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EVOLUÇÃO DA PRÁTICA CLÍNICA DOS ONCOLOGISTAS PORTUGUESES EM RELAÇÃO À PRESERVAÇÃO DA FERTILIDADE DAS DOENTES ONCOLÓGICAS

Evolution of Portuguese oncologists' practices regarding fertility preservation of female cancer patients

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Artigo científico

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Resumo

Introdução: A maior incidência de cancro em idades jovens, associada ao aumento da sobrevivência, dá origem a um número crescente de doentes oncológicas em idade reprodutiva. A Infertilidade é reconhecida como um efeito a longo prazo do tratamento oncológico, pelo que os médicos devem estar preparados para informar as doentes desta possibilidade e discutir opções disponíveis para Preservação da Fertilidade (PF). A necessidade de reforçar o conhecimento e as competências de comunicação sobre este assunto já foi reconhecida por diversas entidades e, recentemente, foram desenvolvidas, em Portugal, ferramentas informativas e de apoio à tomada de decisão, tais como folhetos informativos, *websites* e cursos pós-graduados. O principal objetivo deste estudo é avaliar a evolução das práticas dos médicos portugueses que tratam patologia oncológica em relação à PF, comparando os resultados obtidos em 2018 com os de um estudo de 2013-2015.

Métodos: Foi aplicado um questionário de auto-resposta a médicos de todas as especialidades que tratam doentes oncológicas. Estes foram recrutados pessoalmente em instituições clínicas portuguesas ou *online* através da divulgação do link do questionário via *e-mail* pela Sociedade Portuguesa de Oncologia, a todos os seus membros, e em grupos de médicos do *Facebook*.

Resultados: Em comparação com o estudo anterior, um número maior de médicos refere que "frequentemente ou sempre" informa os seus doentes do sexo feminino sobre o risco de infertilidade relacionada com o cancro e sobre a possibilidade de PF; menos médicos dizem que o fazem "quase nunca" e nenhum dos médicos relatou "nunca" ter informado as suas doentes sobre o risco de infertilidade relacionada com o cancro e sobre PF. Um maior número de clínicos relatou referenciar um maior número de doentes a um médico de medicina reprodutiva. A maioria dos clínicos não reconhece a falta de leis de gestação de substituição como uma barreira às suas práticas de PF, tal como, discorda que deve ser implementada como um método para alcançar uma gravidez após PF.

Conclusões: O presente estudo revelou uma melhoria nas práticas globais dos médicos em relação à saúde reprodutiva das doentes oncológicas, comparativamente ao estudo de 2013-2015. Assim, podemos hipotetizar que as estratégias implementadas foram importantes e eficazes, tendo contribuído para aumentar o conhecimento dos clínicos sobre a saúde reprodutiva das doentes oncológicas e para facilitar a comunicação médico-doente.

PALAVRAS-CHAVE: Oncofertilidade, oncologia, práticas dos oncologistas, ferramentas informativas, tomada de decisão.

Abstract

Background: The increase of cancer in younger ages, as well as the increase in survival rates, leads to a growing number of cancer patients of reproductive age. Infertility is known to be a long-term effect of cancer treatment, which means that doctors must be prepared to inform and discuss issues concerning Fertility Preservation(FP). It has been recognized that discussion and referrals concerning this matters in female cancer patients has been insufficient. Thus, in Portugal, measures such as information pamphlets, websites and post graduate courses were conceived with the aim of increasing clinicians' knowledge and communication skills about FP. It is the purpose of this study to evaluate the evolution of the practices of Portuguese clinicians that treat cancer patients in relation to FP, comparing the results obtained in 2018 with those of a study in 2013-2015.

Methods: A questionnaire distributed to clinicians' who treat cancer patients were recruited face-to-face in Portuguese clinical institutions and online through a secure Internet-based survey (hosted by https://www.google.com/forms) whose web link was promoted by e-mail by the Portuguese Society of Oncology (SPO) to all of its members and advertised on Facebook groups of physicians.

Results: In comparison to a previous study, a higher number of clinicians' report that they inform their female patients about the risk of cancer-related infertility and FP "very often" or "always"; a smaller number report that they "almost never" never do this; and none of them reported "never" having informed their female patients about the risk of cancer-related infertility and FP. A greater number of oncologists report having referred their female child-bearing aged cancer patients to a reproductive medicine doctor. The majority of clinicians do not consider that the lack of surrogacy laws constitutes a barrier to their FP practices. In fact, the majority, to a degree, disagree that surrogacy should be implemented as an alternative method for obtaining a pregnancy after FP.

Conclusions: The present study revealed an improvement in the overall practices of physicians regarding the reproductive health of cancer patients, compared to the 2013-2015 study. Thus, we can hypothesize that the strategies implemented were important and effective, contributing to increase the knowledge of oncologists on the reproductive health of cancer patients and to facilitate physician-patient communication.

KEYWORDS: oncofertility, oncology, oncologists' practices, information tools, decision-making

Cancer and Infertility

Cancer is the second leading cause of death worldwide [1-3]. Over the past years, the number of cancer survivors in childbearing age without their parental project completed has increased, due to (1) the increasing number of new cancer cases, as well as its survival rates [3-5] and (2) the social trend in developed countries to postpone pregnancy to a later age [6]. Cancer is more prevalent in women that in men in childbearing age [7]. Specifically in Portugal, and according to the Portuguese National Registry of Oncology, in 2008, less than 7% of the cancer in men occurred in patients between 0 and 44 years, were approximately 13% of the female cancers occurred between 0 to 44 years of age [8]. Infertility risk is one concern that needs to be taken into account in these young cancer survivors.

The effects in fertility detected in cancer patients are mostly due to iatrogenic factors, chemotherapy, radiotherapy and/or surgery. The highest risk of permanent infertility is due to treatments with alkylating agents, rather than cancer itself [9-11]. This leads to a significant number of cancer patients who have not yet completed their family project, and who reach reproductive age with their fertility impaired.

Fertility Preservation Options

The term oncofertility describes a discipline that bridges oncology and reproductive medicine in order to discover and apply new fertility preservation (FP) options for young patients with cancer [12, 13]. It is important to note that no FP method can completely assure pregnancy after a cancer-related treatment. Nonetheless, there are techniques that may provide a future opportunity to those with treatment-induced infertility.

An individualized approach towards options of FP is recommended, taking into consideration patient's age, cancer type and stage, proposed treatment regime, time before it is initiated and availability of partner. The most established and clinically approved methods for FP are sperm cryopreservation for men and embryo cryopreservation for women. The clinical pregnancy rate per transfer of frozen embryos is approximately of 23%[9,14]. Embryo cryopreservation for FP purposes, however, is not available in Portugal since 2015 due to ethical, moral and legal issues [15]. Other options include oocyte cryopreservation for later IVF (globally, more than a 1000 children have been born through IVF with frozen oocytes [14]) and ovarian tissue cryopreservation [9, 15]. In women, the preferential option is oocyte cryopreservation. This method requires ovarian stimulation lasting up to 2 weeks and the storage of the collected oocytes without being fertilized. The second preferential option is ovarian tissue cryopreservation, that requires a laparoscopic extraction of a partial or complete ovary, and subsequent dissection into small fragments and freezing of the ovarian cortex. Female FP methods are more time-consuming and

physically more demanding and complex than in men. Thus, patients' referral must occur as soon as possible after the cancer diagnosis and prior to the decision regarding the cancer therapy [15, 16].

Patients Perceptions about the Decision-Making Process regarding Fertility Preservation

Surveys of cancer patients' perceptions indicate that most patients have a strong desire to be informed about FP options. As a matter of fact, the majority of childbearing aged cancer patients who survive cancer treatments want to have children [17]. A recent study concluded that, overall, cancer patients rely mainly on their clinicians for fertility information [18]. However, several patients are left with insufficient information about their reproductive issues [11, 17]. Chiefly, women are less likely to be informed and/or referred to a reproductive medicine doctor for fertility counselling and they tend to report a more negative experiences concerning patient-provider communication of fertility-related aspects of cancer treatments [19]. On the contrary, female patients who have a higher quality decision in FP have a better experience in the overall decision-making process[17]. It was also found that Portuguese women were more dissatisfied, when compared to American women, with their physician's explanations about fertility and that these patients underwent less FP techniques[18].

Hence, newly cancer diagnosed Portuguese women are at risk of not being informed about cancer-related infertility and their FP options. This can result in a higher probability of not preserving their fertility before cancer therapy and thus leading to a future permanent infertility.

Oncologists' Barriers in Fertility Preservation Practices

In Portugal, as around the world, it is recommended that all clinician should discuss with their childbearing aged cancer patients their reproductive future, before initiating any infertility-inducing treatment for cancer [20]. These patients should be informed about the risk of infertility before treatments and about possible FP options, and should be referred to fertility specialists to make an informed decision. Specifically, in Portugal, childbearing aged cancer patients should be referred to gynecologists with the sub-specialty of reproductive medicine to be informed and make their decision about FP before cancer therapy [21].

According to recent studies, clinicians regard FP as mainly a women's issue feeling knowledgeable only about sperm storage and no other FP method, expressing a need for more information. Most clinicians report discussing the risks of infertility cancer treatment with patients, but few report providing patients with written information or ever having referred patients to a specialist on fertility[21, 22].

Specifically, in Portugal, a cross-sectional study was conducted between 2013 and 2015 assessing the practices of oncologists and it was found out that although the majority of clinicians' report discussing the reproductive future with their patients, approximately 3% and 7% of these clinicians report never having informed their patients about the risk of infertility and about FP,

respectively. In fact, 76% of the clinicians had referred fewer than 10 patients to a reproductive medicine doctor throughout all their clinical practice years [21].

Several studies worldwide have revealed some barriers to the oncologists' practices regarding FP, namely a) oncologists' knowledge of FP b) oncologists' communication skills; c) patient-related issues; d) time with patients and e) financially related barriers. Lack of information leads to a lack of referral. Several clinicians lack knowledge about cancer-related infertility, FP options and their efficacy and about where to refer patients to perform these techniques. Moreover, many of them reveal lack of communication skills, referring feeling uncomfortable when discussing fertility with patients. Patient-related issues are documented as an obstacle in engaging in fertility discussions, being it less likely to occur in poor prognosis patients, those with an emergent need to start cancer therapy, or with low cancer-related infertility risk. This indicates that doctors feel that cancer patients who face a severe illness are less likely to be interested in fertility, therefore they do not initiate fertility discussions. The same was reported concerning certain socio-demographic patient traits, with clinicians being less likely to discuss FP with female patients, with those under the age of adulthood, those who are single, homosexual or who already have children. Time with patients was reported as another important barrier, with most oncologists expressing being pressured to consult a great number of patients in a short amount of time, topics beyond the cancer diagnosis and treatment become a lower priority. In spite of financial barriers being also referred as important, in Portugal FP methods are offered cost free to both male and female young patients facing cancer-related infertility risk[21, 23].

In Portugal, and in terms of barriers to the oncologists' practices, the 2013-2015 cross-sectional study found out that "time with patients" was significantly strongly endorsed and "oncologist's knowledge about FP" was significantly poorly endorsed ($p<.001$, $n^2=0,43$) by these clinicians. However, the strength of the endorsement of oncologists' intrinsic barriers (i.e. their knowledge, communication skills and their subjective perception of discussing fertility with patients with different clinical and socio-demographic characteristics) proved to be more strongly associated with each other than with extrinsic barriers (lack of time with patients) and a stronger endorsement of the barriers "oncologists' communication skills" and "patient-related factors" was related to a lower frequency of informing about both the risk of cancer-related infertility and about FP, making it very important to develop and implement strategies to overcome such barriers [12, 21].

Implemented Strategies for Oncologists

It is believed that increasing clinicians' knowledge about FP methods and cancer-related infertility results in an increment in clinicians informing practices about cancer-related infertility and FP as well as referral to reproductive medicine [12, 15, 20].

In line with other countries, several actions were undertaken in Portugal to increase the oncologists' knowledge regarding cancer-related infertility and FP options. Portuguese clinical

societies (e.g. the Portuguese Society for Reproductive Medicine, the Portuguese League Against Cancer) developed several information tools for oncologists regarding the reproductive future of cancer patients (e.g. pamphlets, websites) [20]. Some materials from the Oncofertility Consortium (eg, iSaveFertility app, Web site http://www.myoncofertility.org, and Repropedia tool) were translated into Portuguese to allow a better knowledge about FP, thereby aiding in the decision-making process. The Portuguese Centre of Fertility Preservation, CFP, Coimbra Hospital and University Centre, CHUC, EPE, also aimed to better inform health professionals about the impact of cancer in fertility, the techniques available for FP, and how to assemble a team that can provide counselling and assistance in decision making. In order to achieve such goals, information fact-sheets for clinicians were created and a Website was launched with information and tools tailored specifically to Portuguese health professionals [12]. In cooperation with the Portuguese League Against Cancer, LPCC, a Portuguese non-profit cancer patients' organization, the CFP conducted a project to develop and disseminate oncofertility information resources, directed to health professionals and in collaboration with the Portuguese Society for Reproductive Medicine, organized postgraduate courses to oncologists, the first having occurred in October 2013. The Portuguese Society for Reproductive Medicine, SPMR, and the Portuguese Oncology Society, SPO, in cooperation with the national hematology and andrology professional societies, published and endorsed the ‘‘Portuguese Recommendations for Preserving the Reproductive Potential of Cancer Patients’’ [13, 15, 20].

Portuguese Surrogacy Laws

Recent developments regarding surrogacy laws in Portugal have occurred. The prior Portuguese 32/2006 law provided as medically assisted procreation techniques the following: a) Artificial insemination; b) In vitro fertilization; c) Intracytoplasmic sperm injection; (d) transfer of embryos, gametes or zygotes; e) Pre-implantation genetic diagnosis; f) Other laboratory techniques of equivalent or subsidiary gametic or embryonic manipulation.

The 25/2016 law arouse to change the 32/2006 law, by adding "gestation of substitution" as a medically assisted procreation technique. "Gestation of substitution" or "surrogacy" is comprehended as any situation in which the woman is willing to support a pregnancy on behalf of others and to deliver the child after childbirth, renouncing the powers and duties proper to maternity. The celebration of a legal business of surrogacy is only possible exceptionally and with a gratuitous nature, in cases of absence of uterus or injury of this organ that absolutely and definitively prevents the pregnancy of the woman or in clinical situations that justify it.

Surrogacy may only be authorized by means of a medically assisted procreation technique using the gametes of at least one of the respective beneficiaries, and in no case may the replacement pregnant woman be the donor of any oocyte used in the concrete procedure in which it is a participant.

The conclusion of legal business of replacement pregnancy requires prior authorization from the National Council for Medically Assisted Procreation (CNPMA), which oversees the entire process, which is always preceded by hearing from the Medical Association. If the request to access the replacement gestation is accepted, the beneficiary couple and the substitute pregnant woman must abide to a contract made available by CNPMA with a mandatory content to which subscribers may add clauses if they so wish.

Objectives

The main objectives of this study were: 1) to assess the current practices of a sample of medical doctors with different clinical specialties that treat cancer patients regarding the reproductive future of female cancer patients of childbearing age; 2) to describe the strength of endorsement of the main barriers to clinicians' practices; 3) to examine the individual characteristics of the clinicians and how they relate to their clinical practice; 4) to examine the oncologists' perceptions regarding surrogacy as an implication for FP practices and the role of its individual characteristics in these perceptions.

The present study was part of an integrated medical master's degree of a sixth year medical student at the Faculty of Medicine of the University of Coimbra.

Measures

A self-report questionnaire combining 43 items, organized in seven sections, was created based on the previous study developed during 2013-2015, in Portugal [21]. A research team, including a reproductive medicine doctor and a psychologist with clinical experience in FP and a sixth year medical student, adapted the questionnaire due to new important information regarding Portuguese law towards FP methods. A Linkert scale was used to assess the oncologists responses. A complete version of the questionnaire can be seen in attachment 1.

After adaptation, the questionnaire was piloted with six clinicians with different clinical specialties (e.g., medical oncology, gynaecology and haematology), so that the items could be examined and revised for clarity and comprehensibility before the beginning of the study. The final self-report questionnaire took approximately seven minutes to complete.

The following topics describe the questionnaire:

- Personal Information

The inclusion criteria were being a doctor that assists female cancer patients of childbearing age in a Portuguese clinical institution and having knowledge and understanding of Portuguese.

Socio-demographic (gender and age) and clinical practice-related (clinical specialty, number of female cancer patients of childbearing age assisted per year) information was collected.

- Practices Regarding Female Fertility Preservation

Doctors were asked about:

1) the frequency of informing about the risk of cancer-related infertility — *"How often do you inform your female cancer patients of childbearing age about the potential impact of cancer treatment on their fertility*?"

2) the frequency of informing about FP — "*How often do you inform your female cancer patients of childbearing age who are at risk of cancer-related infertility about the possibility to preserve their fertility?".*

These questions were answered using a 5-point Likert scale ranging from 0 (Never) to 4 (Always).

Doctors were asked about the number of patients referred to a reproductive medicine doctor (i.e. in Portugal, this is the fertility specialist to whom patients need to be referred to discuss

FP, make a decision and implement it) — "How many female cancer patients of childbearing age do you remember referring to a reproductive medicine doctor to preserve their fertility in all your years of clinical practice?". An open-ended answer was obtained.

- Barriers to Practices Regarding Female Fertility Preservation

A total of 19 question items were presented to assess the barriers towards the practice of female FP. This section began with the query "*How much do you identify with the following sentences?"* and doctors were asked to evaluate their agreement within the items using a 5-point Likert scale ranging from 0 (Entirely disagree) to 4 (Entirely agree).

These 19 items, that were developed based on those used in prior studies [21], as well as new questions based on the recently modified Portuguese law, were organized along four dimensions, as in the previous study[21]. Each dimension refers to a different type of barrier in oncologists' practices regarding FP:

1) Oncologists' knowledge of FP (seven items; e.g. "*I do not know reproductive medicine doctors to whom to refer patients for FP.*");

2) Oncologists' communication skills (two items; e.g. "*I only inform the patient about the risk of cancer-related infertility when she initiates the topic.*");

3) Patient-related factors (nine items; e.g. *"I do not inform the patient about the risk of cancer-related infertility when she already has children.*");

4) Time with patients (one item; "*I have little available time with the patients to discuss the risk of cancer-related infertility.*").

- Clinicians Perception Regarding Surrogacy

Two items were developed by the research team to assess the clinicians' perception regarding surrogacy: "*The lack of clear regulations in Portugal on surrogacy prevents me from referring patients with cervical cancer, uterus cancer or absence of it, to a specialist in reproductive medicine for decision-making regarding their preservation of fertility*" and "*If surrogacy was legalized in Portugal, I would approach this hypothesis with cancer patients in need of this technique as a gestational alternative"*. Clinicians were asked to evaluate their agreement within the items using a 5-point Likert scale ranging from 0 (Entirely disagree) to 4 (Entirely agree).

Procedures and Disclosure

A total of 68 male and female doctors who assist female cancer patients at clinical institutions in Portugal were recruited face-to-face (n = 26; 38,2% response rate, based on the total number of surveys delivered) and online (n = 42; 61,8%) between September 2018 and November 2018. Face-to-face recruitment was performed in different clinical institutions, Coimbra's Portuguese Oncology Institution (IPO) and Coimbra's University Hospital (CHUC), after the

authorization of the Ethics Committee of these institutions. All of the participants were individually approached by a researcher to be invited to participate in the study and they were given information concerning the research goals, the anonymity of the answers provided, the participants' role and the researchers' obligations, and they expressed their consent in participating in the study in the beginning of each survey. The participants received the survey in an envelope and were instructed to complete it at that moment or later on and to return it to the researchers in a pre-addressed sealed envelope. Online recruitment was performed through a secure Internet-based survey (hosted by https://www.google.com/forms/) whose web link was advertised on Facebook groups of physicians and promoted by e-mail by the Portuguese Society of Oncology (Sociedade Portuguesa de Oncologia, SPO) to all of its members. Participation was voluntary and no remuneration was provided.

Statistical analyses

Analysis were conducted using IBM Statistical Package for the Social Sciences, version 23.0 (SPSS Inc., Chicago, IL, USA). A first descriptive analysis of the data was made. $\chi 2$ and non-parametric tests (when appropriate) were used, due to lack on normal distribution, to identify possible associations between variables. Associations were made to group different response options (per example, "Very often" and "Always") as well as age (0-39 and 40-150).

Preliminary Analysis of the Participants

A total of 68 doctors who assist female cancer patients in different clinical institutions in Portugal participated in the present study. Approximately two-thirds of the oncologists were women (n = 49, 72.10%) and had a mean age of 41,00 years old (SD = 11.20). The most frequent clinical specialty was medical oncology [n = 31, 45.60%; with a mean number of female cancer patients assisted per year of 108,21 (SD = 131,99, ranging from 5 to 500)], followed by gynecology [n = 23, 33.80%; with a mean number of female cancer patients assisted per year of 125.74 (SD = 196.44, ranging from 2 to 800)] and hematology [n = 9, 13.20%; with a mean number of female cancer patients assisted per year of 24.44 (SD = 16.67, ranging from 4 to 50)]. The less frequent clinical specialties were grouped together in the “Other” category [n = 5, 7.40%; with a mean number of female cancer patients assisted per year of 23.80 (SD = 14.50, ranging from 7 to 40)].

Oncologists' Practices Regarding Patients’ Reproductive Future

The majority of clinicians reported discussing with their female childbearing aged cancer patients about their reproductive future; 91,2% (*n* = 62) "very often" or "always" declared informing them about the risk of cancer-related infertility, and 83,8% (*n* = 57) "very often" or "always" reported informing them about their FP options. However, 1,5% (*n* = 1) and 5,9% (*n* = 4) of the clinicians "almost never" inform about their female patients about their risk of cancer-related infertility and about FP options respectively. None of the clinicians stated "never" informing their patients in childbearing age about the risk of cancer-related infertility nor about FP options.

Physicians report that, in all their years of clinical practice, they have referred, on average, 18,89 (SD = 34.44, ranging from 0 to 200) female cancer patients to a reproductive medicine doctor to make a decision about FP. A great proportion of clinicians (65.2%, n = 43) report that they had referred fewer than 10 female cancer patients, and only 5 (7.60%) oncologists indicated that they had "never" referred any patient to a reproductive medicine doctor.

Significant and positive correlations between clinicians’ practices regarding patients’ reproductive future were found. Specifically, a higher frequency of informing about the risk of cancer-related infertility was strongly associated with a higher frequency of informing about FP options (r = .679, p < .001). A higher frequency of informing about FP was also moderately associated with a higher number of patients referred to a reproductive medicine doctor (r = .247, p < .05).

Barriers to Physicians Regarding Fertility Preservation

Table 1 presents information about the explored barriers to the clinicians'' practices regarding FP. Differences concerning clinicians' relative strength of endorsement of such barriers were found, specifically the barrier "time with patients", the most positively endorsed barrier, when compared to "oncologist's knowledge", the most poorly endorsed barrier, ($r=0.293$; $p<0.05$).

Table 1 - Barriers to oncologists' practices regarding FP

	Entirely disagree n(%)	Slightly disagree n(%)	Somewhat agree n(%)	Mostly agree n(%)	Entirely agree n(%)	Dimension Medin min-max
Oncologists Knowledge of FP						0 0-2
1. The success rates of the FP techniques are so low that it is not important to refer patients to a reproductive medicine doctor	55 (76,5)	9(13,2)	6(8,8)	1(1,5)	0	
2. I do not discuss fertility with my cancer patients, taking into account the risk of a cancer recurrence and/or of offspring malformation	61(89,7)	5(7,4)	2(2,9)	0	0	
3. Most of the FP techniques are still experimental, so I should not refer cancer patients to a reproductive medicine doctor	54(79,4)	11(16,2)	3(4,4)	0	0	
4. I do not discuss the risk of cancer-related infertility with my patients, because I do not know where to refer them	54(79,4)	12(17,6)	2(2,9)	0	0	
5. I do not know reproductive medicine doctors where to refer patients to FP	54(79,4)	8(11,8)	5(7,4)	0	1(1,5)	
Oncologists' communication Skills						2 0-4
6. I only inform the patient about the risk of cancer-related infertility when she initiates the topic	49(72,1)	10(14,7)	8(11,8)	0	1(1,5)	
7. I feel comfortable discussing the risk of cancer-related infertility with my cancer patients.	3(4,4)	4(5,9)	8(11,8)	21(30,9)	32(47,1)	
Patient-related Factors						1.11 0-2.22
8. Cancer patients are not interested in the fertility topic, because they	38(55,9)	18(26,5)	9(13,2)	2(2,9)	1(1,5)	

are facing a severe illness. So I do not talk about it						
9. I only inform patients about the risk of cancer-related infertility when they are married.	60(88,2)	6(8,8)	1(1,5)	1(1,5)	0	
10. I discuss the risk of cancer-related infertility with all my cancer patients.	2(2,9)	8(11,8)	8(11,8)	23(33,8)	27(39,7)	
11. I do not discuss the risk of cancer-related infertility with patients with a bad prognosis.	14(20,6)	18(26,5)	23(33,8)	12(17,6)	1(1,5)	
12. I do not discuss the risk of cancer-related infertility with patients under de age of majority	42(71,2)	10(16,9)	3(5,1)	3(5,1)	1(1,7)	
13. I do not discuss the risk of cancer-related infertility with patients in emergent need to start cancer therapy	40(58,8)	16(23,5)	8(11,8)	3(4,4)	1(1,5)	
14. I do not inform the patient about the risk of cancer-related infertility when she already has children	48(70,6)	17(25)	2(2,9)	1(1,5)	0	
15. I do not inform the patient about the risk of cancer-related infertility when she is homosexual	52(76,5)	9(13,2)	2(2,9)	5(7,4)	0	
16. I always discuss the risk of cancer-related infertility, even when the patient has a high probability of being fertile after cancer treatment	6(8,8)	9(13,2)	13(19,1)	23(33,8)	17(25)	
Time with Patients						1 0-4
17. I have little time available with the patients to discuss the risk of cancer-related infertility	33(48,5)	12(17,6)	17(25)	5(7,4)	1(1,5)	

The role of oncologists' individual characteristics in their practices regarding the reproductive future and in the strength of endorsement of barriers to these practices

Table 2 presents information about the role of the clinicians' individual characteristics (i.e. gender, age, clinical specialty) in their practices regarding patients' reproductive future (i.e. frequency of informing about the risk of cancer-related infertility, frequency of informing about FP). Visually analyzing the frequencies (n, %) of each group, it is possible to verify gender differences concerning the frequency of informing about the risk of cancer-related infertility. Female clinicians revealed being more prone to inform than male clinicians. Moreover, it is also possible to visualize

that older oncologists reported informing about FP more frequently than younger oncologists. The clinical specialty that revealed less informing about the risk of cancer related infertility and about FP were the hematologists.

Table 2 - Clinicians' practices regarding the reproductive future of female cancer patients

		Gender		Age		Clinical Specialty			
		Male n(%)	Female n(%)	</=40 n(%)	>40 n(%)	Medical Oncology n(%)	Gynecology n(%)	Hematology n(%)	other n(%)
Frequency of informing about risk of cancer related infertility	Never/Rarely	4 (21.1%)	2 (1.1%)	2 (6.3%)	3 (11.1%)	2 (6.5%)	2 (8.7%)	2 (22.2%)	
	Oftentimes	9 (47.4%)	21 (42.9%)	18 (56.3%)	12 (33.3%)	18 (58.1%)	6 (26.1%)	4 (44.4%)	2 (40.0%)
	Always	6 (31.6%)	26 (53.1%)	12 (37.5%)	20 (55.6%)	11 (35.5%)	15 (65.2%)	3 (33.3%)	3 (60.0%)
Frequency of informing about FP	Never/Rarely	2 (10.5%)	9 (18.4%)	6 (18.8%)	5 (13.9%)	2 (6.5%)	5 (21.7%)	3 (33.3%)	1 (20.0%)
	Oftentimes	12 (63.2%)	16 (32.7%)	14 (43.8%)	14 (38.9%)	18 (58.1%)	3 (13.0%)	5 (55.6%)	2 (40.0%)
	Always	5 (26.3%)	24 (49.0%)	12 (37.5%)	17 (47.2%)	11 (35.5%)	15 (65.2%)	1 (11.1%)	2 (40.0%)

Table 3 presents information about the role of the clinicians' individual characteristics (i.e. gender, age, clinical specialty) in the strength of endorsement of the barriers towards FP practices. Visually analyzing the frequencies (n, %), it is possible to verify that there were age and clinical specialty differences concerning the barrier theme of "Time with patients", with older clinicians more strongly endorsing this barrier to their practices regarding FP compared to younger clinicians, as well as the group of "gynecologists" and "other" comparing to the group of "Hematology". Visually, it is not possible to detect any differences concerning gender.

Table 3 - The role of oncologists' individual characteristics in their practices regarding the reproductive future and in the strength of endorsement of barriers to these practices.

	Barriers to practices regarding FP							
	Oncologist's Knowledge of FP Md(Q1;Q3) min-max	**p**	**Oncologists' communication skills** Md(Q1;Q3) min-max	**p**	**Patient-related factors** Md(Q1;Q3) min-max	**p**	**Time with patients** Md(Q1;Q3) min-max	**p**
Individual characteristics								
Gender								
Male	2.00(1.50;2.0)	0.455	2.00(1.50;2.0)	0.027	2.00(1.50;2.0)	0.798	1(0;2)	0,869

	1.50-4.0		1.50-4.0		1.50-4.0		0-3	
Female	2.00(1.50-2.0) 0.00-2.50		2.00(1.50-2.0) 0.00-2.50		2.00(1.50-2.0) 0.00-2.50		1(0;2) 0-4	
Age								
≤40	2.00(1.50;2.0) 1.50-3.0	0.463	2.00(1.50;2.0) 1.50-3.0	0.578	2.00(1.50;2.0) 1.50-3.0	0.816	2(0;2) 0-4	0.017
>40	2.00(1.50;2.0) 0.00-4.0		2.00(1.50;2.0) 0.00-4.0		2.00(1.50;2.0) 0.00-4.0		0(0;1) 0-3	
Clinical Specialty								
Medical oncology	2.00(1.50;2.0) 0.00-3.0	0.268	2.00(1.50;2.0) 0.00-3.0	0.675	2.00(1.50;2.0) 0.00-3.0	0.341	1(0;2) 0-3	0.024
Gynecology	2.00(1.00;2.0) 0.00-4.0		2.00(1.00;2.0) 0.00-4.0		2.00(1.00;2.0) 0.00-4.0		0(0;2) 0-3	
Hematology	2.00(1.50;2.0) 0.00-2.50		2.00(1.50;2.0) 0.00-2.50		2.00(1.50;2.0) 0.00-2.50		2(1;3) 0-4	
Other	2.00(1.50;2.0) 1.50-2.00		2.00(1.50;2.0) 1.50-2.00		2.00(1.50;2.0) 1.50-2.00		0(0;0) 0-1	

Oncologists' Perceptions Regarding Surrogacy

Table 4 presents the perceptions of the clinicians regarding surrogacy and the role of its characteristics in these perceptions. In general, the majority of the clinicians (45.5%) disregards the lack of regulation about Surrogacy as a prospective barrier to their FP practices. In terms of the role of oncologists' characteristics in their perceptions, visually analyzing the frequencies it is possible to detect that medical oncologists and hematologists more strongly agreed with this perception (36.7% and 50% respectively), when compared to other specialties. When asked about their receptivity about surrogacy as a gestational alternative, most of the oncologists "disagreed" to "somewhat disagreed" (53%) and only 20.3% "entirely agreed". Visually analyzing the frequencies, we detected differences in gender and clinical specialty regarding the valorization of surrogacy as a gestational alternative. Gynecologists female oncologists reported more strongly agreeing with these option, when compared to men and other clinical specialties.

Table 4 - oncologists' endorsement to surrogacy as a fertility preservation barrier and future practice

		Sex		Age		Clinical Specialty			
	(%)	Male	Female	</=40	Male	Female	</=40	Male	Female
The lack of clear regulations in Portugal on replacement gestation prevents me	Entirely Disagree (45.5%)	9	21	15	15	12	13	2	3
		47,4%	44,7%	50,0%	41,7%	40,0%	56,5%	25,0%	60,0%
	Slightly Disagree (19.7%)	3	10	4	9	6	5	1	1
		15,8%	21,3%	13,3%	25,0%	20,0%	21,7%	12,5%	20,0%
		6	11	7	10	11	1	4	1

from referring patients with cervical cancer to the uterus and /or absence of it, to a specialist in reproductive medicine for decision-making regarding their preservation of fertility	Somewhat Disagree (25.8%)	31,6%	23,4%	23,3%	27,8%	36,7%	4,3%	50,0%	20,0%
	Mostly Agree (6.1%)	1	3	3	1	0	3	1	0
		5,3%	6,4%	10,0%	2,8%	0,0%	13,0%	12,5%	0,0%
	Entirely Agree (3.0%)	0	2	1	1	1	1	0	0
		0,0%	4,3%	3,3%	2,8%	3,3%	4,3%	0,0%	0,0%
If gestation of substitution was legalized in Portugal, I would approach this hypothesis with oncological patients needing this technique as a gestational alternative	Entirely Disagree (18.2%)	3	10	7	6	5	5	2	1
		15,8%	20,4%	21,9%	16,7%	16,1%	21,7%	22,2%	20,0%
	Slightly Disagree (12.1%)	3	5	4	4	6	1	1	0
		15,8%	10,2%	12,5%	11,1%	19,4%	4,3%	11,1%	0,0%
	Somewhat Disagree (22.7%)	6	10	5	11	11	1	2	2
		31,6%	20,4%	15,6%	30,6%	35,5%	4,3%	22,2%	40,0%
	Mostly Agree (16.7%)	4	7	7	4	4	3	3	1
		21,1%	14,3%	21,9%	11,1%	12,9%	13,0%	33,3%	20,0%
	Entirely Agree (20.3%)	3	17	9	11	5	13	1	1
		15,8%	34,7%	28,1%	30,6%	16,1%	56,5%	11,1%	20,0%

The main goal of this study was to assess the current practice and barriers of the Portuguese clinicians' regarding FP and how they were affected by the implemented measures to improve past practices, according to the 2013-2015 study.

The main findings of this study were: 1) A higher number of clinicians report that "very often" or "always" inform their female patients about the risk of cancer-related infertility and FP; a smaller number of clinicians say "almost never" and none of the clinicians' report "never" having informed their female patients about the risk of cancer-related infertility and about FP; 2) A greater number of clinicians report referring their female child-bearing aged cancer patients to a reproductive medicine doctor. The number of doctors that never have referred or have referred less than 10 being inferior than the results obtained in past studies. 3) "time with patients" still is the most endorsed barrier; 4) the majority of clinicians' disregard lack of surrogacy laws as a prospective barrier to their FP practices, and "disagree" to "somewhat disagree" that it should be implemented as an alternative method for obtaining a pregnancy after FP.

Oncologists' Practices Regarding Fertility Preservation

The majority of clinicians reported having the childbearing female cancer patients' reproductive future into account in their clinical practice, discussing with these patients their cancer-related fertility risks and FP options. However, the frequency of patients' referral to the reproductive medicine doctor was low. We can hypothesize that, although clinicians had already begun to understand the importance of addressing this issue, the patients' referral to a reproductive medicine doctor is not yet rooted to their daily clinical practice. This can be due to the patients' reserved prognosis and the emerging need to start cancer therapy. However, comparing our results with the 2013-2015 study results, the number of clinicians that "very often" or "always" informed about the cancer-related infertility risk and about FP options has increased from 65.7% to 91.2% and from 59.3% to 83.8%, respectively [21]. No oncologist reported having "never" informed about the cancer-related infertility risk and about FP. This awareness improvement was also observed in the total of patients' referral to the reproductive medicine doctor, from, in average, 7.38 to 18.89, reducing the number of doctors that have never referred any patients (17.50 % to 7.60%) or that have referred less than 10 female patients (75.80% to 65.20%). These results highlight the importance and the impact of the measures applied in Portugal between the 2013-2015 study and our study, in order to improve clinicians' awareness and their practices regarding FP in child bearing aged female cancer patients. Increasing clinicians' knowledge about FP methods and cancer-related infertility leads to an increment in clinicians´ informing practices about cancer-related infertility and FP as well as overall patients' referral to the reproductive medicine doctor to make an FP decision. The results found amongst the group of hematologists, a specialty that endorses cancers with high

prevalence in reproductive-age patients, should be interpreted with caution. In spite of this clinical specialty appeared to have poor informing practices, the number of hematologists in our sample was very small.

Oncologists' Barriers Regarding Fertility Preservation

As the 2013-2015 study concluded, "time with patients" was still the most endorsed barrier by the oncologists to their FP practices [21]. We hypothesize that the reason for these results remains the same as in the 2013-2015 study, as meanwhile no change had occurred in the Portuguese public-health system regarding time per consultation. In order to overcome this context, we propose that FP discussions should occur with more than one clinician. In Portugal, cancer patients tend to be followed by more than one physician, going from the general practitioner, the oncological surgeon, up to the clinician that defines, in a multidisciplinary counseling, the course of treatments. Therefore, if at least one of these clinicians talks about FP, before treatment begins, it will allow to spend less time per consult in the subject of FP. The existence of referral strategies will also facilitate this practice. In oncological treatment centers who have reproductive medicine consultations, time used to manage FP and cancer treatment is shorter, as it is easier to refer patients to such consultation. Therefore, it is recommended that every oncologic treatment center should have a reproductive medicine specialist. "Oncologists communication skills" were in the 2013-2015 study, and still are in this study, the least endorsed barrier by the clinicians. In addition to the reasons hypothesize in the previous study, we hypothesize that this can be now also a result of the implemented measures to improve clinicians' practices. The differences detected visually concerning oncologists' age, with older oncologists having better FP practices, may be related to the fact that the mean age of our sample was low.

Oncologists' Perceptions Regarding Surrogacy

This is the first study, to our knowledge, that assessed Portuguese clinicians' perceptions about surrogacy as a barrier to FP practices and their approval to its use as a gestational option. The majority of clinicians disregarded the lack of regulation laws allowing surrogacy as a barrier to informing their female cancer patients about the risk of cancer-related infertility and about FP. However, 9,1% of the clinicians "mostly" or "entirely agreed" that it is a barrier towards their practice. When asked about their perceptions about the implementation of surrogacy as a gestational technique, the majority of clinicians "disagreed" to "somewhat disagreed" it should be implemented. It is possible to hypothesize it to be due to a cultural perspective, as well as to lack of information about surrogacy, its applicability in reproductive medicine, as well as the clinicians' communication skills to inform about such issue. This is supported by the fact that there was a group of clinicians that supported its practical application, mostly gynecologists, who are perceived to be the most knowledgeable clinical group about surrogacy. Therefore, taking into account that the majority of the clinicians reported that it will not affect their practice, there is the need to inform clinicians about the subject and capacitate them to communicate with their patients about it.

Limitations

The main limitation of this study was the low number of participants. Therefore, conclusions may not be representative of the Portuguese scenario. In addition, it is possible that the clinicians with more interest in the subject in question have been more inclined to respond to the survey, which affects the generalization of the results, being a potential selection bias.

As expected, due to the implemented strategies increasing clinician's knowledge about FP methods and cancer-related infertility, the present study found an improvement in the overall clinicians' practice towards female child-bearing aged cancer patients, improving the information practices about cancer related fertility risk and about FP, as well as enhancing the number of referrals to reproductive medicine doctors.

This study also added information about the clinicians' perspective about surrogacy as a barrier and a future practice. It was noted that few but some clinicians regard the lack of regulation allowing surrogacy as a gestational alternative as a barrier towards their practice and that the majority of clinicians' disregard the implementation of surrogacy as an important reproductive alternative. Therefore, a continuous need for increasing clinicians' knowledge about surrogacy is imperative.

However, there is still space for improvement, as some clinicians' still "almost never" inform about cancer related treatment-induced infertility risk and about FP, and referrals can be improved by developing referral strategies.

"Recomeça...
Se puderes
Sem angústia
E sem pressa.
E os passos que deres,
Nesse caminho duro
Do futuro
Dá-os em liberdade.
Enquanto não alcances
Não descanses.
De nenhum fruto querias só metade.
..."
Sísifo de Miguel Torga

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