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Embryo donation for research:

A patient-centred approach

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Abbreviations

ART	Assisted Reproductive Technologies
ASRM	American Society for Reproductive Medicine
βhCG	Beta-Human Chorionic Gonadotropin test
CBCR	Cross-border reproductive care
CNPMA	Conselho Nacional de Procriação Medicamente Assistida [National Council for the Assisted Reproductive Technologies]
ESF	European Science Foundation
ESHRE	European Society of Human Reproduction and Embryology
hESCs	Human Embryonic Stem Cells
ICMART	International Committee for Monitoring Assisted Reproductive Technology
IVF	In Vitro Fertilization
IFFS	International Federation of Fertility Societies
ICSI	Intracytoplasmic Sperm Injection
IVF	In Vitro Fertilization
PCOS	Polycystic Ovary Syndrome
PGD	Preimplantation Genetic Diagnosis
WHO	World Health Organization

Abstract

Background

Most couples enrolled in Assisted Reproductive Technologies' (ART) treatments need to make decisions regarding embryo disposition, as they are asked to sign a consent form concerning embryo donation for research. Decision-making on embryo donation for research is influenced by three main iterative and dynamic dimensions: (i) hierarchisation of the possible options regarding embryo disposition, framed on patients' beliefs about what should be done or their representations regarding the moral and social status of embryos; (ii) patients' understanding of expectations and risks of the research on human embryos; (iii) and patients' experiences of information exchange and levels of trust in the medical-scientific institutions. Results relating to the influence of sociodemographic characteristics and reproductive and gynaecological history were mostly inconclusive **(PAPER I)**.

In the context of clinical practices involving informed consent on embryo disposition, it is crucial to ground legal and regulatory frameworks on patients' values, preferences, choices and expressed needs to lend credence and robustness to the consent that the couples give. Further research on patients' experiences and perspectives about the healthcare system, and on the human factors involved in the decision-making process regarding embryo donation for research, is needed to contribute to the implementation of informed relational ethics in clinical practice and to improve patient-centredness in the field of ART at three main levels. First, the circumstances under which the informed consent should be delivered, explained and signed, considering that patients' attitudes about embryo disposition evolve over time; second, the sociodemographic, reproductive and psychosocial characteristics and reasons associated with willingness to donate embryos for research; lastly, the perceptions about storage limit for embryos, taking into account that they may shape decision-making on embryo disposition and that there is no evidence justifying the current storage periods.

Objectives

To produce evidence to sustain the development of patient-centredness regarding embryo donation for research. To accomplish this aim, four studies were performed, with the following specific objectives:

1) To assess the psychosocial, demographic and reproductive factors and socioethical reasons associated with willingness to donate embryos for research among IVF couples.

2) To analyse IVF couple's willingness to donate cryopreserved embryos for over time, taking into account the influence of psychosocial, demographic and reproductive factors.

3) To assess IVF patients' opinions about the storage limit for embryos and to explore their perceptions of the criteria underlying the establishment of the storage period offered to them.

4) To analyse the perceptions of IVF couples regarding the factors that contextualize informed consent regarding embryo cryopreservation.

Methods

This is an observational and longitudinal mixed-methods study. The methodological strategy relied on three evaluation moments: (1) quantitative questionnaire with couples in IVF/ICSI treatments, over 12 consecutive months (baseline); (2) semi-structured interviews to a subsample of couples, conducted 3 months after baseline; (3) quantitative questionnaires 12 months after baseline. Between August 2011 and August 2012, 221 heterosexual couples and 92 women undergoing IVF were systematically recruited in a Portuguese public fertility centre (participation rate=95.1%). Data on sociodemographic characteristics, reproductive history, psychosocial variables, willingness and reasons to donate embryos for research were collected by self-report questionnaires. No statistically significant differences were found in the self-reporting of depression, anxiety, social support and partner relationship or in sociodemographic and obstetric characteristics between women interviewed alone or with the partner (**PAPER II**). Approximately three months after completing the questionnaire, semi-structured interviews with 34 couples took place between March and December 2012. About 12 months after completing the quantitative questionnaire applied at baseline, all the participants who previously agreed to be invited to participate in the third phase of the study were contacted. Those who agreed to be included in the 12-months after evaluation were sent the self-administered part of the questionnaire by mail. At this moment, 221 participants (114 women and 107 men) returned the questionnaires (participation rate=41.4%), in a total of 104 couples.

Descriptive and inferential statistics were used to analyse the quantitative data. In qualitative data, content analysis protocols, with an iterative and reflexive process, were implemented according to the objectives of each paper.

Results

The majority of the 213 couples who had information on the outcome variable was willing to donate embryos for research (87.3%; 95%CI: 82.1-91.5), expecting benefits for science, health and

infertile patients. Almost all couples reached consensus regarding the decision (94.3%; 95% CI: 89.8-96.7). Willingness to donate was more frequent among women below 36 years old (OR=3.06; 95%CI: 1.23-7.61) and who considered embryo research to be very important (OR=6.32; 95%CI: 1.85-21.64); and in Catholic men (OR=4.16; 95%CI: 1.53-11.30). Those who were unwilling to donate reported the conceptualization of embryos as children/lives, lack of information or fears about embryo research to justify their decision. Men with higher levels of trait anxiety (OR=0.90; 95%CI: 0.84-0.96) were less frequently willing to donate (**PAPER III**).

Over time, a significant decrease in patients' willingness to donate embryos for research was registered (86.5% to 73.6%; RR= 0.85; 95% CI: 0.76-0.95). Participants with more than 12 years of education and who considered research with human embryos to be important (vs very important) were less frequently willing to donate embryos for research over time ($RR_{interaction}$= 0.77; 95% CI: 0.63-0.95 and $RR_{interaction}$= 0.70; 95% CI: 0.50-0.98, respectively) (**PAPER IV**).

In this sample of women and men undergoing IVF, 38% of participants preferred the duration of 4-5 years for embryo storage limit, 38% extended it beyond 5 years and 23% indicated 3 years. Having experienced at least one previous cycle was directly associated with agreeing with a duration of storage longer than 5 years, for both women and men (OR=2.94; 95% CI: 1.51–5.71 and OR=2.44; 95% CI; 1.17–5.08, respectively). Having children was inversely associated with longer duration of storage, among women. One third of the 34 interviewed couples stated that their knowledge concerning embryo storage was insufficient. Nevertheless, all the interviewees reported at least one possible reason for the legal establishment of the storage period offered to them, highlighting financial costs and decreased embryo quality. There were misconceptions and gaps in awareness of cryopreservation which may shape patients' opinions (**PAPER V**).

Data gathered through the 34 semi-structured interviews revealed a perception of informed consent as a formality, signed in an inadequate period of time and often administered by non-qualified professionals. The following needs have been identified: timely provision of detailed, accurate and intelligible information about the costs of cryopreservation, embryo storage limit and effective options for embryo disposition; reinforcement of physical privacy; availability of time to reflect about embryo disposition and the disclosure of users' identities (**PAPER VI**).

Conclusion

This thesis provided evidence to sustain the development of patient-centredness on embryo donation for research, with implications for clinical practice and regulation. Looking at patient-centred care through the lens of public health, this study contributes to advance knowledge in

three key areas: openness and information about research with human embryos; suitability of research projects using cryopreserved embryos; policies and guidelines regarding informed consent process on embryo donation for research. Data provided by this study was also important to deconstruct ideas regarding the influence of being Catholic on embryo donation for research. Its innovativeness also relies on the assessment of psychosocial variables as anxiety, depression and quality of partner relationship, and the inclusion of both members of the couple, considering that these methodological features are absent from most of the studies on embryo disposition.

Achievements from this study revealed a high receptivity to scientific and technological progress and trust in medical institutions and their professionals. Lack of information and gaps and misconceptions reported by patients highlighted that attention should be drawn to the responsibility of scientific and medical institutions, health professionals and researchers regarding the provision of accurate and timely information that is attentive, responsive, and tailored to patients' needs. The communication of realistic expectations as well as discussions about the risks and limitations of research with human embryos should be central topics in the ethics of clinical research, care and doctor-patient relationships centred on patients.

Lastly, this study calls on the one side for the inclusion of the subject of decision-making on embryo disposition in general guidelines for psychosocial care in infertility and ART, and, on the other side, to the need to improve clinical practices involving informed consent in order to make them more patient-centred. Our achievements may help to inform ethical debates on the credence and robustness of informed consent given by couples and on the circumstances under which the informed consent should be delivered, explained and signed, including the establishment of storage periods and the reasons for limitations in these periods.

Resumo

Introdução

A maioria dos casais envolvidos em técnicas de Procriação Medicamente Assistida (PMA) são confrontados com a necessidade de tomar uma decisão quanto ao destino dos embriões criopreservados, sendo-lhes solicitada a assinatura de um consentimento informado sobre a doação de embriões para investigação. Esta decisão é influenciada por três dimensões dinâmicas e iterativas: (i) hierarquização das opções possíveis para o destino dos embriões, enquadrada nas crenças dos pacientes acerca do que deve ser feito e nas suas representações acerca do estatuto moral e social dos embriões; (ii) forma como os pacientes compreendem as expectativas e os riscos associados à investigação com embriões de origem humana; (iii) experiências dos pacientes a nível da informação e respetivos níveis de confiança nas instituições médico-científicas. Globalmente, os resultados sobre a influência das características sociodemográficas, reprodutivas e da história ginecológica são inconclusivos (**ARTIGO 1**).

No âmbito das práticas clínicas que envolvem o consentimento informado na criopreservação, é crucial que os enquadramentos legais e regulatórios se enraízem nos valores, preferências, escolhas e necessidades expressas pelos pacientes, de forma a conferir credibilidade e robustez ao consentimento. Neste contexto, conhecer as experiências e perspetivas dos pacientes quanto aos fatores humanos e do sistema de saúde que estão envolvidos no processo de decisão em relação à doação de embriões para investigação científica é fundamental para informar a ética relacional na prática clínica e para melhorar a prestação de cuidados centrados no paciente no contexto da PMA, principalmente a três níveis. Em primeiro lugar, as circunstâncias em que o consentimento deve ser entregue, explicado e assinado, considerando que as atitudes quanto à doação de embriões para investigação evoluem ao longo do tempo; em segundo lugar, as características sociodemográficas, reprodutivas e psicossociais e as razões associadas à doação de embriões para investigação científica; e, por fim, as perceções acerca do período máximo de criopreservação, aspeto que pode influenciar a decisão, e cuja delimitação não assenta em evidência científica.

Objetivos

Produzir conhecimento que sustente o desenvolvimento de práticas de saúde centradas no paciente quanto à doação de embriões para investigação. Neste sentido, foram realizados quatro estudos com os seguintes objetivos específicos:

1) Avaliar os fatores psicossociais, demográficos e reprodutivos, bem como as razões associadas à doação de embriões para investigação em casais envolvidos em FIV.

2) Analisar as atitudes dos casais em FIV quanto à doação de embriões para investigação, ao longo do tempo, tendo em conta a influência de fatores psicossociais, demográficos e reprodutivos.

3) Explorar as opiniões dos pacientes sobre o período máximo de criopreservação de embriões e as suas perceções acerca dos critérios subjacentes ao estabelecimento do limite de criopreservação que lhes é oferecido.

4) Analisar as perceções de casais em FIV sobre o consentimento informado para a criopreservação de embriões.

Métodos

Com base numa metodologia mista, este estudo observacional e longitudinal incluiu três momentos de avaliação: (1) questionário quantitativo com casais envolvidos em fertilização *in vitro* e injeção intracitoplasmática de espermatozoides, durante 12 meses consecutivos; (2) entrevistas semiestruturadas a uma subamostra de casais, realizadas 3 meses após o primeiro momento de avaliação; (3) reavaliação 12 meses após o contacto inicial, com questionários quantitativos. Entre agosto de 2011 e agosto de 2012, 221 casais heterossexuais e 92 mulheres envolvidos em fertilização *in vitro* e injeção intracitoplasmática de espermatozoides foram recrutados sistematicamente numa Unidade Pública de Medicina da Reprodução (proporção de participação=95,1%). Recolheram-se dados sociodemográficos e da história reprodutiva; dados psicossociais; e atitude e razões quanto à doação de embriões para investigação, através de questionários. Não se encontraram diferenças estatisticamente significativas no reporte de depressão, ansiedade, suporte social e relação com o parceiro, ou nos dados sociodemográficos e obstétricos, entre as mulheres que foram entrevistadas sozinhas ou com o parceiro (**ARTIGO II**). Aproximadamente três meses após o preenchimento do questionário, realizaram-se 34 entrevistas semiestruturadas em casal, entre março e dezembro de 2012. Cerca de 12 meses após o primeiro momento de avaliação, todos os participantes que aceitaram continuar no estudo foram contactados. Entre estes, os que concordaram em participar na reavaliação receberam por correio o mesmo questionário autoadministrado que tinham preenchido no primeiro momento, bem como os consentimentos informados, com um envelope para devolução. Devolveram os questionários 221 participantes (114 mulheres e 107 homens), num total de 104 casais (proporção de participação=41,4%). Foi utilizada estatística descritiva e inferencial para analisar os dados quantitativos. Os protocolos de análise de conteúdo de dados qualitativos foram escolhidos de acordo os objetivos de cada estudo, num processo reflexivo e iterativo.

Resultados

A maioria dos 213 casais com dados sobre a atitude quanto ao destino dos embriões criopreservados aceitou doar embriões para investigação (87,3%; IC95%: 82,1-91,5), referindo os benefícios esperados para a ciência, a saúde e os casais inférteis. A grande maioria dos casais chegou a consenso quanto à decisão tomada (94,3%; IC95%: 89,8-96,7). A doação de embriões para investigação foi mais frequente em homens católicos (OR=4,16; IC95%: 1,53-11,30) e em mulheres com menos de 36 anos (OR=3,06; IC95%: 1,23-7,61) e que atribuíram muita importância à investigação com embriões (OR=6,32; IC95%: 1,85-21,64). Aqueles que não aceitaram doar reportaram mais frequentemente falta de informação ou receios acerca da investigação com embriões e conceptualizaram o embrião como criança/ser vivo. Os homens com níveis mais elevados de ansiedade-traço (OR=0,90; IC95%: 0,84-0,96) tenderam a não doar (**ARTIGO III**).

Uma análise da evolução da atitude quanto à doação de embriões para investigação, ao longo do tempo, mostrou uma descida significativa na tendência para doar (86,5% a 73,6%; RR= 0,85; IC95%: 0,76-0,95). Os pacientes mais escolarizados (> 12 anos de escolaridade) e que consideraram importante a investigação com embriões (por comparação com os que consideraram muito importante) doaram menos para investigação no segundo momento ($RR_{interação}$= 0,77; IC95%: 0,63-0,95 e $RR_{interação}$= 0,70; IC95%: 0,50-0,98, respetivamente) (**ARTIGO IV**).

O estudo das opiniões dos pacientes acerca do limite máximo da criopreservação de embriões revelou que 38% dos participantes defenderam a extensão do limite para 4-5 anos e 38% defenderam a extensão para além dos 5 anos, sendo que 23% defenderam o atual limite legal de 3 anos. Os participantes que realizaram pelo menos um tratamento referiram, mais frequentemente, um período máximo de criopreservação superior a 5 anos (OR=2,94; IC95%: 1,51–5,71 e OR=2,44; IC95%; 1,17–5,08, em mulheres e homens, respetivamente). Ter filhos associou-se inversamente à preferência por longos períodos de criopreservação, entre as mulheres. Um terço dos 34 casais entrevistados referiram ter um conhecimento escasso sobre os critérios usados para estabelecer um limite temporal na criopreservação de embriões. No entanto, todos os entrevistados reportaram pelo menos uma razão possível para o estabelecimento legal do limite máximo que lhes é oferecido, salientando os custos da criopreservação e a diminuição da qualidade dos embriões. Encontraram-se conceções erradas e lacunas no conhecimento sobre criopreservação de embriões, aspetos que podem moldar as opiniões dos pacientes (**ARTIGO V**).

Os dados obtidos através das 34 entrevistas semiestruturadas revelaram que o consentimento é percecionado como um formalismo, é assinado num momento inadequado e muitas vezes aplicado por profissionais não qualificados. Emergiram as seguintes necessidades: provisão atempada de informações detalhadas e coerentes sobre os custos e duração da criopreservação e o destino dos embriões; reforço da privacidade física; tempo para refletir sobre o destino dos embriões e sobre a divulgação da identidade dos beneficiários (**ARTIGO VI**).

Conclusão

Esta tese gerou conhecimento que sustenta o desenvolvimento de políticas e cuidados centrados no paciente no âmbito da doação de embriões para investigação, com implicações para a prática clínica e a regulação. Perspetivando os cuidados centrados no paciente do ponto de vista da saúde pública, este estudo contribui para o avanço do conhecimento em três áreas principais: recetividade à doação e informação sobre a investigação em embriões; adequação dos projetos de investigação com embriões de origem humana às perspetivas dos casais; políticas e orientações para o processo de consentimento informado na criopreservação. Os resultados obtidos foram ainda importantes para a desconstrução de ideias acerca da influência da crença na religião Católica na doação de embriões para investigação. O caráter inovador deste trabalho apoia-se também na avaliação de variáveis psicossociais como ansiedade, depressão e qualidade da relação conjugal, incluindo ambos os membros do casal, num contexto em que estas componentes metodológicas estão ausentes da maioria dos estudos que avaliam os fatores associados à doação de embriões para investigação.

Este estudo revelou uma recetividade elevada ao progresso científico e tecnológico e confiança nas instituições e profissionais de saúde. O facto de os pacientes reportarem falta de informação e conceções erradas sobre a criopreservação e a investigação em embriões humanos alerta para a responsabilidade das instituições científicas e médicas, dos profissionais de saúde e dos investigadores quanto à prestação de informação adequada e oportuna, que seja responsiva e adaptada às necessidades dos pacientes. A comunicação de expectativas realistas e a discussão dos riscos e limitações da investigação com embriões devem ser tópicos centrais da ética na investigação e nos cuidados de saúde centrados no paciente.

Por fim, este estudo apela, por um lado, à inclusão deste tópico nas diretrizes para o cuidado psicossocial em infertilidade e PMA e, por outro, à necessidade de melhorias nas práticas clínicas que envolvem o consentimento informado, de forma a torná-lo mais centrado no paciente. Os dados deste estudo contribuem para informar os debates éticos sobre a credibilidade e robustez do consentimento informado, bem como as circunstâncias em que o mesmo deve ser entregue, explicado e assinado, incluindo a definição do limite máximo de tempo para a criopreservação e as razões subjacentes.

1. Introduction

The introductory chapter of this thesis aims to provide a comprehensive overview of the psychosocial, clinical, regulatory and legal frameworks where embryo donation for research occurs. It is argued that further research on patients' experiences and perspectives about the healthcare and regulatory systems, and on the human factors involved in the decision-making process regarding embryo donation for research, is needed to contribute to the implementation of informed relational ethics in clinical practice and to improve patient-centredness in the field of ART.

The first section briefly summarizes the quantitative indicators about the prevalence of infertility and the number of ART cycles, advocating the need to devote more attention to psychosocial, ethical and relational issues of involuntary childlessness in public health research on infertility in a context where an increasing number of embryos has been storage.

The second section presents the contours of a responsible governance of human embryo research in a scenario characterized by differences in national and transnational laws and policies regarding the use of human embryonic stem cells in research and the maximum length for embryo storage, and uncertainties on whether the informed consent should be signed by IVF patients prior to the first treatment, during treatment or after treatment is completed, detailing the Portuguese legal and regulatory landscape that frames the present work. Research needs to find a balance between expectations and controversies, empirically grounded on the assessment of the moral and ethical spectrum involving both scientists and stakeholders and the public, in particular those people who must make embryo disposition decisions, whose perspectives and experiences are a core need for patient-centred care and policies on human embryo research.

The last section explores the theoretical, methodological and pragmatic challenges raised by the conceptualization and implementation of patient-centredness on infertility and ART, calling for a renewed debate that includes the subject of decision-making on embryo disposition, namely embryo donation for research, and looks at patient-centredness through the lens of public health. Knowledge on patient's perspectives and experiences with regard to embryo donation for research is essential for the conceptualization of patient-centred policies and for ethics in clinical practice at the following levels: to analyse openness and information about research with human embryos; to sustain stakeholders' decisions regarding the suitability of research projects using cryopreserved embryos; and to disseminate ethically robust evidence to inform policies and guidelines on embryo cryopreservation and embryo disposition.

1.1 Infertility and Assisted Reproductive Technologies

1.1.1 Definition and prevalence

According to the World Health Organization (WHO) and the International Committee for Monitoring Assisted Reproductive Technology (ICMART)[a], infertility is considered "a disease of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse"[1]. In 2013, the American Society for Reproductive Medicine (ASRM) proposed to include in such definition the cases where the failure to achieve a clinical pregnancy occurs after therapeutic donor insemination[2]. In addition, recent guidelines have shortened the period of 12 months to 6 months of unprotected sexual intercourse without achieving a pregnancy when there is a medical history and physical evidence, previously known to potentially compromise fertility (e.g., cancer patients; in women, oligomenorrhea, amenorrhea, advanced stage endometriosis), or when women are aged above 35 years[3].

Despite the definition previously presented, there are differences regarding the threshold considered in the diagnosis of infertility when comparing clinical and epidemiological studies: while 1 year has become the gold standard for clinical purposes[1], epidemiological studies use a time horizon of 5 years, "in order to reduce the likelihood of misclassifying fertile unions as infertile"[4]. In fact, there is no biological basis for the establishment of 1 year of regular unprotected sexual intercourse as a clinical criterion for the diagnosis of infertility, since a considerable proportion of spontaneous pregnancies occurring after the first 12 months of trying is observed. Besides the time threshold, the present definition of infertility includes an ambiguous criterion - the "regular" intercourse, in the sense that it does not adequately account for how time and frequency of sexual intercourse may influence conception and the quality of gametes[5, 6], which claims for more attention to psychosocial and relational aspects of involuntary childlessness.

While in females, the common biological causes of infertility are ovulatory dysfunction, ovarian abnormalities, abnormalities of cervical mucus production or sperm/mucus interaction and abnormalities of uterine anatomy or function and endometriosis[3], in males, the reduction in the number of sperm (oligospermia), low sperm motility (asthenoteratospermia); sperm with abnormal

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[a] The International Committee Monitoring Assisted Reproductive Technologies (ICMART) is an independent, international non-profit organization that has taken a leading role in the development, collection and dissemination of worldwide data on Assisted Reproductive Technologies (ART). It is supported by the following organizations: American Society for Reproductive Medicine (ASRM), Society for Assisted Reproductive Technology (SART), European Society for Human Reproduction and Embryology (ESHRE), Latin American Network for Assisted Reproduction (REDLARA), Fertility Society of Australia (FSA), Japan Society for Reproductive Medicine (JSRM), and Bertarelli Foundation.

morphology (teratospermia); absence of a measurable level of sperm in semen (azoospermia) or inability for vaginal ejaculation are the established causes[7].

According to the cause of infertility, clinical subtypes are commonly defined as due to a male factor (40% of cases), female factor (40%), couple factor (10%) or unknown factor (10%)[8, 9]. However, these estimates vary across studies, being influenced by physician's practices, extensiveness of clinical testing and their sensitivity and specificity, and the limited information about what constitutes normal variations in human fecundity[9]. Previous studies have shown variations of infertility from an unknown factor ranging from 15 to 30%[10], with women over 35 years of age having the double probability to present unexplained infertility[11]. When the cause of infertility is unexplained, the probability of achieving a spontaneous pregnancy seems to be higher among younger women and who performed a smaller number of In Vitro Fertilization (IVF) attempts[12].

Infertility is currently seen as a global public health issue[13], considering the challenges imposed by declining fertility rates on population renewal in various developed countries for the last century[14] and the promotion of universal access to sexual and reproductive health in the context of the primary healthcare approach[15]. Arguments as a decline in sperm concentration and quality over time[9, 16, 17], secular events such as changes in the availability of contraception and new legislation about abortion[18], economic factors affecting education, employment and family life[19], or changes in the attitudes and cultural values of men and women[20] have been pointed out to justify the decline in fertility and number of births. Research has also focused on the influence of environmental exposures, as toxins, pesticides and other pollutants, on fertility[17, 21, 22]. A recent study has found that higher levels of stress as measured by salivary alpha-amylase are associated with a longer time-to-pregnancy and an increased risk of infertility[23]. An increase in the incidence of age-related subfertility in women and, to a lesser extent in men, is associated with delaying the birth of the first child[24]. However, the question of a possible decline in human capacity to conceive remains unanswered[16], being important to continue studying the interactions between reproductive capacity and social changes[14].

A main challenge in this field is related to the estimation of infertility prevalence rates. Population-based studies are scarce and the few high-quality studies available used inconsistent definitions, with different numerators and denominators[4, 25]. In order to overcome these difficulties and synthesize data on the prevalence of infertility, a systematic review with 277 demographic and reproductive health surveys was performed applying a consistent algorithm to measure infertility using household survey data[26]. Global trends in infertility prevalence (both primary and secondary) were estimated in the absolute number of 48.5 million (95% confidence interval (95% CI): 45.0-52.6) infertile couples. Primary infertility prevalence[b] among child-seeking women varied by region in 2010, from 1.5% (95%CI: 1.2%, 1.8%) in the Latin America/Caribbean region, to 2.6% (95% CI: 2.1%, 3.1%) in the North Africa/Middle East region. Twenty-year trends in infertility prevalence were not statistically significant in most regions[26]. In Portugal, a study with the EPIPorto cohort estimated a lifetime infertility prevalence of 11.9% (95% CI: 10.4%-13.7%)[27c].

While primary infertility is mainly registered in high income countries, low income countries present higher rates of secondary infertility (inability to conceive among couples with a previous pregnancy, regardless of outcome), mostly due to untreated or poorly managed reproductive tract infections, including sexually transmitted infections, and also because infertility is deemed a low-priority issue in the context of scarce healthcare resources[15, 28]. For example, in the Arab Gulf and South Asia, a new "infertility epidemic is raging", which is linked to overweight/obesity, insulin resistance/diabetes and polycystic ovary syndrome (PCOS), the global solution of which is still obscure[28].

In the last decades, there is a focus on high-tech treatments or procedures that include the in vitro handling of both human oocytes and sperm, or embryos, for the purpose of establishing a pregnancy – the Assisted Reproductive Technologies (ART)[1], as the preferable option to deal with infertility[29]. Although ART should not jeopardize the acknowledgement of the importance of prevention and lower tech solutions, as well as the awareness about adoption or foster care, or the cessation of treatment and the acceptance of infertility[30-32], the use of ART seems to have increased in the last years in Europe. In 1997, 203 893 ART cycles (including intrauterine insemination) were registered, being 1183 of these recorded in Portugal[33], while in 2010, a total of 550 296 ART cycles were performed in Europe, and 7179 cycles in Portugal[34d]. The proportion of children conceived through ART per national births has also increased in the two last decades, among the countries providing data to the European Society of Human Reproduction and Embryology (ESHRE), ranging from 1.0% in Switzerland to 3.5% in Iceland, in 1997[33] and from 0.6% in Moldova to 5.9% in Denmark, in 2010[34]. In Portugal, the proportion raised from 1.2% in 2007[35]

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[b] Primary infertility was defined as the absence of a live birth for women who desire a child and have been in a union for at least five years, during which they have not used any contraceptives. The prevalence of primary infertility was calculated as the number of women in an infertile union divided by the number of women in both infertile and fertile unions, where women in a fertile union have successfully had at least one live birth and have been in the union for at least five years at the time of the survey.

[c] In this study, primary infertility was defined as the absence of pregnancy after a year trying to get pregnant, in a women who was never pregnant (or who were more than one year trying to get pregnant before the first pregnancy).

[d] It is important to note that these values may lead to a biased interpretation, due to the fact that between 1997 and 2010 a huge investment in monitoring and quality control was observed in infertility care, forcing the registration of cycles. Thus, the number of cycles performed in 1997 may have been under-registered.

to 1.9% in 2010[34e]. Among the total number of ART treatment cycles performed in Europe in 2010, approximately 20% (n=114 593) resulted from frozen embryo replacement. In Portugal, in the same year, the proportion of ART treatment cycles with frozen embryo replacement was 12.8% (n=921)[34].

Besides infertile couples, ART treatments also involve people who are seeking for prevention of transmission of genetic or infectious diseases through Preimplantation Genetic Diagnosis (PGD)[34f]. This is the case of carriers of genetic diseases or individuals chronically infected with HIV or hepatitis C virus, as these individuals can transmit the genetic disease or infection to their offspring or to an uninfected partner during the process of conception, in the case of communicable diseases.

1.1.2 Psychosocial issues

The importance of developing evidence-based guidelines for psychosocial care in ART treatments has been recently recognized by the ESHRE and the ASRM[36, 37]. This call for high-quality psychosocial care is based on evidence about the benefits of counselling to reduce stress and concerns about medical procedures[38, 39], to improve lifestyle outcomes[40] and patient well-being[41, 42], and compliance with treatment[43]. However, the psychosocial burden of ART and infertility goes beyond these dimensions, and includes feelings of result self-blame and guilt, fear, economic hardship due to treatment costs, social isolation, loss of social support, divorce and social stigma[30, 32, 44, 45].

Also, some patients discontinue treatment without achieving a live birth because of the physical and psychological burden of treatment, relational and personal problems, treatment rejection and organizational and clinic problems (as language problems; therapeutic programme difficult to integrate with work; insufficient or poorly formulated explanations about healthcare or fertility problem; poor management of psychological aspects) and also due to poor prognosis to achieve a pregnancy (based on the older age of women, problems with semen quality or the menstrual cycle, for example)[36, 46, 47].

The burden of infertility and ART is worsened in contexts where childbearing is a societal and cultural imperative[48]. In fact, different meanings attributed to infertility and to gender roles have

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[e] It is important to note that the number of clinics reporting data to ESHRE, in Portugal, increased from 22, in 2007[35], to 25, in 2010[34].

[f] The "analysis of polar bodies, blastomeres or trophectoderm from oocytes, zygotes or embryos for the detection of specific genetic, structural and/or chromosomal alterations" before embryo transfer.

implications on how individuals deal with this health condition[31, 49]: some couples experienced infertility as a life-crisis that brought them together and strengthened their relationship[41, 50], while other couples often cited difficulties in the partner relationship[30, 51].

At the same time, experience of infertility is socially determined: patients with a low occupational status experience higher infertility stress and anxiety than patients with a medium or high occupational status[52]; and patients with lower education level may take more treatment-related hours off work[53], with harder consequence to the familial resources.

Different socioeconomic, cultural and political contexts also underlie searching for cross-border reproductive care (CBRC), often referred to as 'reproductive tourism'[54], 'reproductive exile'[55, 56] or 'transnational reproduction'[57]. The main reasons underlying the movement of persons from one jurisdiction to another in order to access or provide ART may be grouped into four broad categories: 1) law evasion - avoidance of legal, religious, and ethical restrictions and regulations from a departure country; 2) the access to more resources, including shorter waiting lists or lower costs of treatment; 3) the search for more extensive higher quality of care and safety concerns; and 4) personal preferences or privacy[58-61].

Involving patients at the intersection of medicine, law, business and travel[58], CBRC presents two main challenges for public health: the need to protect patients from poor quality and unsafe services abroad; the need to protect disadvantaged individuals from being exploited for their reproductive tissues or capabilities[62, 63] and to prevent the exploitation of existing global inequalities and hierarchies in the service of new reproductive technologies[64]. More specifically, an international surveillance system[65] and a system of certification of centres may be developed, considering equity, safety, efficiency, effectiveness (including evidence-based care), timeliness and patient-centredness[66] at the following dimensions: preventing the transmission of infectious diseases or genetic disorders; provision of understandable information and adequate translation of informed consent; avoidance of lack of medical records; provision of legal advice in the event of patient harm abroad; and provision of best-practice psychosocial counselling support and development of counselling guidelines[60, 61, 67]. At the same time, host countries may witness an increase in the costs of some services or they can be of harder access for local patients[61], while a decrease on the pressure for law reform internally may occur in home countries[59].

This is particularly relevant in a context where all phases of treatment require psychosocial care in response to specific needs[36]. In fact, it is now widely recognized that many IVF patients find it difficult to manage the usually lengthy diagnostic and treatment period, and the uncertainty of achieving parenthood[68], while experiencing some degree of emotional distress during treatment[69]. Several moments had been identified as the most stressful: oocyte retrieval, the waiting period for the pregnancy test, the day of a negative pregnancy result and after a miscarriage[70, 71].

At the 'pre-treatment' period, that begins at the first visit to the clinic up to the start of the first treatment cycle, previous research showed that patients are not more depressed than the general population or matched controls, while data concerning anxiety is inconsistent when comparing IVF patients with the general population[36]. In both women and men, unexplained infertility seems to be harder to cope with than when a cause is identified[69].

Stress during treatment has been described as multi-dimensional[69], being connected to three main aspects: chronic stress caused by the threat of infertility and the loss of hope; stress from the prospect treatment; and the stress of the actual enrolment in the treatment with its daily injections, scans and invasive procedures[g][72]. About one-third of patients did not achieve pregnancy or a live birth within 5 years of the start of treatment[73] and many experience difficulties adjusting to their unmet parenthood goals[74]. The relatively low chance of success is one of the greatest restraints of ART[75][h], being women and men at high risk for major depressive disorder during the course of unsuccessful treatments[76]. Anxiety and stress are also higher when patients are anticipating results and they experience high emotional distress when they are informed that the treatment was unsuccessful[36].

While involving the couple, the fact that most medical procedures in ART occur on women's bodies[i] represents an additional burden for women, who tended to experience a disciplinary regime based on individual responsibility for the maximization of the probability of a successful treatment[6]. The medical and scientific recognition of limitations, uncertainties and risks is an

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[g] These procedures may, in some cases, lead to biological complications. This is the case of ovarian stimulation that is the use of medications, oral or injectable, for hormonal manipulation to enhance ovulation during the ovulatory cycle so that the ovary is stimulated to release multiple oocytes, instead of one[8, 78]. Although this process increases the chance of getting a higher number of eggs to fertilize, it also implies the risk to induce an excessive reaction of the ovaries, which become swollen and painful - ovarian hyperstimulation syndrome (OHSS)[1]. The OHSS is a serious complication of induction of ovulation, which can lead to hospitalizations, due to rapid weight gain and abdominal pain, vomiting or lack of appetite, among other symptoms[1, 77]. According to the last report of the European Society of Human Reproduction and Embryology, 1500 cases of OHSS were recorded in Europe in 2010, being 47 of these registered in Portugal[34].

[h] Although lack of data prevents the last report from ESHRE to present fully precise measures of the success of treatments (evaluated as the proportion of clinical pregnancies and deliveries per initiated cycle), it revealed indicative data regarding ART success rates in Europe, in 2010[34]: among IVF cycles, 29.2% of patients achieved a pregnancy and 22.4% delivered a baby; among ICSI cycles, 28.8% achieved a pregnancy with 21.1% delivering a baby; and among frozen embryo transfers, 20.3% of patients got pregnant and 14.1% delivered a baby.

[i] Usually, the diagnostic begins by a complete medical and reproductive history of the couple, namely a detailed sexual history[3, 7]. After that, the majority of the diagnostic techniques are focused on women's bodies, involving techniques as laparoscopy, hysteroscopy, hysterosalpingogram, hysterosalpingography, hormonal analysis and blood testing[8], while men typically performed a semen analysis[7].

important element underlying patient-centred care, in the sense that it may contribute "to minimize the negative feelings that many patients might have, especially women, that they are to blame for an unsuccessful IVF treatment cycle" (6, p540).

Embryo cryopreservation

With the purpose of eliminating high order multiple gestations, a restrictive embryo transfer policy, of two embryos per cycle, is recommended[77, 78], with European countries currently transferring 2 embryos per cycle in most treatments (56.7%)[34]. A single embryo transfer in selected groups of patients – based on woman's age, number of previous IVF/Intracytoplasmic Sperm Injection (ICSI) cycles and embryo quality – has been also advocated[78], corresponding to 25.7% of all registered treatments in ESHRE's report, in 2010[34]. In this context, cryopreservation of better quality embryos is routinely available as an integral part of infertility services[78][j]. These policies have contributed to an increase of cryopreserved embryos, in the cases where more embryos than those transferred to the uterus were generated.

The cryopreservation technique offers patients undergoing IVF extra chances to conceive without the need to go through a new stimulation cycle[49, 79]. However, storing an increasing number of embryos raises concerns surrounding disputes over ownership or disposition[80, 81], and poses problems and ethical questions to address for clinics and for patients who are requested to decide on the disposition of their cryopreserved embryos. While patients' decision with regard to embryo disposition can involve some less problematic choices, like the transfer of cryopreserved embryos to the uterus in another treatment cycle, there are also controversial options, such as the physical destruction of embryos, the donation to another couple or donation to research. Literature has consistently shown that decision-making on embryo disposition is a complex and difficult decision-making process, being described as a source of moral and emotional distress[82-85]. Some couples report high decisional conflicts[81] and some delay the decision for as long as possible[82]. Yet others report feeling pressure to make a decision[86]. Research also suggests that decisions on embryo disposition are subject to change over time[80, 87], as will be further explored in this thesis.

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[j] Two days after the egg retrieval, the fertilized egg has divided to become a 2- to 4-cell embryo. By the third day, a normally developing embryo contains approximately 6 to 10 cells and by the fifth day a fluid cavity forms in the embryo, and the placenta and fetal tissues begin to separate, being called a 'blastocyst.' Embryos are graded, and a cumulative embryo score is obtained according to several morphologic characteristics (number and symmetry of blastomeres, degree of fragmentation and presence of granulity)[8]. Transfer of embryos with 'best quality' may occur between one and six days after the egg retrieval[8].

1.2 Embryo donation for research

1.2.1 Legal and regulatory framework

The legal and regulatory landscape on human embryo research was recently analysed by the European Science Foundation (ESF)[88], the ESHRE[89] and the International Federation of Fertility Societies (IFFS)[90]. Considering the 58 countries with coherent data on national policies or guidelines regarding research on human embryos in these three sources of information, more than one-third (n=22) bans such research[k], and 19 countries permit research only on surplus IVF embryos, prohibiting the creation of embryos solely for research purposes[l]. Six countries allow the creation of human embryos for research purposes[m], while four permit research only on imported embryos[n]. The remaining seven countries have no legislation on human embryo research[o].

A consensual trend in regulations, guidelines and healthcare policies of countries permitting research on human embryos is the need to obtain consent from the woman and the man that their embryos can be used in scientific studies[90-92]. Notwithstanding, there are differences between countries regarding whether the informed consent should be signed prior to the first treatment[93], during treatment[94] or after treatment is completed[95]. There are also differences regarding the maximum length for embryo storage[96] (Figure 1), which may influence cross-border reproductive care services[62, 65, 97, 98]. Embryo storage limit ranges from a period of 3 years in Portugal, 5 years in Denmark, Egypt or Norway to 10 years in Austria, Australia or Taiwan[90]. It is possibly longer in some countries, such as the UK, where a maximum storage period of 55 years is provided[99], and it is unlimited in Canada and Finland[90].

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[k] The following countries bans research on human embryos: Cameroon, Chile, China, Colombia, Croatia, Democratic Republic of the Congo, Dominican Republic, Ireland (Republic), Ivory Coast, Kazakhstan, Lithuania, New Zealand, Peru, Philippines, Senegal, Singapore, Slovakia, Taiwan, Tunisia, Uruguay, Venezuela, and Vietnam.

[l] The following countries permit research only on surplus embryos: Brazil, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Greece, Hungary, Iceland, Norway, Portugal, Slovenia, South Africa, Spain, The Netherlands, USA, UK.

[m] Belgium, Egypt, Japan, Mexico, South Korea and Sweden allow the creation of human embryos for research purposes.

[n] Austria, Germany, Italy and Switzerland permit research only on imported embryos.

[o] Northern Ireland, Luxembourg, Poland, Romania, Russia, Turkey and Ukraine have no legislation on human embryo research.

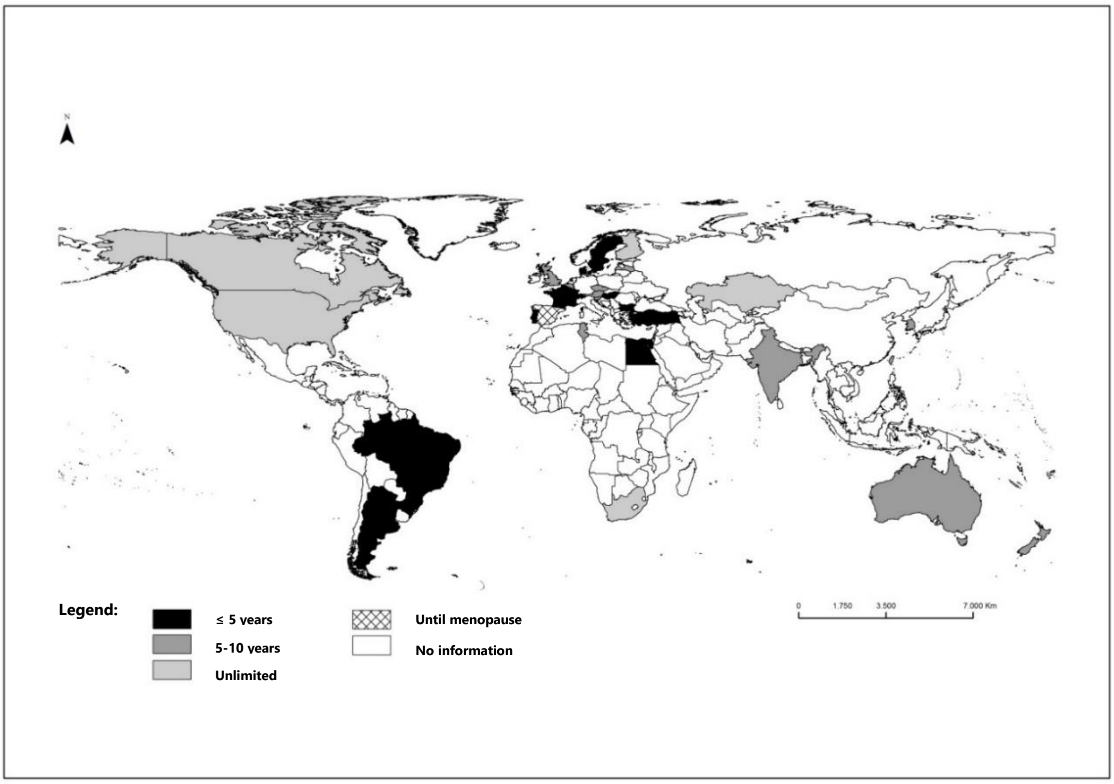


Figure 1. Maximum length of embryo storage, by country[90]

In Portugal, until 2006, the year in which a law regulating ART was enacted - Law No. 32 of July 26, 2006[100], there was no specific regulation on human embryo research. Since then, cryopreserved embryos may be used for scientific research, being prohibited their deliberate creation for research purposes. Experiments using these embryos must be authorized by the Conselho Nacional de Procriação Medicamente Assistida [National Council of Medically Assisted Reproduction], since they would result in present or future benefits for humanity[100]. Obtaining informed consent from the woman and the man for using their embryos in scientific studies is needed.

According to the informed consent form actually in force in Portugal (see Appendix 2), couples are asked for giving broad consent to donate or not to donate embryos to research project and to other infertile couples[101]. Patients must write 'Yes' or 'No' in a blank square in front of the following statements: 1) "We consent to the use of our embryos for donation to other infertile couples"; 2) "We consent to the use of our embryos in scientific research projects". This consent might be revoked by either member of the couple. Embryos must be kept for a maximum period of three years and if, within this period, the embryos are not used by the couple or have not been given other of the uses consented by them (donation for other couples or for research), embryos will be thawed and eliminated. There is no national guidelines concerning the adequate moment for signing the informed consent.

These principles reflect the main international trends in the legal and regulatory landscape of countries allowing human embryo research, particularly on the following aspects: authorization of research projects using only surplus embryos; requirement of evaluation of human embryo research projects prior to implementation by regulatory authorities and ethics committees; prohibition of the sale of embryos and their production solely for research; and the need to obtain informed consent from patients [90-92].

There is a wide debate about the meaning of the informed consent and what is needed to guarantee its legitimacy and validity [102, 103], in a context where the relationship between freedom of action and choice, on the one hand, and influence of the medical expertise and advice, and the social context, on the other, emerge as an important topic of reflection. Overall, it is important that the consent is effectively informed (which requires an understanding of its content as well the comprehension of the oral and written information provided), voluntary (without any pressure or coercion, external or internal, concerning decision-making) and reflected (preceded by time to think about the decision) [91, 95, 104, 105]. These elements are especially relevant when the decision process involves the search for consensus among partners[81]. However, critical approaches arising from social sciences and humanities discuss the conditions under which informed, voluntary and reflected consent is conceptualized and implemented.

The rational-choice theory[106] assumes that each individual makes their decisions in an intentional and objective-oriented way. Individuals hierarchically ordered their set of preferences and make rational calculations of costs and benefits before acting, comparing systematically all the options available in order to maximize utility, which is the last aim of their action. This approach is largely based on the postulate of autonomy, defined as the ability to act freely without constraint or coercion[107]. The individual is thus seen as an autonomous being with his or her own rights, and with little or no influence of social, contextual or structural factors.

Contrasting with this perspective, social constructivist theory assumes that individuals are active participants in learning processes involving the social construction of knowledge which underlies their decisions[108]. Patients have access to information that is socially constructed, resulting from the relationships established with health professionals, being influenced by professionals' skills to explain, respect and support[109]. Consent is regarded as a perceived and experienced process constructed through interactions between individuals and their social contexts, where emotions, desires and feelings shape patients' responses and decision-making. Consent is conceived as an ongoing process rather than as a discrete act of choice taking place in a given moment of time[102], which calls attention for the importance of being revocable at any time.

It has been suggested that informed consent should not be seen as the result of a purely rational and autonomous process of decision-making, based on a deep assessment and understanding of the information provided by health professionals, as it is also guided by feelings of trust in these professionals[103]. Interactions and relationships can enhance as well as restrict the autonomy to consent[109]. Thus, it is important to understand, in depth, the clinical context and the social and political aspects that influence the consent process[102].

In sum, the process of informed consent may constitute an opportunity for humanization, democratization, accountability and transparency of processes and decisions[95, 110] concerned with ART by fostering dialogue and trust between health professionals and patients[111, 112] and providing a space for reflecting about cryopreservation and decision-making regarding embryo disposition. However, it can also be reduced to a formality that may be guided by legitimate medical strategies to manage risks, expectations and responsibilities in the field of ART[113, 114].

In the context of clinical practices involving informed consent on embryo disposition, it is crucial to ground legal and regulatory frameworks on patients' values, preferences, choices and expressed needs in order to lend credence and robustness to the consent that the couples give. This thesis will contribute to this discussion, by analysing three inter-related issues: first, the perceptions of couples undergoing IVF regarding the circumstances that contextualize the delivery and signing of the informed consent; second, patients' opinions about the cryopreservation storage period offered to them; third, the existence of change in their attitudes over time.

1.2.2 Expectations and controversies

Human embryonic stem cells (hESCs) were firstly reported in November 1998, when two independent teams of US scientists succeeded in isolating and culturing stem cells obtained from human embryos and foetuses[115]. In 2006, researchers identified conditions that would allow some specialized adult cells to be "reprogrammed" genetically to assume a stem cell-like state – the induced pluripotent stem cells[116]. Since then, hundreds of stem cell lines have been derived worldwide using mainly remaining embryos generated after IVF treatments, and recently scientists in the UK have been granted permission to edit the genomes of human embryos for research[117].

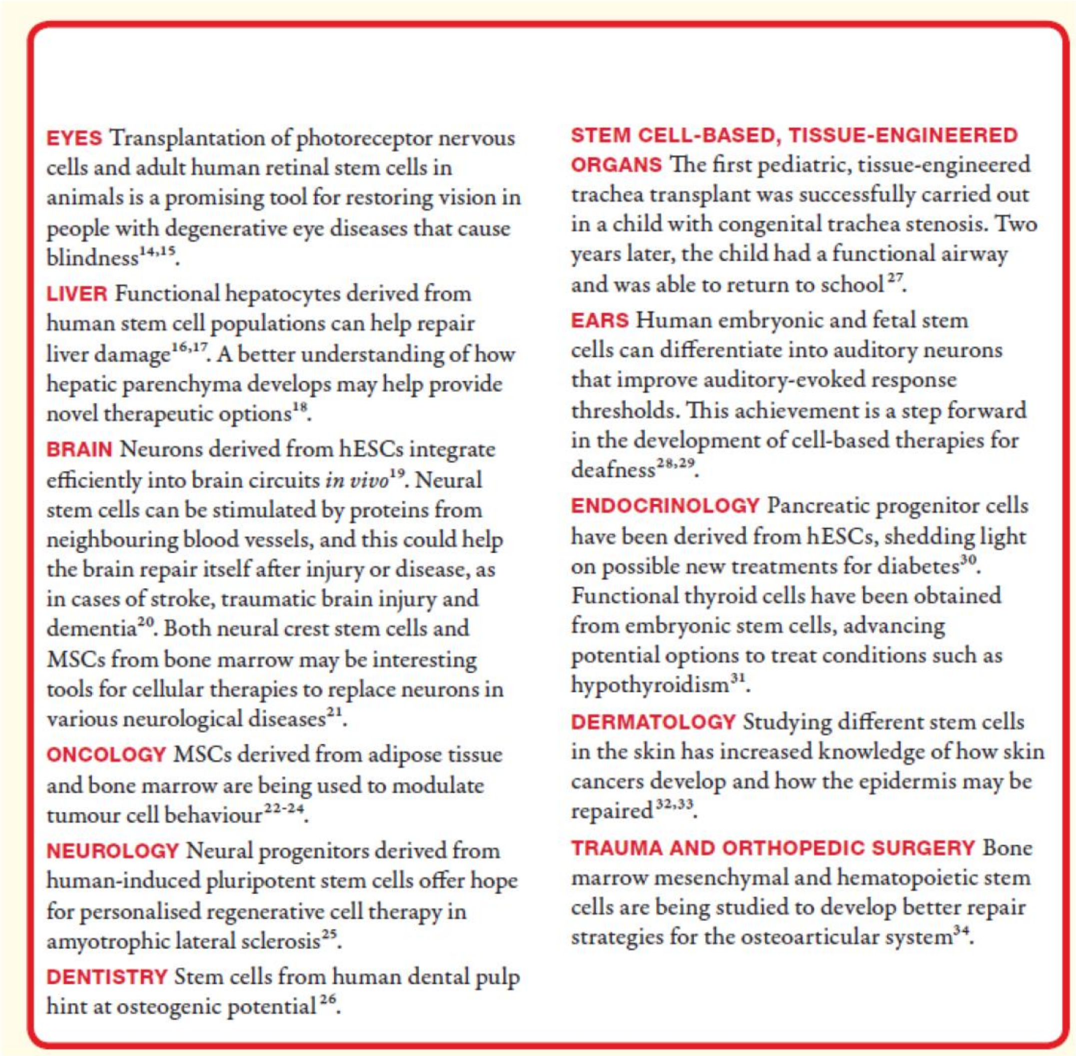
Research on human embryos, and in particular on hESCs, has engendered promising results and high expectations in society, but also controversial issues in ethics, practices and policies[30, 88, 118].

The development of innovative clinical solutions aiming to improve public and individual health is expected[119], with eventual impact on the levels of satisfaction and confidence among both caregivers and patients[120]. The value of recent achievements of research on hESCs is widely recognized (Figure 2), in particular for neurodegenerative disorders[121], transplants onto damaged human corneas[122] or organ transplantation[123].

Despite the promising results and potential clinical applications, differences in national and transnational laws and policies on human embryo research have given rise to reflections concerning the governance of global flows of embryos, scientists and capital[124-127]. Critical approaches also focus on issues related to the management of institutional and individual responsibilities and the protection of human rights, namely in the following domains: status and protection of human embryos[124, 128, 129]; lack of public involvement in decision-making regarding funding for hESC research[130] and in regulation of the information conveyed by the media in this process[131, 132]; and dissemination of unrealistic expectations concerning the results of research on human embryos[133]. In fact, contrary to what IVF patients who donate embryos for research expect, a recent critical review on the clinically validated stem cell-based therapies for reproductive diseases revealed that, to date, there are no stem cell-based therapies available to the larger public and outside of clinical trials directed at ameliorating or solving reproductive medicine issues[134].

Responsible governance on human embryo research needs to find a balance between expectations and controversies, empirically grounded on the assessment of the moral and ethical spectrum involving both scientists and stakeholders[88] and the public[135], in particular those people who must make embryo disposition decisions.

According to the Eurobarometer survey on biotechnology carried out in February 2010[136], 42% of the participants believe it is ethically wrong to use human embryos in medical research even if it might offer promising new medical treatments, while 47% disagree with such sentence and 11% have no opinion on this topic. Data from Portugal point to 40% of the participants considering human embryo research to be ethically wrong, while 42% consider that it is not ethically wrong and 18% do not express an opinion. Although there are differences among countries, these data illustrate the sensitive nature of this topic, with the public opinion being split almost evenly between those who agree and those who disagree that it is ethically wrong to use human embryos in medical research. In this context, it is important to deepen the understanding of the reasons for such opinions, in particular about how the public understands science and technology.



EYES Transplantation of photoreceptor nervous cells and adult human retinal stem cells in animals is a promising tool for restoring vision in people with degenerative eye diseases that cause blindness[14,15].

LIVER Functional hepatocytes derived from human stem cell populations can help repair liver damage[16,17]. A better understanding of how hepatic parenchyma develops may help provide novel therapeutic options[18].

BRAIN Neurons derived from hESCs integrate efficiently into brain circuits *in vivo*[19]. Neural stem cells can be stimulated by proteins from neighbouring blood vessels, and this could help the brain repair itself after injury or disease, as in cases of stroke, traumatic brain injury and dementia[20]. Both neural crest stem cells and MSCs from bone marrow may be interesting tools for cellular therapies to replace neurons in various neurological diseases[21].

ONCOLOGY MSCs derived from adipose tissue and bone marrow are being used to modulate tumour cell behaviour[22-24].

NEUROLOGY Neural progenitors derived from human-induced pluripotent stem cells offer hope for personalised regenerative cell therapy in amyotrophic lateral sclerosis[25].

DENTISTRY Stem cells from human dental pulp hint at osteogenic potential[26].

STEM CELL-BASED, TISSUE-ENGINEERED ORGANS The first pediatric, tissue-engineered trachea transplant was successfully carried out in a child with congenital trachea stenosis. Two years later, the child had a functional airway and was able to return to school[27].

EARS Human embryonic and fetal stem cells can differentiate into auditory neurons that improve auditory-evoked response thresholds. This achievement is a step forward in the development of cell-based therapies for deafness[28,29].

ENDOCRINOLOGY Pancreatic progenitor cells have been derived from hESCs, shedding light on possible new treatments for diabetes[30]. Functional thyroid cells have been obtained from embryonic stem cells, advancing potential options to treat conditions such as hypothyroidism[31].

DERMATOLOGY Studying different stem cells in the skin has increased knowledge of how skin cancers develop and how the epidermis may be repaired[32,33].

TRAUMA AND ORTHOPEDIC SURGERY Bone marrow mesenchymal and hematopoietic stem cells are being studied to develop better repair strategies for the osteoarticular system[34].

Figure 2. Examples of promising results and potential clinical applications of frontier research on stem cells in Europe[88]

The science literacy model assumes that knowledge boosts public acceptance of the scientific worldview and that science literacy is the driving force behind public evaluations[137]. Contrasting with the idea of promoting a well-informed public opinion[138], a contextualist approach to the public understanding of science focuses on the interactions between social context, forms of knowledge, the actions of “experts” and/or media use (e.g., [139-141]). Literature shows that trust in those conducting and regulating scientific research - universities, scientists and governments - has been significantly associated with positive attitudes towards embryonic stem cell research[142]. Higher levels of trust are most frequently observed when research is carried out by public universities, which are typically perceived to serve public over and above political and business interests. At the individual level, news media use and religion seemed to influence the relationship between the public and science and technology[137]. On the one hand, Christian conservatism and social ideology were directly associated with more negative views of embryonic stem cell research. On the other hand, reading about this type of research in the newspapers was associated with more positive views of embryonic stem cell research[137].

Beyond the public opinion, listening to the patients' voice and assessing their real-world experiences is a core need for patient-centred policies on human embryo research, as they are key actors in this research practice[112, 143, 144]. A literature review on this topic will be presented in the next section.

1.2.3 Paper I. Factors associated with the donation and non-donation of embryos for research: a systematic review

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Factors associated with the donation and non-donation of embryos for research: a systematic review

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BACKGROUND: Systematic knowledge on the factors that influence the decisions of IVF users regarding embryo donation for research is a core need for patient-centred policies and ethics in clinical practice. However, no systematic review has been provided on the motivations of patients who must decide embryo disposition. This paper fills this gap, presenting a systematic review of quantitative and qualitative studies, which synthesizes the current body of knowledge on the factors and reasons associated with IVF patients' decisions to donate or not to donate embryos for research.

METHODS: A systematic search of studies indexed in PubMed, ISI WoK and PsycINFO, published before November 2013, was conducted. Only empirical, peer-reviewed, full-length, original studies reporting data on factors and reasons associated with the decision concerning donation or non-donation of embryos for research were included. Eligibility and data extraction were performed by two independent researchers and disagreements were resolved by discussion or a third reviewer, if required. The main quantitative findings were extracted and synthesized and qualitative data were assessed by thematic content analysis.

RESULTS: A total of 39 studies met the inclusion criteria and were included in the review. More than half of the studies ($n = 21$) used a quantitative methodology, and the remaining were qualitative ($n = 15$) or mixed-methods ($n = 3$) studies. The studies were derived mainly from European countries ($n = 18$) and the USA ($n = 11$). The proportion of IVF users who donated embryos for research varied from 7% in a study in France to 73% in a Swiss study. Those who donate embryos for research reported feelings of reciprocity towards science and medicine, positive views of research and high levels of trust in the medical system. They described their decision as better than the destruction of embryos and as an opportunity to help others or to improve health and IVF treatments. The perception of risks, the lack of information concerning research projects and the medical system and the conceptualization of embryos in terms of personhood were the most relevant motives for not donating embryos for research. Results relating to the influence of sociodemographic characteristics and reproductive and gynaecological history were mostly inconclusive.

CONCLUSIONS: Three iterative and dynamic dimensions of the IVF patients' decision to donate or not to donate embryos for research emerged from this review: the hierarquization of the possible options regarding embryo disposition, according to the moral, social and instrumental status attributed to embryos; patients' understanding of expectations and risks of the research on human embryos; and patients' experiences of information exchange and levels of trust in the medical-scientific institutions.

Key words: embryo disposition / human embryo research / *in vitro* fertilization / assisted reproductive technologies / systematic review

Introduction

Research on human embryos, and in particular on embryonic stem cells (hESCs), has engendered promising results and high expectations in society, but also controversial issues in ethics, practices and policies (Vayena *et al.*, 2002; UNESCO, 2008; European Science Foundation, 2013). The development of innovative clinical solutions aiming to improve public and individual health is expected (Lancet, 2013), with eventual impact on the levels of satisfaction and confidence among both caregivers and patients (Genuis, 2008). The value of recent achievements through research on hESCs for neurodegenerative disorders (Marchetto *et al.*, 2010), transplants onto damaged human corneas (Hanson *et al.*, 2013) or organ transplantation (Elliott *et al.*, 2012), is widely recognized. However, differences in national and transnational laws and policies on human embryo research have given rise to reflections concerning the governance of global flows of embryos, scientists and capital (Zarzeczny and Caulfield, 2009; Salter and Faulkner, 2011; Salter and Salter, 2012; Nielen *et al.*, 2013). Critical approaches also focus on issues related to the management of institutional and individual responsibilities and the protection of human rights, namely in the following domains: status and protection of human embryos (Mulkay, 1997; Leist *et al.*, 2008; Zarzeczny and Caulfield, 2009); lack of public involvement in decision-making regarding funding for hESC research (Árnason *et al.*, 2007) and in regulation of the information conveyed by the media in this process (NHS, 2011; Vicsek, 2011); and dissemination of unrealistic expectations concerning the results of research on human embryos (Burns, 2009).

The legal and regulatory landscape on human embryo research was recently analysed by the European Science Foundation (2013), the European Society of Human Reproduction and Embryology (ESHRE, 2013) and the International Federation of Fertility Societies (International Federation of Fertility Societies (IFFS), 2013). Considering the 58 countries with coherent data on national policies or guidelines regarding research on human embryos in these three sources of information, more than one-third ($n = 22$) bans such research, and 19 countries permit research only on surplus IVF embryos, prohibiting the creation of embryos solely for research purposes. Six countries allow the creation of human embryos for research purposes, while four permit research only on imported embryos. The remaining seven countries have no legislation on human embryo research.

Responsible governance of hESC research needs to find a balance between expectations and controversies, empirically grounded on the assessment of the moral and ethical spectrum involving both scientists and stakeholders (European Science Foundation, 2013) and the public (Etchegary *et al.*, 2013), in particular those people who must make embryo disposition decisions. Listening to the patients' voice is a core need for patient-centred policies on hESC research, as they are key actors in this research practice (WHO, 2007; Dancet *et al.*, 2010; European Comission, 2012).

Existing literature reviews on the factors that influence the decisions of couples to donate embryos, both for research and to other couples, are not systematic reviews. The review authored by de Lacey (2013) mainly focuses on the perception of the embryo status and its implications for counselling, while Hug (2008) only provides information about studies published between 2002 and 2007, with a more specific focus on prospective donors and their motivation to donate or not to donate cryopreserved embryos for medical research. Additionally, these reviews did not identify essential dimensions involved in the decision-making process concerning embryo donation for research. This could serve as a relevant tool for future research and policy on hESCs, allowing the comparison of real-world decisions among different cultural, economic and political contexts.

We aimed to synthesize the current body of knowledge about the motivations of IVF patients to donate or not to donate embryos for research, by providing a systematic review on the factors and reasons associated with such a decision.

Methods

We followed the PRISMA principles and our reporting complies with this approach (Moher *et al.*, 2009). Qualitative data analysis followed the main guidance for qualitative research and Cochrane reviews, by the Cochrane Qualitative Research Methods Group (Noyes *et al.*, 2008), and a protocol for content analysis (Stemler, 2001) and for thematic analysis (Mays *et al.*, 2005). A review protocol was developed in advance.

Search strategy

A search of the publications on three electronic databases (PubMed, ISI WoK and PsycINFO) was undertaken in November 2013, with no restriction set for language or time of publication, using the MeSH term 'embryo disposition', which was adapted according to the requirements of each database (e.g. PubMed syntax: (embryo disposition[mh] OR 'embryo disposition') NOT (Animals[mh] NOT Humans[mh])). Embryo disposition was introduced as a MeSH term in 1999, defined as the 'utilization or disposal of an embryo that is fertilized but not immediately transplanted and resulting course of action'. The search was followed by reference tracking, examining the references of the selected publications based on full-text assessment.

Study selection

The inclusion criteria allowed only empirical, peer-reviewed, original full-length studies that: (i) reported the proportion of IVF patients (couples or individuals) who agreed to donate embryos for research; or (ii) assessed factors associated with the decision concerning donation of embryos for research; or (iii) explored the reasons reported by IVF patients to justify their decision regarding the donation or non-donation of embryos for research.

The exclusion criteria disallowed: studies focusing on donation to other couples, studies of the ethical or legal issues surrounding embryo donation to research or medical procedures, as well as studies about the decision to continue/discontinue storage. Non-original full-length studies (reviews, meta-analyses, comments, editorials, notes, newspapers articles, conference proceedings, reports and guidelines) were also excluded.

Screening and quality assessment

The first two authors (C.S. and M.P.) independently screened all the papers retrieved initially, based on the title and abstract, and afterward, based on the full-text; this was crosschecked in both phases. The study selection was guided by the research question, inclusion/exclusion criteria and consensus by both authors. Agreement was reached >92% of the time. Disagreement was solved by joint discussion until consensus could be reached or, when consensus was not achieved, by the assessment of a third author (S.S.), based on the implementation of the same inclusion and exclusion criteria defined for study selection.

Quality assessment on the included articles was based upon the protocol recommended by the Cochrane Database of Systematic Review. It was grounded on the following criteria, according with the characteristics and objectives of this review: (i) Database: studies should be peer-reviewed and be available in an electronic database; (ii) Selection of participants: study participants should be clearly defined as couples or individuals who have been involved in an IVF treatment and have effectively or hypothetically decided about embryo donation or non-donation for research; (iii) Outcome measurements: they should include values of statistical significance in quantitative studies, and research questions in qualitative studies; and (iv) Study methodology: the methods should be clearly described in sufficient detail, including the recruitment of participants, method, time of assessment and outcome measures.

Data abstraction

A standardized data extraction sheet was developed and completed by two independent researchers (C.S. and M.P.), including both quantitative and qualitative data. Descriptive data for the characterization of studies included: information about the authors and publication year; type of methodology (quantitative, qualitative and mixed-methods); period of data collection, country and setting where the study was developed; sample size; and time of assessment (categorized as 'pre-decision' and 'post-decision', the latter being when patients had already formalized their decision on embryo disposition, or both pre- and post-decisions).

Data concerning the proportion of patients who agreed to donate embryos for research (in percentage) were gathered only from quantitative studies. Specific choices were made: (i) in longitudinal studies, where data from the last evaluation were extracted; and (ii) when the response options included mutually exclusive categories, where all the proportions were retrieved and added up.

Quantitative data on variables whose association with embryo donation for research was statistically tested were retrieved and the directions of the associations were registered. Whenever adjusted Odds Ratios (ORadj) were provided, these were extracted.

Based on the protocol for content analysis developed by Stemler (2001), the first two authors analysed, independently, all the studies presenting data about the reasons to donate or not to donate embryos for research, aiming to identify, quotation by quotation, all the reasons reported by IVF patients to justify their decision. These quotations were synthesized into categories, defined as 'a group of words with similar meaning and connotations', by the first and the last authors (C.S. and S.S.), and the number of papers where each category emerged was recorded. Such categories were then grouped into three main themes by C.S. and S.S., according to the protocol for thematic analysis developed by Mays *et al.* (2005): 'sociotechnical context', which included the IVF patients' understanding of science, technology and medicine, and the leading values in the doctor-patient relationship; 'societal benefits', when quotations pointed out the advantages of research on human embryos for the society, for IVF patients, and for individuals; and the 'views about embryos' where the reasons included references to their moral status and quality, as well as to the hierarchization of the fates of embryos. Disagreements in abstractions were discussed and resolved by consensus. An almost perfect strength of agreement between reviewers was achieved (>0.80) (Stemler, 2001).

Results

Search strategy and study selection

The titles of 978 records were initially screened. The search included publications dating from 1985 until November 2013. After the removal of the duplicates ($n = 486$), 492 records were examined. This led to the exclusion of 442 records based on title and abstract assessment, mainly because they were neither related to the research questions nor original full-length studies. Of the 50 fully read papers, 28 met the inclusion criteria. After the reference tracking, 11 papers were included and the final systematic review was composed of 39 papers, published between 1995 and 2012. The screening process is summarized in the study flowchart (Fig. 1).

Study characteristics

The main characteristics of the 39 studies included can be found in Table I. Studies were grouped by type of methodology and ordered by the year of publication.

Research design

More than half of the studies ($n = 21$) used a quantitative methodology, 15 used a qualitative approach and 3 used mixed-methods. In quantitative studies, 13 used questionnaires to collect data (Lornage *et al.*, 1995; Asensio *et al.*, 2001; McMahon *et al.*, 2003; Bangsboll *et al.*, 2004; Burton and Sanders, 2004; Hammarberg and Tinney, 2006; Karpel *et al.*, 2007; Mohler-Kuo *et al.*, 2009; Lyerly *et al.*, 2010, 2011; Provoost *et al.*, 2011, 2012a, b), and 8 used medical records, including consent forms (Choudhary *et al.*, 2004; Newton *et al.*, 2007; Luna *et al.*, 2009; Van Voorhis *et al.*, 2009; Lanzendorf *et al.*, 2010; Hill and Freeman, 2011; Sharma *et al.*, 2011; Provoost *et al.*, 2012c). All the qualitative studies relied on semi-structured and in-depth interviews (Lyerly *et al.*, 2004, 2006; Parry, 2006; Fuscaldo and Gillam, 2007; Haimes and Taylor,

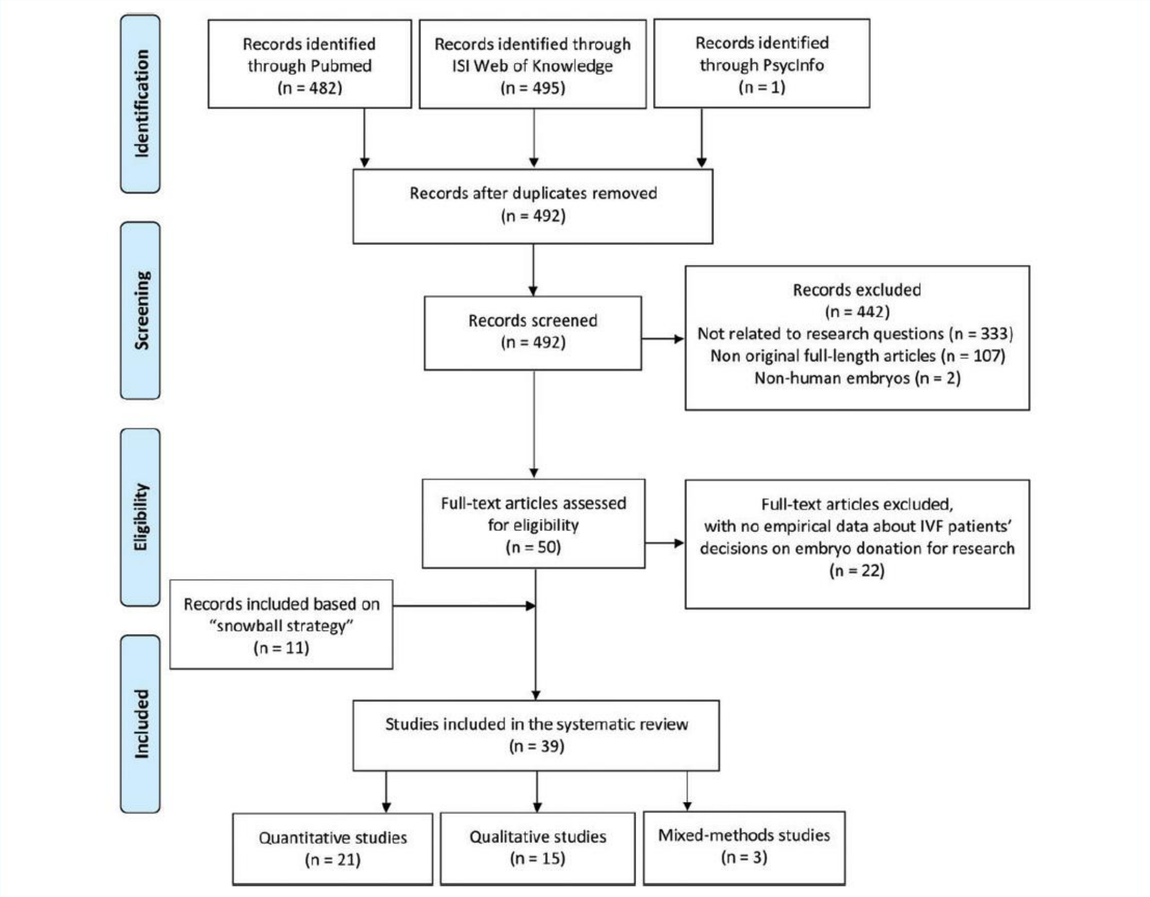

Figure 1 Flowchart showing the search results and screening process for the systematic review on embryo donation for research.

2009; Kufner *et al.*, 2009; Melamed *et al.*, 2009; Peddie *et al.*, 2009; Provoost *et al.*, 2009, 2010; Mitzkat *et al.*, 2010; Nachtigall *et al.*, 2010; Frith *et al.*, 2011; Kato and Sleeboom-Faulkn, 2011; Takahashi *et al.*, 2012). Focus groups were also used in two cases (Parry, 2006; Fuscaldo and Gillam, 2007). Mixed-methods studies used a questionnaire, an informed consent document and a psychological interview (Laruelle and Englert, 1995); in-depth interviews in a narrative style, followed by statistical analysis (Jin *et al.*, 2013); and qualitative and quantitative interviews (Zweifel *et al.*, 2007). Regarding the outcomes under analysis in this review, 23 papers had reliable information on the proportion of IVF patients who agreed to donate embryos for research; 18 provided quantitative information on the factors associated with such a decision; and 22 provided information about the reasons underlying the decision to donate and not to donate embryos for that purpose (Supplementary data, Table SI).

Country of study origin

Empirical studies about the proportion of embryo donation for research or its associated factors, or reported reasons underlying IVF patients' decision derived from 13 countries: USA (*n* = 11), Belgium (*n* = 7), Australia (*n* = 4), UK (*n* = 4), China (*n* = 2), France (*n* = 2), Japan (*n* = 2), Spain (*n* = 2), Brazil (*n* = 1), Canada (*n* = 1), Denmark (*n* = 1), Germany (*n* = 1) and Switzerland (*n* = 1).

Setting

Most of the 39 studies were performed in University Hospitals (*n* = 22). Ten studies were performed in private clinics, 1 in a public centre, 1 in a fertility clinic, 2 in mixed centres (private and public), and 3 did not mention the setting. Two studies gathered data from various centres: Mohler-Kuo *et al.* (2009) presented data from 11 of the 19 Swiss IVF centres in existence in 2004 and Lyerly *et al.* (2010) reported data from 9 fertility clinics operating in the USA between June 2006 and July 2007.

Sample size

In quantitative studies sample sizes varied from 149 individual patients (Lanzendorf *et al.*, 2010) to 2334 couples (Provoost *et al.*, 2012c). In qualitative studies, the samples varied from 5 women (Mitzkat *et al.*, 2010) to 184 participants (110 women and 74 men) (Nachtigall *et al.*, 2010); and in mixed-methods studies, there were from 45 couples (Zweifel *et al.*, 2007) to 363 couples (Jin *et al.*, 2013). In the total of

Table I **Main characteristics of the included studies in the systematic review on embryo donation for research: period of data collection, country, setting, sample size and time of assessment ($n = 39$).**

Authors, year of publication	Period of data collection	Country	Setting	Sample size	Time of assessment (pre/post decision)
Quantitative studies					
Lornage *et al.* (1995)	1987–1992	France	Public centre	145 couples	Pre
Van Voorhis *et al.* (1999)	NR	USA	University hospital	365 patients	Post
Asensio *et al.* (2001)	2000	Spain	University hospital	89 couples	Pre
McMahon *et al.* (2003)	NR	Australia	Private clinic	152 women; 123 men	Pre
Bangsboll *et al.* (2004)	NR	Denmark	University hospital	207 couples	Pre
Burton and Sanders (2004)	May 03	Australia	Private clinic	235 couples	Pre
Choudhary *et al.* (2004)	Jan-Feb 02; Mar-Dec 03	UK	Mixed	300 couples	Post
Hammarberg and Tinney (2006)	Jan 02–Jun 03	Australia	Private clinic	88 women; 35 couples	Post
Karpel *et al.* (2007)	Oct 04	France	University hospital	84 couples	Pre/post
Newton *et al.* (2007)	2002–2005	Canada	University hospital	88 couples	Post
Luna *et al.* (2009)	NR	Spain	University hospital	236 couples	Post
Mohler-Kuo *et al.* (2009)	Mar and Dec 04	Switzerland	NR	458 men; 468 women	Pre
Lanzendorf *et al.* (2010)	Jan 02–Jul 07	USA	University hospital	149 patients	Post
Lyerly *et al.* (2010)	Jun 06–Jan 07	USA	Private clinic	795 women; 225 men	Pre
Hill and Freeman (2011)	Jan 98–Dec 08	USA	Private clinic	364 patients	Post
Lyerly *et al.* (2011)	Jun 06–Jan 07	USA	Private clinic	786 women; 219 men	Pre
Provoost *et al.* (2011)	NR	Belgium	University hospital	326 couples	Pre/post
Sharma *et al.* (2011)	May 08–Apr 09	USA	University hospital	400 patients	Post
Provoost *et al.* (2012a)	NR	Belgium	University hospital	200 women	Post
Provoost *et al.* (2012b)	NR	Belgium	University hospital	326 couples	Pre/post
Provoost *et al.* (2012c)	1992–2006	Belgium	University hospital	2334 couples	Pre/post
Qualitative studies					
Lyerly *et al.* (2004)	NR	USA	University hospital	31 women; 7 couples	Pre
Lyerly *et al.* (2006)	Sept 02 – May 04	USA	University hospital	31 women; 8 men; 7 couples	Pre
Parry (2006)	Jun 01	UK	Fertility clinic	50 participants[a]	Pre
Fuscaldo and Gillam (2007)	Apr–Sept 04	Australia	Mixed	11 men; 31 women	Pre
Haimes and Taylor (2009)	2005–2006	UK	Private clinic	30 couples	Post
Kufner *et al.* (2009)	2005	Germany	University hospital	9 women; 9 men	Pre
Melamed *et al.* (2009)	NR	Brazil	Private clinic	50 couples	Pre
Peddie *et al.* (2009)	Aug 07–Jan 08	UK	University Hospital	15 couples	Pre/post
Provoost *et al.* (2009)	May–Jul 06	Belgium	University hospital	7 couples; 11 women	Pre
Mitzkat *et al.* (2010)	NR	China	Private clinic	5 women	Post
Nachtigall *et al.* (2010)	NR	USA	Private clinic	110 women; 74 men	Post
Provoost *et al.* (2010)	NR	Belgium	University hospital	7 couples; 11 women	Pre
Frith *et al.* (2011)	Sept 08–Dec 09	USA	NR	18 couples; 7 women	Post
Kato and Sleeboom-Faulkn (2011)	2006–2008	Japan	NR	40 women; 18 men	Pre
Takahashi *et al.* (2012)	NR	Japan	University hospital	10 women	Pre/post
Mixed-methods studies					
Laruelle and Englert (1995)	NR	Belgium	University hospital	200 couples	Post
Zweifel *et al.* (2007)	Aug 04–May 05	USA	University hospital	45 couples	Post
Jin *et al.* (2013)	Jan–Apr 12	China	University hospital	363 couples	Pre

NR, not referenced.

[a] This study included five focus groups and seven interviews, in a total of 50 participants. Data were retrieved from the focus groups with fertility support groups.

the 39 papers, samples were composed mostly of couples (*n* = 17), followed by samples of both women and men (*n* = 8), couples and women/men (*n* = 6), and only women (*n* = 3). In five studies, the gender of the participants is not specified.

Time of assessment

Almost half of the studies (*n* = 18) used pre-decision information, 15 studies used post-decision information and 6 studies combined pre- and post-decision information. The majority of studies (*n* = 36) were cross-sectional. Studies by Lornage *et al.* (1995), Newton *et al.* (2007) and Provoost *et al.* (2012c) evaluated more than one moment in time.

Proportion of IVF patients who agreed to donate embryos for research

Figure 2 presents the proportions of IVF patients who donated embryos for research retrieved from the 8 quantitative studies which assessed the proportion of donation through a dichotomic answer (yes or no to donation for research). In these studies, proportions of donation to research varied from 10% in a study conducted in the USA between 1998 and 2008 (Hill and Freeman, 2011) to 73% in a Swiss study based on data collected in 2004 (Mohler-Kuo *et al.*, 2009). Proportions varied among studies conducted in the same country and published in the same or contiguous years in the cases of the USA and Australia. In the USA, the studies published in 2010 and 2011 presented proportions between 10% (Hill and Freeman, 2011) and 50% (Lyerly *et al.*, 2011). In Australia, two papers published in 2003 and 2004 presented proportions from 27% (Burton and Sanders, 2004) to 44% (McMahon *et al.*, 2003).

Figure 3 presents the proportions of IVF patients who donated embryos for research retrieved from 12 quantitative studies where these proportions were assessed through the hierarquization of the available options for embryo disposition. Proportions of donation to research in these studies varied from 7% in a study conducted in France between 1987 and 1992 (Lornage *et al.*, 1995) to 59% in a study developed in the USA from 2002 to 2007 (Lanzendorf *et al.*, 2010). Two studies conducted in Belgium, both published in 2012, presented proportions of 26% in a study collecting information about embryo disposition over 15 years (Provoost *et al.*, 2012c) and 51% in a study best described as cross-sectional (Provoost *et al.*, 2012a).

Proportions were extracted by using as the denominator all the participants who answered the question about embryo disposition in each study. Two proportions were retrieved from the studies that presented results regarding the donation of embryos for research stratified by 'research to improve techniques' and 'stem-cell research' (Burton and Sanders, 2004) and 'infertility research' and 'stem cell research' (Bangsboll *et al.*, 2004).

The sum of all proportions is presented when the response options included mutually exclusive categories regarding donation of embryos for research: 'a possible decision' and 'a likely decision' (McMahon *et al.*, 2003); 'yes, in principle' and 'yes, with some restrictions' (Mohler-Kuo *et al.*, 2009); 'donation and experimentation' and 'experimentation' (Laruelle and Englert, 1995). Because of the fact that articles by Lyerly *et al.* (2010, 2011) and Provoost *et al.* (2011, 2012a, b) were based on the same sample, only the overall proportion of non-stratified results was extracted from one paper (Lyerly *et al.*, 2011; Provoost *et al.*, 2012a).

Factors associated with the donation and non-donation of embryos for research

The quantitative synthesis of the factors associated with the decision to donate or not to donate embryos for research is presented in Table II.

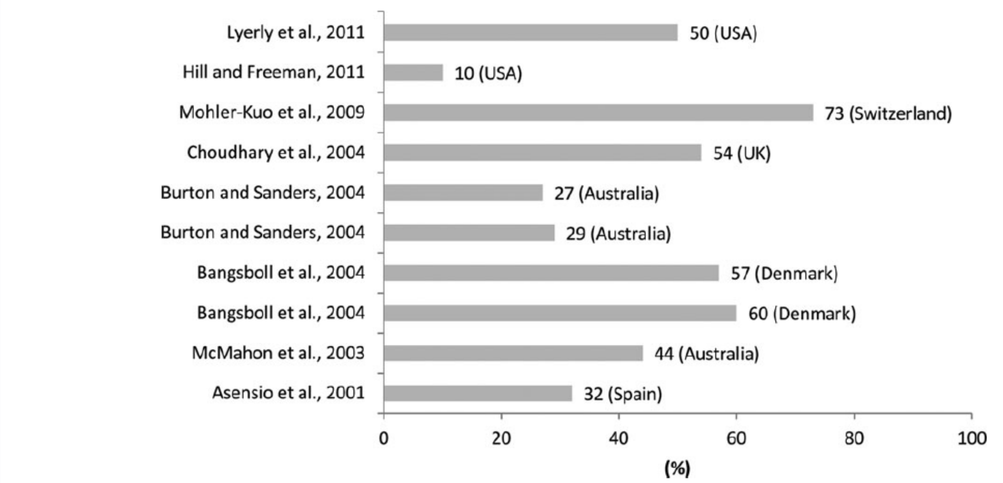

Figure 2 Proportion of IVF patients who agreed to donate embryos for research, in the studies where the proportion was estimated through a dichotomic answer (yes/no to donation for research). Notes: Two proportions were retrieved from the studies that presented results stratified by 'donation to research to improve techniques' (29%) and 'stem-cell research' (27%) (Burton and Sanders, 2004) and 'infertility research' (60%) and 'stem cell research' (57%) (Bangsboll *et al.*, 2004). The proportion of donation to research, in Hill and Freeman (2011), was calculated by adding the absolute frequencies of participants who agreed to donate to research in two groups of patients: 'patients using autologous oocytes' (41 out of 364) and 'donor oocyte recipients' (6 out of 110), which was divided by the total number of participants (*n* = 474). Proportions are rounded to units.

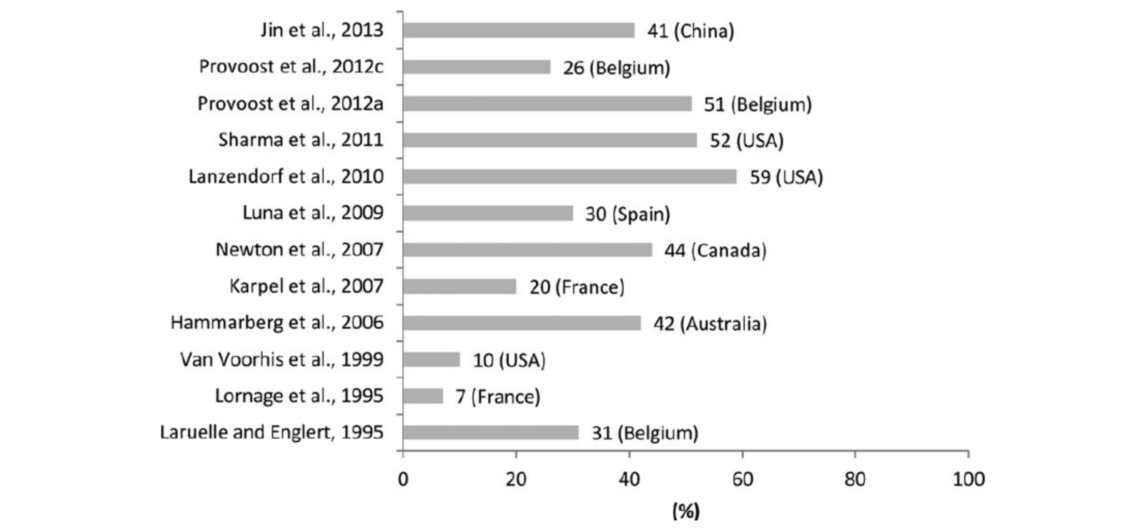

Figure 3 Proportion of IVF patients who agreed to donate embryos for research, in the studies where the proportion was assessed through the hierarquization of the possible options for embryo disposition. Note: Proportions are rounded to units.

Factors related with reproductive and gynaecological history and sociodemographic characteristics were more frequently addressed, followed by other factors such as storage length and perception of embryo status.

The donation of embryos for research was consistently less frequent among IVF patients who conceptualized embryos in terms of personhood, a life or as having a high moral status, or among those who viewed embryos as a symbol of the relationship of the couple. The donation of embryos for research was also associated with: the country of birth (being an Asian born inside the USA versus an Asian born outside the USA); giving a high importance to altruism in the decision about embryo disposition; a higher decisional conflict; a joint decision by partners; and having an interest in participating in clinical research. There were no statistically significant associations between the decision to donate or not to donate embryos for research and the duration of infertility, numbers of previous cycles, types of treatment, parity, types of funding, concerns about family/finances, or consultation with someone other than the partner regarding the decision.

Results about the decision to donate or not donate with regard to having children or not, the number of embryos, the use of homologous/heterologous techniques, unsuccessful cycles, age, education levels, religion beliefs, ethnicity and embryo storage lengths were contradictory.

However, 14 out of 22 variables were assessed once or twice, resulting in inconclusive data. Additionally, most of the quantitative studies were descriptive, which does not allow conclusions to be reached about the isolated effect of a specific variable in the decision about embryo donation or non-donation for research. Odds ratios and respective 95% confidence intervals (OR, 95% CI) for the associations between factors and the decision to donate or not to donate embryos for research were presented in four studies (Bangsboll *et al.*, 2004; Mohler-Kuo *et al.*, 2009; Lyerly *et al.*, 2010, 2011). Three of them clearly stated that adjusted ORs (ORadj) were calculated, i.e. the observed associations had been adjusted for multiple confounders (Bangsboll *et al.*, 2004; Mohler-Kuo *et al.*, 2009; Lyerly *et al.*, 2011). Considering that the variables analysed with ORs were not measured in a standardized way and that the same outcome was assessed in a maximum of two studies, a meta-analysis was not conducted.

Reproductive and gynaecological history

Having children after an IVF treatment (versus no children) was predictive of donating embryos for stem cell research (ORadj = 3.80, 95% CI: 1.40–10.20) (Bangsboll *et al.*, 2004), while having children conceived naturally was associated with donating less often for research in one study, compared with those having children from IVF or Intracytoplasmic Sperm Injection (ICSI) (ORadj = 0.60, 95% CI: 0.40–0.90) (Mohler-Kuo *et al.*, 2009). Having had a live birth was associated with donating less frequently for research than discarding (30 versus 52%; $P = 0.05$) (Newton *et al.*, 2007). No association between the decision to donate and having (or not) IVF children was found by Choudhary *et al.* (2004), Hammarberg and Tinney (2006) and Lanzendorf *et al.* (2010). Also the decision to donate embryos for research was not influenced by whether the patients had children, regardless of being or not conceived by IVF (Burton and Sanders, 2004; Lyerly *et al.*, 2010; Sharma *et al.*, 2011) or being children of only one of the members of the couple (Sharma *et al.*, 2011).

Results regarding the impact of the number of embryos were contradictory. Choudhary *et al.* (2004) showed that those with a higher number of embryos donate more frequently to research (7.25 ± 4.91 versus 5.73 ± 3.98; $P = 0.004$), but Provoost *et al.* (2012c) found the opposite association, with those with a lower number of embryos donating more (4.08 versus 4.51; $P = 0.020$). No association between these variables was found by Hammarberg and Tinney (2006) and Newton *et al.* (2007).

Couples who used their own gametes (versus donor gametes) were more willing to donate embryos for research in one study (56.9 versus 42.9%; $P < 0.05$) (Luna *et al.*, 2009). However, another study showed that couples treated with donor (versus the husband's) sperm are

Table II **Main findings on the factors associated with the donation of embryos for research, identified on the quantitative and mixed-methods studies (n = 18).**

Factors (number of papers)	Main findings
Reproductive and gynaecological history	
Having children ($n = 9$)	Children after IVF treatment (versus no children): predictive of agreement to embryo donation for stem cell research (ORadj = 3.80, 95% CI: 1.40–10.20) (Bangsboll *et al.*, 2004[a]) Children conceived naturally (versus children from IVF/ICSI): less likely to donate (ORadj = 0.60, 95% CI: 0.40–0.90) (Mohler-Kuo *et al.*, 2009[b]) Live birth: 52% discard versus 30% donate for research ($P = 0.05$)(Newton *et al.*, 2007) No association with having (or not) IVF children (Choudhary *et al.*, 2004; Hammarberg and Tinney, 2006; Lanzendorf *et al.*, 2010) No association with having (or not) previous children (Burton and Sanders, 2004; Lyerly *et al.*, 2010; Sharma *et al.*, 2011)
Number of embryos ($n = 4$)	Higher number of embryos: more likely to donate (7.25 ± 4.91 versus 5.73 ± 3.98; $P = 0.004$) (Choudhary *et al.*, 2004) Lower number of embryos: more likely to donate (4.08 versus 4.51; $P = 0.020$) (Provoost *et al.*, 2012c) No association (Hammarberg and Tinney, 2006; Newton *et al.*, 2007)
Homologous/heterologous techniques ($n = 3$)	Couples treated with donor (versus husband sperm): more likely to donate to infertility research (OR = 1.30, 95% CI: 1.20–1.50) (Bangsboll *et al.*, 2004[a]) Couple's own gametes (versus donor gametes): more likely to donate (56.9% versus 42.9%; $P < 0.05$) (Luna *et al.*, 2009) No association with donation for stem cell research (Bangsboll *et al.*, 2004[a]; Sharma *et al.*, 2011)
Unsuccessful cycle ($n = 2$)	Previous failed fertilization: less likely to donate ($P = 0.009$) (Choudhary *et al.*, 2004) No association (Sharma *et al.*, 2011)
Duration of infertility ($n = 2$)	No association (Bangsboll *et al.*, 2004[a]; Choudhary *et al.*, 2004)
Number of previous cycles ($n = 2$)	No association (Choudhary *et al.*, 2004; Sharma *et al.*, 2011)
Type of treatment ($n = 2$)	No association (Bangsboll *et al.*, 2004[a]; Choudhary *et al.*, 2004)
Parity ($n = 1$)	No association (Sharma *et al.*, 2011)
Sociodemographic characteristics	
Age ($n = 8$)	Older (>40 versus ≤40 years old): more likely to donate to medical research (ORadj = 1.80, 95% CI: 1.10–3.00) (Mohler-Kuo *et al.*, 2009[b]) No association (Asensio *et al.*, 2001; Burton and Sanders, 2004; Choudhary *et al.*, 2004; Hammarberg and Tinney, 2006; Lanzendorf *et al.*, 2010; Sharma *et al.*, 2011; Provoost *et al.*, 2012c)
Education level ($n = 3$)	College and University education and Vocational School + 2 years versus mandatory/vocational school): more likely to donate (ORadj = 1.80, 95% CI: 1.10–3.00 and ORadj = 2.00, 95% CI: 1.20–3.40, respectively) (Mohler-Kuo *et al.*, 2009[b]) No association (Hammarberg and Tinney, 2006; Jin *et al.*, 2013)
Religion beliefs ($n = 3$)	Moderate to strong beliefs (versus not very strong beliefs): less likely to donate in both women (20 versus 42%; $P = 0.008$) and men (18 versus 41%; $P = 0.01$) (Burton and Sanders, 2004) Perceived (high) importance of religious principles on attitude toward reproductive medicine: less likely to donate (ORadj = 0.40, 95% CI: 0.20–0.60) (Mohler-Kuo *et al.*, 2009[b]) No association: commitment to religion (versus non-religious) (McMahon *et al.*, 2003)
Ethnicity ($n = 2$)	Caucasian (versus Asian): donate more (56 versus 27%; $P = 0.022$) (Choudhary *et al.*, 2004) Caucasian (versus Asian): donate more (41.6 versus 57%; $P < 0.001$) (Sharma *et al.*, 2011) No association (Lyerly *et al.*, 2010)
Country of birth ($n = 1$)	Asians born outside the USA (versus Asians born inside the USA): less likely to donate (37.9 versus 57.6%; $P = 0.001$) (Sharma *et al.*, 2011)
Other factors	
Storage length ($n = 6$)	Longer periods of storage: more likely to donate (35.7% among 5–10 years, 34.9% among >10 years versus 19.1% among ≤4 years; $P < 0.05$) (Luna *et al.*, 2009) No association (Asensio *et al.*, 2001; Hammarberg and Tinney, 2006; Newton *et al.*, 2007; Lanzendorf *et al.*, 2010; Lyerly *et al.*, 2010)
Embryo status ($n = 5$)	View of the moral status of the embryo as a cluster of cells versus life, potential child: 86.2 versus 13.6% donate to medical research and therapy ($P < 0.05$) (Jin *et al.*, 2013) Lower moral status to human embryos (versus higher): more likely to donate (OR = 0.69, 95% CI: 0.60–0.79) (Lyerly *et al.*, 2010) Strong agree/agree with embryo as a human being (versus strong disagree/disagree): less likely to donate (ORadj = 0.30, 95% CI: 0.20–0.50) (Mohler-Kuo *et al.*, 2009[b])

Continued

Table II *Continued*

Factors (number of papers)	Main findings
	Embryo as a child (versus others): less likely to donate(16 versus 36%; $P < 0.05$) (Laruelle and Englert, 1995)
	Patients without the Symbol of One's Relationship (SOR) view[c] (versus patients with the SOR view): more willing to donate (87.2 versus 65.1%; $P = 0.018$) (Provoost *et al.*, 2012b)
Type of funding ($n = 2$)	No association (Choudhary *et al.*, 2004; Sharma *et al.*, 2011)
Altruism ($n = 1$)	High importance of altruism in the decision about the fate of embryos (versus less importance): more likely to donate than to discard (OR = 1.65, 95% CI: 1.47–1.85) (Lyerly *et al.*, 2010)
Concerns about family/finances ($n = 1$)	No association (Lyerly *et al.*, 2010)
Consultation of others regarding the decision ($n = 1$)	No association (Provoost *et al.*, 2012a)
Decisional conflict[d] ($n = 1$)	Higher decisional conflict (versus lower): more likely to donate embryos for research (ORadj = 1.66, 95% CI: 1.12–3.46) (Lyerly *et al.*, 2011)
Joint decision ($n = 1$)	Joint decision made by partners (comparing with decision by woman alone/by woman after consulting man or by man after consulting woman): more often in couples who donated for science (87.9% versus 12.1%; $P = 0.014$) (Provoost *et al.*, 2012a)
Research interest ($n = 1$)	Interest in participating in clinical research (versus no interest): more proportion of donation (62.5% versus 31.8%; $P < 0.008$) (Sharma *et al.*, 2011)

OR, odds ratios; CI, confidence interval.

[a] Only factors associated with donation to infertility research or stem cell research were retrieved.

[b] Only factors associated with donation to medical research were retrieved.

[c] Couples were asked to take a position on the statement: 'Embryo is a symbol of the relationship between me and my partner', being the answers 'yes' or 'no/neutral'.

[d] Defined as 'The extent to which patients with cryopreserved embryos reported personal uncertainty about disposition decisions and related deficits in knowledge and values clarity'.

more likely to donate to fertility research (OR = 1.30, 95% CI: 1.20–1.50) (Bangsboll *et al.*, 2004). No association was found concerning donation for stem cell research (Bangsboll *et al.*, 2004; Sharma *et al.*, 2011).

A previous failed fertilization was associated with donating less frequently for research ($P = 0.009$) (Choudhary *et al.*, 2004), but Sharma *et al.* (2011) found no association between unsuccessful cycles and the donation for research.

The number of previous cycles (Choudhary *et al.*, 2004; Sharma *et al.*, 2011), the duration of infertility (Bangsboll *et al.*, 2004; Choudhary *et al.*, 2004), the type of treatment (Bangsboll *et al.*, 2004; Choudhary *et al.*, 2004), and parity (Sharma *et al.*, 2011) were not significantly associated with the decision to donate embryos for research.

Sociodemographic characteristics

Age was assessed in eight studies. While Mohler-Kuo *et al.* (2009) observed that the prevalence of embryo donation to medical research was significantly higher among those older than 40 years (ORadj = 1.80, 95% CI: 1.10–3.00), none of the other seven studies observed any effect of age on the decision to donate embryos for research, regarding either the women's age (Lanzendorf *et al.*, 2010; Provoost *et al.*, 2012c) and the women's and men's ages (Asensio *et al.*, 2001; Burton and Sanders, 2004; Choudhary *et al.*, 2004; Hammarberg and Tinney, 2006; Sharma *et al.*, 2011).

One study showed that participants with higher educational levels were more likely to donate embryos for research than those with lower educational levels (Mohler-Kuo *et al.*, 2009). Those with college and university studies and those with vocational school plus 2 years were more likely to donate than those with mandatory/vocational school (ORadj = 1.80, 95% CI: 1.10–3.00 and ORadj = 2.00, 95% CI: 1.20–3.40, respectively) (Mohler-Kuo *et al.*, 2009). Two other studies found no association between these variables (Hammarberg and Tinney, 2006; Jin *et al.*, 2013).

Religious beliefs were assessed in three studies (McMahon *et al.*, 2003; Burton and Sanders, 2004; Mohler-Kuo *et al.*, 2009). Both women and men with moderate to strong religious beliefs were less likely to donate embryos for research, compared with those with not very strong beliefs (20 versus 42%; $P = 0.008$ and 18 versus 41%; $P = 0.01$, respectively) (Burton and Sanders, 2004). Those who attributed a higher importance to religious principles in their attitudes toward reproductive medicine were less likely to donate embryos for research (ORadj = 0.40, 95% CI: 0.20–0.60) (Mohler-Kuo *et al.*, 2009). In the study of McMahon *et al.* (2003), having commitment to religion (religious affiliation/moderate or high commitment), in comparison with a non-religious commitment (no religious affiliation/religious affiliation but slight or no commitment), was not shown to be associated with the decision to donate/not to donate embryos for research.

Concerning ethnicity, two studies showed that Caucasians donate embryos for research more often than Asians: 56 versus 27%; $P = 0.022$ (Choudhary *et al.*, 2004) and 57 versus 42%; $P < 0.001$ (Sharma *et al.*, 2011). One study found no association between the decision and being 'white' or 'non-white' (Asian, African American and Other) (Lyerly *et al.*, 2010).

Only one study evaluated country of birth (Sharma *et al.*, 2011), concluding that Asians born outside the USA (versus Asians born in the USA) were less likely to agree with embryo donation for research (37.9 versus 57.6%; $P = 0.001$).

Other factors

The association between the storage period of cryopreserved embryos and their donation for research was quantified in six studies. While Luna *et al.* (2009) found that couples with older cryopreserved embryos were more likely to donate (35.7% among 5–10 years and 34.9% among >10 years versus 19.1% among ≤4 years; $P < 0.05$), the other five studies found no association between such variables (Asensio et al., 2001; Hammarberg and Tinney, 2006; Newton et al., 2007; Lanzendorf et al., 2010; Lyerly et al., 2010).

The five studies that quantitatively assessed embryo status evaluated it by different means: by measuring the perception of their moral status, from low to high (Lyerly et al., 2010) or a cluster of cells versus life/potential child (Jin et al., 2013), or by agreement with the statement that an embryo is a human being (Mohler-Kuo et al., 2009), a child (Laruelle and Englert, 1995), or a 'Symbol of One's Relationship' (Provoost et al., 2012b). Couples were less likely to donate embryos for medical research (OR = 0.30, 95% CI: 0.20–0.50) when they perceived embryos as human beings (Mohler-Kuo et al., 2009), as life/potential child (versus as a cluster of cells: 86.2 versus 13.6%; $P < 0.05$) (Jin et al., 2013), or as children (versus other perceptions: 16 versus 36%; $P < 0.05$) (Laruelle and Englert, 1995), as well as when they attributed a higher moral status to human embryos, in comparison with those who attributed a lower moral status (OR = 0.69, 95% CI: 0.60–0.79) (Lyerly et al., 2010). Patients who did not classify embryos as a symbol of the relationship (versus those who did) were more likely to donate embryos for research (87.2 versus 65.1%; $P = 0.018$) (Provoost et al., 2012b).

The type of funding (Choudhary et al., 2004; Sharma et al., 2011), having concerns about family/finances (Lyerly et al., 2010), and consulting someone other than the partner to make the decision about embryo disposition (Provoost et al., 2012a) were not associated with the decision to donate or not to donate embryos for research.

The interest in participating in clinical research (Sharma et al., 2011) and altruism (Lyerly et al., 2010) were significantly associated with the decision to donate embryos for research. Those who reported an interest in participating in clinical research, comparing to those who declared no interest, were more likely to donate embryos for research (62.5 versus 31.8%; $P < 0.008$) (Sharma et al., 2011). Those who agreed with donating also more frequently attributed a high importance to altruism in the underlying decision-making process than those who did not donate embryos for research (OR = 1.65, 95% CI: 1.47–1.85) (Lyerly et al., 2010).

One quantitative study mentioned decisional conflict as influencing the non-donation of embryos for research, being described as the extent to which patients with cryopreserved embryos reported personal uncertainty about disposition decisions and related deficits in knowledge and values clarity (Lyerly et al., 2011). Couples with a higher decisional conflict were more likely to donate embryos for research, compared with those with lower decisional conflict (OR = 1.66, 95% CI: 1.12–3.46) (Lyerly et al., 2011). Couples who donated for science significantly more often made a joint decision (compared with cases where the decision is made by the woman alone, by the woman after consulting the man or by the man after consulting the woman) (87.9 versus 12.1%; $P = 0.014$) (Provoost et al., 2012a).

Reasons for donating and not donating embryos for research

The qualitative synthesis of the reasons for donating and not donating embryos for research is presented in Table III. The donation of embryos for research is rooted in reasons related to the individual's contribution to society (helping others or improving health and IVF treatments and research), the perception of such a decision as better than the destruction of embryos, and in positive views about research and the medical system. The conceptualization of cryopreserved embryos in terms of personhood, the perception of risks, and the lack of information about research projects proved to have the highest relevance as motives for not donating embryos for research.

Sociotechnical context

Patients who agreed to donate embryos for research reported 'a sense of gratitude to reproductive medicine' (Mitzkat et al., 2010), a feeling of reciprocity for being able to 'give back' (Lyerly et al., 2006) or being able 'to give a little to take a little' (Provoost et al., 2010), as well as a sensation of 'obligation in terms of returning the favour' (Fuscaldo and Gillam, 2007), which is the opportunity afforded to them of having a child of their own, which is offered by science and technology, in six studies (Lyerly et al., 2006; Parry, 2006; Fuscaldo and Gillam, 2007; Karpel et al., 2007; Mitzkat et al., 2010; Provoost et al., 2010). This decision was also framed in a context where the desire of the medical team or the need of scientists regarding the use of embryos for scientific purposes were presented as reasons to donate embryos for research, as described by Fuscaldo and Gillam (2007), Haimes and Taylor (2009), Lyerly et al. (2006), McMahon et al. (2003), Parry (2006), Provoost et al. (2010) and Zweifel et al. (2007).

In eleven studies, the participants who did not donate embryos for research justified their decision with the perception of risks related to research, like 'the fear that someone needed an embryo and they would give it to somebody, or they would mix it up' (Lyerly et al., 2006) or that 'researchers would allow the embryo to go on developing' (Provoost et al., 2010) (see also Choudhary et al., 2004; Parry, 2006; Fuscaldo and Gillam, 2007; Kufner et al., 2009; Provoost et al., 2009; Mitzkat et al., 2010; Nachtigall et al., 2010; Takahashi et al., 2012; Jin et al., 2013). Issues linked with the lack of information concerning the objectives of the research projects requiring embryos were highlighted in eight studies (McMahon et al., 2003; Lyerly et al., 2006; Parry, 2006; Fuscaldo and Gillam, 2007; Mitzkat et al., 2010; Nachtigall et al., 2010; Provoost et al., 2010; Jin et al., 2013), while the need for regulation which guarantees that research remains 'within a defined [legal] frame' was referred to in two studies (Kufner et al., 2009; Melamed et al., 2009).

Views about embryos

The moral status of the embryo emerged as a key explanation for not donating embryos for research in thirteen studies, being described in different perspectives: embryo as 'a child'/'children' (McMahon et al., 2003; Kufner et al., 2009; Provoost et al., 2009, 2010; Frith et al., 2011; Kato and Sleeboom-Faulkn, 2011; Takahashi et al., 2012); 'life' (Lyerly et al., 2004, 2006; Provoost et al., 2009, Takahashi et al., 2012); 'a early life' (Hammarberg and Tinney, 2006); 'not just a bunch of cells' (Provoost et al., 2009); a 'potential person', 'potential life' or 'potential children' (McMahon et al., 2003; Parry, 2006; Provoost et al., 2010; Frith et al., 2011; Jin et al., 2013); 'a baby' (Fuscaldo and Gillam, 2007; Provoost et al., 2009); or 'brothers and sisters' of the daughters who are already born (Kato and Sleeboom-Faulkn, 2011). The preference for donating embryos to other couples was described in six studies as a reason for not donating embryos for research (McMahon et al., 2003; Hammarberg and Tinney, 2006; Parry, 2006; Fuscaldo and Gillam, 2007; Provoost et al., 2010; Frith et al., 2011), while their use for the 'sole purpose' of having a baby was reported in three studies (Parry, 2006; Haimes and Taylor, 2009; Kato and Sleeboom-Faulkn, 2011).

Table III **Qualitative synthesis of the main reasons for donating and not donating embryos for research (n = 22).**

	Donate (n)	**Not donate (n)**
Sociotechnical context		
A sense of gratitude to reproductive medicine	6 (Parry, 2006; Lyerly et al., 2006; Fuscaldo and Gillam, 2007; Karpel et al., 2007; Mitzkat et al., 2010; Provoost et al., 2010)	
If you [medical team] really want it [cryopreserved embryos], then take it	4 (Lyerly et al., 2006; Fuscaldo and Gillam, 2007; Haimes and Taylor, 2009; Provoost et al., 2010)	
Research has to be done	4 (Zweifel et al., 2007; McMahon et al., 2003; Parry, 2006; Provoost et al., 2010)	
Have that irrational fear (. . .) that they would mix it up		11 (Choudhary et al., 2004; Lyerly et al., 2006; Parry, 2006; Fuscaldo and Gillam, 2007; Kufner et al., 2009; Provoost et al., 2009; Mitzkat et al., 2010; Nachtigall et al., 2010; Provoost et al., 2010; Takahashi et al., 2012; Jin et al., 2013)
You have no idea what kind of research will be done with them		8 (McMahon et al., 2003; Lyerly et al., 2006; Parry, 2006; Fuscaldo and Gillam, 2007; Mitzkat et al., 2010; Provoost et al., 2010; Nachtigall et al., 2010; Jin et al., 2013)
It [embryo research] has to stay within a defined [legal] frame		2 (Kufner et al., 2009; Melamed et al., 2009)
Views about embryos		
If people are only going to destroy embryos, I can't see why research isn't a good way of using them	14 (McMahon et al., 2003; Lyerly et al., 2004; Hammarberg and Tinney, 2006; Fuscaldo and Gillam, 2007; Karpel et al., 2007; Haimes and Taylor, 2009; Kufner et al., 2009; Peddie et al., 2009; Provoost et al., 2009; Lyerly et al., 2010; Provoost et al., 2010; Kato and Sleeboom-Faulkn, 2011; Takahashi et al., 2012; Jin et al., 2013)	
Embryos with bad quality: *They [embryos] wouldn't have progressed anyway (. . .)*	4 (Parry, 2006; Haimes and Taylor, 2009; Peddie et al., 2009; Mitzkat et al., 2010)	
That's not just a bunch of cells, right? That's life you know		13 (Lyerly et al., 2004; Hammarberg and Tinney, 2006; Lyerly et al., 2006; Parry, 2006; Fuscaldo and Gillam, 2007; Kufner et al., 2009; Provoost et al., 2009; Provoost et al., 2010; Frith et al., 2011; Kato and Sleeboom-Faulkn, 2011; Takahashi et al., 2012; Jin et al., 2013)
I'd rather give someone a chance of having a baby than giving some to research		6(Frith et al., 2011; Fuscaldo and Gillam, 2007; Hammarberg and Tinney, 2006; McMahon et al., 2003; Parry, 2006; Provoost et al., 2010)
[Our] 'sole purpose' is to have a baby		3 (Parry, 2006; Haimes and Taylor, 2009; Kato and Sleeboom-Faulkn, 2011)
Societal benefits		
We will be happy that they [cryopreserved embryos] could help others	12 (McMahon et al., 2003; Lyerly et al., 2006; Lyerly et al., 2004; Zweifel et al., 2007; Haimes and Taylor, 2009; Kufner et al., 2009; Provoost et al., 2009; Mitzkat et al., 2010; Provoost et al., 2010; Kato and Sleeboom-Faulkn, 2011; Takahashi et al., 2012; Jin et al., 2013)	
I did contribute to make this world a healthier place	10 (Hammarberg and Tinney, 2006; Lyerly et al., 2006; Fuscaldo and Gillam, 2007; Zweifel et al., 2007; Kufner et al., 2009; Peddie et al., 2009; Provoost et al., 2009; Mitzkat et al., 2010; Provoost et al., 2010; Takahashi et al., 2012)	
Maybe advance the technology and knowledge about IVF treatment	4 (Lyerly et al., 2006; Parry, 2006; Mitzkat et al., 2010; Provoost et al., 2010)	
I did not do all this [hard work and expensive treatment] for the benefit of others		1 (Kato and Sleeboom-Faulkn, 2011)

n, number of papers.

Otherwise, the belief that donating embryos for research is better than their destruction was mentioned in fourteen studies as a motive for donating embryos for that purpose (McMahon et al., 2003; Lyerly et al., 2004, 2010; Hammarberg and Tinney, 2006; Fuscaldo and Gillam, 2007; Karpel et al., 2007; Haimes and Taylor, 2009; Kufner et al., 2009; Peddie et al., 2009; Provoost et al., 2009, 2010; Kato and

Sleeboom-Faulkn, 2011; Takahashi *et al.*, 2012; Jin *et al.*, 2013). Additionally, having embryos considered to be of poor quality was reported in four studies as an explanation for donating embryos for research, because they would not develop into an eventual pregnancy (Parry, 2006; Haimes and Taylor, 2009; Peddie *et al.*, 2009; Mitzkat *et al.*, 2010).

Societal benefits

Societal benefits constituted the first group of reasons cited by those who agreed to donate embryos for research. These motives were presented in three forms: (i) answers like 'We will be happy that they [cryopreserved embryos] could help others' (Jin *et al.*, 2013) proved to have the highest relevance, and were described in twelve studies (McMahon *et al.*, 2003; Lyerly *et al.*, 2004, 2006; Zweifel *et al.*, 2007; Haimes and Taylor, 2009; Kufner *et al.*, 2009; Provoost *et al.*, 2009, 2010; Mitzkat *et al.*, 2010; Kato and Sleeboom-Faulkn, 2011; Takahashi *et al.*, 2012; Jin *et al.*, 2013); (ii) in ten studies, there was a reference to the opportunity of contributing to make this world a healthier place (Hammarberg and Tinney, 2006; Lyerly *et al.*, 2006; Fuscaldo and Gillam, 2007; Zweifel *et al.*, 2007; Kufner *et al.*, 2009; Peddie *et al.*, 2009; Provoost *et al.*, 2009, 2010; Mitzkat *et al.*, 2010; Takahashi *et al.*, 2012); and (iii) the perception that the donation of embryos for research may advance the technology and knowledge about IVF treatment was cited in four studies (Lyerly *et al.*, 2006; Parry, 2006; Mitzkat *et al.*, 2010; Provoost *et al.*, 2010).

The avoidance of benefiting others was indicated in one study as a motive for not donating embryos for research: 'I did not do all this [hard work and expensive treatment] for the benefit of others' (Kato and Sleeboom-Faulkn, 2011).

Discussion

Current state of research and future direction

The aim of this systematic review was to synthesize the current body of knowledge about IVF patients' motivations to donate or not to donate embryos for research, based on quantitative and qualitative studies. It suggested that IVF patients' decision-making process about embryo donation for research is influenced by several factors from individual, social and structural levels. Three main iterative and dynamic dimensions emerged: (i) hierarquization of the possible options regarding embryo disposition, framed on patients' beliefs about what should be done or their representations regarding the moral and social status of embryos; (ii) patients' understanding of expectations and risks of the research on human embryos; (iii) and patients' experiences of information exchange and levels of trust in the medical-scientific institutions.

Qualitative studies reported consistent data about the influence of the sociotechnical context, which included the IVF patients' understanding of science and medicine and the leading values in the doctor-patient relationship, and of the perception of the societal benefits of research on human embryos for the society, for IVF patients, and for individuals. Qualitative synthesis showed that those who donate embryos for research reported feelings of reciprocity towards science and medicine, revealed a positive vision of research and high levels of trust in the medical system. Additionally, they described such a decision as an opportunity to help others, by contributing to a healthier world and to the improvement of IVF treatments. Those who do not donate embryos for research perceive the embryo as a potential life or person or intended to use embryos for reproductive purposes, including donation to other couples. They also revealed low levels of confidence in science and a lack of information concerning the specific research projects in which embryos will be used, reporting the need for a clear legal framework.

Quantitative papers were based on specific sets of variables, mainly about sociodemographic characteristics and reproductive and gynaecological history, for which the assessment varied among studies. Furthermore, 14 out of 22 variables were analysed in very few studies (a maximum of two papers), resulting in inconclusive data. Contradictory results were reported concerning seven of the eight remaining variables: having children, number of embryos, use of homologous/heterologous techniques, age, education level, religion beliefs and the storage length.

The influence of the views about embryos was simultaneously assessed in quantitative and qualitative studies. The perception of embryos in terms of personhood with a moral and social status is a factor influencing the non-donation of embryos for research, while viewing the embryo as an entity with a high instrumental value was positively linked with donation for science (Provoost *et al.*, 2009). Attributing the status of person to one's embryos was not linked with an absolute objection to any action that leads to the destruction of the embryo (Frith *et al.*, 2011; Provoost *et al.*, 2010). At the same time, results coherently revealed that heterogeneous classifications were attributed to cryopreserved embryos by IVF users, reinforcing the idea that embryos are not universal and fixed entities (Haimes *et al.*, 2008). For example, embryos were classified in terms of the level of their moral status, from low to high (Lyerly *et al.*, 2010). In other studies, embryos were defined as a cluster of cells (Jin *et al.*, 2013), as life/potential child (Frith *et al.*, 2011; McMahon *et al.*, 2003; Lyerly *et al.*, 2004, 2006; Hammarberg and Tinney, 2006; Parry 2006; Provoost *et al.*, 2009, 2010; Takahashi *et al.*, 2012; Jin *et al.*, 2013), as a human being (Kufner *et al.*, 2009; Mohler-Kuo *et al.*, 2009; Provoost *et al.*, 2009), as a child (Laruelle and Englert, 1995; McMahon *et al.*, 2003; Fuscaldo and Gillam, 2007; Kufner *et al.*, 2009; Provoost *et al.*, 2009, 2010; Frith *et al.*, 2011; Kato and Sleeboom-Faulkn, 2011; Takahashi *et al.*, 2012), or as a 'Symbol of One's Relationship' (Provoost *et al.*, 2012b). Embryos were thus simultaneously perceived as epistemic or medical objects for research and clinical practices, and ontological objects for reproduction.

Although for many citizens, embryos were described as potential lives, this did not override their views about the preference of 'using' embryos rather than discarding them, as found by de Lacey *et al.* (2012). Additionally, embryos were perceived as having both an intrinsic moral and social status and an instrumental value for IVF patients (Provoost *et al.*, 2009). How these dimensions intertwine varies according to historical and geographical contexts and the social position of those who classified embryos (Lyerly *et al.*, 2006; Haimes and Taylor, 2009; Silva and Machado, 2010a).

This review also highlights the relevance of the balance between expectations and fears about research with human embryos on IVF patients' motivations to donate or not donate embryos for such a purpose, which involves issues of trust, hope, power, knowledge and responsibilities, both of medical and scientific institutions, and citizens (Silva and Machado, 2011). These results are particularly relevant in a context where embryo donation for research has become increasingly popular during the last two decades, as the positive trend on the proportion of users donating embryos for this purpose illustrates (Provoost *et al.*, 2012c).

This may have implications on the patients' motivation and choice regarding embryo disposition, in three complementary ways. Firstly, attention should be drawn to the responsibility of scientific and medical institutions, health professionals and researchers that shape the choices of IVF users, namely by providing accurate and timely information, in accordance with patients' needs. For raising information and confidence, it is essential to use routine medical practices with the intention to carefully deal with ethically sensitive decisions (Gerrits *et al.*, 2013). Informed consent should include accurate information about all the available options on embryo disposition, with detailed data being provided about the research projects aiming to use human embryos (de Lacey, 2007). Secondly, referencing risks and their implications in the actions of social and/or professional groups, including IVF patients and researchers, should be central topics in the debates of biomedicine in a broader sense and in the local ethics of clinical research and doctor-patient relationships (Silva and Machado, 2010b). Finally, the increased popularity of the donation of embryos for research may be reconfigured as a new morality that presses IVF patients to donate embryos for research as a contribution to a healthier society (Rose and Novas, 2005; Burns, 2009).

Some psychosocial factors generally associated with patients' experiences of IVF treatments are absent from most of the studies included in this systematic review, in particular those associated with the couples' relationship (Peterson *et al.*, 2008), the meanings of parenthood (Fisher and Hammarberg, 2012) and social support (Martins *et al.*, 2011), as well as personal well-being and psychopathological symptoms (Hammarberg and Tinney, 2006; Boivin *et al.*, 2011). Evidence produced by studies on the cognitive dimension underlying the decision-making process regarding the fate of embryos reveals feelings of conflict, often between the members of the couple, with psychological implications, such as anguish and anxiety (de Lacey, 2005; Hammarberg and Tinney, 2006). In a decision where the couple is most frequently the key element, the incorporation of these variables must be taken into account.

An analytic tool could serve as a basis for comparative intercultural studies covering different regulatory, economic and political contexts. It would be relevant for the definition of patient-centred policies on hESC research, as well as for ethics in clinical practice. It could also allow the comparison of the real-world decisions among different cultural, economic and political contexts that influence access, care and decision-making in reproductive medicine.

Methodological features

There are some methodological limitations in the studies included in this systematic review that should be taken into account when interpreting the results. Although 11 out of the 39 papers were found through reference tracking, all of the relevant studies were identified. It is important to stress the need to include the MeSH term 'embryo disposition' in papers published about the utilization or disposal of an embryo that is fertilized but not immediately transplanted and resulting course of action.

A relatively small number of empirical studies conducted in few countries and specific settings are available. White Western countries are over-represented in this review sample, although research with hESCs is allowed in many countries worldwide. National regulations and guidelines vary widely in issues as the access criteria to infertility treatments, the available options for embryo disposition and the policies concerning funding or the governance of hESC research (ESHRE, 2013; European Science Foundation, 2013; International Federation of Fertility Societies (IFFS), 2013). Some countries included in this review have legislations which permit research only on surplus IVF embryos, prohibiting the creation of embryos solely for research purposes. This is the case in Brazil, Denmark, France, Spain, the UK and the USA. The retrieved proportions of donation for research can be affected by the varied legislations of the countries but can also be biased by the different measures used to assess it (dichotomic answers versus hierarquization of the possible options for embryo disposition).

Taking into account the sensitive nature of the decision under analysis and its dependence on national or local policies on hESC research, more information on regulation and policies concerning counselling processes and the available options on embryo disposition is required to contextualize the assessment of the outcome in the studies. In fact, the evidence cannot be generalized as the conditions of social policy or clinical practice may vary significantly between countries, in states within countries, or even in individual clinics (de Lacey, 2007).

Additionally, more detailed information about the sampling and time of assessment within IVF treatments' stage should be provided, in order to increase reliability and to allow data comparison and weighing of the studies, which was not possible in this systematic review.

Finally, a dynamic analysis of the interactions between qualitative and quantitative data calls for the development of more mixed-methods studies, which represented only a small portion of the studies included in this review (3/39). This methodology would lead to a wider understanding of the decision-making process, taking into account the factors influencing the donation and non-donation of embryos for research.

Conclusion

The aim of this study was to synthesize the current body of knowledge about the motivations of IVF patients to donate or not donate embryos for research, based on quantitative and qualitative studies. Three iterative and dynamic dimensions of the decision-making on embryo donation emerged from this review: the hierarquization of the possible options regarding embryo disposition, according to the moral, social and instrumental status attributed to embryos; the patients' understanding of expectations and risks of the research on human embryos; and the patients' experiences of information exchange and levels of trust in the medical-scientific institutions. Results relating to the influence of sociodemographic characteristics and reproductive and gynaecological history were mostly inconclusive. Further research is needed for the development of a theoretical framework, contributing to a deeper understanding of real-world decisions about embryo disposition. An analytical tool could serve as a basis for the definition of patient-centred policies on hESCs research, benefiting informed relational ethics in clinical practice.

Supplementary data

Supplementary data are available at http://humupd.oxfordjournals.org/.

Authors' roles

C.S. and S.S. contributed significantly to all stages of the preparation of this manuscript. C.S. and M.P. did the data extraction. H.M. and B.F. provided important intellectual content in the design and analysis. All authors approved the final version of this manuscript.

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Conflict of interest

The authors declare no financial or commercial conflicts of interest in this study.

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1.3 Patient-centred care

1.3.1 Conceptual framework

In 2001, the Institute of Medicine of the United States National Academies of Science established the *patient-centred care* as an indicator of high-quality healthcare that is respectful of and responsive to individual patient preferences, needs, and values[145]. Currently, patient-centred care has become an important global issue in health, permeating the literature and policy discourse internationally. The WHO´s global strategy on integrated people-centred health services for 2016-2026 calls for a fundamental paradigm shift in the way health services are funded, managed and delivered[146]. The European Union also set out integrated, sustainable and citizen-centred care as a topical theme in the European Work Programme for the H2020´s Societal Challenge of Health, calling for action-oriented research to develop new, or improve on existing, models for health systems in order to make them more patient-centred[147], and the International Alliance of Patients' Organizations advocates and ensures its implementation worldwide[148].

The call for a patient-centred care represents a significant shift in terms of clinical practice, the conceptualisation of healthcare user, and the doctor-patient relationship in Western countries, against the predominantly paternalistic model of healthcare delivery (Figure 3). The paternalistic model assumes that the professional's role is one of authority and of applying technical knowledge while having the obligation to keep emotional detachment from patients' experiences[149]. Patients are regarded as helpless and passive in need of doctors' expert knowledge, who are in total control of the situation and have to make the decisions for the patient[150]. According to this approach, which is still in force nowadays[151, 152], the "sick person" (the patient) is expected to assume his/her condition of disabled, which releases him/her from fulfilling normal social obligations, and to cooperate fully with the doctor, while doctors are expected to apply their specialist knowledge and skills for the benefit of the patient[149]. Parsons, following structural-functionalist principles, viewed health as a functional prerequisite of society and illness as a form of social deviance, where doctor and patient assumed complementary roles[149]. In this way, the "sick role" is acknowledged by Parsons also as a social role and not only as a "condition", in the sense that both roles fit into the general equilibrium of the social system.

The paternalistic model is underpinned by a biomedical conception of illness[153], in which patients are approached as physical beings whose signs and symptoms indicate the presence or absence of illness after being evaluated and diagnosed by the medical doctor[154]. According to this perspective, disease exists as a distinct entity and the individual patient is a passive site of disease manifestation[154].

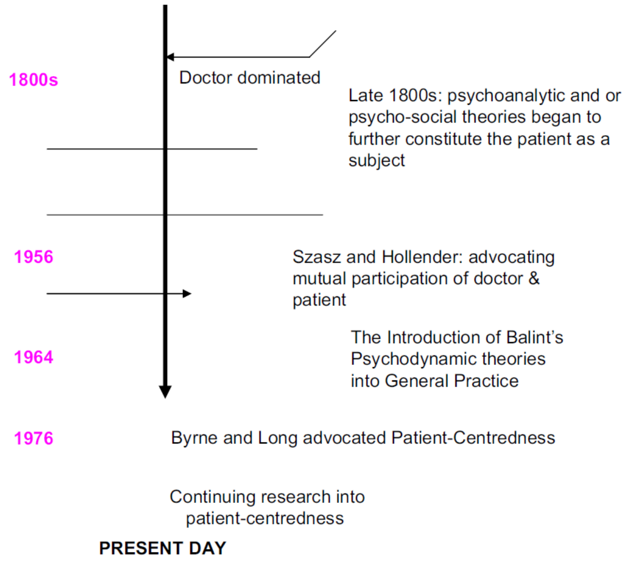

Figure 3. A timeline indicating the evolution of the doctor-patient relationship since 1800s[155]

The assumptions of the paternalistic model were initially challenged by the emergence of psychology, in particular the psychoanalytical and psychosocial theories of Breuer and Freud[156], as well as Carl Rogers' distinctive approach to understand personality and human relationships[157] - the person-centred therapy, which highlighted the importance of listening to the patient as a subject, developing a genuine communicative relationship and viewing the patient as an active agent. Moreover, the importance of analysing the patient's unique psychological and social context and developing an emotional relationship to create good therapeutic and diagnostic processes was also argued by Balint[158].

This move towards a biopsychosocial understanding of disease broadened the biomedical explanatory perspective on illness to include social and psychological factors and mutual participation of doctor and patient in the caring relationship[153]. The figure of "doctor-as-a-person", rather than simply a total expert, emerged in this context, henceforth viewed as someone who shared power and responsibility with the patient[159]. At the same time, a renewed focus on understanding patients' experiences was observed[160], along with changes in the way the patient is conceptualised, with his/her role moving from one of passive recipient of care to one of "co-producer of health" (162, p8), an active subject in self-care management, and also in the governance and improvement of services[159, 161, 162]. Being seen as a social, emotional and physical being, the "patient-as-a-person" makes interpretations of treatment and attributes meanings to illness according to his/her individual experience[159], which is fundamental to evaluate the quality of healthcare and to understand how health systems can better respond to the needs of all healthcare stakeholders and constituencies in a holistic manner[112]. The assessment of the quality of healthcare system then began to include the patients' right to be fully informed, to be treated with respect and to be actively involved in the decision-making processes about treatment.

Shifts in care paradigms occur in parallel with wider social, policy and healthcare system changes. Reconfigurations in public expectations about healthcare delivery were observed[112, 161] due to higher levels of education, increased availability of information (namely through internet), a move towards market models of care, growing consumerism and larger access to goods and services, and an increasing emphasis on democratic values (e.g., citizens as with the right to claim quality healthcare). A discourse based on the idea of greater humanization of services coexists with an increasing emphasis on patients' responsibilities and the individualisation of health, which have given rise to a redefinition of patients as consumers in scenarios circumscribed by neoliberalism and market-orientated models of care and [163]. The concept of healthcare users as consumers inspired several policy documents in countries such as the United Kingdom, the United States and Australia[161, 164, 165], being translated in an appeal to the health authorities to make services which are more responsive to patients through consultation processes.

The rhetoric underlying these proposals suggests the possibility of achieving "a higher level of performance and adopt a more humanistic and holistic approach to healthcare, where the individual who needs care is viewed and respected as a whole person with multidimensional needs" (137, p4). However, it might form a moral landscape that points to the duty of all citizens to exercise an "active citizenship", masking class and gender differences or socioeconomic inequalities that may limit or even prevent their effective exercise[166]. It is also claimed that the emphasis on patient choice, individual responsibility and agency with respect to personal health and wellbeing asks patients to use their own resources (e.g., time and knowledge) to self-regulate and to ensure they remain healthy[163, 167], in line with the idea of an "expert patient", i.e., patient as an expert of his own health condition, as an 'engaged', 'empowered' or 'activated patient'. This idea has been promoted, to a large extent, by the underlining connection made between 'self-care management', better health outcomes and cost effectiveness of interventions[168, 169], which mobilization is often triggered in contexts where the scarcity of resources supports constraints in healthcare provision[170].

Patient-centredness was firstly advocated in 1976 by Byrne and Long[171]. Their work started with the assessment of doctor's verbal behaviour in the consultation, in order to summarize the doctor's interview style. From the analysis of about 2000 audiotaped consultations, carried out over three years and a half, these authors found a continuum of general practitioner consulting styles ranging from “doctor-centred” to “patient-centred”[171]. The “doctor-centred” consultations were characterized by a predominance of doctor’s medical knowledge, who gave direction to patients. On the opposite side, “patient-centred consultations” recognized patient’s needs and preferences; doctors listened and encouraged patients to express their needs. In this perspective, patient-centredness was firstly defined as a style of doctor-patient interaction in which the main elements to take into account were how medical power was shared between doctors and patients and how patients were involved in consultations. Later, Mead and Bower[159] referred to these interactions, characterised by the power and responsibility exchange between doctor and patient, as “therapeutic alliance” in which the patient involvement in treatment decisions became possible.

The patient-centred care was included as a Medical Subject Heading (MeSH) in 1995 and has been conceptualized through the following core dimensions[145, 159, 172, 173]:

- *Respect for patients’ values, preferences, choices, and expressed needs* (where attention is required to aspects such as quality of life, involvement in decision-making, dignity, needs and autonomy). The health system should be designed to meet the most common types of needs, but should also have the capability to respond to individual patient choices and preferences. Also, it should be able to accommodate differences in patient preferences and encourage shared decision-making.

- *Patient involvement in health policy*. Patients and patients’ organizations have a valuable role to play in healthcare policy-making through meaningful and supported engagement in all levels and at all points of decision-making to ensure that they are designed with the patient at the centre.

- *Coordination and integration of care* (importance of assuring that accurate and timely information reaches those who need it at the appropriate time).

- *Information, communication, and education* (trustworthy and accurate information that is attentive, responsive, and tailored to an individual’s needs). Patients should have access to their own medical information and to clinical knowledge; and clinicians and patients should communicate effectively and share information. Patients should also receive care based on the best available scientific knowledge and it should not vary from clinician to clinician or from place to place.

- *Physical comfort* (timely, tailored, and expert management of symptoms of pain, shortness of breath, or some other discomfort).

- *Emotional support* – intended as relieving fear and anxiety (taking into account all the distressing symptoms and the significant emotional and spiritual dimensions of the individual. Attention is required on the impact of the illness on self and family; and over the financial impact of the illness). The health system should anticipate patient needs, rather than simply react to events.

- *Involvement of family and friends* (accommodation of family and friends, involving family in decision-making, supporting the family as caregiver, recognising the needs and contributions of the family). This should include information describing the system's performance on safety, evidence-based practice, and patient satisfaction.

The implementation and evaluation of these dimensions of patient-centred care are complex and context-dependent, they are neither consensual nor are necessarily translated in the improvement of health care[174-176]. On the one side, the evaluation of patient-centred care has been defined and implemented by the healthcare services themselves, which may hamper the search for a grounded understanding about how people experience health, illness, treatment and the delivery of care[160]. Therefore, the inclusion of patients' voices in guidelines and quality standard development processes[176, 177] is essential to promote service responsiveness, particularly when neoliberal rationalities underlying policy and services can prevent patients from seeing themselves as subjects of rights, including the right to quality care[167].

On the other side, the implementation of patient-centred care requires individual, organizational and political changes in order to promote adjustments in the established social and professional roles, in attitudes and in the knowledge which traditionally sustains the interactions and decisions in the healthcare system[178, 179]. The different healthcare professional groups, as well as patients, need to incorporate the principles and goals of patient-centredness as pillars of their existing professional and social identities[174]. This requires changes in the power and knowledge hierarchies underlying doctor-patient relationship[176], which are able to support the development of collaborative relationships[180]. However, the engagement of healthcare professionals might be undermined by the new public management principles, which are intended to meet increasing needs and demands of patients, while simultaneously achieving the most rational and efficient performance at the lowest cost[181, 182] by directing professionals for productivity aims[183] rather than encourage them to listen to the views and perspectives of patients. In this sense, while patient-centred care may liberate the medical encounter from paternalistic power, at the same time it introduces a new complex of power relations between doctors and patients[103].

1.3.2 Patient-centredness in infertility and ART

It is now widely recognized that high quality infertility care comprises more than just the effectiveness of care[146, 184] and should be patient-centred[36, 42, 185]. However, its implementation is faces particular challenges. For example, the fact that the subject of treatment is most often a couple involves reconfigurations on the medical procedures, on the type of information that should be provided and on the type of interactions upheld, creating a different sort of doctor-patient relationship, which moves from a dyad to a triad[186]. Also the search for cross-border care in reproductive medicine, particularly in Europe[59, 187], adds additional concerns regarding the development and implementation of policies and guidelines to guarantee the delivery of optimal care and patient-centred treatments among the different local, cultural, socioeconomic and political contexts regulating ART[143].

Studies on patient-centredness in infertility and ART have mainly focused on the following topics: i) evaluation of patients' experiences with infertility care[188-191], with an emphasis on gender differences[192-194], and respective comparison with health professionals' perceptions of patients' experiences[195-197]; ii) association between patient-centred care and health outcomes, in particular patients' quality of life and feelings of distress[39, 42]; iii) development of guidelines for the implementation of patient-centred care[198]; iv) evaluation of the effect of physician training in empathic skills[199], as well as giving feedback to health professionals about patients' experiences on patient satisfaction and healthcare quality improvement[195, 200].

Most of these studies were conducted in European countries and the great majority was carried out in the Netherlands and Belgium. The assessment of the concept has relied on quantitative instruments[39, 42, 188, 189, 193-197, 199-207] , on the qualitative analysis of patients' experiences and narratives[191, 198, 208-215] and on mixed-methods studies[190, 200]. Quantitative assessment has been based on self-report instruments. The most used valid and reliable instrument is the "Patient Centredness Questionnaire – Infertility (PCQ-Infertility)"[188] (see also e.g., [39, 42, 193, 195, 200, 204]). PCQ-Infertility consists of a 46-items questionnaire, divided in an overall score of patient-centredness and seven subscales: accessibility, information, communication, patient involvement, respect for patients' values, continuity and transition, and competence. Another questionnaire is the "Quality from the Patient's Perspective of In Vitro Fertilization" (QPP-IVF)[192]. It is divided into 10 subscales: pain relief and physical care, waiting time, care room characteristics, information during treatment, information after treatment, participation, responsibility/continuity, the staff's respect/commitment/empathy, atmosphere and environment and availability. The measurements consisted of two kinds of evaluations: the rating of the importance of various aspects of treatment (subjective importance) and the rating of perceived quality of care (perceived reality). Other authors used questionnaires designed for their studies[194, 196, 197, 199] or specific to conditions, such as endometriosis[201, 202]. Qualitative studies relied on the use of interviews[211, 213-215], focus groups[190, 198, 208, 209], the Delphi technique[191] and ethnographic observation[103].

The few studies examining IVF patients' perspectives on care as their primary aim concluded that patients expressed the need for medical skills but also for respect, coordination, accessibility, information, comfort, support, partner involvement and a good attitude of and relationship with fertility clinic staff (Figure 4)[143].

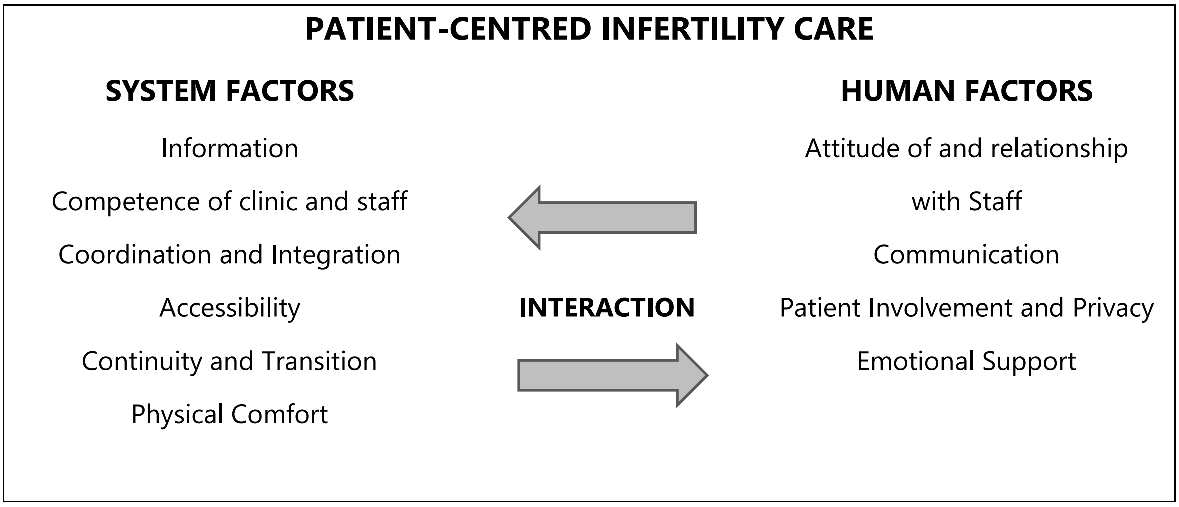

Figure 4. The interaction model of patient-centred infertility care[208]

Some studies showed that patients considered that respect, autonomy and partner involvement were strengths in their fertility centre[190] while waiting times, information provision, emotional support[188] and doctors' continuity during the treatment[188, 190] were valuable dimensions that needed improvement in order to attain a higher level of patient-centredness[189, 190]. Provision of information and accessibility were ranked as top priorities for IVF patients[209]. They also presented a desire to have free access to their own medical record[188]; the need to have a report on treatment outcomes and complications, and on the results of semen analyses in a standardized way; to be provided with information on the negative consequences for achieving a pregnancy in case of a high BMI; and to have counselling about the positive effects of the elimination of a 'harmful lifestyle' on their chance of getting pregnant[191]. Importance of medical care and ‘information after treatment’ were emphasized by both partners in a study from Holter et al.[192]. Patients appreciated the opportunity to question and clarify doubts with the health professionals, as well as the time they dedicate to communicate in a reliable and comprehensive way, stressing the importance of the communication skills (e.g., do not induce fear, introduce themselves at the beginning of treatment or provide information on what is expected to happen during treatment)[208].

Patients and health professionals tended to agree on the perception of the overall level of patient-centredness in infertility care[195], with both groups attributing the highest value to indicators of information and communication[198]. Notwithstanding, differences in the perspectives of doctors and patients on the specific valued dimensions of patient-centredness of a fertility centre were registered[191, 195, 196]. While patients emphasized accessibility of care, professionals emphasized coordination and integration as important quality measures for patient-centredness in infertility care[191]. Also, patients valued the physicians’ attitude as the highest priority relative to other attributes, but physicians underestimated the importance of their own attitude and overvalued treatment effectiveness[196, 197].

Moreover, significant gender differences were found within heterosexual couples in the evaluation of the most important dimensions of patient-centredness: women rated all the aspects of care during IVF as more important than their partners, except ‘responsibility/continuity’[192]. Other study found that although no differences were observed in the PCQ-Infertility total score between women and their partners, men scored higher on the subscales ‘respect for patients values’ and ‘staff’s competence’[193]. The narratives of women undergoing treatment also revealed the importance attached to relational dimensions, highlighting the need for social support as an integral part of strategies to deal positively with the difficulties along the process[211]. Regarding the association between level of patient-centredness and patient outcomes, patient-centred care was associated with wellbeing during treatment[103, 191]. Higher levels of patient-centredness in infertility care seemed to be associated with better quality of life and lower levels of anxiety and depression among women undergoing infertility treatment[42]. Information provision and continuity of care were indirectly associated with better individual wellbeing[39, 103, 191, 204, 207], the first via lower treatment concerns and the second via higher treatment tolerability[39]. Positive experiences regarding information received, respect from staff about values and preferences, continuity in treatment and competence of staff were also directly associated with higher compliance intentions[204]. Competence, accessibility, continuity and communication were indirectly associated with better relational wellbeing via higher treatment tolerability[39], as well as with higher levels of trust in health professional[103]. Moreover, the level of patient-centred care significantly influenced patients' choice of a fertility clinic[200], with the lack of patient-centredness emerging as the most cited non-medical reason for changing fertility clinics[197].

However, Gerrits[103] also explored the "unintended effects" from patient-centredness. While patient-centred practices are reported to facilitate informed decision-making and to provide emotional support for couples, they may also have unintended disciplining and normalizing effects. This can happen, for example, when the intention to provide the patients with the ability to cope with all the adverse outcomes of treatment contributes, paradoxically, to "normalize" the burden of treatment, which is one of the undesirable effects of the implementation of patient-centred care[103].

Training empathic physicians' skills seemed to have resulted in higher patient satisfaction levels on the perceived information quality, communication skills and time dedicated at first consultation for infertility treatment[199]. Besides that, Aarts and colleagues[195] pointed as a possible tool to start improvement of patient-centredness and quality of care to provide detailed feedback of patients' opinions to health professionals. However, a recent study showed that merely providing auditing and feedback to professionals in infertility care about their performance on patient-centeredness may not be sufficient to increase the level of this important dimension of quality of care[193] as well as to increase the fit between the care provided at different points in treatment and patients' needs[39].

In sum, assessing the level of patient-centredness is essential for clinics to have detailed insight into their performance in the perspective of patients. That will allow them to tailor quality improvement and benchmarking[188]. Beyond individual clinicians, it is also fundamental to provide actionable feedback to stakeholders in health systems and public health practitioners about what needs to be changed to achieve patient-centred care[185]. This includes the discussion of broader political changes needed to empower people to manage their own health, such as the social determinants of health[175].

Although methods for determining the level of patient-centredness of care are proposed to rely on assessing patients' specific experiences with care delivery, rather than on surveys measuring global satisfaction[190, 195], and most research evidence sustains the development of a relational ethics in the clinical practice, existing studies using a patient-centred approach do not explore the specific process of decision-making on embryo disposition, namely embryo donation for research. Taking into account the centrality of adequate and timely information, communication and patient involvement to promote patient-centredness, the informed consent is a fundamental tool and process on embryo disposition, which study has been scarce in this context.

Knowledge on patient’s perspectives and experiences with regard to embryo donation for research is essential for the conceptualization of patient-centred policies and for ethics in clinical practice at the following levels: to analyse openness and information about research with human embryos; to sustain stakeholders’ decisions regarding the suitability of research projects using cryopreserved embryos; and to disseminate ethically robust evidence to inform policies and guidelines on embryo cryopreservation and embryo disposition, namely concerning the informed consent design and its implementation. Thus, a renewed debate that includes the views of patients about the legal and regulatory contexts that frame the clinical practice is needed. This thesis’ results intend to contribute to answer to this challenge by analysing embryo donation for research, based on a patient-centred care approach.

2. Objectives

Research on human embryos, and particularly on hESCs, has engendered promising results and high expectations in society regarding the improvement of public and individual health, but also controversial issues in ethics, practices and policies[30, 88, 118]. Reflections concerning the responsible governance of human embryo research sustain the relevance of listening to the patients' voice and assessing their experiences as a core need for patient-centred care and policies on human embryo research, as they are key actors in this research practice[112, 143, 144].

In fact, most couples enrolled in ART treatments need to make decisions regarding embryo disposition[216-218], as they are usually asked to sign a consent form concerning embryo donation for research. The consent should be informed (which requires an understanding of its content as well the comprehension of the oral and written information provided additionally), voluntary (without any pressure or coercion, external or internal, concerning decision-making) and reflected (preceded by time to think)[91, 95, 104, 105].

Beyond implementation of evidenced-based practices in the field of informed consent on embryo disposition, it is crucial to ground legal and regulatory frameworks on patients' values, preferences, choices, and expressed needs in order to lend credence and robustness to the consent that the couples give. However, existing studies using a patient-centred approach do not explore the specific process of decision-making on embryo disposition, namely embryo donation for research, and there is no available evidence on this topic to ensure feasibility to guideline development[36].

Thus, knowledge on patients' experiences and perspectives about the healthcare and regulatory system, and on the human factors involved in the decision-making process regarding embryo donation for research, is needed to improve patient-centredness in the field of ART. This thesis will focus on the following three main levels underlying decision-making on embryo disposition that cross the boundaries between evidenced-based practices for clinical purposes and evidence regarding political, legal and regulatory contexts: the sociodemographic, reproductive and psychosocial characteristics and reasons associated with willingness to donate embryos for research; the perceptions about storage limits for embryos; the circumstances under which the informed consent should be delivered, explained and signed.

Results relating to the influence of sociodemographic characteristics and reproductive and gynaecological history on the decisions of IVF patients regarding embryo donation for research are mostly inconclusive. Moreover, some psychosocial factors generally associated with patients' experiences of IVF treatments, in particular those related to couples' relationship, the meanings of parenthood and social support, as well as personal well-being and psychopathological symptoms, are absent from most of the studies[219]. Obtaining knowledge on these factors is a core need to identify the determinants of the decision and to better understand how partner dynamics and gender differences affect couples' decision, providing valuable insights into psychosocial care in ART. It also contributes to analyse openness and expectations about research with human embryos, and to sustain stakeholders' decisions regarding the suitability of research projects using cryopreserved embryos in accordance with patients' expectations.

Beyond data provided by the cross-sectional studies, those with a longitudinal design call attention to the fact that decision-making on embryo disposition is subject to change over time. From the few existing longitudinal studies about the factors associated with patients' willingness to donate embryos for research none focused on the influence of psychosocial, demographic and reproductive characteristics. At the same time, patients' needs for information and support are likely to vary across treatment stages[36]. In this context, the timing set to obtain consent, as well as the embryo storage time limits, constitute two key regulatory issues which are likely to influence the type of decisions made regarding embryo donation for research. Currently, there is no consensual evidence on whether the informed consent should be signed prior to the first treatment[93], during treatment[94] or after treatment is completed[95], and the establishment of current storage limit for embryos has been based more on social and political criteria, with no scientific evidence underlying the implemented storage periods[96, 220-223]. Thus, obtaining knowledge on how patients' attitudes about embryo disposition evolve over time, as well as on patients' opinions about the storage limit for embryos, is needed to guide patient-centredness in infertility and ART. This data can be useful in developing knowledge and patient-centred information concerning storage periods and the reasons for limitations, in a context in which patients' views are taken into consideration across legal and political boundaries. Such knowledge may also help in enacting guidelines to regulate applications to define embryo storage, as well as to set the timing for obtaining informed consent.

Overall, the literature on patients' perspectives on embryo donation for research has neglected the analysis of the conditions in which the informed consent is implemented. The process of informed consent may constitute an opportunity for humanization, democratization, accountability and transparency of processes and decisions[95, 110], concerned with ART by fostering dialogue and trust between health professionals and patients[111, 112] and providing a space for reflecting about cryopreservation and decision-making regarding embryo disposition. However, it can also be reduced to a formality that may be guided by medical strategies to manage risks, expectations and responsibilities in the field of ART[113, 114]. Given the inconsistency in the guidelines for clinical practices regarding informed consent, a central tool in decision-making process, knowledge on the perceptions of IVF couples regarding the factors that contextualize informed consent on embryo disposition, in particular the circumstances under which it should be delivered, explained and signed, are essential to guide patient-centredness in infertility and ART.

This thesis aims to produce evidence to sustain the development of patient-centredness regarding embryo donation for research, by the accomplishment of the following specific objectives:

1) To assess the psychosocial, demographic and reproductive factors and socioethical reasons associated with willingness to donate embryos for research among couples undergoing IVF.

2) To analyse IVF couple's willingness to donate cryopreserved embryos for research over time, taking into account the influence of psychosocial, demographic and reproductive factors.

3) To assess IVF patients' opinions about the storage limit for embryos and to explore their perceptions of the criteria underlying the establishment of the storage period offered to them.

4) To analyse the perceptions of IVF couples regarding the factors that contextualize informed consent regarding embryo cryopreservation.

3. Methods

3.1 Study design

This work is based on an observational and longitudinal mixed-methods study. This design involves collecting quantitative and qualitative data, alternating between sides over time[224]. The methodological strategy relied on three evaluation moments: (1) quantitative questionnaire with couples in IVF/ICSI treatments, over 12 consecutive months (baseline); (2) semi-structured interviews to a subsample of couples, conducted 3 months after baseline; (3) quantitative questionnaires 12 months after baseline (Figure 5).

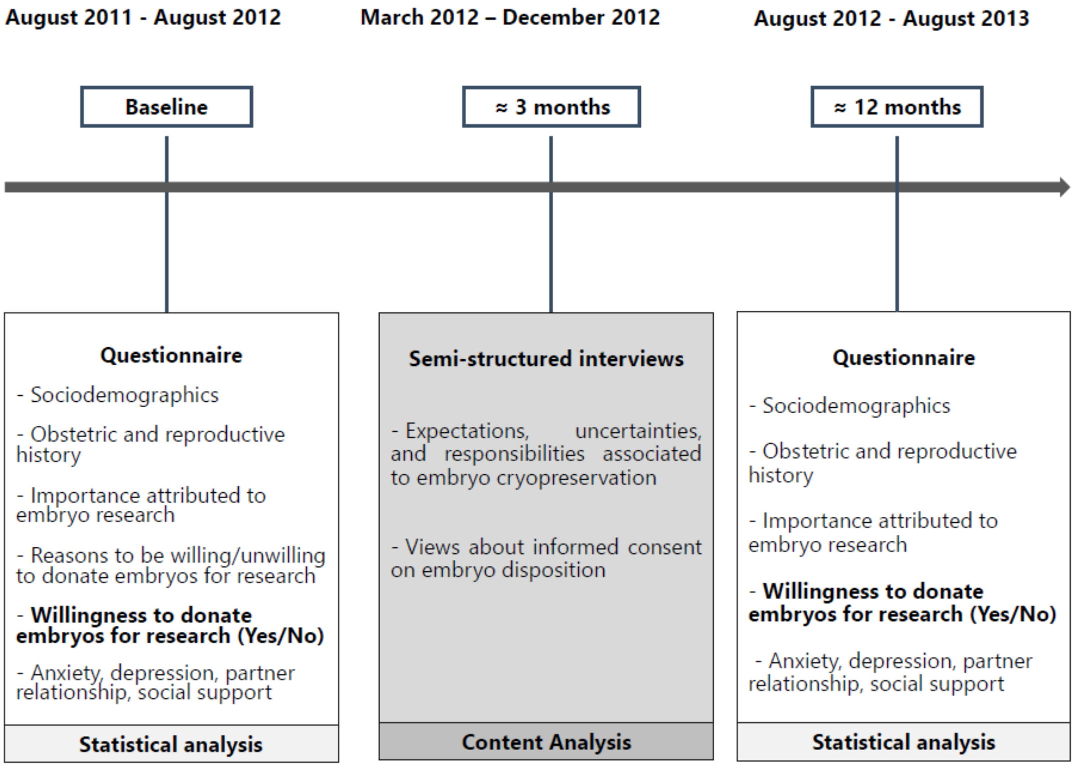

Figure 5. Study design

3.2 Participants and data collection

3.2.1 Questionnaires at baseline

Between the 17th of August 2011 and the 16th of August 2012, all patients undergoing IVF or Intracytoplasmic Sperm Injection (ICSI) in one reproductive medicine centre in Porto, Portugal, were consecutively and systematically invited to participate in the study on the day biological samples were collected to diagnose pregnancy, using the Human Chorionic Gonadotropin test – βhCG (N=329 tests), about 15 days after embryo transfer, being interviewed while awaiting for the results (Figure 6). In this centre, couples with cryopreserved embryos had signed the informed consent about embryo disposition after embryo transfer. This fertility centre is located in a public University Hospital that performs IVF/ICSI homologous cycles and does not conduct research projects using human embryos.

The research protocol was designed to recruit heterosexual couples because, in Portugal, IVF users must be heterosexual and married (or be in a stable relationship for at least 2 years)[225]. The choice of the day of the diagnosis of pregnancy was based on the fact that this procedure may require the presence of the couple, after a physically and emotionally challenging treatment[226, 227].

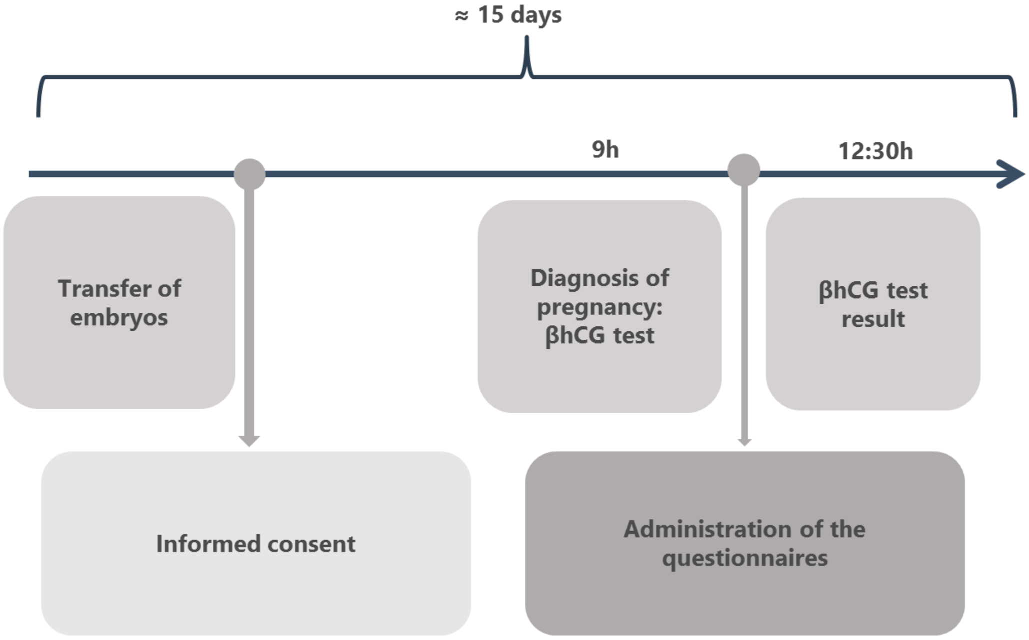

Figure 6. Moment of administration of questionnaires at baseline

Patients were first approached by nurses and given a study information sheet (see Appendix 1). This sheet had several sections, namely: 1) explanation on the purposes and design of the study; 2) potential risks and benefits of participating, issues of privacy and confidentiality, including duration of the questionnaire (30 minutes on average); and 3) information about patients' right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal or any influence in their treatment. Patients read the information sheet and one member of the research team then invited the potential participants to participate in the study, responding to all of their questions. Patients who decided to participate in the study were accompanied to a private room in the reproductive centre, where they read and signed the informed consent, and the data gathering started afterwards.

Of the 329 eligible patients, 226 visited the hospital with a partner and 103 women went to the hospital alone. Of the 226 couples invited, 221 agreed to participate in the study and among women alone, 92 participated, with participation rates of 97.8% and 89.3%, respectively (Figure 7). The global participation rate was 95.1%.

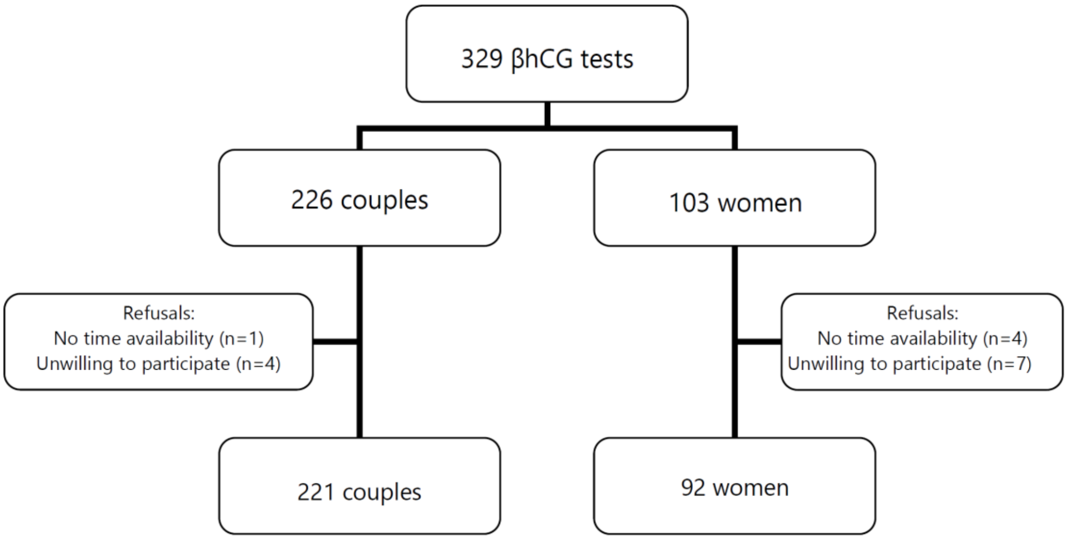

Figure 7. Flowchart for sample recruitment

The characteristics of the participants, stratified by gender, are presented in Table 1. Regarding couples' characteristics (n=221 couples), most of them were in a relationship for more than 5 years (73.7%) and had a household income higher than 1500€/month (58.1%). Most couples had never been pregnant (67.0%), had a duration of infertility superior to 3 years and had performed at least one previous cycle (56.1%). Regarding the causes for using ART, 27.6% had a female cause, 32.1% had a male cause and 40.3% had a mixed (female and male) or unexplained cause.

Table 1. Demographic, reproductive and psychosocial characteristics of the participants, stratified by gender

	Women (n=313)	Men (n=221)
Age (years), n (%)		
≤35	199 (63.6)	117 (52.9)
>35	114 (36.4)	104 (47.1)
Education level (years), n (%)		
≤12	181 (57.8)	155 (70.1)
>12	132 (42.2)	66 (29.9)
Country of origin, n (%)		
Portugal	280 (89.5)	195 (88.2)
Other	33 (10.5)	26 (11.8)
Catholic, n (%)		
Yes	281 (89.8)	185 (83.7)
No	32 (10.2)	36 (16.3)
Religious practice[a], n (%)		
At least once a month	86 (27.6)	40 (18.2)
Less than once a month	226 (72.4)	180 (81.8)
Parental status, n (%)		
No children	273 (87.2)	195 (88.2)
Children	40 (12.8)	26 (11.8)
Importance of embryo research, n (%)		
Very important	225 (72.3)	167 (75.6)
Important	86 (27.7)	54 (24.4)
State anxiety[b], M (SD)	47.12 (12.65)	34.55 (6.94)
Trait anxiety[b], M (SD)	38.47 (7.91)	38.15 (9.73)
Depression[c], M (SD)	9.49 (4.58)	6.41 (4.51)
Social support, Md (P25-P75)	76.00 (68.00-81.00)	71.00 (63.00-78.00)
Partner relationship – positive[d], Md (P25-P75)	30.00 (27.00-31.00)	29.00 (27.00-31.00)
Partner relationship – negative[e], Md (P25-P75)	8.00 (7.00-10.00)	9.00 (7.00-10.00)

[a]The total does not add 313, in women, and 221, in men, due to missing cases; [b]Lower values indicate lower anxiety symptoms (range: 20-80); [c]Lower values indicate fewer depressive symptoms (range: 0-30); [d]Higher scores mean that positive relationship dimensions are more present (range: 8-32); [e]Higher scores mean that negative relationship dimensions are more present (range: 4-16).

Two trained female interviewers conducted face-to-face interviews with the couples, using structured questionnaires. The outcome - willingness to donate embryos for research - was assessed by the question: "[When you are no longer using your embryos for your own treatment] Did you consent/ Would you consent the use of your embryos in scientific research projects?" and was categorized as "yes" or "no" to donation. The agreement between the couple to donate/not to donate embryos for research was also assessed. Data was also collected on: demographic characteristics (age, education level, country of origin, religion, household monthly income, subjective social class and length of relationship) and reproductive history (parental status, duration of infertility, number of previous cycles and causes of infertility) and the importance attributed to embryo research. Religious belief was categorized as a yes/no response to being Catholic, given the high prevalence of Catholic religion in Portugal[228]. Religious practice was assessed through the frequency of participation in religious services. Answers were categorized as "at least once a month" (including the options "many times a week", "once a week", "two or three times a month" and "at least once a month") or "less than once a month" (including the options "many times a year", "once a year", "less than once a year" and "never"). The importance attributed to human embryo research was measured through the answer to the following question: "How important is research with human embryos for you?". The original scale had the following categories: "Very important", "Important", "A little important" and "Not important". Given the fact that all participants answered "Very important" or "Important", the variable was dichotomized into "Very important" and "Important".

The two main individual reasons underlying their willingness to donate embryos for research were assessed through one open-ended question, which was included to collect more detailed and complete responses and to develop appropriate response categories[229]: "In your opinion, what are the main reasons to donate/not to donate embryos for research?".

Data on anxiety (state and trait), depression, partner relationship and perceived social support were collected through self-administered questionnaires that were completed individually and consisted of scales validated in Portuguese samples. The State-Trait Anxiety Inventory (STAI)[230] is composed of two scales of twenty items each, Trait (a permanent condition of anxiety) and State (anxiety in a specific situation), on a 4-point Likert scale (scale range: 20 to 80). Lower values indicate lower anxiety symptoms. The Portuguese STAI[231] has shown good internal consistency (α= 0.93 for the State Scale and α= 0.89 for the Trait Scale).

The Edinburgh Postnatal Depression Scale (EPDS)[232] consists of 10 items on a 4-point Likert scale (scale range: 0 to 30). Lower values indicate fewer depressive symptoms. It is reliable for the evaluation of depression not only in the postnatal period but also in the prenatal period[233], and addresses symptoms of depression within the previous 7 days. The Portuguese EPDS presented good internal consistency (α= 0.85).

The Relationship Questionnaire (RQ)[234] is comprised of 12 items on a 4-point Likert scale. The questionnaire was designed to assess two independent dimensions of the partner relationship: 1) the positive relationship subscale, which includes a sense of support and care, as well as affection, closeness and joint interests and activities, and 2) the negative relationship subscale, which includes anxiety, irritability and criticism. Higher scores, in the positive relationship subscale, mean that positive relationship dimensions are more present (range: 8-32), while higher scores, in the negative relationship subscale, mean that negative relationship dimensions are more present (range: 4-16). The questionnaire presented a good internal consistency (α= 0.79 for the total scale, α= 0.90 for the positive sub-scale and α= 0.72 for the negative sub-scale) and test–retest reliability (r= 50.74 for the total scale).

The Multidimensional Scale of Perceived Social Support[235] measures the perceived social support received from a significant other, family and friends, through 12 items on a 7-point Likert scale (total scale range: 12-84). Each subscale has four items (range: 4-28). Higher values indicate the perception of a better social support.

3.2.2 Questionnaires at 12 months

Approximately 12 months after completing the quantitative questionnaire applied at baseline, at the period starting one year after patients undergo their last treatment cycle, i.e. in ESHRE's "after treatment" stage[36], all the participants who previously agreed to be invited to participate in this phase of the study were contacted by telephone or email (according to their preference). Those who agreed to be included in the 12-months after evaluation were sent the questionnaire, as well as the informed consent form, by mail. This questionnaire included the same question regarding the willingness to donate embryos for research, questions about reproductive and obstetric data of the last year and the same self-administered scales for collecting data on anxiety (state and trait), depression, social support and partner relationship. Prepaid return envelopes were sent together. A total of 221 participants (114 women and 107 men) returned the questionnaires (participation rate=41.4%), in a total of 104 couples.

Longitudinal analysis was only performed with the couples who participated both at baseline and 12 months later, in a total of 82 couples (164 patients). Comparing participants who participated in the evaluation 12 months later with those who did not participate, the non-participants presented higher scores in the negative dimensions of the partner relationship than participants (respectively, Md [P25-P75]= 9.00 [8.00-10.00] vs 8.00 [7.00-10.00], p = 0.023). Besides that, no significant differences were found regarding psychosocial and reproductive characteristics and the willingness to donate embryos for research between these groups (Table 2).

Table 2. Comparison between the demographic, reproductive and psychosocial characteristics of the participants and the non-participants in couple, at time 2.

	Participants (n=164)	**Non-participants (n=278)**	***p***
Willingness to donate embryos for research			
Yes	240 (88.9)	132 (84.6)	0.260
No	30 (11.1)	24 (15.4)	
Age (years), n (%)			
≤35	93 (56.7)	172 (61.9)	0.332
>35	71 (43.3)	106 (38.1)	
Education level (years), n (%)			
≤12	97 (59.1)	190 (68.3)	0.064
>12	67 (40.9)	88 (31.3)	
Household monthly income (€)[a,b], n (%)			
≤1500	60 (38.0)	120 (44.1)	0.253
>1500	98 (62.0)	152 (55.9)	
Country of origin[a,b], n (%)			
Portugal	144 (92.9)	252 (95.1)	0.474
Other	11 (7.1)	13 (4.9)	
Catholic, n (%)			
Yes	150 (91.5)	235 (84.5)	0.051
No	14 (8.5)	43 (15.5)	
Religious practice[a]**,** n (%)			
At least once a month	36 (22.2)	60 (21.6)	0.970
Less than once a month	126 (77.8)	218 (78.4)	
Parental status, n (%)			
No children	149 (90.9)	244 (87.8)	0.400
Children	14 (9.1)	34 (12.2)	
Importance of embryo research[a], n (%)			
Very important	119 (73.0)	216 (77.7)	0.318
Important	44 (27.0)	62 (22.3)	
State anxiety[c], M (SD)	43.51 (12.50)	42.24 (11.54)	0.290
Trait anxiety[c], M (SD)	36.74 (7.58)	36.7 (8.52)	0.957
Depression[d], M (SD)	7.86 (4.56)	7.83 (4.90)	0.946
Social support, Md (P25-P75)	75.00 (67.00-80.00)	73.00 (66.00-80.00)	0.723
Partner relationship – positive[e], Md (P25-P75)	29.00 (27.00-31.00)	30.00 (27.00-31.00)	0.688
Partner relationship – negative[f], Md (P25-P75)	8.00 (7.00-10.00)	9.00 (8.00-10.00)	0.023

[a] The total does not add 164 in participants due to missing cases; [b] The total does not add 278 in non-participants due to missing cases; [c] Lower values indicate lower anxiety symptoms (range: 20-80); [d] Lower values indicate fewer depressive symptoms (range: 0-30); [e] Higher scores mean that positive relationship dimensions are more present (range: 8-32); [f] Higher scores mean that negative relationship dimensions are more present (range: 4-16).

3.2.3 Semi-structured interviews

Approximately three months after completing the questionnaire, at baseline, a sub-sample of the participants who agreed to participate in a qualitative interview were contacted by telephone or email, according to their preference, to confirm their availability to collaborate in the study. Between February and November 2012, 56 couples were consecutively invited to participate in the interview, and 34 accepted. Of the 22 couples who refused to be interviewed, more than half (n = 13) did not show the reasons for such refusal, 4 alleged lack of availability, 3 mentioned emotional obstacles, one couple invoked illness of one of the partners and another couple reported being separated.

Participants were purposively sampled to include pregnant and non-pregnant women, and couples who donated and who did not donate embryos for research. In addition, a heterogeneity sampling was used for maximum variation of views and experiences, until thematic saturation was reached. Therefore, recruitment continued until no new themes emerged from the interview data[236]. The characteristics of the interviewees are summarized in Table 3.

Semi-structured interviews took place between March and December 2012, and all were conducted by the same female interviewer. These occurred at the university department responsible for the study (n=16), couples' home (n=17) and at workplace (n=1). Interview duration ranged from 62 to 111 minutes, with an average of 81 minutes. All were taped, transcribed verbatim and accuracy has been checked.

The interview guide covered the following issues: meanings of parenthood; views, values, and knowledge actualised to understand the status of embryos; expectations, uncertainties, and responsibilities associated to the embryos cryopreservation; awareness of the processes of evaluation and classification of the embryos' quality and viability; how IVF couples made their decisions about donating embryos and their views of the consent process; and their understandings and knowledge of embryo research.

Table 3. Characteristics of the interviewed couples

Interview*	Age		Education level (years)		Embryo donation for research	Pregnancy
	Women	Men	Women	Men		
E1	28	27	>12	≤12	Yes	Yes
E2	36	28	>12	>12	Yes	Yes
E3	34	40	>12	≤12	Yes	Yes
E4	37	41	>12	>12	Yes	No
E5	38	36	>12	>12	Yes	No
E6	35	43	>12	>12	No	No
E7	35	38	>12	>12	Yes	Yes
E8	33	33	12	≤12	Yes	Yes
E9	38	39	>12	≤12	Yes	No
E10	25	30	>12	>12	Yes	No
E11	26	29	≤12	≤12	Yes	No
E12	37	35	≤12	≤12	No	No
E13	31	36	>12	≤12	Yes	Yes
E14	27	34	≤12	≤12	Yes	No
E15	40	37	≤12	≤12	Yes	No
E16	34	36	>12	>12	Yes	No
E17	36	36	>12	>12	Yes	No
E18	33	32	≤12	≤12	Yes	Yes
E19	38	35	>12	>12	No	No
E20	39	42	>12	>12	Yes	Yes
E21	38	38	>12	>12	Yes	No
E22	30	40	>12	>12	Yes	Yes
E23	37	40	≤12	≤12	No	Yes
E24	38	35	≤12	≤12	No	Yes
E25	26	33	≤12	≤12	Yes	No
E26	34	33	>12	>12	No	Yes
E27	37	41	>12	>12	No	No
E28	38	34	≤12	≤12	No	Yes
E29	33	33	>12	>12	Yes	Yes
E30	35	46	≤12	≤12	Yes	Yes
E31	39	39	≤12	>12	No	Yes
E32	34	35	>12	>12	Yes	No
E33	36	38	>12	>12	Yes	No
E34	32	34	>12	>12	Yes	No

*Participants are described in the table following the order of interview; the alphanumeric code assigned to each couple corresponds to the number of interview order.

3.3 Data analysis

Quantitative data

Statistical analyses were performed using the IBM Statistical Package for the Social Sciences (SPSS) Statistics for Windows (versions 20.0 and 21.0), Armonk, NY, USA, Stata V.11.0 (College Station, Texas, USA, 2009) and the R Software (2013). Data was described as counts and proportions for categorical variables, mean and standard deviation for normally distributed continuous variables, and median and interquartile range for non-normally distributed continuous variables. The prevalence of the outcomes was presented with 95% Confidence Interval (95% CI).

According to the specific objectives of each paper, different analytic approaches were considered. Chi-square test or Fisher's exact test were used to assess the independent associations between the categorical variables (demographic and reproductive characteristics) and the outcome. For continuous variables (STAI, EPDS, RQ and social support), mean or median differences were compared by the Independent Samples t-test or the Mann-Whitney test, according to data distribution. For these variables, the scores for each individual were calculated using its arithmetic mean for each scale.

The associations between explanatory variables and the outcomes were estimated by crude and adjusted odds ratios (OR) and the corresponding 95% CI using using binary logistic regression or multivariate logistic regression models, adjusting for possible confounders in each study.

Moreover, generalized Estimation Equation models with exchangeable correlation structure were performed. Relative Risks (RR) and the corresponding 95% confidence intervals (95% CI) were estimated by a log link function with a Poisson distribution.

Qualitative data

Semi-structured interviews were analysed using NVivo10 (QSR International, USA, 2013). Protocols for content analysis were selected according to the objectives of each study. Stemler's protocol[237] was useful when we intended to categorise data and determine the frequencies of categories. It differs from more 'qualitative' methods in that it requires categorization to be sufficiently precise to allow multiple coders to achieve the same results, relying on the systematic application of rules and drawing on the concepts of validity and reliability[238]. The protocol for thematic analysis developed by Mays et al.[239] was used to identify prominent or recurring themes, and to summarize the findings under thematic headings using summary tables[238]. The principles of grounded theory were also followed to constantly compare, contrast, synthesise and code data by theme and subsequently by thematic category, based on Charmaz[240] and Clarke[241]. It was used to identify patterns in primary data, being an inductive approach to analysis, that allows the theory to emerge from the data. Data was then interpreted by a qualitative content analysis approach, based on Mayring[242].

Coding was independently conducted by two researchers and disagreements in abstractions were discussed with a third researcher and resolved by consensus. Internal reliability and reflection were maximized though comparing coding between multiple researchers.

3.4 Methodological issues

Research on reproductive themes often deals with the main challenge of having the couple as unit of analysis, rather than an individual[16], which involves methodological and ethical dilemmas in study design, participants' recruitment, data collection, and analysis and interpretation of the data gathered. Qualitative studies show that being alone or in the presence of the partner shape the reporting of experiences and emotions[243, 244]; data collection may be affected when one person dominates the interview[245, 246] ethical dilemmas may occur if tensions/disagreements happen between partners[244, 245]. Quantitative studies have focused on the preferential mode of questionnaire completion by women in infertility surveys[247], the interaction and mutual influence of both members of the couple[248], the heterogeneity across individuals[249], and the strengths and weaknesses of the use of dyadic data analysis when the participant is a couple[250].

This thesis involved collecting quantitative and qualitative data with couples, alternating between sides over time, with a quantitative-dominant approach characterized by *complementarity*[224, 251]. The use of quantitative and qualitative methods aimed to maximize the understanding of the topic under research by looking for answers to different research questions in order to contribute to produce evidence to sustain the development of patient-centred policies and for ethics in clinical practice[251]. A quantitative approach was used to respond to the first two specific objectives of this thesis, while the third and fourth objectives claim for a mixed-methods and a qualitative approach, respectively.

Protocols for qualitative data analysis were selected according to the objectives and methodological approaches of each manuscript. When analysing data related with the open-ended questions included in the questionnaire and with the topic interview-guide question about the storage period for embryos, a protocol for content analysis[216] that differs from more 'qualitative' methods was chosen, because it relies on the systematic application of rules and draws on the concepts of validity and reliability[217], in accordance with the quantitative approach used in the first three specific objectives of this thesis.

When analysing the narratives enacted by IVF couples regarding their perception about the factors that contextualize informed consent in the field of embryo disposition, the grounded theory[240, 241] was used to identify patterns in primary data, based on an inductive analysis that allows the theory to emerge from the data.

Taking into account the fact that the present study involved joint quantitative and qualitative interviews with couples, researchers were aware of the response effect or partner effect, which happens when interviewees change or hinder their answers as a result of the interview situation, by withholding information or changing presentation style, for example, even if it is unintentional[245, 252]. This process often boosts a greater agreement between the opinions of both partners on a variety of attitudinal and behavioural items[253]. Additionally, there were situations when one of the elements of the couple had a dominant attitude, by speaking most of the time, despite the attempts by the researcher to question the other directly and obtain his/her opinion[244]. This may affect the opinions of the other and the opportunity to express them[245, 254].

There is also the possibility that researchers have induced more reflexivity about the topic of embryo donation for research, and, thus, have also motivated participants to search for more information, with an influence on their attitudes and, eventually, on the decision to participate in the study at time 2. Although there is no evidence regarding the motivations to complete or not a second questionnaire, it could be hypothesized that those who most reflected on embryo donation for research were more motivated to remain in the study. This highlights the importance of considering ethics in practice[243], emphasizing the ethical responsibility of the researchers to disseminate the results of the research among participants[255].

In this work, the fact that several women attended the medical appointment without their male partner raised two main concerns: was it helpful, from a basic research perspective, not having to exclude the women who went alone in a setting where they are available, and if so, were there differences in self-reporting of psychosocial variables when women or couples were recruited? To answer these questions, **PAPER II** was performed, with the objective of comparing the self-reporting of sociodemographic and psychosocial characteristics by female IVF patients interviewed alone or with the partner in heterosexual couples. This study concluded that no statistically significant differences were found in the self-reporting of depression, anxiety, social support and partner relationship or in sociodemographic and obstetric characteristics between women interviewed alone or with the partner. Thus, having a male partner present in the research setting during a self-administered questionnaire seems not to influence women's responses to psychosocial measures.

The development of evidence-based guidelines for conducting research on health conditions involving more than one person claims for studies assessing other outcomes and being conducted in other settings and sociocultural and economic contexts. It would be useful to assess the influence of differences in reproductive control and access to reproductive healthcare in a context of "stratified reproduction"[256]. Notwithstanding, these results contribute with important information that should be taken into account when planning studies on infertility and in the psychosocial assessment of IVF patients in clinical psychology practice.

3.5 Ethics

In data collection, storage, analysis and dissemination, procedures were developed in order to guarantee data confidentiality and protection. Ethics approval was granted by Ethics Committee for Health of the Centro Hospitalar de S. João.

Patients were first approached by the nurses and given a study information sheet, with an explanation on the purposes and design of the study. One member of the research team then invited the potential participants to take part in the study, responding to all of their questions. Patients who decided to participate in the study were accompanied to a private room in the reproductive centre, where they read and signed the informed consent. All participants formalized their collaboration through a written informed consent form according to the World Medical Association's Declaration of Helsinki.

All materials were anonymous and confidential. Each participant was identified with a numerical code, in the questionnaires and in databases. Data protection was guaranteed in accordance with the usual rules of confidentiality and only the research team had access to the data. Personal data, consents, questionnaires, interview tapes and transcripts were coded and kept separately from one another in locked file cabinets. Audio files will be destroyed at the end of the study. Interview transcripts are archived at the Institute of Public Heath of the University of Porto for 5 years. Once archived, transcripts were subject to strict protection and were not available, unedited, to any second party.

The interviewers were trained using a structured protocol addressing all the questionnaires' queries and periodic supervision of their work was undertaken by a senior social sciences researcher. A multidisciplinary team, with experience in national and international projects, was responsible for the staff training and the development of the questionnaire and the interview guide. Transcription of the interviews was performed by a professional, reliable service with a strict confidentiality policy in operation. Identifiable information was inevitably captured on the audio recordings but only the research team and transcription service had access to these files.

3.6. Paper II. Self-reported psychosocial factors among In Vitro Fertilization patients interviewed alone or with the partner

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Self-reported psychosocial factors among in vitro fertilization patients interviewed alone or with the partner

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ABSTRACT

The purpose of this study was to compare the sociodemographic and psychosocial characteristics reported by female *in vitro* fertilization (IVF) patients interviewed alone or with the partner in heterosexual couples. During 12 months (2011–2012), all patients undergoing IVF or intracytoplasmic sperm injection at one public reproductive medicine unit, in Portugal, were interviewed on the day of the diagnosis of pregnancy, being recruited 221 women interviewed with the partner and 92 interviewed alone. Interviewers collected data on sociodemographic and obstetric characteristics; and anxiety, depression, social support and partner relationship were collected by self-administered questionnaires. χ^2 test was used to assess the independent association between the categorical variables and being interviewed alone or with the partner. For continuous variables, mean or median differences were compared by the *t*-test or the Mann–Whitney test, according to data distribution. No statistically significant differences were found in the self-reporting of depression, anxiety, social support and partner relationship or in sociodemographic and obstetric characteristics between women interviewed alone or with the partner. Although women interviewed alone were older and more frequently had children than women interviewed with the partner, no significant associations were observed. Thus, having a male partner present in the research setting during a self-administered questionnaire seems not to influence women's responses to psychosocial measures. Other outcomes and settings need to be evaluated to support evidence-based guidelines for research on infertility.

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Introduction

Qualitative studies show that being alone or in the presence of the partner shape the reporting of experiences and emotions (Bjornholt & Farstad, 2014; Machado & Silva, 2010).

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Psychological variables should be addressed when a holistic approach is intended to the care of infertile women (Batool & Visser, 2014) and men (Schmidt, 2009). However, there is no quantitative data about the influence of participating alone or with the male partner in self-reporting in research on infertility. Studies have focused on the preferential mode of questionnaire completion by women in infertility surveys (Morris, Edwards, Doyle, & Maconochie, 2013), the interaction and mutual influence of both members of the couple (Donarelli et al., 2012), the heterogeneity across individuals (Weinberg & Wilcox, 2008), and the strengths and weaknesses of the use of dyadic data analysis when the participant is a couple (Peterson et al., 2009).

This study seeks to contribute to fill this gap, by exploring whether having a male partner present in the research setting during a self-administered questionnaire influences women's responses to psychosocial measures, taking advantage of an opportunity that emerged during fieldwork conducted within an observational cross-sectional project about embryo disposition. The research protocol was designed to recruit heterosexual couples on the day of the diagnosis of pregnancy. This choice was based on the fact that, in Portugal, IVF users must be heterosexual and married (or in a stable relationship for 2 years) (Silva & Barros, 2012). Furthermore, this procedure may require the presence of the couple, after a physically and emotionally challenging treatment (Boivin, Griffiths, & Venetis, 2011; Hammarberg, Fisher, & Wynter, 2008). However, several women attended this medical appointment without their male partner. It raised two main concerns: was it helpful, from a basic research perspective, not to have to exclude the women who went alone in a setting where they are available? If so, were there differences in self-reporting of psychosocial variables when women or couples were recruited?

Therefore, the objective of this study was to compare the self-reporting of sociodemographic and psychosocial characteristics by female IVF patients interviewed alone or with the partner in heterosexual couples.

Methods

Participants and procedures

Between 16 August 2011 and 15 August 2012, all patients undergoing homologous IVF or Intracytoplasmic Sperm Injection (ICSI) at a public reproductive medicine unit in Porto, Portugal, were consecutively and systematically recruited and interviewed on the day of Human Chorionic Gonadotropin test – βhCG ($n = 329$). In most situations, both members of the couple attended this medical appointment ($n = 226$), while 103 women went to the hospital alone. In the first case, women and men were invited to participate in the study; in the latter, women were invited to participate alone, with participation rates of 97.8% among couples and 89.3% among women alone. The final sample comprised two independent groups: 221 'women interviewed with the partner' and 92 'women interviewed alone'.

Ethical approval was granted by the Ethics Committee for Health of the S. João Hospital. All participants signed an informed consent.

Measures

Self-reported data on sociodemographic characteristics and obstetric history were assessed in face-to-face interviews conducted by two female trained interviewers using structured questionnaires. Women interviewed alone were asked to report their partners' sociodemographic characteristics. When at least one member of the couple had a child, participants were classified as having 'children'.

The following data were collected through self-administered questionnaires fulfilled individually, and partners did not talk to each other during the administration.

The State-Trait Anxiety Inventory (Gonçalves, Almeida, Machado, & Simões, 2006) is constituted by two scales of 20 items each, trait (permanent condition of anxiety) and state (anxiety in a specific situation), on a 4-point Likert scale. Good internal consistency was achieved in the Portuguese validation ($\alpha = .93$ [State]; $\alpha = .89$ [Trait]) and in the present study ($\alpha = .94$ [State]; $\alpha = .89$ [Trait]).

The Edinburgh Postnatal Depression Scale (Areias, Kumar, Barros, & Figueiredo, 1996) consists of 10 items on a 4-point Likert scale, presenting good reliability, both originally ($\alpha = .85$) and in this study ($\alpha = .84$). It is reliable for the evaluation of depressive symptoms not only in the postnatal period but also in the prenatal (Tendais, Costa, Conde, & Figueiredo, 2014).

The Relationship Questionnaire (Figueiredo et al., 2008) comprises 12 items on a 4-point Likert scale and assesses two dimensions: positive dimension (sense of support and care, affection, closeness, joint interests and activities); and negative dimension (anxiety, irritability and criticisms). It is reliable originally ($\alpha = .90$ [positive subscale]; $\alpha = .72$ [negative subscale]) and in the present study ($\alpha = .81$ [positive subscale]; $\alpha = .58$ [negative subscale]).

The Multidimensional Scale of Perceived Social Support (Zimet, Dahlem, Zimet, & Farley, 1988) measures the perceived social support from a significant other, family and friends, through 12 items on a 7-point Likert scale . A good internal consistency was registered originally (α [total scale] = .88; α [significant other] = .91; α [family] = .87; α [friends] = .85) and in the present study (α [total scale] = .91; α [significant other] = .90; α [family] = .92; α [friends] = .94).

Data analyses

χ^2 test was used to assess the independent association between the categorical variables and being interviewed alone or with the partner. For continuous variables, mean or median differences were compared by the independent samples *t*-test or the Mann–Whitney test, according to data distribution. Analyses were conducted using SPSS, version 20.0 for *Windows*.

Results

There were no statistically significant associations between the sociodemographic and obstetric characteristics of women interviewed alone or with the partner (Table 1). Although not reaching statistical significance, women interviewed alone were older (>35 years) and more frequently had children than women interviewed with the partner (44.5% vs. 33.0%, and 18.5% vs. 10.4%, respectively). Comparison between sociodemographic data of the partners of women interviewed alone and women interviewed with the partner showed no significant differences in any of the variables (data not shown).

Regarding anxiety, mean value was similar between the groups, both in state-anxiety and in trait-anxiety. Likewise, no statistically significant differences were found regarding

Table 1. Sociodemographic characteristics and obstetric history in female IVF patients being interviewed alone or with the partner in heterosexual couples.

	Overall	Women interviewed alone *n* (%)	Women interviewed with the partner *n* (%)	
	N = 313	*n* = 92	*n* = 221	*p*
Age (years)				
<30	41	11(12.0)	30(13.6)	.152
30–35	158	40(43.5)	118(53.4)	
>35	114	41(44.5)	73(33.0)	
Education level				
≤12 years	181	49(53.3)	132(59.7)	.352
>12 years	132	43(46.7)	89(40.3)	
Household monthly income (€)[a]				
≤1000	48	17(18.7)	31(14.4)	.618
1001–2000	157	44(48.3)	113(52.6)	
>2000	101	30(33.0)	71(33.0)	
Length of relationship (years)				
≤5	83	25(27.2)	58(26.2)	.910
6–7	87	24(26.1)	63(28.5)	
>7	143	43(46.7)	100(45.2)	
Cause of infertility				
Female	83	22(23.9)	61(27.6)	.887
Male	102	31(33.7)	71(32.1)	
Combined	66	19(20.7)	47(21.3)	
Unexplained	62	20(21.7)	42(19.0)	
Duration of infertility (months)				
≤24	56	17(18.5)	39(17.6)	.962
25–36	64	18(19.5)	46(20.8)	
>36	193	57(62.0)	136(61.6)	
Previous cycles				
0	130	33(35.9)	97(43.9)	.413
1–2	126	40(43.5)	86(38.9)	
≥3	57	19(20.6)	38(17.2)	
Previous pregnancy				
No	203	54(59.3)	149(67.4)	.190
Yes, without children	70	21(23.1)	49(22.2)	
Yes, with children	39	16(17.6)	23(10.4)	
Parental status				
No children	273	75(81.5)	198(89.6)	.078
Children	40	17(18.5)	23(10.4)	

[a] The total does not add 313 due to missing information.

depression symptoms among those interviewed alone or with the partner. Partner relationship dimensions were similar between both groups, with no statistically significant differences in the median of positive or negative subscales. Perceived social support was similar among women interviewed alone and those interviewed with the partner concerning the total score and the significant other, family and friends subscales scores (Table 2).

Discussion

In this study, the self-reporting of anxiety, depression, social support and partner relationship did not differ between women interviewed alone and those interviewed with the

Table 2. Anxiety and depression symptoms, partner relationship and perceived social support in female IVF patients interviewed alone or with the partner in heterosexual couples.

	Overall	Women interviewed alone	Women interviewed with the partner	
	N = 313	*n* = 92	*n* = 221	*p*
STAI-state anxiety[a] (mean, ± SD)	47.07(12.84)	46.69(13.89)	47.22(12.42)	0.760
STAI-trait anxiety[a] (mean, ± SD)	38.62(8.00)	37.99(8.29)	38.88(7.88)	0.405
EPDS Depression Scale[b] (mean, ± SD)	9.51(4.58)	10.04(4.54)	9.29(4.59)	0.187
Partner relationship – positive subscale[c] (median, P25–P75)	30.0(27.0–31.0)	30.0(27.0–31.0)	30.0(27.0–31.0)	0.449
Partner relationship – negative subscale[d] (median, P25–P75)	8.5(7.0–10.0)	9.0(7.0–10.0)	8.0(7.0–10.0)	0.794
Social support scale (total)[e] (median, P25–P75)	76.0(68.0–81.0)	76.0(68.8–81.0)	76.0(68.0–81.0)	0.838
Significant other subscale[f] (median, P25–P75)	28.0(25.0–28.0)	28.0(24.0–28.0)	28.0(26.0–28.0)	0.143
Family subscale[f] (median, P25–P75)	26.0(21.0–28.0)	26.0(21.0–28.0)	26.0(22.0–28.0)	0.639
Friends subscale[f] (median, P25–P75)	24.0(20.0–27.0)	24.0(20.0–28.0)	24.0(20.0–27.0)	0.659

[a] Lower values indicate lower anxiety symptoms (range: 20–80).
[b] Lower values indicate fewer depressive symptoms (range: 0–30).
[c] Higher scores mean that positive relationship dimensions are more present (range: 8–32).
[d] Higher scores mean that negative relationship dimensions are more present (range: 4–16).
[e] Higher values indicate better social support (range: 12–84).
[f] Higher values indicate better social support (range for each subscale: 4–28).

partner. Additionally, women's sociodemographic and obstetric characteristics were not significantly different, as well as those of their male partners. Findings from this study have implications mainly in two areas: firstly, data sustain the idea that researchers and clinical psychologists working on infertility can assess anxiety, depression, social support and partner relationship through the measures used in this study, regardless the presence of the couple; second, these results support an overall analysis of all the female IVF patients when assessing self-reported psychosocial factors, independently of being interviewed alone or with the partner.

Although the association between being interviewed alone or with the partner and both age and parental status hadn't achieved statistical significance, we cannot understate the risk estimate obtained. Women interviewed alone were older and more frequently had children than women interviewed with the partner. This may be explained by the fact that the experience of being a mother may help diminishing the psychological distress (Mckenzie & Carter, 2013) and the negative emotional consequences of infertility (Cousineau & Domar, 2007).

A high number of hospital visits in a short period of time prior to the pregnancy diagnosis, in articulation with the organization of public health care services in Portuguese fertility centers, may have hampered the male availability to attend all the medical appointments, because they occur on working days, usually during the morning. Additionally, the perception of infertility as a female problem (Chachamovich et al., 2010; Inhorn & Patrizio, 2015) and the election of the female body as the main factor underlying the success of IVF treatments (Silva & Machado, 2010) may explain the sub-representation of males in this study.

All the interviewees were heterosexual couples involved in homologous techniques, which may dissipate any possible differences resulting from single motherhood and the use of heterologous techniques. Furthermore, in studies aiming to analyze the interdependence between both members of the couple and the magnitude of its influence on the results (e.g. the analysis of the impact of one partner's coping on the stress of the other partner), the unit of observation should be the couple and a dyadic data analysis cannot be disregarded (Peterson et al., 2009).

The development of evidence-based guidelines for conducting research on health conditions involving more than one person claims for studies assessing other outcomes and being conducted in other settings and sociocultural and economic contexts. It would be useful to assess the influence of differences in reproductive control and access to reproductive health care in a context of 'stratified reproduction' (Greil, McQuillan, Shreffler, Johnson, & Slauson-Blevins, 2011). In conclusion, these results contribute with important information that should be taken into account when planning studies on infertility and in the psychosocial assessment of IVF patients in clinical psychology practice.

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4. Results

4.1 Paper III. Factors associated with willingness to donate embryos for research among couples undergoing IVF

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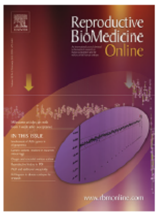

ARTICLE

Factors associated with willingness to donate embryos for research among couples undergoing IVF

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Abstract Between 2011 and 2012, 213 heterosexual couples undergoing fertility treatments in a Portuguese public fertility centre were systematically recruited to assess factors associated with willingness to donate embryos for research. Data were collected by questionnaire. Most couples (87.3%; 95% CI 82.1 to 91.5) were willing to donate embryos for research, citing benefits for science, health and infertile patients. Almost all couples (94.3%; 95% CI 89.8 to 96.7) reached consensus about the decision. Willingness to donate was more frequent in women younger than 36 years (adjusted OR 3.06; 95% CI 1.23 to 7.61) and who considered embryo research to be very important (adjusted OR: 6.32; 95% CI 1.85 to 21.64), and in Catholic men (adjusted OR 4.16; 95% CI 1.53 to 11.30). Those unwilling to donate reported conceptualizing embryos as children or living beings and a lack of information or fears about embryo research. Men with higher levels of trait anxiety (adjusted OR 0.90; 95% CI 0.84 to 0.96) were less frequently willing to donate. Future research on embryo disposition decision-making should include the assessment of gender differences and psychosocial factors. Ethically robust policies and accurate information about the results of human embryo research are required.

KEYWORDS: cryopreserved embryos, embryo disposition, embryo research, IVF, patient-centred care

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Introduction

Most couples enrolled in IVF and intracytoplasmic sperm injection (ICSI) cycles need to make decisions about embryo disposition (Provoost et al., 2010; Wånggren et al., 2013). It has been consistently shown that this is a complex decision-making process, involving different sequential stages that can change over time (de Lacey, 2005; Provoost et al., 2009, 2012a). Patients undergoing IVF usually reveal multifaceted views about embryo status (Haimes and Taylor, 2009; Provoost et al., 2009), disagreements between partners (Provoost et al., 2012b) and emotional distress (de Lacey, 2005; Fuscaldo et al., 2007).

Embryo donation for research is a controversial option for embryo disposition (Samorinha et al., 2014). Although unavailable in several countries, such as Argentina, Chile, Croatia, Lithuania, Slovakia and Russia (European Science Foundation [ESF], 2013; Ory et al., 2013; Kupka *et al*, 2014), it is offered in most European countries (ESF, 2013), and current US federal law allows research with donated embryos (Ory et al., 2013). Recent studies have revealed that over 59% of IVF patients are willing to donate their embryos for research in Switzerland (Mohler-Kuo et al., 2009), the USA (Lanzendorf et al., 2010) and Sweden (Wånggren et al., 2013). In Belgium, Provoost et al. (2012a) reported a positive trend in donating embryos for research between 1992 and 2006.

Embryo donation for research is supported by optimistic expectations concerning its potential to improve assisted reproductive techniques (Provoost et al., 2010), public health, clinical solutions for several diseases, or both (Svendsen, 2007), and by feelings of reciprocity (Lyerly et al., 2006) and trust in medical-scientific institutions (Priest et al., 2003). Patients undergoing IVF, however, have also reported a perception of risks (Provoost et al., 2009), a lack of information about research projects using human embryos (Fuscaldo et al., 2007; Provoost et al., 2010) and mixed feelings about embryo status (Lyerly et al., 2006; Provoost et al., 2010). These appraisements arise within ongoing socioethical and legal debates regarding embryo status, over-expectations concerning the results from stem cell research and public funding of embryonic stem cell research (Burns, 2009; ESF, 2013).

A recent systematic review analysed 39 empirical quantitative and qualitative studies that examined the factors associated with donation and non-donation of embryos for research, from the perspective of IVF patients. The associations between sociodemographic and reproductive characteristics and willingness to donate embryos for research were inconclusive. The authors concluded that the assessment of psychosocial factors, in particular well-being and psychopathological symptoms, were absent from most of the studies (Samorinha et al., 2014) and would provide valuable insight into psychosocial care in assisted reproductive techniques. Further research on these psychosocial factors will also give a better understanding of how partner dynamics and gender differences between couples affect embryo disposition (Sydsjö et al., 2005).

As the embryo disposition decision is influenced by both circumstances of daily life and structural drivers (CSDH, 2008), research on factors influencing disposition decisions should go beyond the assessment of the elements typically addressed in studies on patient-centred care in infertility: level of satisfaction with care delivery, information provision, emotional support, attitude of and relationship with staff, competence of clinic and staff, communication, autonomy and privacy, clinic's organization and accessibility (den Breejen et al., 2013; Dancet et al., 2011; Huppelschoten et al., 2013; van Empel et al., 2010). A public health approach to patient-centred care is required to produce knowledge on the determinants of the disposition decision, to disseminate ethically robust evidence that informs policies on embryo disposition and to increase awareness of public understanding of science and technology. These are necessary issues to promote the responsible regulation of embryo research and to achieve health policies respectful of, and responsive to, patient preferences, needs and values (Institute of Medicine, 2001).

In Portugal, IVF–ICSI is only available to heterosexual couples who are married or have been living together for at least 2 years (Government of Portugal, 2006). Embryos not used in treatment can be cryopreserved under two conditions: first, they must be considered to be suitable for cryopreservation by health professionals and, second, IVF couples must jointly sign an informed consent agreeing to cryopreservation (National Council for the Assisted Reproductive Technologies, 2013). In accordance with the current informed consent form in Portugal, couples are asked for an immediate decision on embryo disposition by giving broad consent to donate or not to donate embryos to research or to other infertile couples. Patients must write "Yes" or "No" in a blank square in front of the following statements: "We consent to the use of our embryos for donation to other infertile couples"; and "We consent to the use of our embryos in scientific research projects" (National Council for the Assisted Reproductive Technologies, 2013). This consent can be revoked by either member of the couple. Embryos must be kept for a maximum period of 3 years and if, within this period, the embryos are not used by the couple or have not been given to either of the consented uses (donation to other couples or for research), the embryos are thawed and destroyed (National Council for the Assisted Reproductive Technologies, 2013). The state pays for the freezing and storage for up to three cycles per couple (Government of Portugal, 2011).

This study aimed to assess the factors associated with willingness to donate embryos for research among IVF couples, to better understand how to sustain the development of patient-centred care.

Materials and methods

Participants

Between 17 August 2011 and the 16 August 2012, all patients undergoing IVF or ICSI in one reproductive medicine centre in Porto, Portugal, were consecutively and systematically invited to participate in the study on the day biological samples were collected to diagnose pregnancy using the beta HCG test. The fertility centre is located in a public University Hospital that carries out IVF–ICSI homologous cycles and does not conduct research projects using human embryos.

Of the 329 eligible female patients, 226 visited the hospital with a partner and 103 women attended alone. Of the 226 couples invited, 221 agreed to participate in the study (participation rate: 97.8%). Because we intended to assess an outcome that is shared by the members of a couple, i.e. willingness to donate embryos for research, the analysis was restricted to couples. Eight couples without information on the outcome variable were excluded from these analyses, resulting in a final sample of 213 couples.

Study design

This is an observational cross-sectional study designed to be exploratory and hypothesis-generating, because data about the association between sociodemographic and reproductive history and the decision about embryo donation for research is inconclusive, and little is known about the role of psychosocial variables (Samorinha et al., 2014).

Patients were first approached by the nurses and given a study information sheet. One member of the research team then invited the potential participants to take part in the study, responding to all of their questions. Patients who decided to participate in the study were accompanied to a private room in the reproductive centre, where they read and signed the informed consent according to the World Association's Declaration of Helsinki.

Two trained interviewers conducted face-to-face interviews with the couples, using structured questionnaires. The questionnaire was designed to accommodate the particular social context within which the research was conducted. This was achieved by including two main dimensions to the questionnaire. First, psychosocial variables were collected (including symptoms of anxiety and depression, the partner relationship, and importance of embryo research), that went beyond the sociodemographic and reproductive/obstetric history variables that were often collected in research on this topic (gender, age, education level, country of origin, religion, household monthly income, subjective social class and length of relationship; parental status, duration of infertility, number of previous cycles and causes of infertility). Second, participants freely reported the main reasons underlying their willingness to donate embryos for research through one open-ended question, which was included to collect more detailed and complete responses (McDonald et al., 2003): "In your opinion, what are the main reasons to donate/not to donate embryos for research?". The outcome – willingness to donate embryos for research – was categorized as "yes" or "no" to donation, and the agreement between the couple to donate or not to donate embryos was also assessed. Religious belief was categorized as a yes/no response to being Catholic, given the high prevalence of the Catholic religion in Portugal (INE, 2012). The importance attributed to human embryo research was measured through the question: "How important is research with human embryos for you?". The original scale had the following categories: "very important", "important", "slightly important" and "not important". As all participants answered "very important" or "important", the variable was dichotomized into these two categories.

Data on anxiety (state and trait), depression and partner relationship were collected through self-administered questionnaires that were completed individually and consisted of scales validated in Portuguese samples. The State-Trait Anxiety Inventory (STAI) (Gunning et al., 2010) is composed of two scales of 20 items each, trait (a permanent condition of anxiety) and state (anxiety in a specific situation), on a four-point Likert scale (scale range: 20 to 80). The Portuguese STAI (Silva, 2006) has shown good internal consistency (α = 0.93 for the State Scale and α = 0.89 for the Trait Scale). The Edinburgh Postnatal Depression Scale (EPDS) (Areias et al., 2006) consists of 10 items on a four-point Likert scale (scale range: 0 to 30). It is reliable for the evaluation of depression in the postnatal and prenatal periods (Tendais et al., 2014), and addresses symptoms of depression within the previous 7 days. The Portuguese EPDS presented good internal consistency ($\alpha = 0.85$). The Relationship Questionnaire (Figueiredo et al., 2008) is composed of 12 items on a four-point Likert scale. The questionnaire was designed to assess two independent dimensions of the partner relationship: the positive relationship subscale, including a sense of support and care, as well as affection, closeness and joint interests and activities; and the negative relationship subscale, which included anxiety, irritability and criticism. A higher score on a relationship subscale meant that these aspects were more present in the partner relationship. The questionnaire presented good internal consistency ($\alpha = 0.79$ for the total scale, $\alpha = 0.90$ for the positive subscale and $\alpha = 0.72$ for the negative subscale) and test-retest reliability ($r = 50.74$ for the total scale).

Ethics approval was granted by the Ethics Committee for Health of the Centro Hospitalar de S. João on 11 March 2009.

Data analysis

The association between the categorical variables and willingness to donate embryos for research was quantified through a chi-squared test. For the continuous variables (STAI, EPDS and the Relationship Questionnaire), the scores for each individual were calculated using the arithmetic mean of the scale. Separated scores were calculated for the STAI subscales (state and trait) and for the two subscales of the Relationship Questionnaire (positive and negative dimensions of the relationship). Mean differences were compared using an Independent Samples t-test or Mann–Whitney test, according to data distribution. All variables statistically significant at a $P < 0.01$ significance level, by gender, were included in multivariate logistic regression models (Enter method) and the odds ratios (ORs) and corresponding 95% confidence intervals (95% CI) were estimated. The first two models used gender to explore which female and male variables were associated with the outcome. The final model, for analysis by couple, included all significant variables in the first two models. Trait anxiety and depression were not adjusted, owing to high intercorrelation. The IBM Statistical Package for the Social Sciences (SPSS) Statistics for Windows, version 21.0, Armonk, NY, USA, was used for all analyses.

Answers to the open-ended question about the two main reasons to be willing to donate embryos for research were synthesized into categories after emergent coding, i.e., categories were established after preliminary examination of data according to Stemler's protocol for content analysis (Stemler, 2001). The first and the last authors independently conducted emergent coding, and disagreements in classification were resolved by consensus.

Results

The sociodemographic, reproductive and psychosocial characteristics of the participants are shown in Table 1. Most participants were younger than 36 years old, had less than or equal to 12 years of education, were Portuguese and Catholic. Most of the couples did not have children, had been infertile for more than 3 years and had undergone at least one previous treatment cycle.

Most of the couples were willing to donate embryos for research (87.3%; 95% CI 82.1 to 91.5). The embryo disposition decision was consensual for most of the couples (94.3%; 95% CI 89.8 to 96.7). Among those who reported a lack of consensus within the couple (*n* = 12 couples), the opinion of the man prevailed in eight couples (seven couples chose to donate and one opted for non-donation) and the opinion of the woman prevailed in four couples (two couples chose to donate and two chose not to donate). Catholic women and men ($P = 0.002$ and $P = 0.005$, respectively), and participants who considered human embryo research to be very important ($P < 0.001$ for women and $P = 0.001$ for men), were more likely to be willing to donate embryos for research. Younger women ($P = 0.002$), women without children ($P = 0.008$) and whose country of origin was Portugal ($P = 0.006$) were more likely to be willing to donate. Men with lower levels of trait anxiety ($P < 0.001$) and depression

Table 1 Sociodemographic, reproductive and psychosocial characteristics of the participants.

Individual characteristics	*Women (n = 213)*	*Men (n = 213)*	P
Age (years), n (%)			
>35	68 (31.9)	99 (46.5)	
≤35	145 (68.1)	114 (53.5)	0.003
Education level (years), n (%)			
≤12	126 (59.2)	151 (70.9)	
>12	87 (40.8)	62 (29.1)	NS
Country of origin, n (%)			
Other	20 (9.4)	26 (12.2)	
Portugal	193 (90.6)	187 (87.8)	NS
Catholic, n (%)			
No	21 (9.9)	35 (16.4)	
Yes	192 (90.1)	178 (83.6)	NS
Religious practice, n (%)			
At least once a month	54 (25.5)[e]	39 (18.4)[e]	
Less than once a month	158 (74.5)[e]	173 (81.6)[e]	NS
Parental status, n (%)			
Children	21 (9.9)	26 (12.2)	
No children	192 (90.1)	187 (87.8)	NS
Importance of embryo research, n (%)			
Important	48 (22.6)[e]	51 (23.9)[e]	
Very important	164 (77.4)[e]	162 (76.1)[e]	NS
State anxiety[a], mean (SD)	42.7 (11.9)	38.2 (9.7)	<0.001
Trait anxiety[a], mean (SD)	36.6 (7.7)	34.6 (6.9)	<0.001
Depression[b], mean (SD)	7.8 (4.8)	6.4 (4.5)	<0.001
Partner relationship - positive[c], Md (P25-P75)	30.0 (27.0–31.0)	29.0 (27.0–31.0)	NS
Partner relationship - negative[d], Md (P25-P75)	9.0 (7.0–10.0)	9.0 (7.0–10.0)	NS
Couple's characteristics	(*n* = 213)		
Duration of infertility (years), n (%)			
≤3	84 (39.4)		
>3	129 (60.6)		
Number of previous cycles, n (%)			
0	96 (45.1)		
≥1	117 (54.9)		
Cause of infertility, n (%)			
Female	56 (26.3)		
Male	68 (31.9)		
Other	89 (41.8)		

[a] Lower values indicate lower anxiety symptoms (range: 20–80).
[b] Lower values indicate fewer depressive symptoms (range: 0–30).
[c] Higher scores mean that positive relationship dimensions are more present (range: 8–32).
[d] Higher scores mean that negative relationship dimensions are more present (range: 4–16).
[e] The total does not add up to 213 owing to non-responses.
Md, mean difference; NS, not statistically significant; P25, 25th percentile; P75, 75th percentile.

(*P* = 0.005) were more frequently willing to donate embryos (Table 2).

The main factors associated with willingness to donate embryos for research by women, men and the couple are presented in Table 3. After adjustment, women who were willing to donate embryos for research were more likely to be younger than 36 years of age (OR 3.01; 95% CI 1.12 to 8.06) and to consider embryo research to be very important (OR 6.58; 95% CI 2.42 to 17.90). Men who were willing to donate embryos for research were more likely to be Catholic (OR 4.10; 95% CI 1.60 to 10.47), to consider embryo research to be very important (OR 4.60; 95% CI 1.93 to 10.96) and to present lower levels of trait anxiety (OR 0.90; 95% CI 0.84 to 0.97) and depression (OR 0.87; 95% CI 0.79 to 0.96). In the final model, after adjustment, willingness to donate embryos for research was more frequent among women below 36 years of age (OR 3.06; 95% CI 1.23 to 7.61), Catholic men (OR 4.16; 95% CI 1.53 to 11.30) and women who considered embryo research very important (OR 6.32; 95% CI 1.85 to 21.64). Men with higher levels of trait anxiety (OR 0.90; 95% CI 0.84 to 0.96) and depression (OR 0.86; 95% CI 0.78 to 0.96) were less frequently willing to donate embryos for research.

Participants who were willing to donate embryos for research presented reasons mainly related to contributions for scientific progress (48.4% of women and 42.5% of men) and to improvements in IVF treatments (37.6% of women and 39.8% of men). Almost one-third (31.2% of women and 32.3% of men) claimed that "helping others/altruism" was a reason to donate embryos for research. Other mentioned reasons included improving human health (11.3% of women and 9.1% of men), feelings of "reciprocity" towards science and medicine (5.4% of women and 5.9% of men) and considering that donation to research was a "way to give utility to embryos", which was "better than wasting" them (6.5% of women and 3.8% of men).

The most frequently mentioned reasons among those unwilling to donate embryos for research were the conceptualization of embryos as "children", a "baby" or a "living being" (29.6% of women and 37.0% of men), a lack of information about embryo research (29.6% of women and 33.0% of men), the need to transfer the cryopreserved embryos (25.9% of women and 22.2% of men), fears about what could happen to the embryos (18.5% of women and 22.2% of men) and non-specified issues related to "personality" or "education" (22.2% of women and 18.5% of men).

Discussion

Data provided in this study may be helpful in the development of ethically robust patient-centred policies about decision-making on embryo donation for research, in the following ways. First, the results call for the development of guidelines for psychosocial care in the field of embryo donation decision-making that should be sensitive to women's, men's and couples' age, religion, trait anxiety, and conceptualization of cryopreserved embryos. Additionally, it highlights the responsibility of health professionals and researchers to communicate realistic expectations about the results from research on human embryos, as the patients who were willing to donate embryos for research believed it was highly important and based their decision primarily on the expected benefits for science, health and IVF patients. There is also room to disseminate accurate information about research on human embryos, including their specific goals, objectives and procedures, to improve the robustness of the informed consent given by couples.

This study revealed one of the highest proportions of IVF patients willing to donate embryos for research among similar studies, in which willingness to donate was also assessed by a yes/no answer (Samorinha et al., 2014). A positive attitude towards the donation of embryos for research was also illustrated by the fact that none of the couples considered research on human embryos to be of slight importance. Most patients believed that human embryo research would result in scientific progress and benefits for health and for IVF couples in particular.

The high perceived value of embryo research is consistent with the changing social context in which legislation in several countries allows and regulates the use of human embryos in research (ESF, 2013). A high receptivity to scientific and technological progress and trust in medical institutions and their professionals characterizes would-be-parents' assessment of the benefits and risks of assisted reproduction techniques, which was described in previous studies as being imbued with hope, trust and altruism (Silva and Machado, 2009, 2010, 2011). The reported reasons for donating embryos in this study reflect the incorporation of this assessment and are aligned with findings from other studies: willingness to contribute to scientific progress in general (Fuscaldo et al., 2007; Lyerly et al., 2006), to the development of IVF treatments in particular (Lyerly and Faden, 2007; Provoost et al., 2010) and to the improvement of human health (Fuscaldo et al., 2007; Provoost et al., 2009). These motives may also reflect the perception that minimal risks are associated with human embryo research, as mentioned by Priest et al. (2003), which conflicts with the report of fears by patients who were unwilling to donate embryos for research. Consistent with results obtained in previous studies (Fuscaldo et al., 2007; Lyerly et al., 2006; McMahon et al., 2003; Provoost et al., 2010), participants who were willing to donate embryos for research in our study also revealed a "sense of gratitude" to science and an "altruistic desire" to help others.

These feelings might be simultaneously driven by external constraints and internal motivations, which have been previously described in the donation of biological material in Portugal (Machado and Silva, 2015; Silva and Machado, 2009). This socioethical framework redefines human embryos as a gift for the common good in the context of embryo disposition (Mauss, 1954; Rose and Novas, 2005), pointing to the conceptualization of embryo donation for research as an act of individual responsibility for collective well-being (Machado and Silva, 2014). This framework is useful in understanding why the Catholic men in our study were significantly more willing to donate embryos for research. Previous studies about the role of religion in IVF patients' decision about embryo disposition reported inconsistent data; studies in Australia (McMahon et al., 2003) and in Belgium (Provoost et al., 2009, 2010) found no association between an individual's religion and the disposition decision, although other studies in Switzerland (Mohler-Kuo et al., 2009) and Australia (Burton and Sanders, 2004) suggested that having moderate or strong religious beliefs (versus not very strong beliefs) was associated with a lower likelihood of donating embryos for research. In a qualitative study in the USA (Lyerly et al., 2006), pa-

Table 2 Willingness to donate embryos for research, according to the sociodemographic, reproductive and psychosocial characteristics of the participants.

	Willingness to donate		
	Yes (n = 186)	*No (n = 27)*	*P*
Women (N = 213)			
Age (years), n (%)			
>35	52 (28.0)	16 (59.3)	
≤35	134 (72.0)	11 (40.7)	0.002
Education level (years), n (%)			
≤12	109 (58.6)	17 (63.0)	
>12	77 (41.4)	10 (37.0)	NS
Country of origin, n (%)			
Other	13 (7.0)	7 (25.9)	
Portugal	173 (93.0)	20 (74.1)	0.006
Catholic, n (%)			
No	13 (7.0)	8 (29.6)	
Yes	173 (93.0)	19 (70.4)	0.002
Religious practice, n (%)			
At least once a month	45 (24.3)[e]	9 (33.3)	
Less than once a month	140 (75.7)[e]	18 (66.7)	NS
Parental status, n (%)			
Children	14 (7.5)	7 (25.9)	
No children	172 (92.5)	20 (74.1)	0.008
Importance of embryo research, n (%)			
Important	32 (17.3)[e]	16 (59.3)	
Very important	153 (82.7)[e]	11 (40.7)	<0.001
State anxiety (M [SD])[a]	46.9 (11.8)	51.5 (12.9)	NS
Trait anxiety (M [SD])[a]	38.4 (8.1)	40.8 (6.6)	NS
Depression (M [SD])[b]	9.3 (4.6)	9.15 (4.91)	NS
Partner relationship – positive (Md [P25-P75])[c]	30.0 (28.0–31.0)	30.0 (28.0–31.0)	NS
Partner relationship – negative (Md [P25-P75])[d]	8.0 (7.0–10.0)	9.0 (8.0–10.0)	NS
Men (N = 213)			
Age (years), n (%)			
>35	87 (46.8)	12 (44.4)	
≤35	99 (53.2)	15 (55.6)	NS
Education level (years), n (%)			
≤12	133 (71.5)	18 (66.7)	
>12	53 (28.5)	9 (33.3)	NS
Country of origin, n (%)			
Other	20 (10.8)	6 (22.2)	
Portugal	166 (89.2)	21 (77.8)	NS
Catholic, n (%)			
No	25 (13.4)	10 (37.0)	
Yes	161 (86.6)	17 (63.0)	0.005
Religious practice, n (%)			
At least once a month	34 (18.4)[e]	5 (18.5)	
Less than once a month	151 (81.6)[e]	22 (81.5)	NS
Parental status, n (%)			
Children	20 (10.8)	6 (22.2)	
No children	166 (89.2)	21 (77.8)	NS
Importance of embryo research, n (%)			
Important	37 (19.9)	14 (51.9)	
Very important	149 (80.1)	13 (48.1)	0.001
State anxiety (mean [SD])[a]	37.5 (9.6)	42.1 (10.2)	NS
Trait anxiety (mean [SD])[a]	33.9 (6.5)	38.9 (8.3)	<0.001
Depression (mean [SD])[b]	6.0 (4.2)	8.6 (5.4)	0.005
Partner relationship – positive (Md [P25-P75])[c]	29.0(27.0–31.0)	30.0(27.0–31.0)	NS
Partner relationship – negative (Md [P25-P75])[d]	8.0 (7.0–9.0)	9.5 (7.8–10.3)	NS
Couple characteristics (*n* = 213)			
Duration of infertility (years), n (%)			
≤3	73 (39.2)	11 (40.7)	
>3	113 (60.8)	16 (59.3)	NS
Number of previous cycles, n (%)			
0	80 (43.0)	16 (59.3)	
≥1	106 (57.0)	11 (40.7)	NS
Cause of infertility, n (%)			
Female	50 (26.9)	6 (22.2)	
Male	61 (32.8)	7 (25.9)	
Other	75 (40.3)	14 (51.9)	NS

[a] Lower values indicate lower anxiety symptoms (range: 20–80).
[b] Lower values indicate fewer depressive symptoms (range: 0–30).
[c] Higher scores mean that positive relationship dimensions are more present (range: 8–32).
[d] Higher scores mean that negative relationship dimensions are more present (range: 4–16).
[e] The total does not add up to 186 owing to one non-response.
Md = mean difference, P25 = 25th percentile; P75 = 75th percentile.

Table 3 Factors associated with willingness to donate embryos for research among couples undergoing IVF.

	Willingness to donate	
	Crude OR (95% CI)	*Adjusted OR (95% CI)*
Model 1: women		
Age		
>35	1	1
≤35	3.75 (1.63 to 8.61)	3.01 (1.12 to 8.06)[a]
Country of origin		
Other	1	1
Portugal	4.66 (1.67 to 13.03)	3.53 (0.84 to 14.79)[a]
Catholic		
No	1	1
Yes	5.60 (2.06 to 15.23)	3.26 (0.71 to 14.92)[a]
Parental status		
Children	1	1
No children	4.30 (1.55 to 11.91)	2.98 (0.77 to 11.39)[a]
Importance of embryo research		
Important	1	1
Very important	6.96 (2.95 to 16.39)	6.58 (2.42 to 17.90)[a]
Model 2: men		
Catholic		
No	1	1
Yes	3.79 (1.56 to 9.20)	4.10 (1.60 to 10.47)[b]
Importance of embryo research		
Important	1	1
Very important	4.34 (1.88 to 10.01)	4.60 (1.93 to 10.96)[b]
Trait anxiety	0.90 (0.85 to 0.96)	0.90 (0.84 to 0.97)[c]
Depression	0.88 (0.81 to 0.97)	0.87 (0.79 to 0.96)[c]
Model 3 – Couple		
Age (women)		
>35	1	1
≤35	3.75 (1.63 to 8.61)	3.06 (1.23 to 7.61)[d]
Catholic (men)		
No	1	1
Yes	3.79 (1.56 to 9.20)	4.16 (1.53 to 11.30)[d]
Importance of embryo research (women)		
Important	1	1
Very important	6.96 (2.95 to 16.39)	6.32 (1.85 to 21.64)[d]
Importance of embryo research (men)		
Important	1	1
Very important	4.34 (1.88 to 10.01)	1.09 (0.32 to 3.74)[d]
Trait anxiety (men)	0.90 (0.84 to 0.97)	0.90 (0.84 to 0.96)[e]
Depression (men)	0.87 (0.79 to 0.96)	0.89 (0.71 to 1.12)[e]

[a] Adjusted for each other.
[b] Adjusted for each other.
[c] Adjusted for being Catholic and the importance of embryo research.
[d] Adjusted for each other.
[e] Adjusted for age (women), being Catholic (men) and the importance of embryo research (women and men).

tients noted that religion affected their decision-making and identified themselves as Catholic (Evangelical) Christian, or Baptist, stating that they considered embryo destruction, including research, to be prohibited. These results indicate that religious faith and an understanding of scientific facts and methods are not mutually exclusive and can coexist, with religion as a "perceptual filter" that moderates the ways in which scientific knowledge affects attitudes (Allum et al., 2014).

It is worth noting that the main argument used by the Catholic Church to criticize human embryo research, that human life begins at conception (United States Conference of Catholic Bishops, 2011), was also observed in this study in participant's reasons to not donate embryos for research, as shown by their conceptualization of embryos as living beings or children. This perspective, however, is not always a barrier for donating embryos for research, as research may be perceived to be preferable to discarding embryos, as previously described (de Lacey et al., 2012; Lyerly et al., 2004). Furthermore, the perception that human life begins at conception may increase the value of an embryo, which could justify their use in research, as presented by de Lacey et al. (2012) and Provoost et al. (2009). Patient's preference is not often that their remaining embryos have a chance at life, but rather that they can "be used in a way" (Lyerly and Faden, 2007). Therefore, the meanings of the moral status of embryos seem to be varied and context-dependent, not fixed entities (de Lacey, 2005; Haimes et al., 2008), with couples using a complex and dynamic system of embryo classification (Haimes and Taylor, 2009). Patients undergoing IVF perceive embryos simultaneously as epistemic or medical objects for research and clinical practices, and ontological objects for reproduction (Samorinha et al., 2014), with an instrumental value (Provoost et al., 2009) that should not be wasted (Luna et al., 2009; Provoost et al., 2010).

The complex relationships between the conceptualizations of embryos, scientific research and individual ethical responsibilities may explain the contradictory results described in empirical studies examining the association between sociodemographic characteristics and the (un)willingness to donate embryos for research. Although our study showed that age was a significant factor in women's willingness to donate embryos for research, several studies have found no association between the age of IVF female patients and their donation decision (Lanzendorf et al., 2010; Provoost et al., 2012a). Our study showed that younger women were more willing to donate embryos for research. This may be related to the perception that younger women have more opportunities to become pregnant owing to age-related decline in fertility (American Society for Reproductive Medicine, 2014a), and therefore it would not be necessary to transfer the cryopreserved embryos.

Regarding the psychosocial factors, an anxious state seemed to have had a significant influence only on men's opinion. Higher levels of trait anxiety were found among men who were unwilling to donate embryos for research, which can be associated with the fact that individuals with high anxiety levels are more likely to avoid perceived threats, especially future events (Spielberger and Vagg, 1984). Patients who were given extensive information in fertility care services have presented less psychopathological feelings (Mourad et al., 2010). In this context, donation of embryos for research can be perceived as a threat. This perception occurs when participants report a lack of information about research projects, as previously found (Fuscaldo et al., 2007; Lyerly et al., 2006; Provoost et al., 2010), or when they have fears about what could happen to their embryos (Fuscaldo et al., 2007; Provoost et al., 2009). Additionally, those who were unwilling to donate may feel they did not accomplish the desirable action within a context mostly receptive to scientific and technological progress (Rose and Novas, 2005), which can generate higher levels of anxiety.

The present study was the first to evaluate the association between willingness to donate embryos for research and patient anxiety, depression and quality of partner relationship, while also including variables from both members of the couple. Although no association between donation decision and depression and quality of partner relationship was found in this study, further studies should be conducted to validate these results.

Furthermore, this study provides preliminary results about the development of a public health approach to patient-centred care in embryo disposition, contributing to an analysis of open-mindedness towards and level of information about research with human embryos. It also deconstructs stereotypes about the influence of religious beliefs on embryo donation for research. It sustains stakeholders' decisions about the suitability of research projects using cryopreserved embryos, and contributes to maximize public understanding of science and technology. This study, however, does have some limitations. Participants were recruited from only one public reproductive medicine centre located in a university hospital. Although it was the largest centre in the Northern region of Portugal, the prevalence of embryo donation for research may be overestimated in this setting, as trust increases when research is conducted in universities compared with the private sector (Critchley, 2008). The recruitment of participants in private clinics, as well as couples involved in heterologous techniques, would be enriching. Nevertheless, 25% of the participants had already undergone at least one cycle in a private centre. The timing of data collection may have contributed to increased levels of state anxiety in this study. The fact that all of the individuals were exposed to the same situation, however, mitigates the possible biasing effect of a differential exposure on the main outcome of this study – the willingness to donate embryos for research. In addition, some participants were in the midst of treatments, which could affect their disposition decision-making process. The fact that couples in this centre were asked to give informed consent on embryo disposition after embryo transfer, at a time when they show increased levels of state anxiety (ESHRE, 2015), suggests that we should consider the circumstances under which the informed consent should be delivered, explained and signed. National practice in this area could be made more ethically robust by removing disposition decisions away from that point during treatment and permitting the decision to be made at a later, less stressful time. As patients' willingness to donate embryos for research may change over time, future research would benefit from a prospective analysis, with more longitudinal studies to assess causality, and with national representative samples. On the other hand, a deeper understanding of the decision-making process relating to embryo donation for research could be obtained by more studies focusing on in-depth qualitative analyses of couples, in their particular cultural context (de Lacey, 2007).

In conclusion, opportunities exist for research to assess gender differences and psychosocial factors involved in embryo disposition decisions, and these findings should be included in the guidelines for psychosocial care for infertility and assisted reproduction techniques. Ethically robust policies and practices that are sensitive to patient's information needs are required, including the provision of accurate information on the results of human embryo research that will promote a fully informed consent (ASRM, 2014b).

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4.2 Paper IV. Couple's willingness to donate embryos for research: a longitudinal study

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Couple's willingness to donate embryos for research: a longitudinal study

Running title: Willingness to donate embryos for research

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Abstract

Introduction: Decision-making on embryo disposition is a source of distress and is subject to change over time. This paper analyses in vitro fertilization couple's willingness to donate cryopreserved embryos for research from 15 days after embryo transfer to 12 months later, taking into account the influence of psychosocial, demographic and reproductive factors. *Materials and Methods:* Prospective longitudinal study, with 74 heterosexual couples undergoing in vitro fertilization in a public fertility centre in Portugal, recruited between 2011 and 2012. Participants were evaluated at two times: 15 days after embryo transfer and 12 months later. ***Results:*** A significant decrease in patients' willingness to donate embryos for research over time was observed (86.5% to 73.6%; relative risk (RR)=0.85; 95%CI; 0.76-0.95). A higher education level (>12 years) (RRadj=0.79; 95%CI; 0.64-0.96), considering research on human embryos to be important (vs. very important) (RRadj=0.59; 95%CI; 0.39-0.85) and practicing a religion less than once a month (vs. at least once a month) (RRadj=0.73; 95%CI; 0.53-1.00) seemed associated with unwillingness to donate embryos for research over time. Change towards non-donation happened mainly among couples who firstly considered that it was better to donate than wasting the embryos. Change towards donation occurred mostly among those stating their priority at time 1 was to have a baby and who became pregnant in the meantime. *Conclusions:* Quality of care guided by patients' characteristics, values, preferences and needs calls for considering the factors and reasons underlying couples' willingness to donate embryos for research over time as a topic in psychosocial guidelines for infertility and medically assisted reproductive care.

Key words

IVF, cryopreserved embryos, embryo disposition, decision making, longitudinal study, patient-centered care

List of abbreviations

CI	confidence interval
ICSI	intracytoplasmic sperm injection
IVF,	in vitro fertilization.
RR,	relative risk
RRadj	adjusted relative risk

Key Message

Willingness to donate embryos for research is dynamic among patients undergoing in vitro fertilization. The importance of psychosocial and reproductive factors, and time, in explaining variations in decision-making regarding embryo donation is highlighted, with implications for ethics in clinical practice. The idea that informed consent should be signed after the infertility treatment is completed is reinforced.

Introduction

In vitro fertilization (IVF) couples are asked, in several countries, to sign an informed consent form regarding embryo donation for research. This entails a decision involving both members of the couple, who are requested to make it together. Differences in regulations, guidelines and health care policies between countries determine whether the informed consent should be signed prior to the first treatment (1), during treatment (2) or after treatment is completed (3). Patients' needs for information and support are likely to vary across these three treatment stages (4), which means that the timing set to obtain consent is likely to influence the type of decisions made. Thus, obtaining knowledge on how patients' attitudes about embryo disposition evolve over time is needed to guide patient-centredness in infertility and medically assisted reproduction.

Decision-making on embryo disposition is described as being difficult, as well as a source of moral and emotional distress (5,6). Some couples report high decisional conflicts (7) and some delay the decision for as long as possible (5). Yet others report feeling pressure to make a decision (8). Research also suggests that decisions on embryo disposition are subject to change over time (9-11). A study carried out in Belgium observed a positive trend towards embryo donation for research over time (11). Yet other studies carried out in the USA and in Canada found that patients who firstly chose to donate embryos for research later changed their choice to use or discard embryos (9,10). Having experienced a live birth was associated to discard embryos rather than use them for research purposes in Canada (10), but studies in France and in the USA found no significant association between change in willingness to donate embryos for research and having a child (9,12).

From the few existing longitudinal studies about the factors associated with patients' willingness to donate embryos for research none focused on the influence of psychosocial, demographic and reproductive characteristics. Therefore, the objective of this longitudinal study was to analyse IVF couple's willingness to donate cryopreserved embryos for research from 15 days after embryo transfer to 12 months later, taking into account the influence of psychosocial, demographic and reproductive factors.

Material and methods

This is a prospective longitudinal study. Between August 2011 and August 2012, all patients undergoing IVF or intracytoplasmic sperm injection (ICSI) in one reproductive medicine centre in Porto, Portugal, were consecutively and systematically invited to participate in a study on embryo disposition (time 1) and reevaluated 12 months later (time 2). The fertility centre is located in a public University Hospital that carries out IVF-ICSI homologous cycles and does not conduct research projects using human embryos. In Portugal, these techniques are available for heterosexual couples, married or living together for at least two years (13). The state pays for IVF-ICSI treatments, embryo freezing and storage, for up to three cycles per couple, and covers 69% of the total cost of infertility medication (13). Couples with cryopreserved embryos are required to make a joint consensual decision about embryo disposition, saying 'Yes' or 'No' to donation to other infertile couples and to scientific research (14). For this reason, participants were asked as a couple whether they would donate embryos for research at time 1 (about 15 days after embryo transfer). Embryos should be used within a maximum period of three years, otherwise, embryos will be thawed and discarded. The consent might be unilaterally revoked by either member of the couple. Taking this into account, obtaining data on the individual opinion of the members of the couple at time 2 is fundamental to assess change in willingness to donate embryos for research.

Of the 221 couples invited, 97.8% agreed to participate at time 1 and 215 accepted to be reevaluated one year later. At time 2, a participation rate of 38.1% was obtained (N=82 couples). Eight couples without information on the outcome variable were excluded from these analyses, being the final sample constituted by 74 couples. No significant differences were found regarding psychosocial, demographic and reproductive characteristics and willingness to donate embryos for research between the patients included in the analysis and those who did not participate at time 2.

At time 1, two trained interviewers conducted face-to-face interviews with the couples, using structured questionnaires. Willingness to donate embryos for research was assessed by the question: "[When you are no longer using your embryos for your own treatment] Did you consent/Would you consent the use of your embryos in scientific research projects?". Data on sociodemographic characteristics (age, education level, country of origin, religion, household monthly income) reproductive and obstetric history (parental status, duration of infertility, number of previous cycles and reasons for using IVF-ICSI), and on the importance attributed to embryo research was collected at time 1. Parental status was categorized as "children" and "no children", based on whether at least one member of the couple had a child. Religious belief was categorized as Catholic: "yes" or "no", taking into account the high prevalence of the Catholic religion in Portugal (15). The importance attributed to human embryo research was measured through the question: "How important is research with human embryos for you?". The original scale had the following categories: "very important", "important", "little important" and "not important". As all participants answered "very important" or "important", the variable was dichotomized into these two categories. The two main reasons underlying the decision on embryo donation for research were assessed through one open-ended question.

Data on anxiety (state and trait), depression, social support and partner relationship were collected through self-administered questionnaires completed individually. The State-Trait Anxiety Inventory (STAI) (16) is composed of two scales of twenty items each, trait (a permanent condition of anxiety) and state (anxiety in a specific situation), on a four-point Likert scale (scale range: 20-80). The Portuguese STAI (17) revealed good internal consistency (α= 0.93 for the State Scale and α= 0.89 for the Trait Scale). The Edinburgh Postnatal Depression Scale (EPDS) (18) consists of 10 items on a four-point Likert scale (scale range: 0-30) and presented good internal consistency (α= 0.85). EPDS is reliable for the evaluation of depression symptoms in the pre- and postnatal period (19). The Multidimensional Scale of Perceived Social Support (20) measures the perceived adequacy of social support received from a significant other, family and friends, through 12 items. Respondents reported their agreement on a seven-point Likert scale (scale range: 12-84) (α[total scale]=0.88). The Relationship Questionnaire (21) comprises 12 items on a four-point Likert scale and assesses two independent dimensions of the partner relationship: the positive relationship subscale, including a sense of support and care, as well as affection, closeness and joint interests and activities; and the negative relationship subscale, which included anxiety, irritability and criticisms. The questionnaire presented good internal consistency: α= 0.79 (total scale), α= 0.90 (positive subscale) and α= 0.72 (negative subscale).

At time 2, self-administered questionnaires to be completed individually were sent by mail to the couples who agreed to participate. These questionnaires included the same question regarding willingness to donate embryos for research, one item about parental status as well as the self-administered questionnaires for collecting data on anxiety, depression, social support and partner relationship.

Ethics approval was granted by the Ethics Committee for Health of the Centro Hospitalar de S. João on 11 March 2009. All participants formalized their collaboration through a written informed consent form according to the World Medical Association's Declaration of Helsinki.

Statistical analysis

Willingness to donate embryos for research was described according to the psychosocial, demographic and reproductive factors, and the importance attributed to embryo research, stratified by time of evaluation. In order to assess the association between the different factors and willingness to donate embryos for research, at time 2, model 1 was performed. Data was adjusted for the decision at baseline in order to observe if the effect of each variable was independent of willingness to donate at time 1. After, we measured the effect of time on willingness to donate embryos for research (model 2). Generalized Estimation Equation models with exchangeable correlation structure, within couple (model 1) and couple and time (model 2), were performed. The gee model estimates the correlation between the opinion of women and men within a couple. To estimate the Relative Risks (RR) and the corresponding 95% confidence interval (95% CI), a log link function with a Poisson distribution was used. The analyses were conducted using the R Software (2013) and the "gee package", version 4.13-18.

Answers to the open-ended question about the two main reasons to be willing to donate embryos for research were synthesized into categories following *a priori* coding (i.e. categories were established before data analysis), according to those proposed on a recent systematic review regarding the reasons to donate and not to donate embryos for research (22), and following Stemler's protocol for content analysis (23). The first and the last author independently classified the reported reasons and disagreements were resolved by consensus. Reasons to be willing to donate embryos for research were analysed according to the following categories: a wish to contribute to improve health, IVF treatments and research; helping others; positive views about research and the medical system and the perception of such a decision as better than the destruction of embryos. Reasons to be unwilling to donate embryos for research were analysed according to these categories: the perception of risks; lack of information about the research projects using human embryos; conceptualization of embryos in terms of personhood; having a baby is the priority.

Results

Table 1 describes willingness to donate embryos for research according to the participants' psychosocial, demographic and reproductive characteristics, by moment of evaluation. The majority of patients agreed to donate embryos for research (86.5% at time 1 and 73.6% at time 2). However, a significant decrease in couples' willingness to donate embryos for research over time was observed (RR_{time}= 0.85; 95% CI; 0.76-0.95).

More than a fifth of participants changed the opinion regarding embryo donation for research (n= 33/148): 26 changed from donation to non-donation and 7 changed from non-donation to donation. Overall, change happened in 25 couples. Among these couples, change happened in both members of the couple in 8 cases: 3 couples changed from non-donation at time 1 to donation at time 2; 5 couples changed from donation at time 1 to non-donation at time 2. Among the remaining 17 couples, only one member of the couple changed his/her opinion: 7 women and 9 men changed from donation at time 1 to non-donation at time 2; and 1 man changed from non-donation at time 1 to donation at time 2 (data not shown).

A higher education level (adjusted RR (RRadj)= 0.79; 95% CI; 0.64-0.96), considering research on human embryos to be important (vs. very important) (RRadj= 0.59; 95% CI; 0.39-0.85) and practicing a religion less than once a month (vs at least once a month) (RRadj= 0.73; 95% CI; 0.53-1.00) seemed to be associated with higher probability of being unwilling to donate embryos for research at time 2 (table 2). These effects were independent of willingness to donate embryos for research at time 1. No association was found between the psychosocial factors (anxiety, depression, social support and partner relationship) and changing willingness to donate embryos for research (data not shown).

Education level, religious practice and the importance attributed to embryo research showed an interaction with time (table 3). While less educated participants (≤12 years of education) did not have a significant evolution on willingness to donate over time, more educated participants (>12 years of education) appeared to be less frequently willing to donate embryos for research over time ($RR_{interaction}$= 0.77; 95% CI; 0.63-0.95). Moreover, those with a more frequent religious practice did not change willingness to donate embryos over time, but participants whose religious practice occurred less than once a month seemed to be less willing to donate embryos at time 2 ($RR_{interaction}$= 0.75; 95% CI; 0.56-1.00). Finally, those who considered research with human embryos to be very important kept their willingness to donate embryos for research, while those who considered research important seemed to be less frequently willing to donate embryos for research over time ($RR_{interaction}$= 0.70; 95% CI; 0.50-0.98).

Participants who justified willingness to donate embryos for research at time 1 based on reasons such as contributing for scientific progress, human health and improvements in IVF treatments; the desire to help others; or by feelings of “reciprocity” towards science and medicine, more often kept their initial positive attitude towards embryo donation for research at time 2. Those who firstly donated embryos for research considering that option as “better than waste” more frequently changed their opinion towards non-donation.

The majority of participants who were unwilling to donate embryos for research at time 1 due to the conceptualization of embryos as a “child”, a “baby” or a “living being did not change their attitude towards donation over time. Most of those who reported the priority “to have a baby” as a reason not to be willing to donate embryos at time 1 changed to a more favorable opinion towards donation, mainly the participants who had babies or became pregnant in the meantime.

Discussion

This study showed that more than one fifth of the participants changed the opinion about embryo donation for research in a 12-month follow-up, with change mostly occurring from donation at time 1 to non-donation at time 2. Disagreements between partners’ opinions at follow-up were found among 17 couples.

In addition, it identified factors eventually associated with this change towards non-donation: being more educated, practicing a religion less than once a month, considering research with human embryos to be important and firstly considering that donation for research was better than wasting embryos. This study also identified patients who changed from being unwilling to donate, at time 1, to being willing to donate embryos for research at time 2. This type of change was mostly present among couples whose priority at time 1 was to have a baby and who got pregnant in the meanwhile. From the participants who were unwilling to donate embryos for research at time 1, those who performed at least one previous cycle were significantly more willing to donate embryos for research at time 2.

These achievements generate hypothesis to be further studied, in order to contribute to the development of patient-centredness in infertility care at two levels. First, data from this study call attention to the need to launch a debate on what are considered widely acceptable timings to request informed consent. The existence of change in the willingness to donate embryos for research supports the idea of a two/three-stage process to obtain full informed consent, as suggested by other studies (10,11). Moreover, it reinforces the argument that informed consent should be signed only after the infertility treatment is completed, in accordance with the recommendations of the Ethics Committee of the American Society for Reproductive Medicine (3). This study also draws attention to the fact that implementing good quality infertility care guided by patients' characteristics, values, preferences and needs (24) calls for considering the factors and reasons underlying couples' willingness to donate embryos for research over time as a topic to be included in the guidelines for psychosocial care in infertility and medical assisted reproduction.

This longitudinal quantitative study shows an association between willingness to donate embryos for research over time and the education level, religious practice and the importance attributed to human embryo research. A higher level of education is a predictor of support for science and technology (25). However, the influence of education can be moderated by the individual's interest in science and medicine (26). This appears to be also the case with decision-making on embryo donation. A recent systematic review about the factors associated with the donation and non-donation of embryos for research among IVF patients shows that valuing the expected societal benefits of research on human embryos for society, IVF patients and other individuals is associated with being more prone to donate embryos for research (22). The influence of religion should be further explored, taking into account its possible relation with this ethically challenging decision, namely through the couples' conceptualization of embryos (27). It may play a role independent of frequency of attendance and the predominantly Catholic culture in Portugal (15) may influence embryo disposition.

This study provided longitudinal data about willingness to donate embryos for research, while controlling for the effect of willingness to donate at time 1. Being conducted with couples, it allowed the inclusion of variables related with partner relationship, evaluating its association with willingness to donate embryos for research as well as with the role of other psychosocial variables not previously studied, such as anxiety, depression and social support. Although no significant associations were found between willingness to donate embryos for research over time and anxiety, depression, social support and partner relationship, there is a need for more studies in other contexts, and including different measures of these variables, to validate these results. Also, the fact that there is no research project with human embryos being currently developed in Portugal calls attention to the level of informed choice regarding IVF couples willingness to donate embryos for research (28). In fact, ethically robust policies and practices sensitive to patient's information needs are required, including the provision of accurate information on human embryo research (28).

This study is limited by the reduced response rate in the follow-up, though no differences were found regarding the psychosocial, demographic and reproductive characteristics and willingness to donate embryos for research between those who participated and those who did not. The obtained response rate is quite similar to the ones described in other studies focusing on IVF couples decision on embryo disposition with more than one evaluation moment (6,9,10). It has also been reported that the loss of participants is more common in studies aiming to collect data on sensitive topics (29). Notwithstanding, it would be valuable to understand the reasons underlying the non-response at time 2. Another limitation of this study is the fact that data derives from only one public reproductive medicine centre, located in a university hospital. Although this is the biggest reproductive centre in the Northern region of Portugal and our sample includes couples who had already performed at least one cycle in a private centre, this means that data generalizability should be approached with caution.

In conclusion, this study reveals that IVF couple's willingness to donate embryos for research is dynamic, changing one year after patients undergo their last treatment cycle. This study also calls attention to the importance of psychosocial and reproductive factors, and time, in explaining variations in decision-making concerned with embryo donation. Further studies, with more time intervals and larger samples, should be developed. Data on this field is essential to contribute to rethinking timings for obtaining full informed consent and the additional topics that need to be addressed by guidelines for psychosocial care in infertility and medically assisted reproduction, from which decision-making on embryo disposition should not be excluded.

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Legends

Table 1. Willingness to donate embryos for research according to participants' psychosocial, demographic and reproductive characteristics, by moment of evaluation.

Table 2. Crude and adjusted Relative Ratios (RR) for the effect of sociodemographic and reproductive factors on the willingness to donate embryos for research, at time 2.

Table 3. Effect of time on the willingness to donate embryos for research and the respective interactions.

Table 1. Willingness to donate embryos for research according to participants' psychosocial, demographic and reproductive characteristics, by moment of evaluation

	Embryo donation for research			
	Time 1		**Time 2**	
	Yes ***n* (%)**	**No** ***n* (%)**	**Yes** ***n* (%)**	**No** ***n* (%)**
Overall	128 (86.5)	20 (13.5)	109 (73.6)	39 (26.4)
Age (years)				
≤35	73 (88.0)	10 (12.0)	59 (71.1)	24 (28.9)
>35	55 (84.6)	10 (15.4)	50 (76.9)	15 (23.1)
Education level (years)				
≤12	75 (85.2)	13 (14.8)	71 (80.7)	17 (19.3)
>12	53 (88.3)	7 (11.7)	38 (63.6)	22 (36.7)
Country of origin[a]				
Portugal	114 (89.1)	14 (10.9)	95 (74.2)	33 (25.8)
Other	6 (54.5)	5 (45.5)	8 (72.7)	3 (27.3)
Household monthly income[a]				
≤1000	8 (80.0)	2 (20.0)	7 (70.0)	3 (30.0)
>1000	118 (89.4)	14 (10.6)	98 (74.2)	34 (25.8)
Catholic				
Yes	122 (89.1)	15 (10.9)	102 (74.5)	35 (25.5)
No	6 (54.5)	5 (45.5)	7 (63.6)	4 (36.4)
Religious practice				
At least once a month	28 (82.4)	6 (17.6)	19 (55.9)	15 (44.1)
Less than once a month	100 (87.7)	14 (12.3)	91 (79.8)	23 (20.2)
Duration of infertility (years)				
≤3	54 (87.1)	8 (12.9)	40 (64.5)	22 (35.5)
>3	74 (86.0)	12 (14.0)	69 (80.2)	17 (19.8)
Previous cycles (no.) at time 1				
0	48 (80.0)	12 (20.0)	40 (66.7)	20 (33.3)
≥1	80 (90.9)	8 (9.1)	69 (78.4)	19 (21.6)
Cause of infertility				
Female	40 (95.2)	2 (4.8)	30 (71.4)	12 (28.6)
Male	46 (85.2)	8 (14.8)	37 (68.5)	17 (31.5)
Other	42 (80.8)	10 (19.2)	42 (80.8)	10 (19.2)
Parental status at time 1				
No children	116 (86.6)	18 (13.4)	101 (75.4)	33 (24.6)
Children	12 (85.7)	2 (14.3)	8 (57.1)	6 (42.9)
Parental status at time 2[a]				
No children	-	-	56 (74.7)	19 (25.3)
Children	-	-	45 (70.3)	19 (29.7)
Importance of embryo research[a]				
Very important	100 (91.7)	9 (8.3)	18 (16.5)	91 (83.5)
Important	27 (71.1)	11 (28.9)	21 (55.3)	17 (44.7)
	Mean (SD)	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
State anxiety[b]	42.64 (12.25)	45.35 (12.32)	36.43 (9.97)	35.30 (10.91)
Trait anxiety[b]	36.46 (7.53)	37.35 (8.67)	35.98 (9.47)	36.29 (11.03)
Depression[c]	7.73 (4.45)	6.79 (4.33)	6.98 (4.62)	5.49 (4.46)
	Median (P25-P75)	**Median (P25-P75)**	**Median (P25-P75)**	**Median (P25-P75)**
Social support[d]	75.00 (67.00-80.00)	76.50 (63.25-79.00)	72.00 (62.50-78.00)	71.00 (65.00-79.00)
Partner relationship – positive[e]	29.00 (27.00-31.00)	30.00 (29.00-31.00)	29.00 (27.00-31.00)	29.00 (25.00-31.00)
Partner relationship – negative[f]	8.00 (7.00-9.00)	8.00 (6.00-9.00)	9.00 (7.00-9.00)	8.00 (7.00-10.00)

[a]The total does not add 148 due to non-responses; [b]Lower values indicate lower anxiety symptoms (range: 20-80); [c]Lower values indicate fewer depressive symptoms (range: 0-30); [d]Higher values indicate the perception of a better social support (range: 12-84); [e]Higher scores mean that positive relationship dimensions are more present (range: 8-32); [f]Higher scores mean that negative relationship dimensions are more present (range: 4-16).

Table 2. Crude and adjusted Relative Ratios (RR) for the effect of sociodemographic and reproductive factors on the willingness to donate embryos for research, at time 2

	RR – Crude (95% CI)	RR - Adjusted (95% CI)
Age (years)		
≤35	REF	REF
>35	1.11 (0.91-1.36)	1.13 (0.93-1.37)
Education level (years)		
≤12	REF	REF
>12	**0.80 (0.64-1.00)**	**0.79 (0.64-0.96)**
Country of origin		
Portugal	REF	REF
Other	1.11 (0.74-1.65)	1.30 (0.87-1.93)
Catholic		
Yes	REF	REF
No	0.96 (0.64-1.44)	1.15 (0.81-1.63)
Religious practice		
At least once a month	REF	REF
Less than once a month	0.71 (0.50-1.01)	**0.73 (0.53-1.00)**
Duration of infertility (years)		
≤3	REF	REF
>3	1.24 (0.97-1.60)	1.25 (0.98-1.59)
Previous cycles (no.)		
0	REF	REF
≥1	1.18 (0.92-1.51)	1.10 (0.89-1.37)
Cause of infertility		
Female	REF	REF
Male	0.96 (0.70-1.32)	1.02 (0.77-1.36)
Other	1.13 (0.85-1.50)	1.24 (0.95-1.62)
Parental status - time 1		
No children	REF	REF
Children	0.84 (0.51-1.39)	0.85 (0.54-1.32)
Parental status - time 2		
No children	REF	REF
Children	1.16 (0.87-1.56)	-
Importance of embryo research		
Very important	REF	REF
Important	**0.53 (0.35-0.80)**	**0.58 (0.39-0.85)**

Note: All the variables were adjusted for the willingness to donate embryos for research at time 1.

Table 3. Effect of time on the willingness to donate embryos for research and the respective interactions

Willingness to donate	**RR (95% CI)**
Model without interaction	
Time	
1	REF
2	**0.85 (0.76-0.95)**
Model with the interaction for time and education level	
≤12	REF
>12	1.02 (0.94-1.11)
Time	
1	REF
2	0.94 (0.84-1.06)
Time*education level	**0.77 (0.63-0.95)**
Model with the interaction for time and religious practice	
At least once a month	REF
Less than once a month	0.97 (0.82-1.02)
Time	
1	REF
2	0.91 (0.82-1.02)
Time*religious practice	**0.75 (0.56-1.00)**
Model with the interaction for time and importance of embryo research	
Very important	REF
Important	0.81 (0.70-0.94)
Time	
1	REF
2	0.92 (0.82-1.03)
Time*importance of embryo research	**0.70 (0.50-0.98)**

Notes: RR = Relative Ratios; 95% CI = 95% Confidence Intervals.

4.3 Paper V. Patients' views on the embryo storage time limits

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ARTICLE

Patients' views on the embryo storage time limits

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Abstract The establishment of the length of embryo storage has been based on socio-political criteria. There are different regulations, guidelines and health care policies worldwide. This mixed-methods study aimed to assess the opinion of patients about the embryo storage time limit, and the perception of the criteria underlying the establishment of the storage period offered to them. Between August 2011 and December 2012, 534 IVF patients from Portugal participated in a quantitative questionnaire and 34 couples were interviewed. Overall, 38% of participants preferred the duration of 4–5 years, 38% extended it beyond 5 years and 23% indicated 3 years. Having experienced at least one previous cycle was directly associated with agreeing with a duration of storage longer than 5 years, for both women and men. Having children was inversely associated with longer duration of storage, among women. One-third of the 34 interviewed couples stated that their knowledge concerning embryo storage was insufficient. Nevertheless, all the interviewees reported at least one possible reason for the legal establishment of the storage period offered to them, highlighting financial costs and decreased embryo quality. There are misconceptions and gaps in awareness of cryopreservation, which may shape patients' opinions. Accurate information regarding policy on storage of embryos is needed.

KEYWORDS: cryopreservation, embryo disposition, IVF, public policy

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Introduction

Storage of embryos has been in widespread use for over 30 years, after successful achievement of the first pregnancy from frozen embryos in 1983 (Trounson and Mohr, 1983). Cryopreservation offers patients undergoing IVF extra chances to conceive without the need to go through a new stimulation cycle (Capalbo et al., 2011; Silva and Machado, 2011). A recent review demonstrated that frozen embryo transfers reduce the risk of ovarian hyperstimulation syndrome and improve health outcomes, not only in terms of achieving higher pregnancy rates, but also in terms of lower maternal and infant morbidity and mortality (Evans et al., 2014). However, embryo viability may be threatened either in the process of freezing or thawing (Ashrafi et al., 2011; Michelmann and Nayudu, 2006), by cross-contamination (Bielanski, 2012) or by osmotic shock, cryoprotectant toxicity and intracellular ice formation (Saragusty and Arav, 2011), respectively. Despite evidence showing that the storage period does not interfere with the quality of cryopreserved embryos (Marietta, 2011; Riggs et al., 2010), qualitative studies indicate that patients believe that the quality of the embryo diminishes throughout cryopreservation (Provoost et al., 2010, 2011c). Additionally, little is known about the impact of long-term storage on children's and parents' health and well-being (Marietta, 2011).

Storing an increasing number of embryos raises concerns surrounding disputes over ownership or disposition (Lyerly et al., 2011; Provoost et al., 2012), and poses problems and ethical questions to address for clinics (Ethics Committee of the American Society for Reproductive Medicine, 2013; Provoost et al., 2011b). These situations draw attention to the need to establish a storage limit for embryos, which until now has been based more on social and political criteria (Edwards and Beard, 1997; Englert and Revelard, 1997; Fasouliotis and Schenker, 2000; Reproductive Technology Council, 2010; Ron-El, 1997). There are different regulations, guidelines and health care policies among countries on this matter (Bielanski, 2012) which may influence cross-border reproductive care services (Brezina and Zhao, 2012; Deonandan, 2010; Provoost et al., 2011a). Embryo storage limit ranges from a period of 3 years in Portugal, 5 years in Denmark, Egypt or Norway to 10 years in Austria, Australia or Taiwan (Ory et al., 2013). It is possibly longer in some countries, such as the UK, where a maximum storage period of 55 years is provided (The Human Fertilization and Embryology [Statutory Storage Period for Embryos and Gametes] Regulations, 2009), and it is unlimited in Canada and Finland (Ory et al., 2013).

Knowledge about patients' views on embryo storage is necessary for the conceptualization of patient-centred policies and for ethics in clinical practice (Dancet et al., 2011). Although data on how patients' attitudes towards cryopreserved embryos influence embryo disposition is available, which highlights the importance of disseminating accurate information about cryopreservation throughout IVF treatments (Fuscaldo et al., 2007; Lyerly et al., 2004; Provoost et al., 2010), there are, to the best of our knowledge, no studies on patients' views regarding the embryo storage limit. This mixed-methods study contributes to fill this gap by assessing IVF patients' opinions about the storage limit for embryos and exploring their perceptions of the criteria underlying the establishment of the storage period offered to them.

Materials and methods

This mixed-methods, observational and cross-sectional study was designed to be exploratory and hypothesis-generating since little is known about patients' views on embryo storage limit. It comprises a quantitative questionnaire and qualitative interviews with women and men undergoing IVF/intracytoplasmic sperm injection (ICSI) in one reproductive medicine centre in Porto, Portugal. This fertility centre is located in a public university hospital that performs IVF/ICSI homologous cycles. According to Portuguese law, these techniques are only available for heterosexual couples, married or living together for at least 2 years (Silva and Barros, 2012).

Between 17 August 2011 and 16 August 2012, all patients were consecutively and systematically invited to participate in both parts of the study, a total of 226 couples and 103 women. Among the patients invited, 97.8% of couples ($n = 221$) and 89.3% of women ($n = 92$) agreed to participate in the questionnaire, while 94.7% of couples ($n = 214$) and 88.3% of women ($n = 91$) agreed to participate in a qualitative interview. Participants were approached by the team in the hospital, about 15 days after embryo transfer.

Questionnaire: participants and data collection

Among the patients invited, 221 couples and 92 women participated in this part of the study. After exclusion of the participants who did not answer, did not know or presented missing values on the opinion regarding the embryo storage limit, 206 couples and 83 women were included in the quantitative analysis.

Self-reported data on demographic and socio-economic characteristics (age, educational level and household income), reproductive and obstetric history (reasons for using IVF/ICSI, duration of infertility, previous cycles and parental status), having cryopreserved embryos and opinion on embryo storage limit, were collected by two trained female interviewers using a structured questionnaire.

Reasons for using IVF/ICSI were reclassified as female, male or other (mixed, genetic or unknown). Parental status was defined by the existence of offspring, biological or adopted. The opinion question on the embryo storage limit included the following options: ≤ 3 years, 4–5 years and >5 years (sum of the categories 6–7 years, 8–9 years and ≥10 years).

Statistical analysis

Statistical analysis was performed using Stata 11.0 (College Station, TX, 2009), and statistical significance was defined as $P < 0.05$. Opinion about the embryo storage limit according to female and male participants' characteristics is presented as counts and proportions and was compared using the chi-squared test. Adjusted odds ratios (OR) and 95% confidence intervals (95% CI) were estimated by multinomial logistic regression models, stratified by gender, to assess the association between demographic, socio-economic, reproductive and obstetric characteristics of the participants, and the opinion on the embryo storage limit.

Qualitative interviews: participants and data collection

Approximately 3 months after completing the questionnaire a sub-sample of those who agreed to participate in a qualitative interview was contacted by telephone or email, according to their preference, to confirm their availability to collaborate in the study. Between February and November 2012, 56 couples were invited to participate in the interview, and 34 accepted. Participants were purposively sampled to include pregnant and non-pregnant women, and couples willing to donate and not to donate embryos for research. In addition, a heterogeneity sampling was used for maximum variation of views and experiences, until thematic saturation was reached, thus recruitment continued until no new themes emerged from the interview data (Guest, 2006).

Semi-structured interviews took place between March and December 2012. Interview duration ranged from 62 to 111 min, with an average of 81 min. All were taped, transcribed verbatim and checked for accuracy.

The interview guide covered the following issues: views, values and knowledge mobilized to give meaning to the status of embryos; expectations, uncertainties and responsibilities associated with embryo cryopreservation, including the perception of the criteria underlying the establishment of the storage period offered to them; awareness of the processes of evaluation and classification of embryo quality and viability; how couples made their decisions regarding embryo disposition and their views of the consent process; and their understanding and knowledge of embryo research. For the purposes of this paper, data relating to the core theme of embryo storage limit will be discussed by exploring the answers obtained from the following topic question: 'How long should the storage period for embryos last? Why?'

Content analysis

Content analysis of qualitative data was carried out according to the protocol established by Stemler (Stemler, 2001) and was performed using NVivo 10 (QSR International, USA, 2013). Emergent coding was independently conducted by the first and last authors aiming to identify, sentence by sentence, the criteria invoked by the interviewees to justify the storage period offered to them. The categories were then grouped into the following analytical themes: (i) 'scientific and technical reasons', which includes references to embryo quality and viability, women's reproductive age or efficiency of technology; (ii) 'financial reasons', which contains references to financial costs of cryopreservation; (iii) 'policy decisions', comprising answers related with fertility promotion policies; and (iv) 'socio-ethical issues', which encompass arguments such as social representation of the appropriate time between deliveries or for embryo disposition decision, and statements of ethics committees. Disagreements in abstractions were discussed and an almost perfect strength of agreement was achieved. The findings are reported below with verbatim anonymized quotes from interview transcripts translated by the authors.

Ethical approval

Ethical approval was granted by Ethics Committee for Health of the Centro Hospitalar de S. João on 11 March 2009. All participants formalized their collaboration through a written informed consent according to the World Association's Declaration of Helsinki.

Results

Opinion about the embryo storage limit

More than 40% of the women who participated in the questionnaire stated that the embryo storage limit should be between 4 and 5 years, while 41.7% of men responded more than 5 years (Table 1). Both women and men who had experienced at least one previous cycle were more likely to agree with a storage limit above 5 years ($P = 0.001$ and $P = 0.043$, respectively). Women with higher education and monthly household income tended to extend the limit of embryo storage, whereas those who answered that embryos should not be cryopreserved for more than 3 years tended to have a lower educational degree. Also, women with a duration of infertility longer than 36 months, with no children and without cryopreserved embryos were more likely to extend the limit of storage. A length of storage above 5 years was more frequently chosen by men with a duration of infertility over 36 months and those who reported other reasons for using assisted reproduction techniques, apart from female and male causes.

After adjustment, having experienced at least one previous treatment cycle was directly associated with agreeing with a storage limit longer than 5 years, for both women and men (OR = 2.94; 95% CI 1.51–5.71 and OR = 2.44; 95% CI 1.17–5.08, respectively) (Table 2). Women with higher educational degrees more frequently preferred a storage limit above 5 years (OR = 1.90; 95% CI 0.97–3.74). Women with children preferred the shorter storage limit.

Perception of the reasons for limiting embryo storage

One-third of the interviewed couples stated that their knowledge concerning embryo cryopreservation was insufficient, in particular relating to embryo storage limit. Catherine and Andrew's dialogue shows that they did not know about the storage limit, asking questions about the nature of the limit – 'technical' or 'legal':

> Catherine: 'I had no idea that there is a limit for it [embryo storage]. (. . .)'
> Andrew: 'But is there a technical limit? Or a legal limit?'

Nevertheless, all the interviewees reported at least one possible reason for the establishment of the storage period

Table 1 Characteristics of the participants according to the opinion about the embryo storage time limits, by gender ($n = 495$).

	Women				*Men*			
	Total	*≤3 years*	*4-5 years*	*>5 years*	*Total*	*≤3 years*	*4-5 years*	*>5 years*
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Overall	289 (58.4)	66 (22.8)	120 (41.5)	103 (35.6)	206 (41.6)	50 (24.3)	70 (34.0)	86 (41.7)
Age (years)								
≤35	189 (65.4)	43 (65.2)	79 (65.8)	67 (65.0)	111 (53.9)	26 (52.0)	42 (60.0)	43 (50.0)
>35	100 (34.6)	23 (34.8)	41 (34.2)	36 (35.0)	95 (46.1)	24 (48.0)	28 (40.0)	43 (50.0)
Educational level								
≤12 years	172 (59.5)	46 (69.7)	71 (59.2)	55 (53.4)	144 (69.9)	33 (66.0)	52 (74.3)	59 (68.6)
>12 years	117 (40.5)	20 (30.3)	49 (40.8)	48 (46.6)	62 (30.1)	17 (34.0)	18 (25.7)	27 (31.4)
Household income (€/month)								
≤1500	118 (40.8)	32 (48.5)	51 (42.5)	35 (34.0)	83 (40.3)	18 (36.0)	36 (51.4)	29 (33.7)
>1500	171 (59.2)	34 (51.5)	69 (57.5)	68 (66.0)	123 (59.7)	32 (64.0)	34 (48.6)	57 (66.3)
Reasons for using ART								
Female	77 (26.6)	17 (25.8)	33 (27.5)	27 (26.2)	65 (31.6)	16 (32.0)	24 (34.3)	25 (29.1)
Male	95 (32.9)	18 (27.3)	41 (34.2)	36 (35.0)	57 (27.7)	15 (30.0)	22 (31.4)	20 (23.3)
Other	117 (40.5)	31 (47.0)	46 (38.3)	40 (38.8)	84 (40.8)	19 (38.0)	24 (34.3)	41 (47.7)
Duration of infertility (months)								
≤24	54 (18.7)	13 (19.7)	28 (23.3)	13 (12.6)	38 (18.4)	11 (22.0)	13 (18.6)	14 (16.3)
25-36	57 (19.7)	13 (10.8)	23 (19.2)	21 (20.4)	42 (20.4)	11 (22.0)	15 (21.4)	16 (18.6)
>36	178 (61.6)	40 (38.8)	69 (57.5)	69 (67.0)	126 (61.2)	28 (56.0)	42 (60.0)	56 (65.1)
Previous cycles [a]								
0	122 (42.2)	35 (53.0)	58 (48.3)	29 (28.2)	90 (43.7)	27 (54.0)	34 (48.6)	29 (33.7)
≥1	167 (57.8)	31 (47.0)	62 (51.7)	74 (71.8)	116 (56.3)	23 (46.0)	36 (51.4)	57 (66.3)
Parental status								
No children	256 (88.6)	54 (81.8)	109 (90.8)	93 (90.3)	183 (88.8)	42 (84.0)	66 (94.3)	75 (87.2)
Children	33 (11.4)	12 (18.2)	11 (9.2)	10 (9.7)	23 (11.2)	8 (16.0)	4 (5.7)	11 (12.8)
Cryopreserved embryos								
No	169 (58.5)	43 (65.2)	70 (58.3)	56 (54.4)	122 (59.2)	28 (56.0)	39 (55.7)	55 (64.0)
Yes	107 (37.0)	20 (30.3)	43 (35.8)	44 (42.7)	75 (36.4)	19 (38.0)	26 (37.1)	30 (34.9)
Don't know	13 (4.5)	3 (4.5)	7 (5.8)	3 (2.9)	9 (4.4)	3 (6.0)	5 (7.1)	1 (1.2)

ART = assisted reproduction techniques.

[a] $P = 0.001$ for women and $P = 0.043$ for men.

offered to them. The vast majority highlighted financial costs. The expense involved in the maintenance of embryo storage facilities was one of the most frequently reported arguments:

> Betty: 'I think (. . .) is not only [a matter of] facilities but also a question of money, which in Portugal may define a three year period as limit [for embryo storage], because there is no money to extend it.'

Interviewees also perceived the decrease in quality of embryos as a main reason for the storage limit. Harry's narrative, for example, illustrates the misconceptions and fears the patients have regarding the 'degradation' of embryos throughout cryostorage:

> Harry: 'I have the idea that two years would be the period considered reasonable to maintain the quality of a cryopreserved embryo. (. . .) Right or wrong, I believe that from then on degradation [of embryo] could occur.'

The national policy on fertility promotion was mentioned by few participants as a possible reason for the storage limit offered to them. Nielson distinguished national legal frameworks according to the fertility rates, concluding that countries with 'normal' fertility rates tended to shorten the storage limit:

> Nielson: 'Some countries want to raise their fertility rates, while other countries discourage this, as happens in Portugal (. . .) because our fertility rates can be considered normal, can't they?'

Angela invoked the appropriate time frame for making the decision regarding embryo disposition as the criteria for the storage limit offered to the couple:

> Angela: 'I think that [the storage limit] is enough time for a couple to decide [embryo disposition].'

Philippe and Sarah's testimony shows how storage limits may be seen as similar to any process of freezing, in the sense that any 'frozen product' has an 'expiry date', after which it loses quality or might be 'weakened', and, thus, cannot be used:

Table 2 Adjusted odds ratios for the association between socio-demographic characteristics and obstetric history, and opinion about the embryo storage time limits, among women and men undergoing IVF/ICSI ($n = 495$).

	Opinion about the embryo storage time limits [a]			
	Women		*Men*	
	4–5 years	*>5 years*	*4–5 years*	*>5 years*
	Adjusted OR (95% CI) [b]	*Adjusted OR (95% CI)* [b]	*Adjusted OR (95% CI)* [b]	*Adjusted OR (95% CI)* [b]
Age (years)				
≤35	1	1	1	1
>35	1.07 (0.55–2.05)	1.05 (0.53–2.09)	0.82 (0.38–1.80)	1.01 (0.48–2.14)
Educational level				
≤12 years	1	1	1	1
>12 years	1.64 (0.85–3.15)	1.90 (0.97–3.74)	0.70 (0.31–1.60)	0.80 (0.37–1.73)
Previous cycles				
0	1	1	1	1
≥1	1.24 (0.67–2.31)	2.94 (1.51–5.71)	1.43 (0.67–3.05)	2.44 (1.17–5.08)
Parental status				
No children	1	1	1	1
Children	0.40 (0.16–1.00)	0.35 (0.14–0.92)	0.34 (0.09–1.24)	0.69 (0.24–1.95)

95% CI = 95% confidence interval; OR = odds ratio.
[a]Reference class: ≤ 3 years; [b]Adjusted for all the variables in the table.

> Philippe: 'It's almost like buying a frozen product. (. . .)'
> Sarah: 'It has a[n] [expiry] date; it has a[n] [expiry] date.'
> Philippe: '[After some time] you cannot keep it in the fridge, because it deteriorates.'

This 'expiry date' view tended to be used as an argument that sustains the idea that there is an evidence-based limit for embryo storage. Interviewees also talked about other criteria allegedly based on scientific knowledge, such as the 'efficiency of technology' and 'women's reproductive age'. Andrea considered that 'the embryo storage limit should be extended until the end of the woman's reproductive age', while Charles believed that legal frameworks are grounded on evidence assuring that embryos are 'in a good condition':

> Charles: 'To be regulated in the law [embryo storage limit], it should be the period that medicine considers acceptable for maintaining embryos in a good condition.'

Assuming that an embryo in Portugal should be like an embryo wherever, Mathew highlighted how the establishment of different storage limits may reproduce social inequalities between countries:

> Mathew: 'I also think that it [cryopreservation] is related with institutional funds and with its importance for assuring future generations in each country. (. . .) An embryo here [in Portugal] should be like an embryo in Germany (. . .) or wherever. . . They are embryos, [but] there could be differences in funding to keep them and to carry out [embryo] research.'

Aiming to mitigate some of these inequalities, Anthony proposed the publication of transnational legislation establishing a storage limit which includes alternatives for storage fees:

> Anthony: 'I think that this issue [storage limit] should be ruled by a European Code (. . .). If we are talking about [financial] costs, an alternative should be offered to families after [public] funded treatments.'

The flexible stipulation of a storage limit, according to couple's reproductive trajectories (namely the 'appropriate time between deliveries', either because women's bodies need to 'normalize' or because it is the 'ideal gap between siblings'), was also invoked, as the dialogue between Harry and Annabelle illustrates:

> Harry: 'The embryo storage limit is also related with the time that one must give for women's [bodies] to get back to normal, I suppose.'
> Annabelle: '(. . .) even if we want more children, we always want some time [from one baby to another], like three years, for a baby to grow (. . .).'

Discussion

This mixed-methods study reveals several aspects that can be useful in implementing patient-centred policies on embryo storage. It may help in developing patient information and understanding around storage periods and the reasons for limitations, in a context where the views of the patients apply across legal and political boundaries. The qualitative finding that the majority of the interviewed couples believed that financial costs and decreased embryo quality were the main reasons for the establishment of the storage limit draws attention to patients' educational and informational needs. Quantitative data suggest that having experienced at least one previous cycle influence the option for an extended storage limit, while the shortest period was more often preferred by female participants with children. These features support the need of flexibility and sensitivity in enacting guidelines to regulate applications to extend embryo storage, taking into account reproductive trajectories and life conditions of patients. Knowledge about patients' perspectives and misconceptions helps in providing timely, consensual and relevant information to IVF patients. In this sense, these results challenge current clinical practices worldwide, including countries who currently have storage limits for embryos in storage.

In Portugal, the cost of embryo cryopreservation in private reproductive medicine centres is about €600 per 3 years, and there is no information about financial costs in the case of public storage facilities. In fact, financial costs of a storage facility depend upon the size of the facility and the number of embryos stored (ECASRM, 2013). Additionally, evidence shows that duration of embryo storage does not interfere with the quality of cryopreserved embryos (Marietta, 2011; Riggs et al., 2010), but patients' perception about diminishing embryo quality throughout storage has also been reported previously, grounded on similar metaphors associated with food freezing processes (Provoost et al., 2010, 2011c). What this study adds to the literature is the idea that the 'expiry date' view might be triggered by storage limits, in the sense that patients could construct a parallelism between storage limit and embryos' expiry date, calling attention to the policy and organisational aspects that influence patients' experiences (van Empel et al., 2011).

In a context where participants reported lack of knowledge about cryopreservation and embryo storage, the election of evidence-based criteria for justifying the establishment of the storage limit (namely financial costs and decreased embryo quality) might reveal the search for certainty and objectivity by which patients reinforce trust and hope in medicine and technology (Silva and Machado, 2010; Thompson, 2005). Furthermore, using food metaphors and financial reasoning might represent a way by which patients understand and make sense of highly specialized technologies and medical jargon conveyed by empirical knowledge and country's economic situation (Silva and Machado, 2011; Webster, 2007).

In this scenario, patient-related factors tended to be undervalued as criteria for limiting storage. This may explain the low number of interviewees mentioning the appropriate time frame for making the final decision regarding embryo disposition as a criteria for the storage limit. Conversely, the extension of the storage limit was prompted by personal experiences of previous cycles and not having children. These findings suggest that the opinion on the embryo storage limit might be influenced by the perception of the probability of using cryopreserved embryos for their own treatment – would-be parents could see reasons to hold on to their cryopreserved embryos as long as possible for maximizing the probability of achieving a pregnancy (Thompson, 2005), while women with children could feel more pressure to use cryopreserved embryos in a shorter period of time, in line with the belief in the existence of an age range for women to conceive (Campbell, 2011).

A limitation of this study is that data were collected at a single reproductive centre, which limits the generalizability of the results. Furthermore, answer options regarding the opinion about storage limit may have an effect on the answers of the participants, in the sense that they may presume that it is more usual to have longer storage periods and that 3 years is about a set minimum.

In conclusion, this mixed-methods study shows how reproductive trajectories influence IVF patients' appraisal of embryo storage time limits and indicates misconceptions and gaps in awareness of cryopreservation among IVF patients. Findings suggest that the patients ought to be informed of the facts regarding cryopreservation of embryos, grounded on a practical ethical reasoning about embryo storage. This study also contributes to informing decision-making by all the participants in the health care system, including policy-makers. Although it does not aim to significantly influence current storage limits, this study calls attention to a critical discussion around the need of developing practice guidelines on embryo storage limits. However, future research is needed on patients' preferences regarding timing and volume of information about embryo storage.

The provision of accurate information regarding policy on embryo storage and the development of consensual guidelines regarding storage limit may contribute to raise awareness about cryopreservation, both among patients and among health professionals. Taking into account the consistent tendency to follow the international recommendations in the field of reproductive medicine, the development of guidelines could attenuate differences between countries (Brezina and Zhao, 2012), by standardizing the initial storage period and providing clear guidance on when it is lawful to extend storage beyond such a period (RTC, 2010).

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4.4 Paper VI. [Consenting on embryo cryopreservation: perception of infertile couples]

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(submitted)

Consentir na criopreservação de embriões: perceção de casais inférteis[16]

Consenting on embryo cryopreservation: perception of infertile couples

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RESUMO

A criopreservação de embriões é precedida da assinatura de um consentimento informado por parte dos usuários de técnicas de procriação medicamente assistida. Este estudo analisou as perceções de casais inférteis quanto aos fatores que contextualizam o consentimento livre e esclarecido na criopreservação de embriões. Explorou-se a provisão de cuidados de saúde

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centrados no paciente, com implicações para a prática clínica e a regulação. Realizaram-se, em 2012, 34 entrevistas semiestruturadas a casais envolvidos em técnicas de Procriação Medicamente Assistida numa Unidade Pública de Medicina da Reprodução, em Portugal. Procedeu-se à análise dos dados segundo os princípios da teoria fundamentada. Os resultados revelaram uma perceção do consentimento como um formalismo, que é assinado num momento inadequado e muitas vezes aplicado por profissionais não qualificados. Emergiram as seguintes necessidades: provisão atempada de informações detalhadas, rigorosas e coerentes sobre os custos e a duração máxima da criopreservação e o destino efetivo dos embriões; reforço da privacidade física; dispor de tempo para refletir sobre o destino dos embriões e sobre a divulgação da identidade dos beneficiários. As condições em que o consentimento foi aplicado parecem ameaçar três elementos fundamentais do consentimento - informação, voluntarismo e ponderação. Importa desenvolver orientações profissionais e éticas que assegurem a prestação de um consentimento assente em práticas de aconselhamento e de prestação de informação adequadas às necessidades e expectativas dos pacientes.

Palavras-chave - Consentimento esclarecido; criopreservação; assistência centrada no paciente; fertilização in vitro; destinação do embrião.

Consenting on embryo cryopreservation: perception of infertile couples

ABSTRACT

Cryopreservation of embryos is preceded by the signature of an informed consent by those benefiting from assisted reproductive technologies. This study analysed infertile couples' perceptions of the factors that contextualize informed consent regarding embryo cryopreservation. Patient-centred care delivery was also explored with implications for clinical practice and regulation. In 2012, 34 semi-structured interviews were conducted with couples involved in Assisted Reproductive Technologies at a public reproductive medicine unit, in Portugal. Data were analysed according to the principles of grounded theory. Data gathered revealed a perception of informed consent as a mere formality, signed in inadequate period of time and often administered by non-qualified professionals. The following needs have been identified: timely provision of detailed, accurate and intelligible information about the costs of cryopreservation, embryo storage limit and effective embryo disposition; reinforcement of physical privacy; availability of time to reflect about embryo disposition and the disclosure of users' identities. The conditions under which the informed consent was administered appear to threaten three fundamental elements of the consent - information, voluntarism and reflection. It is necessary to develop professional and ethical guidelines that can ensure the implementation of a consent process characterized by practices of advice and information adapted to patients' needs and expectations.

Keywords - Informed consent; cryopreservation; patient-centered care; fertilization in vitro.

INTRODUÇÃO

A criopreservação de embriões é, na maioria dos países, acompanhada da assinatura de um consentimento informado por parte de usuários de técnicas de procriação medicamente assistida (Ory e col., 2013; Leite e Henriques, 2014). Em Portugal, o modelo de consentimento informado é aprovado e revisto pelo Conselho Nacional de Procriação Medicamente Assistida (Portugal, 2013), e inclui informações sobre os benefícios, riscos e limitações da criopreservação de embriões e menciona a duração máxima da criopreservação (3 anos) e os destinos dos embriões criopreservados - utilização pelo casal, doação para outros casais inférteis, doação para investigação e destruição.

O consentimento é assinado pelo/a médico/a e pelo casal beneficiário, sendo passível de revogação por qualquer um dos membros do casal. O casal formaliza a decisão quanto ao destino dos *seus* embriões criopreservados e à divulgação da *sua identidade* nas situações legalmente previstas ao escrever "sim" ou "não" à frente das seguintes afirmações: "consentimos no uso dos nossos embriões para doação a outros casais inférteis"; "consentimos no uso dos nossos embriões em projetos de investigação científica"; e "autorizamos que o Conselho Nacional de Procriação Medicamente Assistida divulgue as nossas identidades, nos casos excecionalmente previstos no n.º 3 do artigo 15.º da Lei n.º 32/2006 de 26 de julho", ou seja, quando as pessoas nascidas em consequência da dádiva de embriões solicitem informações que lhes digam respeito para averiguar eventual existência de impedimento legal a projetado casamento.

A decisão sobre o destino dos embriões criopreservados é particularmente desafiadora e difícil (Fasoulitis e Schenker, 1996; Autor, 2014a). A possibilidade de doar embriões pode ser enquadrada numa ética de solidariedade e altruísmo e perspetivada como um contributo para o desenvolvimento científico ou para a saúde e bem-estar de casais inférteis ou da população em geral (Autor, 2013b; Autor, 2014a). No entanto, esta hipótese também pode originar preocupações quanto à proteção e estatuto do embrião criopreservados (Fasoulitis e Schenker, 1996; Schuster e col., 2003; Haimes e col., 2008), discordância entre os membros do casal (Hammarberg e Tinney, 2006) e, ainda, questionar a confiança depositada nos médicos ou investigadores, por escassez de informação e/ou de aconselhamento (Autor, 2013a; Lyerly e col, 2006). Neste contexto, há casais que tentam prolongar a criopreservação, adiando a decisão em relação ao destino dos embriões criopreservados (de Lacey, 2005) enquanto sentem inconstância nas suas preferências (Lyerly e col., 2006).

A obtenção do consentimento pode consubstanciar uma estratégia de humanização, democratização, prestação de contas e transparência de processos e decisões (O'Neill, 2004) ao favorecer o diálogo entre profissionais de saúde e beneficiários (WHO, 2007) e ao proporcionar uma reflexão sobre a criopreservação por parte de todos os atores envolvidos. No entanto, pode também reduzir-se a uma formalidade ou revelar-se uma prática problemática ao transferir responsabilidades complexas para o casal (Menegon, 2004; Autor, 2008, 2014b). Globalmente, importa que o consentimento seja informado/esclarecido (o que exige a compreensão do respetivo conteúdo e das informações orais e escritas facultadas adicionalmente), voluntário (sem qualquer tipo de pressão ou coação, externa ou interna, na tomada de decisão) e ponderado (precedido de tempo para refletir), elementos especialmente relevantes quando o processo de decisão passa pela procura de consenso entre os elementos do casal (Entidade Reguladora da Saúde, 2009; Consumers Health Forum of Australia, 2013).

Assegurar a qualidade das práticas que envolvem a prestação do consentimento para a criopreservação de embriões afigura-se, assim, como um elemento central na provisão de cuidados centrados no paciente, ou seja, cuidados respeitadores e responsivos às necessidades, valores e preferências dos casais (Institute of Medicine, 2001; Fortes, 2004). Para esse efeito, importa conhecer as perspetivas dos beneficiários quanto aos fatores organizacionais (por exemplo, provisão de informação, competência, coordenação e integração dos profissionais de saúde, conforto físico e acessibilidade) e humanos (entre outros, atitude e relação com os profissionais de saúde, comunicação, envolvimento dos pacientes, privacidade e suporte emocional) que contextualizam o consentimento (Mourad e col., 2010; Dancet e col., 2012). Este conhecimento é relevante considerando a ausência de orientações e de guias de prática clínica, em Portugal, com indicações sobre as circunstâncias em que o consentimento deve ser entregue, explicado e assinado (Leite e col., 2014).

No entanto, a escassa literatura sobre as visões dos usuários em torno da criopreservação de embriões tem descurado a análise do consentimento informado, focalizando a atenção nas perceções sobre a segurança dos procedimentos envolvidos na criopreservação e repercussões na viabilidade e qualidade dos embriões e na eficácia dos tratamentos (Bankowsky e col., 2005; Provoost e col., 2010), nas opiniões sobre a duração máxima da criopreservação (Autor, 2015), e nos fatores que influenciam o processo de decisão quanto ao destino dos embriões criopreservados (Autor, 2014a).

Neste artigo, a análise das perceções de casais inférteis sobre o consentimento informado para a criopreservação de embriões servirá de mote para refletir sobre reconfigurações na prática clínica e respetiva regulação, enquadradas na provisão de cuidados de saúde centrados no paciente.

MÉTODOS

Entre 17 de agosto de 2011 e 16 de agosto de 2012, todas as mulheres e homens que recorreram a Fertilização *In Vitro* ou Injeção Intracitoplasmática de Espermatozoides numa Unidade Pública de Medicina da Reprodução, em Portugal, foram convidados a participar num estudo sobre as decisões dos casais em torno do destino dos embriões, aprovado pela Comissão de Ética para a Saúde do Centro Hospitalar de S. João, EPE. Aplicou-se um questionário no dia em que realizaram o exame para confirmar uma eventual gravidez e, nessa altura, solicitou-se autorização para estabelecer um contato posterior, após 3/4 meses, no sentido de serem entrevistados.

Com base nos participantes que aceitaram ser contatados para agendar uma entrevista, constituiu-se uma amostra intencional, considerando a inclusão de casais com diferentes decisões em relação à doação de embriões para investigação científica (aceitação versus recusa) e com estatutos parentais diferenciados (gravidez versus não gravidez). Entre fevereiro e novembro de 2012 convidaram-se 56 casais para participar numa entrevista semiestruturada, 22 dos quais recusaram (13 não mencionaram o motivo, 4 alegaram falta de disponibilidade, 3 referiram obstáculos emocionais, 1 invocou doença e 1 casal reportou estar separado). Foram assim realizadas 34 entrevistas em casal, conduzidas pela mesma entrevistadora. As características dos entrevistados encontram-se descritas na Tabela 1.

Todos os casais formalizaram a sua colaboração através da assinatura de um consentimento informado, de acordo com a Declaração de Helsínquia da Associação Médica Mundial, em situação de copresença física. As entrevistas, com uma duração média de 81 minutos (mínimo-máximo: 62-111 minutos), aconteceram nas instalações das instituições de acolhimento do projeto (n=16), em casa (n=17) ou no local de trabalho dos participantes (n=1), entre março e dezembro de 2012. Todas as entrevistas foram gravadas com autorização dos participantes e integralmente transcritas, sendo a qualidade das transcrições verificada pela equipa de investigação.

Neste artigo analisam-se as respostas às seguintes questões: Vocês assinaram um consentimento onde declararam a vossa decisão sobre o destino dos embriões. Podem falar-me um pouco desse momento? Como reagiram? O que sentiram? Alguém vos informou ou aconselhou nesse processo? De que forma?

As respostas obtidas foram sistematicamente comparadas, sintetizadas e codificadas por temas e por categorias, de acordo com os princípios da teoria fundamentada (Clarke, 2005; Charmaz, 2006). A análise de conteúdo e a interpretação dos resultados basearam-se numa abordagem qualitativa (Mayring, 2004), explorando a provisão de cuidados de saúde centrados no paciente (Mourad e col., 2010; Dancet e col., 2012) através da dissecação de um conjunto selecionado de extratos ilustrativos das perceções dos casais entrevistados em torno do consentimento informado na criopreservação de embriões. Os dados foram analisados por dois investigadores independentes e todas as dúvidas foram resolvidas por discussão conjunta até se obter consenso. Utilizou-se o NVivo 10 nesta análise.

RESULTADOS

No discurso dos entrevistados prevaleceu a perceção do consentimento como um formalismo, diluído em memórias associadas a outras fases do tratamento. Destacou-se a inadequação do momento em que o consentimento é assinado (após a transferência de embriões, quando imperavam outras preocupações associadas ao sucesso do tratamento) e a escolha de profissionais não qualificados para o entregar. Os casais realçaram a necessidade de investir nos seguintes aspetos: provisão atempada de informações detalhadas, rigorosas e coerentes sobre os custos e a duração máxima da criopreservação e os destinos dos embriões criopreservados; reforço da privacidade física; e dispor de tempo para refletir sobre as suas decisões quanto ao destino dos embriões criopreservados e à divulgação da identidade do casal. Estas condições parecem ameaçar elementos fundamentais do consentimento – informação, voluntarismo e ponderação, como se mostrará de seguida.

Um formalismo (sem) sentido

A perceção de que o consentimento constituiu um instrumento formal, diluído num conjunto de memórias associadas a outras fases do tratamento, foi dominante nas narrativas dos entrevistados. Estes utilizaram frequentemente expressões como *"papéis"*, *"papelada"*, *"folhinha"*, *"questionário"* e *"documentos"* para se referirem ao consentimento, situando de forma difusa a sua assinatura entre "*os momentos vários em que lá vamos [ao centro de PMA]*" [E34]. Anabela, por exemplo, perspetivou o consentimento como "*mais um formulário*", enquadrando a sua opinião na falta de informação detalhada sobre o mesmo e no tempo que esperou para ser atendida:

> Anabela - *Não houve uma informação detalhada e (...) as pessoas estão ali (...) três horas à espera. (...) Salvo as pessoas que estejam mais sensibilizadas e que até tenham algum*

> *conhecimento de causa, [as outras preenchem o consentimento como] mais um formulário.* [E6]

Um dos fatores que, na perspetiva dos entrevistados, contribui para a concetualização do consentimento como uma formalidade é a inadequação do momento em que é assinado. A grande maioria mencionou ter assinado o consentimento *"à toa"*, *"em cima do joelho"* ou *"à pressa"*, após a transferência de embriões, num contexto de relativa sonolência e desgaste – "*uma altura em que eu estava ainda (…) meia abananada"* [E5] – e onde imperavam outras preocupações, como assegurar a maximização da probabilidade de confirmar uma gravidez. Os relatos seguintes alertam para a necessidade de considerar um eventual estado de dissonância cognitiva e/ou afetiva dos casais na definição do momento adequado para assinar o consentimento sobre a criopreservação de embriões (Lyerly e col., 2006), ao evidenciar como o foco no sucesso do tratamento (Kato e Sleebom-Faulkner, 2011) não favorece a reflexão nem a decisão autónoma sobre questões que não visem diretamente o alcance da gravidez:

> Rita – *Ali foi uma pressão: assinem, leiam, assinem! E uma pessoa está tão focada na gravidez, quer um bebé…* [E29]

> Mónica - *Foi uma época um bocadinho complicada para mim, porque eu tinha tanta coisa na cabeça que, realmente, quando [os profissionais de saúde] me diziam para assinar [um documento] eu era quase de cruz.*
> Nilton - *Sim, é verdade!* [E33]

> Maurício - *Agora, que as coisas já estão bem encaminhadas [gravidez confirmada], acho que temos outra disponibilidade para pensar sobre o assunto e, com clareza, dizer o que é que queríamos e o que é que gostávamos em função daquilo que sabemos ou que nos informaram.* [E1]

Também a escolha de profissionais não qualificados para aplicar o consentimento sustentou a perceção de que este se reduz a um instrumento formal. De acordo com as situações relatadas pelos entrevistados, tal tarefa coube maioritariamente à rececionista e muito raramente a biólogos. A maioria dos casais enquadrou a delegação da entrega do consentimento a um profissional menos qualificado na falta de tempo dos médicos para o fazer, devido ao excesso de trabalho. O recurso a este argumento coexistiu com o reconhecimento da ausência de competências dos profissionais administrativos para proporcionar informações adicionais e esclarecer dúvidas específicas sobre o conteúdo do consentimento, como ilustra o diálogo estabelecido entre Nicolau e Rosana.

> Nicolau - *A rececionista não foi, de maneira nenhuma, mal-educada nem nada dessas coisas, nem [nos] despachou. (...) Só que ela tem sempre muita coisa que fazer e pode haver certas coisas que...*
> Rosana - *Há coisas que ela não consegue explicar, não é?* [E22]

> Os entrevistados alertaram para a necessidade de contemplar tais competências na definição do perfil adequado dos profissionais responsáveis pela aplicação do consentimento sobre a criopreservação dos embriões, independentemente do grupo profissional que o faça - médicos, enfermeiros, biólogos ou embriologistas.

Experiências em torno da provisão de informação

Os entrevistados salientaram a necessidade de investir na provisão atempada de informações detalhadas sobre os seguintes tópicos: 1) quem suporta os custos financeiros da criopreservação e qual o montante; 2) vantagens e desvantagens associadas aos diferentes destinos dos embriões criopreservados, nomeadamente informações adicionais sobre os projetos de investigação que os pretendem utilizar e sobre a eventual ocorrência de nascimentos de embriões doados a outros casais, assim como sobre o destino efetivo dos embriões doados; 3) possibilidade de poder alterar as decisões formalizadas no consentimento. Mariana, por exemplo, preocupou-se em esclarecer o destino efetivo dos embriões após os três anos de criopreservação, indagando a possibilidade de os embriões serem eliminados:

> Mariana - *A minha pergunta foi: E passados os dois anos ou três (...) deitam fora? (...) Eles [profissionais de saúde] disseram: "Não, (...) se quiser continuar com eles criopreservados é só informar-nos que continuam".* [E1]

A informação oral sobre a oportunidade de prolongar a criopreservação para além do período legalmente previsto, com base na simples solicitação do casal, contraria a seguinte informação escrita no consentimento: "Compreendemos que, de acordo com a legislação em vigor, os embriões serão conservados por um período máximo de três anos e que, decorrido este prazo, se os embriões não tiverem sido por nós utilizados ou não lhes tiver sido dada outra utilização por nós consentida, serão descongelados e eliminados". Também o relato de Antónia evidencia contradições no esclarecimento de dúvidas acerca dos custos financeiros a suportar pelo casal no âmbito da criopreservação:

> Antónia – *Lemos [o consentimento] (…) e perguntamos: "Olhe, ninguém nos informou sobre os custos. Qual é o custo?". E a senhora [rececionista] também não sabia dizer e foi perguntar ao enfermeiro, que depois acabou por dar a resposta errada. Nós depois tivemos que pagar (…), mas a resposta que nos deram era que não haveria custos. (…) Não sei se foi 20€, se foi 25€ por cada um [embrião] que pagamos. Mas eu depois ainda perguntei: "Mas isso é por ano ou é para os três anos?". Não me sabiam dizer!* [E13]

Estas situações alertam para a importância de assegurar o rigor e a qualidade das informações prestadas pelos profissionais de saúde, elementos que facilitam a obtenção de consenso entre os elementos do casal e têm sido associados à diminuição dos seus níveis de ansiedade (de Lacey, 2005; Hammarberg e Tinney, 2006; Lyerly e col., 2006). O investimento no reforço da informação é especialmente relevante num contexto em que a maioria dos entrevistados realçou a confiança depositada em todos os profissionais que os acompanharam, ainda que elegessem os médicos e, esporadicamente, os biólogos como os profissionais melhor posicionados para prestar informações no âmbito da criopreservação de embriões - *"um médico ou um biólogo; quem esteja dentro [do assunto]"* [E27].

A otimização da prestação de um consentimento na criopreservação de embriões passa, na perspetiva dos entrevistados, por um processo bidirecional contínuo e dinâmico que envolve, simultaneamente, os casais e os profissionais de saúde, em particular o/a médico/a responsável pela assinatura do consentimento. O acesso a informação pormenorizada e coerente surgiu frequentemente articulado com a necessidade de promover a disponibilidade, solicitude e sensibilidade dos profissionais de saúde para: explicar conteúdos de natureza técnica e científica; esclarecer dúvidas; e proporcionar aconselhamento no processo de decisão em torno das questões colocadas no consentimento (o destino dos embriões criopreservados e a divulgação da *identidade* dos beneficiários nos casos legalmente previstos). Estes processos ocorrerão, sobretudo, nos casos em que os casais sentem tais necessidades e deverão respeitar a liberdade das escolhas individuais:

> Maurício – *Eu, agora que volto atrás, digo que o facto de não ser apoiada a decisão permite total anonimato e liberdade aos decisores, que somos nós, de tomarem a sua decisão.* [E1]

Os entrevistados também salientaram a sua própria responsabilidade na procura ativa de informações, questionando diretamente os profissionais de saúde e/ou utilizando diversas fontes de informação (por exemplo, internet e folhetos disponíveis em diversos centros), existindo casais que se culpabilizaram por não o ter feito:

> Mariana - *Se nós tivéssemos mais perguntas para fazer, de certeza que [os profissionais de saúde] nos respondiam.* [E1]

> Rita – *Realmente, nós somos uns inconscientes! Devíamos ter pensado nisto [decisão em torno do destino dos embriões criopreservados], devíamos ter falado disto em casa os dois.*
> Joel - *Bom, eu não senti que fossemos inconscientes. A questão é que teria sido, de facto, melhor.* [E29]

O papel da privacidade física

Nas narrativas dos entrevistados emergiu a necessidade de reforçar a privacidade física no contexto da assinatura do consentimento, ou seja, o direito do casal a estar sozinho ou num espaço físico com acessibilidade limitada. A maioria dos casais manifestou "*incómodo*" ou "*desconforto*" por ter assinado o consentimento na sala de espera, diante de outras pessoas e muitas vezes a pé e junto ao balcão de atendimento, local de passagem obrigatória para aceder à porta que dá acesso aos consultórios, gabinetes e salas de exame:

> António – *[Assinei o consentimento] Na receção, depois de ter estado quatro horas à espera e já com outras pessoas ali que estavam a ser chamadas, e têm que passar por aquele guiché para entrar. Portanto, sem condições, com poucas, com fracas condições para poder tomar uma decisão.* [E6]

> Rita - *Estarmos ali os dois ao balcão a falar [sobre a nossa decisão]... Imagine o que é uma sala cheia de gente: aquela sala é pequenina, uma pessoa tem os bancos, mas está sempre cheia, e estamos ali a assinar! (...) Pois, eu nem me senti bem!* [E29]

Alguns casais referiram ter saído da sala de espera para ler e assinar o consentimento num espaço público imediatamente contíguo, junto aos elevadores, com o objetivo de conquistar alguma reserva e recolhimento enquanto dialogavam sobre as decisões a tomar: "*Fomos para junto dos elevadores para falarmos um bocadinho, mas foi uma coisa de dois minutos*" [Carina, E9].

Avaliação do tempo para refletir

De acordo com os entrevistados, o tempo proporcionado para refletir sobre o consentimento informado foi escasso, considerando a sensibilidade das questões colocadas sobre o destino dos embriões criopreservados e sobre a divulgação da *identidade* dos beneficiários, assim como as eventuais dificuldades associadas à procura de consenso entre os membros do casal.

> Rita - *Não foi uma coisa [assinar o consentimento] muito refletida.*
> Joel - *Sim. Com essa formalidade de termos objetivamente ali aquilo apresentado, falarmos sobre qual é que ia ser a nossa decisão e de pensarmos um bocadinho o que é que queríamos.* [E29]

> Horácio - *Eu acho que é um tema muito delicado e não pode ser pensado nem decidido logo na hora. Devíamos ter mais tempo (...) e tirarmos as nossas dúvidas.* [E23]

Alguns entrevistados sugeriram abrir a possibilidade de levar o consentimento para casa antes de o assinarem, maximizando desta forma o tempo de reflexão, discussão e eventual aconselhamento. Marco, por exemplo, mencionou não ter sentido dificuldades em assinar o consentimento de imediato, mas reconheceu que outras pessoas poderão necessitar de mais tempo para solidificar o processo de tomada de decisão:

> Marco – *[Para nós] Foi fácil [decidir de imediato], mas acho que há pessoas que ficam ali a pensar se estão a tomar uma decisão correta ou não. Se calhar, queriam voltar para casa, aconselhar-se com alguém. (...) Aí as decisões seriam mais sólidas, mais seguras.* [E3]

De fato, a maioria dos entrevistados recordou a "surpresa" que sentiu perante a solicitação da assinatura do consentimento informado - *"foi uma surpresa, porque nunca achei que fosse ali naquela hora, sem apoio, sem mais explicações. Por isso é que, entretanto, acho que já mudei de ideias"* [E32]. As suas narrativas expressam, frequentemente, a necessidade de dispor de mais tempo para refletir, o que possibilitaria uma melhor gestão das emoções e mais certeza e segurança nas decisões a tomar:

> Daniela - *Mas quando se começa a ler [o consentimento]...*
> Manuel - *Assusta!*

Daniela - *Assusta, assusta! (…) É a decisão sobre aquilo que pode ser, na minha conceção, um ser humano.* [E7]

Américo - *Fui eu que preenchi o papel [consentimento] e assinalei sim nos dois casos [doação para outros casais e doação para investigação científica]. Mas depois, quando dei [à companheira] para assinar, ela leu melhor (…) e começou a chorar. (…) E depois foi pedir o papel novamente [à secretária] para alterar a decisão para [não doar a outros] casais.* [E30]

Leandro - *Eu realmente não pensei muito naquele momento. (…)*
Sónia - *Eu já tinha posto a cruz e ele só assinou. (…)*
Leandro – *Concordei [com a decisão dela]. Fui um bocado empurrado a concordar, mas concordei.* [E4]

DISCUSSÃO

As perceções de casais inférteis sobre as práticas que envolvem o consentimento informado para a criopreservação de embriões convidam a refletir sobre três dimensões centrais na provisão de cuidados de saúde centrados no paciente, com implicações para a prática clínica e para a regulação.

Primeiro, este estudo salienta a necessidade de investir no desenvolvimento de orientações que regulem o momento da entrega e da assinatura do consentimento informado, assim como o perfil dos profissionais de saúde com competência e qualificações para acompanhar os casais nessas situações. Ainda que alguns países prevejam a assinatura do consentimento antes do primeiro tratamento (Pennings, 2007), durante o tratamento (Bjuresten e Hovatta, 2003) ou após a conclusão do tratamento (Ethics Commitee of American Society for Reproductive Medicine, 2014), não existe estandardização deste procedimento entre países e a legislação é omissa a este respeito em Portugal. Na definição desses momentos importa considerar as trajetórias reprodutivas dos casais e proporcionar-lhes tempo para refletir sobre as decisões a tomar. Estudos prévios mostram que o nascimento de um filho pode estar associado a uma mudança na decisão em relação ao destino dos embriões criopreservados (Hammarberg e Tinney, 2006), tendo em conta que a perspetiva dos casais sobre o simbolismo atribuído ao embrião criopreservado muda, tornando-se este uma "criança virtual" (de Lacey, 2005). Neste sentido, o pedido do consentimento numa altura em que, para os casais, ainda não é evidente se os seus embriões serão "excedentários", pode pôr em causa a tomada de decisão consciente e a qualidade do consentimento informado (Scott e col., 2012).

Os resultados obtidos evidenciam, ainda, a necessidade de providenciar atempadamente informações precisas e detalhadas sobre a duração máxima da criopreservação de embriões e os custos financeiros envolvidos nesse procedimento (Autor, 2015) e sobre os destinos efetivos dos embriões criopreservados. Importa clarificar, em especial, os objetivos dos projetos de investigação que pretendem usar os embriões (Autor, 2013b), como recomendado pelo Ethics Commitee of American Society for Reproductive Medicine (2014), num contexto em que a falta de informação é um dos aspetos apontados pelos pacientes como tendo tido mais influência na sua decisão (Lyerly e col., 2006; Silvestre, 2015). Além disso, a informação sobre as circunstâncias em que pode ocorrer o descongelamento e a destruição dos embriões, bem como sobre os moldes em que os casais podem alterar as decisões formalizadas no consentimento informado, constitui um direito fundamental dos pacientes (Nelson, 2008). Importa assegurar a coerência, rigor e qualidade das informações prestadas pelos profissionais de saúde e treinar as respetivas competências comunicacionais para esclarecer dúvidas e aconselhar os casais que manifestem tais necessidades, potenciando uma comunicação efetiva entre médicos e pacientes (Institute of Medicine, 2001) e a prestação de cuidados centrados no paciente.

Este estudo mostra, por último, a importância de reforçar a privacidade física no âmbito da assinatura do consentimento. A existência de espaços físicos confortáveis e com acesso limitado é fundamental, para que cada casal possa expressar as suas sensações e as respetivas decisões de forma autónoma e privada.

A prática de um consentimento informado que potencie o fornecimento de cuidados de saúde centrados no paciente requer que os vários aspetos que contextualizam este procedimento sejam atendidos. Considerando que a comunicação é particularmente difícil em situações que podem causar *distress*, moral e emocional (de Lacey, 2005; Hammarberg e Tinney, 2006), e que a tomada de decisão dos casais no contexto do consentimento informado na criopreservação de embriões é fortemente influenciada pelo aconselhamento (Shehab e col., 2008), importa disponibilizar o apoio de profissionais qualificados e devidamente treinados (Doyal, 2001) e também de grupos de pares (Soini, 2006) para minimizar a ocorrência de conflitos decisionais. Os profissionais são responsáveis por explicar conteúdos baseados na evidência e devem respeitar a liberdade de decisão dos casais (Soini, 2006), convidando-os a expressar as suas preferências e necessidades (Charles e col., 1999). Já o apoio dos pares contribui para atenuar sentimentos de isolamento e estigmatização e potencia o acesso a informações enraizadas em experiências comuns (Shehab e col., 2008).

Constituindo um importante contributo para a reflexão sobre reconfigurações na prática clínica e regulação em torno do consentimento informado para a criopreservação de embriões, importa ter em conta que estes resultados são válidos no contexto em que foram recolhidos, devendo ser analisados como um estudo de caso que procurou compreender e explorar a perspetiva de casais inférteis sobre este tema.

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Tabela 1. Características dos casais entrevistados

Entrevista*	Pseudónimos	Idades	Níveis de escolaridade	Doação de embriões para investigação	Gravidez
E1	Mariana e Maurício	28 e 27	Licenciada e 12º ano	Sim	Sim
E2	Andreia e Amaro	36 e 28	Licenciados	Sim	Sim
E3	Sandra e Marco	34 e 40	Bacharel e 12º ano	Sim	Sim
E4	Sónia e Leandro	37 e 41	Bacharel e Licenciado	Sim	Não
E5	Joana e Jorge	38 e 36	Licenciados	Sim	Não
E6	Anabela e António	35 e 43	Mestre e Licenciado	Não	Não
E7	Daniela e Manuel	35 e 38	Licenciados	Sim	Sim
E8	Isabel e Tomás	33 e 33	12º ano e 9º ano	Sim	Sim
E9	Carina e Rui	38 e 39	Licenciada e 12º ano	Sim	Não
E10	Carolina e Miguel	25 e 30	12º ano e 9º ano	Sim	Não
E11	Camila e Augusto	26 e 29	6º ano	Sim	Não
E12	Sara e Fausto	37 e 35	6º ano	Não	Não
E13	Antónia e Adalberto	31 e 36	Licenciada e 12º ano	Sim	Sim
E14	Ana Maria e Roberto	27 e 34	6º ano	Sim	Não
E15	Sílvia e Mariano	40 e 37	9º ano e 12º ano	Sim	Não
E16	Dalila e Jaime	34 e 36	Licenciada e Bacharel	Sim	Não
E17	Aurélia e André	36 e 36	Licenciados	Sim	Não
E18	Maria e Cláudio	33 e 32	9º ano e 6º ano	Sim	Sim
E19	Madalena e Josué	38 e 35	Licenciados	Não	Não
E20	Cátia e Justino	39 e 42	Mestre e Licenciado	Sim	Sim
E21	Manuela e Gustavo	38 e 38	Licenciados	Sim	Não
E22	Rosana e Nicolau	30 e 40	Licenciados	Sim	Sim
E23	Soraia e Horácio	37 e 40	6º ano e 12º ano	Não	Sim
E24	Idalina e Nelson	38 e 35	12º ano	Não	Sim
E25	Ana e Moisés	26 e 33	6º ano	Sim	Não
E26	Ivone e Rogério	34 e 33	Licenciados	Não	Sim
E27	Patrícia e Ernesto	37 e 41	Licenciada e Mestre	Não	Não
E28	Tanya e Denys	38 e 34	12º ano	Não	Sim
E29	Rita e Joel	33 e 33	Licenciados	Sim	Sim
E30	Célia e Américo	35 e 46	12º ano	Sim	Sim
E31	Laurinda e Hernâni	39 e 39	12º ano e Licenciado	Não	Sim
E32	Erica e Daniel	34 e 35	Licenciados	Sim	Não
E33	Mónica e Nilton	36 e 38	Licenciada e Mestre	Sim	Não
E34	Eugénia e Marcos	32 e 34	Licenciada e Mestre	Sim	Não

* Os participantes são descritos na tabela pela ordem de realização das entrevistas; no código alfanumérico atribuído a cada casal, os algarismos correspondem ao número de ordem da entrevista.

5. Conclusion

This observational and longitudinal mixed-methods study provided evidence to sustain the development of patient-centredness on embryo donation for research, with implications for clinical practice and regulation. Looking at patient-centred care through the lens of public health, this study contributes to advance knowledge in three key areas: openness and information about research with human embryos; suitability of research projects using cryopreserved embryos; policies and guidelines regarding informed consent process on embryo donation for research. Its innovativeness also relies on the assessment of psychosocial variables as anxiety, depression and quality of partner relationship, and the inclusion of both members of the couple, considering that these methodological features are absent from most of the studies on embryo disposition[219]. The high response rate at baseline, with the use of a consecutive and systematic recruitment strategy in the largest centre in the Northern region of Portugal, emerged as an additional strength of this project.

Regarding openness about research with human embryos, achievements from this study revealed a high receptivity to scientific and technological progress and trust in medical institutions and their professionals. More than three quarters of patients in this study were willing to donate embryos for research. This positive attitude was reinforced by the fact that none of the couples considered research on human embryos to be of slight importance. The high perceived value of embryo research is consistent with the changing social context in which legislation in several countries allows and regulates the use of human embryos in research[88], and with previous studies conducted in Portugal that show how would-be-parents' assessment of the benefits and risks of ART are imbued with hope, trust, altruism, and receptivity to progress[6, 114, 257].

This framework is translated into the reasons invoked by IVF patients for donating embryos to research in this study, which are aligned with findings from other studies: willingness to contribute to scientific progress in general[83, 258], to the development of IVF treatments in particular[216, 259] and to the improvement of human health[83, 260]. These motives may also reflect the perception that minimal risks are associated with human embryo research, as mentioned by Priest et al.[140], which contrasts with the report of fears by patients who were unwilling to donate embryos for research. Consistent with results obtained in previous studies[83, 216, 258, 261], participants who were willing to donate embryos for research in our study also revealed a "sense of gratitude" to science and an "altruistic desire" to help others. These feelings, predominantly reciprocity, solidarity and altruism, might be simultaneously driven by external constraints and internal motivations, which have been previously described in the donation of biological material in Portugal[257, 262]. This socioethical framework redefines human embryos as a gift for the common good in the context of embryo disposition[263, 264], pointing to the conceptualization of embryo donation for research as an act of individual responsibility to contribute to the collective good and wellbeing[265].

IVF patients' willingness to donate embryos for research should also be framed in the context of the setting where this study occurred - a public reproductive medicine centre located in a university hospital. The prevalence of embryo donation for research may be overestimated in this setting, as trust in the medical professionals, one of the key issues influencing the process of decision-making[103], tended to increase when research is conducted in universities compared with the private sector[142, 266]. It calls attention to the need of promoting an in-depth analysis of the relational and interactional aspects involved in the informed consent[103], including the understanding of changes over time due to fluctuations on the information exchanged with the health professionals, to variations on the social network or in the reproductive trajectories of patients, among other factors[80, 87].

Data provided by this study was also important to deconstruct ideas regarding the influence of being Catholic on embryo donation for research. The majority of the Catholics were willing to donate embryos for research. Religious beliefs and the understanding of scientific facts and methods are not mutually exclusive and can coexist, with religion as a 'perceptual filter' that moderates the ways in which scientific knowledge affects attitudes[267]. In fact, the perspective associated with Catholic religion that human life begins at conception[268] was also observed in participants' reasons for not donating embryos for research. However, at the same time, this perception may also increase the value of an embryo, which can justify their use in research, as presented by de Lacey et al.[269] and Provoost et al.[260]. Patients' preference is justified by the idea that remaining embryos can "be used in a way"[259]. Thus, the meanings of the moral status of embryos seem to be varied and context-dependent, not fixed entities[82, 270], with couples using a complex and dynamic system of embryo classification[271]. IVF patients perceive embryos simultaneously as epistemic or medical objects for research and clinical practices, and ontological objects for reproduction[219], with an instrumental value[260] that should not be wasted[217, 272].

Regarding information, this study showed that patients felt fears about what could happen to the embryos, and frequently mentioned having lack of information about research on human embryos, namely regarding the specific projects for which they were donating their embryos, their aims and expected results. Lack of information about embryo research was reported as one of the main reasons to be unwilling to donate embryos for research. Moreover, gaps and misconceptions in awareness of cryopreservation were found, and our findings suggest that the patients ought to be more fully informed of the facts regarding cryopreservation of embryos, namely the storage periods and the reasons for limitations in these periods. Attention should be drawn to the responsibility of scientific and medical institutions, health professionals and researchers regarding the provision of accurate and timely information that is attentive, responsive, and tailored to patients' needs, in a context where a decrease in patients' willingness to donate embryos for research over time was observed in our sample. Investment in information provision is especially important taking into account that the majority of patients highlighted feelings of trust and reciprocity towards the health professionals who contacted with them, as well confidence in the medical and scientific institutions.

In what concerns the contributions of this study to sustain stakeholders' decisions regarding the suitability of research projects using cryopreserved embryos, our data showed that patients who were willing to donate embryos for research expected benefits for science, for IVF patients through the improvement of ART treatments, and for health in general. In this circumstance, the responsibility of health professionals and researchers to communicate realistic expectations concerning the results from research on human embryos is highlighted. Additionally, references to risks and limitations of research with human embryos should be central topics in the ethics of clinical research, care and doctor-patient relationships centred on patients.

This study also adds important achievements to the development of policies and guidelines regarding informed consent practices and decision-making process on embryo donation for research. First, by claiming for the inclusion of the subject of decision-making on embryo disposition in general guidelines for psychosocial care in infertility and ART, taking into account this is an ethically sensitive issue. Second, by showing that psychosocial care in the field of embryo donation decision-making should be sensitive to women's, men's and couples' age, religion, trait anxiety, and conceptualization of cryopreserved embryos.

While several studies have found no association between the age of patients and their donation decision[80, 85], this study showed that younger women were significantly more willing to donate embryos for research. This may be related to the perception that younger women have more opportunities to become pregnant owing to age-related decline in fertility[273], and therefore it would not be necessary to transfer the cryopreserved embryos.

Regarding the psychosocial factors, an anxious state had a significant influence on men's opinion in this study. Higher levels of trait anxiety were found among men who were unwilling to donate embryos for research, which can be associated with the fact that individuals with high anxiety levels are more likely to avoid perceived threats, especially future events[274], in a context where donation of embryos for research can be perceived as a threat. This perception occurs mainly when participants report a lack of information about research projects, as previously found[83, 216, 258], or when they have fears about what could happen to their embryos[83, 260]. Additionally, those who were unwilling to donate may feel they did not accomplish the desirable action within a context mostly receptive to scientific and technological progress[264], which can generate higher levels of anxiety. Although no association between donation decision and depression and quality of partner relationship was found in this study, further studies should be conducted to validate these results.

This study also contributes to inform socioethical debates about the establishment of storage periods and the reasons for limitations in these periods. Quantitative data on patients' views on the embryo storage time limits showed that having experienced at least one previous cycle influenced the option for an extended storage limit, while the shortest period was more often preferred by female participants with children. These findings suggest that the opinion on the embryo storage limit might be influenced by the perception of the probability of using cryopreserved embryos for their own treatment – would be parents could see reasons to hold on to their cryopreserved embryos as long as possible for maximizing the probability of achieving a pregnancy[275], while women with children could feel more pressure to use cryopreserved embryos in a in a shorter period of time, in line with the belief in the existence of an age range for women to conceive[276]. These features support the need of flexibility and sensitivity in enacting guidelines to regulate applications to extend embryo storage, taking into account reproductive trajectories and life conditions of patients.

Additionally, while evidence shows that duration of embryo storage does not interfere with the quality of cryopreserved embryos[277, 278], patients believed that embryo quality diminishes throughout storage, as previously described, grounded on similar metaphors associated with food freezing processes[217, 279]. What this study adds to the literature is the idea that the 'expiry date' view might be triggered by storage limits, in the sense that patients could construct a parallelism between storage limit and embryos' expiry date, calling attention to the policy and organisational aspects that influence shorter period of time, in line with the belief in the existence of an age range for women to patients' experiences[207]. In a context where participants reported lack of knowledge about cryopreservation and embryo storage, the election of evidence-based criteria for justifying the establishment of the storage limit (namely financial costs and decreased embryo quality) might reveal the search for certainty and objectivity by which patients reinforce trust and hope in medicine and technology[6, 275]. Furthermore, using food metaphors and financial reasoning might represent a way by which patients understand and make sense of highly specialized technologies and medical jargon conveyed by empirical knowledge and country's economic situation[49, 280]. The provision of accurate information regarding policy on embryo storage and the development of consensual guidelines regarding storage limit may contribute to raise awareness about cryopreservation, both among patients and among health professionals.

Our data consistently points to the need to improve clinical practices surrounding informed consent in order to make them more patient-centred. Patients reported the need of timely provision of detailed and intelligible information about the costs and duration of cryopreservation and embryo disposition, considering that information about the circumstances under which thawing and destruction of embryos may occur, and the ways in which couples can change their formalized decisions on the informed consent, is a fundamental right of patients[281]. This study also highlighted the importance of reinforcing physical privacy and having more time to reflect about embryo donation for research. The fact that, in some cases, couples' willingness to donate embryos for research changed one year after undergoing their last treatment cycle calls for a renewed discussion around the idea of a two/three-stage process to obtain full informed consent, as previously suggested[80, 87].

These achievements may help to inform debates on the credence and robustness of informed consent given by couples and on the circumstances under which the informed consent should be delivered, explained and signed, including the establishment of storage periods and the reasons for limitations in these periods, in a context where the views of the patients apply across legal and political boundaries. Moreover, it sustains the argument that informed consent should be signed only after the infertility treatment is completed, in accordance with the recommendations of the Ethics Committee of the American Society for Reproductive Medicine[95].

The challenges identified throughout this thesis were raised by the conceptualization of patient-centredness on infertility and ART through the lens of public health, and call for a renewed debate on embryo donation for research. This approach goes beyond the current assessment of patients' individual experiences and level of satisfaction with care delivery[193, 195], while comprising the analysis of real circumstances under which decisions on embryo disposition are being made, including psychosocial and reproductive factors and structural drivers[282], as norms and values within society, global and national economic and sociolegal policy, processes of governance at the global, national, and local level, as well as the health care system characteristics.

With the purpose of enriching patient-centredness in embryo donation for research, further work needs to be developed around the following issues. First, the meanings attributed by IVF couples to the possibility of visualizing their cryopreserved embryos and how these meanings influence decision-making on embryo donation for research. Second, the opinion of IVF patients about what should happen when there is no agreement between partners concerning embryo disposition. Third, the factors and reasons associated with IVF patients' willingness to donate embryos for other infertile couples, evaluating how this can influence a hierarchisation of the possible options regarding embryo disposition. Fourth, the development of comparative studies including public and private fertility centres, as well as different cultural settings.

Additionally, considering that the implementation of patient-centredness includes the involvement of clinic staff, their perspectives and experiences also need to be addressed, in order to acquire an integrated view about the human and system factors that influence patient-centred care. The opinions and experiences of health professionals are essential to understand how different forms of organisation, more or less based on the new public management principles, might undermine healthcare professionals' engagement with patient-centred principles.

This future work would be relevant for the definition of patient-centred policies and regulations on decision-making on embryo donation for research, as well as for ethics in clinical practice. It would also allow the comparison of the real-world decisions among different cultural, economic and political contexts that influence decision-making in embryo disposition.

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Appendices

APPENDIX 1. Study Information Sheet

Quais serão os benefícios da minha participação?

Será participante de um estudo inovador no nosso país que procura compreender as experiências e opiniões dos casais que têm que decidir o destino dos seus embriões, contribuindo para definir políticas que visem melhorar as práticas ao nível do acompanhamento destes processos de decisão. A sua participação também permitirá conhecer as opiniões destes casais quanto à investigação científica em embriões.

Sou obrigado a participar?

Não. Caso decida não participar, esta decisão não terá qualquer influência em nenhum dos serviços de que usufrui. Mesmo depois de aceitar, poderá, em qualquer altura e sem justificação, desistir.

Como será usada a investigação?

Os resultados deste estudo serão divulgados junto de várias pessoas, incluindo os profissionais que trabalham nestas áreas e aqueles que podem tomar decisões em relação à melhoria dos serviços prestados, nomeadamente políticos, médicos e os membros do Conselho Nacional de Procriação Medicamente Assistida.

Obrigado por ter lido este folheto!

A sua participação será muito valiosa.

A aplicação do questionário apenas prosseguirá depois de colocadas todas as questões pelo participante e após assinatura do consentimento informado.

Ser-lhe-á dado este folheto informativo e uma cópia do consentimento informado.

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Universidade do Minho
Instituto de Ciências Sociais

Estudo sobre saúde, governação e responsabilidade na investigação em embriões: as decisões dos casais em torno do destino dos embriões

Folha de informação sobre o estudo

Bom dia!

Está a ser desenvolvido um estudo com casais envolvidos em tratamentos de fertilização in vitro (FIV) e injeção intracitoplasmática de espermatozoides (ICSI), sobre as suas decisões em relação aos destinos dos embriões in vitro.
Gostaríamos de contar com a sua participação.

Antes de decidir se quer participar, é importante que saiba mais acerca deste estudo e do que lhe é pedido se aceitar participar.

Por favor leia atentamente este folheto informativo e coloque todas as perguntas que achar necessário.

Obrigado pelo tempo concedido à leitura desta informação!

Por que queremos falar consigo?

A finalidade deste estudo é conhecer as experiências e opiniões dos casais quanto aos destinos dos seus embriões. Em Portugal, este é o primeiro estudo nesta área.

Serão convidados a participar neste estudo os casais que recorrem a fertilização in vitro (FIV) ou injeção intracitoplasmática de espermatozóides (ICSI) no Hospital de São João.

Entre outros aspectos, a informação recolhida será útil para:

- A saúde, na tentativa de melhorar a eficácia e a qualidade do acompanhamento disponibilizado aos casais;

- A justiça, em situações de desacordo quanto ao destino dos embriões congelados;

- A ciência, para compreender as perspetivas dos casais sobre a investigação científica em embriões.

Quem é responsável pelo estudo?

O estudo é financiado pela **Fundação para a Ciência e a Tecnologia** e está a ser executado por investigadores da Universidade do Porto (Faculdade de Medicina e Instituto de Saúde Pública) e da Universidade do Minho (Instituto de Ciências Sociais).

O que é que este estudo envolve?

Gostaríamos que respondesse a um questionário, que será maioritariamente aplicado por uma investigadora. Uma parte será preenchida por si, no final.

No total, terá uma duração máxima de 30 minutos. Será inquirida/o sobre a sua decisão em torno do destino dos embriões e sobre a sua opinião quanto à investigação científica em embriões humanos.

Durante a aplicação do questionário, pode colocar todas as dúvidas e questões que deseje.

Como participante não terá que falar sobre assuntos que prefira não abordar.

A pesquisa é confidencial?

Sim. Toda a informação que partilhar connosco será vista somente pelos membros da equipa de investigação.

A informação será armazenada de forma segura. Isto significa que, sempre que se utilizar alguma informação mencionada no questionário, nunca será usado o seu verdadeiro nome.

APPENDIX 2. Informed Consent

CRIOPRESERVAÇÃO DE EMBRIÕES

Consentimento Informado

No decurso de um ciclo de tratamento de Fertilização *In Vitro* (FIV) ou de Microinjeção Intracitoplasmática de Espermatozoides (ICSI) existe a possibilidade de se obterem mais embriões do que aqueles que são necessários para realizar a transferência para o útero, já que o número de ovócitos fecundados e o número de embriões obtidos podem ser diferentes dos previstos, mesmo tendo em conta todos os fatores clínicos que podem influenciar estes processos (por exemplo, idade da mulher, duração da infertilidade, fatores de infertilidade, qualidade dos ovócitos). Nestas condições, os embriões excedentários (não utilizados) podem ser criopreservados (conservados através do frio) e, se possível e desejado, usados posteriormente.

Do mesmo modo, em certas situações clínicas, como um risco excessivo de síndroma de hiperestimulação ovárica, pode ser aconselhável adiar a transferência e proceder à congelação da totalidade dos embriões viáveis obtidos.

A congelação dos embriões pode permitir fazer transferências para o útero, sem necessidade de uma nova estimulação dos ovários. No entanto, a existência de embriões excedentários será considerado um efeito não desejado e não um objetivo deliberadamente procurado.

Alguns pontos fundamentais merecem ser salientados:

- Alguns ou mesmo a totalidade dos embriões excedentários podem não apresentar as características necessárias para serem criopreservados.
- Alguns ou a totalidade dos embriões podem não sobreviver ao processo de criopreservação e descongelação.
- A transferência de embriões descongelados não garante a obtenção de gravidez.
- A utilização de embriões humanos criopreservados não revelou até agora um risco superior de anomalias fetais, mas não é possível garantir a absoluta segurança da técnica.
- As gestações resultantes desta técnica estão sujeitas a complicações como quaisquer outras, incluindo a implantação do embrião fora do útero, como por exemplo numa trompa.
- Os embriões criopreservados devem ser utilizados pelo casal em novo processo de transferência embrionária no prazo máximo de três anos. De acordo com a lei em vigor, decorrido este prazo, os embriões podem ser doados a outro casal e/ou utilizados na investigação científica e/ou descongelados (o que significará a sua eliminação).
- As crianças nascidas com recurso a embriões doados podem obter informação sobre eventual existência de grau de parentesco, mantendo-se a confidencialidade acerca da identidade dos dadores, exceto se estes expressamente o permitirem (n.º 3 do artigo 15.º da Lei n.º 32/2006, de 26 de julho).
- Acidentes imprevistos, como incêndios ou outro tipo de calamidades, podem, apesar dos cuidados de segurança adotados, levar à perda ou destruição dos embriões criopreservados.

CONSENTIMENTO

Nós, abaixo assinados, declaramos que:

- Lemos e compreendemos este documento, tal como as informações verbais e escritas que nos foram fornecidas, incluindo a informação sobre os custos inerentes à criopreservação dos embriões.
- Foram esclarecidas as dúvidas e respondidas as perguntas por nós colocadas.
- Reconhecemos que este texto não pode descrever de forma exaustiva a totalidade das situações que possam vir a ter lugar no futuro.
- Compreendemos que, de acordo com a legislação em vigor, os embriões serão conservados por um período máximo de três anos e que, decorrido este prazo, se os embriões não tiverem sido por nós utilizados ou não lhes tiver sido dada outra utilização por nós consentida, serão descongelados e eliminados.

  Se os embriões não tiverem sido por nós utilizados (escrever **Sim** ou **Não** em cada uma das opções seguintes):

  - Consentimos no uso dos nossos embriões para doação a outros casais inférteis ☐
  - Consentimos no uso dos nossos embriões em projetos de investigação científica ☐
- Compreendemos que, independentemente do número de ciclos terapêuticos, este consentimento é válido e eficaz até ser revogado por qualquer um dos membros do casal.
- Compreendemos e aceitamos as condições, riscos e limitações da criopreservação de embriões.
- Fomos informados que os dados referentes ao(s) tratamento(s) efetuado(s) e seus resultados terão obrigatoriamente que ser registados e conservados durante 30 anos e que esses dados poderão, em regime de completo anonimato, ser utilizados em trabalhos científicos para apresentação pública e/ou publicação.

Por isso, esclarecidos e de livre vontade, assumimos as obrigações decorrentes da celebração do presente acordo e damos o nosso consentimento para a eventual criopreservação de embriões resultantes do ciclo terapêutico de FIV ou ICSI.

Mais declaramos que (escrever **Sim** ou **Não**):

No caso de doação a outros casais inférteis, autorizamos que o CNPMA divulgue as nossas identidades, nos casos previstos no n.º 3 do artigo 15.º da Lei n.º 32/2006 de 26 de julho. ☐

NOME ______________________________

ASSINATURA ______________________________

N.º ID CIVIL/PASSAPORTE ______________________________

NOME ______________________________

ASSINATURA ______________________________

N.º ID CIVIL/PASSAPORTE ______________________________

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