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Revista de cercetare și intervenție socială

ISSN: 1583-3410 (print), ISSN: 1584-5397 (electronic)

Selected by coverage in Social Sciences Citation Index, ISI databases

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Revista de cercetare și intervenție socială, 2015, vol. 51, pp. 90-102

The online version of this article can be found at:

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Published by:

Expert Projects Publishing House



On behalf of:

„Alexandru Ioan Cuza” University,

Department of Sociology and Social Work

and

Holt Romania Foundation

REVISTA DE CERCETARE SI INTERVENTIE SOCIALA

is indexed by ISI Thomson Reuters - Social Sciences Citation Index

(Sociology and Social Work Domains)



Social Issues and Medical Challenges in Optimising Access and Outcome of Assisted Reproductive Technology Procedures

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Abstract

Assisted Reproductive Technology techniques (ART) have been raising psychological controversies since the beginning, from contesting the procedure itself to challenging the various situations and ways in which ART could be performed. For many of those issues the verdict is mainly influenced by cultural, religious and political differences amongst countries. It is unlikely to reach a consensus on these matters in the near future. At the same time, there are several ethical challenges concerning the individual medical management of the very heterogeneous population of patients referred to *in vitro* fertilization (IVF)/ART which could be easier brought to a common point of view of the specialists involved in ART. Practically, about one in 5-6 child-seeking couples confronts primary or secondary fertility issues. Comparing the level of secondary infertility (frequently reproductive ageing and gynecological disorders related) in Romania (and Eastern European countries) versus high income countries we might associate the important difference observed with the socio-economic and medical access differences between those groups of countries. Our study analyzed the social issues regarding optimal access to ART and the medical and ethical challenges involved in providing optimal individualized ART treatments to infertile patients /couples.

Keywords: Assisted Reproductive Technology, socio-economic factors, individualized protocols, *in vitro* fertilization, reproductive medicine.

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Introduction

There are more than three decades since the first in vitro conceived child was born, in 1978. Since then, assisted reproductive technology (ART) has achieved enormous progress. Along with the technical and scientific progress, medical, ethical and social concerns regarding ART have been raised, from contesting the procedure itself (Zegers-Hochschild, 2013) to questioning various situations and ways in which ART should or should not be performed. In the world in which we live today, it is common for women to postpone childbearing well into their fourth or fifth decade. New family types have also emerged (CDC, 2010). Advanced fertility diagnosis and treatment technologies continue to develop in accordance with these new social realities. ART represents nowadays a widespread medical procedure, but access is still suboptimal in terms of populational categories which should benefit of this modern medical approach, and also in terms of providing access to what is considered quality, evidence-based, medical care (Ferraretti, 2013).

Access to ART procedures has variable limitations in different countries, mostly due to economic, political, cultural and religious differences. There are many aspects that can generate controversies, but for a large amount of them – even if they are of great importance and actuality (third-party donors, surrogacy, single parent, gay couples, etc.) – their medical and social impact involves a significant geographical and political-cultural-religious variability that would lead us to a broad sociological and cultural-religious debate which will not provide us anytime soon with definitive and universal verdicts (De Wert, 2014; Chatzini Nikolaou, 2010).

There is an important emerging trend in ART onto tailoring the therapeutic protocols to the individual, given the important patient heterogeneity and the fact that etiopathogenic mechanisms of infertility are far from complete acknowledgment but rapidly evolving. Consequently, consecutive emergence of new potential therapeutic methods and a tendency to apply them before has been proven to be effective and harmless, under the more or less recognized - but obvious - competition pressure, in terms of success rates. ART is a medical field in which, in many ways, the “expert opinion” approach prevails to the detriment of the “evidence-based”. To a certain point this is justified by the fact that an “one size fits all” approach is excluded due to significant heterogeneity of the infertile patients/couples; It is also a very difficult task to design large randomized trials to prove the benefits and no harms of a certain strategy because of the same patient heterogeneity, the ethical limitations in designing such studies, and of the pressure of time and results; in many situations the financial limitations are also of significant importance (Fishel, 2013). The major issues related to the individualization of ART management that also have a pronounced socio-economic impact are: the decision “to treat or not to treat”, the use of fertility preservation techniques,

decreasing the ART related morbidity and providing widespread access to quality medical care, once taken the decision to refer to such procedures.

There is a certain zone of the ART domain where improved management might be easier to achieve, in order to provide better access to medical care to a larger population in need for this kind of procedures. In this context it is necessary to highlight a series of psychosocial aspects which impact ART access. In the same time, some key medical guidelines required in the direct ART specialist-patient relationship for customizing the medical care should be pointed, most of them universally accepted in theory, but “suffering” in the implementation, largely due to objective difficulties in the standardization of therapeutic behavior. These principles must take into account the fundamental right to medical care, the best interests of the resulted children and the medical fundamental principle “primum non nocere”. It is important to reach a common standpoint concerning the best decisions at least in terms of the direct physician-patient relationship. Optimum medical care influences the results and the cost-efficiency of ART procedures, an important issue, especially when public health system support for these techniques is brought into question.

The Analysis of the factors affecting access to ART procedures

The study highlights the importance of factors influencing optimal access to ART procedures. We analyzed the impact of social and economic status, education level, prohibitive costs and religious beliefs that influence individual access to optimal treatment (ART) for patients/couples presenting infertility.

Research methodology

The study included 350 cases of patients that had received counselling for infertility issues at Ominiclinic Fertility Center Iasi in two years (2011 – 2012) and had indication for in vitro fertilization (IVF) procedures. Only 255 of those patients effectively accomplished IVF procedures. Consequently, two groups of patients were formed: a group of patients with medical indication for IVF that followed the recommended management (lot control, n=255) and a second group of patients (lot study, n=95) that discontinued the treatment for various reasons.

Statistical analysis

Data were analyzed using SPSS V.21 - SPSS Inc, Chicago, IL. The results of the univariate analysis were reported as mean \pm standard deviation for continuous variables and median with interquartile ranges for variables with significant outliers. Total count and percent were reported for categorical variables. Chi-square test was performed for categorical variables and Mann–Whitney test or

Student's t test performed for continuous variables. Associations of selected variables with the outcomes were assessed with Chi-square tests, Fisher exact tests, logistic regression models, and proportional odds models. Risk ratios for different outcome variables were estimated using multivariate logistic regression analysis. Those independent factors which showed statistical significance in a univariate analysis were entered into multivariate analysis. P-values of ≤ 0.05 were considered statistically significant.

Results

A study of factors that influenced the patients' decision to undergo IVF procedures was conducted comparing the two previously defined groups. Characteristics of the patients from all the study groups are presented in table I. The mean age of the patients in the study groups was 33.55 years old \pm 3.64SD. The study included patients between 26 and 40 years old, 50% of the women being under the age of 33.

Table 1. *Characteristics data of women*

Characteristics of the participants	lot study † n = 95	lot control † n= 255	p-value‡ (95%CI)
Age (years)	34.6 \pm 3.84	32.5 \pm 4.61	p=0.281 (NS)
Economic status (average income)	68 (71.6%)	83 (32.5%)	p=0.0173 (SS)
Education (high school)	78 (82.1%)	55 (21.6%)	p=0.0068 (SS)
Rural environment (rural)	80 (84.2%)	45 (17.6%)	p=0.0039 (SS)
Prohibitive costs (patient's perception)	88 (92.6%)	56 (22%)	p=0.0128 (SS)
Strict religious and moral beliefs against IVF prior to counselling	71 (74.7%)	24 (9.4%)	p=0.0025 (SS)

† Values were expressed as number (%) mean \pm SD, or percent at%; NS, not significant; SS statistically significant
‡ Student's t-test, ANOVA, Kruskal-Wallis; Chi-square test or Fisher's exact test.

Univariate analysis of the factors influencing the decision to undergo IVF showed significant differences between the economic status of patients ($p = 0.017$), education level ($p = 0.0068$), residence ($p = 0.0039$), the perception regarding the cost of the procedure as too expensive ($p = 0.0128$). There were also significant differences in terms of religious beliefs ($p = 0.0025$).

To identify predictors of access to ART procedures, multivariate analysis was performed based on logistic regression. In the analysis, independent variables (covariates) were considered the characteristics that had presented significant differences between the two study groups in the previous univariate analysis. Multivariate analysis has allowed a model to define significant predictors affecting

access to ART procedures. Logistic regression provides a useful mean for modelling dependence of a variable dichotomous response to one or more explanatory variables called “predictors” that can be categorical or continuous. The risk is mathematically modelled as a collection of equations as predictor variables. Modelling can have a single step in which all covariates are included at the same time or may be carried out stepwise by gradually including a number of predictors or gradually excluding some.

The “ENTER” method in which all predictors were included in a single step had been applied; Hosmer-Lemeshow test results ($\chi^2 = 9.641$, $df = 6$, $p = 0.482$, 95% CI) indicates that the model is correct. Nagelkerke R^2 value was 0.761, suggesting that the model is very useful in predicting the contribution of explanatory variables in the prediction is statistically significant and the effect size is large.

Table 2. The coefficients calculated and Wald test in logistic regression

	β	S.E.	Wald	Sig. p-value	Exp(β) Odds ratio	95% CI for EXP(β)	
						Lower	Upper
Age (years)	5.156	0.249	1.331	0.0874	1.516	0.336	9.098
Economic status (average income)	5.887	0.865	9.457	0.0015	6.884	4.821	9.677
Education (high school)	2.361	0.071	6.804	0.0031	3.633	1.537	5.609
Rural environment (rural)	0.874	1.035	3.987	0.0185	1.847	1.614	7.972
Prohibitive costs (patient's perception)	2.574	1.049	8.221	0.0257	4.681	1.854	6.387
Strict religious and moral beliefs against IVF prior to counselling	1.571	1.022	5.317	0.0000	2.455	1.253	5.052
<i>CI – confidence interval, SE - standard error, Exp(B) - the odds ratio associated with each predictor</i>							

The result of logistic regression demonstrated that the most important factor influencing patient decision to attend the ART procedure was the economic status (OR = 6.88, 95% CI: 4.82-9.67) followed by the perception of the patient about the prohibitive costs (OR = 4.68, 95% CI: 1.85-6.38) and educational level (OR = 3.63, 95% CI: 1537-5609). The results showed a moderate influence exerted by religious convictions and area of residence. The study revealed that the age of the patient has no significant influence on the decision to undergo the IVF procedure.

Infertility represents a social and public health issue, considering dramatic decrease of natality and overall population. United Nations and World Health Organization (WHO) data reveal a global alarming trend of population ageing, doubled by an increased prevalence of infertility in modern, occidental countries. Romania makes no exception, this trend being even more abrupt due to a lack in counterbalancing policies and suboptimal medical approach to infertility issues.

WHO data estimating the prevalence of primary infertility in child-seeking women aged 20-44 years report values of in high income occidental countries of 1.8% [CI95%: 1.3% - 2.6%] in high income occidental countries, for Central / Eastern Europe countries the estimated prevalence being of about 2.3% [CI95% 1.6%-3.4%] – estimation for the year 2010.

When it comes to secondary infertility, numbers are more spectacular, with an estimated prevalence of 8.1% [CI95% 5.6%-11.3%] in high income countries and 17.9% [CI95% 13.6%-23.9%] in Central/Eastern European countries.

Data for Romania show an increasing prevalence of both primary and secondary infertility in 2010 (primary 1.5%, CI95% 0.7%-3.0%; secondary 17.1%, CI95% 8.9%-28.0%) when compared to the year 1990 (primary 1.2%, CI95% 0.6%-2.3%; secondary 14.3%, CI95% 7.7%-23.3%). Practically, about one in 5-6 child-seeking couples confronts primary or secondary fertility issues. Comparing the level of secondary infertility (frequently reproductive ageing and gynecological disorders related) in Romania (and Eastern European countries) versus high income countries we might associate the important difference observed with the socio-economic and medical access differences between those groups of countries. ART – very important instrument of correcting this trend, if optimal access and medical care are provided, especially due to aging population contributing to higher prevalence of infertility.

Countries that confronted this issue achieved a significant percent of their natality through IVF. In Belgium, the Czech Republic, Denmark, Estonia, Iceland, Norway, Slovenia and Sweden more than 3.0% of all babies born were conceived by ART (ESHRE, 2008). When comparing the number of ART procedures for the year 2010 (data collected from 31 European countries by The European Society of Embryology and Assisted Reproduction – ESHRE) Romania bottoms the list of the reporting countries (669 ART procedures/ million population), with only Hungary (557/million) being behind. Denmark (2893), Belgium (2736) and Iceland (2667) are at the top of the list comparing the total number of IVF procedures with the population, being in the same time countries where a very significant number of all children born are conceived through ART.

Legal constraints – present with variations from one country to another - limiting the access of certain population groups to ART (single mother, gay couples, advanced maternal age) or to certain ART procedures (gamete and embryo donation, surrogacy, PGD /PGS, cryopreservation) – the main consequence of the legal and financial constraints is the cross-border reproductive care. At the time of our study, Romania still does not have a specific legislation concerning assisted human reproduction procedures.

Religious and cultural elements are also involved in the suboptimal referral to ART procedures. An important part of the population are rejecting ART procedures on religious and moral bases, interpreting the discard of low quality embryos as a

form of abortion. Another „cultural” drawback is the fact that infertility of the couple is still largely seen as a medical problem of the female partner, in contradiction with the medical facts revealing that male factor is also involved in at least 20-30% of infertility cases (ESHRE, 2005). The practical consequence is delayed referral to reproductive specialists and the late medical investigation of the male partner, frequently after important reproductive ageing of the female partner with dramatic negative impact on success rates of ART techniques.

Individual reluctance to appealing to ART derives from above-mentioned issues and may be highly surpassed by optimal access to informations regarding ART techniques and their indications as well as by public health support for infertile couples / patients as in any other condition requiring medical assistance. The main questions asked are “Which/ what are my chances?”, “How much it costs?”, “what are the risks for my health and for the future baby’s health?” – this is the point where some general medical and ethical guidelines must be defined and applied with a major role for the clinician and professional detailed counselling (Pennings, 2013). Establishing optimal individualized strategy has consequences for the best clinical attitude, involving also a social impact (optimal chances of success, reduce in financial burden of the patients, public health and social costs of ART related morbidities – severe OHSS, multiple pregnancy and consecutive obstetrical complications, prematurity, neonatal mortality, morbidity and long term sequelae). In our opinion, good medical practice guidelines detailed below for an optimal individualised strategy, represent the “share” of the reproductive specialists required in the advocacy of public health support / financing of ART procedures (Shenfield, 2011, Nyboe, 2008).

Discussion

The decision “to treat or not to treat”

The decision “to treat or not to treat” requires an important ethical judgement by the reproductive medicine specialist in a situation with an important and particular psycho-emotional burden – the desire to have children, accumulated time and frustration, the potential emotional shock of failure; an appropriate psychological counselling is needed (Kaliarnta, Nihlen-Fahlquist, & Roeser, 2011), the final decision should be taken by the patient/couple, but after a very objective assessment made by the physician. The challenge of “overtreatment” - the ART specialist should not recommend excessively complex solutions, inducing the idea of a worse problem than in reality to patients generally receptive to this idea due to strong emotional impact of waiting unsuccessfully to conceive for a time considered to be “too long” in a subjective manner. “Heroic” treatment - encouraging patients with minimal chances of success to perform a procedure

whose outcome would only be an unnecessary financial effort, exposure to medical risks and additional psychological trauma. Promoting fertility desire in patients for whom a pregnancy represents a major medical risk by itself with regard to their medical condition. All these situations involve taking an important joint physician-patient decision that requires a careful assessment and especially a more objective overview from the fertility counsellor of the *de facto* medical situation and therapeutic possibilities. Parental age - age-related limitations also include numerous ethical, legal and social challenges regarding third-party donor procedures (gametes, embryos for postmenopausal women) - assessed and legislated variously in different countries, as well as the fundamental principle of the best interests of the resulted child who may have parents of very advanced age (Pennings, 2013). Lack of consensus concerning this matter can lead to quite tragic and bizarre consequences (Gulino, 2013; Vasireddy & Bewley, 2013).

Fertility Cryopreservation

The so-called “social egg-freezing” – the possibility of freezing the gametes/embryos brought about by a visible trend in the modern society, socioeconomic and lifestyle changes, has caused an increase in the average parental age and, therefore, delayed family planning – raises ethical debates (Ethics, Law *et al.*, 2012). The possibility for healthy women to cryopreserve their oocytes in order to counter future infertility has gained momentum in recent years. However, women tend to cryopreserve oocytes at a time that is suboptimal from a clinical point of view - in their late thirties - when both oocyte quantity and quality have already been considerably diminished and success rates for eventually establishing a pregnancy are thus limited (Lockwood, 2011).

This also gives rise to social and ethical concerns, as the procedure is seen as giving false hope to (reproductively speaking) older women. Measures can be taken to turn social freezing into a procedure that is both clinically and ethically better than the current practice, and three different steps can be taken into account: creating public awareness; offering individualized, age-specific information and counselling; and offering predictive tests such as anti-Müllerian hormone measurements or antral follicle count (Nardo, 2011). The main objective of these measures is to convince the women who are most likely to benefit from social freezing to use this procedure before the age of 35 and to discourage fertility clinics from specifically targeting women who have already surpassed the age at which good results can be expected (Mertes & Pennings, 2011).

Cryopreserving the fertility in oncological patients - the decision should take into account (Wunder *et al.*, 2012): (1) The right of all patients to have this option, given the fact that modern multimodal cancer therapy significantly increase the survival rates of oncological patients, but have a serious potential of damaging fertility (Patrizio & Caplan, 2010); (2) Assessing the risk the patient may be

exposed to by ovarian stimulation treatments or possible delay of cancer therapy; (3) Potential risks that might occur to the offspring of patients with a specific oncological problem; (4) The issue of false hope, some of the procedures used – *in vitro* maturation of oocytes, ovarian tissue cryopreservation - being still considered experimental (Deepinder & Agarwal, 2008); (5) Ethical and legal issues concerning informed consent in minor patients (Deepinder, Agarwal, 2008).

Public health system support for ART access - involves: (1) Acknowledgment of infertility as a disease and consequently the right to healthcare; (2) Criteria for selection of cases that receive public financial support involves an ethical discussion, but is mainly influenced by political particularities.

Reducing ART related morbidity

Reducing ART related morbidity – ovarian hyper stimulation syndrome (OHSS), oocyte retrieval incidents, ovarian torsion, comorbidities, pregnancy related complications (birth defects, multiple pregnancy, prematurity, embryo reduction), risk of vertical viral transmission by IVF / ICSI (Lutgens *et al.* 2009); adverse effects of fertility drugs. Fundamental medical ethical principle “*primum non nocere*” must also be respected in ART. Also taken into consideration should be the fact that the elective character of the procedure brings about a voluntarily agreed medical risk, but this assent should be the result of a very professional counselling. This informed consent refers to a protocol which needs individualization and though requiring a special degree of trust in the physician – patient relationship; hence, the particular responsibility of the ART specialist not to expose the patient to unnecessary risks by individualizing the protocols.

According to the ethical, legal, and social issues, the importance of this decision is even greater as there is an opposite decisional pressure – the pressure of time and results, augmented also by financial reasons (frequently the costs involved limit the number of attempts available for a patient). Countries where demographic and health policies are supportive for ART have accomplished, on one hand, a diminished burden for the physicians involved, on the other hand, the implementation of regulatory measures capable of reducing the main morbidities related to ART (OHSS, multiple pregnancies) without altering the chances of success for the patients involved (Voelker, 2011). These policies allowed the concepts of OHSS-free clinic (Devroey & Adriaensen, 2011), mild stimulation (Casano *et al.*, 2012), and single embryo transfer to become part of the current practice without a major drawback in the overall results (Min, 2010; Voelker, 2011).

Regarding the long-term risks related to fertility medication and those for the resulted children, it is still early to draw definitive conclusions, considering that there have been less than four decades since the first “test tube baby” was born and an even shorter period since ART has become widely available to current

practice. However, most studies conducted so far converge to the opinion that increased incidence of certain morbidities in IVF / ICSI offspring is mostly influenced by some infertility causes and advanced parental age rather than by the procedure itself (Fauser *et al.*, 2014).

Providing access to quality medical care, once taken the decision to treat, involves additional ethical tasks determined by: (1) Prohibitive costs – in certain cases, the ART specialist is forced to choose a protocol that requires a smaller financial effort from the patient, but also with a lower success rate, rather than a protocol the patient could not afford at all (Aleyamma *et al.*, 2011); (2) Individual tailoring of protocols is often “expert opinion” determined, more than “evidence-based”, in a situation in which: (a) there is a relatively rapid evolution of new therapeutically options with good potential, but confirming the benefits by large randomized trials proves frequently very difficult, with a supplementary time related pressure. The patients cannot afford the “long” period required to prove the efficiency and long term risks of these new options; (b) the silent, but strong competition between ART centers (in what has become a billion dollars industry) induces additional pressure to appeal to innovations as soon as possible, to be one step ahead from the competitors, given the lack / impossibility of standardization, but this could also mean supplementary risks and costs for the patients; (3) Genetic testing - preimplantation genetic diagnosis (PGD) and preimplantation genetic screening (PGS) of embryo quality raises additional ethical issues (De Wert, 2014; Dickens, 2014) because it can generate sex and eugenic selection for non-medical reasons (Alviggi, 2012; Dondorp, 2013), but could also avoid major medical disorders in the resulted children (De Wert, 2014). At stake are three main ethical, legal, and social principles. Firstly, the technology is justified by referring to the welfare of the child by avoiding harm to the future offspring. Secondly, the application of PGD increases the autonomy of the parents, both by allowing them to choose a technique that better fits their moral principles and reduces the psychological burden (by avoiding repeated terminations of pregnancy) and by giving them the possibility to protect their interest in favoring the health of their offspring (Shenfield, 2008).

Conclusions

Medically assisted human reproduction has attracted massive ethical, legal, and social concerns from the beginning, amplified by the major progress and spreading of ART. The debates extended from questioning the procedure itself to whom it is addressed to and the methods used. An important part of the controversies related to ART are legislated differently from one country to another, the political and cultural-religious factor often having a major influence. It is unlikely that in the near future a uniform attitude could be reached related to:

third-party donor procedures, single parents, gay couples, advanced maternal age. One of the most obvious results in the globalization era is the so called cross-border reproductive care, which has an important extent, due to some other factors such as the financial one and the competition among ART centers in their success rates, all of them contributing to patient migration along with country-specific legal limitations (Shenfield, 2011; Ethics Committee of American Society, 2013).

In terms of good practice regulations generally available, the involvement of specialized medical organizations and the state can increase the chance of providing a safer medical environment and act in the best interest of the patients. A safer medical management also requires an individualized approach, due to the variety of medical situations and heterogeneity of patients appealing to ART techniques, as discussed above.

Infertility represents a large scale medical condition with important social and public health impact. Optimal ART access – meaning optimal access of targeted populations to optimal medically individualized treatments – might prove an efficient strategy to partially overcome this issue, with appropriate public health system support, as proven in countries that focused on this problem in a serious manner before us.

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