came for fertility preservation services and utilisation rate was 10.2% and a pregnancy rate was 50%. Goeckenjan *et al*.[25] observed a utilisation rate of 1.6% among 59 patients, with a spontaneous pregnancy rate of 20%. Druckenmiller *et al*.[26] reported a 6% return rate for oocyte usage and a 44% live birth rate. A systematic review by Wnuk *et al*.[27] noted a return/usage rate ranging from 3.1% to 8.7% for oocytes, 9% to 22.4% for embryos and 6.9% to 30.3% for ovarian tissue. Cobo *et al*.[28] documented a 12.1% return rate for planned oocyte cryopreservation, while Leung *et al*.[29] reported a lower return rate of 7.4% over 14 years. These comparisons illustrate a broader spectrum of return and success rates across different studies.

The clinical pregnancy and live birth rates using cryopreserved semen demonstrate variable outcomes according to different studies. In the current study, a clinical pregnancy rate of 66.66% and a live birth rate of 33.33% were observed among male cancer survivors. Comparatively, Shin *et al*.[30] reported a lower clinical pregnancy rate of 35% and a live birth rate of 27%. Furthermore, Kobayashi *et al*.[31] identified a clinical pregnancy rate of 41.7% among Japanese men with cancer using cryopreserved semen for assisted reproductive technology (ART), which is slightly lower than that observed in the current study. In addition, an earlier study by Ping *et al*.[32] showed an overall live birth rate of 22.7%. These findings highlight the varying success rates of ART using cryopreserved semen across different populations and studies.

The present study observed a clinical pregnancy rate of 50% and a higher live birth rate of 50% in females using cryopreserved embryos. Kol *et al*.[33] reported a lower ongoing pregnancy rate of 23.9% in their first thawing cycles. Kawamura *et al*.[34] documented considerably clinical pregnancy rates, ranging from 40.4% to 43.1%, after transferring cryopreserved-thawed embryos. Meanwhile, Fraison *et al*.[35] found live birth rates of 21% following *in vitro* fertilisation and 33% from spontaneous births after ovarian tissue transplantation, highlighting variability in success rates depending on the reproductive techniques employed. These findings illustrate the diverse efficacy of reproductive technologies in females using cryopreserved embryos across various studies.

The cost of cryopreservation of gametes represents a substantial financial commitment. Cryopreservation costs vary significantly depending on the tissue type and the desired storage duration. Semen freezing costs around 80,000 INR for 5 years of storage. Oocyte freezing, which involves a more complex process, costs approximately 275,000 INR, including controlled ovarian stimulation and vitrification. Embryo preservation costs around 375,000 INR for 5 years. OTC costs 125,000 INR, plus additional charges for the required laparoscopic surgery. These costs underscore the financial considerations patients must weigh when considering cryopreservation options.

Furthermore, the low utilisation rate of cryopreserved gametes represents a significant burden on hospitals and clinics as they must maintain the samples indefinitely without the assurance of future use. This ties up valuable storage space and requires ongoing maintenance and monitoring, all without the revenue generated by the eventual use of the samples. Whether to continue or discard the gametes when the patients have not used or, in some cases, never communicated is a hard decision. Giving weightage to the sensitive nature of the requirement, the hospital continues the preservation, which in turn casts a huge burden on the system regarding costs and storage space. This expense is a critical consideration in fertility treatments as it adds to the overall financial burden faced by individuals opting for assisted reproductive technologies (ART). The economic implications of cryopreservation and the

low utilisation rate of stored gametes pose significant challenges and considerations for both patients and healthcare providers in reproductive medicine. The challenges lie in the inability to predict outcomes related to individual survival, the likelihood of gonadal recovery leading to spontaneous conception, and the uncertainty surrounding social acceptance of cancer survivors' health. These factors significantly impact their efforts to build a family, and unless these concerns are addressed, the trend of low utilisation of fertility preservation options is likely to persist.

Conclusion

Cancer patients' rate of use of cryopreserved gametes was 1.8%, which is notably low. Contributing factors to this low utilisation include patient mortality, higher-than-expected spontaneous pregnancy rates following cancer treatment, disease progression and various social reasons. The significant volume of stored unused reproductive cells and tissues poses an increased burden and financial cost for the storage facilities. This necessitates a refined paradigm for provisioning of fertility preservation, ensuring that services are extended to those with a defined and foreseeable need for future use.

Author contributions

DG: Writer, AN, YS, D: Data collection.

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Conflicts of interest

There are no conflicts of interest.

Data availability statement

Data is confidential.

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