Fertility preservation to prevent age-related fertility decline: Systematic review

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Abstract

Background: Fertility Preservation (FP) to prevent age-related fertility decline has been subject of great discussion, concerning ethical, legal and religious questions. The present study aims to provide a systematic revision of the contributes in the literature on fertility preservation to prevent age-related fertility decline, namely on 1) what characterize women that consider FP but did not make a decision yet and the women that have actually done it, specifically their individual characteristics and reasons, as well as 2) the knowledge and attitudes of the general practitioners (GPs) about FP, since they are the first-line agents in its disclosure.

Methods: An electronic search in three databases was performed, following the procedure of PRISMA, using the keywords: ("*oocyte freezing*", "*cryopreserve oocytes*", "*fertility preservation*", "*oocyte vitrification*") and ("*age-related fertility decline*", "*age-related fertility loss*", "*decline in fertility age*"). Nine studies were selected and included in this systematic review.

Results: The percentage of women who considered FP as a future option varied according to the studies (15.1% - 31.5%). Women generally performed cryopreservation of oocytes at a later age (approximately 36 to 38 years old) from the recommended period to optimize the technique. The desire to find a suitable partner to share parenting was the main reason that led the women to perform this procedure. In general, GPs have a limited knowledge on FP.

Conclusions: In order to provide the necessary conditions for women of childbearing age to make conscious and informed reproductive decisions, fertility procedures need to be more disseminated, namely toward GPs.

Keywords: Fertility preservation, cryopreserve oocytes, age-related fertility decline, general practitioners, reproductive health.

1. Introduction

Fertility preservation (FP) is an assisted reproductive technique (ART) that allows the cryopreservation of gametes (sperm and oocytes) for long periods of time at temperatures below zero, providing the opportunity to have genetic offspring later (1, 2). Harvesting requires an ovarian stimulation and subsequently oocyte collection (4). There are two main strategies: slow freezing and vitrification, the second presenting higher success rates (5). Later, when women decide to have genetic offspring, they will undergo through a process of in vitro fertilization (IVF) with their cryopreserved oocytes (6). To perform this procedure, Cobo and colleagues (6) suggested that at least eight to ten Metaphase II oocytes should be cryopreserved to ensure a reasonable success rate when using IVF.

FP has been used with at least two different purposes. Firstly, due to medical reasons, particularly cancer patients, because the treatments could affect their ovarian reserve, or women with other medical conditions that may lead to an earlier menopause (1). Secondly, because of non-medical reasons, for healthy women who want to postpone maternity (1).

Given the cost-effectiveness of this technique, IVF with cryopreserved oocytes have a better cost-effectiveness relation than IVF with fresh eggs or natural conception, being more cost-effective as older women have lower chances of conceiving naturally (7). Regarding the cost, a study conducted by van Loendersloot and colleagues (7) showed that when women undergone three cycles of ovarian hyperstimulation at the age of 35 the average cost of this procedure cost was €10 419, with a live birth rate of 84.5%, at age 40. When women cryopreserve their oocytes at the recommended age range, there is a higher success rate and a lower rate of health risks to offspring, comparing with using fresh but age-compromised oocytes (4).

Indeed, when women decided to undergo by IVF at age 37, the probability of live birth with cryopreserved oocytes (before their 34 years) was much higher (51.6%), comparing with no action (21.9%). The live birth rate is highest when FP is performed at a younger age, preferably before 34 years (>74% probability of live birth) (8).

In the last years, the average age at which women decide to start a family is increasing and the number of women that decide to be a mother for the first time after 35 years old has been increasing significantly (9), due to sociological and demographic factors (10). Actually, with the impact of social changes in lifestyle, a group constituted by women mostly at 40 years old, heterosexual, highly skilled, confident and financially independent is appearing, although without a stable partner (6). Therefore, FP could be an opportunity to delay motherhood until they feel that they gathered all the conditions they aspire to have genetic offspring.

During the last years, the number of women that are interested in ART is growing (11). The use of FP for social purposes has only recently been discussed. This issue raises some controversy, as it deals ethical, legal, and religious concerns (2, 10). However, it is currently a technique in progress, which may provide many benefits in the future (2). Actually, ART specialized clinics are suggesting that FP can be used by women that are not prepared to start a family, because they do not have the right partner, financials issues, are not emotional prepared or have other life plans (11). However, it is unclear how women make decisions about FP and which professionals they consult. Therefore, it would be important to understand how well-informed professional are, especially those at the primary services level, providing women and men with accurate information upon which to base their fertility timing decisions.

Women fertility starts to decline with the increase of age, beginning to decrease at the age of 30, accelerating the decline after 35 years old (12), affecting the number

and quality of available oocytes and, finally, a total decline after 40/45 years old (4, 12). With the increase of age, the risk of developing other disorders increases as well (e.g., fibroids, endometriosis) (13). Thus, the optimum period to do FP is before fertility starts to decline. A study conducted by Cil and colleagues (5) suggested that the optimal age to do it is before 36 years old. However, women can cryopreserve their eggs at a later age, according to their preferences, values and available resources (5). Regarding the limit age to use this procedure, a study by Cil and colleagues (5) argues that the interval between 42 and 45 years old should be carefully considered.

Procreation decision is a complex and long process that includes a lot of stages. It is important to improve women awareness of the costs and limitations of ART, since this could influence their fertility planning decision (14). This need to be done in the right time (late 20s or early 30s), in order to optimize the cryopreservation technique. GPs' knowledge and attitudes regarding FP techniques influence the whole women´s decision process, from the moment of the decision to the end of the procedure, due to their involvement in the process, both informative and supportive. For this, it is also important that GPs understand the perceptions, barriers and reasons that lead these women to perform this procedure.

This study aims to provide a systematic review of the literature on FP to prevent age-related fertility decline, namely on 1) what characterize women that consider FP but did not make a decision yet and the women that have actually done it, specifically their individual characteristics and reasons, as well as 2) the knowledge and attitudes of the general practitioners (GPs) about FP, since they are the first-line agents in its disclosure.

Other revisions have been made on FP due to social reasons (2, 3, 5, 10). Although, as far as we know, no one included the individual characteristics and reasons

of women that did not intend to do the procedure, women that intend but did not make a decision yet and studies with women that actually did the procedure, as well as including the health professionals' attitudes and knowledge toward FP, in the same systematic revision. This is an important novelty of this systematic revision, providing a comprehensive framework on the role of health professionals in the parenthood decision of these women. Therefore, this revision is helpful to a future psychoeducational programme for GPs toward FP.

2. Methods

Data sources and search methodology. Based on PRISMA procedures "Preferred Reporting Items for Systematic Reviews and Meta-Analysis" (15), an electronic search in three databases it was performed: PubMed [Title/Abstract], Web of Science [Title] and PsycINFO [Title], using the following keywords related to the review subject, combined with standard MeSH terms ("*oocyte freezing*", "*cryopreserve oocytes*", "*fertility preservation*", "*oocyte vitrification*") and ("*age-related fertility decline*", "*age-related fertility loss*", "*decline in fertility age*").

Study selection (screening). In order to meet the purpose of this study, only empirical articles about the association between FP and declining fertility with advancing age, namely about the intentions, attitudes or knowledge of women about it, were analyzed.

Data extraction. Eligibility. At first, the titles and abstracts of all the initially identified articles (n = 41) were analyzed, in order to have access to all the potentially relevant references. Articles that did studied FP for other reasons (e.g., cancer, ovarian stimulation) were excluded (n = 12). Then, the full articles were analyzed (n = 23), excluding the ones that did not meet the inclusion and exclusion criteria: non-original

research (n = 15). Finally, during this analysis, a study that fulfilled the previously defined criteria was included.

Inclusion. The final articles included in this systematic review (n = 9) were analyzed and their results were described according to a standardized data extraction table, extracting information regarding the authors, date of publication, study objectives, sample size, study design, measures and, finally, the results.

The search and selection were performed by the first author. The complete procedure was separately done by the second author and selected studies were confirmed with no disagreement between them.

Data analysis. Qualitative results of each study regarding the association between FP and the age-related fertility decline (ARFD), namely about the intentions, attitudes or knowledge of women about it, were retrieved (n = 9).

Then, when analyzing these qualitative results, the knowledge and attitudes of the GPs toward FP were also incorporated, because of the extreme importance that these papers gave to the role of these professionals in the discussion of the FP.

3. Results

From these three databases, 41 relevant studies with relevant references were identified. Duplicated studies were removed (n = 6). After that, 12 studies were removed based on the analysis of the title and abstract, and 15 based on analysis of the complete text. During the analysis of the nine articles previously included, one of those suggested another relevant empirical study, which was included afterwards. In the end, nine studies were included in this systematic review. A flow diagram of the search selection for the included studies is presented in Fig. 1, and the procedures are described below.

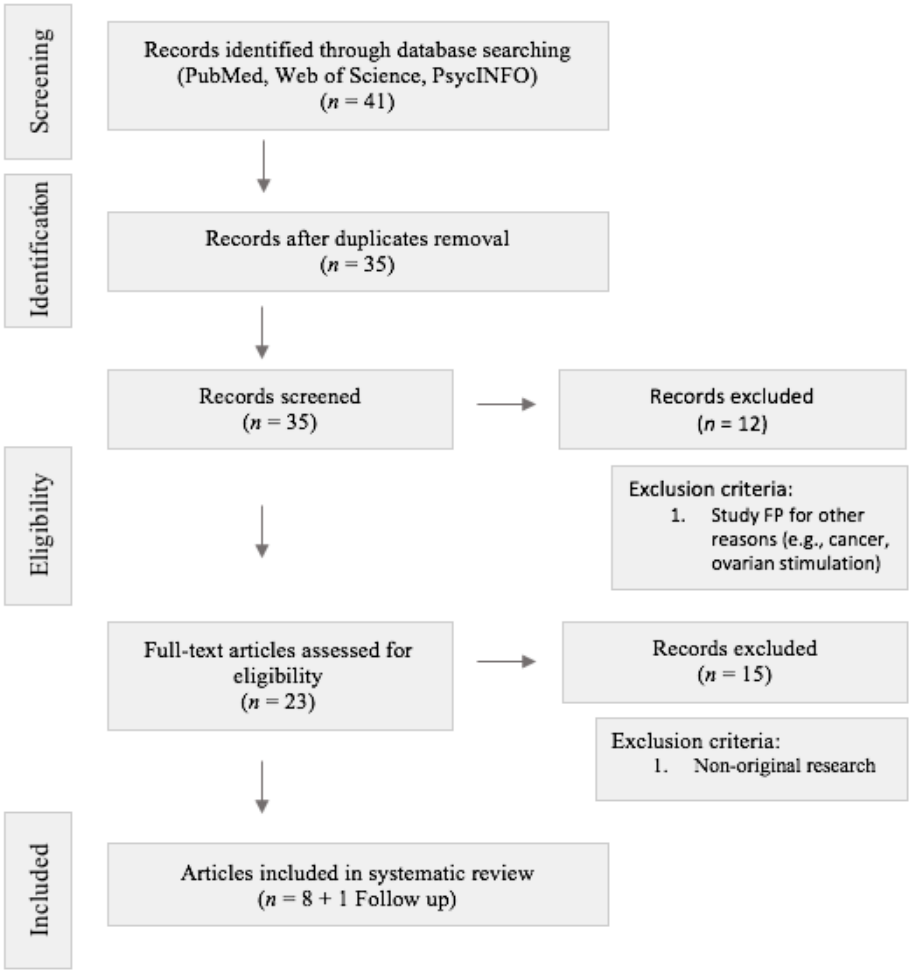

Fig.1. Search strategy flow diagram.

Characteristics of included studies:

Studies focusing social factors associated with the consideration or accomplishment of FP have increased during the last decade. In this research, the majority of the studies used a cross-sectional design (n = 6) with self-reported measures, mostly online (n = 5).

The studies revealed a wide range of proportion (15.1% - 31.5%) of participants that were considering this procedure as a future option (16, 17, 18).

Concerning the studies included in this systematic review we found two subgroups of studies. The first one, which includes women that only considered the procedure as a future option [Table 1] and the second one, including women who have already made a step toward FP (were in the waiting list or did at least one treatment cycle) [Table 2].

Assuming the consideration of FP for social purposes as an outcome, the studies surveying samples with women who only considered the procedure as a future option, comparing with women who did not considered FP as an option, revealed that it was associated with some sociodemographic and psychological variables as individuals' characteristics and motives not to do the procedure [Table 1].

Regarding sociodemographic variables, comparing with the women that did not intend to do FP in the future, women that considered it had a lower age, lower number of children, and were less likely to be married. Additionally, they revealed less background of divorce and more infertility experience.

Regarding the individuals' characteristics, studies showed that women who considered FP had a higher number of desired children, were more available to receive information, revealed higher susceptibility and severity towards infertility implications,

higher expectations to have children at a later age, higher perceived control and subjective norms, lower ethical concerns and optimistically sense about the prognosis.

Regarding the motives not to do the procedure, women indicated financial motives, time commitment, uncertainty about available options, potential health implications and social stigma.

Insert Table 1

Assuming the consideration of FP as an outcome, studies surveying samples with women who were in the waiting list or have done at least one treatment showed some sociodemographic variables and psychological variables as individuals' characteristics. Regarding sociodemographic variables, the majority of these women were single, full-time employed and financially independent. Concerning individuals' characteristics, these women were more optimistic about their prognosis, not concerned about possible risks and revealed a "binary thinking" (the changes of success were as likely as the changes of failing) and an "anticipatory regret" (were afraid of regret later if they have not done it) [Table 2].

Insert Table 2

Almost all studies (n = 5) [table 1 and 2] showed some psychological variables as motives to delay motherhood (n = 2), as the relationship status, the career and the finances; and motives that lead women to do the procedure (n = 3), as the lack of a suitable partner (n = 3) and the career (n = 1). The lack of a partner was the most mentioned reason to do this procedure, due to the reduction of the available time and the pressure to meet a partner. This relation is mediated by the age-related fertility decline.

GPs knowledge about FP:

Studies were very focused on the important role of the GPs in this process. These studies tried to understand the knowledge of these health professionals about the FP procedure as well as their attitudes about doing it to prevent age-related fertility decline [Table 3]. These studies used medical students and house staff, obstetricians (OB), gynecologists (GYN), other physicians and nurses.

Relatively to the knowledge, the studies showed that the majority of the professionals were not familiarised with FP procedures and revealed a lack of knowledge about it. Also, one study showed that the older the participant was, the lower the likelihood of answering correctly and that the GYN were the group with the more adequate and correct knowledge. Also, one study indicated that the majority of the participants heard about FP through formal education and media.

Regarding their attitudes toward FP procedures, GYN revealed being the more conservative group. The results showed that the majority of the professionals disagreed with the possibility of discussing about FP with their patients, but agreed with the discussion about ARFD. Although the level of support was higher for medical reasons (e.g., cancer), rather than non-medical reasons, the percentage of health professionals against FP was very low (4.2 %)

In fact, almost all participants considered important to the health professionals to be informed about ARFD and FP.

Insert Table 3

4. Discussion

In recent times, FP has been discussed among experts. The use of FP technique allows extraordinary advantages and possibilities, as it is an important and not very much studied topic nowadays.

In order to understand human behavior, Uri Bronfenbrenner (25) argued that it is important to consider not only the active individual, but also the direct and indirect environment, as well as their mutual and progressive interactions. This perspective indorses an interdependent, multidimensional, multilevel and interactional view on human behavior and development (26). Structured levels (environments) were conceived in a chain of concentric structures, from the individual with specific characteristics in the center to social and cultural forces.

In this systematic review, the majority of women that were considering or have actually done FP procedure had a lower age, were single and financially independent. However, the women who consider the procedure in the future had a higher number of desired children, more availability to receive information, higher susceptibility and severity towards infertility implications, higher expectations to have children at a later age, higher perceived control and subjective norms and lower ethical concerns. Otherwise, the women that have actually done the procedure were not concerned about possible risks and were afraid of regret later in life. Still, this two groups had an optimistically sense about the prognosis.

Some of these characteristics of the individuals are the consequence of the general lack of knowledge, both in women in a fertile age that have done or considered the procedure, as well as in health professionals.

These professionals are in the immediate context of these women, in the microsystem of Uri Bronfenbrenner model, in which they play a determinant role, and

where the individuals establish close relationships. These professionals, namely the GYN, are the first-line health professionals with whom the women used to contact in order to have counselling about infertility questions as well as the vast different treatments that are available and which ones are more indicated.

In fact, some women (25%) that made at least one oocyte cryopreservation treatment cycle assumed they did not have an adequate education before the first appointment. Also, of the 75% that assumed they had an adequate education, only 29% were from de GYN/OB (20). Also, although one-third of the patients indicated that they did discuss with their GYN before doing the FP (20), the knowledge was not easily accessed or provided in an useful way for an effective parental decision. This strengthens the importance of adequate formation about this fertility questions for GYN and the importance of including this topic in the annual appointment.

In addition, Yu and colleagues (24) specify the importance of including the partner in this phase of psychological education, when applied, which would probably be an increased value, since they are an active part in the decision making and one of the closest interpersonal relationships. Here, it could be important to include the family, since they also are an active part in the microsystem of these patients, which is the highest level of their social environment that is more likely to influence directly the individuals (26).

The mesosystem represents the interrelationships between these various microsystems where individuals have participated. Thus, the most appropriate way to organize this initial process of psychoeducation would be, first of all, an adequate and rigorous education of the GYN, taking into account their crucial role. Also, it would be important to include the partner, if applicable, as well as the family, so these women could make a conscious decision and have a strong and an adequate support.

Then, the exosystem has an indirect influence in the individuals and includes the various scenarios where they did not participate so actively, but affect their behavior and development. In this system, it is possible to indicate the role of the mass media as an important source in the disclosure of information, since this systematic review enhances its role as one of the main sources in it (19). In this review some women revealed being misinformed about the possibility of doing this procedure, as well as about ARFD. Then, the mass media could be a vehicle to disseminate the possibility of doing this procedure, as well as having an important role in the stereotypes about this question.

Finally, the macrosystem includes the cultural patterns, values, beliefs or ideologies that characterize a given society, which are assimilated during the development. The macrosystem involves all other environments, forming a network of interconnections that differs from one culture to another. The proportion of women who consider oocytes cryopreservation for social reasons as a future option varies according to the studies. A study by Stoop and colleagues (16) revealed a percentage of 31.5% and a study by Tan and colleagues (17) indicated a percentage of 26%. This difference could be explained by cultural issues, as the first study was carried out in Belgium and the second one in Singapore, considering the concept of motherhood in the society in which these women are, as well as their openness to this procedure, since the use of FP for social reasons is closely related to ethical and religious issues (17).

Women are now postponing motherhood, both by the high academic goals that modern women aspire today (19) and by the sociocultural environment that forces women to look at their economic, personal and professional stability before having children (6). Therefore, FP could be a solution to this delay. This systematic review

showed that the desire to find a suitable partner is undoubtedly the main reason why women intend to cryopreserve their oocytes, which is probably related to this sociocultural achievement of personal stability as a family, based on shared parenting.

However, women are using this procedure at an age that undermines its success potential, on average at 38 years old (27). In accordance, studies surveying samples with a wide age-range (21 to 40 years) showed that a significant proportion (31.5%) would consider the use of fertility preservation at some point in the future (16). When taking into account the studies that surveyed samples with women in the recommended age (20 to 35), and asked them about their decisional stage at the moment or if they would consider it at some point in the future, the percentage was lower (15.1% and 26%, respectively) (17, 18). Thus, the intentions to do the FP were as higher as older the woman and the majority did not consider to do the procedure in the optimal age range period. This could be another explanation to this discrepancy.

These data corroborate the increase in the age of women attending the fertility clinics during the last years, as well as the fact that women between the late 30s and the early 40s are overrepresented in fertility clinics (16). Besides the lack of knowledge, this happens because the greater the age (the longer they postpone procreation), the greater their perceived susceptibility and, consequently, the greater their intentionality to use FP (18). In these cases, the later the procedure occurs, the lower the fertility and so the success rate of the procedure is almost inexistent.

In conclusion, it is important to carry out a formal and early educational intervention on FP, based on the different dynamic contexts that influence the individual, directly or indirectly. For example, through public health campaigns or information dissemination by the media (3), on the existence of multiple possibilities of ART, including FP, as well as ARFD, since women have a limited reproductive life. It

is also important to clarify the advantageous impact of the FP procedure on their future fertility, explaining the existence of minimal risks (28), one of the obstacles and impositions mentioned. The vehicle used to disseminate this procedure would be healthcare professionals, particularly the GYN, as they are the first-line professionals that women resort to and with whom they generally contact at least once a year. These professionals could initiate a discussion with their patients about FP, stressing the importance of maximizing their reproductive potential (late 20s, early 30s), which is the most flexible age to make reproductive decisions (24), helping then to think rationally about the best way to achieve their parental goals. Therefore, this systematic review highlights the need of a formal education about the ARFD and the FP, to the GPs, as a very poor knowledge about it is shown. This is extremely important, since these professionals are the first line agents that could give informed and accurate information to these women.

It is important to highlight that the literature about this topic is scarce. In this systematic review, only 9 studies follow the requirements to be included, which did not facilitate the comparison and discussion of results and the generalization was also impaired. Also, the majority of these studies used a cross-sectional design, which does not allow to know if the women that considered the procedure as a future option actually have done the procedure. Moreover, most of the measures used to access the intentions and attitudes of the participants did not evaluate the same concepts, and so do not facilitate comparisons between the studies. Most of the studies have used, as a procedure, an online and anonymous measure, which may reduce the credibility of the answers.

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Key-points

FP is usually a backup plan for women.

FP is important to women looking forward to delay motherhood.

Health professionals are the first-line to support women at an early age in establishing a clear and pre-defined plan, based on their parental goals, but they do need to be further informed and trained.

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Table 1. Factors associated with FP to prevent ARFD, in women at fertility age.

Author/Title	Objectives	Participants	Study design / Methods	Results
Stoop et al. (16)	Attitudes, awareness, view and intentions of women, in fertility age, toward FP	1024 women (Belgium) *Potential oocyte freezers:* (*M* = 28.57 [21-29])	**Study design:** cross-sectional **Measures:** electronic survey	Sociodemographic variables: Lower age, less number of married women, number of children, less divorce history and more experience of infertility. Individuals' characteristics: Higher number of desired children and more available to receive inf.
Tan et al. (17)	Attitudes of female medical student, toward FP.	129 female students (Singapore) (*M* = 23.10 [20 - 31])	**Study design:** cross-sectional **Measures:** online survey	Motives to do the procedure: career and/or no suitable partner.

Table 1. (Continued)

Author/Title	Objectives	Participants	Study design / Methods	Results
ter Keurst et al. (18)	Intentions of women without children, towards FP.	257 women (*M* = 30.60, *DP* = 2.30 [28 - 35]	**Study design:** cross-sectional **Measures:** electronic survey	Individuals' characteristics: higher susceptibility, higher severity towards infertility implications, higher perceived behavior control, higher subjective norms, expecting to have children at a later age, less ethical concerns and positive attitudes toward FP.
Will et al. (19)	Knowledge and perceptions of FP and ARFD, in	53 women (52.80%: 26 - 30)	**Study design:** longitudinal **Measures:** survey (and an	Motives to delay motherhood: educational/career, relationship status, finances (28.6%).

Table 1. (Continued)

Author/Title	Objectives	Participants	Study design / Methods	Results
	medical students' and house staff, before and after an educational intervention.		educational intervention)	Motives not to do the procedure: finances, time commitment, uncertainty about available options, potential health implications, social stigma (15.6%).

Table 2. Factors associated with FP to prevent ARFD, in women who were in the waiting list or did at least one treatment cycle.

Author/Title	Objectives	Participants	Study design / Methods	Results
Hodes-Wertz et al. (20)	Beliefs, priorities, attitudes, and knowledge of women that completed at least one oocyte cryopreservation treatment cycle	183 women (42%: 36-38 years at the time of FP)	**Study design:** cross-sectional **Measures:** electronic survey	Sociodemographic variables: The majority never married and were not in a relation in the time of FP. Motives to delay motherhood: Lack of partner (88%), professional reasons (24%), financial reasons (15%).
Stoop et al. (21)	The nature of the relational status, attitudes and reproductive choices of	138 women (between 2009 - 2011)	**Study design:** retrospective cohort	Sociodemographic variables: The majority were single. Motives to do the procedure:

Table 2. (Continued)

Author/Title	Objectives	Participants	Study design / Methods	Results
	women that considered or actually performed FP.		**Measures:** telephone survey	Secure the future against infertility, more time to find a suitable partner, do not feel regrets later and reduce the pressure to find a partner.
de Groot et al. (22)	How women in the waiting list perceive FP.	20 women – in waiting list to cryopreserve their oocytes (*M* = 35.80 [31 - 39]).	**Study design:** exploratory qualitative study **Measure:** "face-to-face" in-depth interviews	<u>Sociodemographic variables:</u> Single, full-time employed, financially independent. <u>Individual characteristics:</u> optimistic about their prognoses, binary thinking, anticipatory regret, not to concerned

Table 2. (Continued)

Author/Title	Objectives	Participants	Study design / Methods	Results
				about possible risks. <u>Motives to do the procedure:</u> Achieve share parenthood with a future partner.

Table 3. Attitudes and knowledge of health professionals toward FP socially

Author/Title	Objectives	Participants	Study design / Methods	Results
Tan et al. (17)	Attitudes of female medical student, toward FP.	129 female students (Singapore) (*M* = 23.10 [20 - 31])	**Study design:** cross-sectional **Measures:** electronic survey	Knowledge: Only 36.4% had heard about FP. Low accurate knowledge about FP.
García et al. (23)	Attitudes and knowledge of the healthcare professionals about FP.	201 healthcare professionals (*M* = 42.70; *DP* = 11.00): GYN, other physicians and nurses	**Study design:** cross-sectional **Measures:** Presencial survey	Knowledge: The older the participant was, the lower the likelihood of answering correctly. GYN was the group with more adequate and correct knowledge. Attitudes: GYN were the more conservator group toward FP. The percentage that

Table 3. (Continued)

Author/Title	Objectives	Participants	Study design / Methods	Results
				opposed to FP was low (4.2%).
Yu et al. (24)	Knowledge, attitudes and intentions of US OB and GYN residents to discuss with their patients about the ARFD and FP.	238 participants **(**74.90%: [[26 - 30])	**Study design:** cross-sectional **Measures:** electronic survey	Knowledge: Only 25.1% were familiarly with FP. A large percentage revealed being misinformed toward ARFD. Attitudes: The majority disagreed with the possibility of a discussion about FP with their patients, but agreed with a discussion about ARFD. The level of support was higher to the FP due to medical reasons.

Table 3. (Continued)

Author/Title	Objectives	Participants	Study design / Methods	Results
Will et al. (19)	Knowledge and perceptions of FP and ARFD, in medical students' and house staff, before and after an educational intervention.	53 women (52.80%: 26 - 30)	**Study design:** longitudinal **Measures:** **Measures:** survey (and an educational intervention)	<u>Knowledge:</u> Knowledge was limited. The majority already had heard/read about FP. The formal (80%) and the online material or social media (40.0%) education was the most identified source. <u>Attitudes:</u> Almost all participants considered important to health professionals to be informed about FP and ARFD.