

RESEARCH ARTICLE

REVISED Oncofertility awareness among primary care physicians in India [version 2; peer review: 2 approved, 1 not approved]

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Abstract

Background:

Primary care physicians not only coordinate referrals to oncology services but can play a crucial role in successful fertility preservation referrals in cancer-diagnosed patients. Hence, it is important to assess their knowledge and attitudes towards fertility preservation.

Methods:

An eighteen-item oncofertility survey was administered to primary care physicians between May 2019 to September 2020.

Results:

A total of forty-six responses were received and analysed. About 60% of primary care physicians did not have adequate knowledge about available fertility preservation options and only 26-32% were aware of international guidelines recommending fertility preservation in cancer patients.

Conclusions:

Imparting awareness and knowledge of fertility preservation and its options to primary care physicians could enable an integrated cancer care model while also facilitating successful oncofertility referrals in countries like India.



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Keywords

Fertility preservation, oncofertility, primary care physicians, general physicians, paediatricians

article can be found at the end of the article.



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REVISED Amendments from Version 1

The latest version of the manuscript has been revised based on reviewers' constructive comments. The introduction section has been revised with further emphasis on the role primary care physicians (PCPs) can play in improving fertility preservation referrals. While cancer patients are usually referred to specialists, it has been reported in literature that patients prefer involvement of PCPs in their cancer care. There are international cancer care guidelines which recommend the involvement of PCPs in treatment plans and other decisions in cancer- and survivorship care. This brings about a need for PCPs to have a basic knowledge of the short and long term impact of cancer treatments on fertility and the options available to mitigate such risks.

The discussion section has also been revised discussing in detail the barriers faced by the PCPs participating in the study, which were compared with studies from other developing countries. Models-of-care for oncofertility improvement have been suggested to overcome the present challenges.

Any further responses from the reviewers can be found at the end of the article

Introduction

Oncofertility – integrating cancer care with fertility preservation (FP) – is expected to be an essential part of the standard care for patients, with international guidelines recommending fertility preservation counselling as routine for reproductive-age cancer patients and for prepubertal children undergoing gonadotoxic therapies. However, successful implementation of oncofertility care requires a coordinated referral system among healthcare providers. While it is established that the role of oncologists and reproductive specialists is key for successful oncofertility, 4 it is also believed that primary care physicians (PCPs) can play an important role in ensuring successful fertility preservation referrals.

PCPs inclusive of general physicians (GPs) and paediatricians (PEDs), are considered as gatekeepers of the healthcare system who provide comprehensive, individual-centric and coordinated continuous care. PCPs are the initial contact point for most cancer patients, who are then referred to specialists such as medical oncologists or paediatric hemato-oncologists. However, the role of PCPs in cancer care has expanded further across the cancer care continuum from prevention, diagnosis, treatment to cancer survivorship as it has been reported that cancer patients preferred their PCPs to be involved in their cancer care. A recent study has reported patients discussing their cancer treatment options with their PCPs, in addition to their oncologists, demonstrating the important role they play in decision-making. It has been reported that about two thirds of patients with long-term or complex health issues prefer interpersonal continuity with a PCP whom they know, trust and who also knows their medical history. Hence, PCPs not only coordinate referrals, but are also involved in providing general medical care, emotional support and overall decision making for the patient during cancer care. The American Society of Clinical Oncology breast cancer survivorship guidelines, recommend post-treatment physical and psychosocial surveillance by primary care clinicians and expediting referrals to reproductive endocrinologists in survivors experiencing infertility.

Fertility preservation while at times is considered to be a burden for patients and their families, can provide opportunities for maximizing reproductive potential of the patient. A multi-disciplinary team that includes the patient's primary care physician along with the cancer specialists and reproductive specialists will allow for a comprehensive decision-making by the patients. ¹³ This also allows for families to gather the information required for taking informed decisions regarding fertility preservation thereby maximizing the chances for preserving their fertility before initiation of cancer therapy. ¹³ Similar approaches are applicable to patients with non-oncological conditions requiring gonadotoxic treatments. ¹³ It is therefore important for PCPs dealing with cancer patients or patients with non-malignant conditions requiring gonadotoxic therapies, to be knowledgeable both of the adverse gonadotoxic effects of chemo- and radiotherapy as well as the options available to mitigate them. The awareness of PCPs of international fertility preservation guidelines and on the available fertility preservation options are expected to strengthen the likelihood of fertility preservation referrals. ¹¹ Therefore, this study was aimed to assess the awareness, knowledge and perceptions of PCPs towards fertility preservation, along with exploring the existing barriers to oncofertility establishment in India.

Methods

The study was approved by the Institutional Ethics Committee, Kasturba Medical College & Kasturba Hospital, Manipal, India (IEC No: 880/2017), and is in continuation of a previously published study. The earlier work included the use of an eighteen-item survey, which was given to oncologists and gynaecologists to explore their attitudes towards fertility preservation. The survey was designed in collaboration with the Oncofertility Consortium, USA. Content validation for the survey was done by experts in the field and a pilot study was conducted on a small group of healthcare providers to validate the comprehensibility of the survey questions (unpublished). In our new study, the survey was administered randomly to GPs and PEDs of the country at various national conferences and virtual platforms from May 2019 to September 2020. Written informed consent was taken from all the subjects participating in the survey.

Table 1. Demographics of primary care physicians (PCPs) participating in the survey.

	General physicians (%) n=23	Pediatricians (%) n=23
Age groups (years)		
<30	30.4	21.7
31–40	17.3	21.7
41–50	21.7	34.7
51-60	26	21.7
>60	4.3	0
Gender		
Male	86.9	73.9
Female	13	26
Work experience (years)		
<5	39.1	26
5–10	8.6	17.3
11–15	8.6	8.6
16–20	4.3	13
>20	39.1	34.7
Practice setting type		
Academic institution	43.4	60.8
Government/Aided institution	0	4.3
Private practice affiliated with institution	4.3	21.7
Exclusive private practice	52.1	13

In brief, the survey contained a total of eighteen questions, of which ten were aimed at understanding the participants' knowledge, attitudes, and referral trends in oncofertility, including their familiarity with existing oncofertility barriers in India, and sought the respondent's suggestions, if any, for effective use of fertility preservation. The remaining eight questions covered the demographics of the survey respondents and contextual details such as the number of new cancer patients treated in a month and the patient age groups. The questions were of different complexities, including those of a dichotomous nature, assessment tools with grading scales, multiple choice items where only one response could be selected, multiple response items where more than one answer could be selected, and even open-ended questions. During the analysis, the survey responses were assigned numerical values (Yes=1, No=0), and the data was analysed using descriptive statistics calculated with Microsoft Excel. In questions containing grading scales or multiple choice, options such as 'not aware', 'aware but inadequate knowledge', 'knowledgeable', 'very knowledgeable', were clubbed as two categories — 'inadequate knowledge' and 'knowledgeable'. For open-ended questions such as suggestions for oncofertility practice, all the responses were considered and grouped based on similarity of the suggestions made. Questions that showed a high variation in responses, such as more than half of the participants not answering, were not included in the analysis.

Results

Out of 105 survey forms distributed, 23 responses each from general physicians (GPs) and pediatricians (PEDs) were received, with an average response rate of 43.8%. The demographics of the PCPs are shown in Table 1.

Awareness of fertility preservation guidelines and options

About 32% of GPs (7 of 22) and 26% of PEDs (6 of 23) were aware of the American Society for Clinical Oncology (ASCO) guidelines on fertility preservation (Figure 1A). When assessing the knowledge of different fertility preservation options available for both prepubertal and adult cancer patients, about 60% of the PCPs did not have an adequate knowledge on established fertility preservation (FP) options (Figure 1B). However, PEDs had a slightly higher level of knowledge of some of the FP options such as sperm banking (35%; 8 of 23), immature testicular tissue freezing (30%; 7 of 23), ovarian tissue freezing (35%; 8 of 23) and oocyte freezing (39%; 9 of 23), and were more knowledgeable of the time needed to undertake each of the options compared to GPs.

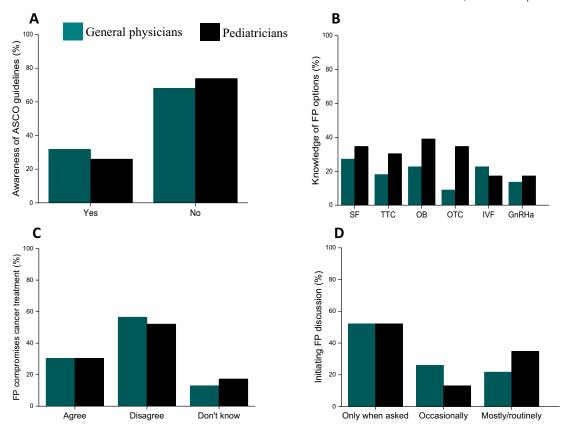


Figure 1. Trends in fertility preservation among primary care physicians (PCPs) – general physicians and pediatricians. (A) Awareness of ASCO fertility preservation guidelines among PCPs. (B) PCPs' knowledge of various fertility preservation options. The various options on the X axis are: Sperm freezing (SF), Testicular tissue cryopreservation (TTC), Oocyte banking (OB), Ovarian tissue cryopreservation (OTC), IVF followed by embryo freezing (IVF) and GnRHa pre-treatment (GnRHa). (C) Opinion on whether fertility preservation compromises cancer treatment. (D) Frequency of initiating fertility preservation discussions with cancer patients (teal bar: general physicians; black bar: pediatricians).

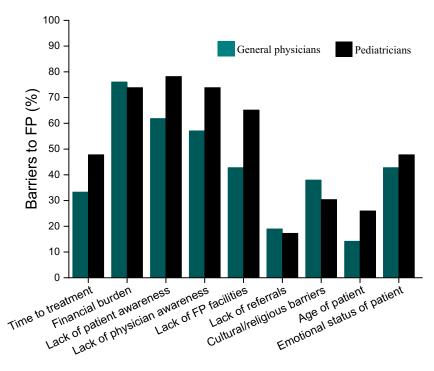


Figure 2. Barriers to effective utilization of fertility preservation services, as perceived by primary care physicians (PCPs). (Teal bar: general physicians; black bar: pediatricians.)

Perception towards FP, referral trends

When asked their opinion on the statement, "offering fertility preservation compromises cancer treatment", 56% of GPs (13 of 23) and 52% of PEDs (12 of 23) disagreed with the statement, indicating a positive attitude towards oncofertility (Figure 1C). Further, the frequency of fertility preservation counselling or referrals showed that 78% of GPs (18 of 23) and 65% of PEDs (15 of 23) initiated FP discussions with the cancer-diagnosed patients only occasionally or when asked; only 21-35% of them reported routine discussions (Figure 1D).

Comfort level in discussing FP

The majority of PCPs (>60%) in both groups were comfortable discussing most of the available FP options. However, when it came to female fertility preservation options, a minority of GPs were not comfortable discussing oocyte freezing (37%; 7 of 19), ovarian tissue freezing (35%; 7 of 17) or IVF (33%; 6 of 18) options, which could be reflective of inadequate knowledge in this area.

Barriers and suggestions towards oncofertility with reference to the Indian context

Participants were asked to select the most appropriate of the listed barriers for effective oncofertility implementation in India. PCPs from both groups felt 'financial burden' (76% of GPs, 74% of PEDs), 'lack of patient awareness' (62% of GPs, 78% of PEDs) and 'lack of physician awareness' (57% of GPs, 74% of PEDs) to be the biggest barriers to FP. PCPs felt that 'lack of FP facilities' (43% of GPs, 65% of PEDs) and 'emotional status of patient' (43% of GPs, 48% of PEDs) were other important barriers (Figure 2).

One of the major suggestions given, in the open-ended questions, was to create 'awareness among primary healthcare providers in fertility preservation' (36% of GPs, 67% of PEDs). More than 40% of GPs and PEDs felt there was a need for bringing about social awareness among the general public about oncofertility programs and educating the patient and their family. Other suggestions included, 'routine medical education', and 'affordable costs', which would help bring about effective implementation of oncofertility programs.

Discussion

This study showed, for the first time, the perceptions and attitudes towards oncofertility among PCPs in India. Lack of knowledge about the current international fertility preservation (FP guidelines) and of the available FP options were key observations made in this study.

In India, the established fertility preservation options include sperm, oocyte and embryo banking for post-pubertal and adult cancer patients while prepubertal options that are available include ovarian or immature testicular tissue cryopreservation, which are still considered experimental. Other options such as gonadal shielding, GnRH analogs are also offered to cancer-diagnosed patients, similar to developed countries. However, the fertility preservation referral rates are only about 4-12% even in European countries. In India, while there are no studies reporting referral rates, the number of patients receiving fertility preservation counselling is quite low. A study reported that only 15% of childhood cancer survivors received information on infertility risks though they were about to receive high-gonadotoxic risk cancer treatment. About 87% of patients with newly diagnosed cancers reported a desire to understand the long-term risks resultant of their disease and treatment.

The majority of PCPs participating in our study reported inadequate knowledge of even the established fertility preservation options along with a reduced awareness of the American Society of Clinical Oncology Fertility Preservation (ASCO-FP) guidelines. This is in line with a cross-sectional study in India on female cancer patients of reproductive age revealing that 68% reported a lack of information received from primary physicians about fertility risks and FP options. There could be several contributing factors to the above finding in our study, one of which could be the lack of knowledge about FP in India, since more than 90% of healthcare workers in other parts of the country reported the need for continued medical education programs or seminars in oncofertility.²⁰ Secondly, the ASCO-FP guidelines are mainly targeted to oncologists and other cancer-care providers,² and not to primary care physicians, though organizations such as the American Academy of Pediatrics have recommended fertility preservation counselling for pediatric and adolescent patients. ¹³ While ASCO has released primary care focused cancer survivorship guidelines for a few cancers, ^{12,21} there is a need for fertility preservation guidelines before the onset of cancer treatment in pediatric and reproductive-age patients, that can be applicable to primary care settings. Also, PCPs' depth of knowledge pertaining to long-term effects of cancer treatment could be limited due to their lack of exposure to relevant literature pertaining to the field, 22 therefore, conducting educational programs for PCPs to increase awareness and knowledge of the various fertility preservation options could aid PCPs in their discussions with patients. In an online survey conducted by Nahata et al., it was seen that the majority of pediatricians felt inadequately trained in fertility risks and sexual function, which was reflective in their comfort level when discussing such issues.²³ Though our study reported a higher comfort level among PEDs in discussing most FP options, a majority of them have suggested the need for fertility preservation awareness programs.

In India, the burden of cancer is steadily increasing, with the Globocan project predicting 1.7 million new cases by 2035. Among children of 0-14yrs and children and adolescents of 0-19yrs, approximately 52,366 individuals and 76,805 individuals develop cancer every year, respectively. However, the ratio of new cancer cases per clinical oncologist is 677:1 and it has been reported that medical oncologists from low- and middle-income countries such as India have a substantial workload compared to high-income countries. However, the onus of FP counselling is placed on oncologists and gynecologists, in the given situation, an integrated care model involving PCPs would be more appropriate. As PCPs have a continual relationship with the patients and are more familiar with their wishes, PCPs can be a part of the FP referrals or discussions, to enable patients to think through their decisions, rather than these discussions taking place only with the oncologists or surgeons. Hor this to succeed however, knowledge dissemination and awareness building of fertility preservation among PCPs in developing countries like India is essential, as emphasized by the findings of the present study. Our earlier study specifically looked at oncologists and gynaecologists' attitude towards fertility preservation, who also emphasized the need for oncofertility awareness.

The scope of oncofertility has started to include fertility preservation in patients with non-oncological conditions who are at high risk of infertility due to gonadotoxic treatments, or individuals with sexual development or auto-immune disorders, and also, in the gender-diverse population.³² The successful establishment of fertility preservation in (non)-oncological conditions therefore requires physicians, both primary care and specialists, to have adequate knowledge of fertility preservation and its related guidelines. A shared care model that facilitates sustained collaborations between healthcare providers, both primary and acute care, will ensure successful execution of fertility preservation goals in patients whose fertility could be impacted. Robust strategies including co-ordinated referral pathways, use of telehealth platforms and decision-aids will promote oncofertility referrals by enabling patients to take informed decisions towards preserving their fertility. Anazodo *et al.*, identified several themes for delivery of oncofertility care such as age-appropriate referral pathways, collaboration between healthcare providers in pediatric or adult hospitals and fertility clinics, and oncofertility training of both cancer and non-cancer HCPs in order to improve the quality of care.

Barriers in providing fertility preservation care can lead to their under-implementation. Our study reported financial burden on the patient, as an important barrier to oncofertility by majority of the PCPs. As fertility preservation procedures are not covered under insurance costs in India,³³ this is one of the biggest hurdles that need to be overcome. Similar economic barriers have been reported in other developing as well as developed countries.^{33,34} Another important barrier reported in the study were lack of fertility preservation awareness among physicians.

This can be overcome by providing educational resources, for e.g., decision aids, brochures or conducting Continuing Medical Education (CME) programs which is expected to increase the knowledge and confidence in healthcare workers thereby improving the frequency as well as quality of fertility preservation discussions.^{35,36}

Strategies for effective implementation of FP services across the country can include formation of fertility preservation consortiums that allow for knowledge and resource distribution among healthcare providers would facilitate successful establishment of oncofertility care in India.³⁷ Development of clinical guidelines with an objective to provide guidance on the gonadotoxicity of (non)-oncological treatments can be focused towards primary care to bridge the knowledge gaps among PCPs in the country.

Conclusions

Our pilot study highlights the dearth of oncofertility awareness among PCPs. With increasing involvement of PCPs in the cancer care continuum, this group could play a crucial role in patient decision-making, thereby helping in the successful establishment of oncofertility as part of standard cancer care. As the scope of fertility preservation is expanding to also include non-oncological patients requiring gonadotoxic therapies the involvement of PCPs whom the patients know and trust and who are also familiar with the patient's wishes or life goals, in fertility preservation discussions could prove beneficial to the cancer-diagnosed patients as well as increase the frequency of fertility preservation referrals. The present study emphasizes the need for knowledge dissemination and awareness about oncofertility among PCPs. This study should contribute to what is currently only limited literature in this area. Limitations of this study include a small sample size and selection bias due to random recruitment of survey participants at conferences. Due to the small sample size conclusions could not be drawn on the characteristics of PCPs with increased knowledge on fertility preservation.

Author contributions

PT: Collected and analyzed the data, wrote paper; SU, RKJ, KSU, GK, NS, TKW: Revised the manuscript critically for important intellectual content; SKA: Conceived and designed the study, wrote paper. PT is the guarantor of this work and as such, had full access to all the data and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors have given final approval for publication.

Data availability

Underlying data

Open Science Framework: 'Oncofertility awareness among primary care physicians in India.' https://doi.org/10.17605/ OSF.IO/N7GVKh.¹²

This project contains the following underlying data:

- Oncofertility survey, data description sheet and content validity analysis (zip file)
- Survey responses (raw data) (zip file)

Data are available under the terms of the Creative Commons Zero "No rights reserved" data waiver (CC0 1.0 Public domain dedication).

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The manuscript entitled "Oncofertility awareness among primary care physicians in India" provides a preliminary survey based analysis highlighting the dearth of oncofertility awareness among PCPs. Specific comments are:

- 1) The discussion section can have the following additional details:
 - Any published estimates of reproductive cancers/prepubertal cancers in India per population/incidences.
 - A paragraph on the current status of fertility preservation in IVF units across the country and gaps in services. Anazodo *et al.* (2019¹) described a model to increase the oncofertility implementation - worth mentioning in the current manuscript.
 - The authors have mentioned about the need for the shared care model for oncofertility referrals. Please explain how this could be achieved in an Indian context tailored to the identified determinants and how the improvement strategies for the guideline-specific barriers should be developed.

References

1. Anazodo A, Laws P, Logan S, Saunders C, et al.: How can we improve oncofertility care for patients? A systematic scoping review of current international practice and models of care. *Hum Reprod Update*. 2019; **25** (2): 159-179 PubMed Abstract | Publisher Full Text

Is the work clearly and accurately presented and does it cite the current literature? Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others? Yes

If applicable, is the statistical analysis and its interpretation appropriate? Yes

Are all the source data underlying the results available to ensure full reproducibility? Yes

Are the conclusions drawn adequately supported by the results? Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Assisted Reproductive Technologies

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 18 Sep 2023

Satish Adiga

We thank the reviewer for the constructive comments. The manuscript has been revised accordingly. Hereby addressing the reviewer's comments:

1) The discussion section can have the following additional details: Any published estimates of reproductive cancers/prepubertal cancers in India per population/incidences.

Ans: Thank you for the suggestion, it has now been added accordingly.

2. A paragraph on the current status of fertility preservation in IVF units across the country and gaps in services. Anazodo et al. (20191) described a model to increase the oncofertility implementation - worth mentioning in the current manuscript.

<u>Ans:</u> Thank you for the suggestion. There is however, currently no data reporting the fertility preservation referral rates in India, but there are a few studies reporting the frequency of counselling for infertility-risk, which has now been added.

The models of care mentioned in the recommended publication have now been added in the discussion section.

3. The authors have mentioned about the need for the shared care model for oncofertility referrals. Please explain how this could be achieved in an Indian context tailored to the identified determinants and how the improvement strategies for the guideline-specific barriers should be developed.

<u>Ans:</u> Thank you for the suggestion. It has been addressed to the best of the author's knowledge and available literature which is limited.

Competing Interests: No competing interests were disclosed.

Reviewer Report 25 August 2023

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I reviewed thoughtfully the manuscript Oncofertility awareness among primary care physicians in India. In this the authors present an exploration of the current knowledge and barriers to fertility preservation in India among PCPs. I congratulate the authors for addressing a topic needing assessment in LMICs.

My main concerns are regarding the paper's impact in the current knowledge, as usually young patients diagnosed with a malignancy are under the care of a specialized team (pediatric oncologist/hematologist), and I do not fully understand if the lack of knowledge of PCP in such a specialized topic is something of importance in their care-continuum. I think if the authors could really justify the importance of understanding the knowledge of PCP in their paper, it could strengthen it.

Overall, I found the paper well-written and understandable.

The data presented was only a description of the obtained answers, were there any correlations made to understand? For example, what are the characteristics of the physicians with the highest knowledge of oncofertility?

During the discussion, there have been other publications in LMICs for example, in Mexico, also in other parts of the world outside the US like Italy. I recommend making a more exhaustive review of the currently published literature to correlate your results with the currently available literature.

During the discussion I would also recommend a deeper exploration of the reported barriers, are these similar to their context? Or as these unique in the Indian population?

In the conclusion, once again I would clearly state why you consider that this is relevant information for the reader.

Is the work clearly and accurately presented and does it cite the current literature? Partly

Is the study design appropriate and is the work technically sound? Partly

Are sufficient details of methods and analysis provided to allow replication by others?

If applicable, is the statistical analysis and its interpretation appropriate? $\ensuremath{\mathsf{No}}$

Are all the source data underlying the results available to ensure full reproducibility?

Are the conclusions drawn adequately supported by the results? $_{\mbox{\scriptsize NO}}$

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Urologic oncology, disparities in cancer care

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Author Response 18 Sep 2023

Satish Adiga

We thank the reviewer for the constructive comments. The manuscript has been revised accordingly. Hereby addressing the reviewer's comments:

1. My main concerns are regarding the paper's impact in the current knowledge, as usually young patients diagnosed with a malignancy are under the care of a specialized team (pediatric oncologist/hematologist), and I do not fully understand if the lack of knowledge of PCP in such a specialized topic is something of importance in their care-continuum. I think if the authors could really justify the importance of understanding the knowledge of PCP in their paper, it could strengthen it.

<u>Ans:</u> We agree with the reviewer's concern. The cancer patients are usually referred to specialized team, but literature as well as discussions with PCPs during the survey distribution have shown that these patients interact with their PCPs during the course of cancer treatment and wish to have their PCPs involved. The introduction section has been revised to emphasize further the role of PCPs in the cancer care continuum.

2. The data presented was only a description of the obtained answers, were there any

correlations made to understand? For example, what are the characteristics of the physicians with the highest knowledge of oncofertility?

<u>Ans:</u> Due to the small sample size in each group conclusions could not be drawn regarding the characteristics of the PCPs with higher oncofertility knowledge. This has now been mentioned as a limitation of the study.

3. During the discussion, there have been other publications in LMICs for example, in Mexico, also in other parts of the world outside the US like Italy. I recommend making a more exhaustive review of the currently published literature to correlate your results with the currently available literature. During the discussion I would also recommend a deeper exploration of the reported barriers, are these similar to their context? Or as these unique in the Indian population?

Ans: Thank you for the suggestion. We agree, there have been other publications about oncofertility trends among oncologists or gynaecologists. However, among PCPs there is very limited literature, and this manuscript is the first of its kind, especially in India. Oncofertility awareness among PCPs is an area with great potential to leverage the role of PCPs in successful oncofertility referrals. Hence, the limited review based on existing literature in this area. However, as per the reviewer's suggestions, the barriers have been compared with other developing countries and revised accordingly.

4. In the conclusion, once again I would clearly state why you consider that this is relevant information for the reader.

Ans: Thank you for the suggestion. It has now been addressed and revised accordingly.

Competing Interests: No competing interests were disclosed.

Reviewer Report 17 July 2023

https://doi.org/10.5256/f1000research.138622.r178270

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It is a well conducted and well written manuscript. It addresses a relevant issue. It is interesting that the authors have gone beyond the specialist and interviewed primary care physicians. It is an important step towards improving awareness about oncofertility. The limitations of the study are the small numbers included.

Is the work clearly and accurately presented and does it cite the current literature? Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others? Yes

If applicable, is the statistical analysis and its interpretation appropriate? \forall_{PS}

Are all the source data underlying the results available to ensure full reproducibility? Yes

Are the conclusions drawn adequately supported by the results?

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Ovarian reserve

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 18 Sep 2023

Satish Adiga

We thank the reviewer for the constructive comments.

Competing Interests: No competing interests were disclosed.

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